Coverage Initiation

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Noxxon Pharma: Unleashing the tumor microenvironment

09/04/2018

Estimated Price:	€17.9
Share Price (€) *	3.9
Market Cap. (€M) *	8.6
Estimated Market Cap. (€M)	39.9
Number of shares (M)	2,229,549
YTD high/low (€)	6,3 / 3,8
3-months average daily vol.	2 946
Free float	7%
Estimated net cash (€M)	1.8

** on 09/04/2018*

Noxxon Pharma is a company specializing in cancer immunotherapy, which develops several products from its technological platform of discovery and production of Spiegelmers.

A unique technology ... that specifically targets the immunological behavior of the tumor microenvironment. The products of Noxxon, particularly NOX-A12 and NOX-E36 address the resistance phenomena observed in solid tumors.

... that renews the vision of the tumor microenvironment ... by offering new perspectives in the management of solid tumors, particularly in metastatic colorectal cancer and pancreatic ductal adenocarcinoma that are resistant to chemotherapy and immunotherapy and bad prognosis.

... thanks to products discovered from its Spiegelmer platform ... all of which have been shown to be effective in clinical trials. Indeed, NOX-A12, the main product of Noxxon has been tested in Phase II in hematological cancers including multiple myeloma and chronic lymphocytic leukemia.

NOX-A12 in combination with an anti-PD-1, pembrolizumab or Keytruda in solid cancers is currently being tested in colorectal cancer and pancreatic cancer. Partial results of this clinical trial demonstrating an increase in the infiltration of tumors by immune cells should be published in the second quarter of 2018. Then, results of efficacy, in combination between NOX-A12 and Keytruda should be available at the end of the year 2018.

Noxxon Pharma's development strategy is to license its products following a Phase III trial. The development of NOX-A12 or NOX-E36 in combined therapy for other indications should represents a significant benefit for both Noxxon and the partner. Based on various indications targeted, colorectal cancer, pancreatic cancer and glioblastoma, we estimate the value of Noxxon Pharma at 17.9€/share.

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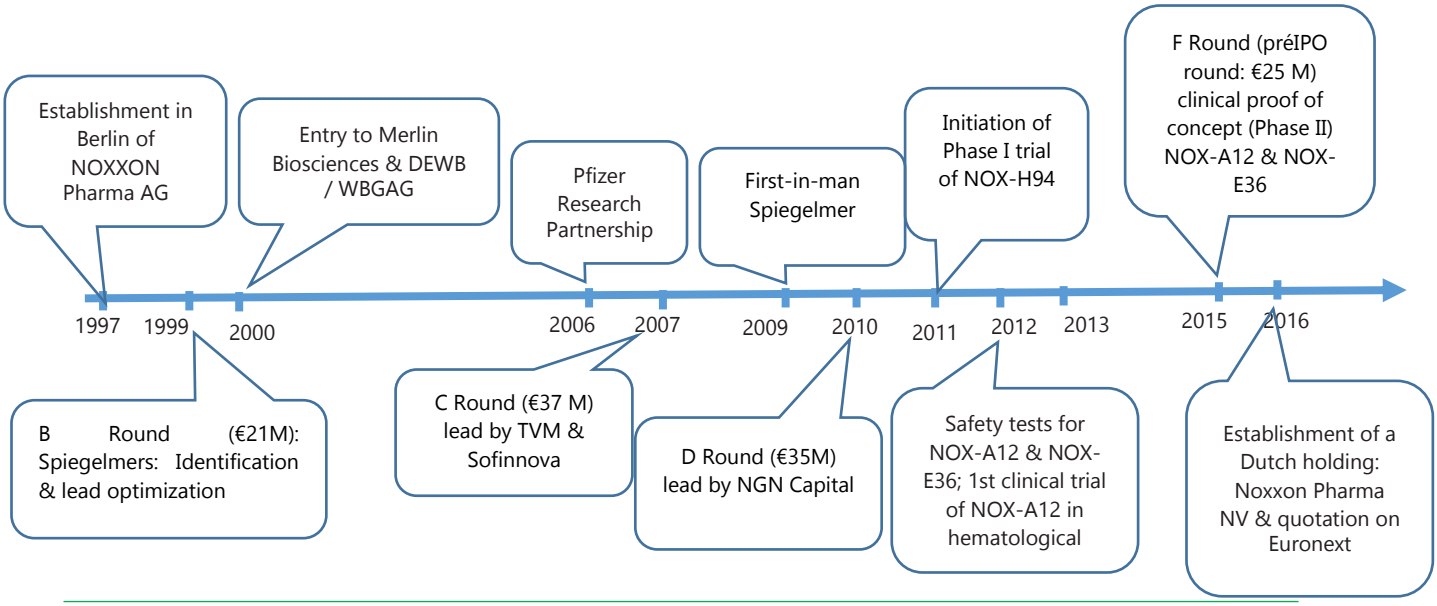
Description of the Company

Noxxon Pharma, which was founded in Berlin in 1997, is a biotechnology company that develops novel and innovative molecules targeting the tumor microenvironment. The Company is focused on developing its portfolio of fully patented products, including two molecules, NOX-A12 and NOX-E36. These chemical molecules belonging to the Spiegelmers class, can bind to biological targets and maximize the effect of immunotherapies inside cancer cells to destroy them more effectively. The drug candidates developed by Noxxon aim to potentially treat a wide variety of solid cancers (including pancreatic cancer, colorectal cancer, glioblastoma ...). NOX-A12, which blocks the activity of the chemokine CXCL12 and its CXCR4 and CXCR7 receptors, is currently being tested in several clinical studies in patients with pancreatic cancer, colorectal cancer. However, NOX-A12 has already been shown to be effective in hematological cancers (chronic lymphocytic leukemia or CLL, multiple myeloma or MM).

Company Timeline



Source: Noxxon Pharma

The second drug candidate is NOX-E36, which binds to the CCL2 chemokine and neutralizes it as well as 3 other chemokines. This chemokine CCL2 or MCP-1 (for Monocyte Chemoattractant Protein-1) has the property like all other chemokines to attract immune cells, in this case monocytes / macrophages. CCL2 and its CCR2 receptor participate in the migration and infiltration of a particular subpopulation of immunity cells. The migration of monocytes from the bloodstream through the vascular endothelium has been shown to be an essential step in immunological tissue monitoring as well as in response to inflammation.

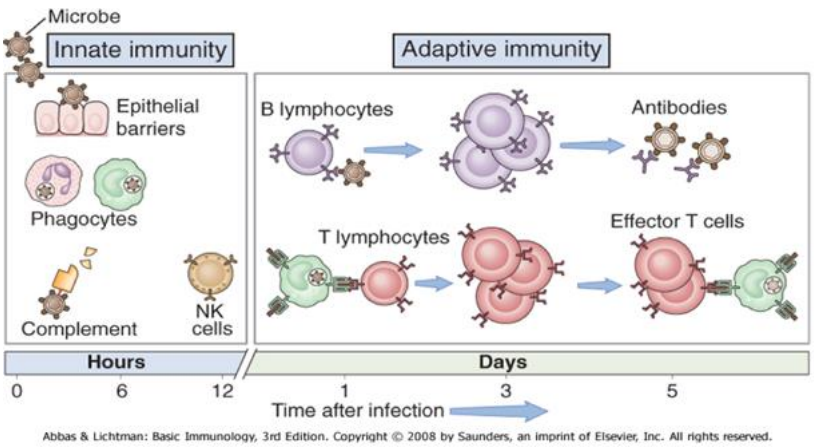
Immunity, immunotherapies and microenvironment

Recent advances in immunotherapy have shown that it is possible to treat and even eliminate some cancers that are not treated by current standards of care[1]. Thus, the arrival of immune checkpoint inhibitors (ICI) has yielded very promising results in the treatment of melanoma and lung cancer[2]. However, depending on the cancer, there is a great variability of results with immunotherapy. Sometimes as Chen & Mellman has been shown in 2017, even in cancers that are considered reactive, the success rate of immune checkpoint inhibitors is often less than 50%. First, let's go back to some notions about the immune system, its biology and its role in protecting against cancer.

Immunity and Immune Checkpoint Inhibitors (ICI)

Immunity refers to the ability of an organism to defend itself against foreign substances such as infectious agents (bacteria, viruses, parasites) or pathological agents. It is manifested by a response, which mobilizes all the cells, tissues and molecules that make up the immune system, which oppose these foreign agents. The body has two defense systems: innate immunity and adaptive immunity. Innate immunity (natural immunity), which is not specific to a foreign agent, can therefore be mobilized immediately by relying on the distinction between self and non-self. This immunity involves natural barriers such as skin or mucous membranes, humoral mechanisms such as complement molecules, cytokines, inflammation proteins and cells (phagocytes, NK cells).

Innate and Adaptive Immunities



Adaptive immunity is specific to an agent already encountered in the past and has been remembered. With a slower onset, because it is based on memory and immune specificity, the acquired immunity is based on a cellular component using T lymphocytes and a humoral component (linked to the blood or lymph) mobilizing soluble molecules, antibodies. Although there are close interactions between innate

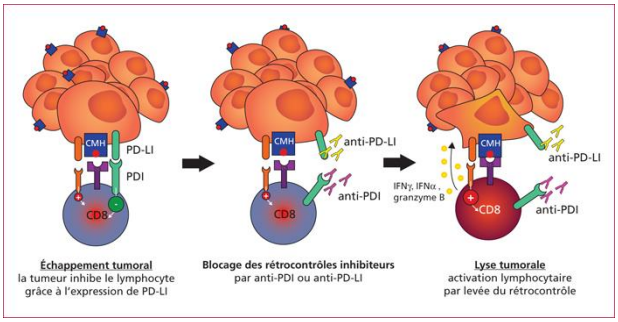
[1] Delitto D, Wallet SM & Hughes SJ. Targeting tumor tolerance: a new hope for pancreatic cancer therapy? *Pharmacology and Therapeutics* 2016; 166: 9–29.
[2] Rafei H, El-Bahesh E, Finianos A, Nassereddine S & Tabbara I. Immune-based therapies for non-small cell lung cancer. *Anticancer Research* 2017; 37: 377–387.

immunity and adaptive immunity that are dependent on each other, and communication between cells in the innate and adaptive system is essential for effective immune response.

Immune Checkpoint Inhibitors (ICI)

Immune Checkpoint Inhibitors (ICIs) have truly revolutionized the immuno-oncological space. Immune checkpoints are a generic term for molecules that limit the proliferation and destruction capacity of T cells.

Co-stimulation or co-inhibition of T cells



Negative co-stimulatory molecules (a sort of immunological brake), Cytotoxic T Lymphocyte Associated Antigen 4 (CTLA-4) or Programmed Cell Death Protein-1 (PD-1), are naturally involved in immune tolerance mechanisms. Immune tolerance is a process that allows the immune system to not react against the body (the self), which prevents T cells from self-activating. CTLA-4 limits T-cell response by initiating co-stimulation of B7, while PD-1 intervenes by another pathway focused on the PD-L1 or PD-L2 ligands. Although CTLA-4 and PD-1 regulate T cell activity, they are thought to exert their function in different stages of T cell activation.

Approval of immune checkpoint inhibitors

Molecule	Brand	Company	Target	Approval date	Market in 2022 ($bn)
ipilimumab	Yervoy	BMS/Ono	CTLA-4	mars-11	2,27
pembrolizumab	Keytruda	Merck & Co	PD-1	sept-14	10,66
nivolumab	Opdivo	BMS/Ono	PD-1	déc-14	11,22
atezolizumab	Tecentriq	Roche	PD-L1	mai-16	4,86
durmalumab	Imfinzi	AstraZeneca	PD-L1	mai-17	2,78
avelumab	Bevancio	Merck KGaA & Pfizer	PD-L1	mars-17	0,59

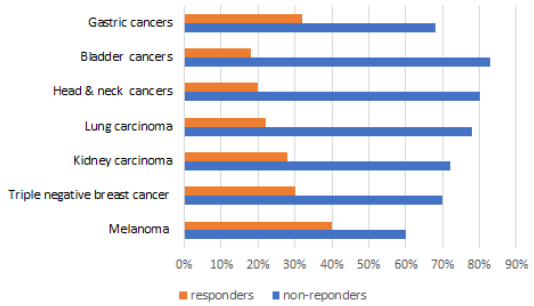
CTLA-4 would primarily regulate cellular immunoactivation responses, while PD-1 would inhibit effector T cells. However, the tumor machinery, which synthesizes ligands for CTLA-4 and PD-1, can maintain T cells in a state of tolerance for antigens carried by tumor cells. This "anergic" state is also reinforced by the tumor microenvironment leading to deficient anti-tumor immunity. Therapeutic anti-CTLA-4 and anti-PD-1 antibodies are intended to overcome this inhibition of T cells. With these new therapies, long-lasting responses have been observed in patients who responded to treatment, although response have been modest. The first FDA-approved checkpoint inhibitor was Bristol-Myers Squibb's Yervoy

(ipilimumab) in 2011, a humanized monoclonal antibody against CTLA-4 for metastatic melanoma. Since Yervoy's approval, four other checkpoint inhibitors have reached the market: Keytruda, Opdivo, Tecentriq and Imflizi, where the first two are antibodies against PD-1 and the last two targeting PD-L1.

Limits to Immunotherapy

ICIs have profoundly modified the treatment of cancers, by increasing the overall survival of patients in difficult-to-treat tumors such as metastatic melanoma, or non-small cell lung cancer. However, only 20 to 40% of patients respond to these anti-PD-1/PD-L1 immunotherapies and therefore non-responders represent the majority. Phenomena that have been observed even for cancers that have demonstrated good sensitivity to ICI such as melanoma, lung carcinoma or renal cell carcinoma. Recent work has shown that the degree of infiltration of the tumor by infiltrating T lymphocytes or TIL (T cells infiltrating) is a good indicator of the patients' response to immunotherapeutic treatment[3], as has been demonstrated in melanoma. In addition, the type of T cells and their location are essential criteria. Tumors with a high level of LTI are called immunogenic, while tumors with a low level are considered non-immunogenic.

Cancers classified as responders and non-responders to ICI



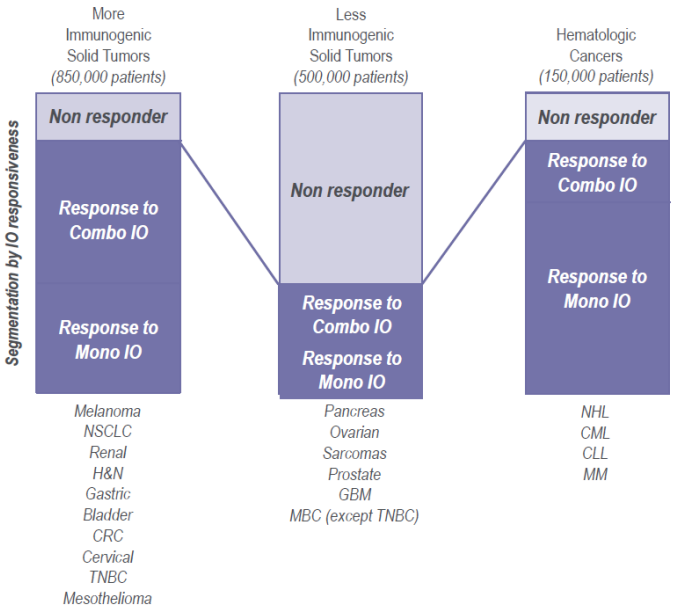
Source: adapted from Teng et al. 2015

Although immunotherapy is rapidly becoming a treatment standard for many cancers, the fact remains that the capacity and quality of the immune response is mainly determined by the interference between the patient's immune system and the tumor. Some cancers resulting from exposure to a mutagen are the conditions that best respond to ICI immunotherapies. Lung cancer (NSCLC) often induced by smoking, melanoma due to UV exposure. These are the indications that saw the first ICI recordings, since Yervoy was first registered for the treatment of melanoma. The response rate observed in hematologic cancers is high both in monotherapy and in combination. This is most likely because leukemias and lymphomas are characterized by a high mutational load. However, for cancers such as pancreatic, ovarian, prostatic, sarcoma and glioblastoma carcinomas, the levels of responses observed with ICI are low and require the use of combination of ICI or ICI with chemotherapy.

Indeed, in these tumors with a low mutational load, there are very few immune infiltrations within the tumor tissues. And these immunosuppressive properties are characteristic from so-called "cold" tumors. It is a question of arousing within these unresponsive tumors the production of unusual and therefore immunogenic proteins to transform them into "hot" answering tumors.

[3] Teng MW, Ngiow SF, Ribas A & Smyth MJ. Classifying cancers based on T-cell infiltration and PD-L1. *Cancer Research* 2015; **75:** 2139–2145.

Classification of cancers according to their response to ICI



Source: Citi Research, American Cancer Society

Therefore, in terms of clinical responses to ICI, we can distinguish two main resistance mechanisms:

- a primary resistance leading to sensitivity phenomenon where the anti-PD1 therapy releases adaptive anti-tumor immunity with a stable disease progression and some complete responses;
- an acquired resistance where the anti-PD1 therapy initially releases tumor-specific immunity, and but eventually fails, ultimately conduct a disease relapse.

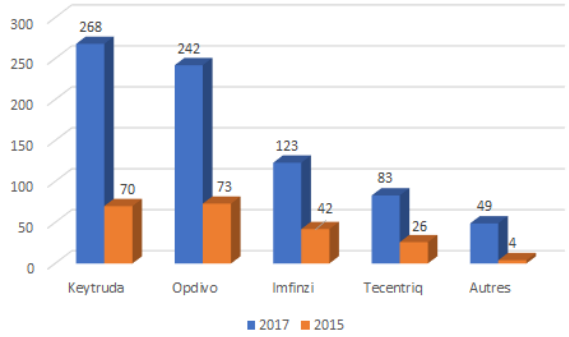
To overcome these resistance occurrence, which result from different categories of resistance to anti-PD1 therapy such as un-tolerance to antigen presentations to antigen presenting cells (APC), exhausted effector T cells, emergence of tumor neoantigens…, there are multiple strategies. One of the most used today is obviously, the increase of synergistic combination between anti-PD-1/PD-L1 therapies with others anticancer molecules.

Combinations: the future of immunotherapy

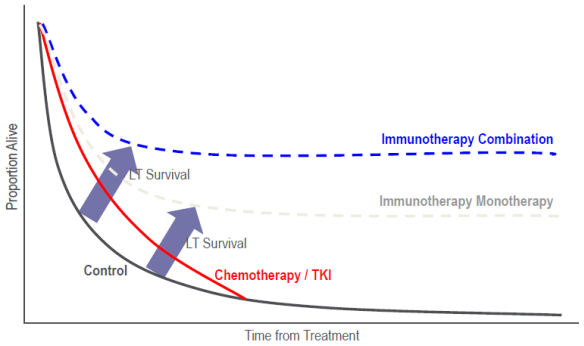
In recent years, there has been an acceleration in the number of combinations involving anti-PD-1 and anti-PD-L1 molecules. According to EP Vantage, with 765 clinical trials with ICI, the number of tests would have been multiplied by more than 3 over 18 months period (765 vs 215). Studies in associations have increased to account for the genomic diversity of tumors, while having the Damocles sword of toxicity, because when we increase the number of molecules, the side effects increase in number and intensity. Several tracks are followed with ICI in combination with targeted therapies or traditional chemotherapy. Checkpoint inhibitors are likely to be an essential part of the anticancer therapeutic arsenal. These compounds induce a memory immune response, which takes longer to settle compared to traditional chemotherapy, but will last longer. Preclinical data from the Noxxon compounds suggest that the combination of PD-1 inhibition with CXCL12 inhibition may result in significant synergies in the tumor microenvironment, repolarizing the tumor microenvironment from an immunosuppressive to an

antitumor state.

Number of association studies Anti-PD-1/anti-PD-L1 between 2015 & 2017



Displacement of survival curves



Source: EP Vantage, Labiotech, Citi Research

Immunotherapy & solid tumors

In recent years, immunotherapy has evolved considerably to emerge as a real therapeutic alternative in oncology. Immunotherapy is to boost, activate or inhibit the immune system, which is the ultimate line of defense of our body against assaults of all types (non-self) so that it destroys cancer cells. Several discoveries are at the origin of this return in force. First, the fact that the immune co-stimulatory mechanisms associated with the presentation of antigens are essential in the antitumor immune response and activation of cytotoxic T cells[4]. Then the blocking of these inhibitory pathways by antibodies, which by reducing the activation of T cells favored tumor growth, provided durable clinical responses in several types of tumors (melanomas, lung cancers ...)[5]. However, despite the positive results that have been observed in many patients, particularly in melanoma or lung cancer, checkpoint inhibitors alone do not yet provide sufficient long-term solutions. Indeed, in indications such as pancreatic cancer, colorectal cancer[6], immunotherapy is no better than standard therapies. In addition, recent work has highlighted the inhibitory effects of the tumor microenvironment on the immune system.

Immune cells: the central components of the tumor microenvironment

Recent scientific work has complicated the vision of the 80s and 90s of a tumor environment simply consisting of cancer cells interacting with each other. Today, it is recognized that several cells adjacent to tumor cells, namely stromal cells, fibroblasts, endothelial cells and immune cells, contribute all to the tumor environment and therefore have an impact on antitumor immunity. Within this heterogeneous set of cells, which constitutes the "tumor microenvironment", we find the immune cells, which play a dual role in cancer: they can promote the progression of the tumor including creating an immunosuppressive tumor microenvironment and induce tumor annihilation by destroying cancer cells. Thus, within the immune cells, those that act against the tumor, such as $CD8^+$ T lymphocytes and CD4 (Th1) helper T lymphocytes, NK cells, M1 macrophages, and dendritic cells, are distinguished. While regulatory T cells

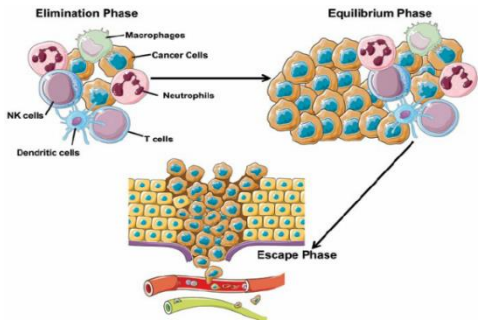
[4] Harding FA, McArthur JG, Gross JA, Raulet DH, Allison JP. CD28-mediated signalling co-stimulates murine T cells and prevents induction of anergy in T-cell clones. Nature. 1992; 356 :607-9.
[5] Garon EB, Rizvi NA, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015; 372 :2018-28.
[6] Sunshine J, Taube JM. PD-1/PD-L1 inhibitors. Curr Opin Pharmacol. 2015 ;23 :32-8.

(Treg), M2 macrophages, TAMs (Tumor Associated Macrophages), myeloid suppressor cells (CDMD), T helper cells 2 (Th2) promote tumor growth[7]. The pro-tumor immune cells and the stromal and endothelial cells form an immunosuppressive network in the tumor microenvironment. The balance between pro-tumor and antitumor immune cells is mainly coordinated by specific chemokines and adhesion molecules.

From immune surveillance to immunoediting

Immune surveillance and immunoediting are two concepts that explain how cancer cells escape the immune system. There is a balance between the pro-tumoral and antitumor action of the immune system, which depends on the initial conditions (immune status of the patient, typology of the tumor). And it is this initial situation which would be the origin of the change in one or the other behavior. According to the concept of immune surveillance, the immune system recognizes and responds to pathogens and abnormal cells present in the body, e.g. tumor cells, and thus acts suppressively on the tumor. In contrast, immunoediting, which may be the exact opposite of immunosurveillance, postulates that the immune system will, by eliminating sensitive cells, select immune-resistant cancer cells to survive, leading to immune escape and tumor progression.

Immune surveillance & immunoediting



Source: Nature

The three phases of immunoediting are elimination, balance and escape. Elimination consists of a series of interactions between innate immune cells of the host and new (cancerous) neoplastic cells. During this first period, the immune system exerts a strong antitumor pressure, which can cause certain neoplastic lesions to survive this pressure. These variants resistant to this elimination phase are therefore counter-selected because they have low immunogenicity as well as immuno-evasion properties. These cells therefore enter an equilibrium phase, where the immune system, by destroying the sensitive cells, will "select" the resistant and weakly immunogenic cells. Then, the tumor will pass from this equilibrium phase to an escape phase during which immune-evasive tumor cell variants that have escaped the immune response are therefore free to multiply in malignant tumors. Immunoediting therefore leads to Darwinian selection of poorly immunogenic cancer cells that can thus escape the immune system of the host. Note that Cytotoxic T Lymphocytes (CTL) are essential in the theory of immune surveillance and immunoediting. CTL recognize tumor cells as foreign by identifying peptides on the surface of cancer cells, called tumor antigens or neoantigens. These peptides, which are not normally expressed on cells, allow the immune system to recognize and eradicate cancer cells. There are several types of tumor

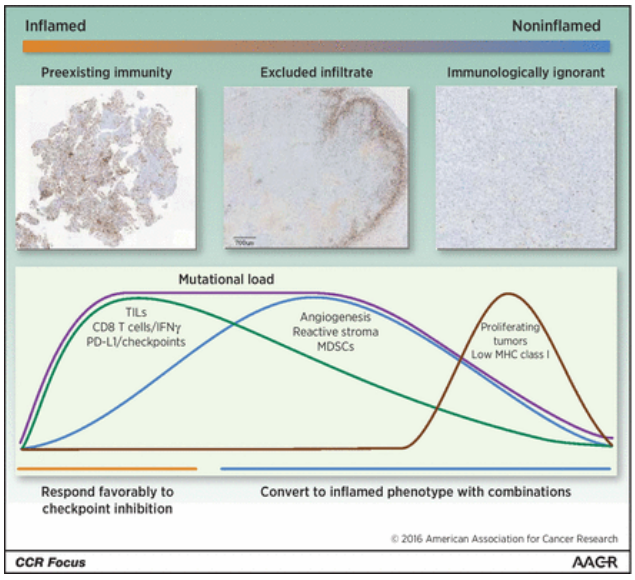
[7] Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumors: impact on clinical outcome. Nat Rev Cancer. 2012; 12:298-306.

antigens: for example, antigens that are mutated gene products, such as RAS and p53, that are tumor specific. Other tumor antigens can be either cellular proteins that are overexpressed by tumors, or genes that are normally silent but are activated by the tumor process. The immune escape by the tumor cells is a major obstacle in the development of immunotherapies and therefore strategies to overcome the immune evasion and go from the equilibrium of the escape to the immunoediting elimination, are studied for the development effective therapies.

Exhaustion of T cells in the tumor microenvironment (TME)

First described in the context of certain chronic conditions, there is a depletion of T cells in the proximity of tumors, which would be due to sustained antigenic stimulation[8]. Chronic exposure to antigens results in increased expression of inhibitory receptors, including programmed cell death protein 1 (PD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4), immunoglobulin T domain, and mucinique domain protein 3 (TIM-3), lymphocyte-activating gene 3 protein (LAG-3) and T cell immunoglobulin and the Inhibitory motifs based on immunoreceptor tyrosine (TIGIT). In addition, there are also hypofunctional CD8 + T cells in the MET. In this state of depletion of T cells, they express high levels of inhibitory receptors, progressively lose their ability to produce cytokines IL-2, TNF-alpha, interferon γ and granzyme and are thus unable to effectively eliminate cancer cells. Blocking these inhibitory receptors may partially restore T cell function enhancing their ability to eradicate cancer cells. The clinical success of PD1 inhibitors and anti-CTLA-4 antibodies validated this concept. These different phenomena make it possible to distinguish three histological typologies for tumors: inflamed tumors, immune excluded tumors and immunologically deserted tumors (immune desert). Inflamed tumors are characterized by the presence of infiltrating T lymphocytes (LIT), cytotoxic $CD8^+$T lymphocytes, interferon γ -producing $CD4^+$T cells (IFNγ), infiltrating lymphocytes expressing the PD-L1 checkpoint, as well as a high mutational load.

Tumoral immunity continuum



Source: Hedge et al. Clin Cancer Res 2016

Despite a high mutational load, tumors with exclusion of infiltration are characterized by an increased

[8] Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. Trends Immunol. 2015; 36 :265-76.

influence of the immunosuppressive stroma, presence of myeloid-derived suppressive cells (MDSC) and angiogenesis. All these characteristics tend to inhibit T cell infiltration in tumors or suppress T cell activation in the tumor medium. Finally, immunologically-ignorant tumors that contain very low T-cell infiltration are genomically stable with highly proliferating tumor cells. These are representative of non-inflamed tumors.

On the other hand, non-inflamed tumors are weakly infiltrated by lymphocytes, under-express PD-L1 all associated with a low mutational load (little or no genomic instability) as well as a low expression of machinery. presenting antigens to immune cells. These non-inflamed tumors are often of poor prognosis. In addition, some innate immune cells secreting growth factors promote the creation of an inflammatory environment. In addition, immune cells also provide the tumor microenvironment with extracellular matrix modifying enzymes for angiogenesis (formation of new blood vessels from already existing ones), invasion and metastasis. The immune cells can also release chemicals that can cause mutagenesis, mainly reactive oxygen species, and thus promote and accelerate the acquisition of genetic alterations that enhance the malignancy of cancer.

On the other hand, infiltration of immune cells can also suppress tumor growth, particularly with tumor-specific CD8 + T cells (CTLs) that recognize and kill tumor cells. CTLs distinguish tumor cells from other cell types by expressing antigens that are not normally expressed on healthy cells (neoantigens). Neoantigens are peptides derived from protein mutations presented on the MHC (Major Histo Compatibility System). LCT infiltration into the tumor has been shown to be a favorable prognostic factor in several cancers, including colorectal cancer, ovarian cancer and melanoma[9].

[9] Gajewski TF et al. Innate and adaptive immune cells in the tumor microenvironment. Nature Immunology 2013: 1014-1022.

Spiegelmers: an innovative and exclusive technological platform

Since their discovery in 1990, aptamers have rapidly developed and become research tools. Generated by the SELEX method (Systematic Evolution of Ligands by Exponential Enrichment), an *in vitro* combinatorial technique of synthetic oligonucleotide libraries, the aptamers are thus modified oligonucleotide sequences. These selected oligonucleotides are capable of selectively binding a given ligand with high and specific affinity. Initially developed with RNAs, this technique was then generalized to DNA oligonucleotides.

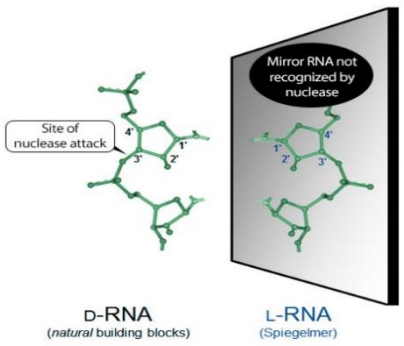
Aptamers

Aptamers are short single-stranded nucleic acid structures between 15 and 60 bases. First described in 1990 by Ellington and Szostak[10], aptamers can bind with high affinity and strong specificity to various targets (small organic molecules, peptides, proteins, nucleic acids or cells). The specific structure features of aptamers that involve three-dimensional folds, result in these high affinities and specificities. The interaction between the aptamer and its target results in a conformational rearrangement of the initial structure of the aptamer to adopt a new structure integrating the target. With these molecular recognition properties, aptamers could be considered an alternative to antibodies.

Noxxon and the Spiegelmers

Since its creation in 1997, Noxxon has developed the proprietary technology of Spiegelmers. These molecules are L-type stereoisomers of aptamers or short nucleic acid sequences that adopt a constrained 3D structure. These molecules, which lie at the interface between biological molecules and small chemical molecules, combine several advantages: an increased affinity for their targets as well as a high specificity (biological aspects) and a simplified chemical synthesis compared to the antibodies. Spiegelmers belong to the class of aptamers, which are synthesized from natural nucleotide blocks in a D-nucleotide conformation.

Comparison D-ARN vs L-ARN

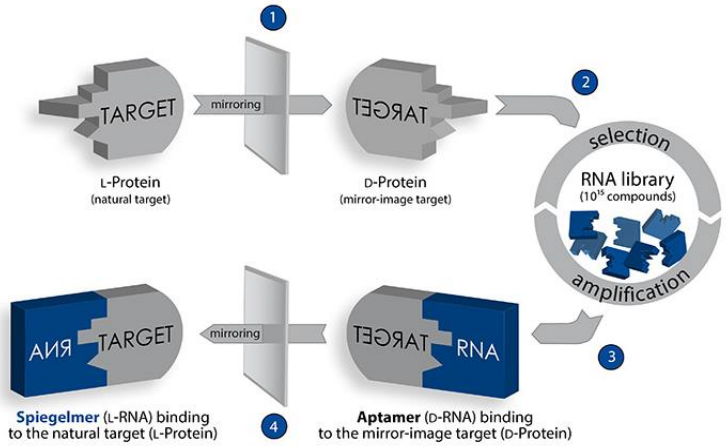


Source: Noxxon Pharma

[10] Ellington AD, Szostak JW. In vitro selection of RNA molecules that bind specific ligands. Nature, 1990. 346: 818-822.

This natural conformation of aptamers can lead to disadvantages such as some biological instability and a propensity to activate the immune system. The transformation of these aptamers into Spiegelmers by a mirror image chemistry allows these structures to no longer be recognized by nucleases (enzymes that cleave the RNA and / or DNA structures) and to no longer be recognized as a foreign RNA by the immune system.

Spiegelmers' Technology



Source: Noxxon Pharma

In addition, it may be necessary to increase the molecular weight of Spiegelmers candidates to modify its bioavailability and thus reduce its elimination of blood and thus keep it longer in the body. For this, the company developed PEGylation procedures, which involves attaching (conjugating) polyethylene glycol (PEG) chains to a biologically active molecule. A PEG of 40kDa was attached to the Spiegelmer[11]. The company uses the SELEX process (Systematic Evolution of Ligands by Exponential Enrichment) to identify Spiegelmers[12]. This method of *in vitro* selection from combinatorial libraries of synthetic oligonucleotides makes it possible to choose molecules capable of binding selectively and very specifically on targets. First, a mirror image of the target is chemically generated, then by screening the 10^{15}-containing oligonucleotide libraries, candidates are identified and amplified by a series of screening and amplification processes, until compounds are obtained. the best affinity and specificity. Then the selected single aptamer is synthesized chemically in mirror image (Spiegelmer). This Spiegelmer, while less sensitive to nuclease attacks and less immunogenic, retains the target attachment properties of the initial aptamer.

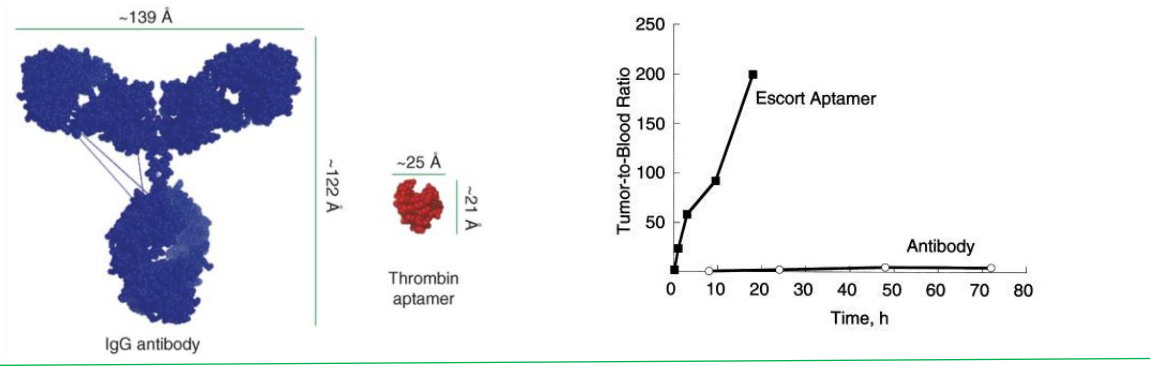
Aptamers / Spiegelmers vs Antibodies

Peptide aptamers are a new type of recognition molecule, whose design is inspired by the structure of antibodies. The selection of aptamers is carried out on a library of 10^{15} compounds by identifying molecules capable of interacting in vivo with a therapeutic target protein and of inhibiting it. Examples of

[11] Hoffmann S et al. RNA aptamers and Spiegelmers: synthesis, purification and post-synthetic PEG conjugation. Curr Protoc Nucleic Acid Chem. 2011; chapter 4; unit 4.46 1-30.
[12] Tuerk C, Gold L, « Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase », *Science*, 1990; 249: 505-510.

therapeutic targets are RAS protein and other proteins in its activation pathway. Inhibition of this pathway blocks the proliferation of cancer cells and leads to their death. Although used extensively in the current pharmacopoeia, antibodies have several disadvantages that have naturally limited their development. Thus, they are very large molecules of nearly 155 KDa (kilodalton unit mass of molecules) against only 15 kDa for aptamers and Spiegelmers. This large size can often be a disadvantage when it comes to touching certain tissues or cell fractions. In addition, the antibodies can be developed only against molecules or immunogenic compounds (capable of developing an immune reaction), while aptamers can be selected against non-immunogenic or toxic molecules for the cells producing the antibodies. The production and manufacture of antibodies is performed in vivo and requires long production steps, which can sometimes lead to reproducibility problems.

Comparison Aptamers vs Antibodies



Source : Aurgalys

While Spiegelmers and aptamers, which are small chemical molecules, have simpler manufacturing processes than antibodies. In addition, they do not generate a toxic reaction or immunogenicity as may sometimes be the case with antibodies.

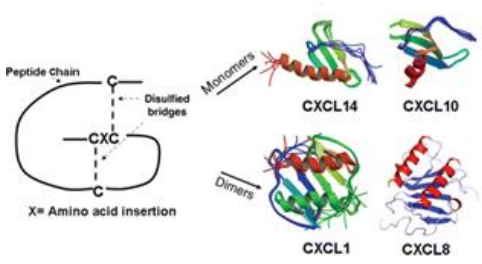
Inhibition of CXCL12 and of CCL2, new tracks

Noxxon Pharma, with its drug candidates NOX-A12 and NOX-E36, has shown that it is possible to block certain chemokines in a durable and non-toxic way. Thus NOX-A12 acts on the chemokine CXCL12 or SDF-1 (Stromal Cell-Derived Factor-1), whose role in cell migration is essential. While NOX-E36 blocks CCL2 or MCP-1, a chemokine involved in tumor development and immune privilege of the tumor. This is a property that some parts of the body, which leads these pathological areas to tolerate the presence of antigens without generating an immune response.

Chemokines & their receptors

Chemokines (or chemo-attracting cytokines) and their membrane receptors have attracted the interest of the scientific community since the mid-1990s. In this family of molecules (48 chemokines known to date and at least as many cloned receptors), almost none was not known in 1991. Chemokines and their receptors are expressed in a wide variety of cells of the hematopoietic system with functions exceeding those of chemotaxis. One of the main functions of chemokines is to attract leucocytes to the inflammatory site from their place of production[13]. Because as emphasized, one author in one of her reviews "the effectiveness of the immune system depends on the mobility of the various cell types that compose it and that never stop circulating between the blood, the peripheral tissues and the lymphoid organs[14]". These capacities of displacement of the immune cells as well as the tumor cells thus depend strongly on the network of chemokines.

Structure of Chemokines CXC



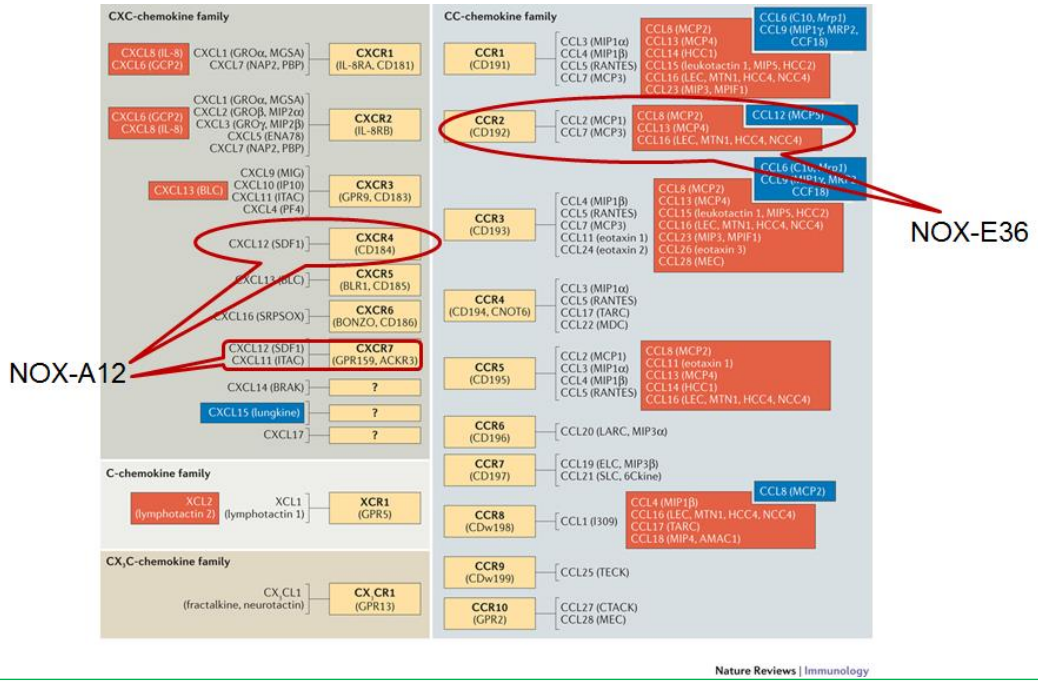
Source: Balestrieri et al.

These small molecules, which are the largest subfamily of cytokines, can be divided into four relatively structurally homogeneous classes. The main difference lies in the location of 2 cysteines, a specific amino acid very important in the structure of these agents. Thus, CXC chemokines (group α), chemokines CC or group β, chemokines C of group γ and chemokines CX3C (group δ) are distinguished. Chemokines are produced by both adherent cells and circulating cells. They can also be produced by the cells they attract. Constitutive or homeostatic chemokines are produced in small amounts by the organs under normal physiological conditions. However, inducible (or inflammatory) chemokines are produced massively in a pathological context (infectious, inflammatory or tumoral) by the tissue itself or by leukocytes infiltrating the tissue. The specificity of action of chemokines is directly related to the cellular distribution of their target receptor (s): the chemokine receptors.

[13] Samson M., Aubry F. et Parmentier M. M/S 2007 : 23, (2) : 173-9
[14] Combadière B., Combadière C. et Deterre P. M/S 2007 : 23, (2) : 173-9

These receptors, numbering 19, have a multiplicity of functions that go beyond the simple migratory phenomena. Although there are differences in primary structure, their tertiary structure composed of 6 extracellular and intracellular loops separated by 7 transmembrane domains makes them belong to the large family of seven-segment transmembrane receptors coupled to G proteins. characterized and grouped into four sub-families corresponding to the CXC, CC, C and CX3C chemokines that they recognize. Noxxon with NOX-A12 which binds to ligand CXCL12 (SDF1α) thus acts the CXCR4 receptor (CD184) and on the CXCR7 receptor (GPR159, ACKR3). CXCR4 plays an essential role during embryonic development, as the expression of CXCR4 on the surface of progenitor cells allows migration from their place of origin to their destination, where they will differentiate into organs and tissues.

Chemokines and their receptors



Source: Nature Reviews

The CXCR4-mediated pathway is important in neo-angiogenesis, immunity, and infections[15], as well as predominantly autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. CXCR4 and CXCL12 thus play decisive roles in tumorigenesis, including enhancement of cell proliferation, migration and invasion, and particularly in the interactions of the microenvironment of cancer cells and angiogenesis[16].

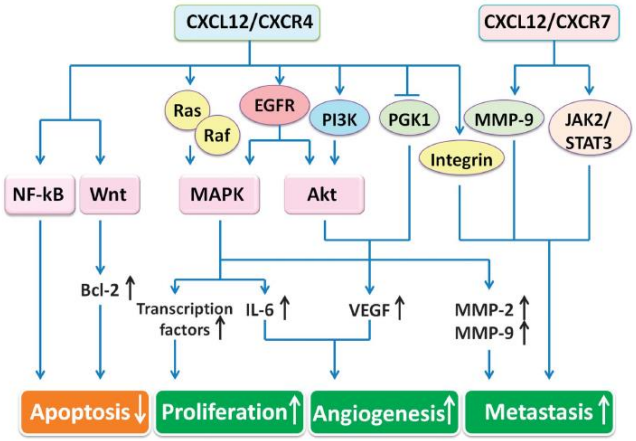
Why CXCL12?

Recent results show that there is indeed a CXCR4 / CXCL12 / CXCR7 axis, involving the chemokine CXCL12 and its two receptors CXCR4 and CXCR7, which play a preponderant role in tumor progression. Like all chemokines, CXCL12 can act in two main directions, either on tumors or on immune cells. In its

[15] Kruizinga RC, Bestebroer J, Berghuis P, et al. Role of chemokines and their receptors in cancer. *Curr Pharm. Des.* 2009 ; 15 : 3396–3416.
[16] Orimo A, Gupta PB, Sgroi DC, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell*. 2005; 121: 335–348.

action on tumors, CXCL12 can intervene directly or indirectly. Thus, by targeting vascular endothelial cells and acting synergistically with vascular endothelial growth factor (VEGF), CXCL12 indirectly promotes tumor angiogenesis[17]. Moreover, in the context of its direct effects on tumor cells, CXCL12 participates in the proliferation and survival of tumor cells[18]. In addition, the CXCL12-CXCR4 signaling pathway promotes cancer cell invasion and metastasis[19]. It has been suggested that $CXCR4^+$ tumor cells may have similar properties to cancer stem cells[20], have high metastatic potential, and show resistance to irradiation[21].

CXCL12's Signaling pathways and its receptors CXCR4 and CXCR7



Source: Guo et al. Oncogene 2016

The binding of CXCL12 to its CXCR4 receptor activates several intracellular signaling cascades that regulate cell proliferation, invasion, migration and "homing" of cancer cells in the liver, bone and brain. In addition to its expression in normal tissues, the overexpression of CXCR4 has been associated with different types of cancers. Thus, in breast cancer, it has been shown that the percentage of $CXCR4^+$ increased from 20% in normal breast tissue to 43% in ductal carcinoma in situ (DCIS) to 67% in invasive cancer[22]. A similar phenomenon has also been shown in lung cancer and prostate cancer[23]. The CXCR4 receptor and its ligand, CXCL12 or SDF1α (Stromal-Derived Factor 1α) are therefore one of the most important chemokine pairs. In addition, CXCL12 also binds to the CXCR7 receptor, which is expressed in both normal (non-pathological) tissue and pathological tissue (inflammation and tumor development)[24]. Recent scientific work shows that CXCR7 is overexpressed in tumor cells as well as in tumor endothelial cells[25]. CXCR7 signaling may also contribute indirectly to angiogenesis by increasing the expression of CXCL8 and VEGF in prostate cancer cells. While CXCR7 is said to influence cell proliferation, angiogenesis and invasion contribute to the development and progression of cancer[26]. Cancer cells expressing the

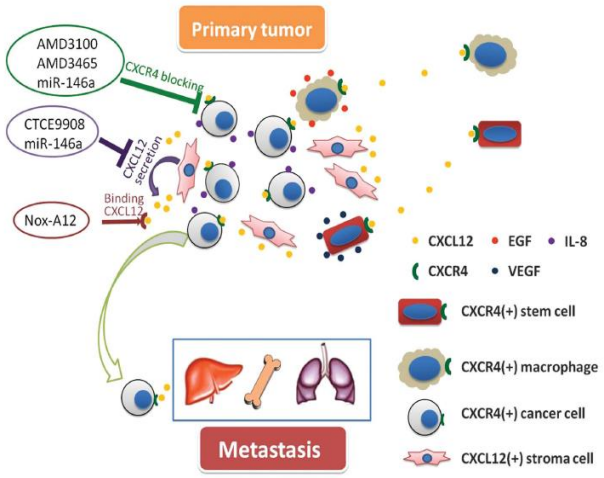
[17] Kryczek, I., Wei, S., Keller, *et al.* Stroma-derived factor (SDF-1/CXCL12) and human tumor pathogenesis. *Am. J. Physiol. Cell Physiol.* 2007; 292, C987–C995.
[18] Scotton, C. J. *et al.* Multiple actions of the chemokine CXCL12 on epithelial tumor cells in human ovarian cancer. *Cancer Res.* 2002; 62, 5930–5938.
[19] Darash-Yahana, M. *et al.* Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis. *FASEB J.* 2004; 18, 1240–42.
[20] Jung, M. J. *et al.* Upregulation of CXCR4 is functionally crucial for maintenance of stemness in drug-resistant non-small cell lung cancer cells. *Oncogene* 2013; 32, 209–221.
[21] Zhang, S. S. *et al.* $CD133^+CXCR4^+$ colon cancer cells exhibit metastatic potential and predict poor prognosis of patients. *BMC Med.* 2012; 10, 85.
[22] Salvucci O, Bouchard A, Baccarelli A, et al. The role of CXCR4 receptor expression in breast cancer: a large tissue microarray study. Breast Cancer Res Treat 2006;97(3):275–83.
[23] Hirata H, *et al.* CXCL12 G801A polymorphism is a risk factor for sporadic prostate cancer susceptibility. Clin Cancer Res 2007;13(17):5056–62.
[24] Sanchez-Martin L, Sanchez-Mateos P, Cabanas C. CXCR7 impact on CXCL12 biology and disease. Trend Mol Med 2013: 19, :12-22
[25] Liu Y, Carson-Walter E, Walter KA. Chemokine receptor CXCR7 is a functional receptor for CXCL12 in brain endothelial cells. PLoS ONE. 2014: 9: e103938.
[26] Lin L, Han MM, Wang F, Xu HX, Yang PY. CXCR7 stimulates MAPK signaling to regulate hepatocellular carcinoma progression. Cell Death Dis 2014: 5, e1488.

CXCR7 receptor, which promote the mechanisms of adhesion, invasion, as well as survival and growth phenomena observed in prostate, breast and lung cancer.

CXCL12/CXCR4 and microenvironment

Recent work has shown that interactions between tumor and stromal cells play a crucial role in the initiation and progression of tumors[27]. The tumor microenvironment is composed of cellular elements (fibroblasts, immune cells and endothelial cells), extracellular matrix, proteins, proteolytic enzymes, growth factors and inflammatory cytokines. All these elements participate in the structure of the tumor, its growth and angiogenesis. The CXCL12 ligand is predominantly expressed by mesenchymal stromal cells in various organs, such as the liver, lungs and bone marrow.

CXCL12 / CXCR4 and the tumor microenvironment



Source: Guo et al Oncogene 2016

In addition, some CXCR4$^+$ cancer cells may be recruited by CXCL12-rich mesenchymal stroma niches to initiate metastases[28]. In addition, CXCL12 can attract CXCR4$^+$ immune cells or fibroblasts to tumor sites. High levels of CXCL12 in tumors attract inflammatory CXCR4$^+$ vascular and stromal cells at the level of the tumor mass. These processes participate in tumor growth by secreting growth factors, cytokines, chemokines and pro-angiogenic factors. A recent study has shown that CXCL12 secreted by multiple myeloma (MM) cells can attract monocytes expressing the CXCR4 receptor. These post-differentiations become M2-type macrophages that significantly increase the proliferation of MM cell lines and protect myeloma cells from chemotherapy and immunotherapy-induced cell death[29]. In addition, macrophages strongly induce the expression of CCL2, CCL5, IL-1β and IL-8 in MM cells, establishing a tumor-friendly microenvironment. CXCL12 induces the production and release of epidermal growth factor (EGF) by mononuclear phagocytes triggering anti-apoptotic mechanisms as well as proliferation signals in cancer

[27] Polyak K, Haviv I, Campbell IG. Co-evolution of tumor cells and their microenvironment. Trends Genet 2009; 25: 30–38.
[28] Wang Z, Ma Q, Liu Q, Yu H, Zhao L, Shen S et al. Blockade of SDF-1/CXCR4 signaling inhibits pancreatic cancer progression in vitro via inactivation of canonical Wnt pathway. Br J Cancer 2008; 99: 1695–1703.
[29] Beider K, Bitner H, Leiba M, Gutwein O, Koren-Michowitz M, Ostrovsky O et al. Multiple myeloma cells recruit tumor-supportive macrophages through the CXCR4/CXCL12 axis and promote their polarization toward the M2 phenotype. Oncotarget 2014; 5: 11283–11296.

cells. Ping et al.[30] showed that CXCL12 could attract $CD133^+$ glioma stem cells and induce the production of vascular EGF (VEGF) by $CD133^+$ cells. These results indicate that CXCL12/CXCR4 promotes cancerous growth as well as angiogenesis by inducing secretion by stromal cells of growth factors

CXCL12 and immunotherapy

Constitutive expression of CXCL12 in bone marrow and other tissues is responsible for regulating the movement and relocation of immature and mature leukocytes to these tissues, preserving tissue homeostasis[31]. In addition, CXCL12, via CXCR4, plays a key role in maintaining neutrophil homeostasis. CXCL12 can thus direct the migration of neutrophils towards the organs, within the framework of the immune surveillance of the body.

Adenocarcinoma

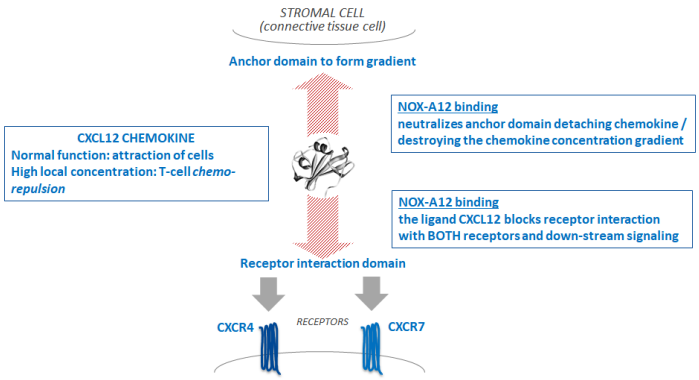
Cancer	Response to antiPD-1/PD-L1	Presence of FAP+ cells	CXCL12 on cancer cells	Absence of T cells inside tumors
Pancreatic Ductal Adenocarcinoma (mouse)	0/8	yes	yes	yes
Pancreatic Ductal Adenocarcinoma	0/14	yes	yes	yes
Colorectal cancer	0/94	yes	yes	yes
Ovarian cancer	1/17	yes	yes	yes

Source: Fearon, Cancer Immunol Res 2014

If CXCR7 is expressed by lymphocytes and granulocytes in bone marrow, it is expressed by monocytes, granulocytes and platelets in the peripheral blood. In the immune system, CXCR7 is expressed in B cells and dendritic cells. It has been shown that CXCR7 was necessary for the functioning of mature B cells and was involved in the initiation of the innate immune response. Other studies have shown that CXCL12 contributes to the immune suppression of tumors by recruiting specific immune cell populations. Within the tumor microenvironment are among the cell populations, a fraction of carcinoma-associated fibroblasts (CAF) that express on their surface, the fibroblastic activation protein (FAP). This CAF FAP is often associated with T cell exclusion from tumor cell proximity as well as a near-zero response rate to ICI (anti-PD-1 / PD-L1). Moreover, it is also associated with the presence of the chemokine CXCL12. FAP-bearing CAFs can block T cells not by creating a physical barrier, but rather by the presence of CXCL12 which, by attaching itself to tumor cells, creates a true biochemical wall. This suggests that any approach to reduce or destroy this blockade by either inhibiting CXCR4 receptors or by blocking the chemokine CXCL12, would release a spontaneous antitumor immune response. It has recently been shown in a breast cancer mouse model[32] that the delivery of an oncolytic virus expressing a CXCR4 receptor antagonist induces a reduction in immunosuppression while decreasing the number of endothelial cells, myeloid cells, of plasmacytoid dendritic cells and regulatory T cells, resulting in a reduction in metastatic proliferation of tumors and an improvement in overall survival. Thus, any antagonistic therapy of the CXCL12 / CXCR4 / CXCR7 pathway may represent an interesting alternative against cancer.

[30] Ping YF, Yao XH, Jiang JY, Zhao LT, Yu SC, Jiang T et al. The chemokine CXCL12 and its receptor CXCR4 promote glioma stem cell-mediated VEGF production and tumor angiogenesis via PI3K/AKT signaling. J Pathol 2011; 224: 344–354.
[31] Karin N. The multiple faces of CXCL12 (SDF-1alpha) in the regulation of immunity during health and disease. J Leuk Biol 2010; 88: 463–473.
[32] Gil M, Komorowski MP, Seshadri M, Rokita H, McGray AJ, Opyrchal M et al. CXCL12/CXCR4 blockade by oncolytic virotherapy inhibits ovarian cancer growth by decreasing immunosuppression and targeting cancer-initiating cells. J Immunol 2014; 193: 5327–5337.

NOX-A12's mechanism



Source: Noxxon

With NOX-A12, Noxxon chose deliberately to target the CXCL12 chemokine instead of the CXCR4 and CXCR7 receptors. Preclinical data and clinical results show that NOX-A12 by blocking the chemokine CXCL12 of the tumor microenvironment acts at multiple levels. Like many chemokines, CXCL12 has two binding sites and more by its structure, the two domains do not overlap. The first binding site, primary and specific, is shared by two chemokine receptors: CXCR4 and CXCR7. Furthermore, CXCL12 also has a nonspecific binding site on the cell surface. It is this interaction with proteoglycans that would allow local CXCL12 gradient formation essential for directed cell migration[33]. On the other hand, as we mentioned above, CXCL12 participates by its action in the immunosuppressive behavior of CAF, while inducing the constitution of a biochemical wall generating an exclusion of cytotoxic T cells within the tumor tissue. In the tumor microenvironment, NOX-A12 by inhibiting CXCL12 reduces or abolishes chemokine binding to tumor cells and will destroy the anti-immunity wall, raised by overexpressing CXCL12 and allowing lymphocyte entry. Numerous publications show that CXCL12 as well as its CXCR4 and CXCR7 receptors, which are often overexpressed in brain tumors, would play a vital role in the resistance of these tumors to therapies. By blocking CXCL12, NOX-A12 inhibits the recruitment of bone marrow cells that participate in the processes of angiogenesis and repair mechanisms of tumor cells damaged by chemotherapy or radiotherapy. The stroma of the bone marrow rich in CXCL12, has the effect of attracting cancerous hematological cells within this compartment thus generating phenomena of therapeutic resistance. Inhibition of CXCL12 by NOX-A12 would therefore reduce the gradient and restore therapeutic sensitivity.

Competitive landscape: CXCR4 inhibitors

The CXCR4 receptor by its implication in many pathological processes has certainly crystallized most of the interest brought to this therapeutic axis. Several small molecule development projects have emerged, but to date, only Genzyme / Sanofi's plerixafor (AMD-3100) or Mozobil ™ has been approved by the FDA. Indicated in association with G-CSF (Granulocyte-Colony Stimulating Factor), Mozobil activates the mobilization of hematopoietic stem cells in peripheral blood prior to collection for autograft in patients with non-Hodgkin lymphoma or multiple myeloma. Most of the products under development in the field therefore address the inhibition of the CXCR4 receptor, with molecular strategies differentiated from

[33] Rueda P, et al. Homeostatic and tissue reparation defaults in mice carrying selective genetic invalidation of CXCL12/proteoglycan interactions. Circulation. 2012; 126(15):1882–1895.

small chemical molecules to monoclonal antibodies via peptides. Noxxon with NOX-A12 targets a blockage of the CXCR4 ligand, the CXCL12 chemokine.

Selection of CXCR4 receptor antagonists in clinical phase

Molécules	Type	Company	Stade de développement
Plerixafor (AMD3100)/mozobil	Petite Molécule	Genzyme/Sanofi	Commercialisé
Ulocuplumab	Anticorps Monoclonal	BMS	Phase II abandon
BL-8040	Peptide	BiolineRx	Phase II
Ly2510924	Peptide cyclique	Lilly	Phase II
USL 311	Petite Molécule	Uspsher-Smith (Proximagen)	Phase II
PF-06747143	Anticorps Monoclonal	Pfizer	Phase I Leucémie myeloide aigue
POL6326	Peptide	Polyphor	Phase I et Phase II
GMI-1359	Petite Molécule	Glycomimetics	Phase I
X4P-001	Petite Molécule	X4 Pharmaceuticals	Phase II/III et Phase I/II

Source: Evaluate, Aurgalys

CCL2: from diabetes to oncology

Although Noxxon initially developed NOX-E36, which inhibits the CCL2 pro-inflammatory chemokine in diabetic nephropathy, the company is considering new developments for this molecule in oncology. It has been shown that monocytes and more particularly macrophages infiltrate the kidneys of patients with nephropathy[34]. This monocyte infiltration was correlated with the overexpression of the chemokine CCL2 (or monocyte-chemotactic protein 1, MCP-1), and its CCR2 receptor. Similarly, renal biopsies confirmed the accumulation of macrophages in renal tissue and its possible pathogenic role in reducing renal function and thus in the evolution of nephropathy. Moreover, in diabetic mouse models, the main species of immune cells infiltrating the kidneys of these mice were macrophages, which play a major role in the inflammation and in the proteinuria (albuminuria) observed in these models[35].

NOX-E36 in diabetic nephropathy

Chronic renal failure is an extremely serious condition, which results in an evolutionary deficit of renal function. Diabetes is certainly one of the major causes of chronic kidney disease (CKD) and even end-stage renal disease (ESRD), because the proportion of people with diabetes in kidney failure is particularly high (40%). CKD has significant unmet medical needs, as no drugs are currently available to stop or slow the deterioration of kidney function. In addition, the natural course of CKD is IRT, which is the ultimate stage of the pathology, and which requires, for survival, the establishment of dialysis or a kidney transplant. The standard of care for diabetic nephropathy is based on molecules controlling blood glucose or / and hypertension that do not change the course of the disease, which will invariably evolve towards the IRT.

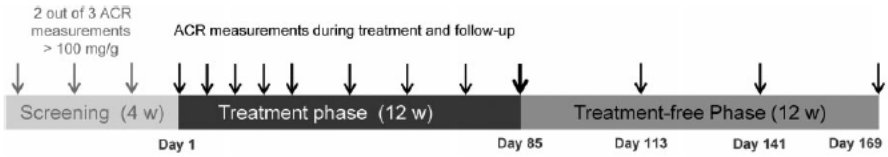
NOX-E36: clinical development

[34] Tesch GH. Macrophages and diabetic nephropathy. Semin Nephrol 2010 ;30: 290–301

[35] Chow FY, Nikolic-Paterson DJ, Ma FY et al. Monocyte chemoattractant protein-1-induced tissue inflammation is critical for the development of renal injury but not type 2 diabetes in obese db/db mice. Diabetologia 2007; 50: 471–480

NOX-E36 was tested in a Phase I trial of 152 subjects with diabetic nephropathy by intravenous (IV) and subcutaneous (SC) injection. Of the 71 subjects who received NOX-E36 IV, the incidence of adverse events was like that of 24 placebo-treated subjects and the incidence of adverse events was independent of the administered dose, which ranged from 0, 03 at 2 mg / kg. Of the 53 subjects who received NOX-E36 in SC, the adverse events observed were like those observed in the four subjects who received placebo. The fraction of monocytes CD14 + CCR2 +, a subset of white blood cells thought to be involved in diabetic nephropathy, decreased in proportion to the dose. NOX-E36 was then tested in an exploratory, randomized, double-blind, placebo-controlled Phase IIa clinical trial. This multi-center trial (5 European countries) explored the NOX-E36 re-protective and antidiabetic potential in type 2 diabetics with proteinuria in combination with the standard of care. The primary endpoint was to characterize the effect of NOX-E36 on variations in albumin / creatinine urinary intake (ACR). Secondary endpoints are the effect of NOX-E36 on glycemic control (HbA1c, glycated hemoglobin: a measure of past glycemic control), as well as safety and tolerability.

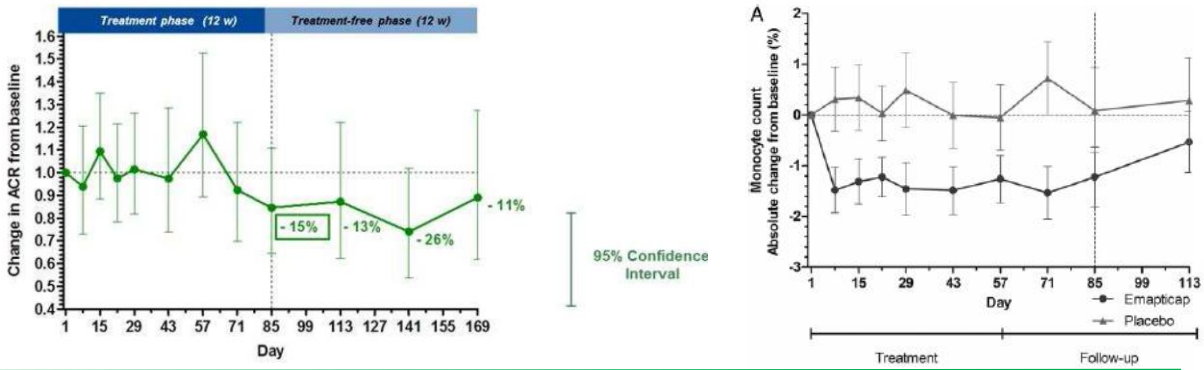
NOX-E36 in diabetic nephropathy



Source: Noxxon Pharma

NOX-E36 or placebo was administered subcutaneously at 0.5 mg / kg twice weekly for 12 weeks to 51 and 25 patients, respectively. At the end of the treatment phase, all patients were followed for one additional 12 weeks without treatment. The main efficacy parameter, ACR (albumin-creatine ratio), was significantly reduced in the NOX-E36 group at the end of treatment by a score of 29% compared to baseline ($p < 0.05$) for the set of evaluable patients. Compared with placebo, a statistically nonsignificant reduction of 15% ($p = 0.221$) at the end of treatment and 26% ($p = 0.064$) eight weeks after the end of treatment were observed. The results of this phase IIa study confirmed the pharmacodynamic effect of NOX-E36 on the monocytes (macrophages) observed in the phase I trial with a reduction in monocytes in the blood count throughout the assay period.

NOX-E36 in diabetic nephropathy



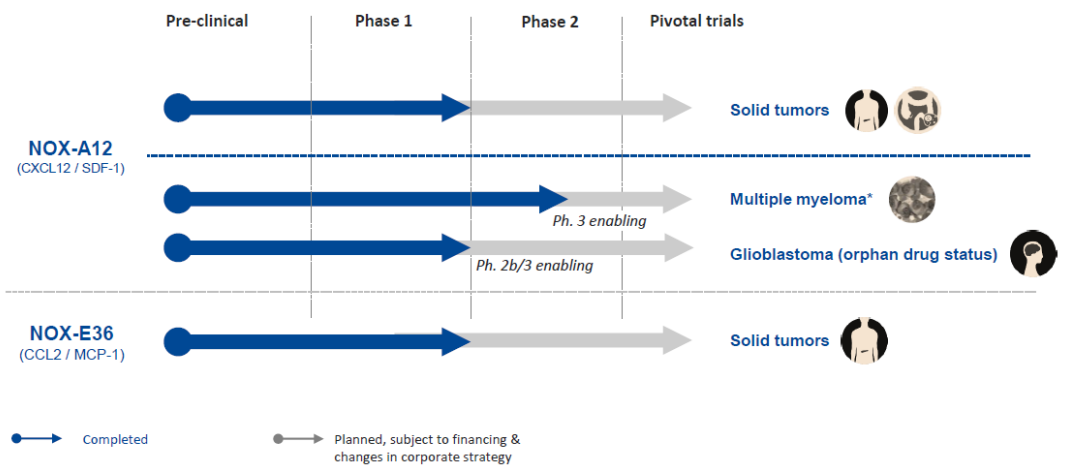
Source: Noxxon Pharma

The results, including animal studies, show that NOX-E36 by binding the CCL2 chemokine prevents the infiltration of pro-inflammatory cells into the kidney and associated pro-inflammatory cytokines. This effect on inflammation is measured by albumin-creatine ratio (ACR) / HbA1c (glycated hemoglobin). In addition, NOX-E36 could be effective in combination with existing therapies. Moreover, the blocking of CCL2 by NOX-E36 would have the effect of inhibiting the displacement ("trafficking") of CCR2 monocytes leading to a quantitative reduction of monocytes in the blood. All these observations suggest that the presence of plasma NOX-E36 which, by binding to the CCL2 present, would result in sequestration of CCR2 monocytes at the level of the bone marrow (MO) due to the inhibition of chemokine-induced MO guidance. Importantly, the beneficial effects on proteinuria, as shown in a diagram below, and glycemic control were maintained for a prolonged period after stopping treatment suggesting a change during the disease.

Pipeline and clinical development

As mentioned above, Noxxon Pharma therefore has a pipeline from which two main products from the Spiegelmers discovery and production platform emerge: the NOX-A12 which targets the CCL12 chemokine and the NOX-E36 which inhibits the CCL2 / CCR2 axis. Although implying distinct chemokines, these products address the tumor microenvironment and its immune components. It should also be noted that Noxxon has already developed several therapeutic molecules up to the end of phase II, including NOX-A12 in hematological malignancies.

Noxxon's Pipeline



Source: Noxxon

NOX-A12, which is currently in a phase II clinical trial in metastatic colorectal cancer and metastatic pancreatic ductal adenocarcinoma in combination with an immune checkpoint inhibitor, may most certainly be indicated in other solid tumors such as lung cancer, breast cancer and ovarian cancer. In addition, the different results obtained during the clinical trials conducted in hematological cancers, support the proof of concept and strongly reduce the technological risk as well as the toxicological risks. **The mechanism of action of NOX-A12 in this case involves a decomposition of the "biochemical barrier" that keeps cytotoxic T cells out of the tumor mass: destruction of the immunological privilege of the tumor.**

NOX-A12 may also be indicated in glioblastoma in combination with radiotherapy for newly diagnosed glioblastomas that are often characterized by resistance to temozolide (TMZ) therapy due to non-methylation of the gene repair promoter. MGMT DNA or O-6-MethylGuanine-DNA MethylTransferase. Indeed, when it is methylated, the gene is not expressed and the TMZ regains its effectiveness. However, in case of non-methylation, the enzyme is activated, and the destruction of tumor cells cannot occur. **In glioblastoma, NOX-A12 by reducing the number of available CCL12 chemokines will block the recruitment of "repairing" myeloid cells that participate in TMZ resistance.**

NOX-A12 in hematological malignancies works by mobilizing a third effect: **by reducing the gradient of CCL12, which attracts both regulatory T cells and CXCL12 + tumor cells in the bone marrow thus creating tumor-protective niches generating resistance chemotherapy treatments.**

NOX-E36, which binds to the CCL2 chemokine, uses another mechanism of action to reduce the immunosuppressive behavior of tumors. **NOX-E36 abolishes the mobilization of bone marrow monocytes.** These monocytes, which, by relocating at the level of tumor masses, differentiate into macrophages associated with tumors and generate an immune anergy that promotes tumor progression. macrophages associated with tumors and generate an immune anergy that promotes tumor progression.

NOX-A12 and hematologic cancers: a first successful development

The role of the chemokine CXCL12 in the progression of hematological malignancies has been amply documented. The CXCR4 / CXCL12 axis is involved in the migration and guidance of myeloma cells to the bone marrow. Indeed, CXCR4 is widely expressed in cells of the hematopoietic lineage ($CD34^+$ HSC, T lymphocytes, B lymphocytes, monocytes, macrophages ...) as well as in various organs such as the brain, lung, colon, heart, kidneys and liver. CXCR4 is also expressed in other cell lines such as endothelial and epithelial cells, microglia and astrocytic cells. All these cells with their functional CXCR4 can migrate and / or invade tissues according to the CXCL12 gradients. CCXCL12 therefore plays a major role in the mobilization and recruitment of these cells at the level of neo-angiogenic niches responsible for the revascularization of ischemic tissues and tumor growth[36]. Thus, the expression of CXCR4 on the cells of several hemopathies shows that the CXCR4 / CXCL12 pathway plays an essential role in the orientation of the metastases of $CXCR4^+$ tumor cells towards organs expressing CXCL12 (lymph nodes, lungs, liver, bone). CXCR4 can also promote tumor vascularization and act as a survival or growth factor.

Rationale NOX-A12 in myeloma

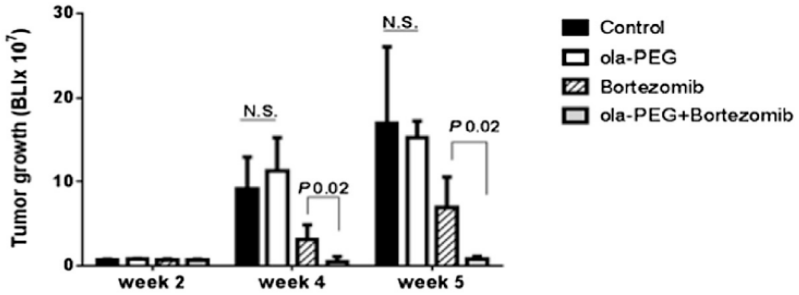
Multiple myeloma (MM) is an incurable hematological cancer characterized by clonal proliferation of plasma cells in the bone marrow. Although representing only about 1% of all cancers, MM is the second most common hematologic cancer after non-Hodgkin's lymphoma. As with all tumors, the survival and expansion of MM plasma cells is dependent on an adequate supply of oxygen and nutrients. In addition, the acquisition of an angiogenic phenotype is a key event in the progression of indolent MM to active MM[37]. CXCL12 is overexpressed by plasma myeloma cells and similarly, circulating levels of CXCL12 are higher in the peripheral blood of MM patients than in healthy people. CXCL12 is therefore an important mediator of several aspects of MM biology, including transendothelial migration, plasma migration and retention. Recent animal studies have shown that blocking the CXCL12 / CXCR4 axis results in a 20% reduction in bone marrow tumor burden[38].

Preclinical data

[36] Petit I, Jin D, Rafii S. The SDF-1-CXCR4 signaling pathway: a molecular hub modulating neo-angiogenesis. Trends Immunol 2007;28: 299–307.
[37] Rajkumar SV, et al. Prognostic value of bone marrow angiogenesis in multiple myeloma. Clin Cancer Res. 2000;6(8):3111–6
[38] Menu E, et al. The involvement of stromal derived factor 1α in homing and progression of multiple myeloma in the 5TMM model. Haematologica. 2006 ;91(5) :605–12.

Noxxon Pharma conducted with the Dana Faber Research Center, a series of preclinical studies in mouse models of multiple myeloma, which showed that NOX-A12 was a drug candidate in the treatment of the microenvironment of this pathology. These studies showed that the combination of NOX-A12 with bortezomib (Velcade®) resulted in a rapid and significant mobilization of bone marrow cancer cells into the blood compartment as well as increased sensitivity to bortezomib.

NOX-A12 Reduces Tumor Growth in Mouse Models of Multiple Myeloma



Source: Noxxon

In the experiment shown in the figure above, the tumor burden was evaluated in 4 groups of mice: untreated control, treated with NOX-A12 alone, treated with bortezomib alone and treated with a combination of NOX-A12 and bortezomib. After 4 to 5 weeks, the NOX-A12 / bortezomib combination significantly inhibited tumor growth compared to other groups. Moreover, the absence of effect of NOX-A12 alone is totally predictable since the molecule acts on the microenvironment and not on the tumor. In addition, these preclinical studies demonstrated that NOX-A12 could inhibit the spread of myeloma cells to the bone marrow. In addition, during these preclinical studies, NOX-A12 was shown to be 1000 times more potent than the CXCR4 antagonist plasterer (Mozobil®) in inhibiting cell migration.

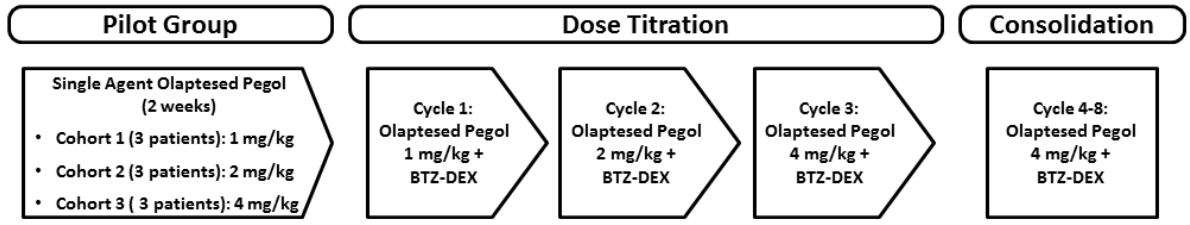
Clinical Programs

Several clinical studies have been conducted with NOX-A12 in hematological cancers and more particularly in multiple myeloma. Thus, a first phase I study was conducted in healthy volunteers to determine the safety of the molecule and its tolerance. 48 healthy volunteers received a single increasing dose of NOX-A12 from 0.05 to 10.8 mg / kg. These doses were well tolerated with no significant side effects. In addition, NOX-A12 was shown to increase concentration of white line cells and hematopoietic stem cells in peripheral blood as a function of concentration. A second phase I study was conducted in 12 healthy subjects receiving repeated increasing doses daily for 5 consecutive days of NOX-A12 (2 mg / kg or 4 mg / kg) to mobilize stem cells. Although the number of mobilized stem cells did not increase as a function of NOX-A12 concentration, an increase in mobilization was observed. If the dose of 2 mg / kg per day for five days seems generally well tolerated, the daily dose of 4 mg / kg on five consecutive days has led to elevated liver enzymes.

A first open-label, single-arm, phase IIa clinical trial was conducted to evaluate the safety and efficacy of a combination of NOX-A12 / bortezomib + dexamethasone (VD) in 28 patients with myeloma multiple recurrent or refractory. These patients received, in a first pilot phase, an infusion of NOX-A12 alone of 1,

2 or 3 mg / kg according to the cohort two weeks before the beginning of the combination treatment. Then the combination is administered in 8 cycles of 21 days with increasing dosage in each patient who will receive a first cycle of 1 mg / kg NOX-A12 + VD, then a second cycle of 2 mg / kg + DV, then a third cycle of 4mg / kg + DV. Then for cycles 4 to 8, patients received 4mg / kg of NOX-A12 + VD.

Overview of the Phase IIa Trial in Multiple Myeloma



Source: Noxxon Pharma

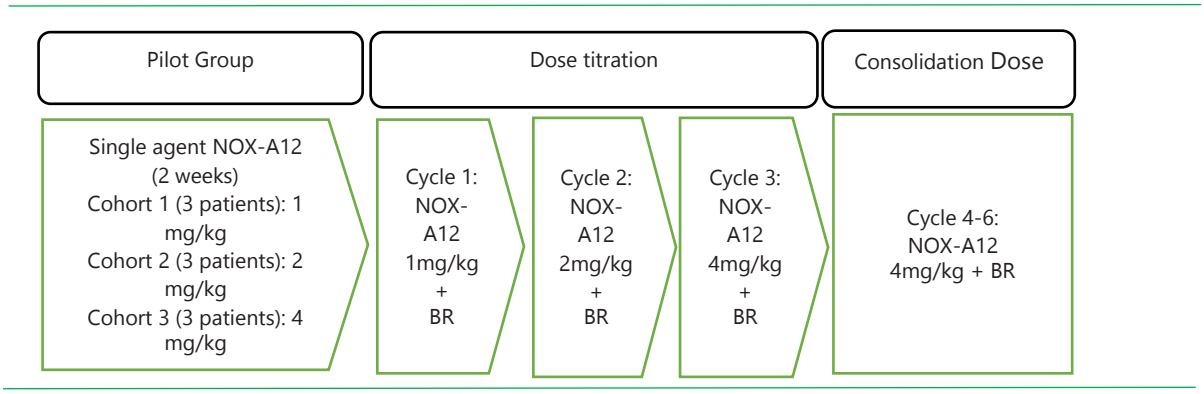
This trial shows that the objective response rate (ORR) is 68%, or 19/28 patients treated. 2 patients (7%) were in complete remission, 5 had a very good partial response (18%), 12 had a partial response (43%) and only 2 patients had a minor response (7%). With only 5 patients in stable disease (18%) and 1 in progression (4%), the clinical benefit of the combination NOX-A12 + VD is 75%. These results are comparable to those of other Phase II studies including bortezomib such as APEX (43%)[39] or BoMER plus dexamethasone (53%)[40]. Moreover, the NOX-A12 + VD combination appears to be more effective than the combination of ulocuplumab + VD which gave a ORR of 40%[41] or the combination of plerixafor + VD with a ORR of 51%[42].

Comparison of multiple trials in multiple myeloma

Source: Noxxon Pharma

[39] Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 2007; 110: 3557–3560.
[40] Harrison SJ, Quach H, Link E, Feng H, Dean J, Copeman M et al. The addition of dexamethasone to bortezomib for patients with relapsed multiple myeloma improves outcome but ongoing maintenance therapy has minimal benefit. Am J Hematol 2015; 90: E86–E91.
[41] Ghobrial IM, Perez R, Baz R, Richardson PG, Anderson KC, Sabbatini P et al. Phase Ib study of the novel anti-CXCR4 antibody ulocuplumab (BMS-936564) in combination with lenalidomide plus low-dose dexamethasone, or with bortezomib plus dexamethasone in subjects with relapsed or refractory multiple myeloma. Blood 2014; 124: 3483.
[42] Ghobrial IM, Shain KH, Laubach J, Henrick P, Vredenburg J, Crilley P et al. Final results of the phase I/II study of chemosensitization using the CXCR4 inhibitor plerixafor in combination with bortezomib in patients with relapsed or relapsed/refractory multiple myeloma. Blood 2015; 126: 425

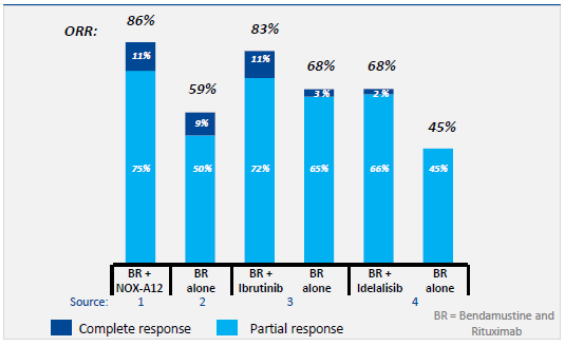
These differences can be credited to the mode of action of NOX-A12 which blocks the chemokine CXCL12, while ulocuplumab and plerixafor are antagonists of the CXCR4 receptor. In addition, studies have shown that blocking CXCR4 in multiple myeloma may be bypassed by CCL12 binding to the CXCR7 receptor, hence the interest of NOX-A12, which targets both CXCR4 and CXCR7.
A second phase IIa study was conducted with NOX-A12 in another hematologic cancer, chronic lymphocytic leukemia, which is characterized by monoclonal lymphoid proliferation resulting in medullary, blood and sometimes lymph node infiltration. Chronic and often incurable, this is the most common leukemia in adults. This multi-center, open-arm, single-arm clinical trial sought to evaluate the safety and preliminary efficacy of a NOX-A12 / rituximab + bendamustine (BR) combination in 28 patients with recurrent or refractory chronic lymphocytic leukemia. These patients received, in a first pilot phase, an infusion of NOX-A12 alone at 1, 2 or 3 mg / kg according to the cohort two weeks before the beginning of the combination treatment.



Overview of the Phase IIa Trial in Chronic Lymphocytic Leukemia

Source: Noxxon Pharma

Then the combination is administered in 6 cycles of 28 days with increasing dosage in each patient who will receive a first cycle of 1 mg / kg of NOX-A12 + BR (IV rituximab 375 mg / m2 and 500 mg / m2, bendamustine in IV between 70-100 mg / m2), then a second cycle of 2 mg / kg + BR, then a third cycle of 4 mg / kg + BR. Then for cycles 4 to 6, patients received 4mg / kg of NOX-A12 + BR. The effectiveness of the combination is determined at the end of cycle 6. The intent-to-treat analysis shows that the overall response rate (ORR) is 82%. 3 patients (11%) had a complete response, 21 had a partial response, or 75%. With only 3 patients progressing (11%), the clinical benefit of the NOX-A12 + BR combination is 86%.



Comparison of multiple trials in Chronic Lymphocytic Leukemia

Source: Noxxon Pharma

The NOX-A12 / BR combination has a clinical benefit equivalent to BR + ibrutinib (Imbruvica®), a targeted Bruton tyrosine kinase inhibitor therapy (83%) tested in phase III[43]. In addition, the combination NOX-A12 / BR is superior to BR alone (59%)[44] tested in an open phase II or the combination BR + idelasib, an inhibitor of a phosphoinositide 3-kinase isoform (PI 3 -kinase) which gave a clinical benefit of 68% in a phase III.

Based on previous results in multiple myeloma and chronic lymphocytic leukemia, Noxxon Pharma has demonstrated that NOX-A12 is effective with an alkylating agent such as bendamustine (LEVACT in France), which is now indicated in 1L in chronic lymphocytic leukemia and in multiple myeloma, as monotherapy in indolent non-Hodgkin's lymphoma. Noxxon remains open to the possibility of an industrial agreement with a partner who could use NOX-A12 as part of a 3L or 4L treatment in these hematological cancers. However, these results show that NOX-A12 is significantly de-risked compared to other products in earlier phases of development.

NOX-A12 and solid tumors: the end of immune privilege

Rationale for NOX-A12 in colorectal and pancreatic cancers

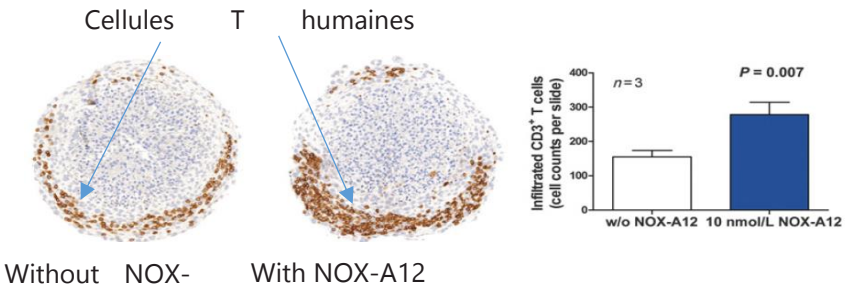
Noxxon develops its main product, NOX-A12 against the chemokine CXCL12 or the factor derived from the stromal cells (SDF1). CXCL12 is naturally present in the processes of angiogenesis (migration of blood vessels) near the tumor as well as in the mechanisms of communication between tumor cells including cancer-associated fibroblasts and their environment. Moreover, not only does CXCL12 act as a cellular attractant, like most chemokines, but also repellent for certain immune cells such as cytotoxic lymphocytes or killer T cells, thus participating in the immunosuppressive behavior observed in solid tumors.

Preclinical data

[43] Chanan-Khan et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (HELIOS): a randomized, double-blind, phase 3 study. Lancet Oncol. 2016 ; 17: 200-11.
[44] Fisher 2011

The activity of NOX-A12 has been studied in multicellular models of tumor spheroids which are considered a good model describing the complexity of the tumor microenvironment.

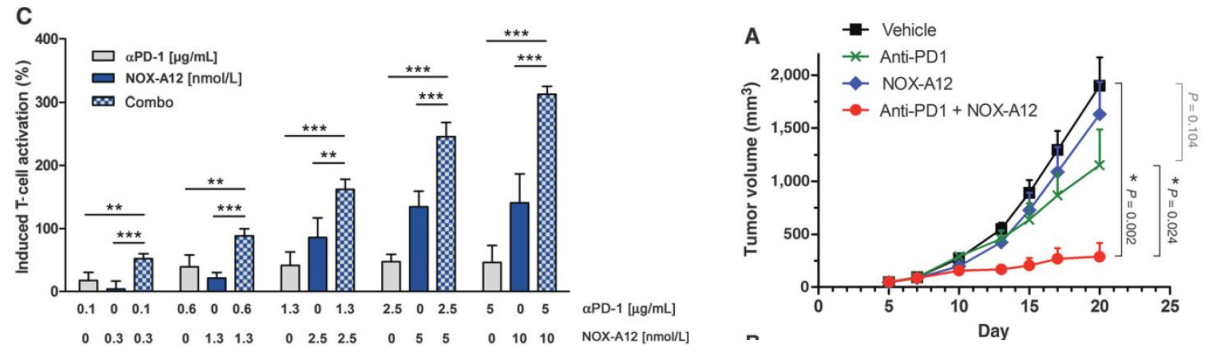
Effect of NOX-A12 on immune cell infiltration



Source: Zboralski D et al. Cancer Immunol Res 2017; 5: 950-56

This pattern, which is characterized by interactions between cancer cells and surrounding cells or the extracellular matrix, is usually accompanied by a decreasing oxygen gradient from the periphery to the center (hypoxia), which makes it very predictive. In this 3D model, NOX-A12 inhibiting CXC12 significantly increases intra-tumor migration of T cells, while increasing their infiltration and activation within spheroids. Similarly, NOX-A12 increases the infiltration of NK cells into spheroids[45]. In addition, these preclinical data show that NOX-A12 acts synergistically with a PD-1 / PD-L1 immune control point inhibitor. Indeed, as shown in the figures below, NOX-A12 alone induces an activation of T cells greater than the anti-PD-1 antibody, but when the two molecules are added, the observed activation is greater than the sum of two. This NOX-A12 induction of T cells is dose-dependent.

Synergy between NOX-A12 & anti-PD-1 *in vitro* (spheroids) & *in vivo*



Source : Zboralski D et al. Cancer Immunol Res. 2017; 5 : 950-56.

One of the hypotheses for explaining the weakness of T-cell activation observed with anti-PD-1 is that most immune cells are located outside the spheroid. When NOX-A12 is added to the anti-PD-1, the improvement of the effector and target contacts is increased. In addition, this synergism between NOX-A12 and anti-PD-1 is confirmed in a murine syngeneic model of CT-26 metastatic colorectal cancer in vivo. This model is particularly relevant since it is often associated with the production of cancer-associated fibroblasts, which contribute to tumor growth and are not controlled by anti-PD-1. The use of

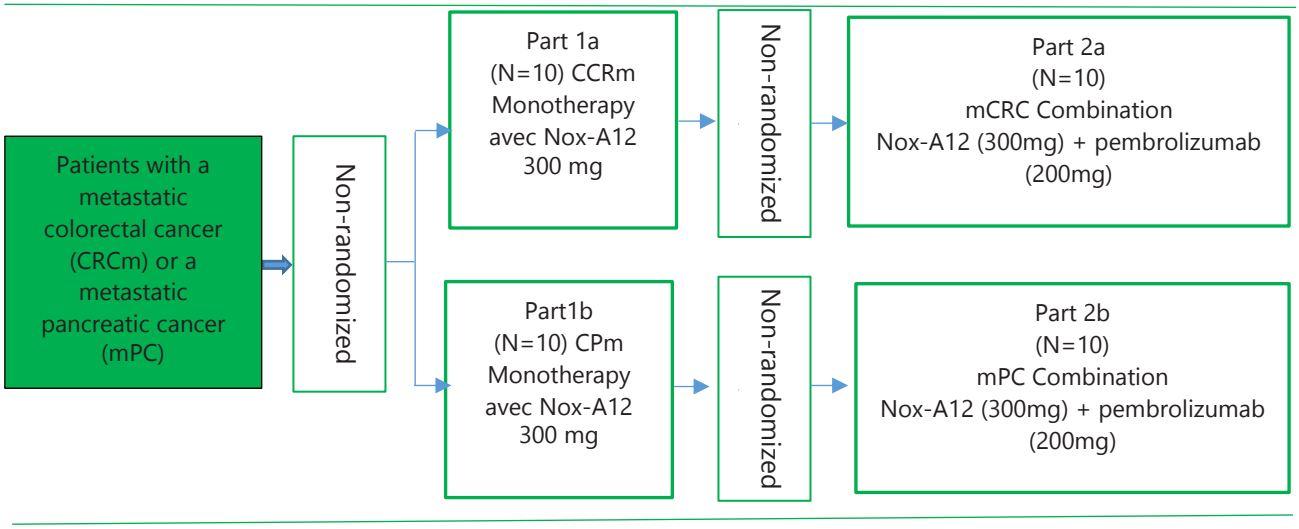
[45] Zboralski D, Hoehlig K, Eulberg D, Frömming A et Vater A. Increasing tumor-infiltrating T cells through inhibition of CXCL12 with NOX-A12 synergizes with PD-1 blockade. Cancer Immunol Res 2017; 5: 950-56.

NOX-A12 alone apparently has no influence on tumor volume as well as anti-PD-1 alone. However, NOX-A12 / anti-PD-1 significantly reduced tumor volume (5 mice / 8 responded). This result confirms the interest of NOX-A12 inhibiting CXCL12 in potentiating the effect of immune checkpoint inhibitors.

Clinical Programs

Noxxon initiated a phase 1/2 clinical trial to demonstrate the effect of NOX-A12 on the tumor microenvironment, particularly on intratumoral infiltration of immune cells, and then the safety and efficacy of NOX-A12. in combination with pembrolizumab (Keytruda®) in patients with metastatic colorectal and pancreatic cancers. This trial of 20 patients (10 patients with metastatic colon cancer and 10 patients with metastatic pancreatic cancer) non-randomized with two arms. A first patient was recruited in May 2017 from the German National Center for Tumor Diseases in Heidelberg, which is part of the Deutsches Krebsforschungszentrum, Heidelberg University Hospital, Heidelberg Medical School and Deutsche Krebshilfe. Two patients have now completed the first part of the study and progressed to the second part. In December 2016, Noxxon Pharma announced a collaboration with Merck under which they will provide the company free of charge, their PD-1 Keytruda® / pembrolizumab checkpoint inhibitor for clinical trials on solid tumors of the group that would test combinations with NOX-A12.

Design of the clinical trial in metastatic cancers



Source: Noxxon et Aurgalys.

By taking biopsies, Noxxon should be able to measure the number of infiltrating T cells. Within these tissue samples from the resected tumor or repeated biopsies of the tumor or its metastases will also be assessed immune cell distribution, as well as changes in the expression pattern of cytokines and chemokines. At the end of this first step taking place on 10 patients with metastatic colorectal cancer and on 10 other patients with a locally advanced or metastatic pancreatic adenocarcinoma, the test will be continued by associating NOX-A12 with the staining inhibitor. Keytruda® / pembrolizumab control system. This second part of the study aims to provide additional information on the safety and therapeutic potential of NOX-A12 / checkpoint inhibitor combinations in a small number of cancer patients. Since these two types of tumors generally do not respond to monotherapy with a Keytruda® / pembrolizumab-type immune-checkpoint inhibitor, Noxxon estimates that even a small proportion of

NOX-A12 + Keytruda® / pembrolizumab responders would be a very relevant result. Depending on the response criteria used for the clinical trial, the second analysis of the tumor response, which will take place approximately six months after the start of the combination therapy, will definitively determine whether each patient responds or not. For responding patients, more time will be required to assess the duration and extent of the response.
Many studies show that the density of infiltrating T cells can be considered as a prognostic factor for advanced solid tumors and their response to immune checkpoint inhibitors. It is particularly well documented for patients with colorectal cancer, which has led to an international recommendation in patient care. Therefore, the company believes that a positive result in this demonstration of the mechanism evidence test is sufficient to support the conduct of a pivotal, randomized, double-blind, placebo-controlled NOX-A12 trial on a control point inhibitor. Immune in a solid cancer indication with primary endpoint, overall survival.

NOX-A12 and Glioblastoma: blocking the recruitment of repair cells

Rationale for NOX-A12 in glioblastoma

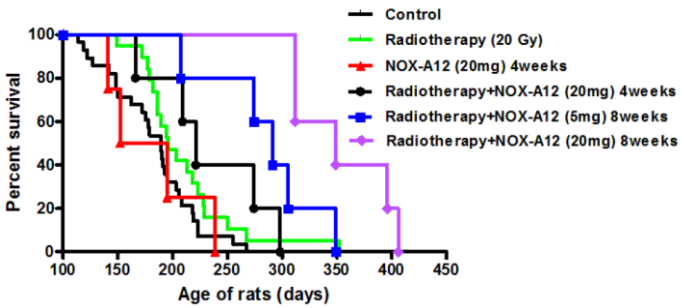
Numerous studies have shown that the chemokine CXCL12 plays a major role in the proliferation and aggressiveness of certain cancers, especially glioblastoma[46]. Several studies of animal models of glioblastoma at Stanford University have shown that radiotherapy induces increased recruitment of bone marrow derived cells while increasing the expression of CXCL12, which increases the number of macrophages associated with bone marrow. the tumor (M2). Still according to researchers at Stanford University, any neutralization of CXCL12 by NOX-A12 would result in stopping the recruitment of these tumor repairing cells that can lead to remission. For patients whose glioblastoma has been recently diagnosed as inoperable, the median overall survival prognosis is approximately one year[47]. In addition, for a significant fraction of these patients, the presence of an unmethylated O6-methylguanine-DNA-methyltransferase (MGMT) promoter prevents them from benefiting from the standard chemotherapy treatment, temozolomide (Temodar®). Inoperable glioblastoma patients who are resistant to Temodar® represent a population for which small improvements in efficacy would be clear after a short period of treatment. In addition, studies have shown that a high rate of lymphocyte infiltration of glioblastoma tumors into $CD8^+$ LTI correlates with longer survival of patients. There would be a higher concentration of $CD68^+$ and $CD8^+$ LT in GBM than in other gliomas (astrocytomas). Other authors have investigated the prognostic value of $CD8^+$ and $CD4^+$ LTIs as well as FOX03 in 90 glioma samples by showing that $CD8^+$ was inversely proportional to grade and that $CD4^+$ was proportional to grade.

Preclinical data

Noxxon Pharma collaborated with a team from Stanford University who had a mouse model of carcinogen-induced glioblastoma. In these preclinical experiments, it was shown that NOX-A12 in combination with radiotherapy induced a significant reduction in the size of tumors below the detection limit in 100% of the animals tested.

[46] Guo F, Wang Y et al. CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. *Oncogene*, 2016 ; **35**, 816–826.
[47] Chauffer et al., 2014

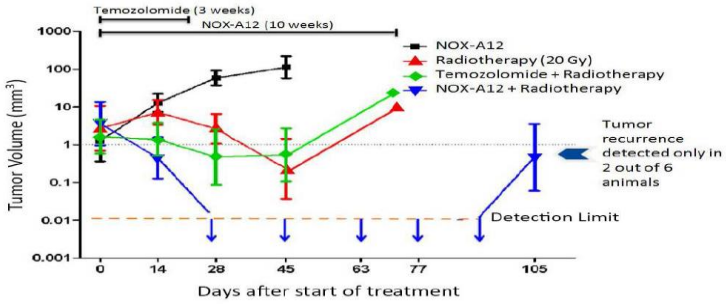
NOX-A12 prolongs survival in rats with glioblastoma



Source: Noxxon Pharma.

In addition, these responses persisted in 2/3 of animals after cessation of treatment[48]. This improvement in survival depends on the dose and duration of treatment since the longest survival was observed with the highest doses and the longest time (20 mg NOX-A12 for 8 weeks). Another preclinical study that was conducted by researchers at Stanford University also showed that treatment with NOX-A12 in combination with radiation therapy leads to a reduction in tumor size at undetectable volume levels by MRI. Four groups of rats were treated with (i) NOX-A12 (10 mg / kg) alone for 10 weeks, (ii) radiotherapy alone (one administration of 20 Gy), (iii) radiotherapy (one administration of 20 Gy) and temozolomide (10 mg / kg) for three weeks or (iv) combination of radiotherapy (20 Gy administration) and NOX-A12 (10 mg / kg) for 10 weeks.

NOX-A12 reduces tumor size in animal models of glioblastoma



Source: Noxxon Pharma.

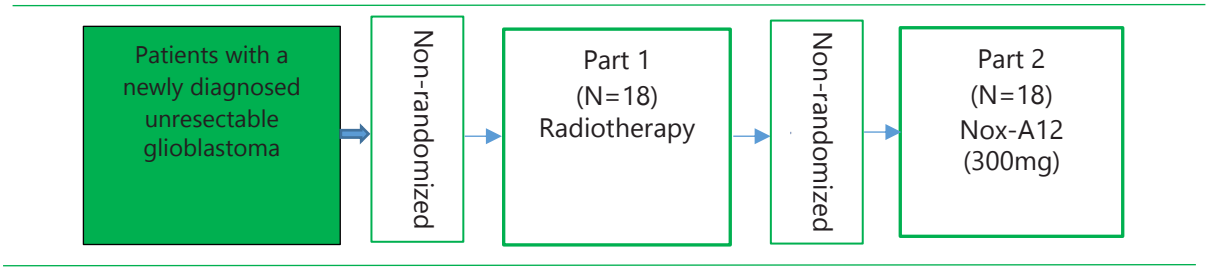
In rats treated only with NOX-A12, the tumor continued to grow as expected, since NOX-A12 does not directly target the tumor, but rather blocks a component of TME, in this case the recruitment of "repairing" cells. For rats receiving radiotherapy alone or temozolomide-mediated radiotherapy for three weeks, the tumors behaved similarly with an initial volume decrease at day 45 followed by recovery. However, the tumors of rats treated with radiotherapy and NOX-A12 for 10 weeks disappeared 28 days after the start of treatment and continued to be undetectable by magnetic resonance imaging until recurrence occurred in two rats 105 days later. treatment initiation and 35 days after stopping treatment with NOX-A12. After stopping treatment, only two out of six rats treated with NOX-A12 and radiation had tumor recurrence.

[48] Liu

Clinical Programs

Noxxon has designed a phase IIb / III Phase I / IIa clinical trial in 18 patients with newly diagnosed glioblastoma. This trial could primarily target patients with a non-methylated MGMT gene promoter, as it is known that these post-surgery patients do not respond to TMZ. The recommended therapeutic strategy is surgical resection at the widest margins possible, because after resection, the size of the tumor residue has a direct influence on survival. Then adjuvant chemotherapy is recommended because there may be residual tumor cells that are not visible on post-surgical MRI. This test of Noxxon could follow two distinct designs. The first would consist of 6 weeks of post-surgical radiotherapy that would start between 4 to 6 weeks after surgery: radiotherapy at the dose of 60 Gy in 30 fractions of 2Gy followed by 4 weeks of rest. Then chemotherapy with NOX-A12 300 mg adjuvant 6 months (based on the Stupp protocol). The interest of this maintenance treatment could show the interest of NOX-A12 monotherapy.

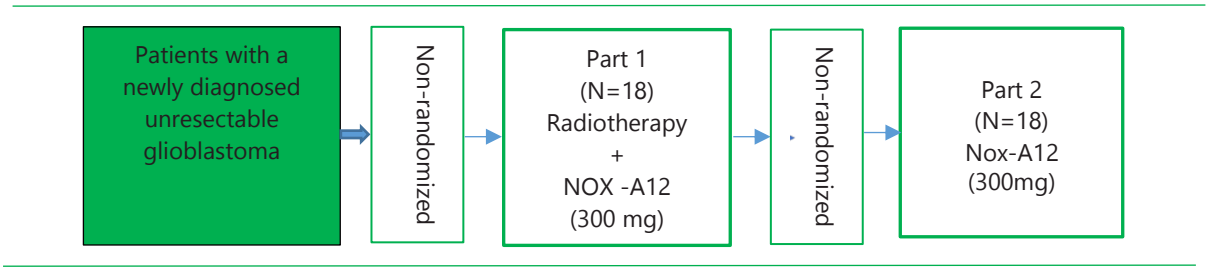
Overview of trial 1



Source: Noxxon Pharma

In this alternative design 1, NOX-A12 is given concomitantly with radiotherapy, replacing temozolomide (TMZ). Indeed, at the end of the surgical excision, the recommended adjuvant treatment is radiochemotherapy according to the Stupp protocol, in which the treatment is started within 4 to 6 weeks after the procedure. Radiotherapy is still 60 Gy (30x2 Gy) + concomitant chemotherapy with NOX-A12. NOX-A12 is taken daily at a dose of 300 mg for the duration of the radiotherapy. Then, NOX-A12 is given 4 weeks after the end of chemoradiotherapy still at 300 mg for 5 days every 28 days for 6 months (see TMZ).

Overview of alternate trial 1



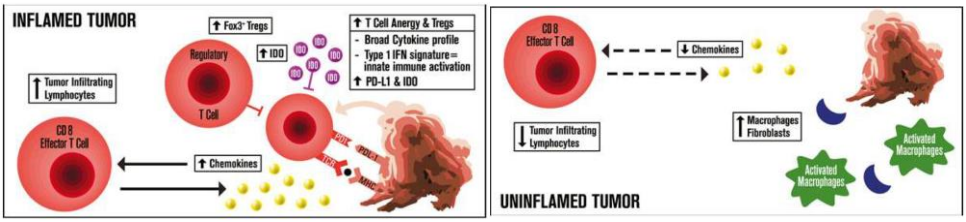
Source: Noxxon Pharma

We believe both designs are favorable for NOX-A12, as in the target population all patients have a non-methylated MGMT gene promoter and are therefore resistant to TMZ. Indeed, with these designs, Noxxon may be able to relatively easily demonstrate the therapeutic benefit of NOX-A12 compared to TMZ since patients recruited post-test methylation of the MGMT gene promoter are all resistant to this type of alkylating agents.

NOX-E36 and pancreatic cancer: targeting the TAM pathway

The rationale for using NOX-E36 in oncology indications is that some tumors have an inflamed phenotype, while others have a sparse immune infiltrate. Despite this pronounced immune infiltration in so-called "inflamed" or inflammatory tumors, the tumor response is not sufficient to halt the progression of the disease. These tumors present a paradoxical situation, with a set of factors that accentuate the migration of T cells (T-cell attracting chemokines) while maintaining a high immunosuppressive activity with FoxP3^{+} regulatory T cells (Treg) coupled to indoleamine-2, 3-dioxygenase (IDO) and PD-L1.

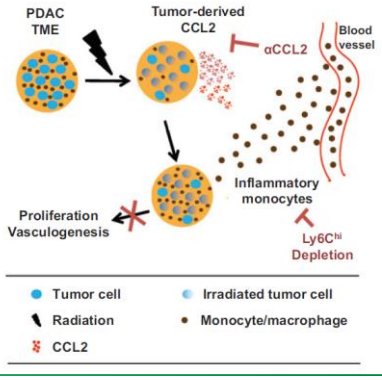
Inflamed tumors and uninflamed tumors



Source: Spencer KR et al. ASCO 2016 Educational book

On the other hand, non-inflamed tumors predominate in an immunosuppressive environment with very few invasive T cells, but markers of chronic inflammation such as tumor-associated macrophages, suppressive cytokines, and myeloid-derived suppressor cells[49]. Therefore, it was assumed that patients with tumors containing T-cell infiltrates could be induced to respond to immunotherapy if the immune cells in the tumor microenvironment could be reactivated. Recent work, particularly in pancreatic cancer[50], shows that it is possible to control the evolution of the tumor in 97% of patients (32/33 patients) using a CCR2 inhibitor in combination with the current standard of care (FOLFIRINOX). Scientific work shows that the CCL2 chemokine is highly expressed in fibroblasts associated with cancer and more particularly in breast cancer. This elevated expression in the CCL2 stroma would be of poor prognosis. Indeed, CCL2 is known to recruit monocytes / macrophages and promote the progression of cancer. The ductal adenocarcinoma of the pancreas is often characterized by an abundant stroma inducing phenomena of therapeutic resistance (chemo or radiotherapy). In the breast, this highly immunosuppressive stroma, where infiltration into T cells is weak, we find innate cells of inflammation such as monocytes and macrophages often in the form of TAMs.

One of the conceptual models proposed to describe the role of monocytes and CCL2



[49] Gajewski TF, Fuertes M, Spaapen R, et al. M resistance mechanisms in the tumor microenvironment. Curr Opin Immunol. 2011; 23:286-92.

[50] Nywening TM et al. Targeting tumour-associ mbination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic car , non-randomized, phase 1b trial. Lancet Oncol 2016; 2045 :78-84

Source: Kalbasi et al. Clinical Cancer Research, June 2018

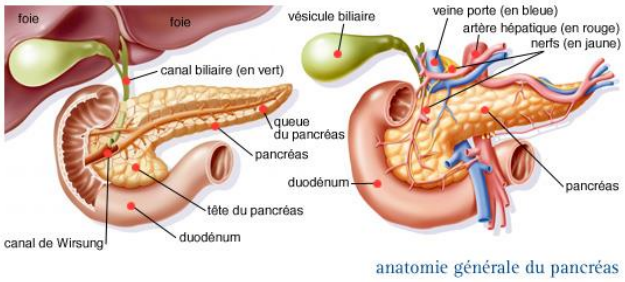
Tumor-associated macrophages play a crucial role in inducing anergy of other immune cells that "penetrate" into the tumor mass lose all ability to produce an immune response against tumor cells. It has also been shown the importance of the relationship between the CCl2 chemokine and its CCR2 receptor in tumor TAM recruitment. Moreover, the other immune cells present are monocytes naturally produced by the bone marrow and which are the precursors of macrophages. There are two types of monocytes: resident monocytes and inflammatory monocytes. Residents that account for 15% of circulating monocytes are weakly expressing the CCR2 receptor, while the inflammatory monocyte population (85% circulating monocytes) strongly expresses CCR2. Then recruited at the site of inflammation, these monocytes leave the bloodstream (extravasation), penetrate the tissues and differentiate into macrophages. In addition, the mechanisms of therapeutic resistance observed with pancreatic adenocarcinoma occur both with chemotherapy and radiotherapy. Because as Kalbasi et al.[51] there is resistance to radiotherapy mediated by CCL2-dependent inflammation. Indeed, following the stress induced by ablative radiotherapy, tumor cells would increase their expression of CCL2 to recruit inflammatory monocytes from the bloodstream. And who upon arrival within the tumor mass would differentiate into pro-inflammatory macrophages and TAMs creating immunosuppressive conditions favorable to the development of the tumor. Therefore, targeting the CCR2 / CCL2 axis reduces the involvement of inflammation cells in the mechanisms of development, progression, resistance and immune suppression observed in most solid tumors. So, any strategy of inhibiting one of the actors, ligand or receptor should reduce or eliminate this process.

[51] Kalbasi A, Komar C, et al. Tumor-derived CCL2 mediates resistance to radiotherapy in pancreatic ductal adenocarcinoma. Clinical Cancer Research

Targeted pathologies

Pancreatic cancer

The pancreas is a vital organ of the body. This elongated and flattened gland, located in the abdomen, behind the stomach and in front of the spine, in the lumbar vertebrae L1 and L2, has an essential action on the digestion of food and the regulation of blood glucose. Therefore, the pancreas has two secretory systems, the so-called exocrine system that allows it to secrete substances that make up the pancreatic juice in the digestive system, particularly in the duodenum.



Anatomy of pancreas

Source : http://www.arcagy.org/infocancer/localisations/appareil-digestif/cancer-pancreas/maladie/un-peu-d-anatomie.html

The other term endocrine, which delivers hormones insulin and glucagon essential for maintaining blood sugar. Through the Wirsung duct, the exocrine function will dump into the duodenum bicarbonate ions that will neutralize the acidity of the bolus or chyme (predigested food) as well as digestive and pancreatic proenzymes that attack lipids, carbohydrates and proteins brought by the diet. β and α cells of Langerhans islets will secrete directly into the bloodstream, insulin which reduces the blood sugar level and glucagon which raises this rate. This dual function of the pancreas shows the central role that the pancreas plays in human physiology and any attack on one or the other system can have devastating consequences. Thus, the destruction of islet cells leads to type 1 diabetes, which results in an abnormal rise in blood glucose levels. Another condition is pancreatitis or inflammation of the pancreas following the presence of stones in the bile ducts, excessive consumption of alcohol, a viral or parasitic infection or an autoimmune disease. Sometimes a malignant tumor can develop in the pancreas, the most common form of which is adenocarcinoma.

Etiology

Primary tumors of the pancreas can affect the exocrine part in 95% of cases[52] and the endocrine part in 5%. They can be subdivided into adenocarcinomas (85% of cases) [53], and neuroendocrine tumors (NET). Adenocarcinomas are mainly tumors of exocrine cells, which produce gastric juices, which participate in digestion. While neuroendocrine tumors affect cells producing pancreatic hormones such as insulin or glucagon. The traditionally aggressive pancreatic cancer is a cancer of bad prognosis, because it is often discovered late. Indeed, the deep localization of the pancreas behind the stomach in front of the spine

[52] http://ncbi.nlm.nih.gov/pubmedhealth/PMHT0024281/
[53] Ryan, DP et al. New England Journal of Medicine 2014: 371, (11):1039-49.

makes it difficult to access almost any means of clinical investigation. In addition, there is no early detection. In addition, it is often discovered at an advanced stage of development because it has few clinical signs early in the disease, making any treatment difficult. Pancreatic cancer is now considered the 4th leading cause of cancer-related death in the United States, with nearly 45,000 deaths each year. Like a large majority of solid tumors, pancreatic tumors maintain a highly immunosuppressive environment, thus escaping immune "surveillance". Therefore, one of the therapeutic approaches to pancreatic cancer could be to target and specifically restore the patient's immune system. Indeed, by modulating the immune response of the host, including reducing the tolerance of the host cells against tumor antigens.

Pancreatic cancer, tumor microenvironment and immunotherapies

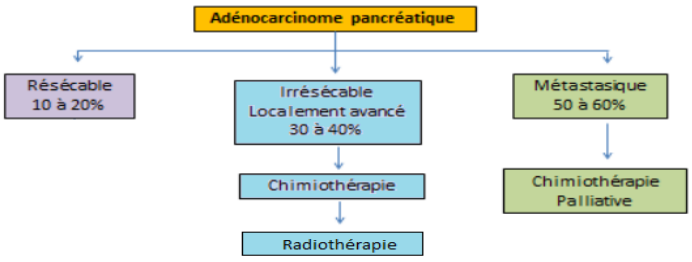
Recent studies have shown that immune checkpoint inhibitors have little therapeutic effect in patients with pancreatic ductal adenocarcinoma[54]. In addition, pancreatic cancer has exclusion profiles of immune infiltrations associated with high levels of TGF-b as well as local production of CXCL12 by Fibroblast activating proteins (FAPs) expressed by CAF or fibroblasts. associated with carcinoma[55]. Therefore, any reduction of FAP + stromal cells, which are the main source of CXCL12 in pancreatic ductal adenocarcinoma, will influence the activity of the control point inhibitors. Similarly, blockade of CXCL12 would restore infiltration of CD8 + T cells within the tumor while acting in synergy with PD-L1 inhibition and cancer cell depletion[56]. The weakness of the responses observed with immunotherapy (ICI) makes it possible to hope that any improvement in response rates would represent a significant advance.

Pancreatic cancer treatments

Treatments for this cancer depend on several factors including the stage of the disease. For cancers limited to the pancreas, surgery is the reference treatment in 15% of cases. The major contraindications for surgery are when the liver, peritoneum or certain lymph nodes have metastases or when the patient cannot be operated on. Post-surgery relapse rates are approximately 70% significant. Surgery is often associated with chemotherapy and / or post-surgery radiotherapy (adjuvant therapy) to prevent relapse. A "neoadjuvant" chemotherapeutic or radiotherapeutic treatment is recommended prior to surgery for "bordeline" tumors. Gemcitabine is one of the standards of care for metastatic pancreatic cancer; it has been registered in combination with erlotinib (Tarceva) and nab-paclitaxel (Abraxane). The combination of gemcitabine + erlotinib increased survival by almost a year compared with gemcitabine alone. Median survival improved from 5.91 months to 6.24 months. Recent studies have shown that the addition of nab-paclitaxel to the gemcitabine + erlotinib cocktail also has the effect of further increasing survival. Data that led the FDA to record these combinations.

[54] Delitto D, Wallet SM & Hughes SJ Targeting tumor tolerance: a new hope for pancreatic cancer therapy? Pharmacology and Therapeutics 2016; 166: 9–29. (doi: 10.1016/j.pharmthera.2016.06.008)
[55] Fearon DT. The carcinoma-associated fibroblast expressing fibroblast activation protein and escape from immune surveillance. Cancer Immunol Res 2014; 2(3): 187-93.
[56] Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci USA 2013; 110: 20212–20217.

Algorithm for the treatment of pancreatic ductal adenocarcinoma



Source : Adapted de Singh et al Biochim Biophys Acta, 2015, Marty, Lasserre and El Alaoui.

FOLFIRINOX (leucovorin + 5-fluorouracil + oxaliplatin + irinotecan) certainly increases the overall survival of patients compared to gemcitabine, but with significant side effects, which lead to recommend it for patients whose general condition allows. In 2015, the FDA approved the release of a new liposomal formulation of irinotecan, Onivyde in combination with fluorouracil and leucovorin. This molecule is indicated for patients with metastatic pancreatic cancer who have not responded to gemcitabine.

Competitive landscape and market

In 2016, there were nearly 49,000 people diagnosed with pancreatic cancer in the US, including just over half with metastatic disease. Globally, this cancer, which is the twelfth in terms of representation in the population, with 338 000 new cases in 2012. With nearly 50% of these patients already in the metastatic stage, because it is a cancer that 'we diagnose late. The 5-year survival rate is particularly low, being less than 14% when localized and less than 1% when metastatic. This condition presents unmet medical needs, particularly in terms of diagnosis and in therapeutic terms, to improve the survival of these patients. Today Gemzar® (gemcitabine) is generic, but it would have generated a little more than 700 million dollars for Eli Lilly, its manufacturer. The other molecules, Tarceva de Roche / Astellas and Abraxane, generated $ 1.2 billion and $ 1.1 billion, respectively, in 2015.

Clinical trials of immunotherapy in pancreatic cancer

Company	Regimen	Target	Target population	design	Phase
Five Prime & BMS	nivolumab + FPA008 (CSF1R inhibitor)	PD-1 + colony stimulating factor-1 receptor	advanced pancreatic cancer	Arm 1- Phase 1a monotherapy Arm 2- Phase1a combination therapy to determine safety data Arm 3- Phase 1b combination therapy to determine clinical activity and safety profile	I
BMS	nivolumab + ulocuplumab (anti-CXCR4)	PD-1 + anti-chemokine receptor CXCR4	metastatic solid tumors	Combination arm in pancreatic cancer	I/II
ARMO Biosciences /Merck	pembrolizumab + AM0010	PD-1 + PEGylated recombinant human IL-10	Advanced solid tumor including pancreatic cancer	Combination therapy	I
Roche	atezolizumab + cergutuzumab amunaleukin (IL-2v with anti-CEA)	PD-L1 + Variant of Interleukin-2 against Carcinoembryonic antigen	Advanced solid tumor including pancreatic cancer	Part 1- Dose Escalation Part 2- Dose expansion	I
City of Hope/Merck	pembrolizumab + Oncolytic virus	PD-1	Solid tumors with failed prior therapy including PDAC	Combination therapy	I

Source: Thind et al. Ther Adv Gastroenterol 2017.

Several strategies have been put in place to reduce the "tumor promotion" performed by the TAMs and improve the prognosis by reducing the number of TAMs present. We will distinguish:

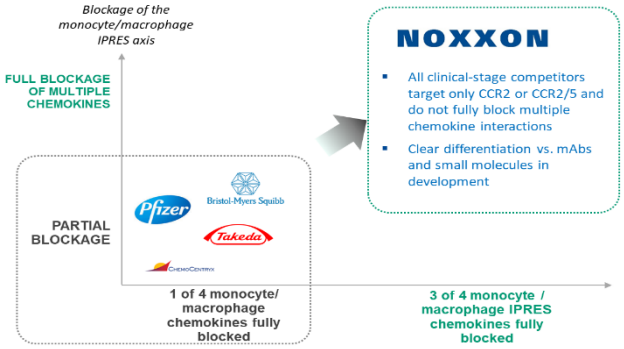
- Agents inhibiting TAM activation such as Novartis MSCI10, Eli Lilly IMC-CS4 (or LY3022855), Amgen AMG820 and GSK PLX6134 / GW2580 all targeting CSF1 and CSFR1, its receptor;
- Agents that reduce the survival of TAMs such as PLX 3397 (a multi-kinase) of Plexxikon, as well as 5-FU or docetaxel or certain immunotoxins that act on FR-β (the β folate receptor);
- Molecules playing on the reprogramming of macrophage polarization such as TLR agonists, anti-CD40 monoclonal antibodies, thiazolidinediones (PPAR-γ agonists);
- Molecules, acting on the CCL2 / CCR2 axis, limit the recruitment of monocytes, either by acting on CCL2 such as carlumab, a monoclonal antibody against CCL2, or on the CCR2 receptor as the CCR2 antagonist, PF-04136309 from Pfizer or CCX872 from ChemoCentryx.

In addition, developments in the concurrent approaches currently under development, CCX140 (ChemoCentryx), PF-04136309 from Pfizer and BMS-813160 (Bristol Myers Squibb) should also be monitored. Indeed, today, the CCL2 / CCR2 path is attracting more and more interest from both major laboratories and biotechnology companies. For example, Pfizer conducted a phase I / IIb clinical trial combining PF-04136309, an oral CCR2 receptor inhibitor, with gemcitabine and nab-paclitaxel. This two-part trial initially (phase Ib) determined the safety and pharmacodynamic and pharmacokinetic properties of PF-04136309. Then, after identifying the dose for phase IIb, 92 patients randomized in 1: 1 receive either PF-04136309 with gemcitabine and nab-paclitaxel (arm A: 46 patients), or gemcitabine and nab-paclitaxel (arm A: 46 patients), or gemcitabine and nab- paclitaxel and placebo (arm B: 46 patients) with the primary endpoint of improving progression-free survival. Recently, ChemoCentryx announced that it has improved the overall survival of patients with locally advanced or metastatic pancreatic cancer with its CCX872 molecule that specifically targets the CCR2 receptor. In this open, multi-center phase Ib trial of 50 patients receiving FOLRIRINOX in combination with CCX872, the overall survival rate was 29% at 18 months compared to 18.6% observed in a previous trial with FOLFIRINOX alone. However, it should be considered that patients in the FOLFIRINOX alone trial had a more advanced metastatic stage than in the ChemoCentryx trial.

The positioning of NOX-E36

Today, it is known that several chemokines (CCL2, CCL7, CCL8 and CCL13) are involved in the PD-1 innate resistance signature. Unlike other developed molecules, which block the recruitment of bone marrow monocytes by inhibiting the CCR5 receptor, Noxxon's NOX-E36 neutralizes 3 out of 4 chemokines, thus reducing the potential for bypass that could be observed. In addition, NOX-E36 is targeting the suppressive myeloid cell (MDSC) pathway. This heterogeneous population of cells that accumulate during tumorigenesis promotes immune escape. But many of these cells share a common trait which is the presence of the CCR2 chemokine receptor as well as the expression of CD11b. In addition, it has been shown that MDSCs also regulate the entry of CD8 cytotoxic T lymphocytes into tumor masses. Noxxon therefore intentionally chose NOX-E36 to block several chemokines that share multiple receptors.

Positioning Noxxon with NOX-E36



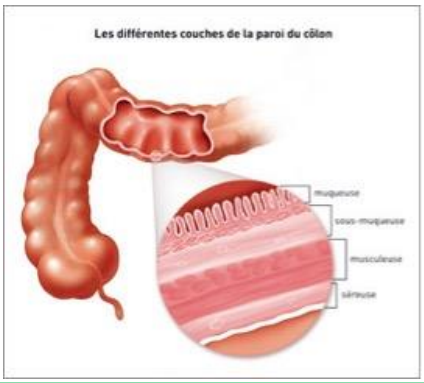
Source: Noxxon

This strategy is highly differentiated from the "natural" competitors of NOX-E36, which almost all target one of the receivers, be it CCR2 or CCR5. This innovative and differentiating approach can, in case of a positive demonstration of clinical efficacy, increase the chances of success for a partnership between Noxxon and a pharmaceutical company.

Colorectal cancer

The colon and rectum make up most of the large intestine, which is the distal part of the digestive tract and provide essential functions in the end of digestion. Indeed, it receives the bolus almost completely digested by the stomach and the small intestine in liquid form. In the colon, residual water is absorbed to desiccate the final food waste and make it semi-solid thus forming the stool that can be stored in the rectum before being evacuated. To perform its essential function of compacting the digested materials in semi-solid stools, the colon is mainly composed of smooth muscles that work autonomously without voluntary intervention. The rectum, located between the colon and the anal canal, is the ultimate part of the digestive tract. Its main function is to store the stool before it is evacuated by the anus. Cylindrical and measuring between 15 and 18 cm long, its inner surface has two or three horizontal folds (valves or valves of Houston) and vertical folds at its junction with the anal canal (rectal columns or columns of Morgagni). Its outer surface is dented and covered by the mesorectum, a fatty tissue that contains blood vessels and lymph nodes. The wall of the rectum, like that of the colon, consists of four different layers that overlap:

The different tissue layers of the colon and rectum

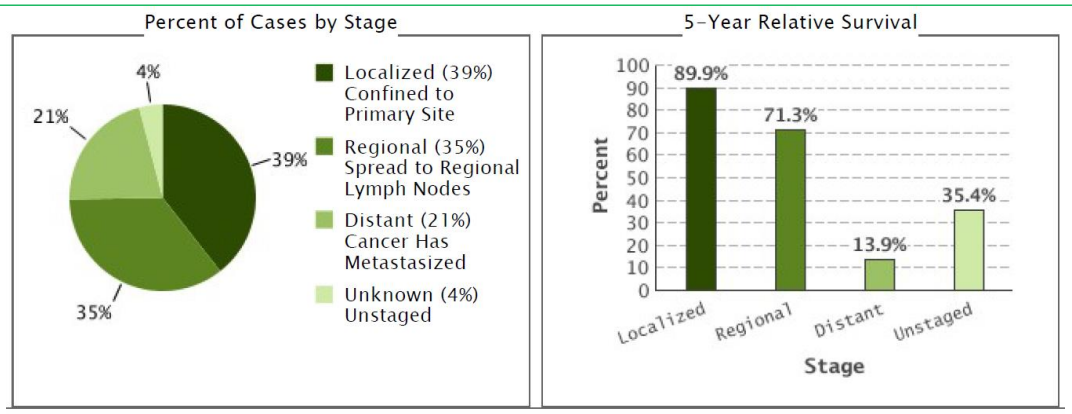


Source : http://chirurgie-digestive-sat.aphp.fr/pathologies/cancer-colorectal/anatomie-du-colon-du-rectum/

Cancer can develop in any portion of the colon. Nevertheless, in more than half of all cases, cancer affects the sigmoid colon. Colon cancers most commonly occur in the mucosa. They then extend to the other deeper layers of the wall as they develop.

Etiology

Sometimes the cells lining the colon and the rectum can adopt anarchic behavior by multiplying rapidly to form outgrowths, polyps. Although polyps do not systematically turn into cancer, the appearance of a tumor is often consecutive to polyps. These cells of these polyps undergo cycles of transformation and mutation of their genetic inheritance leading to malignant tumors. Although screening programs have been introduced and implemented in different countries, there is a high percentage of patients with advanced disease at first diagnosis. As shown by data from the SEER Cancer Statistics US, nearly 39% of patients were at the local stage (stage 0, I and II) when the disease is still restricted to different layers of tissue of the colon or rectum or organs nearby without affecting the lymph nodes.



CRC severity in diagnosis and 5-year relative survival

Source: SEER 18 2007-2013, All Races, both Sexes by SEER Summary Stage 2000

35% of patients diagnosed were at the regional stage which meant that the disease had spread to one or more lymph nodes near the colon or rectum but without reaching the distant organs (stage III) and 21% of patients were at the stage IV or distant when the cancer has spread to distant locations (metastases to the liver, peritoneum and / or lung). In addition, the 5-year survival increases from nearly 90% for local stages (stage 0, I and II) to 71% for the regional stage and 13.9% for the disseminated stage. It should be noted, however, that 50% of patients with local or regional stage relapse after surgery because of the presence of micrometastases[57]. Colorectal cancer is the third most diagnosed cancer worldwide and the second leading cause of death in cancer patients.

Colorectal cancer, tumor microenvironment and immunotherapies

If for many years colorectal cancer (CRC) has been considered as one of the least likely to respond to therapeutic strategies based on immunotherapy, the landscape seems to have changed. Indeed, ICIs have been shown to be effective, including anti-PD-1 therapies as a second line of treatment in patients

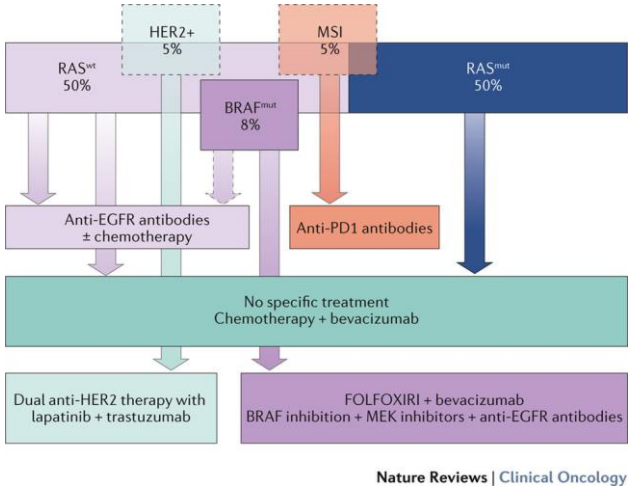
[57] Koido S et al. Immunotherapy of colorectal cancer. World J Gastroenterol. 2013; 19: 8531-8542

with metastatic CRC (mCRC) with high microsatellite instability (MSI-H). In this phase II study examining the use in patients with metastatic CRC of nivolumab (Opdivo) as monotherapy or in combination with ipilimumab (Yervoy). The first arm outcome with Opdivo alone shows the overall response rate was 31.1% with a progression-free survival rate of 48.4% and a 12-month overall survival rate of 73.8%. Unfortunately, these patients represent only 4 to 5% of patients with a mCRC, which unmet medical needs for nearly 95% of mCRC patients. Indeed, MSI-H patients are patients for whom the mutational level is high (hot tumors) and therefore the level of neoantigens generated is also very high. There remains, therefore, unmet medical needs, particularly for colorectal cancers with stable microsatellites and in terms of the use of ICIs, for which it may be essential to identify the best association.

Metastatic colorectal cancer treatments

Historically, metastatic colorectal cancer has been treated in the first line with 5-fluorouracil with leucovorin. Today, the first line of treatment is FOLFOX (leucovorin + 5-fluorouracil + oxaliplatin) sometimes in combination with irinotecan (FOLFIRINOX or FOLFOXIRI). In 2015, a new antineoplastic agent was registered, Lonsurf, which combines trifluridine, a nucleoside analogue of thymidine, and tipiracil, a thymidine phosphorylase inhibitor, that slows the breakdown of trifluridine.

Algorithm for the treatment of metastatic colorectal cancer based on molecular status



Source : Punt, Koopman et Vermulen Nature Reviews Clinical Oncology

However, Lonsurf is offered to patients who are resistant to all available treatments (fluoropyrimidine-based chemotherapy, anti-VEGF treatment and anti-EGFR therapy) and whose general condition is maintained. Several other classes of molecules have been developed such as:

- Angiogenesis inhibitors such as Roche's Avastin (bevacizumab) that blocks intracellular signaling of VEGF.
- EGFR (Epidermal Growth Factor Receptor) inhibitors such as Lilly / Merck's cetixumab (Erbitux) and Amgen / Takeda panitumumab (Vectibix).
- Targeted therapies such as tyrosine kinase inhibitors such as Bayer's regorafinib (Stivarga), which is indicated on the 3rd or 4th line.

However, given the very high heterogeneity of the CCR, the use of diagnostic tests and biomarkers has become widespread to achieve a real stratification of patients. Indeed, depending on the biology of the tumor, it is possible to identify subgroups whose prognosis will vary according to the therapy used. Today only the detection of the RAS mutation is performed in hospital routine. The presence of mutated RAS (RAS-) does not allow the use of anti-EGFR in patients with metastatic CRC. Just as the presence of microsatellite instability (MSI) justifies the use of adjuvant chemotherapy for early stage patients. In addition, patients with high microsatellite instability rates are good candidates for ICI-based anti-PD-1 / PD-L1 immunotherapy. However, in 85% of cases (low microsatellite instability), immunotherapy does not represent a therapeutic alternative.

Competitive landscape and market

It is estimated that there are nearly 1.4 million people with colorectal cancer around the world. This cancer would be the third in number for men and the second for women. It is estimated that 95% of the RCCs are adenocarcinomas. The remainder would be divided between mucinous carcinoma and adenosquamatous carcinoma. Today the therapeutic field of metastatic CRC is mature with Roche's Avastin (bevacizumab), cetuximab (Erbitux®) and Vectibix (panitumumab) all of which have shown an increase in the survival of treated patients. However, as we mentioned earlier, unmet medical needs still exist in the treatment of metastatic CRC and the increase in patient survival, especially for KRAS + patients for whom EGFR inhibitor-based therapies (Erbitux and Vectibix) are not recommended. In addition, the possibility of using immune checkpoint inhibitors is still in its infancy. However, trials involving ICI and the immuno-oncological approach are growing. Several attempts have been made with ICI inhibiting the PD-1 / PD-L1 pathway, but for patients with high MSI expression (MSI-H), which results in several important mutations within the tumor tissue. As Patel and Kurzrock have shown, the expression levels of PD-1 and PD-L1 are low in the MSS CCRs of the order of 20% whereas in the MSI-H CCRs, the level can reach 60%.

Recently, intermediate results from the KEYNOTE-164 Phase II trial showed that pembrolizumab had an overall survival rate of 26.2% in MSI-H patients. Similar results led to the registration of nivolumab in phase II., Which had demonstrated an overall survival rate of 28% in dMMR (DNA Repair Deficiency) or MSI-H patients with metastatic CRC. progression after FOLFOXIRI chemotherapy. The phase III KEYNOTE-177 trial seeks to demonstrate the value of using nivolumab in 1L. As can be seen here there is a real challenge for immunotherapy to treat a larger population in the field of CCR and the contribution of Noxxon with NOX-A12 is essential.

Clinical trials of immunotherapy in colorectal cancer

Company	Regimen	Target	Target population	Line	Phase	Endpoint
BMS	trametinib + nivolumab + ipilimumab	PD-1 +CTLA-4	mCRC MSS		I/II	
BMS	BMS-813160 + nivolumab	PD-1 +CTLA-4	CRC, mCRC		I/II	ORR, PFS, duration of response
Merck	entinostat + pembrolizumab	PD-1	mCRC MSS		I/II	irPFS
BMS	nivolumab +/- ipilimumab +/- cobimetinib ou BMS-813160 + nivolumab ou nivolumab + daratumumab	PD-1 +CTLA-4	mCRC MSI-H & MSS	2L, 3L et 4L	II	ORR
AstraZeneca	durvalumab + tremelimumab	PD-1 +CTLA-4	CRC & mCRC		II	OR
AstraZeneca	durvalumab	PD-L1	mCRC MSI-H & MSS		II	ORR
Merck	pembrolizumab	PD-1	mCRC MSI-H & MSS		II	ORR
Merck	pembrolizumab	PD-1	mCRC & MSI-H		II	irPFS, irORR
Taiho Oncology	TAS-102 (Lonsurf) + nivolumab	PD-1	mCRC MSS	2L, 3L et 4L	II	irORR
Roche	capecitabine + bevacizumab + atezolizumab ou cobimetinib +atezolizumab	PD-L1	mCRC MSI-H & MSS	1L	II	PFS
Roche	atezolizumab + cobimetinib	PD-L1	mCRC		III	OS
Merck	pembrolizumab	PD-1	mCRC MSI-H		III	PFS

ORR=objective response rate; irPFS= immune-response progression free survival; irORR=immune-reponse objective response rate

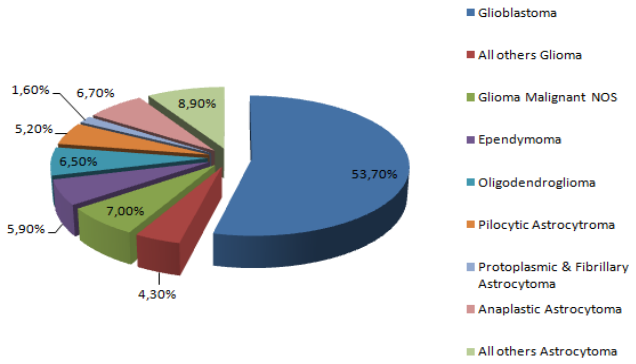
Source: Aurgalys

By destroying the barrier, which is blocking the entry of infiltrating/cytotoxic T cells, NOX-A12 offers a new and particularly relevant pathway for the treatment of CRC. The interest of NOX-A12 is certainly in the fact, that it does not depend on the genetic status of the tumor. The CXCL12/CCR4 pathway allows the recovery of the immune response within the tumor while eliminating the MSI pathway. The specificity and selectivity of NOX-A12 make it a molecule of interest in the treatment of glioblastoma, which can therefore be proposed in combination with various molecules from traditional chemotherapy to ICPI through targeted therapies. In addition, the CCL12 chemokine binding pleiotropy that can indifferently bind to CCR4 or CCR7 militates in favor of chemokine blocking rather than receptor inhibition, a choice that many of Noxxon's competitors make.

Glioblastoma

Primary tumors of the central nervous system come from cells normally found in the brain. According to the American Cancer Society, about 18,500 new cases of malignant brain tumors are diagnosed in the United States each year. Nearly 12,760 deaths are attributable to these brain tumors. In the last three years, with the improvement of the diagnostic procedure, the number of these brain tumors has increased by 300%.

Histological distribution of malignant brain tumors

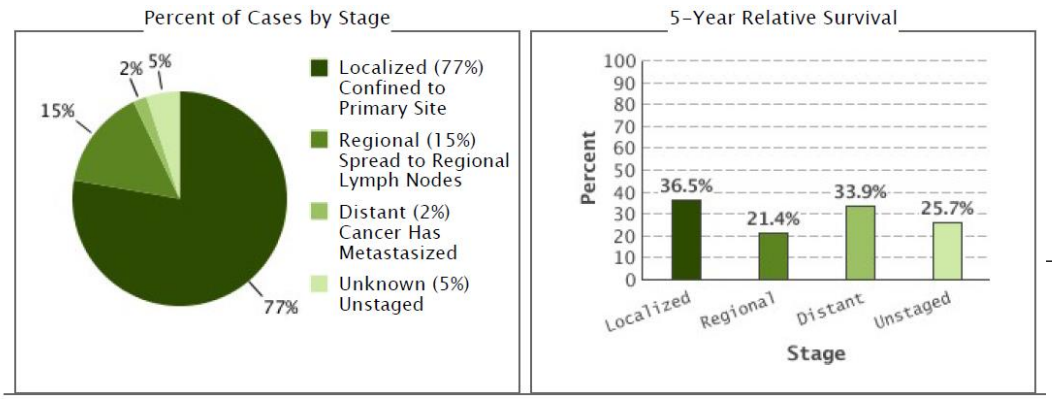


Source: 2006 US Central Brain Tumor Registry 2005-2006 Report based on 25,539 patients 1998-2002.

The most common type of malignant brain tumor is malignant glioma derived from glial cells of neuroepithelial origin in the brain. The main types of brain tumors are: astrocytomas, oligodendromes, oligoastrocytomas and ependymomas, but glioblastomas account for 50% of all malignant tumors. Malignant gliomas are highly invasive tumors, typically containing neoplastic and stromal tissue. This histological composition contributes to their heterogeneity and to variable results. In addition to the tumor itself, inflammation and edema that generate significant neurological deficits should be considered, as the pressure on normal brain tissue increases with the size of the tumor.

Histological analysis of brain tumors based on nuclear atypia, mitosis, microvascular proliferation and necrosis is used by WHO to classify gliomas into four prognostic categories: low grade subtypes (I, II) and high grade (III, IV). The severity (or grade) of a brain tumor is measured according to several criteria, including the similarity of tumor cells to normal cells, the rate of growth or an indication of uncontrolled growth, the presence of dead cells in the center of the tumor, the potential to invade or spread to surrounding tissues and the blood supply to the tumor.

Glioblastoma severity in diagnosis and 5-year relative survival



Source: SEER 18 2007-2013, All Races, Both Sexes by SEER Summary Stage 2000

Grade III and IV malignancies are the most severe, with a high likelihood of recurrence after initial treatment. Glioblastoma multiforme (GBM) is the most aggressive, very malignant and spreads rapidly throughout the brain, but rarely metastasized outside the nervous system.

Glioblastoma multiform (GBM)

GBM is the most common primary brain tumor in adults. GBM is an anaplastic, highly cellular tumor with round cells or pleomorphic cells with little differentiation. In the analysis, GBM may occasionally present multinucleated cells, nuclear atypia, anaplasia and endothelial proliferation. In the WHO classification system, GBM is called grade IV astrocytoma[58]. The signs and symptoms of GBM depend on the location, size and growth rate of the tumor. Primary GBM develops de novo from glial cells, generally has a clinical history <6 months and is more common in elderly patients. This primary tumor exhibits overexpression (> 60% of cases) or amplification (> 40% of cases) of the epidermal growth factor (EGF) gene. Other genetic changes leading to the development of primary glioblastoma include chromosome 10 loss, deletion or mutation of phosphatase and chromosome 10 gene tensin homolog (PTEN), amplification and overexpression. double murine minutes 2 (MDM2). Secondary GBM develops over months or years from low grade preexisting astrocytomas and affects younger patients. The development of secondary GBM is associated with inactivation of the tumor protein gene 53 (TP53) and overexpression of ligands and platelet derived growth factor (PDGF) receptors.

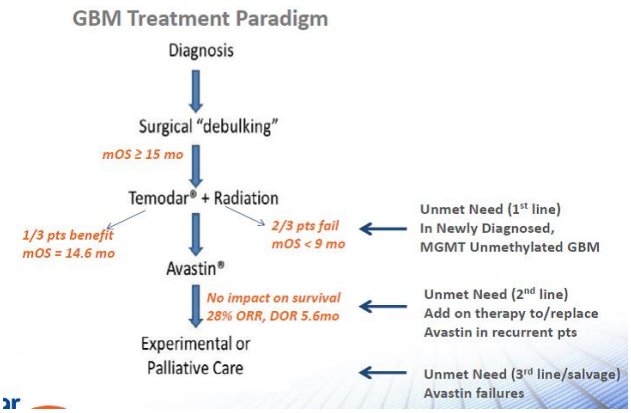
The methylation of the MGMT gene promoter (O-6-methylguanine-DNA-methyltransferase) plays a major role in the level of expression of the gene. Indeed, this modification of gene expression generates a better response to alkylating agents such as TMZ and is associated with a more favorable prognosis of the disease.

GBM treatments

Despite improved diagnostic procedures such as brain imaging, the median survival time of patients with GBM is only 9 to 15 months and the majority die within 2 years. GBM is a very complicated cancer to treat because: 1) Tumor cells are very resistant to conventional therapies; 2) The brain is susceptible to damage from conventional treatments; 3) The brain has a very limited ability to repair itself; 4) Many drugs cannot cross the blood-brain barrier to act on the tumor. In addition, in the GBM, malignant cells spread from the tumor and root deep into the surrounding tissue, making it difficult to kill the tumor without damaging healthy brain cells. While surgery remains the main standard of GBM management, these tumors can often infiltrate the brain to such an extent that complete resection is impossible because it poses an unacceptable risk to the patient.

[58] Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumors. Brain Pathol 1993; 3:255–268.

Algorithm for treatment of glioblastoma



Source: DelMar Pharmaceuticals, Seeking alpha

After surgery, radiotherapy is the second pillar of GBM treatment. Different clinical studies have shown that radiotherapy can prolong survival time in GBM, but rarely eliminates the disease. Surgery + radiotherapy is by far one of the most effective adjuvant approaches and extends the median survival from 14 to 36 weeks. Chemotherapy is a third method to treat glioblastoma. Currently, two chemotherapeutic agents have been approved by the FDA for the treatment of GBM in combination with radiotherapy. These are Temodal® (temozolomide, TMZ) from Merck for newly diagnosed GBM and Avastin® (bevacizumab) from Roche for recurrent GBM. A third chemotherapeutic agent on the GBM market is the Bristol Myers Squibb Carmustine (injection or Wafer). EGFR is a validated target for the treatment of this cancer, with several approved drugs: Tarceva (erlotinib) from Roche, gefitinib (Iressa) from Astra Zeneca and Erbitux (cetuximab) from BMS and nimotuzumab from YM Bioscience.

Competitive landscape and market

It is estimated that there are nearly 25,000 malignant cervical tumors diagnosed per year in the United States and about the same proportion in Europe. Gliomas account for 81% of these malignancies and the GBM about 45% of these, or 9000 GBM in the United States. According to Globocan, in 2012, there were 10x more malignant cervical tumors, or approximately 90,000 GBM worldwide. The standard of chemotherapeutic treatment is temozolomide (Temodar), which is now generic. Temozolomide sales would have increased from $ 1.06 billion in 2010 to $ 312 million in 2015. Roche's Avastin or bevacizumab would have generated sales of approximately $ 170 million per year for this indication. In this indication the unmet medical needs are important, and this brings about an important innovation. There are therefore several molecules in the development phase, including a vaccine approach with DCVax-L from Northwest Biopharmaceuticals, which uses the patient's own dendritic cells to induce an immune response. It is an adjuvant post-surgery strategy, which is currently being tested in Phase III in partnership with BMS (NCT02017717). ICIs (nivolumab and ipilimumab) were also tested in a phase III in recurrent GBM by BMS. EGFR being overexpressed in 40-50% of patients with GBM, makes this condition one of the most angiogenic. In addition, the cells strongly overexpress various pro-angiogenic factors, such as VEGF, bFGF (basal fibroblast growth factor), PDGF, and HGF, which contribute to peritumoral edema and inflammation as well as growth of the primary tumor. Integrins also play a role in the regulation of angiogenesis. This makes it a natural target for Roche's bevacizumab (Avastin), which has shown an increase in progression-free survival of nearly 6 months in patients with recurrent GBM.

Vascular Biogenics VB-111 is an anti-cancer gene therapy that is currently in phase III and targets angiogenesis.

Immunotherapy clinical trials in glioblastoma

Company	Regimen	Target	Target population	Phase
Agios Pharmaceuticals	ivosidenib (AG-120)	isocitrate dehydrogenase	IDH 1 mutated GBM	I
Agios Pharmaceuticals	AG-881	isocitrate dehydrogenase (IDH1/2)	IDH 1/2 mutated GBM	I
DNAtrix, Inc.	DNX-2401 + Interferon γ	Oncolytic virus	recurrent GBM & Gliosarcoma	I
Immatics Biotechnologies	APVAC1 polypeptidic vaccine	immunologic stimulation	Newly diagnosed GBM (1L)	I
Tocagen	Toca 511 retrovirus	5C in 5FU conversion	recurrent GBM	I
VAXIMM	vaccin oral VXM01 activation de cellules T	VEGFR2	GBM	I
Ziopharm Oncology	Ad-RTS-hIL-12 + nivolumab	IL12	GBM	I
ImmunoCellular	ICT-107	dendritic cells activation	GBM	II
Stemline Therapeutics	IL-13 vaccine +/-bevacizumab	immuno	recurrent GBM	I/IIa
Ziopharm Oncology	Ad-RTS-hIL-12	IL12	GBM	I/IIa
DNAtrix, Inc.	DNX-2401 + pembrolizumab	Oncolytic Adenovirus	Gliomat & glioblastoma	II
Symphogen	SYM004 anticorps monclonal αrEGFR	EGFR	relapse GBM post-bevacizumab	II
Vascular Biogenics	VB-111 + bevacizumab	oncolytic virus	Glioblastoma	II
Northwest Biotherapeutics	DCVax-L	Dendritic cells	GBM	III
BMS	nivolumab	PD-1	recurrent GBM	III
Tocagen	Toca 511 + Toca FC		GBM	III
BMS	nivolumab + ipilimumab + bevacizumab	PD-1 +CTLA-4	recurrent GBM	III

Source: Aurgalys

The positioning of NOX-A12 in glioblastoma

The size and chemical structure (small chemical molecule) of NOX-A12 crosses the blood-brain barrier and directly affects intracranial tumor masses. the specificity and selectivity of NOX-A12 make it a molecule of interest in the treatment of glioblastoma. The CXCL12 / CCR4 pathway allows the recovery of the immune response within the tumor. In addition, it is exempt from DNA repair pathways, which follow many of the molecules developed (alkylating agents: TMZ, lomustine, carmustine) or in development (Val-083 from DelMar Pharma). Several vaccine strategies are under development (DCVax-L, ICT-107), as well as gene therapies (Toca511, AdV-tk) or inhibitors of the pathway PI3-kinase coupled or not to the mTOR pathway. But the simplicity of the NOX-A12 mechanism of action has the potential to replace the TMZ as a standard of care. Thus, recently a Belgian team from GIGA Neurosciences has shown that the chemokine CXCL12 is involved in the mechanisms of radio-resistance of the GBM, by allowing the relocation of the glioma-initiating cells to an area of the brain (the subventricular zone). by increasing their mesenchymal character (close to the stroma). The inhibition of the chemokine CXCL12 appears therapeutically more interesting than the blocking of the CXCR4 receptor chosen by Noxxon's competitors such as X4 Pharmaceuticals, Lilly or BMS. Indeed, CXCL12 can be fixed indifferently on the CXCR4 or CXCR7 receptors. Because CXCR7 binds more strongly CXC12 than CXCR4, while being expressed in a multitude of tumor lines (GBM, hepatocellular carcinoma, gastric cancers, lung cancer, breast cancer ...). In addition, CXCR7 participates in tumor development by playing on tumor growth, angiogenesis, migration and the appearance of metastases.

Development plans and marketing strategies

NOX-A12 and NOX-E36 are the backbone of Noxxon's product portfolio. This new class of molecules acts on the tumor microenvironment, where the stromal component is sometimes important, cancers with solid tumors such as pancreatic cancer, colorectal cancer and glioblastoma.

Oncology: drug prices are high

For several years, molecules intended for oncological indications have been facing increased pressure on prices from reimbursement agencies. We estimate that the price of the NOX-A12 and Nox-E36 molecules should be around 45,000 euros in Europe and 65,000 in the United States. Indeed, if we look at the US price of the last molecules recorded since 2013, the average is at $ 10,724 / month is for 6 months of treatment just under $ 65,000. There is no molecule of the class Spiegelmers today that is registered, and we can get the price. The prices suggested above are for the United States. For the European markets, we estimate that the company could charge 70% of the US price. Therefore, in all markets outside the US, we estimate that the price per patient for Noxxon molecules will be € 45,000 per patient.

A sector rich in partnerships

The most sensible strategy for Noxxon would be to license its molecules to one or more pharmaceutical partners. The choice of this partner will be dictated by its ability to support the costs of larger trials and accompany the various regulatory steps to market. With respect to Noxxon's product portfolio, it seems likely that the company could make two agreements, one on NOX-A12 and the other on NOX-E36, which has a different mechanism of action. However, we will conservatively consider that Noxxon will sign an agreement in colorectal cancer. The amount of upfronts and milestones should be determined.

Some deals in the field of immuno-oncology

Date	Buyer	Seller	Sector	Operation	Product	Upfront ($M)	Milestones ($M)	Total Value ($M)
nov-17	Bayer	Loxo Oncology	IO	licence	Kinases	400	650	1 550
oct-17	Amgen	Cytomyx Therapeutics	IO	licence	bispecific T cells	40	455	495
oct-16	Takeda	Cresendo	IO	licence	Humanbody	36	754	790
sept-16	Amgen	Advaxis Immunotherapies	IO	licence	neoantigenes based vaccines	25	770	795
jul 016	Servier	Sorrento	IO	Licence	anti-PD-1 antibodies	28	958	986
juin-16	Janssen	MacroGenics	IO	Licence	antibodies	75	665	740
avr-16	AbbVie	Cytomyx Therapeutics	IO	Licence	bispecific T cells	20	470	490
avr-16	AbbVie	Argenx	IO	Partenariats	antibodies	40	645	685
avr-16	Janssen	Tesaro	IO	Licence	niraparib (PARP inhibitor)	35	415	450
févr-16	Baxalta	Precision Biosciences	IO	Partenariats	CAR-T	105	-	1705
nov-15	Servier	Cellectics	IO	Licence	CAR-T	38	300	338
oct-16	BMS	Five Prime	IO	Licence	Combination Opdivo-CSFR1	350	1388	1738
sept-16	Celgene	Nurix	IO	Partenariats	Ubiquitine proteasome	150	-	555
					Moyenne	**103,23**	**679,09**	**870,54**
					Médiane	**40**	**650**	**740**

Source: Aurgalys

To answer this difficult question, we can examine the terms of recent agreements in oncology or immuno-oncology, which we can use as a reference. The average of our sample is 706 million euros ($ 870 million) with an average upfront of 84 million euros ($ 103 million), or 12% of the total amount of the deal. In addition, the data we were able to consult do not stipulate royalty rates. There are some

agreements for which royalties were given, so we used a rate of 20%. It seems reasonable to include in our assumptions at least one agreement with a large pharmaceutical company in which Noxxon Pharma receives an initial payment (upfront) of the order of 80 million euros ($ 103 million) and milestones at less 400 million euros. As mentioned above, if the results of the Phase IIa trial are positive there is a high probability that Noxxon will be able to approach a large laboratory and conclude a transaction at the levels indicated above. Also we included in our calculations with a probability of 30%, an upfront of 80 million euros between 2019 and 2020 before the initiation of the phase III trial (Pivot) including colorectal cancer.

NOX-A12 + ICI: combination of a new type for solid tumors

It is estimated that there are approximately 384,000 new cases of colorectal cancer each year in the United States and Europe. While the prevalence is nearly one million worldwide, this pathology preferentially affects a relatively old population between 55 and 85 years. Genetic and environmental factors are at the origin of the pathology. The numerous mutations observed (RAS, BRAF, MSS or MSI and HER2) make colorectal cancer, a condition that is particularly difficult to treat. Patients with metastatic CRC account for 20% of cases. The hypermethylation of the promoter of certain genes leading to microsatellite instabilities (MSI) is a favorable factor for the use of immunotherapy. However, most of colorectal cancers do not present microsatellite instabilities and are therefore MMS, prohibiting the use of ICI. The contribution of NOX-A12, which destroys the tumor chemokine wall and promotes the penetration of cytotoxic T lymphocytes, should allow a positive response to ICI. NOX-A12 combined with an ICI could therefore be prescribed in 1L or 2L in colorectal MMS cancers.

Based on initial trials and the strategy adopted by most pharmaceutical companies developing ICI, NOX-A12 + ICI could be either a second-line treatment after chemotherapy (FOLFOXIRI in the CCRm) or a third line treatment after antiangiogenic drugs. As for our estimates of market share, we prefer to remain cautious, as the results of the first part of Phase IIa are not yet known as well as those measuring the effectiveness of the NOX-A12 + Keytruda combination. Moreover, we do not know which treatment line will be preferred (2L or 3L). In addition, the environment of immuno-oncology is today highly competitive and the number of association between an ICI and another class of molecules is very important.

The disclosure in the first half of 2018 of the preliminary results of Phase IIa Part 1a in mCRC and pancreatic cancer on the ability of NOX-A12 to mobilize T cells in the tumor is essential for our prospective schedule. If these first results are positive, they will provide confirmation of the NOX-A12 mechanism of action and proof of concept. Moreover, they will make it possible to differentiate the behavior of NOX-A12 according to the type of solid tumor (CCR or ductal adenocarcinoma of the pancreas). Then, according to the results of the second part of the test that measures the coupled effect of NOX-A12 and Keytruda on the tumor, Noxxon should be able to accelerate its negotiations with a partner.

In colorectal cancer, the potential partner of Noxxon should at least have an immune checkpoint inhibitor. According to the results of the ongoing phase IIa, at least two scenarios are possible. In the first case, Noxxon will have to initiate phase IIb to determine the treatment dose for phase III and confirm the efficacy observed in phase IIa. Then, a phase III will be conducted under the responsibility of the partner of Noxxon. The other possibility could be that following the results of Part 1 and Part 2 of the Phase IIa trial demonstrating the efficacy of NOX-A12 not only in the mobilization of CTL, but also in an

improvement of Keytruda's answer in cancers, that the company can negotiate with the FDA and the support of its partner a passage directly a phase III (pivot). But whatever the scenario, the partner will be responsible for phase III as well as regulatory aspects for registration. In scenario 1, which we favor in a conservative way, the partner will have to finance phase IIb before phase III. In return, the partner will benefit from the exclusive and global rights of NOX-A12 in the JRC. Noxxon will receive a 10% royalty rate from the partner, as well as milestones related to clinical developments and sales.

We expect a registration in 2024 in the United States and Europe and a commercial launch in 2025. As a result, the company is expected to enter into contracts in the United States and Europe because of the Phase III trial and regulatory approval in 2018-2019. The value of the transactions signed, and the amount of milestone payments and the percentage of royalties received by Noxxon Pharma will depend on 1) the benefit demonstrated during Phase III; 2) the labeling given by the regulator. We estimate that 16% market share in the United States and 15% market share in Europe. Based on a price of 45,000 euros in Europe and 65,000 euros in the United States and with a market growth rate of almost 4% per year, we estimate that the maximum sales of NOX-A12 in this indication could reach 2.7 billion euros for Europe and North America.

NOX-A12 and radiotherapy in GBM

There are approximately 11,500 new cases of brain cancer each year in the United States, 45% of which are glioblastomas. The prevalence and incidence of glioblastoma are almost equivalent in Europe. It is estimated that between 61-66% of these new patients have under-methylation of the MGMT gene promoter and do not respond to the combination of radiotherapy + temozolomide post-surgery. TMZ would only work on one third of patients. These unmethylated MGMT patients could receive NOX-A12 as first-line treatment. We estimate that NOX-A12, once approved, could reasonably capture approximately 50% of eligible patients (non-methylated MGMT). Based on a price of 45,000 euros in Europe and 65,000 euros in the United States and with a market growth rate of almost 4% per year, we estimate that the maximum sales of NOX-A12 in this indication could reach 585 million euros for Europe and North America.

Noxxon is planning to conduct a Phase I / IIa trial with NOX-A12 in adjuvant therapy for newly diagnosed patients with non-methylation of the MGMT promoter. This test should confirm the efficacy of the molecule and its mechanism of action, which would make it possible to position NOX-A12 in adjuvant post radiotherapy with / without temozolide, either a 1L treatment or 2L. We believe that Noxxon could partner by terminating the NOX-A12 under two scenarios. The first would be an accelerated registration at the end of the phase II trial in accordance with the orphan drug status. The second hypothesis would lead to a new clinical trial that would be supported by the partner before any registration.

Scenario 1: The results of the Phase IIa trial demonstrate a statistically significant improvement in progression-free survival (PFS) compared to other trials for regulatory agencies to warrant expedited registration. However, for greater safety and to increase the risk reduction inherent in the product, we estimate that Noxxon's potential partner could expect the results of overall survival on a larger number of patients (extension to 35 patients) before initiating the appearance regulation and registration. Marketing is expected to occur in 2023-2024.

Scenario 2: In this scenario, the results of Phase IIa are not sufficient to warrant expedited registration. We believe that in this scenario, a new pivotal phase IIb trial (demonstrating efficacy in a small population) or a phase III trial demonstrating overall survival may be required to record the molecule. At the end of this trial marketing could only take place in 2026, that is 2 years later.

NOX-E36 + ICI: another mechanism for pancreatic cancer

There are approximately 126,672 new cases of pancreatic cancer in the United States and Europe. At diagnosis only 15% are eligible for resection surgery. The rest is divided between locally advanced cancers for 30 to 40% and 40 to 45% are metastatic. For locally advanced patients the standard of care in 1L is gemcitabine associated with nab-paclitaxel (Abraxane®). Sometimes chemotherapy with FOLFIRINOX may also be recommended with or without radiotherapy. For metastatic adenocarcinoma, 1L is also based on the combination gemcitabine + nab-paclitaxel, with 2L erlotinib (Tarceva®) and capecitabine (Xeloda®) in 3L. Like tests conducted by other companies like ChemoCentryx (CCX872 + FOLFIRINOX), Pfizer (PF-04136309 + gemcitabine + nab-paclitaxel) or FivePrime (cabiralizumab + nivolumab, Opdivo®), we estimate that NOX-E36 once approved, could reasonably position itself in 1L. Indeed, the mechanism of action of NOX-E36, which blocks not only the CCL2 chemokine, but also the CCL8 and CLL13 chemokines involved in the TAM-related IPRES, shows a significant improvement over CCR2 inhibitors or other molecules. inhibiting CCL2. NOX-E36 could be prescribed in combination with the current treatment standard (gemcitabine and nab-paclitaxel) or in combination with an ICI to approximately 30% of patients with metastatic pancreatic ductal adenocarcinoma. Based on a price of 45,000 euros in Europe and 65,000 euros in the United States and with a market growth rate of almost 4% per year, we estimate that the maximum sales of NOX-A12 in this indication could reach 1056 million euros for Europe and North America.

Valuation

Noxxon's valuation is based primarily on its product portfolio, in which NOX-A12 and NOX-E36 are the most advanced products. Indeed, NOX-A12 has already demonstrated its efficacy (phase II) in several clinical indications such as multiple myeloma, chronic lymphocytic leukemia. Currently, Noxxon Pharma has a Phase II clinical trial currently underway including solid tumors (metastatic pancreatic adenocarcinoma, metastatic colorectal cancer). The next milestone for society in Q2 2018 will undoubtedly be the communication of the results of the first part of the phase IIa trial in pancreatic cancer and metastatic colorectal cancer, which will initially show the changes in the microenvironment NOX-A12 induced tumor, as well as immunological profile (type of immune cells, cytokines and chemokines). Then, in Q4 2018, the results of Part 2 of the trial, which will disclose the patient response rates to the NOX-A12 + pembrolizumab (Keytruda) combination. In addition, the company is expected to continue developing its other product, the NOX-E36 blocking the CCL2/CCL8/CCL13 chemokines, which are particularly active in the implementation of the PD-1 in-resistance signatures (IPRES).

For the sake of simplification, we estimate that the selling price of NOX-A12 should be around 65 000 EUR / year in the United States and 45 000 EUR / year in Europe. This high price corresponds to the high average of the already registered therapies. However, this seems to us relatively conservative compared to the fact that today NOX-A12 still in phase II and that the results are not yet known. In addition, despite the preclinical results, no one yet knows what the improvement and benefit of the NOX-A12 / ICI combination could be compared to the response observed with ICI alone. However, the first observations are positive and will need to be confirmed.

The retained tax rate of 30% and the discount rate used is 17%.

rNPV NOX-A12 in Colorectal cancer

Our hypotheses are as follows for the evaluation of NOX-A12 in colorectal cancer:

- We believe that Noxxon Pharma will finance the development of Phase IIb NOX-A12 until it reaches an agreement with a partner for the US and Europe. When NOX-A12 is licensed, there should be no additional costs as the partner is responsible for manufacturing and marketing.
- Based on several recent partnership agreements, we estimate that Noxxon could sign a partnership with a pharmaceutical company with an average value of 520 million euros, with an upfront representing 16% of this amount, 78 million euros as royalties.
- Furthermore, we believe that the agreement that could be signed by Noxxon Pharma could be on both colorectal cancer and pancreatic adenocarcinoma.
- While the costs inherent in Phase III are difficult to estimate given the progress of NOX-A12, we can reasonably assume that Phase III clinical trials in colorectal cancer as well as in Pancreatic cancer is estimated at between 10 and 15 million euros per indication.
- We estimate the probability of chance for NOX-A12 at 33% for colorectal cancer and at 9% for pancreatic ductal adenocarcinoma.

European Union (28) + Amérique Nord													
CCR		Phase IIa		Phase IIb		Phase Pivot (Phase III)			Reg.	Marketing EU-28			
	(€M)	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Revenues													
Upfront	78,0			26,0		26,0		26,0					
Milestones	172,0								25,0	87,5	25,0	34,5	
Sales Europe + Amérique du nord										61,1	124,2	252,6	513,9
Royalties from partner	15%									9,2	18,6	37,9	77,1
Total Sales		**0,0**	**0,0**	**26,0**	**0,0**	**26,0**	**0,0**	**26,0**	**25,0**	**157,7**	**167,8**	**325,0**	**591,0**
Costs													
Phase IIb				5	5								
Phase III													
Regulatory									1,5				
Total Costs		**0,0**	**0,0**	**5,0**	**5,0**	**0,0**	**0,0**	**0,0**	**1,5**	**0,0**	**0,0**	**0,0**	**0,0**
Net CF		**0,0**	**0,0**	**21,0**	**-5,0**	**26,0**	**0,0**	**26,0**	**23,5**	**157,7**	**167,8**	**325,0**	**591,0**
Net CF After Tax		0,0	0,0	14,7	-5,0	18,2	0,0	18,2	16,5	110,4	117,5	227,5	413,7
Likelihood		100%	100%	100%	100%	15%	15%	15%	15%	15%	15%	15%	15%
Risk adjusted Net CF		**0,0**	**0,0**	**14,7**	**-5,0**	**2,7**	**0,0**	**2,7**	**2,5**	**16,6**	**17,6**	**34,1**	**62,1**
Discount Factor	17%												
Tax Rate	30%												
NPV 2018 (€M)	**27,1**												

rNPV NOX-A12 in glioblastoma

Our hypotheses are as follows for the valorization of NOX-A12 in glioblastoma:

- As a simplification we keep the same price (see above);
- As previously mentioned, Noxxon should conduct a Phase I / II trial with NOX-A12 adjuvant therapy in glioblastoma for newly diagnosed patients. It is clear to us that Noxxon will have to identify its patients on the basis of methylation of the MGMT gene promoter, since non-methylation is correlated with poor prognosis and resistance to alkylating agents and more particularly to TMZ. .
- This phase I / II confirmatory test of the efficacy of the molecule and its mechanism of action, would allow to position NOX-A12 in adjuvant post radiotherapy without / with temozolide, either a 1L treatment or 2L.
- To establish a partnership by firing the NOX-A12, we estimate that 2 scenarios are possible:
- 1. The first would be an accelerated registration after the phase II trial in accordance with the orphan drug status, where the partner is responsible for manufacturing and marketing.
- 2. The second hypothesis would lead to a new clinical trial that would be supported by the partner before any registration.
- So Noxxon Pharma should establish a licensing partnership to market NOX-A12 in glioblastoma. The partner must be present in the United States and in Europe. However, the value of the agreement and the amount of milestones as well as the percentage of royalties will depend heavily on the benefit demonstrated in the Phase I / II trials and the scenario chosen for development.
- Based on several recent partnership agreements, we estimate that Noxxon could sign a partnership with an average pharmaceutical company of 140 million euros with an upfront representing 28% of this amount, 40 million euros and royalties at the rate of 20%.
- This licensing agreement could take place as early as mid-2021 after the results of progression-free survival and first results on the overall survival of the phase I / II trial.
- The costs inherent in Phase I / II are difficult to estimate given the status of NOX-A12, but we can reasonably assume that Phase III clinical trials in both colorectal cancer and Pancreatic cancer would be around 10 million euros.
- We estimate the probability of NOX-A12 chance at 15% for glioblastoma.

European Union (28) + Amérique du Nord

				Phase II (PFS)		OS	Reg.	Marketing EU-28 +Amérique du Nord				
	(€M)	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
Revenues												
Upfront	40						40					
Milestones	120,0							36,00		36,00		36,00
Sales Europe +Amérique du Nord								8,8	17,8	36,0	73,0	147,9
Royalties from partner	20%							1,8	3,6	7,2	14,6	29,6
Total Sales		**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**40,0**	**46,5**	**21,3**	**79,2**	**87,6**	**213,5**
Costs												
Phase II	9,6			2,88	2,88	3,84						
Regulatory	1,5						1,5					
G&A	10%											
Marketing	10%											
Total Costs		**0,0**	**0,0**	**2,9**	**2,9**	**0,0**	**1,5**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
Net CF		**0,0**	**0,0**	**-2,9**	**-2,9**	**0,0**	**38,5**	**46,5**	**21,3**	**79,2**	**87,6**	**213,5**
Net CF After Tax		0,0	0,0	-2,9	-2,9	0,0	27,0	32,6	14,9	55,4	61,3	149,5
Likelihood		100%	100%	100%	100%	15%	15%	15%	15%	15%	15%	15%
Risk adjusted Net CF		**0,0**	**0,0**	**-2,9**	**-2,9**	**0,0**	**4,0**	**4,9**	**2,2**	**8,3**	**9,2**	**22,4**
Discount Factor	17%											
Tax Rate	30%											
NPV 2018 (€M)	**9,9**											

rNPV NOX-E36 in pancreatic cancer

Our hypotheses are the following for the valuation of NOX-A12 in pancreatic cancer:

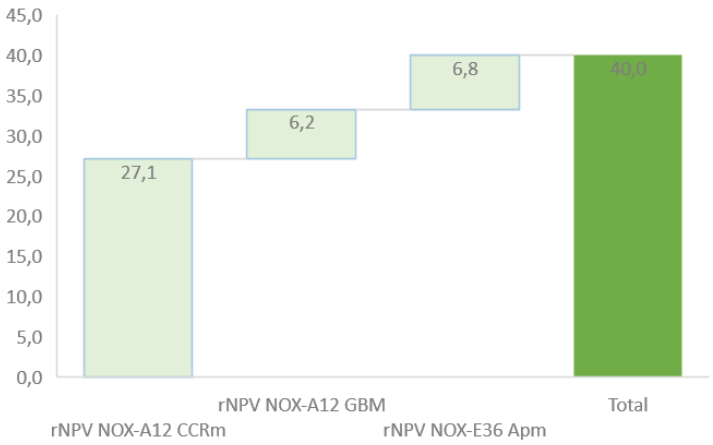
- We believe that Noxxon Pharma will finance the development of Phase IIb NOX-E36 before entering into an agreement with a partner for the US and Europe. When NOX-E36 is licensed, there should be no additional costs as the partner is responsible for manufacturing and marketing.
- Based on several recent partnership agreements, we estimate that Noxxon could sign a partnership with a pharmaceutical company with an average value of 520 million euros, with an upfront representing 16% of this amount, 79 million euros. Noxxon is also expected to receive royalties on sales at the usual rate of 15%.
- While the costs inherent in Phase III are difficult to estimate given the current status of NOX-A12, we can reasonably assume that Phase III clinical trials in both colorectal and pancreas would be around 10 to 15 million euros per indication.
- We estimate the probability of chance for NOX-E36 at 9% for pancreatic ductal adenocarcinoma.

European Union (28)+Amérique du Nord

Apm		Phase IIa		Phase IIb		Phase Pivot (Phase III ou/et licensing)			Reg.	Marketing EU-28/USA				
	(€M)	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
Revenues														
Upfront	78,0	0,0	0,0	0,0	0,0	52,0	0,0	26,0	0,0	0,0	0,0	0,0	0,0	0,0
Milestones	440,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	100,0	200,0	0,0	100,0
Sales Europe												70,6	251,7	916,5
Royalties from partner	10%											7,1	25,2	91,6
Total Sales		**0,0**	**0,0**	**0,0**	**0,0**	**52,0**	**0,0**	**26,0**	**0,0**	**0,0**	**100,0**	**277,7**	**276,9**	**1108,1**
Costs														
Phase IIb	10,0			5,0	5,0									
Phase III	20,0				10,0	10,0								
Regulatory	30,0					15,0	15,0							
Total Costs	60,0	**0,0**	**0,0**	**5,0**	**15,0**	**25,0**	**15,0**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
Net CF		**0,0**	**0,0**	**-5,0**	**-15,0**	**27,0**	**-15,0**	**26,0**	**0,0**	**0,0**	**100,0**	**277,7**	**276,9**	**1 108,1**
Net CF After Tax		0,0	0,0	-5,0	-15,0	18,9	-15,0	18,2	0,0	0,0	70,0	194,4	193,8	775,7
Likelihood		100%	100%	100%	100%	9%	9%	9%	9%	9%	9%	9%	9%	9%
Risk adjusted Net CF		**0,0**	**0,0**	**-5,0**	**-15,0**	**1,7**	**-1,4**	**1,6**	**0,0**	**0,0**	**6,3**	**17,5**	**17,4**	**69,8**
Discount Factor	17%													
Tax Rate	30%													
NPV 2029 (€M)	**6,8**													

Sum of parties

In our model, the indications are valued independently, because the products of Noxxon can be granted to the potential partners according to their interest. Today we estimate the value of Noxxon at 40 million euros, or 17.9 € / share. This valuation is highly dependent on the results of the ongoing phase IIa NOX-A12 in combination with pembrolizumab, which if positive should trigger the interest of the pharmaceutical industry. The NOX-A12 represents 67.7% of the valuation of the company. Indeed, all the actors are looking for new innovative ways to treat solid tumors such as colorectal cancers, but also pancreatic cancers and neuroendocrine tumors.



Sum of parties

	WACC				
	16,0%	16,5%	17,0%	17,5%	18,0%
Valorisation	42,8	41,4	40,0	38,7	37,4
Prix/action	19,21	18,57	17,95	17,36	16,79

Sensitivity analysis

Peer companies

The analysis of comparable companies offers us a tool for comparing the value of several companies active in the field of oncology and more specifically immuno-oncology. However, not all these companies are fully comparable, as there is a great deal of heterogeneity in terms of maturity, funding and capitalization. The list of 12 companies we have established is in our representative estimate of the sector, as they are active in the field of immuno-oncology. Most of them have products in advanced clinical phases (phase II or phase III) in indications like or like those of Noxxon. For example, companies like Threshold Pharmaceuticals or Vascular Biogenics are developing innovative approaches to

glioblastoma or metastatic colorectal cancer.

Peer Companies

Société	Ticker	Monnaie	Capitalisation	EV	Produits en clinique		
					Phase I	Phase II	Phase III
ChemoCentryx	CCXI	USD	733,3	610,7	2	4	3
Clovis Oncology	CLVS	USD	2 930,0	2 671,0	1	1	2
Five Prime Therapeutics	FPRX	USD	575,9	283,2	6	1	-
Innate Pharma	IPH	EUR	314,5	146,5	1	3	-
Kura Oncology	KURA	USD	678,8	592,7	3	1	-
Loxo Oncology	LOXO	USD	3,7	3,1	2	1	-
Molecular Templates (ex-Threshold Pharma)	THLD	USD	0,0	0,0	1	-	-
Newlink Genetics	NLNK	USD	268,4	116,0	2	5	2
Noxxon	ALNOX	EUR	13,0	13,0	-	1 (+2)	-
OSE Immunotherapeutics	OSE.PA	EUR	51,7	35,1	-	-	1
Sierra Oncology	SRRA	USD	115,9	15,6	-	2	-
Vascular Biogenics	VBLT	USD	70,2	15,5	-	2	3
Ziopharm Oncology	ZIOP	USD	609,5	682,5	3	2	-
Moyenne			489,6	398,8	2	2	2
Médiane			291,5	131,3			

Source: FactSet, Aurgalys, companies

Annexes

Management

Aram Mangasarian, PhD, CEO

Aram Mangasarian joined NOXXON in May 2010 as Chief Business Officer of NOXXON and was appointed CEO in July 2015. Aram brings NOXXON more than fifteen years of experience in the biotechnology industry. Previously, Aram held the position of Vice President Business Development at Novexel, where he, among other things, entered into a € 150 million license agreement including an initial payment of € 75 million with Forest Laboratories (NYSE: FRX). Holder of a BS in Biochemistry, Molecular Biology and English Literature, a Ph.D. in Biology from the University of California San Diego and an MBA from INSEAD, Aram held from May 2000 to October 2005, different positions at ExonHit Therapeutics (today Diaxonhit, Euronext: ALEHT).

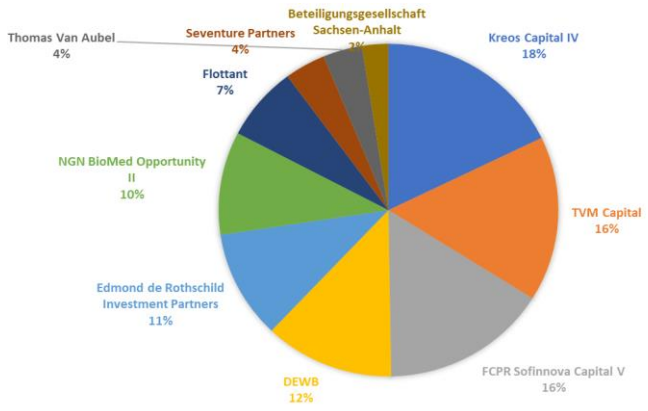
Jarl Ulf Jungnelius, MD, PhD, CMO

Jarl Ulf worked at Celgene from 2007 to 2014 where he was Vice President of Clinical Research and Development in the area of solid tumors. Previously, he held various management positions at Takeda, Pfizer, Eli Lilly & Company and VAXIMM. Jarl Ulf has been responsible for the clinical development of several currently marketed oncology drugs, such as Abraxane®, Gemzar®, Alimata® and Revlimid®. Medical oncologist and researcher of training with more than 25 years of clinical experience and research in large pharmaceutical companies and academic organizations, he combines the understanding of the intimate biochemical mechanisms, the requirement of the clinician. Dr. Jungnelius is currently Director of the Supervisory Board of Isofol Medical AB, Biovica International AB and Monocl AB and has been a director of Oncopeptides AB since April 2011.

J. Donald de Bethizy, Chairman of the Board

J. Donald has thirty years of experience in biotechnology and consumer pharmaceuticals. He was President and Chief Executive Officer of Santaris Pharma A / S in Denmark and the United States until he was sold to Roche in September 2014. He was Executive Chairman of Contera Pharma ApS until he was acquired by Bukwang Pharma in November 2014. Don was co-founder and Chief Executive Officer of Targacept, Inc., a public biotechnology company listed on NASDAQ. He is currently on the Board of Directors of Newron Pharmaceuticals SpA, arGEN-X N.V., Proterris Inc. and Rigontec GmbH and is President of Albumedix A/S.

Capital structure



Source: Noxxon

Income statement (€M)	2014	2015	2016	2017e	2018e	2019e
Revenue	0,0	0,0	0,1	0,0	0,0	0,0
Other incomes	**0,2**	**0,2**	**0,6**	**0,0**	**0,0**	**26,0**
R&D cost	-10,2	-7,6	-5,3	-2,4	-5,0	-5,0
Operating income	**-13,1**	**-14,8**	**-8,6**	**-3,7**	**-6,3**	**19,7**
Income before taxes	-13,7	-16,1	-10,7	-3,8	-6,4	19,6
Income taxes	0,0	0,0	0,0	0,0	0,0	0,0
Net Income	**-13,7**	**-16,1**	**-10,7**	**-3,8**	**-6,4**	**19,6**

Assets (M€)	2014	2015	2016	2017e	2018e	2019e
Non-current assets	1,0	0,7	0,1	0,1	0,1	0,1
Inventories	0,0	0,0	0,0	0,0	0,0	0,0
Receivables	0,0	0,0	0,0	0,0	0,0	0,0
Other Assets	0,501	1,254	0,572	0,312	0,312	0,312
Cash and equivalents	1,5	4,1	2,2	1,1	1,1	1,1
Total Assets	**3,1**	**6,0**	**2,9**	**1,5**	**1,5**	**1,5**

Equity and liabilities (M€)	2014	2015	2016	2017e	2018e	2019e
Equity	-6,2	-7,0	-2,5	-2,5	-2,5	-2,5
Loans	4,2	6,3	0,0	1,6	1,6	1,6
Operating liabilities	2,5	3,2	1,4	1,5	1,5	1,5
Other financial liabilities	2,2	2,6	2,9	0,0	0,0	0,0
Taxes and Social liabilities	0,0	0,0	0,0	0,0	0,0	0,0
Other liabilities	0,5	1,0	1,0	0,9	0,9	0,9
Total Passif	**3,1**	**6,0**	**2,9**	**1,5**	**1,5**	**1,5**

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