

TARGOVAX

Potential immunotherapy champion in the making

We initiate coverage with a BUY recommendation and NOK17 target price. Targovax is an immunotherapy company focused on therapeutic cancer vaccines for solid tumours. Its most clinically developed project TG01 is in phase II, and multiple data events are scheduled for the coming years. We assume Targovax strikes a co-operation deal with a large pharma partner in the years ahead, to help to accelerate its pipeline development.

Potential immunotherapy champion in the making. In mid-2015 Targovax merged with Finnish company Oncos, which also focused on developing new therapeutic cancer vaccines. Their technologies complement each other, and in our view the merger gave Targovax the pipeline depth and breadth to become an attractive partner for large pharma companies active in the space. In our view, immuno-oncology is an attractive area and there have been several high-value biotech/big pharma deals recently.

Data supports future development, despite early stage. The company's oncolytic virus vaccine ONCOS-102 has strong early-stage data suggesting that it triggers an immune response and has a stabilising effect on the underlying disease. Targovax has indicative data of long-term survival benefits going back more than 10 years on its peptide vaccine.

Future pipeline development could be substantial given the breadth and scope of planned clinical trials. We believe the company's first vaccine could be on the market in 2021, but before that several potential events could highlight the product's efficacy: among others, four immune response data points in 2017e.

Risks relate mostly to clinical development. As Targovax is still in the early stage of its clinical trial, the risks relate mainly to the development programme as well as the need for future financing.

Initiating coverage with a BUY recommendation and NOK17 target price. It is challenging to value early-stage companies such as Targovax, as there are numerous possible corporate development routes depending on the strategy chosen. We assume that Targovax makes an out-licensing deal in phase II and that the partner(s) take the products to market. Based on these assumptions and our SOTP NPV, our target price is NOK17.

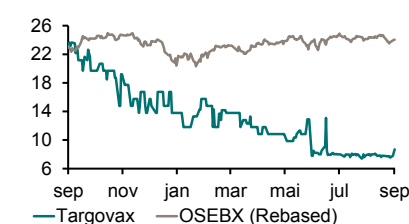
| Year-end Dec | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|-----------------------|-------|-------|-------|-------|-------|-------|
| Revenue (NOKm) | 0 | 0 | 0 | nm | nm | 308 |
| EBITDA adj (NOKm) | -7 | -18 | -90 | -125 | -138 | 128 |
| EBIT adj (NOKm) | -7 | -18 | -90 | -125 | -138 | 127 |
| PTP (NOKm) | -8 | -18 | -90 | -126 | -139 | 127 |
| EPS rep (NOK) | -1.81 | -1.87 | -3.42 | -2.98 | -3.30 | 3.03 |
| Revenue growth (%) | nm | -80.1 | 101.4 | nm | nm | nm |
| EBITDA margin adj (%) | nm | nm | nm | nm | nm | 41.5 |
| EV/Sales adj (x) | | nm | nm | nm | nm | 0.06 |
| EV/EBITDA adj (x) | | nm | nm | nm | nm | 0.1 |
| EV/EBIT adj (x) | | nm | nm | nm | nm | 0.1 |
| ROE (%) | nm | nm | nm | nm | nm | 28.2 |

Source: Company (historical figures), DNB Markets (estimates)

BUY

TP: NOK17.0

TRVX versus OSEBX (12m)



Source: Factset

SUMMARY

| | |
|-------------------------------|------------------|
| Recommendation (prev.) | BUY () |
| Share price (NOK) | 8.70 |
| Target price (previous) (NOK) | 17.0 (N/A) |
| Upside/downside potential (%) | 95 |
| Tickers | TRVX NO, TRVX.OL |

CAPITAL STRUCTURE

| | |
|-----------------------------|------|
| No. of shares (m) | 42.1 |
| Market cap. (NOKm) | 367 |
| NIBD adj end-2016e (NOKm) | -110 |
| Enterprise value adj (NOKm) | 256 |
| Net debt/EBITDA adj (x) | 0.88 |

SHARE PRICE PERFORMANCE

| | |
|--------------------|-----------|
| Abs. 1/3/12m (%) | 12/12/-62 |
| Rel. 1/3/12m (%) | 12/11/-66 |
| High/Low 12m (NOK) | 24/7 |

Source: Company, DNB Markets (estimates)

NEXT EVENT

| | |
|----------------|------------|
| Q3 2016 report | 17/11/2016 |
|----------------|------------|

DNB Markets acted as joint global co-ordinator and joint bookrunner in connection with the recent private placement, listing on Oslo Axess, and subsequent offering of shares in Targovax ASA

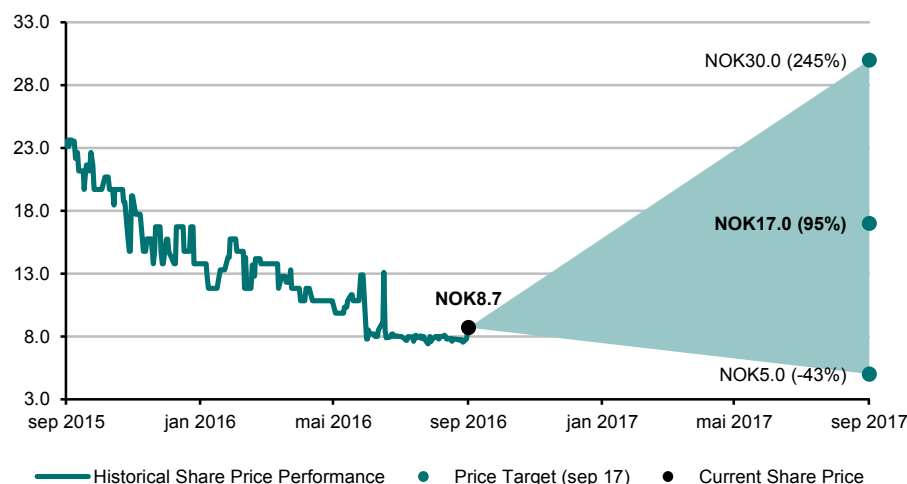
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Investment case overview

Share price performance, DNB Markets' target price, bear- and bull-case scenarios



Source: FactSet, DNB Markets

Downside risks to our investment case

- The main risk at this stage is a delay in the clinical development plan.
- Unexpected results from ongoing/planned clinical trials (mainly related to lack of expected product efficacy or worse side-effects) are also a risk.
- We believe Targovax will need additional financing from its owners and there is always a risk that capital will not be available when needed or at acceptable terms.

Source: DNB Markets

DNB Markets investment case and how we differ from consensus

- We expect Targovax to out-license its products (around phase II) and not to take any of its products or indications to the market on its own.
- We estimate that a deal with a large pharma company could come in 2018.
- In our base-case scenario we have a c5% LOA (likelihood of approval) for the products, as they are still in a very early stage.

Source: DNB Markets

Target price methodology

- We mainly use a SOTP NPV model to value this type of company.
- Our model includes our forecasts for launch dates, drug pricing, probability of reaching the market etc.
- The NPV is calculated using a WACC of 10%.

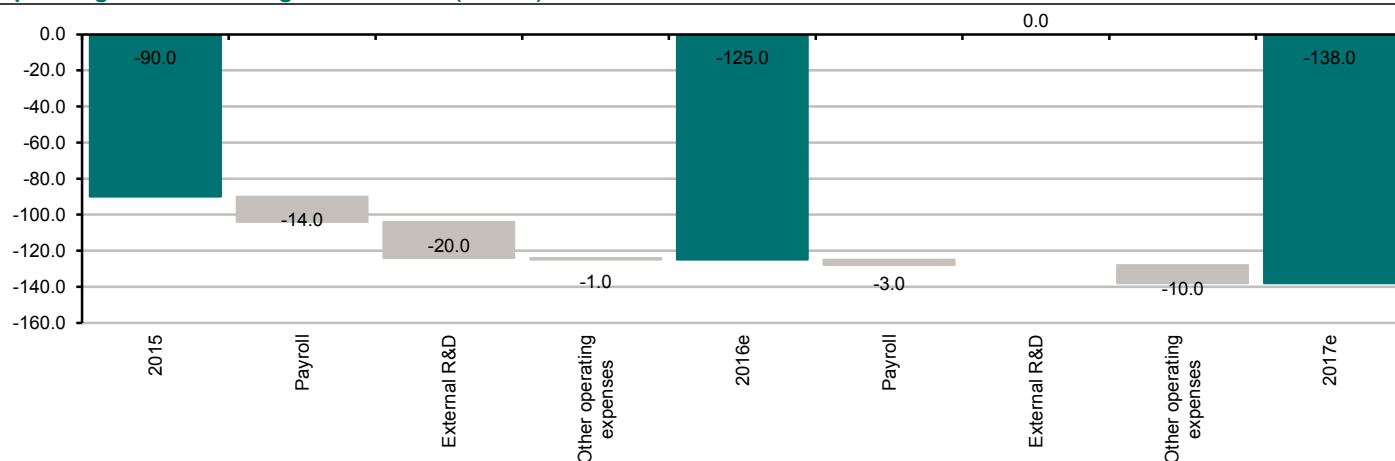
Source: DNB Markets

Upside risks to our investment case

- Our base-case includes a 'standard' regulatory process. If clinical efficacy in some trials is higher than expected, Targovax could well get an expedited review and hence its drugs could reach the market sooner than we expect.
- Targovax could strike an out-licensing deal sooner – and at better terms – than we expect. This would be positive and leave it financially stronger than we assume in our forecasts.

Source: DNB Markets

Operating cost base bridge 2015–2017e (NOKm)



Source: DNB Markets (forecasts), company (historical data)

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Investment case

Immunotherapy company focused on therapeutic cancer vaccines for solid tumours

Targovax has a relatively broad and diversified pipeline in immuno-oncology, focused on therapeutic cancer vaccines. Overall, we find the market areas it addresses to be interesting and we note they have garnered considerable attention from large pharmaceutical companies, in the form of acquisitions, partnerships, and co-development deals in recent years. We believe the consensus view in immuno-oncology is that most diseases will be best served by combination treatments in which therapeutic cancer vaccines could (in one way or the other) play an important role.

Focused on therapeutic cancer vaccines

Two separate technology platforms

We consider the company's pipeline to be reasonably well diversified, with two separate technology platforms for therapeutic cancer vaccines (one based on oncolytic virus vaccines and one peptide-based). The products in the pipeline have the potential to be used in many indications, most likely in combination with checkpoint inhibitors.

Reasonably well-diversified pipeline

Important immune response data in melanoma for oncolytic virus vaccine in H2 2017e

We expect updates on the oncolytic virus vaccine and the peptide vaccine platforms in the coming years. In our view, these events are uncorrelated since the technologies and mechanisms of action differ i.e. we see this as a risk-reducing factor. In addition to important immunological data and interim outcome data, there is likely to be news on the progress of the clinical development programme during 2017, as the company has said is set to initiate around five clinical trials in H2 2016. Hence, we expect considerable news on the pipeline in the coming years. One of the more important events will be the immune response data in melanoma for the oncolytic virus vaccine, expected in H2 2017.

Several potential news events

Partnership deal could accelerate development

In our view, its most likely development path is to strike a partnership deal with a large pharma company within a few years, in order to speed up development and add marketing muscle for the products. We believe that a partnership deal could materialise in 2018. With this in place, we believe a reasonable timeline for the company is to reach the market with its first products is 2021.

Most likely development path, in our view, would be partnership deal with large pharma company

Besides clinical development events, we believe the most likely business strategy is to out-license the products to one or two large pharma companies in the immuno-oncology space. As Targovax's cancer vaccine platforms appear suitable to combine with a checkpoint inhibitor, we believe the most natural partner(s) would be a company active (now or in the future) in the checkpoint inhibitor market. One or more partner deals with big pharma could also be share price triggers – from a financial point of view and (maybe even more so) as confirmation of the technology's value in future combination treatments.

Could out-license products

Patents until end-2029 and possible orphan drug status

The IP situation looks good, in our view, with composition of matter patent protection lasting until end-2029 (with the potential for extensions thereafter). On top of this, the company might benefit from orphan drug status for some indications and the added protection this brings.

Composition of matter patent until at least end-2029

Initiating coverage with a BUY recommendation

Valuing a company at such a relatively early stage is always highly dependent on the assumptions used. We have used mainly a SOTP NPV model, as we believe this best captures the potential of the projects and makes it possible to segment the valuation based on the projects (this is important as the development success or failure should be uncorrelated in Targovax's case – as its projects are based on two different technologies). Our NPV SOTP-based target price of NOK17 suggests significant upside potential from the current share price of cNOK8; we therefore initiate coverage with a BUY recommendation.

NPV SOTP-based target price of NOK17, suggesting substantial upside potential from current share price

Company overview

Targovax was born from the merger of two cancer vaccine companies (Targovax from Norway and Oncos from Finland). There were several similarities between the two companies when it came to research focus and potential product end-markets. For example, both focused on therapeutic cancer vaccines, both focus on solid tumours only, and both see their respective products being used in combination with other products to gain maximum effect. Moreover, both were at roughly the same stage of clinical development of their products.

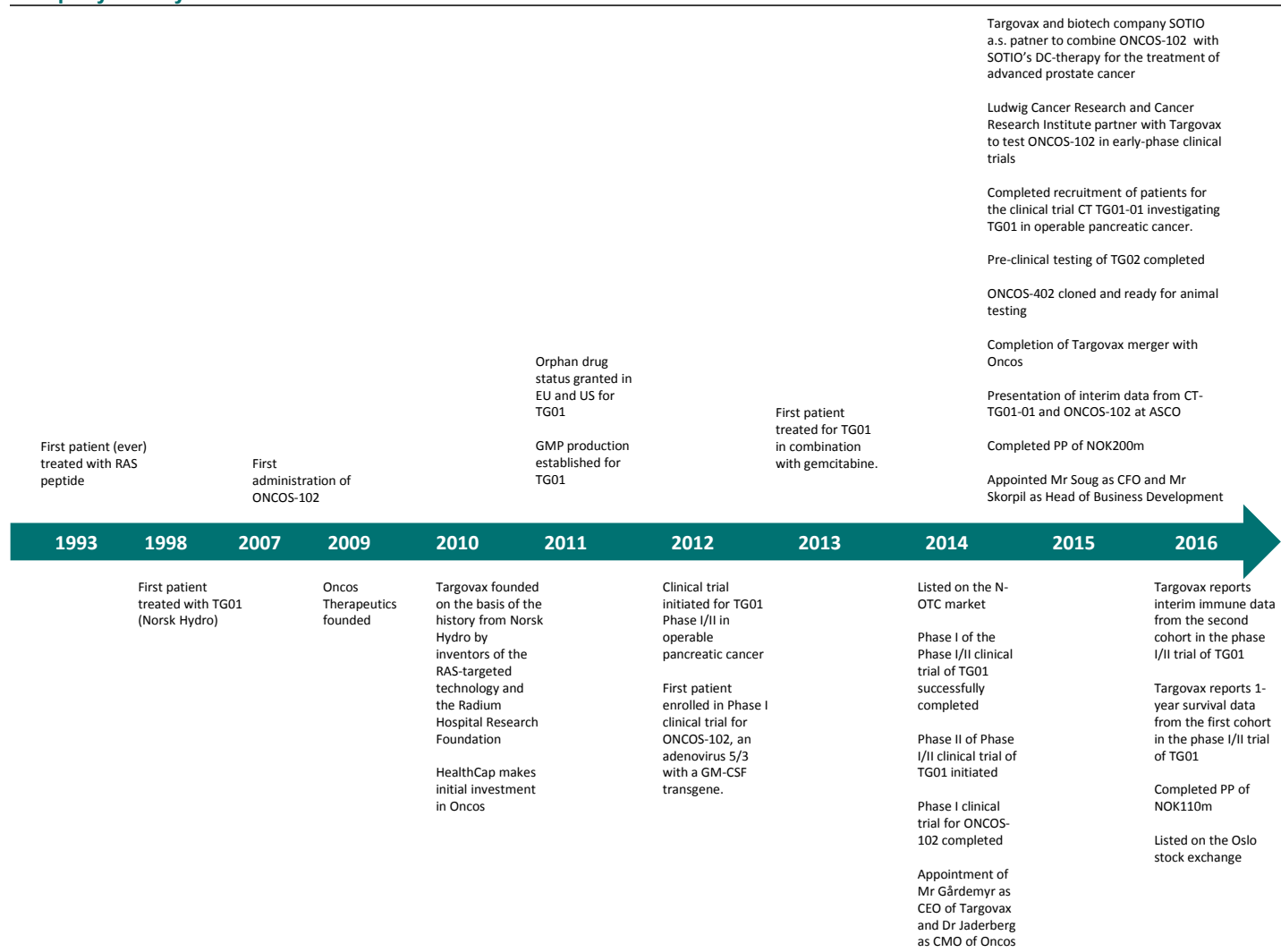
While the products are therapeutic cancer vaccines mainly for solid tumours, the technologies behind the products differ quite a lot, so the development of one product does not have a bearing on another; hence, one could say the pipeline is well diversified in this niche.

As shown below, the development activities have accelerated in recent years and in our view the company is now ready to move along even more quickly. The company listed on the Oslo stock exchange during the summer. In the process leading up to the listing, Targovax raised additional capital to support the future development of its product pipeline during the summer.

Formed from the merger of Targovax from Norway and Oncos from Finland

We consider the pipeline to be well diversified

Company history



Source: Company data

The initial trials or experiments with peptide vaccines in what later on became Targovax were started in the company Norsk Hydro in 1993 as a way of diversifying its business. Norsk Hydro later decided to shelf the project as it did not fit with its strategy. But based on interesting long-term data that showed improved long-term survival in patients treated with the

peptide vaccine (compared with historical data sets), Targovax was founded with the aim of continuing the development of the vaccine platform.

The oncolytic vaccine ONCOS-102 was developed by Professor Akseli Hemminki and his research group at Helsinki University, who started the development of oncolytic viruses in 2002. Oncos Therapeutics was founded in 2009, at which point cancer patients were being treated with the oncolytic virus, ONCOS-102, through a compassionate use programme in Finland that ran from 2007 to 2012, meaning the virus had already proven to be safe. In 2012 the first patient was enrolled to the phase I trial of ONCOS-102. Positive results from this trial later led to the company's merger with Targovax in 2015, which we believe should enable the future clinical development of this vaccine platform.

ONCOS-102 proved safe in humans in a compassionate use programme

Immunology summary

In this section we review the immune system, its biology, and its role in promoting and protecting against the development and progression of cancer. We believe a short background is essential as Targovax's products are based on the scientific rationale of activating cancer patients' immune system to kill cancer cells, and thereby induce durable responses, and hopefully in the long run cure patients.

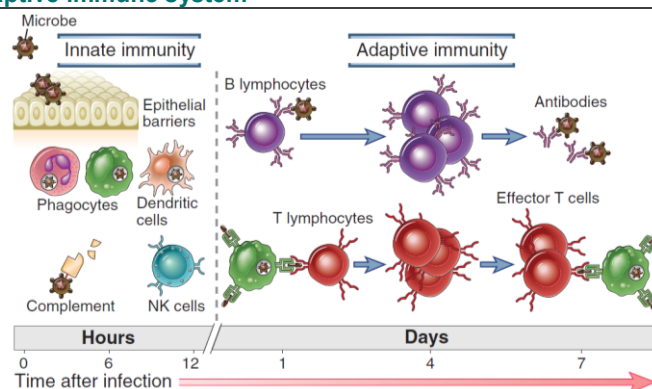
Basic immunology

The role of the immune system is to protect us from pathogens and development of disease. Different types of immune cells play a defined part in managing dangerous pathogens and keeping us healthy.

The definition of immunity is resistance to disease. The cells, tissues, and molecules involved in immunity are defined as the immune system. The function of the immune system is to recognise pathogens, harmful foreign agents, and distinguish them from non-harmful agents. The immune system is commonly divided into the innate and adaptive immune systems:

- **The innate system** is always present in healthy people and mediates a rapid response and protection against infections. This is the body's first line of defence, and protects from entry of infectious agents through barriers, such as epithelial cells of the skin, specialised cells in the skin and natural antibiotics. If a pathogen breaches the barrier and enters the body, other cells of the first line defence attack. However, many pathogens have evolved to resist the innate system, and the adaptive system is needed for combating these.
- **The adaptive system** mediates a slower – but more effective – response to infections. It consists of lymphocytes, B- and T cells, which mediate the humoral immunity and cell-mediated immunity, respectively. The humoral and cell-mediated immunity are two separate immune responses that eliminate different types of microbes. However, both B- and T cells specifically recognise different substances of microbes, called antigens, through their receptors, in order to elicit a protective immune response.

Innate and adaptive immune system



Source: Abul K. Abbas, Andrew H. Lichtman, Shiv Pillai (2011) *Cellular and Molecular Immunology*, 7th edn, : Elsevier Saunders

Although the adaptive and innate systems are separated, they rely on each other, and communication between the cells of the innate and adaptive system is essential for an effective immune response.

T cell biology

We will dig a bit deeper into the biology of T cells, responsible for the cell-mediated adaptive immunity, since they are the end target of immunotherapies. And an effective T cell response, especially CD8+ T cell response, is required for an immunotherapy to be effective.

T cells, or T lymphocytes, are a type of white blood cell and an important part of the immune system, more specifically, of the adaptive immune system. The main purpose of T cells is to eradicate intracellular microbes, which reside in infected cells or phagocytes. The population of T cells consists of functionally different subpopulations, broadly separated as helper CD4+

Immune system is essential for
Targovax's products

Immune system is divided into innate
and adaptive systems, which
complement each other

CD8+ T cell response is required for
immunotherapy to be effective

CD8+ T cells main purpose is to
eradicate infected cells

T cells and cytotoxic CD8+ T cells (CTLs). Helper T cells secrete cytokines, which mediate many of the cellular responses of humoral and cell-mediated immunity, such as B-cell activation, T cell differentiation and proliferation, and macrophage activation. By recognising antigens cytotoxic T cells actively kill infected cells through apoptosis by releasing Granzymes or Perforin, or by binding to the death receptor Fas, which is expressed on many cell types. There is a third group of T cells, regulatory CD4+ T cells, which suppress the function of other T cells, and thereby inhibit immune responses.

T cells stem from hematopoietic stem cells of the bone marrow or foetal liver, which mature in the thymus and are later released into the circulation as naïve T cells. Naïve T cells circulate throughout the body and remain naïve until they encounter an antigen. Antigen Presenting Cells (APCs), primarily Dendritic Cells (DC), and naïve T cells are brought together in the lymph nodes for the activation of T cells with specificity against the antigen presented by the DC. Dendritic cells present antigens derived from endocytosed proteins (proteins actively taken up from the outside of the cell) and antigens from intracellular proteins on Major Histocompatibility Complex (MHC) class II and I, respectively. The T cell receptor (TCR) on CD4+ T cells associates with MHC II, while the TCR of CD8+ T cells associates with MHC I. According to this principle, vaccinations should only be able to activate CD4+ T cells via antigen presentation by MHC II. However, there is a phenomenon called cross-presentation, where exogenous antigens are presented by MHC I instead, and thereby able to activate CD8+ T cells. Some subsets of dendritic cells have higher capacity for this than others.

For a T cell to become activated it has to receive more signals than just via the TCR, these signals are called costimulators, and are molecules expressed by the APC. The best characterised costimulatory molecule is B7 (CD80/CD86) expressed on APCs, which binds CD28 on T cells. B7 is absent or expressed at low levels on resting APCs and induced by a various of stimuli from the innate immune system, including activation of Toll-like receptors by microbial agents, or by cytokines, such as IFN-gamma, in response to an infection. Furthermore, activated T cells express CD40 ligand (CD40L) on their surface. This ligand binds to CD40 on APCs and acts in a feedback loop to enhance the expression of B7; hence inducing the activation of T cells further. For T cells not to become activated by self-antigens and generate autoimmunity, inhibitory receptors associate with B7 and create self-tolerance.

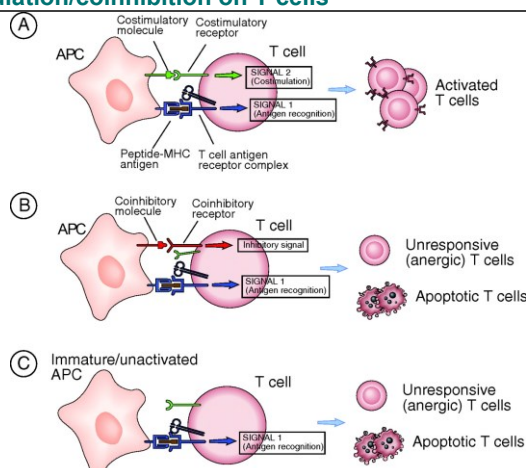
Two of the best characterised inhibitory receptors are CTLA-4 and PD-1. CTLA-4 and CD28 share ligand, but CTLA-4 has a much higher affinity for B7 than CD28. It is therefore postulated that CTLA-4 binds B7 when levels of the ligand are low, while CD28 binds B7 when levels are high (e.g. upon recognition of a pathogenic antigen and exposure to innate immune responses)¹. In the absence of costimulators or in the presence of inhibitory receptors the T cell either becomes anergic (i.e. unresponsive to the antigen) or dies via apoptosis (see below).

Dendritic cells activate T cells in the lymph nodes that are specific for the antigen presented

For activation a T cell must receive additional signals via, so called, co-stimulatory receptors

Co-inhibitory receptors inactivate T cells and protect from autoimmunity, the best characterised inhibitory receptors are CTLA-4 and PD-1

Influence of costimulation/coinhibition on T cells



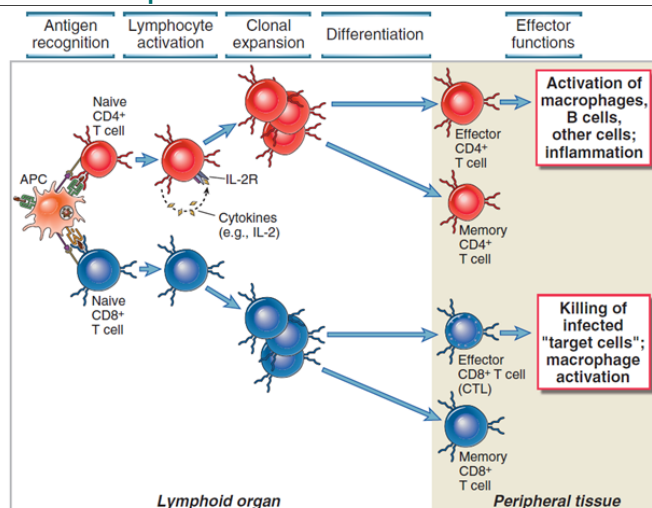
Source: Gotsman I. et al. *Circulation Research*. 2008;103:1220-1231

¹ Abul K. Abbas, Andrew H. Lichtman, Shiv Pillai (2011) *Cellular and Molecular Immunology*, 7th edn, : Elsevier Saunders

Upon activation, a T cell undergoes several functional changes important for proliferation and differentiation, such as changes in expression of surface molecules and secretion of cytokines. One of the most important cytokines produced early on after T cell activation is IL-2, which is a survival and differentiation factor for T cells.

IL-2 also induces proliferation/clonal expansion of T cells, leading to the generation of a high number of T cells required for elimination of infected/cancerous cells. Moreover, CD4⁺ T cells undergo differentiation into one out of primarily three distinct subgroups of CD4⁺ T cells. These three subgroups are called Th1, Th2, and Th17. They secrete different cytokines, have different functions, and fight different types of infectious pathogens. The development of different T cell subsets are driven by cytokines released by APCs, so different types of microbes might cause the release of distinct set of cytokines, which could skew the differentiation of CD4⁺ T cells, and some studies indicate that specific subsets of DCs drive the generation of either Th1 or Th2 T cells. Furthermore, each differentiated subset of CD4⁺ T cells secrete cytokines themselves that promote their own development and inhibit the development of other subsets.

T cell activation and development

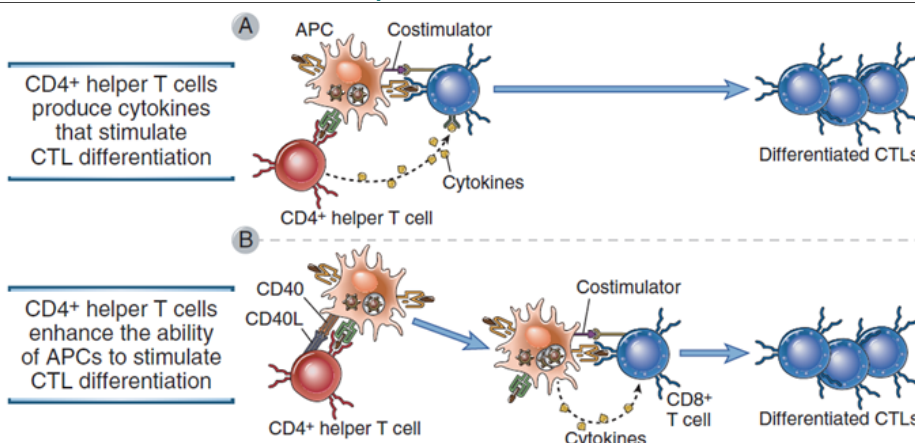


Source: Abul K. Abbas, Andrew H. Lichtman, Shiv Pillai (2011) *Cellular and Molecular Immunology*, 7th edn, : Elsevier Saunders

Activation of CD8⁺ T cells leads to their differentiation to CTLs, and as for CD4⁺ T cells, CD8⁺ T cells also require the recognition of an antigen in the presence of second signals for activation. However, the nature of these second signals can be different from those for CD4⁺ T cells. If the innate immune response is weak, as it tends to be for tumours, CD8⁺ T cells can require the help from CD4⁺ T cells to become activated.

Activation of CD8⁺ T cells generate functional cytotoxic lymphocytes

Different routes for CD4⁺ cells to help to activate CTLs



Source: Abul K. Abbas, Andrew H. Lichtman, Shiv Pillai (2011) *Cellular and Molecular Immunology*, 7th edn, : Elsevier Saunders

It has been established that following activation of naïve T cells, some effector cells generate a pool of memory T cells. Memory T cells are heterogeneous population of long-lived cells, specific for the antigen, which are responsible for protecting the host and initiating an immune response in case of re-exposure to the pathogen or tumour. However, the research field of memory T cells is still lacking the answers to fundamental questions regarding the generation of memory T cells. Better understanding of the mechanism underlying the generation of T cell memory will be crucial to developing more efficient vaccines.

Immune cells – central components of tumour microenvironment

Tumours are complex organs, constituting several distinct cell types, not only tumour cells, which together create the 'tumour microenvironment'. Important cells in the tumour microenvironment are immune cells, which have a dual role in tumorigenesis – tumour promoting and tumour suppressing.

Some tumour-promoting features of immune cells include creation of an inflammatory environment (mainly innate immune cells) that by e.g. releasing growth and survival factors to the tumour cells. Furthermore, the immune cells also supply the tumour microenvironment with extracellular matrix-modifying enzymes that enable angiogenesis (forming of new blood vessels from existing ones), invasion, and metastasis. The immune cells can also release chemicals that cause mutagenesis, mainly reactive oxygen species, and thereby foster and accelerate the acquisition of genetic alterations leading the cancer to become more malignant.

On the other hand, infiltration of immune cells can also suppress tumour growth, especially tumour-specific CD8⁺ T cells (CTLs) that recognise and kill tumour cells. CTLs distinguish tumour cells from other cell types by their expression of antigens that are not normally expressed on healthy cells (neoantigens). Neoantigens are peptides derived from mutated proteins presented on MHC.

Infiltration of CTLs into the tumour has been shown to be a favourable prognostic factor in several cancers, including colorectal cancer, ovarian cancer, and melanoma².

Immune surveillance and immunoediting

The theories of immune surveillance and immunoediting explain how cancer cells evade the immune system. The theory of immune surveillance proposes that the immune system looks for, recognises, and reacts against pathogens and abnormal cells in the body, e.g. tumour cells, and thereby acts in a tumour-suppressive manner. While immunoediting proposes that that eventually immune-resistant cancer cells are selected for survival, leading to immune escape and tumour progression.

Immunoediting has three phases: elimination, equilibrium, and escape, which essentially lead to the Darwinian selection of weakly immunogenic cancer cells that can escape the host's immune system. Elimination includes the stages when CTLs recognise tumour cells as foreign and eliminate them (immune surveillance). Failure to eliminate all cancer cells can lead to equilibrium, where a tumour is kept in check and does not progress. However, this can be overcome by cancer cells that escape the immune system via several mechanisms, including loss of antigen expression, down-regulation of MHC class I (so the cells cannot be recognised by CTLs), low expression of costimulators (resulting in T cell anergy), production of immunosuppressive cytokines, and recruitment of suppressor immune cells (e.g. regulatory T cells and myeloid-derived suppressor cells). Furthermore, tumour cells inhibit immune responses by engaging inhibitory receptors, such as CTLA-4 and PD-1, expressed on activated CD4⁺ and CD8⁺ T cells.

Note that CTLs are central in both the immune surveillance and immunoediting theory. CTLs recognise tumour cells as foreign through identification of peptides on the surface of the cancer cells, termed tumour antigens or neoantigens, which are abnormal peptides not normally expressed on cells, allowing the immune system to eradicate cancer cells.

Some effector T cells differentiate into memory T cells, important for protection in case of re-exposure to the pathogen (or tumour)

Immune cells are central components of the tumour microenvironment

Cancer cells evade the immune system through immunoediting

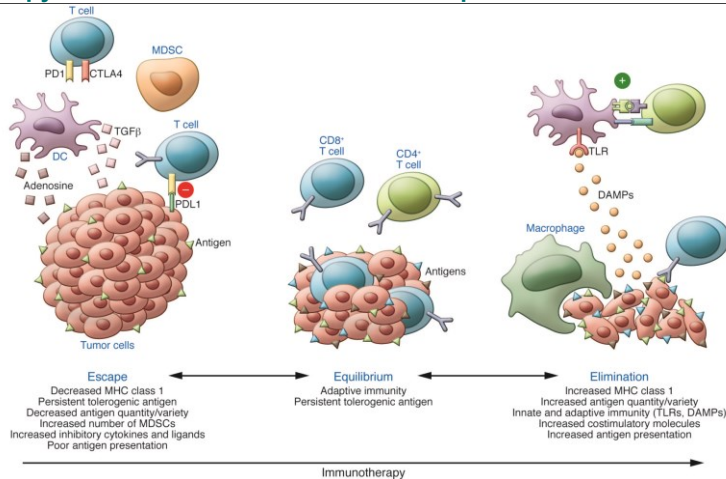
Immunoediting leads to Darwinian selection of weakly immunogenic cells

CTLs recognise cancer cells through neoantigens, i.e. abnormal peptides

² Gajewski TF. et al. *Nature immunology* 14.10 (2013): 1014-1022

There are several types of tumour antigens; e.g. antigens that are products of mutated genes, such as RAS and p53, which are tumour specific. Other tumour antigens include normal cellular proteins that are overexpressed in tumours, or proteins of genes that are normally silent but have become activated in the tumour.

Immunotherapy aims to shift the balance from escape to elimination



Source: Kalbasi A. et al. *The Journal of clinical investigation* 123.7 (2013): 2756-2763

Immune escape by tumour cells is a large hurdle in the development of immunotherapies; therefore strategies to overcome immune evasion, and shifting the balance from escape to elimination in immunoediting, are studied for development of effective therapies. The class of drugs called checkpoint inhibitors have been the most successful in this area, and we will address these later.

Immune escape needs to be overcome for immunotherapies to be effective

Cancer vaccines

Therapeutic cancer vaccines belong to the family of cancer treatments called immunotherapies. Immunotherapies aim to modulate the interactions between the cancer and immune cells, so the cancer is rejected by the patient's own immune system.

Most successful cancer vaccines have so far been prophylactic vaccines, i.e. given before the disease develops, with the aim of reducing the risk of developing a certain cancer later in life. There are two commercially available prophylactic cancer vaccines in the US; hepatitis B and HPV vaccines. As both hepatitis B and HPV have been shown to cause cancer, vaccinating against them is an effective method for preventing cancer. However, Targovax's focus is on therapeutic cancer vaccines and this is what our discussions will focus on, i.e. vaccines given to patients already diagnosed with cancer – and we will call them simply 'cancer vaccines'.

The notion that the immune system can reject tumours has been around since the late 1800s, when physician William Coley discovered that several metastases regressed in a sarcoma patient after suffering a bacterial infection in a wound. Until this day remnants of this approach are seen in cancer therapies, where general immune stimulants are used to activate the immune system, such as attenuated bacteria and interleukins, which are used in bladder cancer and melanoma treatment, respectively.

The discovery of tumour-specific antigens has led to the development of more targeted immunotherapies, in the form of cancer vaccines, some of which target a particular antigen or a subset of antigens (there are also vaccines that target multiple undefined antigens, such as oncolytic viruses).

The objective of cancer vaccines is to boost the body's own immune system to fight the cancer. This is also the definition of active immunotherapy. Passive immunotherapy, on the other hand, involves the administration of exogenously produced components, such as cytokines, antibodies, or lymphocytes, for the generation of an immune response.

Mechanism of action

We will briefly review the main mechanism by which cancer vaccines activate the immune system, i.e. by the activation and maturation of Dendritic Cells (DCs), which eventually leads to the generation of T cells targeted at the cancer.

Background

Cancer vaccines elicit a T cell mediated immune response by initially activating DCs. DCs are an essential bridge between the innate and adaptive immune system, as through sensors they can capture invading pathogens and transmit the information to lymphocytes (T- and B cells). DCs are bone marrow-derived cells and reside in the periphery and in lymph nodes. Antigens can therefore be captured by peripheral DCs that migrate to a lymph node for antigen presentation or by DCs residing in lymph nodes.

There are several distinct subsets of dendritic cells that generate different types of immune responses. DCs are split broadly into myeloid DCs (or 'conventional DCs') and plasmacytoid DCs. Plasmacytoid DCs circulate through the blood and lymphoid tissues, and represent front-line immunity against viral infections by secreting high amounts of IFN α , which stimulates the immune system and can therefore also induce an anti-tumoural immune response. However, the majority of DCs are myeloid and there are distinct classes of myeloid DCs in blood and skin that generate different immune responses, but essentially all of them are very effective at activating adaptive immune cells, such as B- and T cells.

Compared with other antigen presenting cells (APCs), DCs are extremely efficient at generating a T cell response through antigen presentation. As the DC encounters a pathogenic antigen the cell matures and acquires novel functions, such as increased surface levels of MHC II and co-stimulatory molecules, as well as expression of CCR7, which allows the migration of the DC to draining lymph nodes. If the DC does not mature (due to the antigen not being pathogenic or due to low levels of cytokines), the DC induces tolerance through T cell deletion or differentiation of regulatory or suppressor T cells. Therefore, it is

Therapeutic cancer vaccines are given to patients already diagnosed with cancer, in contrast to prophylactic cancer vaccines

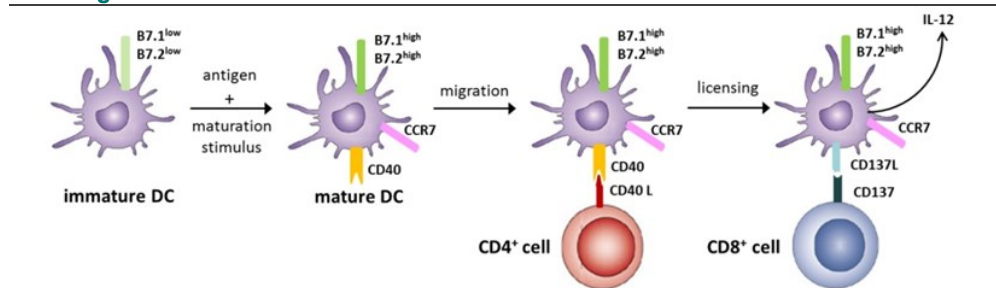
Cancer vaccines boost the patient's immune system to fight the cancer

DCs are the essential bridge between the innate and adaptive immune system

DCs are extremely efficient at activating T cells

important that antigens are immunogenic enough to elicit an innate immune response, which would lead to the maturation of DCs and induced co-stimulation, and thereby activation of T cells. To enhance co-stimulation of T cells in vaccinations, adjuvants are added to the vaccination. Adjuvants mainly act by stimulating DC maturation, and thereby improve their ability to co-stimulate T cells upon antigen presentation. GM-CSF in combination with IFN α , TNF, or IL-15 is known to induce inflammatory DCs, and has therefore been used in vaccines administered to cancer patients³.

Maturing of dendritic cells



Source: Immunodeficiency InTech Europe edited by Krassimir Metodiev, 01/2012

Although the essential mechanism of all cancer vaccines is to activate cytotoxic T cells, many tumour vaccine platforms deliver the antigen and activate DCs by different means.

Oncolytic virus vaccines

Oncolytic viruses are viruses that selectively infect and kill cancer cells. They also induce anti-tumour effects by activating innate and adaptive immune cells targeted at the cancer cells, which helps to eliminate uninfected cancer cells in primary and metastatic tumours, and thereby they act as in situ vaccines. The virus is usually able to generate an immune response targeted at the cancer cells through several immune mechanisms.

The immune responses generated are in many cases robust, long-lasting, and specific, and are often mediated by CD8+ T cells⁴. There is still a lot to learn about the immunogenicity of oncolytic viruses and how to modify the virus to generate the optimal immune response, because not all types of immune responses are beneficial, e.g. chronic inflammation, which might instead promote tumorigenesis (cancer cell growth) and inhibit T cell anti-tumour immunity.

The viruses used for these products under development are mainly adenoviruses or herpes simplex viruses, but there are many more types of viruses that have potential as oncolytic virus vaccines. We address the technology behind oncolytic virus vaccines later.

Protein and peptide vaccines

Vaccination with peptides of tumour-specific antigens was one of the first approaches to cancer vaccination. Initially, short peptides specific for MHC class I together with adjuvants were used for activating CD8+ T cells. However, vaccinations utilising short peptides (8–10 amino acids) do not activate CD4+ T cells, which can largely impair the functionality of CTLs. Therefore, a more recent strategy has been to use long synthetic peptides of 23–45 amino acids, which activate T cells through both MHC class I and II (importantly, MHC class I receptors bind shorter peptides of 8–10 amino acids, while MHC class II bind longer peptides, generally 15–24 amino acids). Vaccinations with multiple peptides activating several T cell clones have also shown to be clinically beneficial⁵, which is also supported by mouse models⁶.

APC-based vaccines

Several APCs have been investigated for the use of cancer vaccines, including peripheral blood mononuclear cells (PBMCs), activated B-cells, and DCs. DC vaccines have shown to be safe, feasible, and immunogenic, and able to promote clinical significant tumour regression in some patients. The idea behind APC-based vaccines is to remove large amounts of PBMCs from the patient and culture them ex vivo in the presence of cytokines and pulse them

Different types of cancer vaccines all aim to activate CTLs, but do so by different means

Oncolytic viruses directly kill cancer cells, as well as act as an in situ vaccine

Immune responses are robust, long-lasting, and specific

Modern peptide vaccines utilise longer peptides that can activate both CD4+ and CD8+ T cells

APC-based vaccines have shown effects in some patients, but are costly and time-consuming

³ Palucka K. et al. Nature Reviews Cancer 12.4 (2012): 265-277

⁴ Chiocca EA. and Rabkin SD. Cancer immunology research 2.4 (2014): 295-300

⁵ Walter S. et al Nature medicine 18.8 (2012): 1254-1261

⁶ Disis ML. et al. Cancer Prevention Research 6.12 (2013): 1273-1282

with tumour antigens to activate the cells without the influence of the immunosuppressive tumour microenvironment, and then reinject them into the patient. A strategy also used for APC vaccines is to transfect the removed DCs with a plasmid expressing a tumour antigen, and the construct may even express adjuvants. However, an important disadvantage of autologous (from the patient) DC vaccines is that they are time-consuming and costly to produce.

Sipuleucel-T (PROVENGE) is an FDA-approved APC-based vaccine for metastatic prostate cancer, which consists of autologous peripheral blood mononuclear cells (PBMCs) that have been activated outside the body with a protein fused to granulocyte-macrophage colony stimulating factor (GM-CSF), an adjuvant.

Tumour cell vaccines

Along with APC-based vaccines, tumour cell vaccines are called whole-cell vaccines. To make the vaccine safe, the cancer cells are killed or weakened so they cannot divide, before being injected into the patient. The idea is that as many tumour antigens are difficult to identify, injecting tumour cells (source of tumour antigens) should elicit an immune response. However, as many tumours are non-immunogenic, whole tumour cells are injected with adjuvants that will enhance the immune response. Tumour cells can even be genetically modified to express high levels of proteins to enhance the immune response, e.g. GM-CSF. Tumour cells used in vaccinations can be autologous (i.e. derived from the patient, and the vaccine should create a highly tumour-specific immune response as the injected tumour cells express identical antigens to the patient's cancer cells) or allogenic (i.e. derived from another person, but the expressed antigens should be similar to the patient's own tumour cells to create a tumour-specific immune response).

An example of a whole-tumour cell vaccine is GVAX, comprising allogenic pancreatic ductal adenocarcinoma cells genetically modified to secrete GM-CSF. The vaccine is in several phase I and II trials in various combinations. Treatment combinations being investigated include nivolumab (Opdivo) and pembrolizumab (Keytruda). However, the vaccine relatively recently failed to meet its primary endpoint of an improvement in overall survival in a phase IIb trial, where it was studied in combination with CRS-207. Hence, we believe the probability of success and continued development of GVAX is low at this point. Algenpantucel-L is another whole tumour cell vaccine, which unfortunately also relatively recently failed in a large phase III trial.

DNA vaccines

DNA vaccines consist of bacterial plasmids (a small DNA molecule separated from chromosomal DNA, which can replicate independently) into which specific genes have been incorporated, e.g. specific tumour antigens. The DNA vaccine is commonly injected into the skin or muscle where the plasmid enters the nucleus of keratinocytes, myocytes, and resident APCs. The host cellular machinery then transcribes and translates the antigen, which have been incorporated into the plasmid backbone. This should result in the synthesised antigen being presented on MHC class I and II receptors and thereby being recognised by the immune system, subsequently leading to an immune response against the selected antigen.

It has also been shown that bacterial plasmids can elicit an innate immune response, due to a specific bacterial genetic sequence is recognised by Toll-like receptor-9 expressed by several cell types, e.g. B cells and dendritic cells. However, the innate immune response to bacterial plasmids is not as strong in humans as was initially observed in mice⁷.

There are several benefits with DNA vaccines over many of the other types of vaccines. Among other things, they should (theoretically at least) have a more beneficial safety profile as they are non-live, non-replicating, and non-spreading. Furthermore, they are easy to manufacture in large-scale and to store, and they can encode several types of genes. However, clinical trials have shown low immunogenicity of DNA vaccines, hence low clinical success, and future DNA vaccines require optimisation of delivery to cells and level of antigen expression. Currently most clinical trials for DNA tumour vaccines are in phase I. DNA vaccines are investigated for melanoma, breast cancer, and prostate cancer, among others⁸.

The idea behind tumour cell vaccines is that injecting patients with tumour cells in combination with adjuvants could elicit an anti-tumour immune response

Two tumour cell vaccines recently failed in late-stage development

DNA vaccines have so far shown only modest effects in clinical trials

⁷ Rice J. et al Nature Reviews Cancer 8.2 (2008): 108-120

⁸ Yang B. Human vaccines & immunotherapeutics 10.11 (2014): 3153-3164

Two main technologies

Following the merger of Targovax and Oncos, the company has two cancer vaccine technologies at its disposal. Targovax's technology focuses on peptide-based cancer vaccines, while Oncos's focuses on oncolytic virus cancer vaccines. Below we delve into the two technologies and consider their main differences.

Oncos's technology – oncolytic virus vaccines

Oncos's technology is based on a so-called oncolytic virus, which selectively infects and kills cancer cells. Apart from directly killing the cancer cells, oncolytic viruses induce anti-tumour effects by activating innate and adaptive immune cells targeted at the cancer cells, which helps to eliminate uninfected cancer cells in primary and metastatic tumours, and thereby they act as in situ vaccines.

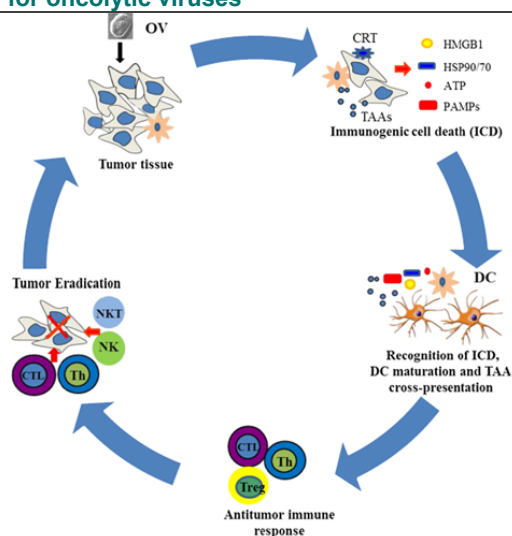
Anti-tumour immunity is elicited by 'immunogenic cell death' (ICD) induced by the oncolytic virus. ICD differs from normal apoptotic cell death, which is non-immunogenic, by the release of damage-associated molecular pattern (DAMP) (danger signals), oncolytic virus-derived pathogen-associated molecular pattern molecules (PAMPs), and inflammatory cytokines, and finally by the release of tumour-associated antigens (TAAs). With these actions, the virus can generate an immune response targeted at the cancer cells. Apart from generating an immune response via ICD, the oncolytic virus is in itself immunogenic through recognition via TLR-9 on innate immune cells, which generates a CD8+ T cell response.

The immune responses generated by oncolytic viruses are in many cases robust, long-lasting, and specific, and are often mediated by CD8+ T cells⁹.

Oncos's technology is based on an oncolytic virus that selectively kills cancer cells, and induces immune response

Oncolytic virus induces immunogenic cell death of cancer cells

Mechanism of action for oncolytic viruses



Source: Bartlett et al. 2013

Broadly speaking, there are two types of oncolytic viruses:

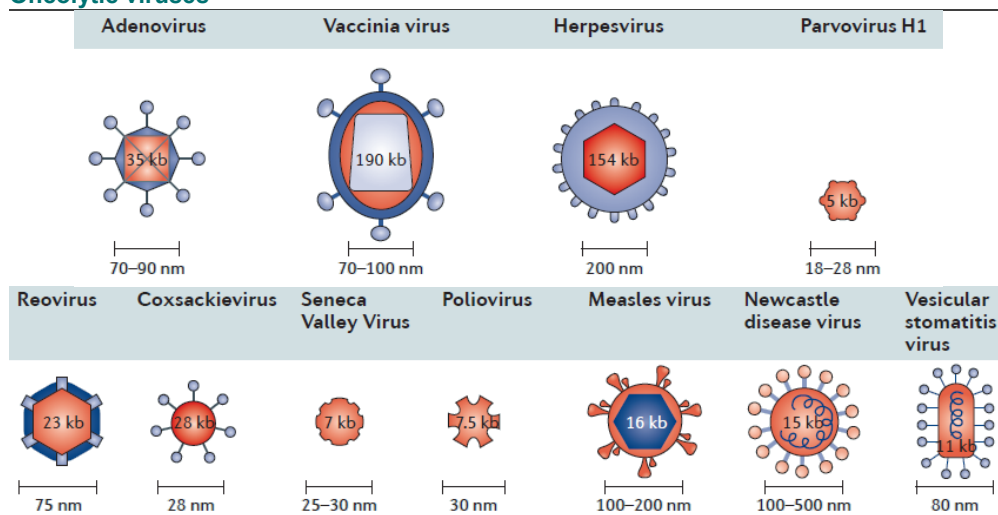
- Those that naturally replicate preferentially in cancer cells and that are non-pathogenic for humans due to high sensitivity to innate antimicrobial signalling or dependence on oncogenic signalling pathways. Examples: reovirus, Newcastle disease virus, parvovirus.
- Those that are genetically manipulated for use as vaccine vectors, such as:
 - Measles virus, poliovirus, and vaccinia virus.
 - Viruses that are genetically engineered with mutations/deletions in genes that are required for replication in normal cells but not in cancer cells. Examples: adenovirus, herpes simplex virus, vaccinia virus, vesicular stomatitis virus.

⁹ Chiocia EA. and Rabkin SD. Cancer immunology research 2.4 (2014): 295-300

Different oncolytic viruses all have their pros and cons and differ in regards to size, viral entry, replication, immunogenicity, transgene capacity, among other features. And current research is highly focused on trying to elucidate the optimal features of an oncolytic virus, which likely though differs between cancer forms.

The figure below illustrates different oncolytic viruses, the viruses on the top are DNA viruses and the ones on the bottom are RNA viruses.

Oncolytic viruses



Source: Kaufman HL, et al. *Nature Reviews Drug Discovery* 14.9 (2015): 642-662.

As the technology of genetic engineering has evolved in the past two decades, there has been rapid expansion of oncolytic viruses, as engineering improves the safety and targeting of the virus, and gives the possibility to insert a transgene into the virus that allows enhancement of the anti-tumour efficacy.

A common group of transgenes used in oncolytic viruses are genes encoding proteins that enhance the activation of the adaptive immune system, for example GM-CSF, which has been incorporated in several viruses, as it has shown to be an effective immune modulator in other types of cancer vaccines (e.g. Sipuleucel-T). Other therapeutic transgenes include IL-2, IL-12, IL-15, IL-18, IFN- α/β .

The tumour microenvironment is in many cases favourable for a virus, as cancer cells sustain proliferation: escape cell death, growth suppressors, and immune destruction. Furthermore, cancer cells commonly experience genomic instability and DNA damage stress, which also provides a benign environment for the virus.

Oncolytic viruses have several advantages over common treatment modalities for cancer, including: 1) a low risk of generating resistance as they use several pathways of cytotoxicity; 2) the treatment generates only minimal systemic toxicities as the virus selectively replicates in cancer cells and is thereby relatively non-pathogenic; 3) in contrast to common cytotoxic drugs, oncolytic viruses increase with time as the virus replicates; and 4) the possibility to insert transgenes in the genome of the virus allows for the insertion of safety features, such as drug and immune sensitivity.

The main issue for oncolytic viruses is administration; although intravenous administration is the most convenient option, and it can be used in multiple tumours, there are several issues with using intravenous administration of oncolytic viruses:

- Pre-existing antibodies against oncolytic viruses for human viruses.
- Generation of antibodies against oncolytic viruses due to multiple injections.
- Sequestration in the liver.
- Lack of extravasation to the tumour.

Technology advancements have led to rapid expansion of oncolytic viruses

Oncolytic viruses have several advantages over common cancer treatments

Oncolytic viruses are better administered by intratumoural injections than by intravenous

For these reasons, intratumoural injections are likely to be the more effective choice for delivery of the oncolytic virus, despite being more laborious. However, the effectiveness varies and depends on the cell phenotype, the permissiveness of the virus infection, and the transfer of the virus to tumour cells.

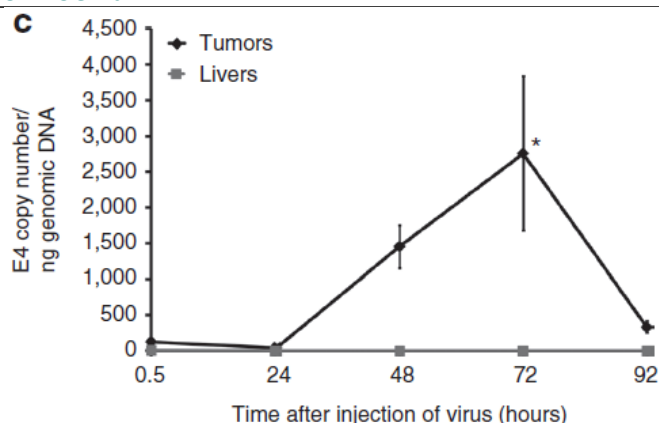
As the field of oncolytic viruses is still relatively novel, there is limited knowledge in certain areas, which could lead to some challenges in the drug development process. For example the dynamics of how oncolytic viruses are cleared and controlled in cancer patients is not yet fully understood. And there are multiple factors that could affect the clearance of the oncolytic virus, e.g. presence of pre-existing neutralising antibodies, virus-specific memory T cell response, and the innate ability of some viruses to evade immune detection, all of which might need consideration to maximise the efficacy of the vaccine. An example of another challenge is the biosafety handling of oncolytic viruses that needs some extra consideration due to no universally accepted standards, and therefore the development plan should include policies for safe handling and storage of the vaccine. Even though there are some challenges in the development process of oncolytic viruses, we believe the favourable risk-benefit ratio makes this class of new drugs highly promising for cancer therapy.

ONCOS-102 product

The oncolytic virus vector vaccines developed by the Oncos technology are based on adapted human serotype 5 adenoviruses. Adenoviruses as vaccine vectors have shown to be effective as they can both prime and boost immune responses. ONCOS-102 is injected directly into the solid tumour; hence, the vaccine candidate cannot be used for tumours that are inaccessible for direct injections. This for reasons explained earlier in the section of oncolytic viruses.

The Oncos virus is genetically altered to impede replication in healthy cells through a 24 base pair (bp) deletion in the E1A gene of the virus at the binding site of the Retinoblastoma (Rb) protein. The Rb protein is a tumour suppressor protein that normally inhibits cell cycle progression until the cell is ready, and the adenovirus protein E1A binds and inactivates Rb to be able to replicate in quiescent cells. Therefore, the deletion leads to the selective replication of the virus in cells with deficient p16-Rb pathway, which is in virtually all cancer cells¹⁰. The safety, efficacy, and bio-distribution of this virus have been widely studied in several preclinical models previously, and the safety and selectivity has also been confirmed by Targovax¹¹. Koski et al showed that ONCOS-102 selectively replicates in tumour cells by measuring the level of the virus in tumour and liver samples from HapT1 tumour-bearing Syrian hamsters. In the tumour samples the virus load increased 23-fold between 0.5 and 72 hours after injection, while in the liver samples the amount of virus particles remained low at all time points (see figure below).

Selectivity of ONCOS-102



Source: Koski A. et al. *Molecular Therapy* 18.10 (2010): 1874-1884

The liver is a good and commonly used model for non-tumour tissue when comparing viral load to confirm selectivity of an oncolytic virus as it is the organ most exposed to blood-borne viruses¹².

¹⁰ Nevins JR. *Human molecular genetics* 10.7 (2001): 699-703

¹¹ Kanerva A. and Hemminki A. *International journal of cancer* 110.4 (2004): 475-480

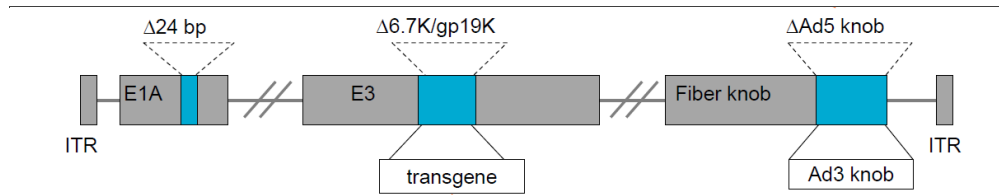
¹² Koski A. et al. *Molecular Therapy* 18.10 (2010): 1874-1884

We believe the risk-benefit profile of oncolytic viruses makes the drug class promising

ONCOS-102 is based on adapted human serotype 5 adenoviruses

ONCOS-102 is genetically modified to restrict its replication to only cancer cells

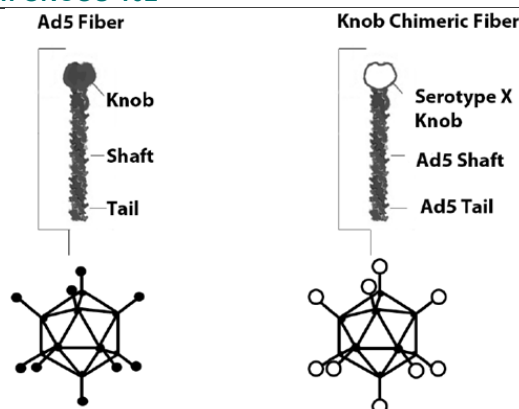
Genetic alterations of ONCOS-102 adenovirus



Source: Company data

Furthermore, the ONCOS-102 harbours two additional genetic changes, the insertion of the transgene GM-CSF and the replacement of the serotype 5 adenovirus (Ad5) fiber knob with Ad3 fiber knob resulting in the Ad5/3 chimera, which consists of the backbone (shaft and tail) from Ad5 and the knob from Ad3 (see figure below). Ad3 binds to an additional receptor, which Ad5 does not bind to, that is commonly overexpressed by cancer cells, while the receptors bound by Ad5 are usually expressed at very low levels in tumours. This genetic modification increases the infectivity of the virus directed towards cancer cells, which has been verified by multiple preclinical assays¹³.

Binding alterations in ONCOS-102



Source: Ranki T. and Hemminki A. *Viruses* 2.10 (2010): 2196-2212

GM-CSF as an adjuvant – in a transgene version

In the ONCOS case the company uses GM-CSF as an adjuvant, which is encoded by a transgene that has been inserted into the viral genome. This means that as the virus replicates within the cancer cells, GM-CSF is produced simultaneously, and in conjunction with the immunogenic cell death of cancer cells caused by the oncolytic virus, GM-CSF will be released and able to further stimulate the immune system by recruiting APCs and natural killer (NK) cells, as well as activating the APCs, which will aid in generating an effective T cell immune response. The safety of GM-CSF in humans is well-established, and ONCOS-102 induces only local levels of the GM-CSF¹⁴.

Numerous oncolytic viruses in clinical development

There are numerous oncolytic viruses in clinical trials, the table below summarises the key viruses that have been developed clinically, not all of them are being investigated now, e.g. Onyx-015 and H101, but as one can see most are adenoviruses or herpesviruses, and only a few have reached later stage of clinical development.

The virus produces immune stimulant GM-CSF as it replicates

Most oncolytic viruses are adenoviruses or herpesviruses, and most of them are still in early development

¹³ Koski A. et al. *Molecular Therapy* 18.10 (2010): 1874-1884

¹⁴ Koski A. et al. *Molecular Therapy* 18.10 (2010): 1874-1884.

Key oncolytic viruses in clinical trials

| Virus | Manufacturer | Number of clinical trials | | | Cancers |
|---------------------|--------------------------|---------------------------|----------|-----------|---|
| | | Phase I | Phase II | Phase III | |
| Adenovirus | | | | | |
| Onyx-015 | Onyx Pharmaceuticals | 6 | 6 | 0 | Head and neck cancer, pancreatic cancer, ovarian cancer, colorectal cancer, gliomas, lung metastases, and liver metastases |
| H101 | Shanghai Sunwaybio | 1 | 2 | 1 | Squamous cell carcinoma and head and neck cancer |
| DNX-2401 | DNAtrix | 4 | 0 | 0 | Glioblastoma, ovarian cancer |
| VCN-01 | VCN Biosciences | 2 | 0 | 0 | Pancreatic cancer |
| Colo-Ad1 | PsiOxus Therapeutics | 1 | 2 | 0 | Colon cancer, NSCLC, renal cancer, bladder cancer, and ovarian cancer |
| ProstAtak | Advantagene | 4 | 1 | 1 | Pancreatic cancer, lung cancer, breast cancer, mesothelioma, and prostate cancer |
| Oncos-102 | Targovax | 1 | 0 | 0 | Solid cancers |
| CG0070 | Cold Genesys | 1 | 1 | 1 | Bladder cancer |
| Vaccinia virus | | | | | |
| Pexa-vac (JX-594) | Jennerex Biotherapeutics | 7 | 6 | 1 | Melanoma, liver cancer, colorectal cancer, breast cancer, and hepatocellular carcinoma |
| GL-ONC1 | Genelux | 4 | 1 | 0 | Lung cancer, head and neck cancer, and mesothelioma |
| Herpesvirus | | | | | |
| IMLYGIC | Amgen | 2 | 3 | 2 | Melanoma, head and neck cancer, and pancreatic cancer |
| G207 | Medigene | 3 | 0 | 0 | Glioblastoma |
| HF10 | Takara Bio | 2 | 1 | 0 | Breast cancer, melanoma, and pancreatic cancer |
| SEPREHVIR | Virttu Biologics | 5 | 1 | 0 | Hepatocellular carcinoma, glioblastoma, mesothelioma, neuroblastoma |
| OrienX010 | OrienGene Biotechnology | 1 | 0 | 0 | Glioblastoma |
| Reovirus | | | | | |
| Reolysin | Oncolytics Biotech | 15 | 9 | 0 | Glioma, sarcomas, colorectal cancer, NSCLC, ovarian cancer, melanoma, pancreatic cancer, multiple myeloma, head and neck cancer |
| Seneca Valley Virus | | | | | |
| SVV-001 | Neotropix | 3 | 1 | 0 | Neuroendocrine-featured tumours, neuroblastoma, and lung cancer |
| Coxsackievirus | | | | | |
| Cavatak | Viralytics | 3 | 1 | 0 | Melanoma, breast cancer, and prostate cancer |

Source: Kaufman HL. et al. *Nature Reviews Drug Discovery* 14.9 (2015): 642-662

In GlobalData records we find that c40 oncolytic viruses are in clinical development, most of which are in phase I or phase I/II development. However, a few are being investigated in phase III: CG0070, Pexa-vac, ProstAtak and Imlygic

c40 oncolytic viruses are in clinical development

The number of oncolytic viruses in clinical development implies fierce competition for ONCOS-102, and suggests that interest in the field has boomed, but not without reason – improved technology and promising pre-clinical and clinical trial results, including Imlygic's approval, have had an impact on interest in oncolytic viruses.

Targovax's technology – peptide-based cancer vaccines

Targovax cancer vaccines are built on peptides that are taken up by dendritic cells (DCs) and by this route presented to the immune system. The peptides used in the TG-platform vaccines are commonly mutated forms of the RAS protein.

Targovax peptide vaccines consists of commonly mutated forms of RAS

The RAS genes (HRAS, KRAS, NRAS) are the most common oncogenes (genes that have the potential to cause cancer if activated) in human cancer; up to 20% of all cancers have a constantly activated RAS gene. This notion is not surprising as RAS is involved in a wide range of signalling pathways controlling several vital functions of the cell, including proliferation, apoptosis, differentiation, and cellular metabolism. It has been reported that RAS is mutated in up to 90% of pancreatic cancer, c40–60% of colorectal adenocarcinomas, c60% of follicular carcinomas of the thyroid, c30% of adenocarcinomas in the lung, c40–60% of biliary tract carcinomas, and c20% of malignant melanomas.

Up to c20% of all cancers have mutations in the RAS gene

RAS mutation

| | |
|--------------------|---------|
| Pancreatic cancer | c90% |
| Colorectal cancer | c40–60% |
| Biliary cancer | c40–60% |
| Thyroid cancer | c60% |
| NSCLC | c20–30% |
| Malignant melanoma | c20–30% |

Source: Miglio, U et al 2014, Vaughn, C.P. et al 2011 D'Arcangelo, M et al 2012, Fernandez-Medarde, A et al, 2011

The vaccine consists of a cocktail of seven or eight, medium long, synthetic peptides that are all aimed at different versions of RAS mutations. The peptides are 17 amino acids long, making them long enough to activate both CD4+ and CD8+ T cells, as demonstrated by several independent laboratories¹⁵. Furthermore, studies have revealed that the RAS peptide can also bind to all three major HLA II forms (DP, DR, DQ)¹⁶, indicating that a lack of RAS presentation by certain HLA types might not be a major constraint in responsiveness against RAS mutations.

RAS protein amino acid sequence

1 12 13

M T E Y K L V V V G A G G V G K S A L T I Q L I Q ...

Source: Company data

Most mutations in RAS are point mutations resulting in a single amino acid substitution

| | | 12 13 | | | | | | | | | | | | | | | | | | |
|---------|---|-------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----|
| Peptide | 1 | ... | K | L | V | V | V | G | A | A | G | V | G | K | S | A | L | T | I | ... |
| | 2 | ... | K | L | V | V | V | G | A | C | G | V | G | K | S | A | L | T | I | ... |
| | 3 | ... | K | L | V | V | V | G | A | D | G | V | G | K | S | A | L | T | I | ... |
| | 4 | ... | K | L | V | V | V | G | A | R | G | V | G | K | S | A | L | T | I | ... |
| | 5 | ... | K | L | V | V | V | G | A | S | G | V | G | K | S | A | L | T | I | ... |
| | 6 | ... | K | L | V | V | V | G | A | V | G | V | G | K | S | A | L | T | I | ... |
| | 7 | ... | K | L | V | V | V | G | A | G | D | V | G | K | S | A | L | T | I | ... |
| | 8 | ... | K | L | V | V | V | G | A | G | C | V | G | K | S | A | L | T | I | ... |

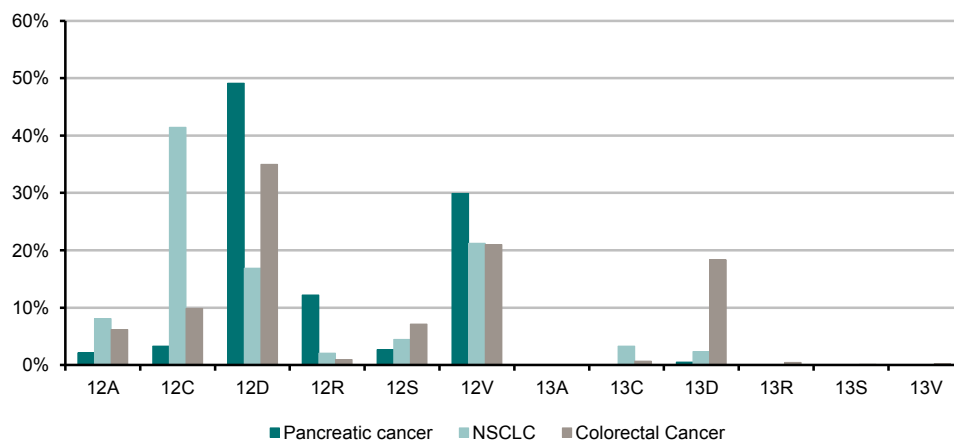
Source: Company data

Below, we have included the different mutations and their frequency for different diseases.

¹⁵ Gedde-Dahl T. et al. Human immunology 33.4 (1992): 266-274, Fossum B. et al. International journal of cancer 56.1 (1994): 40-45, Abrams S. et al. Cellular immunology 182.2 (1997): 137-151, Giersten MK. et al. International Journal of Cancer 72.5 (1997): 784-790

16 Fossum B. et al. *European journal of immunology* 23.10 (1993): 2687-2691. Gedde-Dahl T. et al. *European journal of immunology* 24.2 (1994): 410-414. Johansen BH. et al. *Scandinavian journal of immunology* 39.6 (1994): 607-612

Mutations for various diseases



Source: Prior et al. Cancer Res. 2012 May 15; 72(10): 2457-2467

As shown, including the seven peptides (for TG01) in a cocktail means that such a vaccine should cover >99% of all RAS mutations seen in pancreatic cancer patients. Adding the eighth peptide (in TG02) should mean that >99% of RAS mutations in NSCLC and CRC are covered. Hence, having this peptide cocktail is a much more convenient way of treating patients, since one does not have to do any typing of the mutation in the patient before initiation of treatment.

GM-CSF used as an adjuvant to the vaccine

We know that using peptides as antigens in therapeutic cancer vaccines alone is not immunogenic enough to trigger a long-term immunogenic response in most patients. Hence, in addition to peptides, one has to use some sort of adjuvant to trigger the required T cell response. For TG01 and TG02 Targovax will use GM-CSF as the adjuvant, i.e. the same as in ONCOS-102, but the difference is that in the TG products, the GM-CSF is not produced by the product itself, as in ONCOS-102, but must instead be administered concurrently with the peptide vaccine.

GM-CSF is a cytokine that stimulates the immune system by triggering stem cells to produce granulocytes (white blood cells – neutrophils, eosinophils and basophils) as well as monocytes, which mature into macrophages and dendritic cells. There are two pharmaceutical analogues to the naturally occurring GM-CSF called sargramostim and molgramostim. The sargramostim product is produced in yeast and is glycosylated while the molgramostim product is produced in bacteria (*E. coli*) and is non-glycosylated.

In TG01 and TG02 the pharmacological analogue of GM-CSF, molgramostim, is used. We see one potential issue with using molgramostim in the vaccine: it is no longer available on the market – in Europe it was withdrawn in 2004 and in the US it was never approved. Targovax buys its GM-CSF from a Chinese manufacturer but, over time, plans to start manufacturing it itself in Europe at a CMO. However, Targovax expects to get the GM-CSF registered as a part of the vaccine and has no plans to try to register the molgramostim as a stand-alone product.

TG01 and TG02 cover most mutations of RAS in pancreatic, colorectal and non-small cell lung cancer

Adjuvant GM-CSF given concomitantly with the peptide vaccine

Targovax aims to get the peptide vaccine and the GM-CSF approved as one single product

Why have other cancer vaccines failed?

Historically there have been numerous attempts to develop cancer vaccines; however, most of them have failed in clinical testing. As more is understood about tumour immunology, the reasons for the failed attempts are better understood and include patient selection, clinical trial design, treatment combinations, and design of the vaccine. We believe that one major contributor to failed historical clinical trials is that vaccine trials have often been designed in much the same way as other more traditional drug trials, which might be completely unsuitable.

Onset of action

Over time we have seen that the clinical effect of immunological therapies (not only vaccines) can take some time to materialise. It is not uncommon for there to be no initial significant reduction in tumour size (and in some cases, the immunological processes might even induce tumour growth). Hence, this phenomenon could explain why several phase III vaccine trials have demonstrated no significant change in disease progression (disease-free survival), while the long-term endpoint of overall survival (OS) has significantly improved. This situation, with long-term benefits without immediate and significant reduction in tumour size makes biological sense in terms of immune response but might be difficult to accept for both regulatory agencies and the financial markets.

Patient selection

In the classic development path for new drugs, one usually starts doing the trials in very severely ill patients. Many patients are, for example, heavily pre-treated and have high tumour burdens and in many ways have exhausted all other treatment options.

Greater tumour burden leads to a proportional increase in regulatory T cells (Tregs), as well as increased levels of indoleamine-2,3-dioxygenase, transforming growth factor (TGF)- β and IL-10, all of which can inhibit T cell activation. In addition, severely ill patients, with a very aggressive cancer, might not survive long enough to have time to develop a significant immune response and as a result not see any benefit from the treatment.

Selection of appropriate clinical end-points in trials

Choosing and agreeing on the right end-points in clinical trials for cancer vaccine therapy is very important. Given the effects mentioned above, we have seen several trials where the progression free survival (PFS) between the vaccine and placebo has been non-existent, while at the same time there has been a statistically significant difference in overall survival. In the Sipuleucel-T (Provenge) phase III trial¹⁷ the drug failed to meet its primary endpoint of longer PFS but at the same time displayed a clear improvement in OS (25.8 months versus 21.7 months: $p=0.032$). The same happened with Bavarian Nordic's PROSTVAC-VF phase II trial¹⁸, where the trial did not show any difference in PFS but at the same time showed a clear survival benefit with an increase of 8.5 months ($p=0.016$) in OS.

The figure below tries to capture some of the reasons why it is not uncommon to see a prolonged OS and no increase in PFS. Traditional treatment with cytotoxic drugs can have a dramatic impact on tumour burden, but as soon as treatment is stopped, the tumour growth returns to its old trajectory while the impact of immunotherapy can have a marked impact on the growth trajectory leading to a significantly slower growth rate and as a result display a prolonged OS without any difference in PFS. The crosses in the figure represent time of death of the patients.

Most cancer vaccines have failed in clinical development, historically

Due to slow onset of action, cancer vaccines might not show immediate effects of tumour reduction

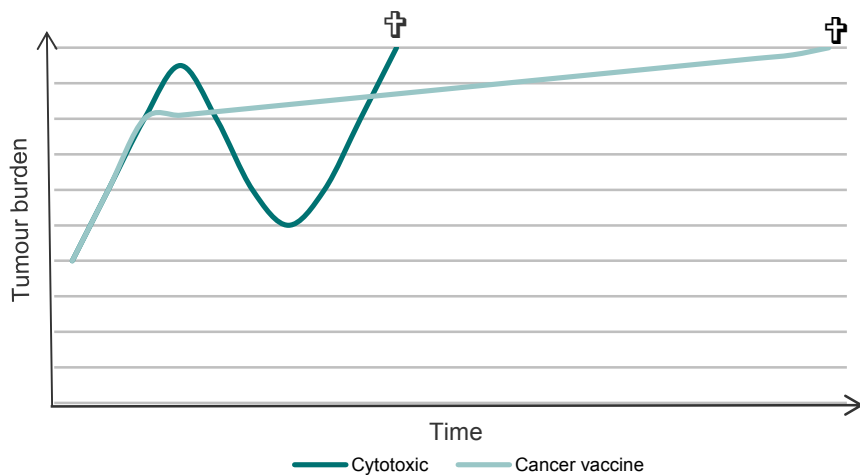
Cancer vaccines might not be suitable for severely ill patients

Selecting the right endpoints is crucial

¹⁷ Kantoff PW. et al. New England Journal of Medicine 363.5 (2010): 411-422.

¹⁸ Kantoff PW. et al. Journal of Clinical Oncology 28.7 (2010): 1099-1105.

Dynamics of tumour growth



Source: Adapted after M Bilusic et al.

In light of the mechanism of action for cancer vaccines and greater focus among payers on improvements in OS for patients, selecting the right end-points in clinical trial programmes and having a thorough understanding of the mechanism behind PFS and OS are important in order to correctly evaluate the clinical outcomes.

Poor choice of adjuvant to the vaccine

This is probably also a contributory factor why older therapeutic cancer vaccines have failed. For example, one classic adjuvant used has been IFA (Incomplete Freund's Adjuvant). Freund's adjuvant is a solution of antigen emulsified in water and mineral oil. The complete form of the adjuvant includes inactivated and dried mycobacteria (usually *M. tuberculosis*) – the incomplete form of the adjuvant excludes the mycobacteria (hence only water in mineral oil emulsion). However, one important problem with this adjuvant is that when it is injected into the skin or subcutaneously, it forms a depot and even if it is effective in creating a local immunological reaction, the antigen presenting cells remains (get trapped) in the depot rather than move to the lymph nodes. As a result, getting a strong immunological reaction to the vaccine is almost impossible.

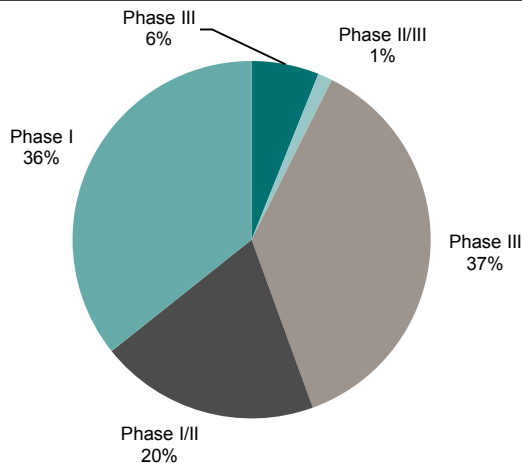
Today, however, almost all therapeutic cancer vaccines under development use GM-CSF as adjuvant so this should not be an issue to the same extent going forward.

Therapeutic cancer vaccines in development

There are several therapeutic cancer vaccines under development from a multitude of companies as well as from publicly financed institutions. We carried out a search in GlobalData's database for products in development with a special focus on cancer vaccines. We found that c150 cancer vaccines are in clinical development worldwide, studied in c380 independent clinical trials, split into the different phases as shown in the figure below.

c150 cancer vaccines are in clinical development

Ongoing cancer vaccine trials, by stage of development



Source: GlobalData

As discussed earlier, competition is fierce in the oncolytic virus vaccine space; and the figure above highlights the great number of cancer vaccines being developed, indicating also great competition on the cancer vaccine market as a whole.

Below we discuss a number of unique cancer vaccines, most of which are in the later stages of development.

Products worth keeping an eye on

Below we highlight some of the more advanced potential competitors for Targovax that we believe the financial markets need to keep an eye on and be updated on their development.

Imlygic (T-VEC/Talimogene laherparepvec)

Imlygic, developed by Amgen and approved in 2015, is an oncolytic virus that – unlike ONCOS-102 – is based on a herpes simplex virus-1 (HSV-1) rather than on an adenovirus. The virus has been genetically modified to allow selective replication in tumour cells and to increase the immunogenicity of the virus. The wild type HSV-1 is widespread in the human population, and it resides latent in sensory ganglia neurons until reactivation, when the virus causes infections of the oral mucosa. To ensure safety and selectivity of Imlygic, the neurovirulence gene ICP34.5 has been disrupted; a strategy that has proven to direct tumour cell lysis in several tumours¹⁹. To increase the immunogenicity of the virus the gene ICP47 that provides immune-evasive properties has also been disrupted, and to further increase the immune recognition, the gene encoding GM-CSF has been inserted in the genome of the virus.

Imlygic is an oncolytic virus based on genetically modified HSV-1

In comparison to adenoviruses and ONCOS-102, HSV activates the innate immune system by different means, and it is mainly recognised by TLR-2 and -4 on innate immune cells, which is not optimal for a CD8+ T cell response.

Imlygic showed significant clinical benefits in a phase III trial for advanced melanoma, and in April 2015 an independent advisory board panel to the US FDA voted 22 to 1 in favour of its approval. And at the end of October 2015 the FDA approved Imlygic for advanced melanoma.

Imlygic is approved for advanced melanoma

The phase III trial, which the FDA based its approval on, was a randomised, open-label study testing the effect of intratumoral Imlygic injections versus subcutaneous GM-CSF in 436

¹⁹ Liu BL. et al. Gene therapy 10.4 (2003): 292-303

patients. The primary outcome was DRR or Durable Response Rate (objective response that lasted 6+ months). Overall survival and overall response rate were secondary end-points. The durable response rate was significantly higher with Imlygic than with GM-CSF (16.3% versus 2.1%) and the overall response rate was higher with Imlygic (26.4% versus 5.7%). The median overall survival was 23.3 months with Imlygic and 18.9 months with GM-CSF.

Imlygic clinical data

| Drugs | Trial | Study population | n | Study design | DRR | ORR | Median OS |
|-----------------------|-------|-------------------|-----|--|-------|-------|-------------|
| Imlygic versus GM-CSF | OPTIM | Advanced melanoma | 436 | Randomised, open-label phase III trial at 64 centres | 16.3% | 26.4% | 23.3 months |

Source: Andtbacka RHI. et al. ASCO Annual Meeting Proceedings. Vol. 31. No. 18_suppl. 2013

When the effects of Imlygic were analysed in different subgroups, the benefit of Imlygic was not realised in patients with stage IVb and IVc melanoma or in those whose melanoma was previously treated²⁰. Furthermore, concerns have been raised about the study's open-label design because of the possibility of bias in the analysis of response. Also, the pharmaceutical drug treatment alternatives for melanoma have increased considerably with several immune checkpoints in recent years – hence GM-CSF is a less relevant comparator today. But even so, the approval is justified by the fact that there is still a great need for additional anticancer drugs in advanced melanoma, as tumours tend to become resistant or fail to respond to drugs, and the treatment did in fact induce a significant rate of durable responses.

The potential of combining Imlygic with immune checkpoint inhibitors is being studied in early-stage trials, and data reported from a phase Ib trial where Imlygic was combined with ipilimumab, in stage IIIB and IV melanoma patients, showed that the treatment regimen achieved an ORR of 56%²¹, which is much higher than that achieved by either agent alone.

Earlier studies of Imlygic have shown evidence of systemic immunity and regression of metastatic lesions²²; however, according to the FDA review, data from the phase III study provided only limited evidence of systemic effects, which was difficult to quantify²³. And the phase III trial did not provide data that demonstrated that Imlygic induced a tumour-specific T cell immune response.

Imlygic has also shown to be safe in the clinical trials; the most frequent adverse events linked to the immunotherapy are low-grade flu-like symptoms²⁴.

Algenpantucel-L

Algenpantucel-L is the most clinically advanced immunotherapy for pancreatic cancer, but due to the recently failed phase III trial, IMPRESS, it reaching the market is highly doubtful.

Algenpantucel-L is a whole-cell vaccine developed by NewLink Genetics containing two pancreatic cancer cell lines that have been genetically modified to express alpha-gal molecules on their cell surface. Even though humans do not normally express alpha-gal on cells, humans have large quantities of natural anti-alpha-gal antibodies. Therefore, vaccination with cells expressing alpha-gal on their surface leads to a hyper-acute rejection through a complement-mediated lysis and antibody-dependent toxicity towards the Algenpantucel-L cells. The idea is that the immune reaction generated by Algenpantucel-L leads to activation of immune cells, targeted at pancreatic cancer specific-antigens expressed by the cell lines, which will attack and eradicate the patients' own pancreatic cancer.

The results of a single-arm, open-label, multi-institutional phase II study (NLG0205) of Algenpantucel-L combined with standard chemotherapy (gemcitabine+5-FU/radiation) after R0/R1 resection where promising. The primary endpoint in the trial was disease-free survival at one year and secondary endpoint was overall survival at one year. In total, 62% of patients achieved the primary endpoint and 86% achieved the secondary endpoint²⁵. These results

Phase III trial did not provide evidence of tumour-specific T cell immune response

Highly doubtful that Algenpantucel-L reaches the market

Algenpantucel-L is a whole-cell vaccine indicated for pancreatic cancer

²⁰ Andtbacka RHI. et al. ASCO Annual Meeting Proceedings. Vol. 31. No. 18_suppl. 2013

²¹ Puzanov I et al. J Clin Oncol. 33, 2015 (suppl; abstr 9063).

²² Kaufman HL. et al. Ann Surg Oncol (2010) 17:718–730

²³ John Carroll FierceBiotech April 27, 2015

²⁴ Johnson DB. et al. Immunotherapy 7:6 (2015): 611-619

²⁵ Hardacre JM. et al. Journal of Gastrointestinal Surgery 17.1 (2013): 94-101

compared favourably with those from the RTOG-9704 trial, in which patients received the same chemo-radiation regimen. In that trial, the 1-year survival was only 69%. Furthermore, the predicted 1-year survival for patients in the NLG0205 study was 55–63%, compared with the observed 86%, representing over 30% improvement in survival. The phase II study also concluded that no serious adverse events were attributed to the immunotherapy.

Algenpantucel-L clinical data

| Drugs | Trial | Study population | n | Study design | DFS at 1 year | OS at 1 year |
|---|---------|----------------------------|----|--|---------------|--------------|
| Algenpantucel-L in combination with standard chemotherapy | NLG0205 | Resected pancreatic cancer | 73 | Open-label, dose-finding, phase II trial at 16 centres | 62% | 86% |

Source: Hardacre JM. et al. *Journal of Gastrointestinal Surgery* 17.1 (2013): 94-101

Algenpantucel-L has since been investigated in two phase III clinical trials: one in patients with resectable pancreatic cancer (IMPRESS) and one in non-resectable pancreatic cancer (PILLAR). The IMPRESS study enrolled 722 patients, making it the largest study ever to be completed in the US for patients with resected pancreatic cancer. The company recently announced that the IMPRESS trial did not meet its primary endpoint of improved overall survival, and the median overall survival was longer in the placebo arm, at 30.4 months, compared with the treatment arm, at 27.3 months. The PILLAR trial is expected to be completed in December 2016; however, a positive outcome is believed to be unlikely, after the failure of IMPRESS. The FDA has given Algenpantucel-L fast-track status and orphan drug designation.

Algenpantucel-L did not meet its primary endpoint of improved overall survival in patients with resectable pancreatic cancer

GV1001

GV1001 is a telomerase peptide vaccine of a 16 amino acid hTERT peptide that binds to multiple HLA class molecules. Telomerase is an enzyme that is expressed in 85–90% of cancer cells, but not in normal cells. One of three components of the human telomerase detected is the human telomerase reverse transcriptase (hTERT), which is a telomeric catalytic subunit. The mRNA levels of hTERT have shown to be high in cancer cells.

GV1001 is a peptide vaccine studied in pancreatic cancer

GV1001 was studied in a phase I/II trial in 48 patients with unresectable pancreatic cancer, the vaccine was given intra-dermally in three dosing groups together with GM-CSF for 10 weeks followed by optional monthly booster vaccines. Of the 27 evaluable patients in the trial the median survival was 8.6 months in the intermediate dose group, which was significantly longer than in the two other dosing groups. Furthermore, the vaccine was well-tolerated, and the 1-year survival in the intermediate dose group was 25%.

GV1001 clinical data

| Drugs | Trial | Study population | n | Study design | Outcomes |
|---|------------------|---|------|---|--|
| GV1001 together with GM-CSF | Bernhardt (2006) | Unresectable pancreatic cancer | 38 | Open-label phase I/II trial | Median OS=8.6 months, 1-year survival=25% |
| GV1001 versus gemcitabine | PrimoVax | Advanced unresectable pancreatic cancer | 360 | Controlled, randomised, open-label, phase III trial | Terminated early due to lack of survival benefit in the GV1001 arm |
| Gemcitabine and capecitabine with sequential/concurrent or without GV1001 | TeloVac | Advanced and metastatic pancreatic cancer | 1062 | Open-label, randomised, phase III trial at 51 centres | Median OS: Chemotherapy alone = 7.89 months, sequential chemoimmunotherapy: 6.94 months, concurrent chemoimmunotherapy = 8.36 months |

Source: Bernhardt SL. et al. *British journal of cancer* 95.11 (2006): 1474-1482. Gunturu KS. et al. *Therapeutic advances in medical oncology* (2012): 1758834012462463. Middleton G. et al. *The lancet oncology* 15.8 (2014): 829-840

GV1001 was thereafter studied in two phase III trials: PrimoVax and TeloVac. The PrimoVax trial analysed the efficacy of the vaccine as a monotherapy in unresectable pancreatic cancer in comparison to gemcitabine. The trial was terminated due to a lack of survival advantage. The TeloVac trial analysed the efficacy of the vaccine in combination with gemcitabine and capecitabine (Xeloda) in patients with advanced and metastatic pancreatic cancer. The trial recruited 1,062 patients in 52 centres throughout the UK. However, there was no significant survival benefit for patients receiving the vaccine. Despite this, the vaccine received

GV1001 development was discontinued after failing two phase III trials

conditional marketing approval in South Korea. The company Kael-GemVax was though encouraged by the finding of two possible biomarkers in the trial that might predict the response to the vaccine and increased survival²⁶.

UV1

UV1 is a peptide vaccine developed by Norwegian company Ultimovacs. The technology is based on the identification of a new set of peptide epitopes from hTERT in long-term surviving patients that had been treated with different forms of telomerase therapeutic cancer vaccine and hTERT transfected dendritic cells. The hypothesis is that since these epitopes elicited an immune response only in patients that had a clinical benefit to the hTERT-based treatments, it could indicate that these epitopes might be responsible for the tumour eradication.

The vaccine is in three early stage clinical trials: two studying its safety and ability to elicit an anti-tumour immune response in patients with metastatic, androgen sensitive prostate cancer and advanced NSCLC, and the third assessing its safety and efficacy when combined with ipilimumab in patients with unresectable or metastatic malignant melanoma.

The difference between TG01/TG02 and the telomerase peptide vaccines is mainly the peptide. The telomerase peptide is a wild type peptide that is overexpressed in cancer cells, but is still expressed to some extent in normal cells. The RAS peptides in TG01/TG02 are not wild type, but are mutated and only present in cancer cells, hence they also more specific than the telomerase products.

Provenge (sipuleucel-T)

This product was developed by Dendreon, and is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. The vaccine consists of the patient's own PBMCs, which includes APCs, which have been activated ex vivo with a recombinant fusion protein (PA2024). The fusion protein consists of prostatic acid phosphatase (PAP) and GM-CSF. PAP is not tumour-specific, but is expressed on the majority of prostatic cancers, and only minimally expressed on other tissues than the prostate gland.

Provenge clinical data

| Drugs | Trial | Study population | n | Study design | Median OS |
|-----------------------------|--------|---|-----|--|-------------|
| Sipuleucel-T versus placebo | IMPACT | Metastatic castration-resistant prostate cancer | 512 | Double-blind, placebo-controlled, phase II trial at 75 centres | 25.8 months |

Source: Kantoff PW. et al. *New England Journal of Medicine* 363.5 (2010): 411-422

Provenge was initially approved for advanced prostate cancer by the FDA in 2010, and in 2013 it was approved in the EU, Norway, Iceland, and Liechtenstein. The approval was based on the results of the phase III trial IMPACT, which showed a significant improvement in overall survival. The trial included 512 patients with metastatic castration-resistant prostate cancer that received either sipuleucel-T or placebo. The median overall survival was 4.1 months longer for patients who received Provenge (25.8 months), than for patients who received placebo (21.7 months). Despite the increase in survival, no significant change in time to disease progression was observed in men who received Provenge compared with controls.

After approval in 2010, Provenge was believed to become a blockbuster, but the vaccine has not lived up to initial expectations, the reasons for which include the USD93,000 price tag, manufacturing hurdles, and competition from new and more convenient drugs for prostate cancer, such as Xtandi and Zytiga²⁷.

PROSTVAC

PROSTVAC is a cancer vaccine containing prime and multiple boosts with recombinant attenuated vaccinia and fowlpox viruses, respectively. Both viruses have been engineered to encode human PSA and several co-stimulatory molecules. The virus stimulates the activation of cytotoxic T-lymphocytes (CTLs) targeted at Prostate-specific antigen (PSA). PSA is

UV1 is a peptide vaccine based on hTERT peptides

Provenge is approved for advanced prostate cancer

PROSTVAC contains viruses that encode PSA

²⁶ <http://www.fiercebitech.com/story/uk-researchers-report-big-immunotherapy-flop-long-sought-cancer-vaccine/2013-06-03>

²⁷ <http://www.fiercevaccines.com/story/dendreon-bankruptcy-weighs-cancer-vaccine-field/2014-11-10>

normally secreted by the epithelial cells of the prostate gland, but the protein's serum quantity is generally elevated in the presence of prostate cancer. It is administered subcutaneously over five months with an initial priming dose, followed by several boosting doses.

PROSTVAC clinical data

| Drugs | Trial | Study population | n | Study design | Median PFS | Median OS |
|----------------------------------|----------------|---|-----|---|------------|-------------|
| PROSTVAC + GM-CSF versus control | Kantoff (2010) | Minimally symptomatic castration-resistant metastatic prostate cancer | 125 | Double-blind, randomised, controlled phase II trial at 43 centres | 3.8 months | 25.1 months |

Source: Kantoff PW, et al. *Journal of Clinical Oncology* 28.7 (2010): 1099-1105

PROSTVAC, developed by Bavarian Nordic in partnership with the National Cancer Institute, showed encouraging results from a randomised, double-blind, placebo-controlled phase II trial and formed the scientific and clinical rationale of the ongoing pivotal phase III study. The phase II trial showed no significant difference in PFS between the PROSTVAC arm (median = 3.8 months) and the control arm (median = 3.7 months). This is similar to what has been observed in clinical trials of Provenge. However, a significant difference in OS between the two treatment groups was recorded, the median OS for patients treated with PROSTVAC was 25.1 months, while for patients in the control group the median OS was only 16.6.

PROSTVAC is in a phase III trial

RINTEGA (rindopepimut)

RINTEGA, developed by Celldex Therapeutics, is a peptide vaccine consisting of mutant EGFRvIII peptides connected to the carrier protein KHL, which aids in the immune activation. The vaccine has been evaluated in EGFRvIII positive glioblastoma, in both recurrent and newly diagnosed patients. Three independent phase II trials showed improved long-term survival benefits in patients treated with RINTEGA, compared with historical datasets (see table below). However, the vaccine recently failed in a large phase III trial (n = 745) in patients with newly diagnosed glioblastoma with minimal residual disease, in which the control arm outperformed the treatment arm (although RINTEGA performed consistently), OS 21.1 months versus OS 20.4 months, in respective arms.

RINTEGA OS across three phase II studies in EGFRvIII-positive glioblastoma versus independent control datasets

| | Median (months) | OS 3 years |
|--|-----------------|------------|
| RINTEGA phase II studies (all data from study entry) | | |
| ACT III (n=65) | 21.8 | 26% |
| ACT II (n=22) | 20.5 | 23% |
| ACTIVATE (n=18) | 20.4 | 33% |
| Independent control datasets (all data from study entry) | | |
| MD Anderson EGFRvIII-positive patients matched1 to ACTIVATE patient population (n=17) (contemporary with ACTIVATE) | 12.22 | 6% |
| Radiation Therapy Oncology Group (RTOG) 0525 study - all EGFRvIII-positive patients (n=142) (contemporary with ACT III) | 15.1 | 18% |
| RTOG 0525 study - all EGFRvIII-positive patients treated with standard dose temozolomide (n=62) (contemporary with ACT III) | 14.2 | 7% |
| RTOG 0525 study - EGFRvIII-positive patients matched1 to ACT III/IV patient population (n=29) (contemporary with ACT III) | 16 | 13% |

Source: <http://ir.celldex.com/releasedetail.cfm?ReleaseID=721828>

Comments about failure of algenpantucel-L and RINTEGA

We believe it is important to comment on the recent failures of algenpantucel-L and RINTEGA, as they cast some shade over the cancer vaccine market as a whole. However, we do not believe they should affect the development of Targovax's vaccine platforms immensely. Algenpantucel-L is, for example, fundamentally different from the Oncos and Targovax platform vaccines, hence there is no scientific rationale why the outcome of its phase III trial should determine the success of any of Targovax's products. RINTEGA on the other hand is a peptide vaccine, comprising mutant proteins, and reminds us somewhat of

We do not believe the recent failures should affect Targovax immensely

TG01/TG02, but it was developed in a different indication, with different biology and conditions for success from the TG01/TG02 vaccines. Hence, we believe direct comparisons between the two vaccines should not be made. That said, we believe the failure of RINTEGA could affect the market's general view on peptide vaccines and therefore be negative for TG01/TG02. But on the other hand we believe these two failures could actually instead boost the positive view on oncolytic viruses, which – unlike other types of cancer vaccines – have proof of concept in the form of the approval of Imlygic.

Checkpoint inhibitors most likely combination for cancer vaccines

Checkpoint inhibitors (CPI) have revolutionised the immuno-oncology space, and although response rates have been modest, perhaps the most exciting feature of the treatment has been the durable responses in patients that have experienced a response to the treatment.

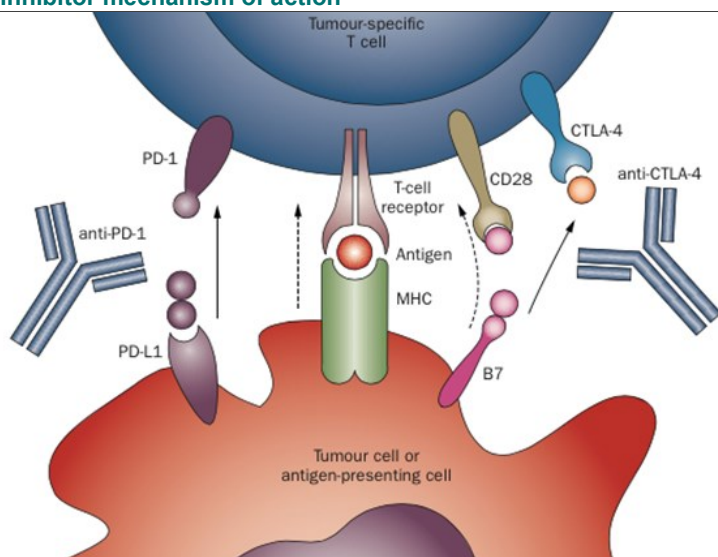
Immune checkpoints are the collective term for molecules that limit the proliferation and killing capacity of T cells. Normally, immune checkpoints function to control excessive immune activation, but tumours often take advantage of these checkpoints to limit the anti-tumour immune response. The two best characterised immune checkpoints are the cells surface receptors CTLA-4 and PD-1, both of which are expressed on T cells, and have shown to be upregulated in some tumours. CTLA-4 limits the T cell response by engaging the co-stimulatory molecule B7 and PD-1 by engaging its ligands PD-L1 or PD-L2. Even though both CTLA-4 and PD-1 regulate the activity of T cells, they are believed to exert their function in different stages of T cell activation.²⁸ CTLA-4 is believed to primarily regulate immune responses early on in T cell activation, while PD-1 is thought to mainly inhibit effector T cells in the effector phase.

To limit immunosuppression mediated by e.g. the tumour, and 'release the brakes' of the immune system, immune checkpoints can be inhibited therapeutically with checkpoint inhibitors.

Checkpoint inhibitors induce durable responses

Checkpoint inhibitors 'release the brakes' on the immune system

Checkpoint inhibitor mechanism of action



Source: Drake CG. et al. *Nature reviews Clinical oncology* 11.1 (2014): 24-37

The first checkpoint inhibitor approved by the FDA was Bristol-Myers Squibb's Yervoy (ipilimumab) in 2011, a humanised monoclonal antibody against CTLA-4, for the treatment of metastatic melanoma. Yervoy was approved based on a randomised (3:1:1) double-blind phase III trial in patients with unresectable or metastatic melanoma. Because no standard therapy exists for these patients, the investigational vaccine gp100 was used as an active control in the study. Patients treated in the trial were therefore randomised to receive Yervoy + gp100 vaccine, Yervoy + vaccine placebo, or gp100 vaccine + placebo. The trial showed that patients treated with Yervoy alone had longer overall survival (OS), at 10.1 months, in comparison to patients treated with gp100 vaccine, with an OS of six months. Patients treated with Yervoy + gp100 vaccine also had an improved OS of 10 months. The overall response rate (ORR) was also highest in patients treated with Yervoy alone, which was 10.9%. Long-term pooled survival data from patients treated with Yervoy in clinical trials show that c20% of patients survive three years or longer, and the longest reported survival reaches 10 years post treatment²⁹.

Anti-CTLA-4 antibody, Yervoy, was first checkpoint inhibitor to be approved

²⁸ Pardoll DM. *Nature Reviews Cancer* 12.4 (2012): 252-264.

²⁹ <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm412861.htm>

Since the approval of Yervoy, three other checkpoint inhibitors have reached the market: Keytruda, Opdivo and Tecentriq, where the first two are antibodies targeted at PD-1 and the third is targeted at PD-L1. Keytruda and Opdivo received breakthrough therapy designation, priority review, and orphan drug designation by the FDA for advanced melanoma. Keytruda was approved for patients with malignant melanoma with disease progression following Yervoy and, if relevant, a BRAF-inhibitor, based on data from 173 patients, which showed an ORR of 24%³⁰. Opdivo was initially approved for patients with advanced melanoma, who no longer responded to any treatment, based on interim data from 120 patients in a phase III trial that showed 32% ORR, compared with 11% for chemotherapy, also with less grade 3–4 treatment-related adverse events, in patients that had progressed after treatment with anti-CTLA4 treatment³¹.

Since then, Opdivo has received expanded approval, and is now approved for front-line treatment in metastatic melanoma in combination with Yervoy, as well as in patients with advanced NSCLC with progression on or after treatment with platinum-based chemotherapy, and as second-line in patients with metastatic renal cell carcinoma (only therapy that has shown improved survival in these patients). While Keytruda, as a single agent, has received expanded approval for first-line treatment in unresectable or metastatic melanoma (as of 15 December 2015). Keytruda has also received expanded approval to treat patients with metastatic NSCLC on or after treatment with platinum-based chemotherapy who also express PD-L1 (companion diagnostics therefore needed).

So far three checkpoint inhibitors have been approved: Yervoy plus two PD-1-inhibitors

Clinical data of checkpoint inhibitors in melanoma (approved and under development)

| Agent | Setting | No. of patients | Response rate, % | OS | Grade 3-4 Adverse Events, % (Frequency of selected events) | Source |
|------------------------|--|-----------------|------------------|---------------------------------------|---|---------------------|
| Ipilimumab | Phase III, previously treated patients | 137 | 10.9 | Median, 10.1 months | 19 (7 fatigue, 5 colitis, 2 hypophysitis) | Hodi et al, 2010 |
| Nivolumab | Phase III, untreated patients | 210 | 40 | 73% at 12 months | 12 (1.5 hepatic, 1 diarrhoea, 0.5 hypophysitis) | Robert et al, 2015 |
| Nivolumab + vaccine | Phase II, prior ipilimumab treatment | 53 | 25 | Not reported | 7 (4 rash, 2 pneumonitis) | Weber et al, 2013 |
| Pembrolizumab | Phase I | 135 | 38 | Not reported | 13 (2 rash, 1 diarrhoea) | Hamid et al, 2013 |
| Pembrolizumab | Phase I, prior ipilimumab treatment | 173 | 26 | 61% at 12 months | 12 (2 immune related) | Robert et al, 2014 |
| MPDL3280A | Phase I | 43 | 30 | Not reported | 13 (2 fatigue, 2 hepatic, 1 hypoxia) | Herbst et al, 2014 |
| Nivolumab + ipilimumab | Phase I | 53 | 40 | Not reported | 53 (15 hepatic, 6 renal failure, 4 colitis, 2 pneumonitis) | Wolchok et al, 2013 |
| Nivolumab + ipilimumab | Phase III | 314 | 57.6 | Not reported (median PFS 11.5 months) | 55 | Larkin et al, 2015 |

Source: Hodi FS. et al. New England Journal of Medicine 363.8 (2010): 711-723, Robert C. et al. New England Journal of Medicine 372.4 (2015): 320-330, Weber JS. et al. Journal of Clinical Oncology 31.34 (2013): 4311-4318, Hamid O. et al. New England Journal of Medicine 369.2 (2013): 134-144, Robert C. et al. The Lancet 384.9948 (2014): 1109-1117, Herbst RS. et al. Nature 515.7528 (2014): 563-567, Wolchok JD. et al. New England Journal of Medicine 369.2 (2013): 122-133, Larkin J. et al. New England Journal of Medicine 373.1 (2015): 23-34.

Another CPI target showing similar promise as PD-1 is PD-L1. PD-L1 is the ligand of PD-1 and is expressed on resting T cells, B cells, macrophages, and dendritic cells, and is further upregulated upon activation. PD-L1 is also found on vascular endothelial cells, pancreatic islet cells, and importantly also on tumour cells³². Targeting PD-L1 instead of PD-1 with a checkpoint inhibitor might result in a different biological effect, as PD-L1 has also been shown to engage the co-stimulatory molecule B7, and through this conveys inhibitory signals to T cells.

PD-L1 is another promising CPI target

The first anti-PD-L1 antibody to show objective tumour response in a variety of solid tumours was BMS-956559, but it is no longer under clinical development. Other anti-PD-L1 antibodies in clinical development that also have shown disease responses in early-phase clinical trials³³ include MPDL3280A, durvalumab (previously known as MEDI4736) and MSB0010718C. In findings from a phase I trial of durvalumab in NSCLC, as an example, the ORR across the full

³⁰ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412802.htm>

³¹ Weber JS. et al. Annals of Oncology 25.suppl 4 (2014): mdu438-34

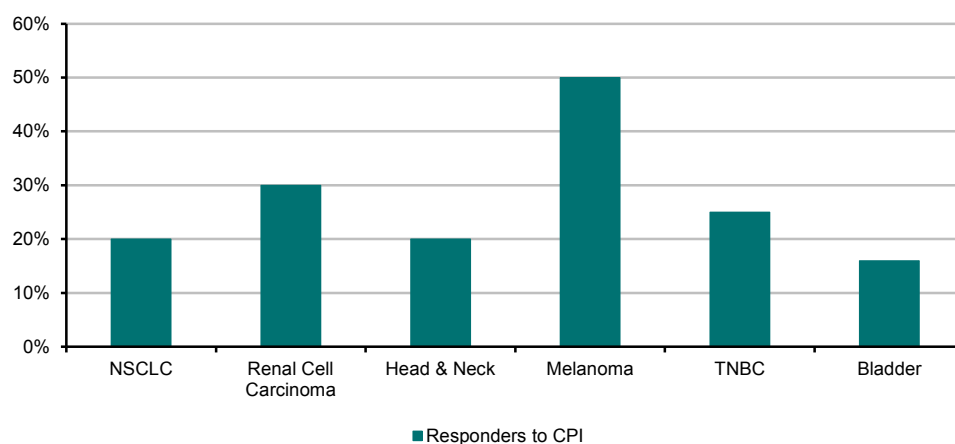
³² Keir ME. et al. The Journal of experimental medicine 203.4 (2006): 883-895, Ahmad SM. et al. Blood cancer journal 4.7 (2014): e230

³³ Postow MA. et al. Journal of Clinical Oncology (2015): JCO-2014

population was 16% (n=200) with a disease control rate at 12 weeks of 42%. In patients with PD-L1 positive tumours in the same trial the ORR was 27% (n=84)³⁴.

The first anti-PD-L1 antibody to be approved is Tecentriq, which received accelerated approval for patients with bladder cancer post progression with a platinum-based chemotherapy; the indication is independent of PD-L1 expression. The approval was based on results that showed tumour response and improved duration of response. The pivotal trial was a phase II trial including 310 patients that received Tecentriq on the first day of 21-day cycles until unacceptable toxicity or either radiographic or clinical progression.

Responders to CPI – various cancer forms



Source: Company data.

Given the commercial success the checkpoint inhibitor class has had, and the numerous products in development for coming generations of products, we suspect this class of drugs will be the main one to be used together with therapeutic cancer vaccines. As mentioned above, the main function of the checkpoint inhibitor class is to 'take the brakes off' the immune system, but taking the breaks off is of no use if the underlying immune system is weak. It is like taking off the brakes of a car without an engine – you won't get very far, very fast. This is shown in the chart above, where we highlight that a large proportion of patients still do not respond in an adequate way to checkpoint inhibitor therapy and these are areas where the company sees great potential of combining its therapeutic cancer vaccines with checkpoint inhibitors.

Looking at the clinical trials planned by the company, we see that the majority involve giving patients a combination of therapeutic cancer vaccines (to boost the immune system – rev the engine) and checkpoint inhibitors (release the brakes). We find the combination logical given the complementary effects these two classes of drugs should have on the immune system.

Cancer vaccines being investigated in combination with CPIs

Several cancer vaccines are already being explored in combination with various types of CPIs, we have summarised some of the ongoing and planned trials with cancer vaccines in combination with CPIs in the table below.

Large proportion of the patients treated with CPIs do not respond

We believe Targovax's product has complementary effects to CPIs

³⁴ Rizvi NA. et al. J Clin Oncol. 2015;33 (suppl; abstr 8032).

Cancer vaccines clinically investigated in combination with CPIs

| Vaccine(s) | CPI | Sponsor/Collaborators | Indication(s) | Trial phase | Status |
|------------------|--------------|--|---|-------------|-------------------------|
| GVAX and CRS-207 | Opdivo | Sidney Kimmel Comprehensive Cancer Center; John Hopkins University | Metastatic Adenocarcinoma of the Pancreas | Phase II | Ongoing, recruiting |
| Vigil | Opdivo | Gradalis Inc. | Lung Cancer | Phase II | Ongoing, recruiting |
| DNX-2401 | Keytruda | DNAtrix, Inc. | Recurrent Glioblastoma Multiforme (GBM) | Phase II | Planned |
| TPIV200 | Durvalumab | TapImmune/AstraZeneca | Ovarian cancer | Phase II | Ongoing, recruiting |
| UV1 | Keytruda | Ultimovacs AS | Melanoma | Phase I/II | Ongoing, recruiting |
| ISF35 | Keytruda | Memgen, LLC.; The University of Texas MD Anderson Cancer Center | Metastatic Melanoma | Phase I/II | Planned |
| WT1 Vaccine | Opdivo | Memorial Sloan Kettering Cancer Center | Fallopian Tube Cancer | Phase I/II | Ongoing, recruiting |
| Cavatak | Keytruda | Viralytics Ltd. | Bladder Cancer | Phase I/II | Ongoing, recruiting |
| CG0070 | Yervoy | Cold Genesys, Inc. | Muscle Invasive Bladder Cancer (MIBC) | Phase I/II | Planned |
| NY-ESO-1 Vaccine | Yervoy | Ludwig Institute For Cancer Research Ltd | Melanoma | Phase I | Ongoing, not recruiting |
| P53MVA Vaccine | Keytruda | Tara Immuno-Oncology | Bladder Carcinoma | Phase I | Ongoing, not recruiting |
| Vigil | Keytruda | Gradalis Inc. | Melanoma | Phase I | Ongoing, recruiting |
| Imlygic | Atezolizumab | Amgen Inc. | Breast Cancer | Phase I | Planned |
| Imlygic | Keytruda | Amgen Inc.; Merck & Co., Inc. | Head And Neck Cancer, Squamous Cell Carcinoma | Phase I | Ongoing, recruiting |

Source: GlobalData, DNB Markets

As shown above, various cancer vaccines are being studied in combination with CPIs, which highlights the industry's interest in and hopes on this treatment modality. For Targovax this again implies fierce competition, but on the bright side also justifies the planned combinations for the company's cancer vaccines, as well as provides a possibility for proof of concept and a better understanding of the mechanism of action to emerge from these trials, which could ease the development of Targovax's vaccines in combination with CPIs.

Most of these cancer vaccines are being developed in partnership with the CPI company, in which the cancer vaccine company does not have to pay for the CPI itself. To our knowledge only one licensing deal has so far occurred, where the CPI developer has acquired the full rights to the cancer vaccine; the subsidiary of AstraZeneca, MedImmune licensed Inovio Pharmaceutical's cancer vaccine, INO-3112, which it plans to study in combination with selected immuno-oncology molecules in its pipeline (most likely CPIs).

Targovax has said that it will pay for the CPI in the planned phase Ib colorectal trial. Whether or not the company pays for the CPI in the melanoma trial is yet to be determined, but a partnership deal would of course be preferred so the company does not have to pay for it. To note, we believe a partnership deal is most likely at this stage, rather than an out-licensing deal, because for this the company would probably need more clinical data.

Several cancer vaccines are studied in combination with CPIs

Measuring immune response

In this section we go through the ways the company can measure immune response among patients. We believe it will be important for the stock market to understand what can be measured, and how it can be done. This is particularly important to understand as the company over the coming years is likely to report immunological data several times and it might be an important trigger for the share price – particularly since the immunological data can be measured much earlier than the clinical outcome data will be available, and has also shown to have great predictive value in several indications.

Immunological responses can be measured long before clinical

Monitoring immune responses

The biological events following vaccination can be divided into three phases, and each can be measured as a clinical endpoint. The three phases are:

- Immune activation and T cell proliferation.
- Clinically measurable anti-tumour effects mediated by activated immune cells.
- A potential delay in patient survival.

An anti-tumour response to vaccination may take up to 2–3 months, compared with chemotherapy where an anti-tumour response might be detected fairly quickly. Therefore monitoring the immune response can be used in early studies for proof-of-principle to the proposed pharmacological effect and the immunogenicity of the antigens. In later studies monitoring immune responses can be used to correlate the duration, type, and magnitude to the clinical benefit. The FDA recommends that, if possible, at least two different assays measuring the immune responses proposed to be involved in the anti-tumour effects of the vaccine should be used. It is also recommended to measure the immune response of both the innate and adaptive immune systems, as the efficacy of the immune system to fight the cancer is based on multiple cells of both these systems.

Immune response data provides proof-of-principle

There are different ways to monitor the immune response to a vaccine, and selection of assays should be based on their possibility to measure the components of the immune system believed to be most important and relevant to the anti-tumour effects of the vaccine.

Delayed type hypersensitivity (DTH)

One of the most used assays to measure antigen-specific immunity is one called delayed type hypersensitivity (DTH). The assay measures the immunological reactivity to the selected cancer antigens in the skin. The test is carried out by injecting antigens, in the form of either soluble proteins or antigens loaded on to antigen-presenting cells. The injected antigens mainly activate CD4⁺ T cells that secrete inflammatory cytokines, leading to recruitment of monocytes and other inflammatory cells to the site, resulting in visible inflammation of the skin. The inflammatory response is measured 48–72 hours after injecting the antigens – similar to a prick test done for allergy. Depending on how large the inflammatory response is after a few days, the test tells you if the patient is positive or negative to the antigen injected.

DTH test measures inflammatory immune response to antigens injected into the skin

Measuring circulating immune cells

Other methods to measure the level of antigen-specific T cells are in vitro, whereas DTH is in vivo. The most commonly used methods to measure T cell responses are:

- Intracellular cytokine staining (ICS).
- ELISPOT.
- HLA-multimer staining assay.

Collectively, these methods are called second-generation ex vivo T cell assays. ICS detects the intracellular production and accumulation of cytokines through flow cytometry and ELISPOT detects single cells actively secreting cytokines, the method is similar to ELISA. Both these methods provide functional information of the cells capability of producing specific cytokines, and the assays allow the use of a suitable control (e.g. an irrelevant peptide). However, a disadvantage with ELISPOT is that tumour-specific T cells frequently produce low

ICS and ELISPOT measures cytokine release by T cells in response to tumour antigens

amounts of cytokines that might be below the detection limit for the assay. IFN- γ , which is secreted by CD4+ Th1 cells and CD8+ T cells upon antigen specific activation, is a common cytokine to measure the activation of T cells.

HLA-multimer staining assay measures the affinity of the T cell receptor to a specific epitope by flow cytometry. The assay has several drawbacks, including the required knowledge of the given epitope, unspecific binding of the epitope, and lack of information of the functionality of the cells.

Assessing immune response in the tumour

To be able to know and measure the type and amount of local immune response in the tumour, one needs to do a biopsy of the tumour. By doing so, several types of immune cells can be analysed. The biopsies need to be correlated with a baseline biopsy in order to be able to say anything about the change in the presence of immune cells. One usually looks at the presence of CD8+ T cells as well as immune-modulating molecules such as PD-1 and PD-L1. If the level of these cells and molecules are increased compared with the baseline, the immune system has been activated.

Changes in the level of immune cells have been shown to be a positive prognostic factor in several cancers, including melanoma, renal, breast, and ovarian cancer³⁵. For example, it was shown in a study that patients (n=285) with primary cutaneous melanoma with brisk or non-brisk infiltration of lymphocytes had improved long-term survival, compared with melanoma patients with no infiltration of lymphocytes (5-year OS: brisk = 77%, non-brisk = 53%, absent = 37%, 10-year OS: brisk = 55%, non-brisk = 45%, absent = 27%).³⁶

The largest drawbacks of these methods are of course that they are invasive and patients need to undergo several biopsies, and if the tumours are inaccessible for biopsies the method will not work. Further, at this point there is no consensus on how to best assess tumour infiltrating cells, e.g. which markers to use. However, it is obvious that infiltration, especially of cytotoxic T cells, in general has a predictive value for multiple cancers. Hence, the interim immune read-outs planned by Targovax in the clinical trials, we believe, will be of great importance and should guide the company's clinical development.

Issues worth considering

Even though it is recognised that monitoring the immune response is important for understanding the immunogenicity of the immunotherapy, there has been a great lack in the correlation between the immunological response and the clinical outcome. One explanation for this might be the complexity of the response required for an actual anti-tumour response, which is not picked up by the common tests used for monitoring the T cell response.

Moreover, it is common to measure the immune response in peripheral blood, due to its convenience, but a lack in response can actually reflect movement of effector cells to the site of tumour. It might therefore be more interesting to measure the activity of tumour-infiltrating cells (or in secondary lymphoid organs), and there is also evidence showing that levels of CD4+ and CD8+ infiltrating T cells correlate with improved outcome for melanoma patients. On the contrary, levels of infiltrating regulatory T cells have been shown to correlate with poor prognosis in ovarian cancer.

Lack of harmonisation of the methodology for monitoring the immune responses has also been a great challenge for monitoring immune responses, as there has been a great variability between laboratories, which has led to irreproducible results, a vital factor for effective biomarker measurement. Work from several international programmes has led to the development of harmonisation criteria for ICS, ELISPOT, and HLA-multimer staining assay³⁷.

To assess the infiltration of immune cells into the tumour one has to do a biopsy

Lymphocyte infiltration is correlated with improved survival

We believe the interim immune readouts planned by the company will be of great importance

Tumour-infiltrating lymphocytes likely to reflect the effect of the treatment better than lymphocytes in the circulation

³⁵ Butterfield LH. et al. *BMJ* 350 (2015): h988

³⁶ Clemente CG. et al. *Cancer* 77.7 (1996): 1303-1310.

³⁷ Hoos A. *Annals of oncology* 23.suppl 8 (2012): viii47-viii52

Clinical data

Targovax is still an early-stage company, so clinical development data is limited, but some development has been going on for quite some time, and due to this we also have some long-term data.

Targovax

Results from two early clinical trials conducted by Norsk Hydro

Since the development of the peptide vaccines in the TG programme started when the project was still at Norsk Hydro, the company has rigid safety data and real long-term data on the outcome in resected pancreatic patients, which was analysed by Wedén et al in 2011.

The company has rigid safety data and real long-term data on the TG platform

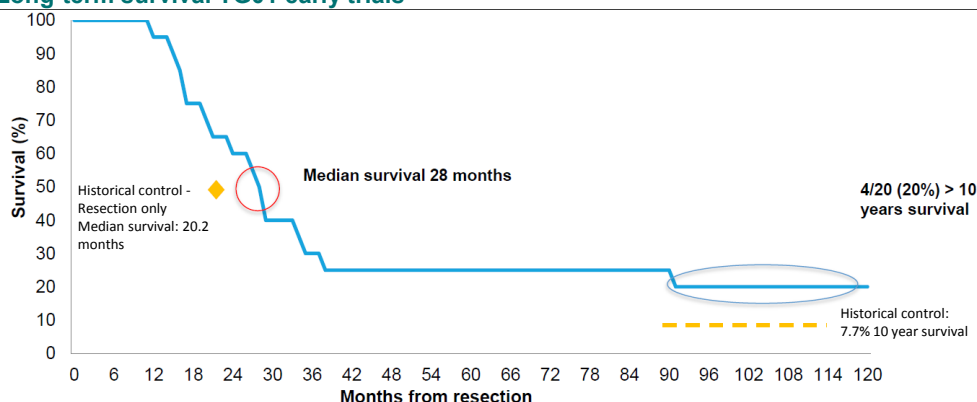
Early clinical trials evaluated the safety and immunogenicity of mutated pancreatic peptides in advanced and operable pancreatic adenocarcinoma, and in colorectal carcinoma. The results of the studies showed that the vaccine was well-tolerated and indicated that the treatment was able to generate CD4+ and CD8+ T cell immune responses³⁸. The earliest studies used RAS peptide pulsed autologous PBMCs for vaccination of patients³⁹. However, this strategy was able to generate a specific T cell response in only two out of five patients. Therefore, it was decided to switch to what was believed to be a more optimal approach (and also a more convenient one): intradermal injections of RAS peptides. Intradermal injections of RAS peptides did also show to be better at generating immune responses than peptide pulsed APCs, as in 2001 Gjersten et al reported that 58% (25 out of 48 patients in trials CTN RAS 95002 and CTN RAS 97004) of pancreatic cancer patients vaccinated with one or four RAS peptides showed a DTH reaction or a T cell response⁴⁰.

Two clinical trials – CTN RAS 95002 and CTN RAS 98010 – conducted by Norsk Hydro with TG01 in 1994–2000 were later analysed for long-term survival. In these two trials patients were treated with one of the TG01 peptides (nine patients) or with the current product TG01 (with the cocktail of seven peptides) – a total of 11 patients in this part of the trial. The CTN RAS 95002 and CTN RAS 98010 trials were initially designed to look only at safety and immune response against the mutated RAS peptides in patients, and not designed to look at the long-term survival.

But in 2011, the investigators published a long-term retrospective analysis of the outcomes for these patients. The figure below shows the Kaplan-Mayer survival curves for the 20 patients in these trials. The median survival for the total group was c28 months and four of the 20 patients (20%) survived for more than 10 years⁴¹.

10-year survival was reported to be 20% in patients treated with TG peptides, better than historical control data

Long-term survival TG01 early trials



Source: Wedén S. et al. *International Journal of Cancer* 128.5 (2011): 1120-1128. Oettle H. et al. *Jama* 297.3 (2007): 267-277. Oettle H. et al. *Jama* 310.14 (2013): 1473-1481

³⁸ Fossum B. et al. *International journal of cancer* 56.1 (1994). Gjersten MK. et al. *International Journal of Cancer* 72.5 (1997): 784-790. Gjersten MK. et al. *Journal of molecular medicine* 81.1 (2003): 43-50

³⁹ Fossum B. et al. *International journal of cancer* 56.1 (1994). Gjersten MK. et al. *British journal of cancer* 74.11 (1996): 1828

⁴⁰ Gjersten MK. et al. *International Journal of Cancer* 92.3 (2001): 441-450

⁴¹ Wedén S. et al. *International Journal of Cancer* 128.5 (2011): 1120-1128

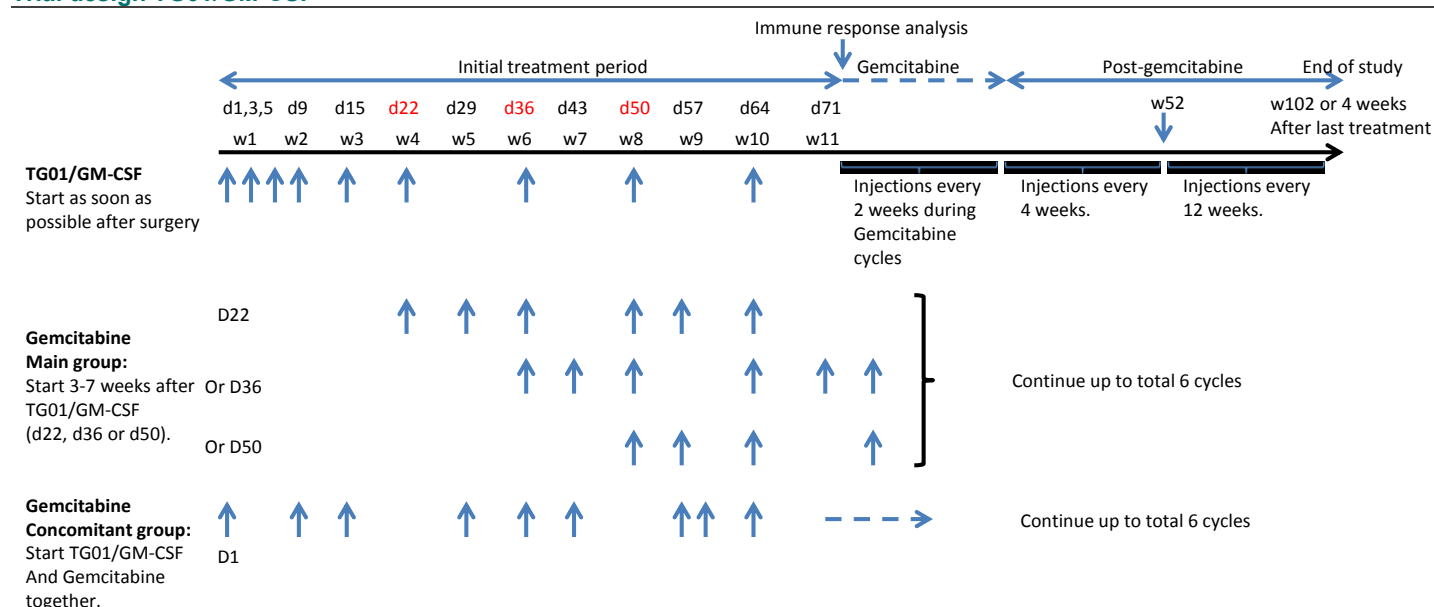
Since they were not designed as outcome trials, no comparators were included. Hence to put this data into perspective one needs to look at historical controls, and as shown above the median survival for resected pancreatic cancer patients is c20.2 months and the historical 10 year survival for resected pancreatic cancer patients is c7.7%. Although it is not scientifically correct to do such comparisons, and particularly to draw any significant conclusions, we believe the data at least indicates that the TG01 vaccine can have a clinical relevant efficacy.

Furthermore, data presented by Wedén et al highlights that 100% of the patients treated with adjuvant TG01 peptide cocktail together with the GM-CSF (11 patients) had an immune response.

Interim results of ongoing clinical trial of TG01 in resected pancreatic cancer

More recent clinical trial results of TG01 have been presented from the ongoing phase I/II trial in resected pancreatic cancer. The ongoing study evaluates the safety and immunogenicity of TG01/GM-CSF given together with Gemcitabine as adjuvant treatment. Patients were given TG01/GM-CSF within 1–8 weeks of surgery, and Gemcitabine was given either 3–7 weeks after the vaccination had started or concomitantly (see the study design in figure below).

Trial design TG01/GM-CSF



Source: Company data

The ongoing TG01 trial consists of three groups: main group, concomitant group, and modified vaccination cohort (not outlined in the figure above). The modified vaccination cohort was added to the trial after two dose-limiting toxicities (grade 4 anaphylactic reactions) observed in the first cohort (main and concomitant groups). In the modified vaccination cohort fewer injections of TG01 will be given and the number of DTH tests has been reduced (as each DTH test increases the risk of allergic reactions due to the injection of antigen peptides); we give details on the trial protocol in the next section.

The preliminary data from the study includes immune and 1-year overall survival data from 19 patients in the initial cohort and immune data from five patients so far recruited into the second cohort. The data shows that TG01 is well tolerated and elicits a RAS-specific immune response in most patients, and the overall survival reported in the interim analysis is so far encouraging.

The 1-year overall survival data was reported by Targovax in March 2016, which showed that that 14 out of 15 evaluable patients (93%) from the initial cohort were alive after 12 months (one dead due to pneumonia deemed unrelated to the treatment). Four patients were not evaluable due to a lack of consent for long-term follow up. The expected 1-year survival based on historical data of patients with resected pancreatic cancer is c75%⁴², hence we believe the 1-

Modified vaccination cohort was added after two dose-limiting toxicities

TG01 is well-tolerated and elicits a RAS-specific immune response

1-year overall survival of 93% in the initial cohort

⁴² Oettle et al JAMA 2013; 310 (14): 1473-1481 and Neoptolemos et al, JAMA 2010; 304 (10): 1073-1081.

year overall survival of patients treated with TG01 is encouraging. However, we also believe one should not draw any large conclusions from this data, as it is still based on only a few patients.

The immunological responses were assessed by DTH and in vitro T cell proliferation (see results in table below).

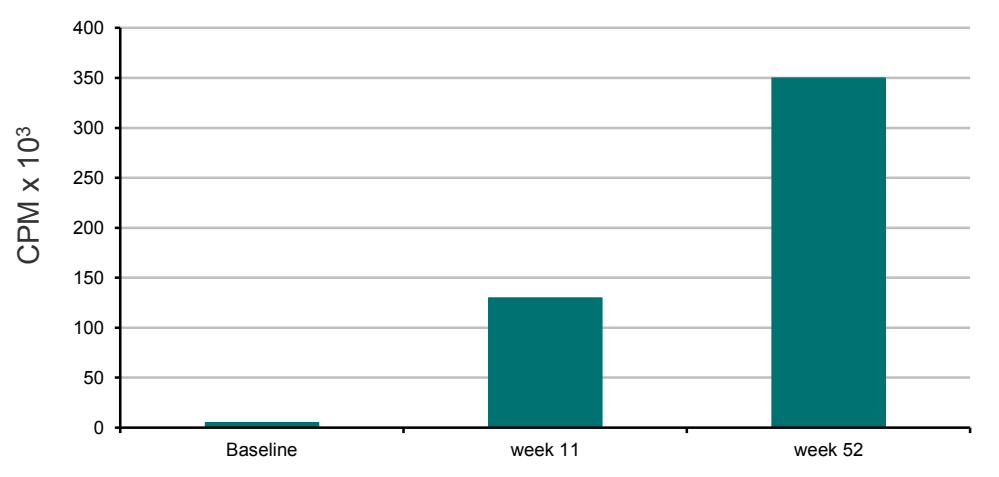
Immune response in TG01 phase I/II trial

| | Positive DTH response n=22 | Positive T-cell response n=8 |
|----------------------------|----------------------------|------------------------------|
| Total | 18/22 (82%) | 6/8 (75%) |
| Main group | 13/14 (93%) | 6/8 (75%) |
| Concomitant group | 1/3 (33%) | 0/0 |
| Modified vaccination group | 4/5 (80%) | Not reported yet |

Source: Company data

What was also shown was that the specific T cell response was maintained and induced by the booster vaccinations in the initial cohort, as shown below.

Immune response in TG01 trial



Source: Company data

The company has total clinical safety data from more than 230 cancer patients (of which c120 have received TG01 peptides), which indicates that the RAS peptides in TG01 are safe and able to elicit an immune response specifically targeted at mutated RAS epitopes. Most adverse reactions reported in the TG01 trial have been related to skin reactions and flu-like symptoms, and are mostly grade 1/2, except for the two anaphylactic reactions that led to the amendment of the trial design (addition of modified vaccination cohort). TG01 seems safe compared with other cancer therapies, which is not very surprising, we believe, as immunotherapies in general have shown to have milder side-effect profiles compared with traditional cancer treatments.

Safety data from more than 230 patients

The data presented so far by the company gives clear indications that the cancer vaccine is able to elicit an immune response mediated by both CD4+ and CD8+. However, data on tumour response and survival is so far limited, but long-term data indicates that the vaccine might have positive effects on survival for pancreatic cancer patients.

Oncos

ONCOS-102 has finished a clinical phase 1 trial (ONCOS C1) in 12 last-line 100% chemo-refractory patients with different types of solid tumours. The main objective of the study was safety and dose finding, and consisted of three cohorts with three dose levels, 3×10^{10} , 1×10^{11} , and 3×10^{11} viral particles, with three, three, and six patients in the cohorts, respectively. The patients were treated with a total of nine intratumoral administrations over six months, with an initial intense priming of the immune system with viral injections on day one, four, eight, 15, 29, and thereafter monthly. To dampen the effects of the immunosuppressive environment of the tumour, concomitant low-dose (50mg) cyclophosphamide was given daily (starting day one to day 169) to downregulate the levels of regulatory T cells. Koski et al. has previously shown that the effect of a daily dose of cyclophosphamide alone is not enough for

an anti-tumour effect; however, the concomitant use of cyclophosphamide and ONCOS-102 is significantly effective⁴³.

ONCOS-102 was shown safe in the phase I trial, no dose-limiting toxicities were recorded, and most of the adverse events were either grade 1 or 2. The most common adverse events were flu-like symptoms and pyrexia; fever was reported in all patients.⁴⁴

Clinical response

Out of 12 patients included in the trial, only 10 were evaluable as two patients passed away before the first clinical assessment. Of these 10 patients, 40% had stable disease at three months, while at six months all patients had progressed, according to RECIST 1.1 criteria.

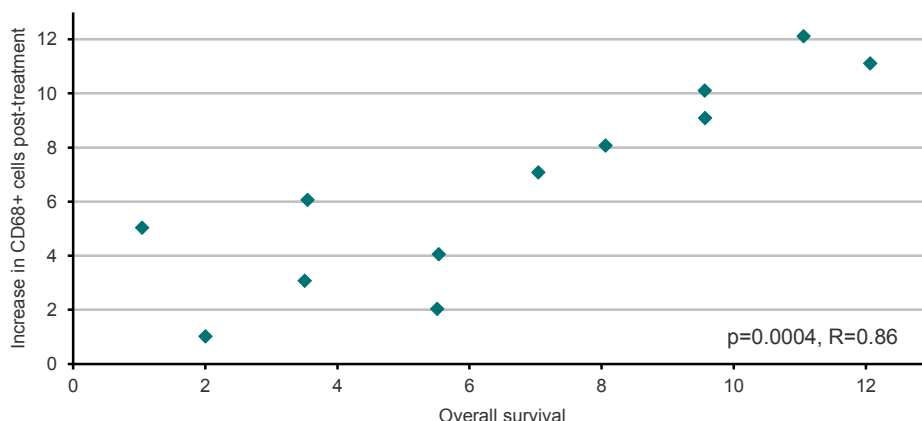
In the per protocol patient population (n=10) the median overall survival was 9.3 months, and in the intention to treat population (n=12) the median overall survival was 8.5 months. The median progression free survival was only 2.9 months, but follows the overall trend for immunotherapies, which tend to take somewhat longer to see a response, and therefore usually have a shorter progression free survival.⁴⁵

Two patients, considering survival, stood out in the trial: patient FI1-14 and FI1-19. Patient FI1-14 with malignant pleural mesothelioma had a late decrease in metabolic activity of the tumour (measured by PET scan). At six months there was a 47% decrease in the glycolytic activity of the tumour, indicating reduced tumour burden, and the patient survived 18 months from ONCOS-102 treatment initiation, and more than 33 months from diagnosis. Patient FI1-19 with epithelial ovarian carcinoma had progressed following seven different chemotherapy treatments and continued to progress during the study. However, after the ONCOS-102 study she started to respond to chemotherapy, and at 22 months after study initiation she showed stable disease, and she was still alive 35 months post study initiation (at the last follow-up). The response could indicate a long-term immune memory kick-started by the subsequent chemotherapy.

Immune response

The immune response results of the study were promising and showed significant innate and adaptive immune responses in most patients. All patients developed fever and increased levels of pro-inflammatory cytokines were induced, furthermore, infiltration of innate immune cells into tumours was detected in 11 out of 12 patients. Importantly, the level of infiltration of these immune cells significantly correlated with the OS (see figure below).

Correlation between innate immune cell infiltration and survival post-treatment



Source: Pesonen S. et al. *European Journal of Cancer* (2014): 47

The adaptive immune response was measured by the levels of infiltrating CD8+ T cells into the tumour pre- and post-injection. An adaptive immune response was also recorded in 11 out of 12 patients, and in one of the patients a CD8+ T cell increase post-treatment was found in

ONCOS-102 was shown safe in the phase I trial

At three months 40% had stable disease

One patient was still alive at the last follow-up, 35 months post study initiation

Most patients had infiltration of innate immune cells into the tumour

11/12 patients had CD8+ T cell infiltration

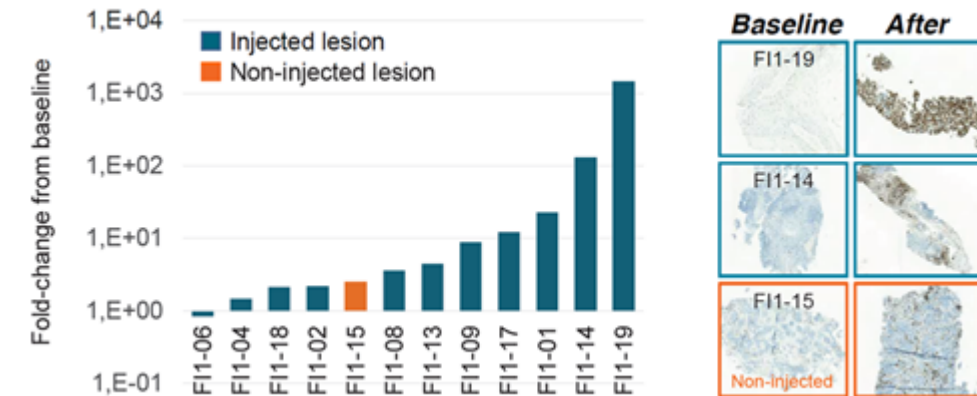
⁴³ Koski A. et al. *Molecular Therapy* 18.10 (2010): 1874-1884

⁴⁴ Ranki T. et al. *Journal for Immunotherapy of Cancer* 4.1 (2016): 1.

⁴⁵ Ranki T. et al. *Journal for Immunotherapy of Cancer* 4.1 (2016): 1.

a non-injected distant metastasis (patient FI1-15), indicating the potential of ONCOS-102 to generate a systemic immune response.

ONCOS-102 clinical efficacy

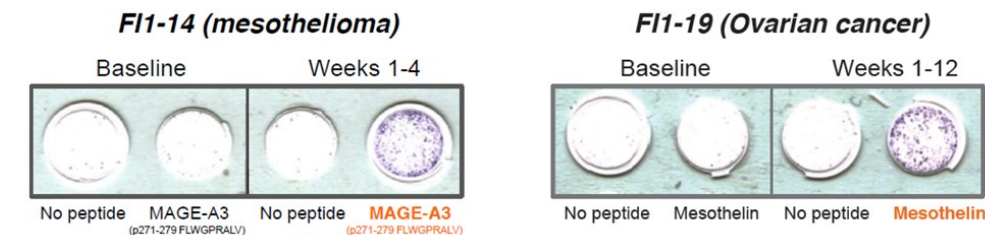


Source: Company data

Importantly, the two patients with a markedly improved survival (patients FI1-14 and FI1-19) also showed systemic induction of tumour-specific CD8+ T cells. Hence, a tumour-specific immune response induced by the vaccine seems to correlate with a clinically significant response of improved survival, which indicates that the immune system fights the cancer.

Systemic induction of tumour-specific CD8+ T cell correlated with prolonged survival

ONCOS-102 results



Source: Company data

The study also suggests that the tumour fights back, as PD-L1 levels increase in response to an increase in INF-gamma levels in several patients. This suggests the potential benefit of combining ONCOS-102 with a checkpoint inhibitor targeting either PD-1 or a third-generation checkpoint inhibitor targeting PD-L1. Furthermore, the induction of infiltrating CD8+ T cells into the tumour, making an initially T cell negative tumour positive, is also an indication that ONCOS-102 sensitises the tumour to other immunotherapies⁴⁶.

Conclusions

- The vaccine seems to be safe, with no grade 4–5 adverse events recorded. Most adverse events were either grade 1 or 2, with flu-like symptoms and pyrexia being the most common.
- 40% of the patients experienced stable disease at three months, considering the state of the patients, the result is encouraging.
 - However, patients might have been too sick for a slower anti-cancer immune response and a durable clinical response to have time to develop in most of the patients, and only three patients completed the full six months of intended treatment.
- Generation of tumour-specific CD8+ T cells seems to correlate with improved survival, and thereby the vaccine's hypothesised mechanism of action seems to hold true.

⁴⁶ Ranki T. et al. Oncoimmunology 3.10 (2014): e958937

Clinical trial programme plan

The company is planning to start several new clinical trials, on top of the TG01 trial in pancreatic cancer already running. In the table below, we summarise the trials expected to run going forward. In the following sections we go into more detail on the different trials.

Targovax will initiate five clinical trials

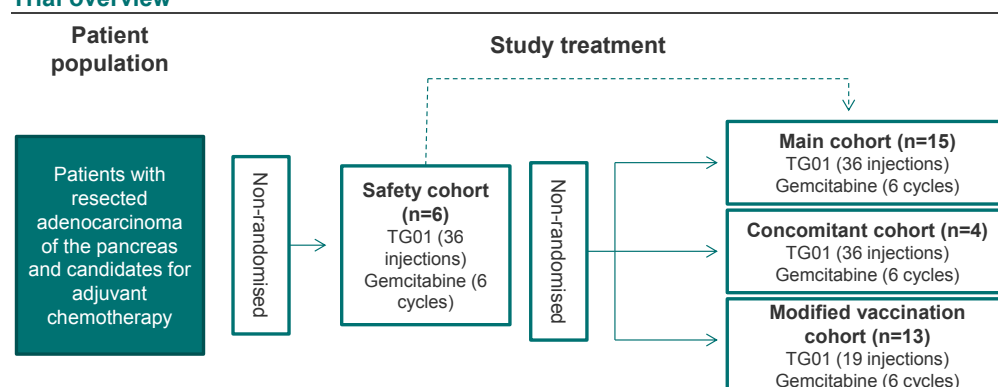
Targovax clinical trial programme plan

| | Phase | Study design | Patients | Sites | Combination |
|------------------------------------|---------------------|---|-----------------------------|---------------------|----------------------|
| TG01 in resected pancreatic cancer | I/II | Single-arm open-label | 19 (Cohort 1)+13 (Cohort 2) | 5 Europe | Gemcitabine |
| ONCOS-102 in mesothelioma | II + Ib safety lead | Randomised open-label (II), non-randomised (Ib) | 30 | 3 Spain & UK | Pemetrexed/Cisplatin |
| ONCOS-102 in melanoma | I/II | Open-label single-arm | 12 | 1 US | CPI |
| TG02 in colorectal cancer | I | Open-label single-arm | 20 | 3 Australia | Pembrolizumab |
| ONCOS-102 in ovarian cancer | I/II | Dose-escalation study with expansion cohorts | 96–102 | 10 US | CPI |
| ONCOS-102 in prostate cancer | I | Single arm | 10 | Czech Republic & UK | DC therapy |

Source: Company data

TG01 in resected pancreatic cancer

Trial overview



Source: Company data

This trial has already started and is running at five sites in Norway, the UK, and Spain. The last patient in the first cohort has been recruited and the company is in the follow-up phase of these patients. And in Q3 2015 the company started to recruit patients to the second cohort, i.e. the modified vaccination cohort.

The trial includes patients with R0 and R1 resection and that are free from metastasis at baseline. The company will (if possible) take a CT at baseline and then every six months from start of vaccination (or when it is clinically indicated) as well as at the end of the trial.

Specifics on the trial design were shown in a figure in the previous section, which outlined the treatment set-up in cohort 1 (main and concomitant group). Apart from what was shown in that figure, cohort 1 included DTH immune measurements at weeks one, two, three, four, six, eight, 10 and 52.

As shown above, the trial also includes a third group, the modified vaccination cohort (cohort 2) added to the treatment protocol due to two severe allergic reactions in cohort 1. This cohort will include 19 injections of TG01 instead of 36, and the DTH measurements will be fewer, and be done weeks one, six, eight, and week eight post chemotherapy. Furthermore, the TG01/GM-CSF vaccinations will begin prior to chemotherapy, and be stopped after six weeks, at which point chemotherapy will be initiated, and once the six cycles of gemcitabine treatment are finished vaccination with TG01/GM-CSF will be reinitiated.

So far the company has reported survival and immune data from cohort 1, as well as DTH responses eight weeks post vaccination in the first five patients recruited into the second cohort (discussed in the previous section); the results are discussed in the previous section of the report.

TG01 trial design

| | |
|-----------------------|---|
| Phase | I/II |
| Study design | Single-arm, open-label |
| Patients | 19 (Cohort 1) + 13 (Cohort 2) |
| Sites | 5 sites in Europe |
| Combination treatment | Combine with gemcitabine |
| Primary objectives | Safety, immune response to TG01, effect in combination with gemcitabine |
| Secondary endpoints | Clinical efficacy at 2 years |
| Timeline | Cohort 1: first patient in Q1 2013 – completed recruitment in Q4 2014 Cohort 2: first patient in Q3 2015 – last patient in H1 2016 |

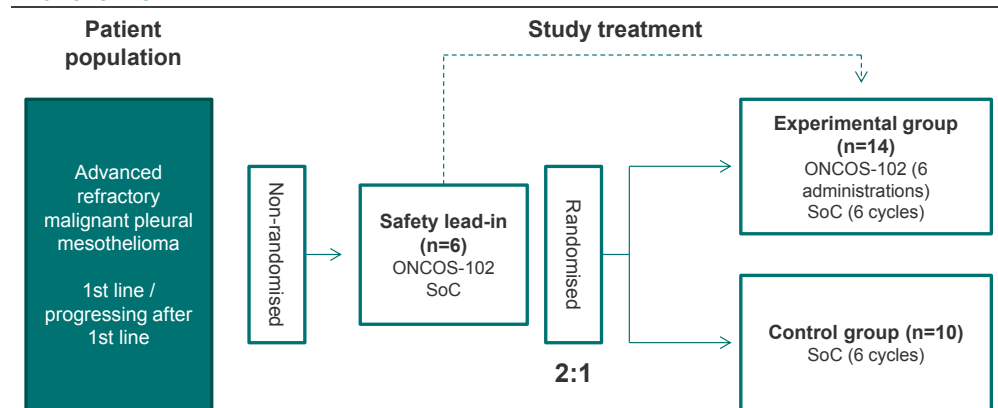
Source: Company data

We expect the company to release 24-month interim survival data from the first cohort in H1 2017, and 24-month survival data from the second cohort in H1 2018.

Upcoming data points in H1 2017 and H1 2018

ONCOS-102 in mesothelioma

Trial overview



Source: Company data

Although this is a small indication, a trial in this indication has several benefits; one of the patients with a significantly good response in the phase I trial was diagnosed with mesothelioma, the company has already received orphan drug designation in the US and Europe in this indication, and due to poor SoC the company should be able to study the vaccine in a first-line setting.

Company has received orphan drug designation

The phase Ib/II trial in mesothelioma is expected to run until H2 2018, and the first patient was dosed in June 2016. The initial part is a non-randomised phase Ib lead-in trial in six patients all with unresectable malignant pleural mesothelioma. In the lead-in phase, the patients will receive 3×10^{11} vp of ONCOS-102 on days one, four, eight, 78, and 120, as well as 500mg/m² pemetrexed and 75mg/m² cisplatin. The phase II part includes 24 randomised patients. Biopsies will be taken at baseline and day 36.

First patient dosed in June 2016

ONCOS-102 in mesothelioma – trial design

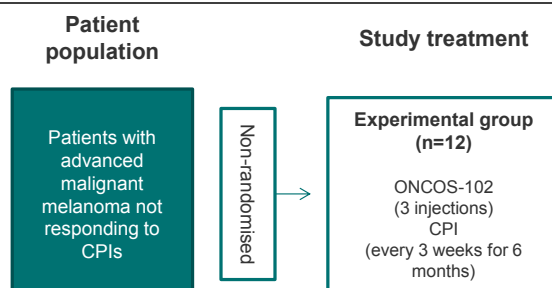
| | |
|-----------------------|--|
| Phase | II + Ib safety lead |
| Study design | Randomised open-label (II), non-randomised (Ib) |
| Patients | 30 |
| Sites | 3 sites in Spain and UK |
| Combination treatment | Pemetrexed /cisplatin |
| Primary objectives | Safety and tolerability, immune response in blood and tumour mass |
| Secondary endpoints | 12 months survival and OS |
| Timeline | First patient H2 2016e, last patient H2 2017e, interim data H1 2018e |

Source: Company data

The company expects to present immune activation data from the trial in H1 2018, and safety data from the 6 lead-in patients in H1 2017.

ONCOS-102 in melanoma patients

Trial overview



Source: Company data

This trial will be an important trial for the company as Targovax vaccines are expected to be used with checkpoint inhibitors quite extensively and the melanoma indication has become something of a checkpoint inhibitor stronghold after more or less all new CPI drugs being documented in this indication. Therefore, the immune activation data will also be of great importance in this study, which is expected to provide significant information on ONCOS-102's potential to induce a tumour immune response, and also provide indicative data on the correlation between immune response and response to the CPI treatment.

This trial is an explorative open-label study to determine anti-tumour immune activation and clinical response to ONCOS-102 given in combination with CPI. The patients to be included have previously failed to respond to the CPI alone. ONCOS-102 will be given at doses of 3×10^{11} vp on days one, four, and eight, and the CPI treatment will be for 24 weeks. Biopsies will be taken at baseline, day 22, and day 64.

Targovax has said that it will pay for the CPI treatment in the majority of cases, but for some patients their healthcare insurance will cover the CPI, and Targovax will not have to pay for the CPI.

Immune data in H1 2018e

The trial aims to provide proof-of-concept of ONCOS-102 in combination with a CPI

ONCOS-102 in melanoma – trial design

| | |
|-----------------------|--|
| Phase | I/II |
| Study design | Open-label single-arm |
| Patients | 12 |
| Sites | 1 site in the US |
| Combination treatment | CPI |
| Primary objectives | Safety and tolerability |
| Secondary endpoints | ORR, changes in immune subsets |
| Timeline | First patient H2 2016e, last patient H1 2017e, interim data H2 2017e |

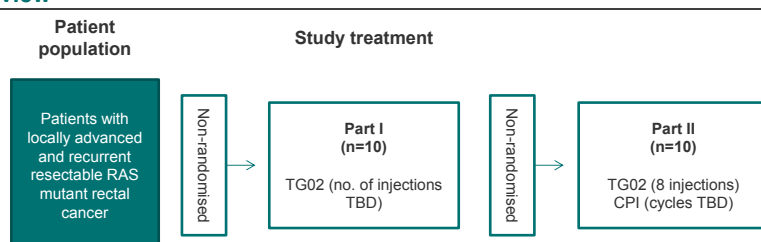
Source: Company data

The interim data expected in H2 2017 will be on the immune activation of the treatment and the company will look at intralesional infiltration of CD4+, CD8+, PD1+ and PD-L1+ cells at days 22 and 64 and compare this to the baseline.

Interim immune data in H2 2017e

TG02 in colorectal cancer

Trial overview



Source: Company data

This is also an explorative open-label study to investigate anti-tumour immune activation as well as clinical response to TG02 in patients with RAS mutant colorectal cancer with progressive disease awaiting surgery for pelvic mass resection. The patients will receive TG02 and GM-CSF on weeks one, two, three, four, and six. The company will look at DTH reactions at week four and eight as well as look at biopsies at week eight and compare it to a baseline biopsy. In the immunological evaluation, the company will look for intralesional infiltration of CD4+, CD8+, PD-1+ and PD-L1+ cells at week eight and compare it to the baseline. In the case of positive immune activation data in part I, the company will move on to part II of the study, which will study the combined safety and efficacy of TG02 and a CPI, more specifically pembrolizumab.

This is the first trial the company will do with the TG02 vaccine. Remember that this vaccine contains an additional peptide compared with TG01. The initial focus for TG02 will be in colorectal cancer, but we also expect that the company over time will look at NSCLC as a potential indication for TG02.

TG02 in colorectal cancer – trial design

| | |
|-----------------------|---|
| Phase | I |
| Study design | Open-label, single-arm |
| Patients | 20 |
| Sites | 3 Australia |
| Combination treatment | Keytruda |
| Primary objectives | Safety and tolerability, immune response in blood and tumour mass |
| Secondary endpoints | PFS, change in immune cell subsets |
| Timeline | First patient in H2 2016e, last patient in H2 2017e, interim data in H2 2017e |

Source: Company data

The interim data read-out is expected in H2 2017 will be related to immune activation primarily, while final clinical data is expected to be reported in H2 2018.

ONCOS-102 in ovarian cancer

This is an indication where the clinical trial will be conducted and coordinated by the Ludwig Cancer Research and Cancer Research Institute (CRI) in the US. Ludwig Cancer Research is an international collaborative of scientists with focus on cancer research, including both basic and translational research. The Ludwig CRI is a non-profit organisation dedicated to improving cancer care by advancing scientific efforts. Ludwig has invested nearly USD2.7bn in cancer research through the institute and the six US-based centres.

The plan is to combine Targovax's oncolytic virus ONCOS-102 with a novel CPI developed and provided by big pharma, which one is not disclosed yet, in patients with ovarian cancer, colorectal cancer and advanced peritoneal malignancies. To note, these are all indications where CPIs have only had limited success so far, and are therefore also indications where there we see room for big improvements, in regards to clinical response to novel therapies.

As we understand it, the Ludwig Cancer Research will take 80% of the costs of the trial, and the rest will be split between Targovax and the big pharma company. Therefore, we do not expect the clinical trial to have a large financial impact on Targovax at this point. In the case of a successful phase I/II clinical trial we see a possibility that Ludwig Cancer Research Institute might continue with a phase III clinical trial. And a partnering deal between Targovax and the big pharma could be possible after either a successful phase II or phase III trial. Furthermore, in the event of successful development, Ludwig Cancer Research Institute would get a payback to cover its investment; quite how this payback would be set up has not been disclosed, but we expect the deal to involve a payback of a certain amounts of the costs for the trial but not a royalty agreement. Furthermore, if the development fails, Targovax has said that it will not have to pay back Ludwig's investment in ONCOS-102.

The trial will look at immune activation in tumour biopsies

Immune data in H2 2017e

Trial co-ordinated by Ludwig Cancer Research and Cancer Research Institute

ONCOS-102 will be combined with a novel CPI

ONCOS-102 in ovarian cancer – trial design

| | |
|-----------------------|--|
| Phase | I/II |
| Study design | Dose escalation study with expansion cohorts |
| Patients | 96–102 |
| Sites | 10 in the US |
| Combination treatment | CPI |
| Primary objectives | Safety and tolerability, ORR |
| Secondary endpoints | Durable clinical benefits, OS, PFS |
| Timeline | First patient in H2 2016e, last patient H2 2018e, interim immune data H2 2017e |

Source: Company data

That said, we find it exciting that Targovax's oncolytic vaccine has been picked by the largest non-profit cancer research institute for further development, and we believe it is a good platform from which to advance ONCOS-102 in various indications. Most excitingly, we believe this partnership could increase the chance of an out-licensing deal if it is successful, but for this we will have to wait and see.

Increases chance of out-licensing deal

Again, the data read-out expected in H2 2017 will be on immune activation.

Immune data in H2 2017e

ONCOS-102 in prostate cancer

This is the second indication where Targovax has an external sponsor for the trial, in this instance Czech biotech company SOTIO that plans to test ONCOS-102 in a small trial in combination with a new dendritic cell therapy product (DCVAC/PCa) for advanced metastatic prostate cancer patients. DCVAC/PCa is in a phase III clinical trial in patients with metastatic castration-resistant prostate cancer, being studied in combination with SoC and compared with placebo.

Trial sponsored by Czech biotech SOTIO

ONCOS-102 will be given with intralesional injections for four weeks alone before the DC therapy, as well as in weeks 14 and 23. We expect the dose to be the same as in the previous trials. The patient population is advanced metastatic castrate-resistant prostate cancer patients. The DCVAC/PCa product consists of dendritic cells activated ex-vivo by allogenic prostate cancer cells. In other words, it is a product similar to Provenge.

This trial will give Targovax the potential to evaluate ONCOS-102 in prostate cancer, as ONCOS-102 will be given alone for four weeks before the DC therapy is initiated (data which Targovax owns the rights to). Furthermore, the trial should also give Targovax good potential to evaluate the efficacy of ONCOS-102 in combination with a DC-therapy, as there is efficacy data available on DCVAC/PCa monotherapy in prostate cancer.

Stand-alone data will give the company a chance to evaluate ONCOS-102 in prostate cancer

Advanced metastatic prostate cancer – trial design

| | |
|-----------------------|--|
| Phase | I |
| Study design | Single arm |
| Patients | 10 |
| Sites | Czech Republic & UK |
| Combination treatment | DC therapy |
| Primary objective | Safety and tolerability |
| Secondary endpoints | Time to disease progression, OS |
| Timeline | First patient in H2 2016, last patient in H2 2017e, interim data in H2 2017e |

Source: Company data

The first outcome data from the trial will be immune activation data in H2 2017e.

Immune data in H2 2017e

Planned clinical trials

The company has one trial running (in resected pancreatic cancer) and has said that it will, either alone or in collaboration with partners, initiate another five trials over the coming 12 months. By end-2016, the company should have six clinical trials running. This significantly adds to the expected newsflow from Targovax, and we expect news on a regular basis about the status of ongoing trials, initiation of new trials, and interim and final data from the trials running.

The majority of data points for the next two years should, we believe, focus largely on immune activation data. Clinical data (on OS, ORR, PFS etc.) will take longer to present. With this said, it is important to remember our comments earlier that for some immune therapies, it might take a long time for the clinical benefits to show through.

Potential events tied to clinical trials

As highlighted earlier, the company is planning to start several clinical trials in the coming 12–15 months and these trials should naturally (as they are early stage and not very large) lead to outcome data relatively quickly. Hence, the majority of the interesting newsflow from the company in the coming years is likely to be centred on news from the clinical trials.

In the table below, we highlight the newsflow related to the clinical development for the pipeline that we expect from the company up to the end of 2018.

Several upcoming data readouts

Clinical development potential events

| | H2 2015 | H1 2016 | H2 2016e | H1 2017e | H2 2017e | H1 2018e | H2 2018e |
|---|---------|---------|----------|----------|----------|----------|----------|
| First patient in Pancreatic cancer | X | | | | | | |
| Last patient in Pancreatic cancer | | X | | | | | |
| Interim data Pancreatic cancer cohort 1 | | X | | | | | |
| Immune data Pancreatic cancer cohort 2 | | X | | | | | |
| First patient in Mesothelioma | | | X | | | | |
| First patient in Ovarian Cancer | | | X | | | | |
| First patient in Prostate cancer | | | X | | | | |
| First patient in Colorectal cancer | | | X | | | | |
| First patient in Melanoma | | | X | | | | |
| Last patient in Melanoma | | | | X | | | |
| 2-year survival data Pancreatic cancer cohort 1 | | | | X | | | |
| Safety data Mesothelioma | | | | X | | | |
| Last patient in Colorectal cancer | | | | | X | | |
| Last patient in Mesothelioma | | | | | X | | |
| Last patient in Prostate cancer | | | | | X | | |
| Interim data Prostate cancer | | | | | X | | |
| Interim data Colorectal cancer | | | | | X | | |
| Interim data Ovarian cancer | | | | | X | | |
| Interim data Melanoma | | | | | X | | |
| 2-year survival data Pancreatic cancer cohort 2 | | | | | | X | |
| Phase I/II data Melanoma | | | | | | X | |
| Interim data Mesothelioma | | | | | | X | |
| Last patient in Ovarian Cancer | | | | | | | X |
| Phase I data Colorectal cancer | | | | | | | X |
| Phase II data Mesothelioma | | | | | | | X |
| Phase I data Prostate cancer | | | | | | | X |

Source: DNB Markets (estimates), company (historical data)

Note: Shaded cells denote interim data points, dark green cells denote clinical data points, and light green cells denote interim immune data points of infiltrating lymphocytes.

During H2 2017 we expect the company to report interim immune data from several trials (data points shaded in light green in the table above), which will be of great importance for the company, as well as the stock market, as these results should prove both ONCOS-102's and TG02's ability to immune activate, i.e. induce lymphocyte infiltration to the tumour site, and thereby possibly predicting the future success of the trials.

Interim immune data in H2 2017e from several trials

All of these interim immune data points are important in their own way:

- Positive results from the melanoma trial would, apart from predicting clinical responses, also provide proof of principle regarding sensitisation of CPI-refractory patients to CPI, as infiltration of tumour-specific lymphocytes has shown to be required for a response to CPIs.
- Positive results from the ovarian cancer trial would, in addition to what was discussed for the melanoma trial, also most likely lead to further discussions with the big pharma that is involved in the trial on future collaboration.
- The stand-alone ONCOS-102 immune data from the prostate cancer trial will be interesting, in our view, as it will give the company a possibility to assess ONCOS-102's immune activating potential in this indication, and the data will therefore also serve as decision point for whether or not to pursue further trials in prostate cancer with ONCOS-102.

- The immune data from the colorectal cancer trial will essentially serve as a go/no go for the TG-platform. If the data is positive the company will continue to develop TG01 and TG02 clinically, as well as initiate CMC activities we believe.
- In H1 2018 the company is expected to report immune data from the mesothelioma trial. In the phase I trial mesothelioma stood out as an indication where ONCOS-102 might have great potential and the company believes this is an indication where it could file for regulatory approval; hence the immune data will be of great value.

Overall, we believe that the long list of events related to the clinical development will be supportive for the share price of the company.

Pipeline summary

In this section we highlight the main components of the company's pipeline and focus areas. The most advanced project has reached phase II – it is the TG01 vaccine from the old Targovax portfolio that is in phase II development for resected pancreatic cancer. The second most advanced project is ONCOS-102, which is scheduled to enter phase II development in 2016, initially for the melanoma indication and for the smaller mesothelioma indication.

Pipeline summary

| | Indication | Programme | Discovery | Pre-clinical | Phase I | Phase II | Phase III |
|-------------|----------------------|-----------|-----------|--------------|---------|----------|-----------|
| Development | Pancreatic cancer* | TG01 | | | | | |
| | Melanoma | ONCOS-102 | | | | | |
| | Mesothelioma* | ONCOS-102 | | | | | |
| | Colorectal and NSCLC | TG02 | | | | | |
| Exploratory | Ovarian cancer* | ONCOS-102 | | | | | |
| | Prostate cancer | ONCOS-102 | | | | | |
| | Melanoma | TG03 | | | | | |
| Discovery | Discovery | ONCOS-402 | | | | | |
| | | ONCOS-802 | | | | | |
| | | ONCOS-902 | | | | | |

Source: Company data

Note: * denotes orphan drug indications

In our discussions with the company we got the impression that it takes approximately one year from starting to plan a clinical trial until patient recruitment begins (due to all the administrative work and co-ordination of centres etc.). Hence even though phase I trials for ONCOS-102 were completed some time ago, phase II trials are only about to begin, and patient recruitment is scheduled to be initiated during H2 2016.

Patient recruitment to start in H2 2016 for several trials

The most advanced discovery phase project is ONCOS-402, which is highly similar to ONCOS-102, except for the transgene the oncolytic virus contains. ONCOS-402 contains CD40L, instead of GM-CSF. CD40L is as GM-CSF, an immune stimulant, although it activates the immune system slightly differently, and is therefore complementary to ONCOS-102. At this stage the company is about to initiate animal testing of ONCOS-402.

One important observation about the pipeline is that the potential indications are broad and the company has multiple shots on goal with: 1) several indications; and 2) two technologies in the pipeline (peptide-based vaccine from Targovax, oncolytic virus vaccine from Oncos). From our point of view, this should lower the overall risk in the development pipeline.

Multiple shots on goal

Disease focus areas

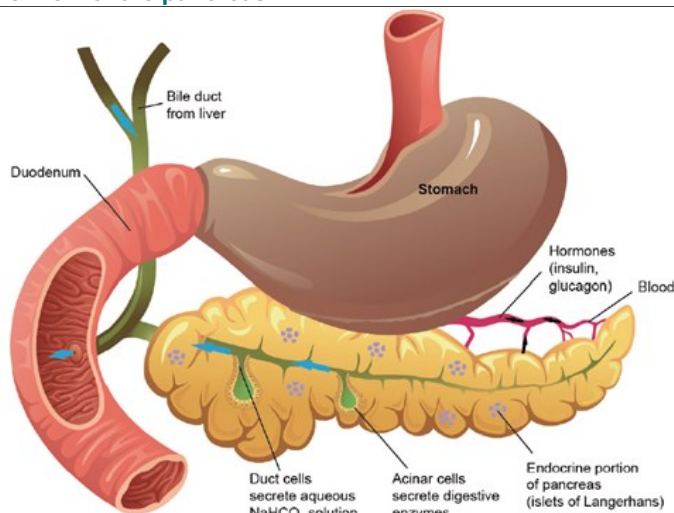
When we look at the pipeline for Targovax (combining the old Targovax pipeline and the Oncos pipeline) we see that the projects are focusing on complementary indications. In all cases the company is focusing on solid tumours, and in the case of the Oncos portfolio only solid tumours that are accessible for injections with the oncolytic virus. Below, we highlight the most important indications and summarise the incidence and prevalence for the various diseases as well as current treatment alternatives and outlook for patients.

Company focuses on treatments for solid tumours

Pancreatic cancer

Pancreatic cancer is a major focus point for Targovax. It encompasses several types of cancers, all arising from the cells of the pancreas. Pancreatic cancer can arise from the endocrine part of the pancreas (which releases hormones directly into the blood stream) or the exocrine part (which releases hormones into ducts). Up to 95%⁴⁷ of pancreatic cancers arise from the exocrine part, including pancreatic adenocarcinoma, the most common form of pancreatic cancer, diagnosed in 85%⁴⁸ of all cases.

Anatomical overview of the pancreas



Source: <http://www.thehsn.org/article/viewFile/2606/3490/10313>

In 2012 c338,000⁴⁹ people were diagnosed with pancreatic cancer, and during the same year around c330,000⁵⁰ people died from it worldwide. In the US it is estimated that there will be c53,000 new cases and c42,000 deaths from pancreatic cancer in 2016⁵¹.

Even though developments have been made in the detection and management of pancreatic cancer, the disease still has an extremely poor prognosis, and the five-year survival rate is only c4–6%⁵²; furthermore, the incidence keeps rising. The only way to cure pancreatic cancer today is by surgical resection, but c80–85% of patients diagnosed with pancreatic cancer present with advanced unresectable disease⁵³. Furthermore, surgical resection with a curative intent increases the five-year survival rate to only c10–15%.

Poor prognosis and incidence keeps rising

Risk factors

Several risk factors for pancreatic cancer have been identified. Pancreatic cancer is to a large extent a disease of the elderly and the disease rarely manifests itself before the age of 40 years. The median age at diagnosis is around 73 years. Apart from age, cigarette smoking is an important risk factor and this is also the leading preventable cause for pancreatic cancer. About c20–25% of all pancreatic cancers are due to tobacco smoking. There are also several other lifestyle related risk factors that have been connected to pancreatic cancer, including

A disease of the elderly

⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0024281/>

⁴⁸ Ryan DP, et al. New England Journal of Medicine 371.11 (2014): 1039-1049

⁴⁹ <http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/pancreatic-cancer-statistics>

⁵⁰ www.cancerresearchuk.org

⁵¹ <http://seer.cancer.gov/>

⁵² Vincent, Audrey, et al. The Lancet 378.9791 (2011): 607-620

⁵³ Vincent, Audrey, et al. The Lancet 378.9791 (2011): 607-620

diets high in meat and fat as well as obesity. There also seems to be a genetic component to the disease, as a person with a first degree relative with pancreatic cancer has around a 9x increased risk of getting the disease compared to the general population. If a person has three or more first-degree relatives with the disease, the risk rises c32-fold.

Risk factors and inherited syndromes associated with pancreatic cancer

| | | Approximate risk |
|--|--|------------------|
| Risk factor (x) | | |
| Smoking | | 2–3 |
| Long-standing diabetes mellitus | | 2 |
| Nonhereditary and chronic pancreatitis | | 2–6 |
| Obesity, inactivity, or both | | 2 |
| Non-O blood group | | 1–2 |
| Genetic syndromes and associated gene or genes (%) | | |
| Hereditary pancreatitis (PRSS1, SPINK1) | | 50 |
| Familial atypical multiple mole and melanoma syndrome (p16) | | 10–20 |
| Hereditary breast and ovarian cancer syndromes (BRCA1, BRCA2, PALB2) | | 1–2 |
| Peutz-Jeghers syndrome (STK11 [LKB1]) | | 30–40 |
| Hereditary nonpolyposis colon cancer (Lynch syndrome) (MLH1, MSH2, MSH6) | | 4 |
| Ataxia-telangiectasia (ATM) | | Unknown |
| Li-Fraumeni syndrome (P53) | | Unknown |

Source: Ryan DP. et al. *New England Journal of Medicine* 371.11 (2014): 1039-1049

Early-stage pancreatic cancer is usually symptomless, and symptoms appear first when the cancer has invaded surrounding tissue or metastasised to distant organs, meaning that patients showing symptoms most likely already have advanced and unresectable disease, and as the cancer is most often detected late it also has a poor prognosis. Symptoms for pancreatic cancers include: abdominal and mid-back pain, obstructive jaundice, and weight loss.

Initial diagnosis and detection of pancreatic cancer is best done through CT scan; CT is also used for staging the disease.

Disease development

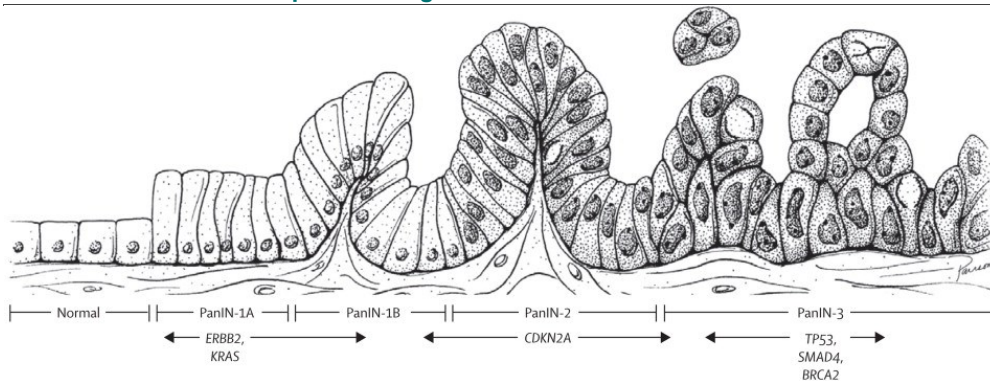
Pancreatic adenocarcinoma arises from the ductal epithelium of the pancreas. A developmental model of pancreatic cancer, in which the cancer arises from precancerous epithelial lesions, termed pancreatic intraepithelial neoplasia (PanIN), is well characterised. Intraepithelial neoplasia denotes a morphologically abnormal epithelium, regarding e.g. size, shape, and nuclear abnormalities of the cell. The neoplastic lesions are classified into three grades: PanIN1 mild cytological and architectural atypia, PanIN2 mild to moderate cytological and architectural atypia, and PanIN3 severe cytological and architectural atypia. The PanINs are normally asymptomatic.

Arises from precancerous epithelial lesions

The progression from PanIN to invasive cancer is a stepwise progress that includes progression from mild neoplasia to severe neoplasia (PanIN1-3), which is accompanied by the accumulation of mutations in oncogenes and tumour-suppressor genes. The most common genetic alterations in invasive pancreatic cancer are mutational activation of KRAS oncogene, and inactivation of tumour-suppressor genes CDKN2A, TP53, SMAD4, and BRCA2, chromosomal losses, and telomere shortening. Mutations in the KRAS gene and telomere shortening are the earliest recorded events in the development of pancreatic adenocarcinoma, and can occur already in stages of PanIN1, while other mutational events occur in later neoplastic stages.

KRAS is the most commonly mutated gene

Pancreatic cancer development and gene involvement



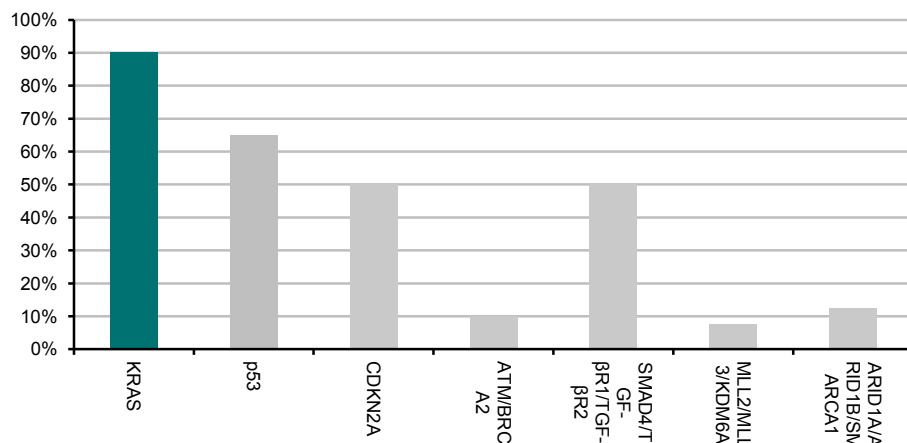
Source: Vincent, Audrey, et al. *The Lancet* 378.9791 (2011): 607-620

Pancreatic cancer can, however, also arise from intraductal papillary mucinous neoplasms (IPMN) or mucinous cystic neoplasms (MCN). IPMNs develop from the epithelium of pancreatic ducts and are a heterogeneous group of precancerous lesions that have increased in incidence lately. The IPMNs show a great variety of genetic alterations, some are similar to the PanINs, as KRAS, CDKN2A, SMAD4, and TP53 mutations. Other genes mutated in IPMNs are PIK3CA and BRAF. Mutations in exon 1 of KRAS have been reported in 31–86% of IPMNs⁵⁴.

MCNs are the most frequent precursor lesions of the pancreas. The exact frequency of lesions is unknown, but it has been reported that MCNs are found in c23% of patients with resected cystic tumours of the pancreas. MCN carries with it only a low risk of developing into malignant tumours and the prevalence of invasive cancer is c13%. The genetic alterations underlying MCNs are not clear, but mutations in KRAS have been detected in low-grade MCNs dysplasia.

In the chart below we show some of the mutations commonly seen in pancreatic cancer patients. Green denotes mutation of an oncogene and grey denotes mutation of tumour suppressor genes.

Common mutations seen in pancreatic cancer patients



Source: Ryan DP, et al. *New England Journal of Medicine* 371.11 (2014): 1039-1049

Disease management

“Pancreatic cancer is a heterogeneous disease at the molecular, pathological, and clinical level. A patient’s response to treatment and outcome depends on many factors, including the biology of their cancer, their performance status, and their pattern of disease progression”⁵⁵. This citation captures the difficulties with managing pancreatic cancer, even though several options are available for treating patients with confirmed pancreatic cancer. However, none of

Difficult to manage the disease

⁵⁴ Schönleben F. et al. *Cancer letters* 249.2 (2007): 242-248

⁵⁵ Vincent, Audrey, et al. *The Lancet* 378.9791 (2011): 607-620

the treatment options can be considered good and the long-term survival for this patient group is dismal, with a 5-year survival rate of only c4–6%.

- **Surgery.** Only c15% of all pancreatic cancers are resectable (i.e. possible to remove surgically), and the major contraindications for pancreatic surgery are liver, peritoneal, or distant lymph node metastases, or if the patient is medically unfit for larger surgery. The risk of recurrence is large after surgery, >70% of patients develop systemic and >20% develop local recurrence.
- **Adjuvant chemotherapy treatment** is recommended for patients undergoing surgery with a curative intent. The standard adjuvant chemotherapy treatment is single-agent gemcitabine. Radiation therapy in addition to chemotherapy has been explored in several trials, but this combination is controversial and most clinical trials have failed to show increased survival. Delayed radiotherapy, to prevent metastatic disease, is being used in clinics, and its efficacy is being investigated in an international phase III trial⁵⁶. Patients most likely to benefit from adjuvant therapy are those who have undergone R0 resection. R0 resection denotes that the pathologist cannot detect any cancer in the resection margin after surgery. R1 resection means the cancer is visible in the resection margin under microscope, but not grossly visible, while a R2 resection has grossly visible cancer in the resection margin. Median survival for patients who have undergone R1 resection is 8–18 months, versus patients who have undergone R0 resection that have a median survival of 20–25 months⁵⁷.
- **Neoadjuvant treatment** is therapy given before surgery. The efficacy of it for pancreatic cancer has not been proven in a randomised controlled trial, and the best treatment option for neoadjuvant therapy is not yet known. However, the therapy can generate partial responses and downstage (decrease the tumour mass, making a surgical approach more manageable) borderline resectable disease and it is therefore also used in this setting.
- **Management of advanced disease.** Patients with advanced pancreatic cancer have a poor prognosis, and median survival of patients with metastatic disease is only 3–6 months. However, survival is markedly better for patients with locally advanced disease, with a median survival of 9–15 months. Standard treatment for patients with advanced pancreatic cancer is gemcitabine; however, patients must have an adequate performance status. Gemcitabine can induce partial responses in some cases and alleviate symptoms.
- **Treatment with chemoradiotherapy** downstages locally advanced pancreatic cancer to resectable in c30% of the cases, and for these patients the survival is equal to patients with initial resectable disease.

Most patients relapse after surgery

Standard treatment is single-agent gemcitabine

Size of patient pool

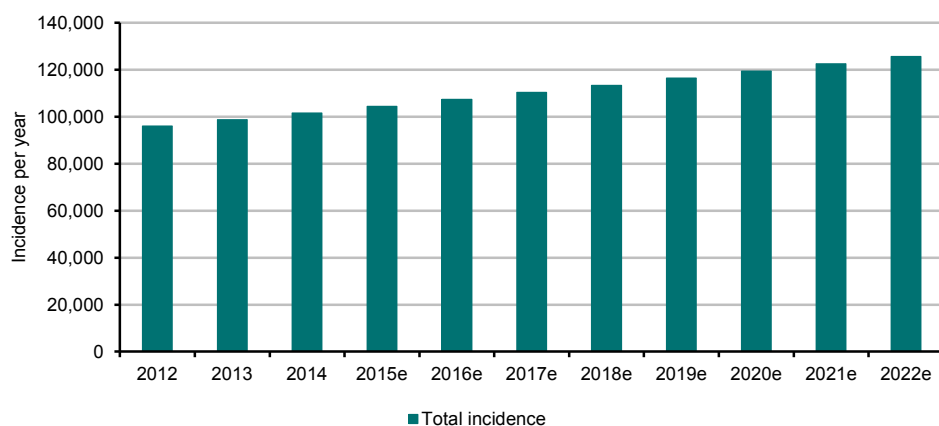
When looking at the incidence and prevalence for pancreatic cancer, the numbers are more or less the same. This is mainly due to the poor prognosis of the disease and the fact that for the majority of patients, survival time is usually less than a year. The figure below shows the incidence of pancreatic cancer in the US and the five largest EU markets. As shown, incidence is expected to grow over time, at c4% p.a. for the coming years. In total just in excess of 100,000 new patients are expected to be diagnosed in these six markets in 2015.

Incidence expected to grow c4% p.a.

⁵⁶ NCT01013649

⁵⁷ Vincent, Audrey, et al. The Lancet 378.9791 (2011): 607-620

Incidence of pancreatic cancer in the US and EU5

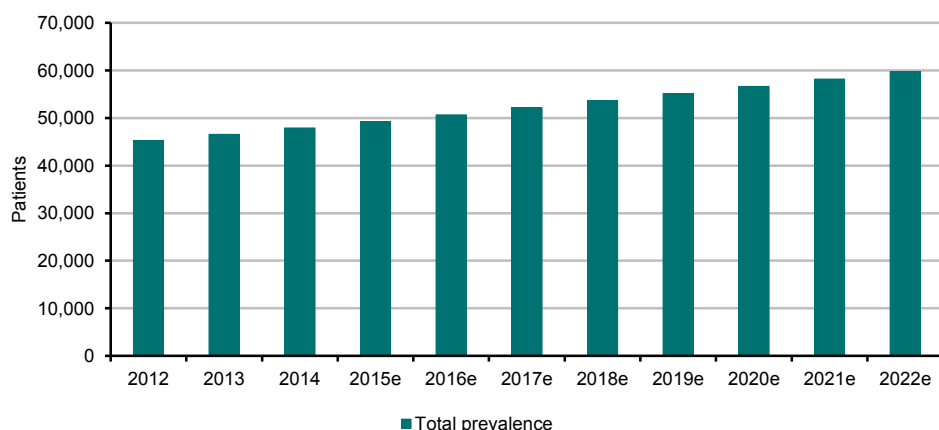


Source: Global Data

Looking at prevalence, one immediately sees the poor prognosis these patients have. As shown below, prevalence is around half of annual incidence (again this is due to the high mortality of the cancer – with an expected survival of on average around six months). All in all, in these six markets, there are some 45,000 patients in prevalence expected for 2015.

Prevalence is around half of the annual incidence due to poor prognosis

Prevalence of pancreatic cancer in the US and EU5

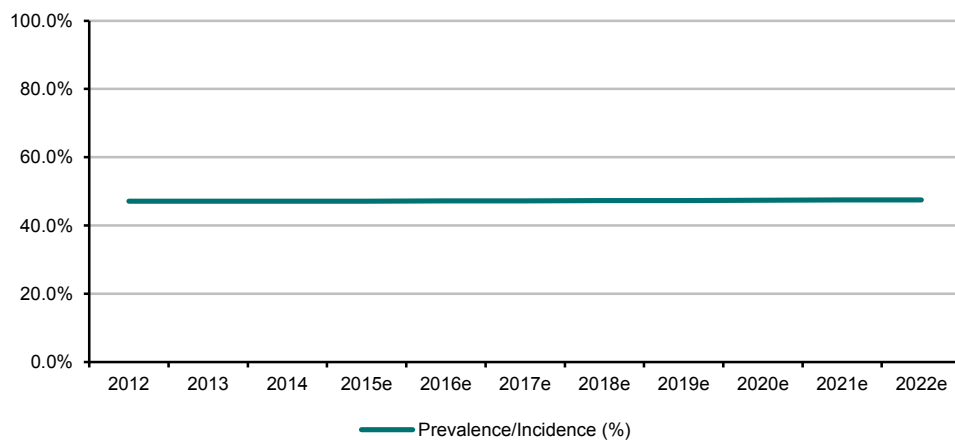


Source: Global Data

Prevalence as a percentage of annual incidence is c47% and, unfortunately over the coming years, the survival for this patient group is not expected to improve significantly. At the end of the forecast period, prevalence as a percentage of incidence is expected to be c47.5% versus c47.1% in 2012, only a marginal improvement.

Survival is not expected to improve significantly during the forecast period

Prevalence as a percentage of annual incidence in pancreatic cancer



Source: Global Data

This tells us that there is significant market potential for new drugs that improve the clinical outcome for this patient group. However, keep in mind that in Targovax's clinical trials for TG01, it is addressing a subset of these patients, namely the c15% of pancreatic cancer patients that can have the tumour surgically removed.

TG01 addresses c15% of the pancreatic cancer population

Melanoma

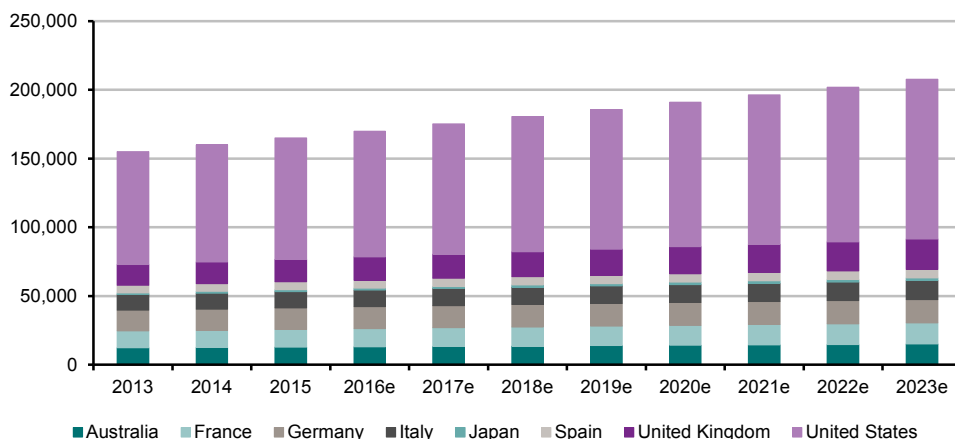
Skin cancer is one of the most common forms of cancer in the world; however, the vast majority of skin cancers are relatively benign. WHO estimates that 2m–3m cases of skin cancer occur globally each year, but only a fraction are melanoma (the more dangerous form of skin cancer). In 2012 c230,000⁵⁸ cases of melanoma were diagnosed worldwide, but the incidence is expected to increase by c3–7% p.a. in fair-skinned Caucasian populations⁵⁹.

Only a fraction of skin cancers are melanomas

The figure below shows the forecast incidence of melanoma in eight major markets until 2023. Melanoma incidence is on the rise, and the main risk factor is exposure to ultraviolet (UV) light. GlobalData predicts that the number of cases will have a CAGR 2013–2023e of c3% in these markets, although there is a great variation between countries, ranging from a growth rate of 1.2% in Germany to 3.5% in the UK.

Melanoma incidence is expected by GlobalData to have a 2013–2023 CAGR of 3% in the eight major markets

Melanoma incidence in eight major markets



Source: Global Data

What makes melanoma dangerous is that when the disease reaches a certain stage, it has a high tendency to cause metastatic tumours, at which point current treatment options are limited and the prognosis for patients is poor. Metastatic melanoma is to a large degree

At a certain stage there is a high risk for metastases

⁵⁸ GLOBOCAN 2012, IARC -8.4.2016

⁵⁹ Lens MB. and Dawes M. The British Journal of Dermatology. 2004;150(2)

refractory to existing therapies, and for patients diagnosed with melanoma that have metastasised to distant organs (stage IV (M1C)) the median survival is only about six months and the 5-year survival rate is <5%.

Survival by stage at diagnosis

| | N | Median OS in months | 1-year survival rate | 2-year survival rate | 3-year survival rate |
|---------------------|------|---------------------|----------------------|----------------------|----------------------|
| Stage IIIB and IIIC | 74 | 24.3 | 67.2% | 42.9% | 32.1% |
| Stage IV (M1A) | 212 | 22.3 | 64.5% | 40.4% | 26.4% |
| Stage IV (M1B) | 292 | 11.2 | 43.8% | 23.4% | 13.8% |
| Stage IV (M1C) | 1104 | 5.1 | 22.3% | 8.9% | 4.7% |

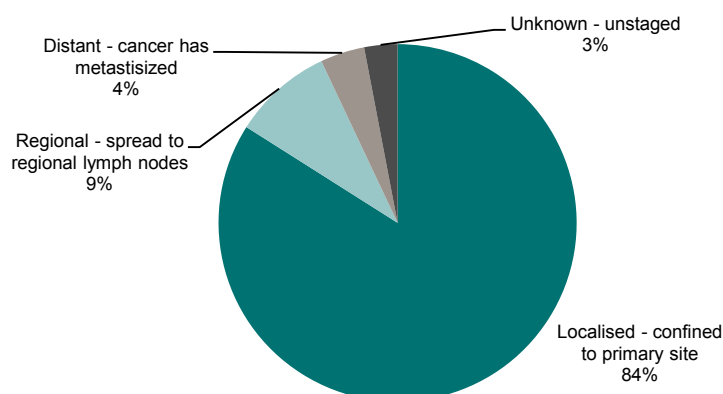
Source: Song et al. CMRO Vol. 31, Number 5, May 2015

There is limited information available in clinical literature as to what stages the patients are at the time of diagnosis, but there are some statistics from the National Cancer Institute that indicate that the vast majority of melanoma cases are localised at the initial diagnosis.

As shown below, c84% of patients have localised disease at the time of diagnosis, while c4% already have metastasised disease at diagnosis.

Most patients have localised disease at the time of diagnosis

Staging of disease at diagnosis

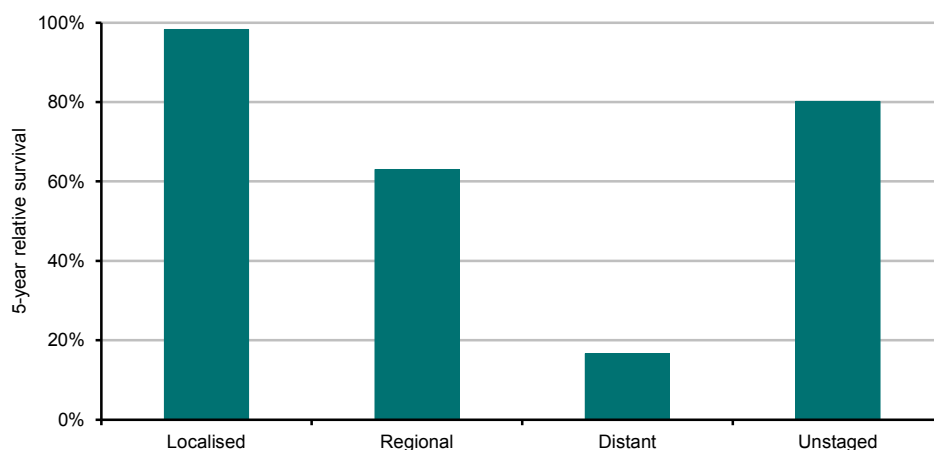


Source: NCI/SEER cancer statistics

The stage of disease is very important for the outcome of the patient as shown in the table above (stage IV is what is called Distant disease). Based on NCI/SEER statistics and their split of the stages of melanoma, the estimated survival for the different stages is shown below. Note that the data shown below are relative survival i.e. in comparison to a healthy age matched population as compared with the data in the table above that refers to absolute survival.

Stage of disease is highly correlated with the outcome

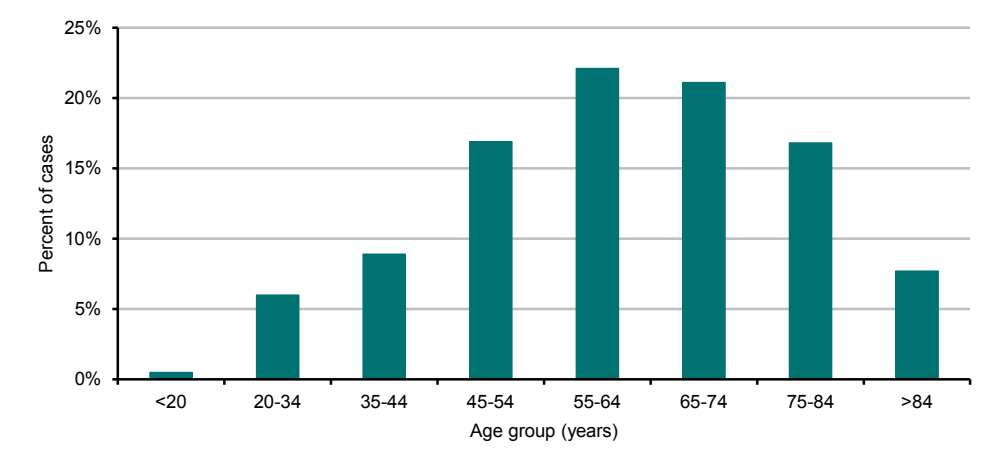
5-year relative survival based on stage at diagnosis



Source: NCI/SEER Cancer statistics

Melanoma, just as with the majority of cancer diseases, is closely correlated with age and the median age at diagnosis is 63 years.

Age at diagnosis of melanoma



Source: NCI/SEER Cancer statistics

Metastatic melanoma

When the tumour has become metastatic one usually finds a considerable number of different mutations and alterations in the tumour cells genomic profile. In the table below, we have listed known changes in the genomic set-up and their frequency.

High number of mutations have been identified in melanoma

Selected genetic alterations in malignant melanoma

| Gene type | Gene | Alteration frequency/type(s) in melanoma (%) |
|--------------------|-----------|--|
| Oncogenes | BRAF | 50–70% mutated |
| | NRAS | 15–30% mutated |
| | ATK3 | Overexpressed |
| Tumour suppressors | CDKN2A | 30–70% deleted, mutated or silenced |
| | PTEN | 5–20% deleted or silenced |
| | APAF-1 | 40% silenced |
| | p53 | 10% lost or mutated |
| Others | Cyclin D1 | 6–44% amplified |
| | MITF | 10–16% amplified |

Source: Gray-Schopfer V. et al. Nature 445.7130 (2007): 851-857

Current treatment options

As for other types of cancer, the treatment for melanoma depends on stage, location of the melanoma, and the health status of the patient.

Treatment depends on stage

- **Stage I–II** – melanomas have not spread to the lymph nodes and are mainly treated by surgery. In some cases, adjuvant interferon therapy is recommended by the physician, or radiation therapy.
- **Stage III** – melanomas have spread to the lymph nodes, so treatment normally requires a wide excision of the primary tumour and lymph node dissection. To decrease the chance of the tumour coming back, adjuvant therapy is most often recommended, which can include interferon therapy, chemotherapy, immunotherapy, or radiation therapy. Also participation in clinical trials can be an option, if current treatments do not offer a cure.
- **Stage IV** – melanomas in this stage are very hard to cure as they have already developed distant metastases. Surgery or radiation therapy is used to alleviate symptoms caused by the tumours or enlarged lymph nodes. Other treatments, such as immunotherapy, targeted

therapy, or chemotherapy, can be used to alleviate symptoms caused by tumours that are not possible to remove by surgery⁶⁰.

In recent years the treatment of advanced melanoma has changed dramatically thanks to the introduction of immune checkpoint inhibitors and targeted therapies that have shown to be more effective than chemotherapy. Chemotherapy usually resulted in responses for 10–15% of these patients, and durable remission occurred rarely. But with targeted treatments, more specifically the small molecule inhibitors targeted at the BRAFV600 and MEK mutations have been effective in the 40–50% of patients that harbour BRAF mutations. BRAF and MEK inhibitors have shown to generate objective responses and prolong survival markedly, compared with conventional chemotherapeutics. Checkpoint inhibitors have also shown to prolong survival and produce durable responses in a significant amount of patients (discussed earlier).⁶¹

Size of patient pool

Melanoma treatments have developed over the past few years, as checkpoint inhibitors have entered the market and been to a large extent documented in this indication. When we look at this market, we estimate c230,000 patients globally that make up the potential market for Targovax. In our model we calculate with annual growth in the number of patients of c3% (in line with the GlobalData) epidemiology estimates.

We believe the company over time might reach penetration of c10% of the pool of patients. In this case we believe the company (together with a partner) could launch the product in 2021.

On the other hand, as we show above, the vast majority of patients are diagnosed at a relatively early stage of the disease and as a result, we believe the patient population that will be eligible for treatment with ONCOS-102 will be the c16% of newly diagnosed patients with advanced disease, in total representing a patient pool of some c40,000 patients per year in the developed markets.

Mesothelioma – an orphan indication

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer caused by neoplastic transformation of mesothelial cells (cells that line the body's serous cavities and the internal organs). In the majority (c90%) of patients with MPM, the tumour appears in the pleural cavity, i.e. between the lungs and the pleura (the protective lining that covers the lungs and the internal organs on the outside).

In general, malignant pleural mesothelioma has a dismal prognosis and was seen as more or less refractory to most local treatments. However, in recent decades, the combination of different chemotherapies has shown it can increase the median survival by a few months and those treatment regimens were gradually introduced in 2003–2006. The treatment consists of a combination of pemetrexed and cisplatin.

Historical, MPM has mostly been associated with exposure to asbestos. It is noteworthy that, regarding MPM's causal relation to asbestos and the fact that asbestos has been banned for some time now, the latency period (time from exposure to development of the disease) can be c40+ years. Hence, a large proportion of patients (especially in the western world) that present with MPM today were exposed to asbestos a long time ago. Despite asbestos having been banned in Europe for some time, the incidence of MPM there has most likely not peaked yet. According to some researchers, the peak in incidence in Europe is expected to come around 2020⁶². However, globally, the MPM population is still expected to rise since asbestos was banned significantly later in many emerging markets (and the full long-term effects in these markets have not yet been seen). This means that the MPM population is ageing rapidly and as it does so, survival rates are declining (as a result of changed demographics and because an elderly population might be too unfit to be treated with the chemotherapy combination).

Treatment landscape for advanced melanoma has changed dramatically since inception of CPIs

c230,000 patients globally

16% of the patient population will be eligible for ONCOS-102

Highly aggressive cancer

Combinatorial chemotherapy treatment has improved survival by a few months

Asbestos exposure is a clear risk factor

⁶⁰ Cancer.org

⁶¹ Johnson DB. and Sosman JA. (2015) JAMA Oncology

⁶² Robinson BWS. and Richard AL. New England Journal of Medicine 353.15 (2005): 1591-1603

Incidence

MPM is a rare disease with a very low incidence. It has been estimated that the new number of patients affected each year is c3,000 in the US. Looking at the incidence per million inhabitants, there is a large deviation between countries – from around seven cases per million people in Japan up to c40 cases per million people in Australia⁶³. In Europe the incidence is around 20 cases per million inhabitants. Overall, we estimate that the global average incidence is around 20 cases per million inhabitants.

c3,000 patients diagnosed yearly in the US

Current treatment

There are several alternative treatments for patients with MPM, although none with good long-term outcomes:

- **Surgery** has unfortunately proven to have a limited success rate. In some quite large clinical trials, the median survival from surgery was only 11.7 months. In cases where the surgery is combined with radiation therapy and/or chemotherapy the overall outcome is almost as dismal as for surgery stand-alone.
- **Radiation** can sometimes be what is called radical treatment, radiation of the hemithorax (more or less the total lung and side of the patient). However, this type of treatment is also associated with significant and severe side effects as the radiation will hit critical organs like the heart, lung, liver, bone marrow etc. The treatment has not been documented to have any curative effects. It can however, from time to time, be used as palliative treatment.
- **Chemotherapy** should be used as soon as possible after diagnosis, even if the patient is a candidate for surgery. The most common treatment regimen is a combination of pemetrexed and some platinum-based compound such as cisplatin. Note that many patients are relatively old at diagnosis and might not be fit enough for chemotherapy. After the documentation showed that a combination of pemetrexed and cisplatin prolonged the median survival for these patients, this treatment has become the standard of care for MPM patients – especially for unresectable patients.

Limited success recorded

Associated with significant side effects

Chemotherapy not suitable for old and frail patients

Clinical outcomes for current treatment

There are several large data registers where real world patients are recorded, among others in the Netherlands, Belgium, and England. In one report⁶⁴, the authors looked at the characteristics, treatments and outcomes for all patients in these markets from 2006–2007 onwards (to ensure the treatment included the pemetrexed plus cisplatin treatment regimen). In the table below we show the patient characteristics in these three registers – the majority of patients are relatively old and there is a clear dominance of male patients (not surprising given the environmental exposure to asbestos in the work place, sometimes 40 years ago).

Patient and treatment characteristics in the registers

| | | Belgium | | Netherlands | | England | |
|-------------|-------------------|---------|----|-------------|----|---------|----|
| | | n | % | n | % | n | % |
| Age (years) | 18–59 | 126 | 14 | 281 | 12 | 520 | 9 |
| | 60–69 | 247 | 27 | 719 | 31 | 1,784 | 31 |
| | 70–79 | 368 | 41 | 937 | 41 | 2,306 | 40 |
| | 80+ | 159 | 18 | 369 | 16 | 1,198 | 21 |
| Gender | Men | 741 | 82 | 2,023 | 88 | 4,788 | 82 |
| | Women | 159 | 18 | 283 | 12 | 1,020 | 18 |
| Treatment | Any chemotherapy | 536 | | 948 | 41 | 2,166 | 37 |
| | Any radiotherapy | 370 | | 234 | 10 | 1,931 | 33 |
| | Any surgery | 147 | | 67 | 3 | 451 | 8 |
| | Surgery and chemo | 98 | | 44 | 2 | 114 | 2 |

Source: Damhuis et al. Lung Cancer 89 (2015) 212-217

⁶³ Lin RT. et al. Lancet. 2007;369:844-9

⁶⁴ Damhuis et al. Lung Cancer 89 (2015) 212-217

As mentioned above, the older the patients are the less likely are they to be treated with chemotherapy due to overall poor health. This is seen quite clearly below, where the authors looked at the proportion that received chemotherapy and correlated it to the age of the patients in the three countries. If we look at the patients aged 70+ years, fewer than 30% receive chemotherapy, most likely due to their poor overall status.

Chemotherapy treatment falls with increasing age (proportion (%) treated by chemotherapy)

| | | Belgium (n=900) | Netherlands (n=2,306) | England (n=5,808) |
|-------------|-------|-----------------|-----------------------|-------------------|
| Age (years) | 18–59 | 87 | 69 | 64 |
| | 60–69 | 79 | 54 | 54 |
| | 70–79 | 55 | 36 | 34 |
| | 80+ | 18 | 7 | 8 |

Source: Damhuis et al. Lung Cancer 89 (2015) 212-217

In the table below, we show the outcomes from these real world registers and we find them useful as they in a way set a benchmark for what any new treatments from the company need to improve upon. The overall survival in none of the countries is especially good. The overall survival ranges from 9.2 months to 10.7 months in the three countries. The older the patient, the lower the survival rate.

Overall survival ranges from 9.2 months to 10.7 months

Overall survival (months) from diagnosis by age group

| | | Belgium (n=900) | | Netherlands (n=2,306) | | England (n=5,808) | |
|-------------|---------|-----------------|--------|-----------------------|--------|-------------------|--------|
| | | Median | IQR | Median | IQR | Median | IQR |
| Age (years) | 18-59 | 16.3 | (9-32) | 13.2 | (7-24) | 13.8 | (7-27) |
| | 60-69 | 13.1 | (7-23) | 11.7 | (5-19) | 12.1 | (5-23) |
| | 70-79 | 10.0 | (4-19) | 8.4 | (4-16) | 8.9 | (3-17) |
| | 80+ | 6.0 | (2-12) | 5.2 | (2-11) | 5.9 | (2-13) |
| | Overall | 10.7 | (5-21) | 9.2 | (4-17) | 9.5 | (4-19) |

Source: Damhuis et al. Lung Cancer 89 (2015) 212-217. IQR=Inter Quartile Range

The authors also looked at the difference between patients that received chemotherapy and the ones that did not and as expected the patient group not receiving chemotherapy had significantly shorter survival.

Patients not receiving chemotherapy have shorter survival

Survival (months) based on chemotherapy or not

| | | Belgium (n=900) | | Netherlands (n=2,306) | | England (n=5,808) | |
|------------------------|---------|-----------------|---------|-----------------------|--------|-------------------|--------|
| | | Median | IQR | Median | IQR | Median | IQR |
| Chemotherapy | | | | | | | |
| Age (years) | 18–59 | 16.7 | (10-30) | 14.5 | (8-24) | 14.6 | (8-28) |
| | 60–69 | 14.1 | (8-24) | 13.0 | (8-20) | 13.8 | (8-25) |
| | 70–79 | 13.0 | (6-21) | 10.3 | (6-17) | 13.2 | (8-22) |
| | 80+ | 7.2 | (4-16) | 9.5 | (4-15) | 11.5 | (4-17) |
| | Overall | 14.0 | (8-23) | 12.3 | (7-20) | 13.5 | (8-23) |
| No chemotherapy | | | | | | | |
| Age (years) | 18–59 | 8.2 | (3-34) | 9.8 | (4-28) | 10.3 | (4-24) |
| | 60–69 | 6.7 | (2-22) | 8.4 | (3-18) | 8.7 | (3-19) |
| | 70–79 | 5.2 | (2-16) | 7.0 | (3-14) | 6.1 | (3-15) |
| | 80+ | 5.2 | (2-12) | 4.9 | (2-10) | 5.6 | (2-12) |
| | Overall | 5.9 | (2-15) | 6.9 | (3-15) | 6.5 | (3-15) |

Source: Damhuis et al. Lung Cancer 89 (2015) 212-217

Note: IQR=Inter Quartile Range

Although the chemotherapy is not really curative, we still see a clear improvement in the overall survival in the group treated with chemotherapy compared with the group not receiving chemotherapy. Given our discussion above about patients being too frail to receive chemotherapy at an older age, it is important to understand that there is most likely a bias in the survival statistics, as the patients that received chemotherapy were also overall more healthy than the group that did not.

Size of patient pool

As mentioned before, this is a rare disease with only c20 patients per million inhabitants per year in most markets (but a large variation between c7 and c40 per million inhabitants). In the most developed markets we estimate that the incidence is c20 per million per year. In total this should give a potential patient population of c25,000 globally for this disease.

We estimate that there are c25,000 patients globally

MPM patients globally – selected markets

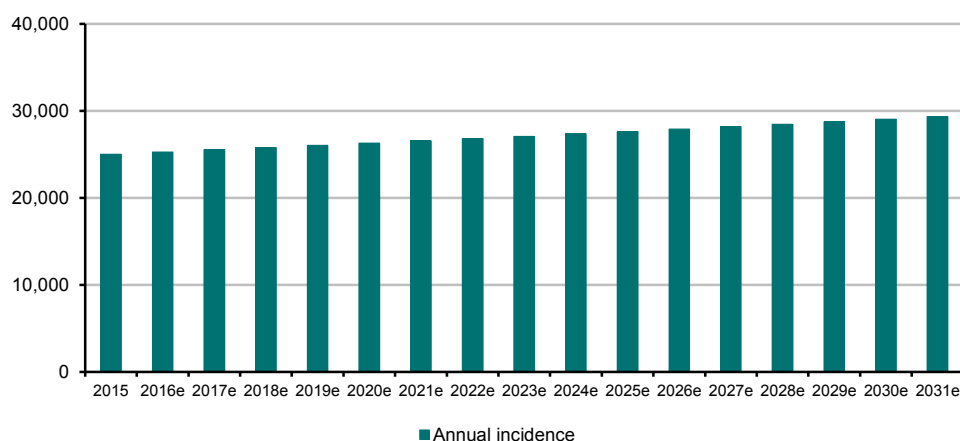
| | Population (m) | Mesothelioma incidence | Mesothelioma incidence/m population |
|-----------------|-------------------|---------------------------|--|
| US | 318.89 | 3,189 | 10 |
| UK | 63.74 | 1,275 | 20 |
| Germany | 81 | 1,620 | 20 |
| Italy | 61.68 | 1,234 | 20 |
| France | 66.26 | 1,325 | 20 |
| Russia | 142.47 | 2,849 | 20 |
| Spain | 47.74 | 955 | 20 |
| The Netherlands | 16.88 | 338 | 20 |
| Poland | 38.35 | 767 | 20 |
| Belgium | 10.45 | 209 | 20 |
| Portugal | 10.81 | 216 | 20 |
| Sweden | 9.72 | 194 | 20 |
| Japan | 126.9 | 888 | 7 |
| Norway | 5.15 | 103 | 20 |
| Finland | 5.27 | 105 | 20 |
| Europe | 739 | 14,780 | 20 |
| EU-27 | 509.37 | 10,187 | 20 |

Source: CDC, WHO

When we look at the potential patients available for the company's products, we estimate that the number of patients will continue to grow by c1% p.a. for 2015–2031.

We estimate the patient population will grow by c1% p.a.

Growth in patient population – MPM



Source: DNB Markets

Clinical development programme

The company finished the planning of a phase I/II trial in mesothelioma in H1 2016. The trial kicked off with announcement that the first patient had been dosed in early July this year.

The clinical development for this indication is the one we associate with the highest risk of delays, as the number of available patients (due to its orphan nature) is relatively low. However, it is our impression that Targovax has planned for slower patient recruitment than the clinics included in the clinical trial expect. Hence, we expect Targovax to recruit all 30 patients within around a year from start of recruitment. With approximately eight centres included in the trial, clinics will need to find approximately one patient per quarter on average to include in the trial.

Slower patient recruitment to expect due to the low number of patients

However, due to the relatively limited competition in this space, we believe most of the upside in this indication relates to the opportunity to become a first-line therapy basically at once if the data is strong.

Colorectal cancer

Colorectal cancer (CRC) is the second leading cause of mortality among cancer patients in the world and the third most diagnosed cancer worldwide. Thus, it represents a huge burden for the global healthcare system. Despite efforts to screen patients more and more in order to find potential CRC cases as early as possible, we still see some 10–20% of newly diagnosed patients being diagnosed with stage IV metastatic disease, and these patients have an overall poor prognosis.

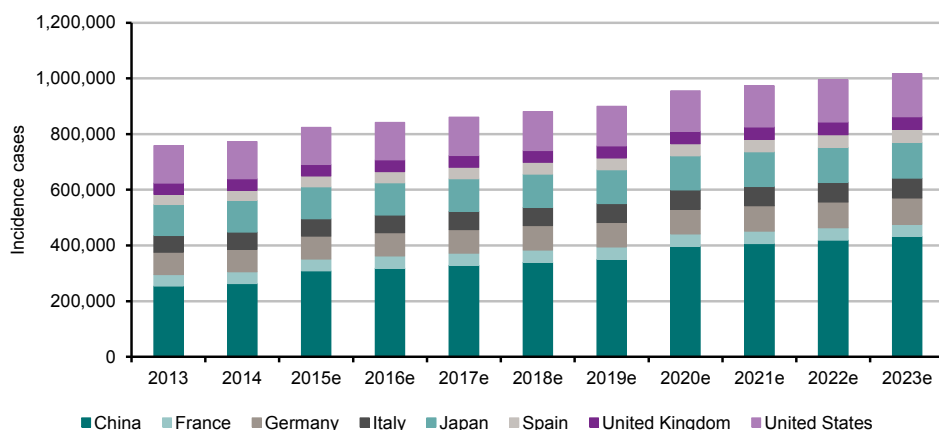
Incidence in major markets

In this section we highlight the expected incidence for CRC in the largest markets (the US, EU5, China and Japan). As shown, the incidence of CRC is expected to grow in the coming years. The annual incidence of CRC in 2023 is expected by GlobalData's epidemiologists to reach more than a million cases in these markets alone. Furthermore, if we look at the expected distribution of CRC in the markets highlighted, we see that China is expected to have the largest number of cases, followed by the US.

Second leading cause of mortality among cancer patients

Incidence expected to grow in the coming years

Incidence in the coming years in the eight major markets



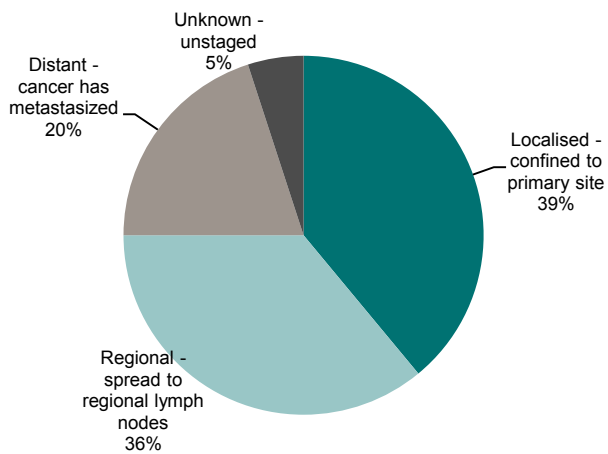
Source: GlobalData

Data from the US gives a good overview of CRC patient characteristics. As shown below, there is a relatively high percentage of patients that already have advanced (metastasised) disease at initial diagnosis of CRC. Patients with more advanced disease also, naturally, have a poorer prognosis and the 5-year relative survival for this group is clearly the lowest. In patients where the CRC has already metastasised, the 5-year relative survival rate is only c13%. Note that despite 80% of patients having localised/regional disease, 50% will relapse after surgery due to the presence of micro-metastases, hence these patients would also benefit from improved systemic treatments entering the market.⁶⁵

Relatively high share of patients are diagnosed with metastatic CRC

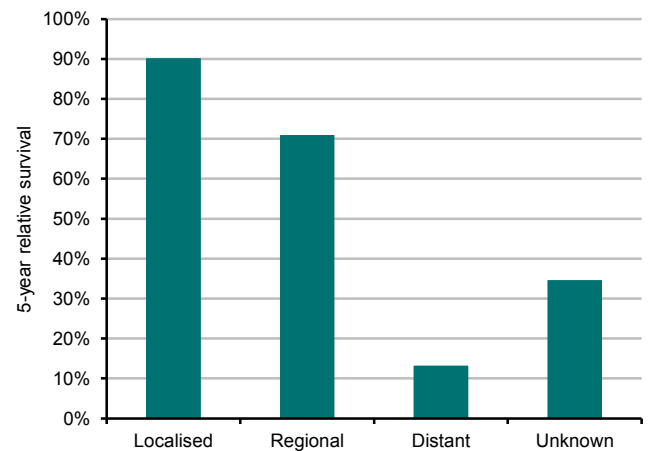
⁶⁵ Koido S. et al. World J Gastroenterol 19.46 (2013): 8531-8542

Disease severity at diagnosis – CRC



Source: NCI/SEER Cancer statistics

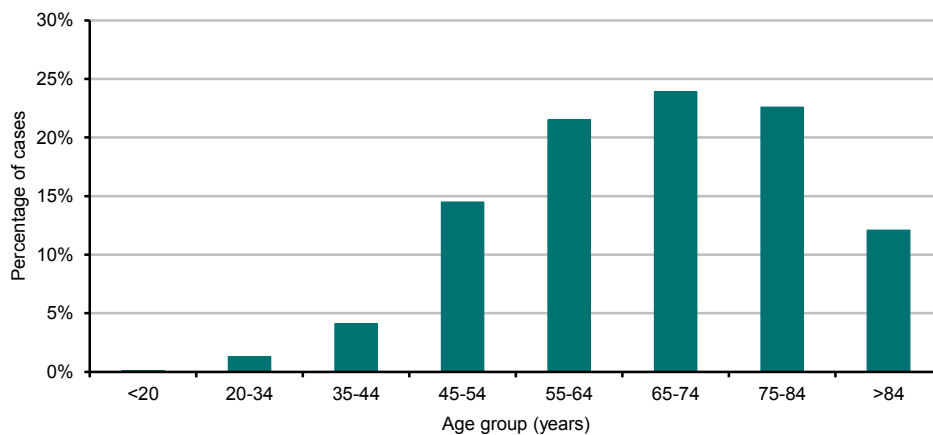
5-year relative survival in CRC based on stage at diagnosis



Source: NCI/SEER Cancer statistics

The median age for diagnosis is c68 years (see below). The median age of death in CRC in the US is 73 years (peaking at 75–84 years, when c27% of diagnosed patients dies).

Diagnosis of CRC based on age at initial diagnosis

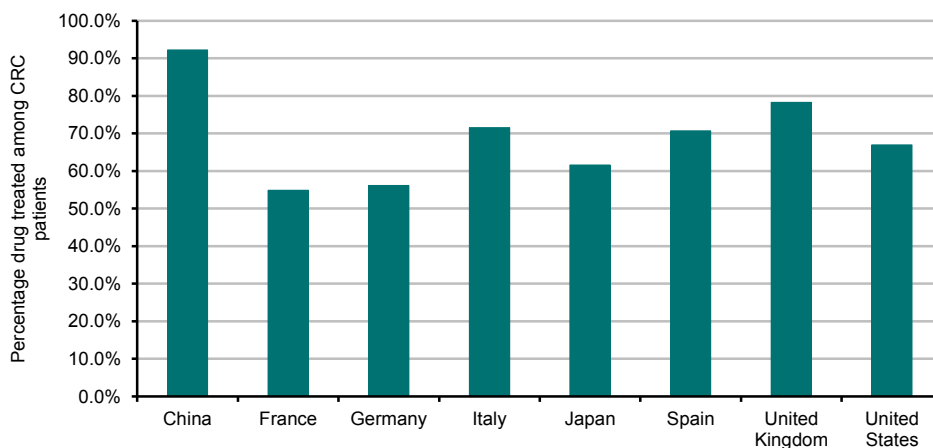


Source: NCI/SEER Cancer statistics

Drug treatment

In a way this market is mature and well established, as shown by the proportion of patients receiving drug treatment for CRC.

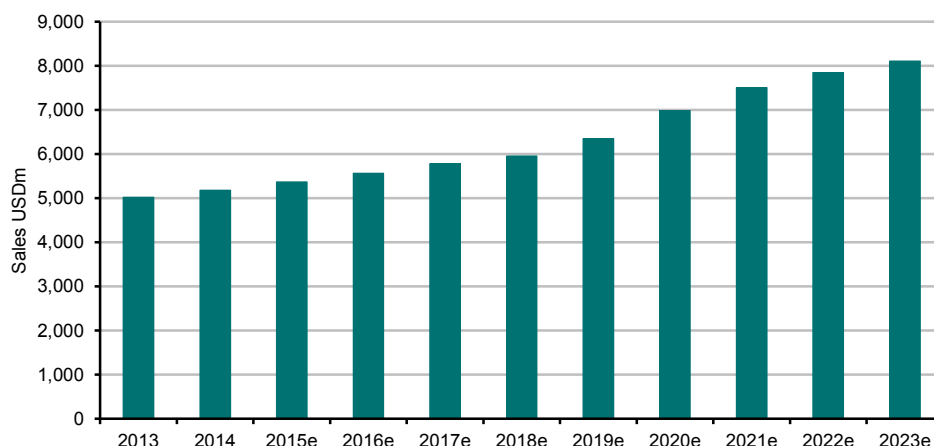
Proportion of patients receiving drug treatment for CRC



Source: GlobalData

In financial terms, it is a large market. In the chart below, we highlight the expected growth in drug sales to the CRC markets highlighted above.

Drug sales in CRC market



Source: GlobalData

In terms of targeted treatments, the metastatic CRC treatment landscape is mature, including branded treatments Avastin (bevacizumab), Erbitux (cetuximab), and Vectibix (panitumumab), which have extended the survival of metastatic patients compared with chemotherapy-only regimens. However, high unmet needs remain for the extension of survival of metastatic patients, particularly those with KRAS mutation-positive disease, for whom the epidermal growth factor receptor (EGFR) inhibitors Erbitux and Vectibix are not recommended.

Size of patient pool

Going back to the data highlighted earlier on how large a proportion of patients in a specific disease have RAS mutations, we saw that in colorectal cancer c40–60% of patients have a RAS mutation, making them suitable for treatment with Targovax RAS peptide vaccine. In this case, the company is planning to use the TG02 vaccine as it contains an additional peptide that makes the product more suitable for the CRC indication.

RAS mutations

| Indication | Percentage with a RAS mutation |
|--------------------|--------------------------------|
| Pancreatic cancer | c90% |
| Colorectal cancer | c40–60% |
| Biliary cancer | c40–60% |
| Thyroid cancer | c60% |
| NSCLC | c20–30% |
| Malignant melanoma | c20–30% |

Source: Miglio, U et al 2014, Vaughn, C.P. et al 2011 D'Arcangelo, M et al 2012, Fernandez-Medarde, A et al, 2011

As we understand it, typing a patient for RAS mutations is already more or less a standard procedure. This implies that the addressable market for Targovax will be the c40% of CRC patients, i.e. the ones that have a RAS mutation. Given the cost of the drugs, we doubt that clinicians will spend a significant amount on vaccines for patients without the RAS mutation. Hence, we believe that the company can address c40% of the colorectal patient population.

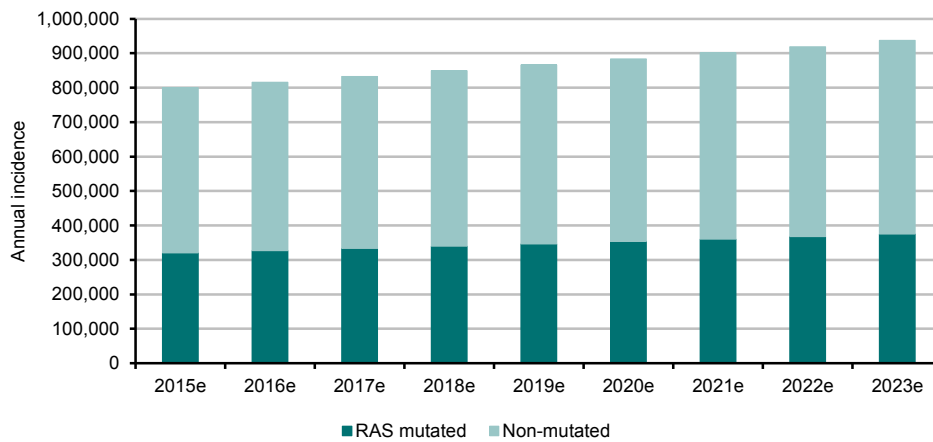
In the figure below, we show the estimated addressable patient pool for CRC (the c40% with RAS mutation) and that the annual incidence of CRC is expected to continue to rise. We have included c1.5% annual growth in the number of new patients diagnosed with CRC.

Several targeted therapies available for CRC

c40–60% of patients have RAS mutations

Addressable market is c40% of the patient population

Patient pool of RAS mutated CRC patients



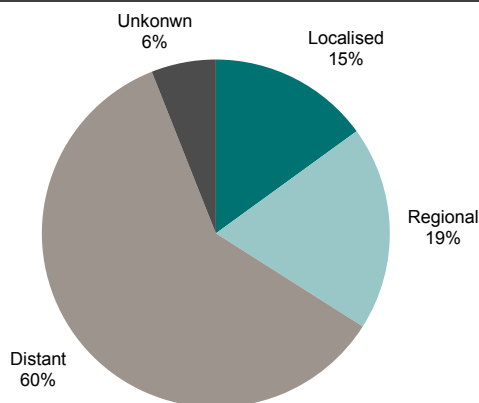
Source: Global Data, DNB Markets

Ovarian cancer

Ovarian cancer is the most common cause of gynaecological cancer-associated death. The disease typically presents in postmenopausal women, with a few months of abdominal pain and distension. Ovarian cancer has a relatively high death rate since patients usually have advanced and disseminated disease at diagnosis, i.e. the cancer has already spread and metastasised.

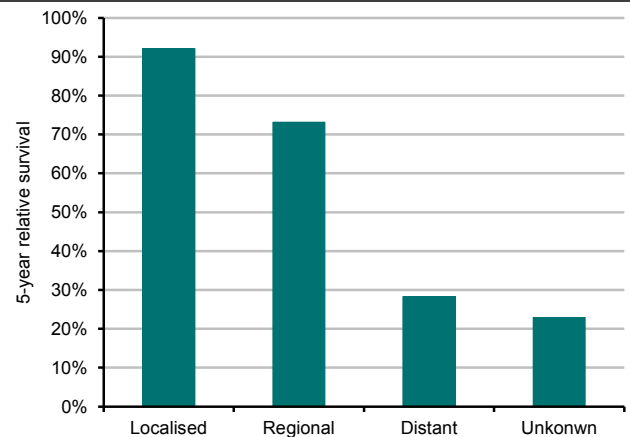
Patients are usually diagnosed with advanced and disseminated disease

Stage at diagnosis



Source: SEER

5-year relative survival based on stage at diagnosis



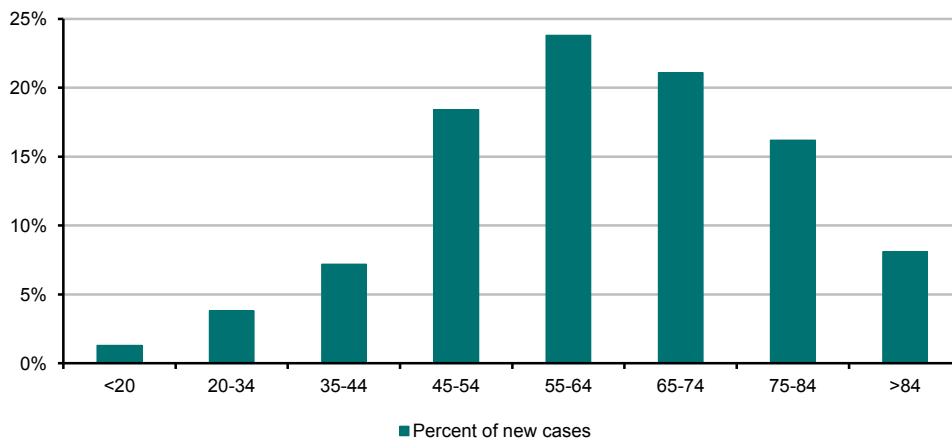
Source: SEER

As shown above, c60% of patients already have cancer that has metastasised at diagnosis and the 5-year relative survival falls quite drastically for patients with more advanced disease.

Long-term survival is poor for patients with advanced disease

The median age at diagnosis is c63 years, and the disease peaks in the 55–64 year age group.

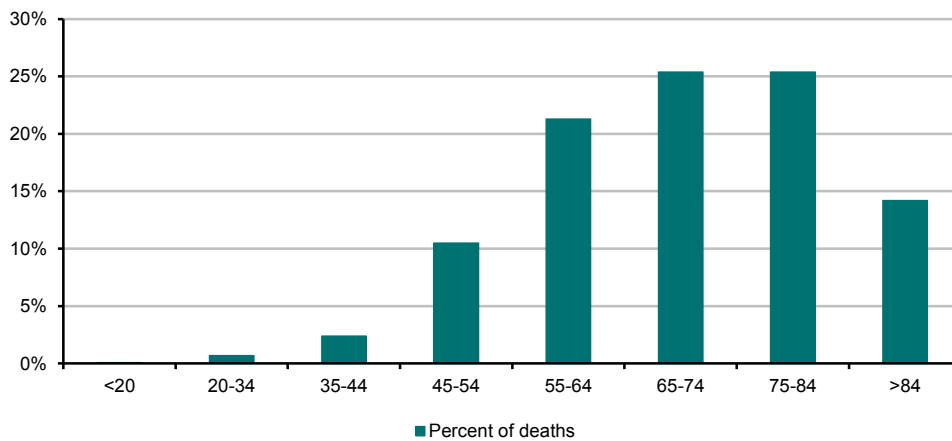
Age at diagnosis of ovarian cancer



Source: SEER

The same age distribution pattern is visible when it comes to death from ovarian cancer as shown below. The median age at death from ovarian cancer is c70 years.

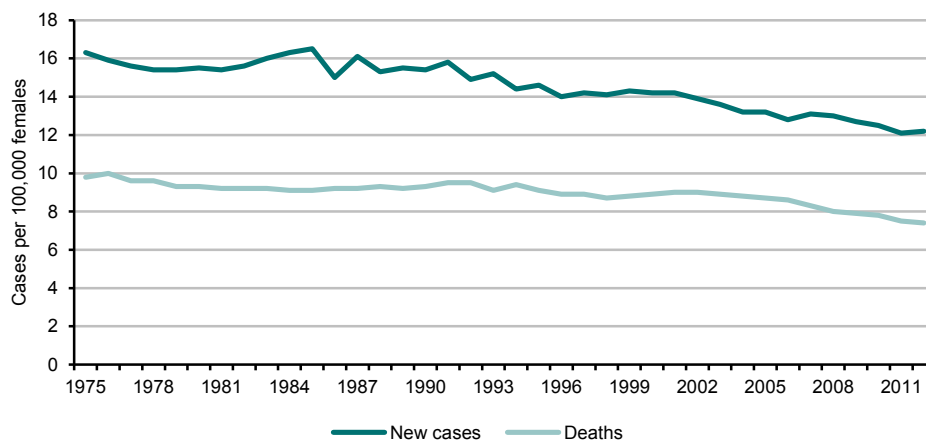
Age at death from ovarian cancer



Source: SEER

When looking at the development in incidence and mortality from ovarian cancer (data from the US only), we see that both incidence and mortality have been decreasing over time.

Incidence and mortality over time

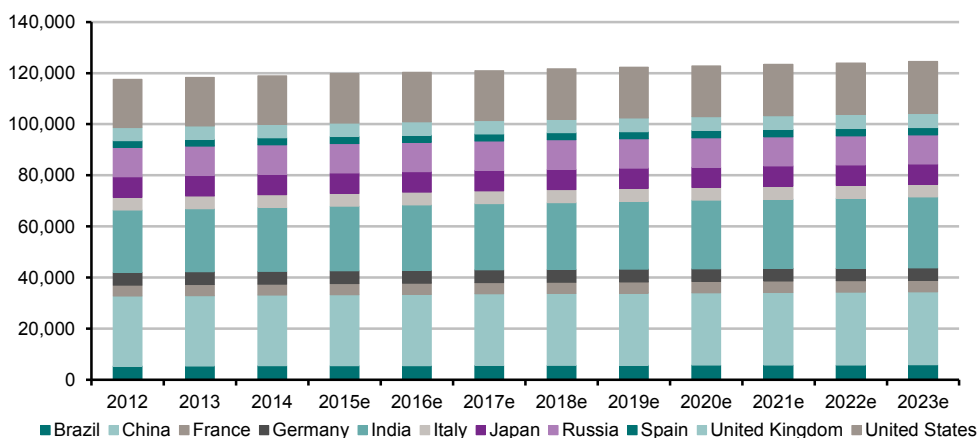


Source: SEER

When looking at the disease from a more global perspective, we used the GlobalData disease database and the prevalence of ovarian cancer in 11 major markets. As shown below, in these markets c120,000 cases were expected in 2015. In total, according to The World Cancer Research Fund International, c239,000 cases of ovarian cases were diagnosed in 2012. Overall, we expect the number of patients to continue to grow over time due to demographic changes (an ageing population) by c1% p.a. going forward.

We expect the incidence to rise globally

Incidence of ovarian cancer 11 major markets



Source: Global Data

Treatment options

Ovarian cancer is treated mainly with surgery and chemotherapy:

- **Surgery** has three main goals: diagnosing, staging, and removing as much of the cancer as possible. Compared with other cancers, surgery is used even in patients with disseminated disease. The rationale is to be able to accurately diagnose the patient, remove tumour tissue that can harbour chemoresistant disease, and to enhance the effectiveness of adjuvant therapy.
- **Chemotherapy** – adjuvant chemotherapy in early-stage disease improves survival by c8%⁶⁶. Some trials have suggested there might be no benefit of treating patients with adjuvant chemotherapy. However, results of long-term follow-up of patients with stage I disease suggest that adjuvant chemotherapy is beneficial for some patient groups.

Surgery is also used for patients with disseminated disease

Standard chemotherapy regimen for patients with advanced disease is carboplatin in combination with paclitaxel or docetaxel, which has been the standard of care for the past 20 years. There have been attempts to add a third chemotherapeutic agent; however, these attempts have been unsuccessful in improving outcomes.

Standard chemotherapy includes carboplatin in combination with paclitaxel or docetaxel

Most patients with recurrent disease receive second-line chemotherapy, but a fraction of these can also be considered candidates for surgery. The choice of second-line chemotherapy depends on if the recurrent tumour is platinum resistant or sensitive. Retrospective studies have defined that cancer progressing within six months of the last platinum-containing treatment is platinum-resistant, and a chance of response to re-treatment with a platinum-containing regimen is less than c15%. Platinum-sensitive disease is treated best with a combination of drugs, such as carboplatin with paclitaxel, gemcitabine or pegylated liposomal doxorubicin. Patients with the worst prognosis are those with platinum-refractory or resistant disease, these patients have been historically treated with either pegylated liposomal doxorubicin or topotecan, which only produce low response rates. The table below outlines the most frequently used agents in platinum-resistant disease.

Patients with platinum- refractory or resistant disease have the worst prognosis

⁶⁶ Jayson GC. et al. The Lancet 384.9951 (2014): 1376-1388

Drugs used in ovarian cancer patients

| Agent | Response rate (%) | PFS (months) | Overall survival (months) |
|---------------------------------|-------------------|----------------|---------------------------|
| Pegylated liposomal doxorubicin | 10–20 | 3–4 | 10–12 |
| Topotecan | 12–18 | 3–4 | 10–12 |
| Docetaxel | 22 | 3.5 | 12.7 |
| Gemcitabine | 15 | 4–5 | 11.8–12.7 |
| Pemetrexed | 15–21 | 2.9 | 11.4 |
| Etoposide | 6–27 | 4–5 | 10–11 |
| Paclitaxel | 10–30 | 4–6 | 13 |
| Nab-paclitaxel | 23 | 4–5 | 17.4 |
| Bevacizumab | 21 | 4.7 | 17 |
| Chemotherapy +/- bevacizumab | 13 versus 31 | 3.4 versus 6.7 | 13.3 versus 16.6 |

Source: Herzog 2013

Novel treatments. The most studied targeted therapy for ovarian cancer is bevacizumab (Avastin), an anti-VEGF antibody that has been approved for use in patients with recurrent platinum-resistant ovarian cancer in combination with chemotherapy. The approval was based on a significant prolongation in PFS seen in patients who received bevacizumab plus chemotherapy (6.8 months) compared with patients who only received chemotherapy (3.4 months); however, no statistically significant difference in OS was shown⁶⁷.

Avastin approved based on improved PFS

Another targeted therapy for ovarian cancer recently approved by the FDA is olaparib (Lynparza), which is a PARP-1 inhibitor (PARPs are enzymes recognised being regulators of survival and cell death). Olaparib is indicated for BRCA-mutated advanced ovarian cancer that has been treated with three or more prior lines of chemotherapy. It was approved based on a phase II study that showed that olaparib improved the PFS significantly in BRCA-mutated patients receiving the drug compared with placebo (11.2 versus 4.3 months). No statistically significant improvement of OS was shown⁶⁸.

Lynparza also approved based on improved PFS

Size of patient pool

As mentioned before, there are c240,000–250,000 cases of ovarian cancer p.a. globally. According to The World Cancer Research Fund International, some 42% of cases were in the more developed parts of the world. Keeping in mind that c60% of patients present with late-stage disease, we believe the available patient population for Targovax will be around 100,000 patients p.a. diagnosed in the developed world, and of this population the 60% with late-stage disease are the patients most relevant or c60,000 p.a. This is particularly true since the company is planning to do the first clinical trials in patients with platinum-resistant ovarian cancer, i.e. in patients with advanced disease where previous treatment with platinum-based chemotherapy has failed.

Patients with late-stage disease will be the most relevant patient population for Targovax in our view

Prostate cancer

Prostate cancer is the fourth most common cancer form globally, and the second most common cancer form in men globally. Below we show the incidence in nine large markets and in these markets alone we are talking about well in excess of 1m patients per year being diagnosed with prostate cancer. These markets make up a large proportion of the diagnosed cases of prostate cancer. In 2012, there were c1.1m cases diagnosed globally and some c0.3m deaths related to prostate cancer⁶⁹.

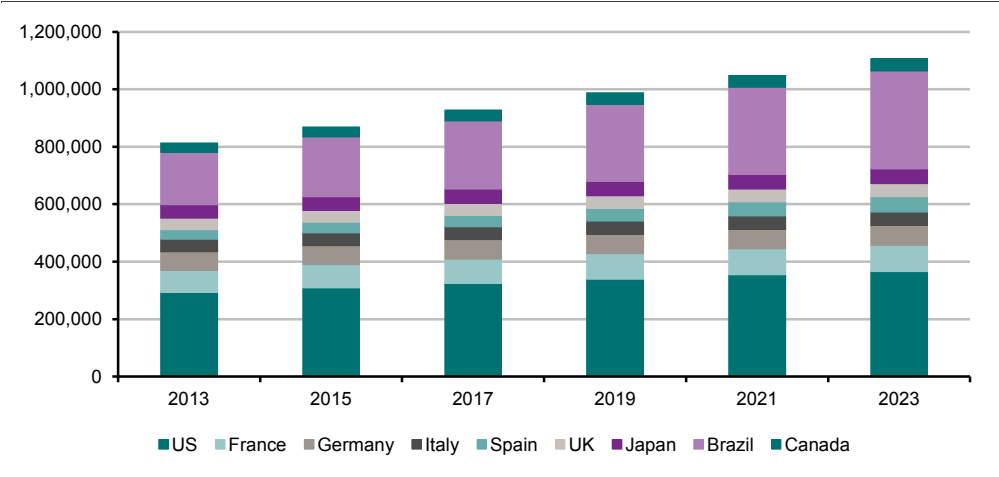
Fourth most common cancer globally

⁶⁷ Pujade-Lauraine E. et al. Journal of Clinical Oncology 32.13 (2014): 1302-1308

⁶⁸ Ledermann J. et al. The lancet oncology 15.8 (2014): 852-861

⁶⁹ World Cancer Report 2014. World Health Organization

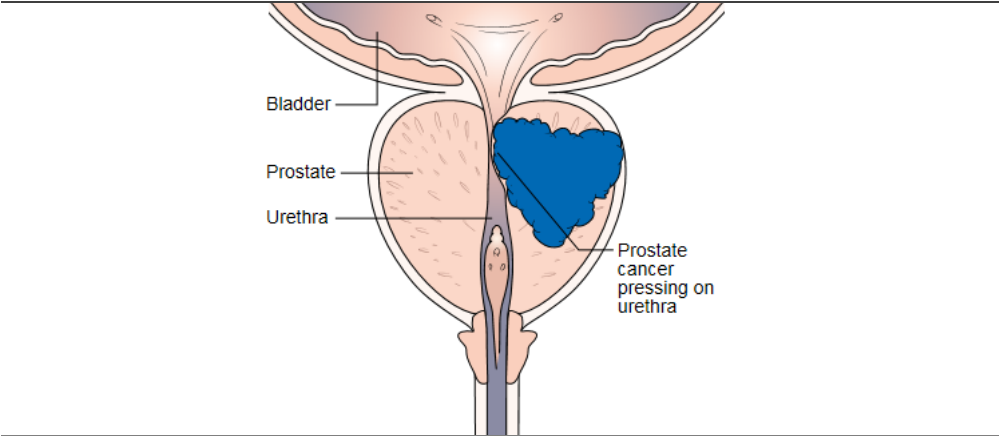
Incidence of prostate cancer in nine major markets



Source: GlobalData

The prostate is a gland in the male urogenital system a gland situated around the urethra.

Anatomical view of the prostate and prostate cancer

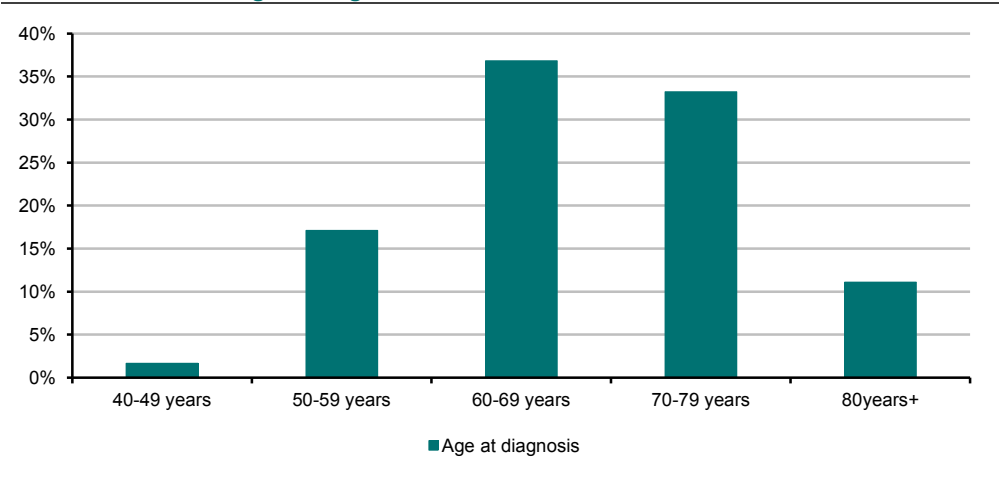


Source: www.wikipedia.org

The disease is highly correlated with age, making it very prevalent in elderly men. It is often said that most men die *with* prostate cancer, not *from* prostate cancer, indicating that with sufficient age more or less all men will get prostate cancer. The high correlation with age can be seen from the figure below.

Highly correlated with age

Prostate cancer and age at diagnosis



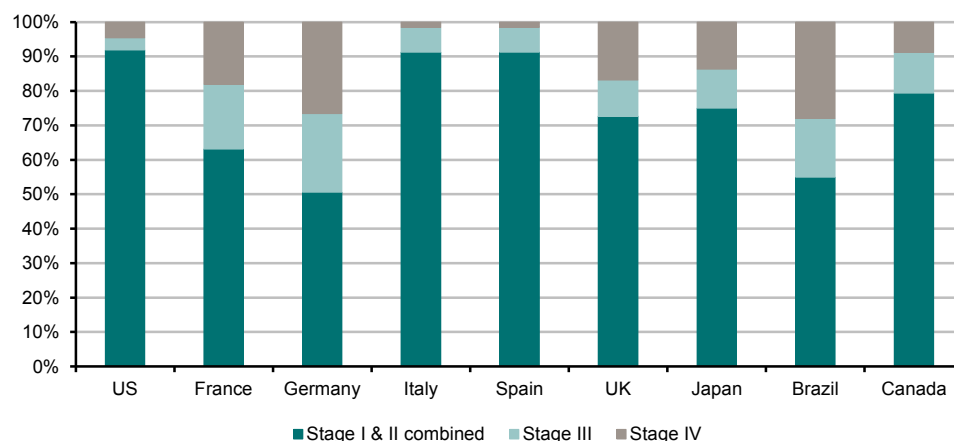
Source: GlobalData

The prostate is a relatively easily accessible tumour type for treatment with the ONCOS-102 vaccine as the gland can easily be reached by injection needle.

There are quite large differences between countries in terms of the stage at which the disease is diagnosed. There are relatively good treatment options for more early-stage prostate cancer cases, and Targovax will most likely concentrate on the more advanced versions ('advanced metastatic castration-resistant prostate cancer').

Targovax will focus on the more advanced forms of prostate cancer

Stages of prostate cancer at diagnosis



Source: Global Data

Treatment options

Most patients are diagnosed with localised disease, but the prognosis can vary a lot. The choice of treatment is therefore based on the stage of the cancer, initial prostate-specific antigen (PSA) levels, Gleason score, urinary function, comorbidities, and the patient's age.

Most patients are diagnosed with localised disease

For stage I–III patients standard therapy includes surveillance, prostatectomy, and radiotherapy. And the outcomes for early-stage patients (stage I/II) is good, with over 90% PFS after five years. Some large clinical trials comparing treatments for localised prostate cancer are shown below. Hormone therapy for prostate cancer is also called androgen suppression therapy or androgen deprivation therapy, and current treatments act by three mechanisms: reduce androgen production by the testicles, block the action of androgens in the body, and block the production of androgens throughout the body. The rationale behind the therapy is that most prostate cancers are dependent on androgen signalling for survival.

The table below summarises the efficacy of current standard therapies for localised prostate cancer.

Influential phase 3 trials for localised prostate cancer

| Trial | Patients | Comparison | OS outcome | HR (95% CI) | p-value |
|--|----------|---|--------------------------------|------------------|---------|
| Trials of radical prostatectomy versus observation | | | | | |
| SPCG4 | 695 | Radical prostatectomy versus watchful waiting | 67% versus 60% at 12 years | 0.82 (0.65–1.03) | 0.09 |
| PIVOT | 731 | Radical prostatectomy versus watchful waiting | 53% versus 50% at 10 years | 0.88 (0.71–1.08) | |
| Trials of hormone therapy with or without radical radiotherapy | | | | | |
| SPCG-7 | 875 | Hormone therapy plus EBRT versus hormone therapy | 70% versus 61% at 10 years | | 0.004 |
| NCIC PR3 | 1205 | Hormone therapy plus EBRT versus hormone therapy | 74% versus 66% at 7 years | 0.77 (0.61–0.98) | 0.033 |
| Trials of radical radiotherapy with or without adjuvant hormone therapy | | | | | |
| EORTC 22863 | 415 | EBRT plus 3 years of hormone therapy versus EBRT | 58% versus 40% at 10 years | 0.60 (0.45–0.80) | 0.0004 |
| RTOG 8531 | 977 | EBRT plus lifelong hormone therapy versus EBRT | 49% versus 39% at 10 years | | 0.002 |
| TROG 9601 | 537 | EBRT plus 6 months of hormone therapy versus EBRT | 70.8% versus 57.5% at 10 years | 0.63 (0.48–0.83) | 0.0008 |

Source: Attard G. et al. Lancet 2015

For all stage IV and high-risk stage III patients, androgen ablation through surgery or chemical castration can result in sustained remission. However, mutations in the androgen receptor develop sooner or later in stage IV prostate cancer, leading to a poor prognosis. However, in the past decade, FDA has approved six new therapeutic agents for castration-resistant prostate cancer that have improved the overall survival.

Poor prognosis for patients for no longer responding to hormonal therapy

Drugs with OS benefit in castrate resistant prostate cancer

| Drug | Trial | Comparator | OS benefit |
|------------------------------------|------------|---------------------------|------------|
| Chemotherapy-naïve patients | | | |
| Abiraterone acetate + prednisone | COU-AA-302 | Placebo + prednisone | 5.2 months |
| Sipuleucel-T | IMPACT | Placebo | 4.1 months |
| Radium-223 | ALSYMPCA | Placebo | 3.6 months |
| Enzalutamide | PREVAIL | Placebo | 2.2 months |
| Post-chemotherapy treatment | | | |
| Abiraterone acetate + prednisone | COU-AA-301 | Placebo + prednisone | 4.6 months |
| Enzalutamide | AFFIRM | Placebo | 4.8 months |
| Cabazitaxel + prednisone | TROPIC | Mitoxantrone + prednisone | 2.4 months |
| Docetaxel + prednisone | TAX 327 | Mitoxantrone + prednisone | 2.4 months |

Source: www.cancernetwork.com

Docetaxel and cabazitaxel are the only cytotoxic drugs to have shown survival benefits in patients with castration-resistant prostate cancer. Enzalutamide (Xtandi), a second-generation androgen receptor inhibitor, and abiraterone acetate (Zytiga), an irreversible cytochrome P17 inhibitor (also an anti-androgen product), were approved in 2012 and 2011, respectively, have represented a major advancement in the treatment of these patients.

Xtandi and Zytiga have improved the treatment of castration-resistant prostate cancer

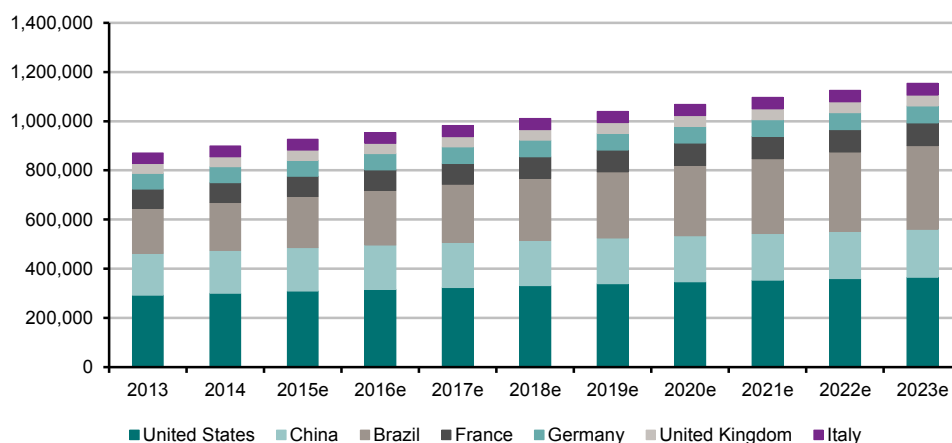
Size of patient pool

The prostate cancer market is large, regardless of how we look at it. The number of patients is high, as prostate cancer is the fourth most common cancer form globally and the second most common in men with c1.1m diagnosed cases in 2012.

As shown above, the vast majority of patients are diagnosed at an early stage and only some c13–15% are present with advanced disease. As the company is planning to document its vaccine in the patient population with advanced metastatic castration-resistant prostate cancer, we believe that of the total prostate cancer population no more than 15% of patients are found in the target population for Targovax. Hence we estimate that the annual available patient group will be around c175,000 patients globally.

Target population c15% of prostate cancers

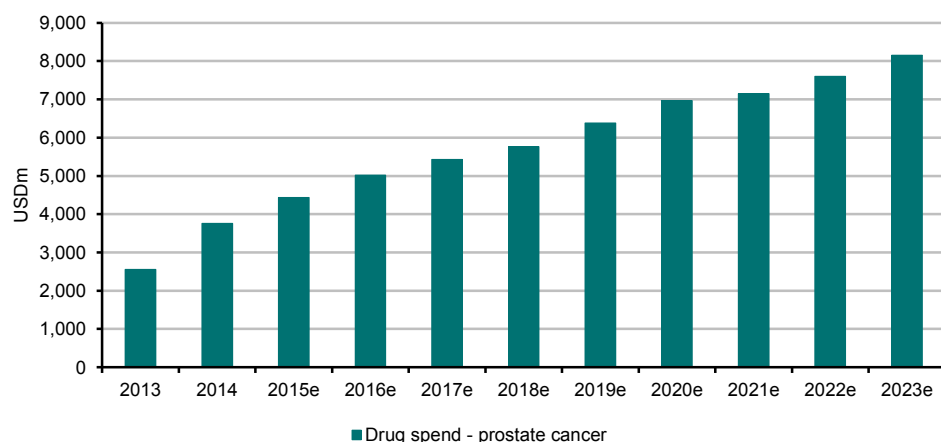
Incidence of prostate cancer – selected markets



Source: GlobalData

Another way of measuring the size of the market is to look at drug spend; and as shown below, this market is expected to reach cUSD8bn in a few years' time.

Spend drugs for prostate cancer – 11 major markets



Source: GlobalData

Non-small cell lung cancer (NSCLC)

Targovax has put this indication somewhat on the back-burner, as it is pushing forward with the colorectal cancer indication instead. However, looking at the product aimed for colorectal cancer (TG02 vaccine) we see the mix of RAS peptides in TG02 would also lend itself to treatment of NSCLC. Keep in mind this is a fairly large indication in number of patients; we believe that over time the company (or its partner) will initiate clinical trials in NSCLC as well.

Background

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. In 2008 1.6m people were diagnosed with lung cancer, and in the same year 1.4m people died from it, or c18% of all cancer deaths that year. In 2010 the number of deaths from lung cancer had risen to 1.5m, or c19% of all cancer deaths that year⁷⁰, and in 2012 1.8m new cases were diagnosed, or c13% of total cancer diagnoses. It is estimated that there will be c224,400 new cases of lung cancer in 2016 in the US⁷¹.

Incidence and prevalence

Lung cancer can be divided into two separate forms: Small Cell Lung Cancer (SCLC) and NSCLC. NSCLC accounts for c85% of lung cancers cases. The incidence of lung cancer in the US is decreasing, directly correlating to a decrease in cigarette smoking, which is the major risk factor for lung cancer. However, smoking is not decreasing everywhere in the world, in China and other developing countries smoking has not yet reached its peak. Below we show the both incidence and mortality in NSCLC in the US over time.

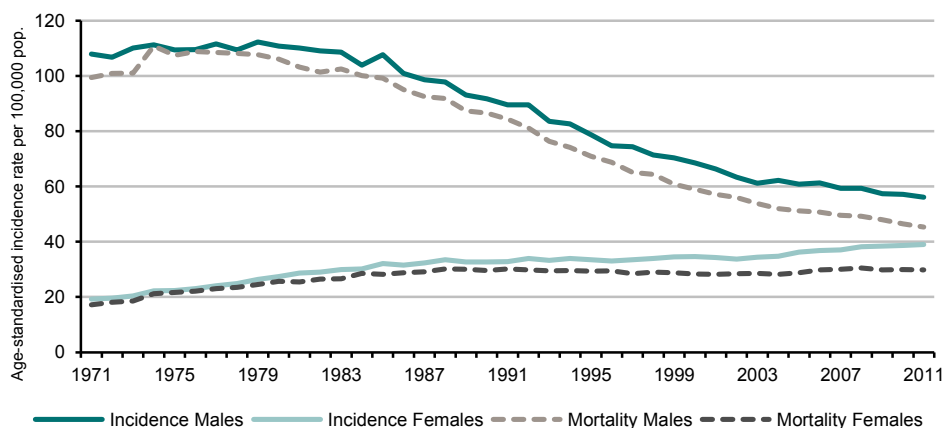
Leading cause of cancer-related deaths worldwide

Smoking is the major risk factor for lung cancer

⁷⁰ Reck M. et al. The Lancet 382.9893 (2013): 709-719.

⁷¹ SEER

Incidence and mortality in NSCLC in the US over time



Source: SEER

The incidence for males has declined since the mid-1970s as a result of fewer people smoking. However, as females started to smoke at a higher rate later than males, the incidence of NSCLC in females is still rising.

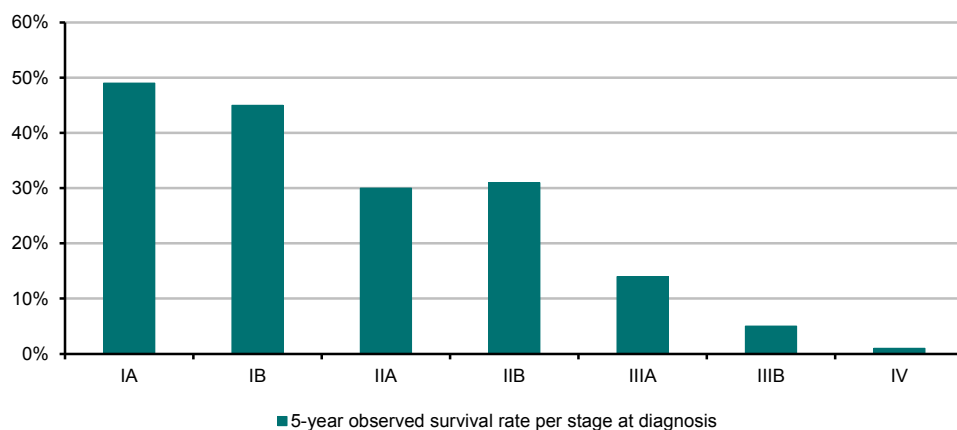
Mortality for NSCLC is tracking the incidence curve quite well and it was not until the last few years that the mortality curves started to deviate slightly more from the incidence curves, indicating that the expected survival has improved slightly. Regardless, NSCLC is still a disease with poor outcomes.

Below we show the predicted 5-year survival for patients depending on stage of the disease at diagnosis. The more advanced the disease at diagnosis, the lower the expected 5-year survival. The median predicted 5-year survival for NSCLC patients is c15.9%. Even though the disease has a bad prognosis, the median survival has increased from eight months to 12 since 2002 because of the introduction of new drugs.

Although mortality is improving NSCLC is still a disease with poor outcomes

Novel drugs have improved the survival

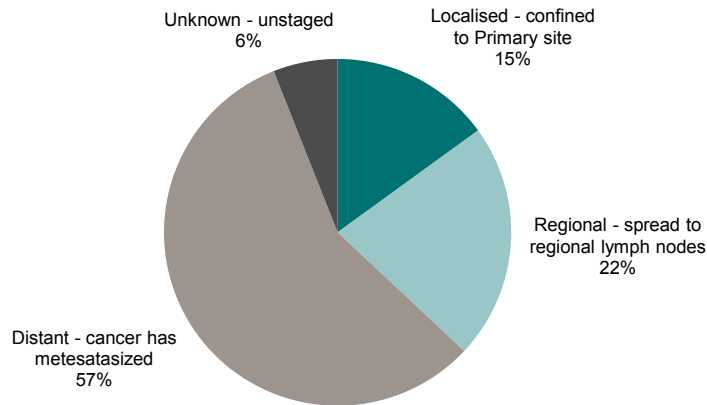
Predicted 5-year survival based on stage at diagnosis



Source: SEER

With this in mind, it is still very problematic for patients and the healthcare system that most patients are diagnosed quite late in the disease. Below we show the proportion of patients in the different stages at diagnosis in the US – the majority are already in stage III at diagnosis.

Stage of NSCLC at diagnosis in the US



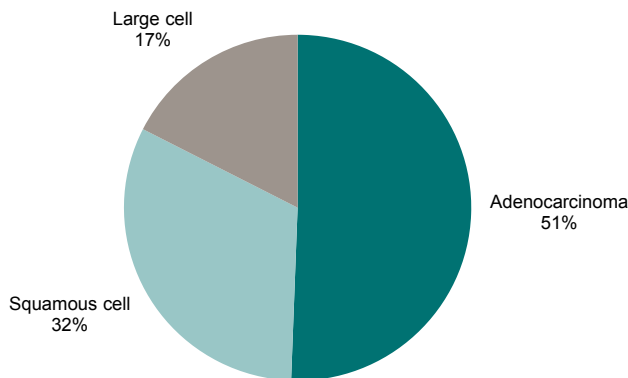
Source: SEER

As c57% of patients already have metastasis at diagnosis and c22% of patients have disease that has spread to the lymph nodes, this makes the disease very hard to treat.

c57% of patients are diagnosed with metastatic disease

The disease can be divided into three major subgroups based on histology: squamous-cell carcinoma, adenocarcinoma, and large-cell lung cancer. The squamous-cell and adenocarcinoma groups are the more common ones.

Split by type of NSCLC



Source: Foster/Rosenblatt. Bloomberg.

In general, adenocarcinoma arise in more distal airways, whereas squamous cell carcinoma arise in more proximal airways and are more strongly associated with smoking and chronic inflammation than adenocarcinoma.

The development of NSCLC involves multistep genetic alterations that leads to the activation of growth promoting proteins (e.g. KRAS, EGFR, BRAF, MEK-1, HER2, and MET) and inactivation of tumour suppressor genes (e.g. TP53 and PTEN).

Targeted therapies developed for NSCLC subtypes

Research has revealed in the past decade that NSCLC is a highly heterogeneous disease with subtypes diverging in morphology and driver mutations. This has led to the development of new targeted therapies.

The most widely recognised genetic alteration is the epidermal growth factor receptor (EGFR) mutations; targeted treatment towards EGFR has improved the outcomes for patients with EGFR mutations markedly. The frequency of EGFR mutations is c10% in adenocarcinomas and 2–3% in squamous cell carcinomas⁷². However, some studies have reported that up to

⁷² Chen Z. et al. Nature Reviews Cancer 15.4 (2015): 247-247

20% of adenocarcinomas have EGFR mutations⁷³. The mutation is more prevalent in females, non-smokers and patients of East Asian ethnicity. EGFR regulates several critical cellular mechanisms, and an activating mutation can lead to inhibition of tumour cell apoptosis (programmed cell death) and tumour progression.

Diagnosis and staging

It is highly important to stage the cancer as this determines the treatment course and prognosis. Most patients are initially diagnosed by chest radiograph, although there are many other techniques for further staging the cancer, such as FDG-PET, CT, MRI, and ultrasound – but to confirm the diagnose a biopsy is usually needed.

Lung cancer is staged based on the TNM classification system, where T is the size of the primary tumour, N is whether nearby lymph nodes are involved, and M is whether there are any distant metastases. The TNM values are combined to determine the stage of the cancer, which range from I to IV, with IV being the most advanced. The stages can be subdivided by the letters A and B, which describe the disease advancement. In the table below, we show one of the more comprehensive staging systems available for NSCLC patients.

TNM staging

| T/M | N0 stage | N1 stage | N2 stage | N3 stage |
|------------------------------------|----------|----------|----------|----------|
| T1a (≤2 cm) | IA | IIA | IIIA | IIIB |
| T1b (>2-3 cm) | IA | IIA | IIIA | IIIB |
| T2a (>3-5 cm) | IB | IIA | IIIA | IIIB |
| T2b (>5-7 cm) | IIA | IIB | IIIA | IIIB |
| T3 (>7 cm) | IIB | IIIA | IIIA | IIIB |
| T3 (invasion) | IIB | IIIA | IIIA | IIIB |
| T3 (same lobe nodules) | IIB | IIIA | IIIA | IIIB |
| T4 (extension) | IIIA | IIIA | IIIB | IIIB |
| T4 (ipsilateral lung nodules) | IIIA | IIIA | IIIB | IIIB |
| M1a (pleural/pericardial effusion) | IV | IV | IV | IV |
| M1a (contralateral lung nodules) | IV | IV | IV | IV |
| M1b (distant metastases) | IV | IV | IV | IV |

Source: International Association for the Study of Lung Cancer (2009)

Note: Shaded denotes unresectable disease

Standard of care

- **Early stage (stage I–II).** The standard of care is surgery for patients medically fit to undergo an operation. Stereotactic body radiotherapy (SBRT) is an alternative, but survival is worse than for surgery in indirect comparisons. However, it is usually patients in a worse condition who receive SBRT. In the past few years clinical trials have shown improved overall survival in stage II and III NSCLCs when using cisplatin-base chemotherapy treatment in an adjuvant setting (after surgery). Adjuvant cisplatin-based chemotherapy has also become the standard of care at clinics. Adjuvant radiation therapy is not standard of care as its role is still unclear, but it is being investigated in clinical trials.
- **Stage III.** Since this patient group highly heterogeneous, and the tumour size and mediastinal involvement varies a lot, there is no clear treatment. However, chemoradiotherapy is the backbone of the treatment. The standard chemotherapy is a platinum-based doublet, which includes a platinum compound, such as cisplatin or carboplatin, and either docetaxel, paclitaxel, vinorelbine, or gemcitabine. The median overall survival is 8–11 months with first-line platinum-based doublet chemotherapy⁷⁴. Whether to use surgery for stage III NSCLC is debated, and it is unclear if it improves survival.
- **Metastatic disease.** Platinum-based doublet chemotherapy has improved the 1-year survival from 20% to 29% in advanced NSCLC, which is also the standard of care for metastatic NSCLC⁷⁵.

Staging determines treatment and prognosis

Staging based on the TNM classification

⁷³ Da Cunha Santos G. et al. Annual Review of Pathology: Mechanisms of Disease 6 (2011): 49-69.

⁷⁴ Dempke WCM. Translational Lung Cancer Research 2.6 (2013): 435.

⁷⁵ Reck M. et al. The Lancet 382.9893 (2013): 709-719.

- **Second-line treatment.** If a patient is treated initially with chemotherapy, second-line treatment usually consists of a single chemotherapeutic agent, such as docetaxel or pemetrexed, or with targeted therapy erlotinib, or chemotherapy plus targeted therapy, e.g. ramucirumab.

Targeted therapies

VEGF antibodies

- **Bevacizumab (Avastin)** is a recombinant humanised monoclonal VEGF antibody that slows the growth of new blood vessels. It is the standard of care for metastatic non-squamous NSCLC, and was approved after a phase III trial that showed improved overall survival when combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone. The median overall survival in the bevacizumab group was 12.3 months, versus 10.3 months in the chemotherapy-alone group. 1- and 2-year survival rates in the bevacizumab group were 51% and 23%, respectively, versus 44% and 15%, respectively, in the chemotherapy-alone group⁷⁶.
- **Ramucirumab (Cyramza)** is FDA approved in combination with docetaxel for metastatic NSCLC after treatment with platinum-based chemotherapy. In the phase III study (REVEL) statistically significant improved survival and progression-free survival (PFS) was shown. Median overall survival (OS) for patients treated with ramucirumab and docetaxel was 10.5 months, while for patients treated with docetaxel and placebo OS was 9.1 months. Median PFS for the ramucirumab group was 4.5 months, and 3.0 months for the placebo group⁷⁷.

EGFR-inhibitors

- **Erlotinib (Tarceva)** is an EGFR tyrosine kinase inhibitor FDA approved for first-line therapy of metastatic NSCLC with EGFR mutations, maintenance therapy for advanced and metastatic NSCLC after four cycles of platinum-based chemotherapy, and second/third-line therapy in advanced NSCLC.
 - In the pivotal phase III trial for second- and third-line approval OS and PFS was extended for patients who received erlotinib. OS for patients receiving erlotinib was 6.7 months, versus 4.7 months in the placebo group. The median PFS was 2.2 months in the erlotinib group and 1.8 months in the placebo group. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group.
 - The pivotal phase III trial, SATURN, evaluated erlotinib as maintenance treatment in advanced NSCLC after first-line chemotherapy. The study showed significantly prolonged PFS for patients treated with erlotinib, 12.3 weeks for patients treated with erlotinib and 11.1 weeks for patients treated with placebo. Overall survival was 12.0 months for patients treated with erlotinib, and 11.0 months for patients treated with placebo.
 - EURTAC, an open-label, randomised phase III trial evaluated the efficacy of erlotinib as first-line treatment in patients with advanced EGFR-mutation positive NSCLC. In the study prolonged PFS was noted in the patient group receiving erlotinib in comparison to the patient group treated with standard chemotherapy (cisplatin with docetaxel or gemcitabine), but no major differences in OS was noted between the two groups (19.3 months versus 19.5 months). The PFS in the erlotinib group was 9.7 months, versus the chemotherapy group where PFS was 5.2 months.
- **Gefitinib (Iressa)** is also an EGFR tyrosine kinase inhibitor. Iressa received accelerated approval by FDA in 2003 after a single-arm phase II trial that shows reduced tumour proliferation in patients with advanced NSCLC who had not responded to previous treatments⁷⁸. However, post market studies failed to show any clinical benefit from gefitinib. Therefore the drug was withdrawn from the US market in 2012⁷⁹. In 2009 the European Commission granted marketing authorisation for gefitinib for treatment of locally

⁷⁶ Sandler A. et al. New England Journal of Medicine 355.24 (2006): 2542-2550.

⁷⁷ EB Garon et al. The Lancet 384.9944 (2014): 665-673.

⁷⁸ Franz S. Nature Reviews Drug Discovery 4.2 (2005): 94-94.

⁷⁹ www.federalregister.gov/articles/2012/04/25/2012-9944/astazeneca-pharmaceuticals-lp-withdrawal-of-approval-of-a-new-drug-application-for-iressa

advanced or metastatic NSCLC of all lines of treatment. Marketing authorisation was based on two phase III pivotal studies, IPASS and INTEREST:

- The IPASS study evaluated the efficacy of gefitinib as first-line treatment and compared it with doublet chemotherapy (carboplatin and paclitaxel) in patients from Asia with advanced NSCLC. The 12-month rates of PFS were 24.9% with gefitinib and 6.7% with chemotherapy.
- The INTEREST study evaluated the efficacy of gefitinib was studied in patients with locally advanced or metastatic NSCLC who had been pre-treated with platinum-based chemotherapy. Gefitinib was compared with docetaxel and the study showed that gefitinib was equivalently effective as docetaxel with similar OS, PFS, and tumour response.
- **Afatinib (Giotrif)** is an EGFR tyrosine kinase inhibitor FDA approved for first-line treatment of metastatic NSCLC with specific EGFR mutations (exon 19 deletion or exon 21 substitution mutations). The exon 19 deletion is the most common EGFR mutation, up to 50% of EGFR mutations is the exon 19 deletion. Its efficacy has been studied in two randomised phase III trials: LUX-Lung 3 and LUX-Lung 6, both studies compared afatinib with doublet chemotherapy regimens in previously untreated NSCLC patients with EGFR mutations. The OS in both studies did not differ significantly between the afatinib and chemotherapy group (LUX-Lung 3: median OS 28.2 versus 28.2 months; LUX-Lung 6: median OS 23.1 versus 23.5 months). However, in patients with exon 19 deletion OS was significantly increased with afatinib treatment (LUX-Lung 3: median OS 33.3 versus 21.1 months; LUX-Lung 6: median OS 31.4 versus 18.4 months). The same effect in OS was not seen in patients with exon 21 substitution. The PFS was significantly improved in the afatinib arm, where median PFS was 11.1 months, in the chemotherapy arm median PFS was 6.9 months.

EML4-ALK inhibitors

- **Crizotinib (Xalkori)** is approved for metastatic NSCLC that are ALK-positive. The clinical efficacy of crizotinib has been evaluated in two randomised phase III trials:
 - One study analysed the effects of the drug compared to chemotherapy in patients with metastatic ALK-positive NSCLC who had previously been treated with one platinum-based chemotherapy regimen. The study showed that crizotinib is superior to standard chemotherapy, PFS was 7.7 months with crizotinib compared to 3.0 months with chemotherapy, and the response rates were 65% with crizotinib and 20% with chemotherapy⁸⁰.
 - The other randomised phase III trial (PROFILE 1014) analysed the effects of crizotinib as first-line treatment and compared it to standard chemotherapy. The primary endpoint was PFS, and the study met the objective as crizotinib was superior to standard chemotherapy and prolonged PFS. PFS for patients treated with crizotinib was 10.9 months, while for patients treated with chemotherapy PFS was 7.0 months. Median OS was not reached for either of the groups⁸¹.
 - Crizotinib received accelerated approval by FDA in 2011 after showing impressive response rates in phase I and II trial, 61% and 51%, respectively, and a favourable side-effect profile⁸².
- **Ceritinib (Zykadia)** was approved by the FDA in April 2014 for ALK-positive metastatic NSCLC that have progressed or in patients intolerant to crizotinib. The drug was granted accelerated approval after showing an overall response rate (ORR) of 43.6% in patients with metastatic NSCLC after progression or intolerance to crizotinib in the phase I trial ASCEND-1⁸³. Recent results from two phase II trials (ASCEND-2 and -3) support the positive results seen in ASCEND-1. The ASCEND-2 study investigated the effect of ceritinib in patients previously treated with chemotherapy and crizotinib, while the

⁸⁰ Shaw AT. et al. New England Journal of Medicine 368.25 (2013): 2385-2394.

⁸¹ Solomon B. et al. Annals of Oncology 25.suppl 4 (2014): iv427-iv427.

⁸² Sahu A. et al. South Asian journal of cancer 2.2 (2013): 91.

⁸³ www.cancer.gov/about-cancer/treatment/drugs/fda-ceritinib

ASCEND-3 study investigated ceritinib in crizotinib-naïve patients. In the ASCEND-2 study the ORR was 38.6% and the PFS was 5.7 months. In the ASCEND-3 the ORR was 63.7% and the median PFS was 11.1 months. Both results are by investigator assessment.

Size of patient pool

The incidence of lung cancer in 2012 in EU-28, North America, East Asia, Australia, and New Zealand was c1,360,000 cases. GlobalData estimates an annual growth rate of the NSCLC incidence of 2.2% during 2012–2022e in the nine major markets (see below), largely driven by a rapid increase in the number of cases in China and India. Excluding China and India, the 2012–2022e CAGR is c1.6%, and the number of cases in the 7MM (China and India excluded) will rise from c440,000 in 2012 to c510,000 in 2022, according to GlobalData estimates.

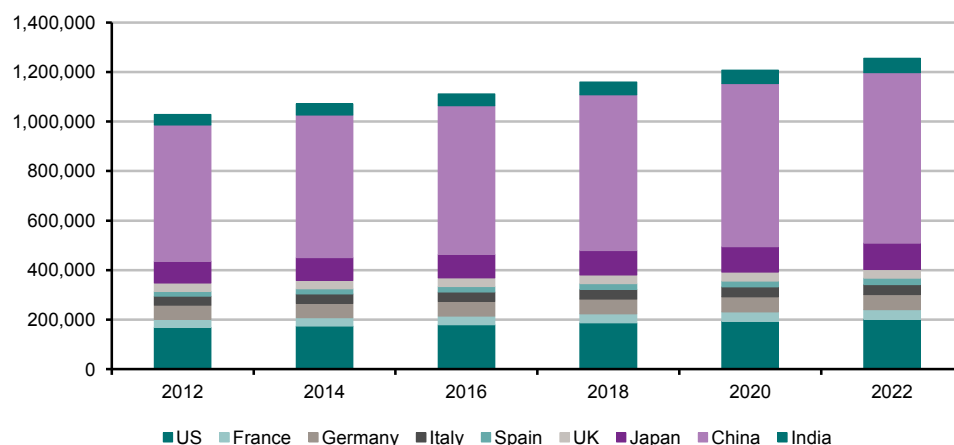
c85% of the diagnosed lung cancer cases are NSCLC, of which c57% are diagnosed at an advanced stage. Approximately c25% of patients with NSCLC have a RAS mutation. Hence, we estimate that the potential market size for Targovax is c300,000 patients (c1.4m cases of lung cancer where c85% are NSCLC and c25% with RAS mutations).

As the chart below shows, China has the highest incidence of NSCLC, which can be explained by the population size, population growth during the forecast period, and the high rate of smoking (e.g. 50% in men)⁸⁴.

Incidence expected to have 2012–2022 CAGR of 2.2% according to GlobalData

c25% of NSCLC patients have RAS mutations

NSCLC incidence 2012–2022e in the nine major markets



Source: GlobalData

⁸⁴ GlobalData

Probability of success

Given the stage of the various research projects as well as the focus areas, we highlight some relevant industry data on overall likelihood of approval (LOA) and the most relevant phase success rates (the probability that a project moves from its current phase to the next).

Latest data covers large set of companies and drugs

There was a large publication in Nature Biotechnology from January 2014 where the researchers had looked at 835 companies, 7,300 indications, and more than 4,400 drugs in various phases. The companies were a mix of large pharma, mid-sized pharma, and emerging biotech companies.

Base-line characteristics

| Company size | Companies | | Indications | | Drugs | |
|--|-----------|------|-------------|------|--------|------|
| | Number | % | Number | % | Number | % |
| Large pharma/biotech (>USD5bn in sales) | 33 | 4% | 3,573 | 48% | 2,075 | 47% |
| Small -to mid-sized pharma/biotech (USD0.1bn–5bn in sales) | 90 | 11% | 1,099 | 15% | 724 | 16% |
| Emerging biotech (<USD0.1bn in sales) | 712 | 85% | 2,700 | 37% | 1,652 | 37% |
| Total | 835 | 100% | 7,372 | 100% | 4,451 | 100% |

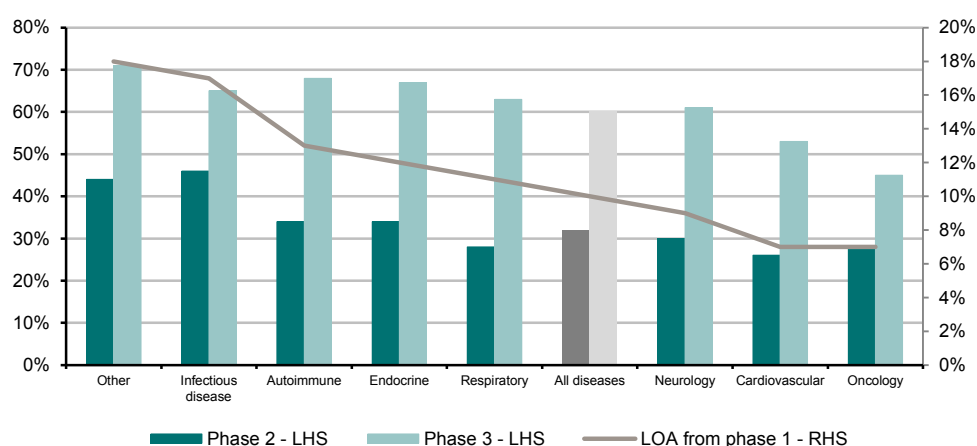
Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-51

The large population of drugs and companies also allowed the authors to split success rates by broad indication and by more narrowly defined diseases in some cases. As in other studies, the authors looked at two types of success: 'phase success' and 'likelihood of approval'. The first metric gives the probability of a development project moving from its current development phase to the next stage, while the LOA gives a probability of the project moving all the way to an approved drug from its current position in the development process.

Two types of success rates: phase success and likelihood of approval

Based on the data in the Hay's study, we show the likelihood of phase success (that a substance moves from current phase to the next phase) when in phase 2 and phase 3 as well as the likelihood of approval (LOA) from phase 1. LOA is the probability that the asset moves all the way from phase 1 to the market. We display the data for selected larger therapy areas.

Phase success and LOA for selected therapy areas



Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-51. Note: LHS=Left Hand Scale and RHS= Right Hand Scale.

Relevant to the development in Targovax, we can see that the overall probability of success in the oncology segment of the drug development market is the lowest of these broad indication areas. The total LOA from phase 1 averages 7% probability for oncology.

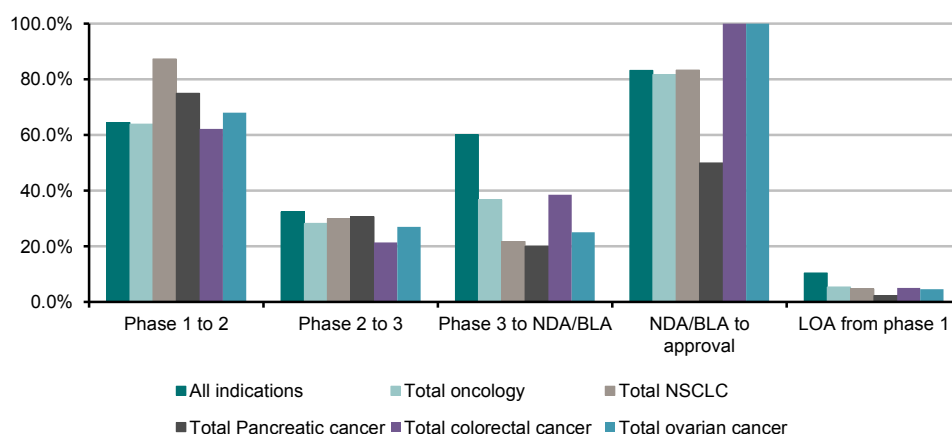
LOA is lower for oncology indications

The fact that the study included more than 4,400 compounds at various stages of development and for a multitude of indications made it possible to display phase successes as well as overall likelihood for approval down to individual indications in certain cases. Below we show the phase success for all indications in the study as well as for total oncology, pancreatic cancer, colorectal cancer, ovarian cancer, and NSCLC. As expected, the phase

Phase success lowest in phase 2

success is lowest in phase 2 and highest in the approval phase. Note that the phase success for NSCLC is clearly higher than the rest of the groups in the phase 1 while it is on average in phase 2. When it comes to the point that matters the most – phase 3 where the outcome data is confirmed in larger trials – NSCLC has among the lowest success rates of the segments. For pancreatic cancer, the pattern is very similar, with a high probability of phase success in phase 1 but clearly the lowest phase success in the most important phase 3. The approval success rate for the pancreatic indication is also clearly lower than the rest of the segments. Hence, the LOA from phase 1 for all pancreatic cancer drugs averages only 2.3%.

Success rates and LOA in the M.Hay study

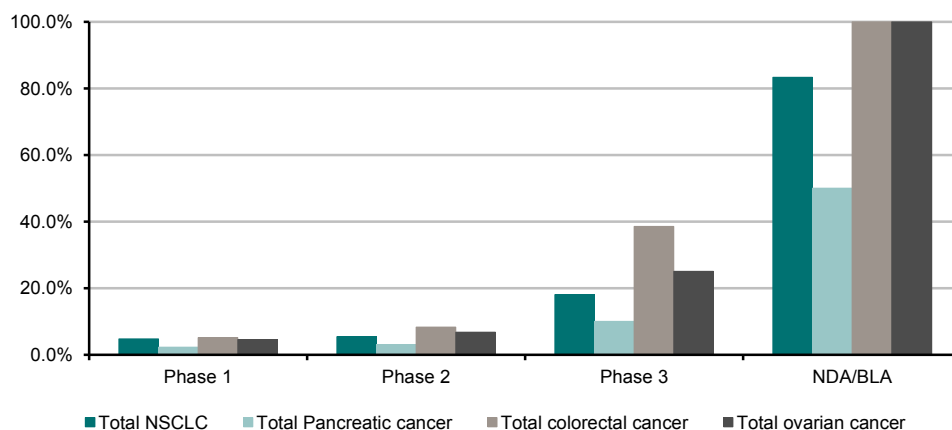


Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-5

Based on the data from the M.Hay study and given the projects in Targovax are mainly in phase 1 or entering phase 2, it is logical to apply a success rate on the projects of c5–10%.

LOA for Targovax's projects are likely to be c5–10%

LOA for Targovax selected areas of development



Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-51

The factor that could change the LOA in a case like Targovax is whether a pipeline drug is approved on pivotal phase 2 data only and does not need to go through the full development programme. However, we remain conservative, as the majority of diseases addressed are large indications and early approval on phase 2 data is more common in orphan indications.

We remain conservative regarding the possibility of approval based on phase 2 data

To summarise the discussions on probabilities for success regarding the different projects in Targovax, we believe that the area of most likely LOA to be used in the valuation should be in c5–10%. The factors affecting the LOA are not only the stage of the current development but also that the therapeutic cancer vaccine market has not been overly successful in delivering strong clinical outcomes in the past, rather the opposite.

Probability of phase success as well as LOA from various stages of development

| | Phase I to phase II | | | | Phase II to phase III | | | | Phase III to NDA/BLA | | | | NDA/BLA to approval | | | |
|-------------------------------------|---------------------|-----------------------|---------------|-----------|-----------------------|-----------------------|---------------|-----------|----------------------|-----------------------|---------------|-----------|---------------------|-----------------------|---------------|-----------|
| | Total in phase | Advanced or suspended | Phase success | Phase LOA | Total in phase | Advanced or suspended | Phase success | Phase LOA | Total in phase | Advanced or suspended | Phase success | Phase LOA | Total in phase | Advanced or suspended | Phase success | Phase LOA |
| All indications | 2,541 | 1,918 | 64.5% | 10.4% | 3,743 | 2,268 | 32.4% | 16.2% | 1,554 | 975 | 60.1% | 50.0% | 908 | 659 | 83.2% | 83.2% |
| Total oncology | 919 | 651 | 63.9% | 5.4% | 1,451 | 827 | 28.3% | 8.5% | 383 | 147 | 36.7% | 30.0% | 142 | 104 | 81.7% | 81.7% |
| Total solid tumours | 668 | 483 | 66.7% | 5.7% | 1,114 | 636 | 26.3% | 8.6% | 299 | 172 | 41.3% | 32.7% | 88 | 67 | 79.1% | 79.1% |
| Renal cell cancer (RCC) | 20 | 15 | 86.7% | 18.4% | 54 | 33 | 30.3% | 21.2% | 15 | 10 | 70.0% | 70.0% | 7 | 6 | 100.0% | 100.0% |
| Head and neck cancer | 6 | 5 | 100.0% | 14.3% | 23 | 12 | 50.0% | 14.3% | 14 | 7 | 42.9% | 28.6% | 3 | 3 | 66.7% | 66.7% |
| Hepatocellular (liver) cancer (HCC) | 18 | 15 | 73.3% | 6.6% | 39 | 25 | 36.0% | 9.0% | 12 | 4 | 25.0% | 25.0% | 1 | 1 | 100.0% | 100.0% |
| Breast cancer | 54 | 47 | 68.1% | 5.7% | 119 | 61 | 21.3% | 8.4% | 34 | 25 | 56.0% | 39.2% | 14 | 10 | 70.0% | 70.0% |
| Non-small cell lung cancer (NSCLC) | 63 | 55 | 87.3% | 5.7% | 161 | 94 | 29.8% | 6.5% | 46 | 23 | 26.1% | 21.7% | 11 | 6 | 83.3% | 83.3% |
| Prostate cancer | 42 | 8 | 71.0% | 5.6% | 103 | 24 | 20.9% | 7.8% | 25 | 8 | 56.3% | 37.5% | 11 | 3 | 66.7% | 66.7% |
| Colorectal cancer (CRC) | 45 | 37 | 62.2% | 5.1% | 87 | 56 | 21.4% | 8.2% | 18 | 13 | 38.5% | 38.5% | 4 | 4 | 100.0% | 100.0% |
| Ovarian cancer | 31 | 25 | 68.0% | 4.6% | 72 | 37 | 27.0% | 6.8% | 15 | 8 | 25.0% | 25.0% | 3 | 1 | 100.0% | 100.0% |
| Pancreatic cancer | 29 | 24 | 75.0% | 2.3% | 66 | 36 | 30.6% | 3.1% | 19 | 10 | 20.0% | 10.0% | 2 | 2 | 50.0% | 50.0% |
| Total haematological tumours | 216 | 152 | 58.6% | 9.9% | 317 | 179 | 34.6% | 16.9% | 78 | 45 | 55.6% | 48.8% | 48 | 33 | 87.9% | 87.9% |
| Multiple myeloma (MM) | 43 | 29 | 69.0% | 9.7% | 48 | 30 | 23.3% | 14.0% | 13 | 5 | 60.0% | 60.0% | 5 | 4 | 100.0% | 100.0% |
| Non-Hodgkin's lymphoma (NHL) | 38 | 28 | 57.1% | 8.5% | 62 | 35 | 40.0% | 14.8% | 19 | 9 | 44.4% | 37.0% | 8 | 6 | 83.3% | 83.3% |
| Chronic lymphocytic leukaemia (CLL) | 17 | 12 | 50.0% | 7.3% | 41 | 24 | 29.2% | 14.6% | 10 | 8 | 62.5% | 50.0% | 7 | 5 | 80.0% | 80.0% |
| Myelodysplastic syndrome (MDS) | 12 | 7 | 71.4% | 4.8% | 22 | 9 | 33.3% | 6.7% | 6 | 5 | 20.0% | 20.0% | 4 | 3 | 100.0% | 100.0% |

Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-51

Manufacturing and logistics

The company has a relatively straightforward manufacturing set-up, with contract manufacturing organisations (CMOs) manufacturing the vaccine products.

GM-CSF used as adjuvant in peptide vaccines

One interesting twist to the manufacturing is that the company is considering, over time, to manufacture its own GM-CSF and sell it as an integrated part of the final vaccine (only when it comes to the peptide-based vaccines). The main reason for this is that the supply situation for global GM-CSF is challenging to say the least. In the clinical trials, Targovax has used a GM-CSF called molgramostim (that is manufactured by a biosimilar supplier in China).

To continue to use molgramostim in the clinical trials, Targovax was buying the product from a biosimilar manufacturer in China, but has planned (if the clinical data supports further development of the TG platform) to proceed with its own manufacturing in Europe. As we understand it, the company has been in discussions with a very well-reputed CMO to manufacture the GM-CSF in Europe (Wacker Chemie AG). The plan is to get the peptide vaccines and the GM-CSF registered as one product and hence not to register the GM-CSF as a stand-alone product. This should reduce the registration risk, we believe, but one should not totally ignore it. It should be noted though that we do not include any costs for these activities in our model as we believe that the company needs to have supportive clinical data from both the TG01 trial and the TG02 trial to proceed with this project.

Peptide vaccines and GM-CSF

The peptides going into the Targovax vaccines are relatively easy to manufacture and production is handled by a well-known and well-reputed CMO in Switzerland (Bachem). We understand that the combined COGS for the peptide vaccines and the GM-CSF will be highly competitive and we expect manufacturing costs for the combined package to be a low/mid single-digit percentage of the estimated sales price. The product already has a proven 3-year shelf life and can be shipped using standard shipment procedures.

Oncolytic virus vaccines

These are manufactured in Finland by a CMO. As with the peptide vaccines, the manufacturing process is relatively straightforward and should generate COGS of a low/mid single-digit percentage of the estimated sales price; hence, for a partner, this should be a true high gross margin product. ONCOS-102 will be an off-the-shelf product. Regarding storage, the product today needs to be stored at minus 60°C but the company has started to document that it is stable at minus 20°C and hence ordinary cold storage and cold shipments should be able to be used in the future. Since the product is based on virus, it is important to note that the company already has an open IND in the US allowing inter-state transportation and distribution.

Company is considering manufacturing its own GM-CSF at a CMO in Europe in the future

Will proceed with discussions about GM-CSF production in case clinical data supports continued development

Peptides easy and relatively cheap to manufacture

Relatively straightforward production

Market models – main indications

In this section we estimate the potential addressable markets for Targovax's vaccines and indications. We present the background information and assumptions that go into the model. In general we have used a NPV SOTP model, which is a type of DCF. As we do probability adjustments on each individual project, we use a relatively normal WACC (10%) when doing the NPV calculations.

Resected pancreatic cancer

For resected pancreatic patients, we start with the total number of potential pancreatic patients but adjust it to the c15% of all patients that are able to have surgery and get the cancer resected. These patients will form the target population for Targovax product TG01.

Historically, pancreatic cancer has been very difficult to treat; hence, we use a relatively low Likelihood of Approval (LOA), only 5%. We estimate that the product will be out-licensed and that the company receives a royalty rate of c20% and that launch takes place in 2021. In our model we have factored in a linear market uptake curve and that peak penetration is reached after five years and at a level of 33% of patients with resectable pancreatic cancer.

Assumptions used in NPV SOTP model

15% have resectable pancreatic cancer

LOA only 5%

Resected pancreatic cancer – model assumptions

| | |
|-----------------------------------|--|
| Product | TG01 |
| Price (per patient per treatment) | USD65,000 in the US USD45,000 in Europe and RoW |
| Resected | 15% of patients |
| Likelihood of Approval (LOA) | 5% |
| RAS-mutations | >90% |
| Total patient base | 105,000 |
| Launch year | 2021 |
| Peak penetration | 33% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 3% |

Source: DNB Markets

Malignant mesothelioma

This is an orphan drug indication. We estimate there are c25,000 patients in the developed world that suffer from malignant mesothelioma. The annual incidence varies a lot between markets but in general we see that c20 people per million inhabitants is an average level of incidence in most countries.

Given the rareness of the disease and the poor treatment outcomes, we believe a decent outcome in clinical trials will open up for rather high penetration in this market segment; hence we estimate that c50% of available patients will be the peak penetration. The Likelihood of Approval (LOA) is set at 10%, slightly above what we use for the other potential indications, again due to the severity of the disease and the lack of treatment options for patients.

Orphan drug indication

Peak penetration of c50%

Malignant mesothelioma – model assumptions

| | |
|-----------------------------------|--|
| Product | ONCOS-102 |
| Price (per patient per treatment) | USD65,000 in the US USD45,000 in Europe and RoW |
| Likelihood of Approval (LOA) | 10% |
| Total patient base | c25,000 |
| Launch year | 2021 |
| Peak penetration | 50% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 1% |

Source: DNB Markets

Melanoma

This is a relatively large indication and has been the focus area for most CPIs reaching the market in recent years. The company is developing ONCOS-102 for this indication and this is a relatively small indication with c40,000 patients in the developed world (assuming the product is only used in patients with advanced and metastatic disease). Again we assume that the company out-licenses the product and receives a royalty based on sales in the market of c20%. Peak penetration is estimated at c33% (but only in the sub-group with metastatic disease) and we use a 5% Likelihood of Approval (LOA) given the current development state of the project.

Central indication for CPIs

Melanoma – model assumptions

| | |
|-----------------------------------|---|
| Product | ONCOS-102 |
| Price (per patient per treatment) | USD650,000 in the US USD45,000 in Europe and RoW |
| Likelihood of Approval (LOA) | 5% |
| Total patient base | c40,000 |
| Launch year | 2021 |
| Peak penetration | 33% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 3% |

Source: DNB Markets

Colorectal cancer

This is a relatively large cancer form today, but only c40% of patients have RAS mutations and hence are suitable for treatment with TG02. Testing patients for RAS mutation is more or less a standard procedure today, and we estimate that a maximum of 40% of the colorectal cancer population will be the target population for Targovax. This is the first indication for the TG02 product, which contains an additional peptide above what is found in TG01, making it slightly more suitable for colorectal cancer and NSCLC patients.

40% have RAS mutations

This is a challenging indication with a lot of competition. We estimate the company has a c5% Likelihood of Approval (LOA) and that the peak penetration could reach c10% five years after launch.

Challenging indication

Colorectal cancer – model assumptions

| | |
|-----------------------------------|---|
| Product | TG02 |
| Price (per patient per treatment) | USD650,000 in the US USD45,000 in Europe and RoW |
| Likelihood of Approval (LOA) | 5% |
| Total patient base | 800,000 |
| RAS mutations | 40% |
| Launch year | 2021 |
| Peak penetration | 10% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 2% |

Source: DNB Markets

Ovarian cancer

Ovarian cancer is again an indication for ONCOS-102. The company is expected to conduct an early stage dose-escalation study in this indication, co-ordinated and sponsored by Ludwig Cancer Research and Cancer Research Institute. The cancer virus, ONCOS-102, will be investigated in combination with a checkpoint inhibitor, provided by an as-yet un-named big pharma company.

Collaborative study

We estimate that the Likelihood of Approval (LOA) is c5% and if the product reaches the market the possible peak penetration could be 20% five years after launch.

Ovarian cancer – model assumptions

| | |
|-----------------------------------|--|
| Product | ONCOS-102 |
| Price (per patient per treatment) | USD65,000 in the US USD45,000 in Europe and RoW |
| Likelihood of Approval (LOA) | 5% |
| Total patient base | 60,000 |
| Launch year | 2021 |
| Peak penetration | 20% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 1% |

Source: DNB Markets

Prostate cancer

The company will proceed on its own initially and is planning to start the first phase I proof of concept trial during 2016. The first trial will take place in the Czech Republic in co-operation with Czech company Sotio.

This is another potentially large indication (number of patients), but competition is intense and Targovax will address only advanced metastatic castrate-resistant prostate cancer. We estimate that up to c15% of the total patient population are in Stage IV at diagnosis.

Large indication with intense competition

Prostate cancer – model assumptions

| | |
|--|--|
| Product | ONCOS-102 |
| Price (per patient per treatment) | USD65,000 in the US USD45,000 in Europe and RoW |
| Proportion of patients with advanced disease | 15% |
| Likelihood of Approval (LOA) | 5% |
| Total patient base | 1,100,000 |
| Launch year | 2021 |
| Peak penetration | 5% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 3% |

Source: DNB Markets

NSCLC

NSCLC is another large patient group, with 20–30% of patients having the RAS mutation. Clinicians do not regularly type patients for RAS mutations, but we believe this will change. So for the TG02 product, c25% of patients with NSCLC are the addressable population. NSCLC is not a prioritised indication, so development and market introduction (if successful) should come later than other indications. TG02 will be the product aimed for this indication.

Not a prioritised indication at this stage

This indication is not one that the company is prioritising, and hence we expect this indication to reach the market later than the other indications (in 2024) and with a lower LOA (2.5%).

NSCLC – model assumptions

| | |
|-----------------------------------|--|
| Product | TG02 |
| Price (per patient per treatment) | USD65,000 in the US USD45,000 in Europe and RoW |
| Likelihood of Approval (LOA) | 2.5% |
| Total patient base | 1,400,000 |
| Launch year | 2024 |
| RAS mutations | c25% |
| Peak penetration | 5% |
| Years from launch to peak | 5 years |
| Royalty rate | 20% |
| Annual growth in patient base | 2% |

Source: DNB Markets

Valuation and forecasts

We consider it important to state that the historical earnings are not representative for the current corporate structure and cost base. In mid-2015 Targovax officially acquired Oncos and hence the historical earnings are not pro-forma based, rather they include Oncos for approximately six months in 2015 and for 2013–2014 include only the costs in Targovax stand-alone (without Oncos). However, for 2016 onwards we have the combined operation for Targovax and Oncos in our estimates.

Valuing a company at Targovax's stage of development is always a challenge, since there are no revenues to speak of and it is expected to be loss-making for many years. Several valuation approaches are possible, including a DCF model for the total company (with a very long forecast period), a SOTP NPV model with a value for each project, or a peer group comparison with other biotech companies at a similar stage of development. Also, one can look at transaction multiples where similar companies have been acquired by larger entities. Approaches that involve a comparison with similar companies will, however, struggle to find something similar and define how similar is similar enough. Another issue is that most similar companies (just as Targovax) are loss-making, so there are no relevant key ratios to look at.

Our preferred valuation approach

Our preferred method of valuing a company like Targovax is to use a SOTP NPV model. Since this is a version of a DCF model it is long-term in its approach but it also specifies a value per project, which we find useful when projects are based on different technologies and/or different mechanisms of action.

The additional information gained by the SOTP NPV model is a feeling for the valuation contributions from the individual projects; and particularly in cases where one or more projects fail or are delayed, it is easy to get an understanding of the implications of such an event on the total company valuation. This is, however, only true when a failure (or success) in one project does not have an immediate impact on other projects in the pipeline portfolio.

Base-case SOTP valuation

In our base-case SOTP valuation of Targovax we have used the following inputs:

- LOA (likelihood of approval) of 2.5–10% depending on project:
 - Resected pancreatic cancer – 5%.
 - Mesothelioma – 10%.
 - NSCLC – 2.5%.
 - Melanoma – 5%.
 - Colorectal cancer – 5%.
 - Ovarian cancer – 5%.
 - Prostate cancer – 5%.
- WACC of 10% (as the probability adjustment reflects the risk of the individual projects, we see no need to increase the WACC to reflect the risk in the projects).
- The cost of developing projects is seen as central costs in our model.
- We expect the company to out-license the products at a relatively early stage and thus receive royalties on global sales of c20% (the same for all products).
- All corporate overheads are deducted from the total NPV value of the sum of the projects.
- Revenue per treatment of cUSD65,000 per patient for all indications in the US and cUSD45,000 outside the US. This gives a blended average of cUSD55,000.
- We expect COGS to be low given Targovax's manufacturing set-up with well-reputed CMOs manufacturing the peptides and GM-CSF. We see a maximum COGS of c5% of sales. A low manufacturing cost for the products also supports a relatively high royalty rate, we believe.

Historical earnings not representative

We use a SOTP NPV model

Assumptions used

The real question is the speed the products might get to the market. As we see it, it is highly unlikely that the company would try to take the products to the market on its own; hence the most reasonable scenario is a partnership with a larger pharmaceutical company. The main reason we do not believe it will take the products to market is that it uses the same products for different indications. Even though it could, theoretically, for example take ONCOS-102 to market in MPM, it would still need a partner for the other indications and we believe that a potential partner would like to take all indications – or none at all.

As mentioned earlier, Targovax has orphan drug designations for several indications and this could speed up the time to market in these indications. However, it is still uncertain what the longer-term clinical data might show and the only ODD indication where the company has come to phase I/II is resected pancreatic cancer. Mesothelioma and ovarian cancer are still in phase I and in the pre-clinical stage. Thus, we believe it is most likely that Targovax will sign a partnership agreement and that the partner will drive more or less all indications in parallel; therefore we expect the vaccines to reach the market in 2021 for all indications except NSCLC (a non-prioritised indication as of now, we expect it to reach the market in 2024).

New cancer drug prices are high

In our valuation we estimate that the global average price for TG01/TG02 and ONCOS-102 is cUSD55,000 per patient treated. The company has not given any indication of the price for TG01/TG02 or ONCOS-102. Rather, we have looked at what prices new drugs are commanding in the oncology space. In the table below, we have included new oncology drugs that have reached the market in the US since 2013. The price per month per patient column indicates that most new cancer drugs are priced at cUSD10,000 per patient per month (except Blincyto, which is priced at cUSD64,000 per month).

Drug prices oncology US

| Brand name | Substance | Year of approval | Indication | Price/month (USD) |
|------------|---------------------------|------------------|-------------------|-------------------|
| Tecentriq | atezolizumab | 2016 | Urothelial cancer | 12,500 |
| Venclexta | venetoclax | 2016 | CLL | 9,125 |
| Imlygic | talimogene laherparepvec | 2015 | Melanoma | 10,800 |
| Farydak | panobinostat | 2015 | Myeloma | 10,035 |
| Ibrance | palbociclib | 2015 | Breast cancer | 9,978 |
| Lenvima | lenvatinib | 2015 | Thyroid cancer | 13,945 |
| Opdivo | nivolumab | 2014 | Melanoma | 12,500 |
| Blincyto | blinatumomab | 2014 | ALL | 64,260 |
| Keytruda | pembrolizumab | 2014 | Melanoma | 8,725 |
| Cyramza | ramucirumab | 2014 | Gastric & NSCLC | 13,256 |
| Zykadia | ceritinib | 2014 | NSCLC | 13,672 |
| Gilotrif | afatinib | 2013 | NSCLC | 6,170 |
| Gazyva | obinutuzumab | 2013 | CLL | 5,973 |
| Imbruvica | ibrutinib | 2013 | Lymphoma | 11,077 |
| Xofigo | radium 223 dichloride | 2013 | Prostate | 12,657 |
| Tafinlar | dabrafenib | 2013 | Melanoma | 9,564 |
| Mekinist | trametinib | 2013 | Melanoma | 8,955 |
| Pomalyst | pomalidomide | 2013 | Myeloma | 11,520 |
| Kadcyla | ado-trastuzumab emtansine | 2013 | Breast cancer | 10,807 |

Source: Memorial Sloan-Kettering, FDA, Bloomberg.

Amgen's oncolytic virus vaccine Imlygic, which was approved for melanoma in 2015 in the US and Europe, commands a price of cUSD65,000 in the US and cUSD45,000 in Europe for a 6-month treatment. We believe that this serves as a good benchmark for the potential price for Targovax products going forward. As the treatment in general takes c6 months, this is also in line with the average price of cUSD10,000 per month per patient.

Based on this we have estimated a price for ONCOS-102 and TG01/TG02 of cUSD65,000 per patient in the US (rather than estimate a price per month or per injection) as this treatment most likely will be conducted during a reasonable short time period and not repeated at a regular interval. There is, however, a discussion in the market about whether these high prices are reasonable and there might be increased pressure downward on prices going

Unlikely to take products to the market on its own

We expect the vaccines to reach the market in 2021

Global average price cUSD55,000

Imlygic a good benchmark for pricing

forward. The prices included above are for the US. For ex-US markets we estimate that the company could charge c70% of the US price. Hence in all markets outside the US we estimate that the price per patient for Targovax's therapeutic cancer vaccines will be cUSD45,000 per patient. Combining the US price estimate of cUSD65,000 per patient with the ex-US price estimate of cUSD45,000 gives us a global average of cUSD55,000 per patient.

Probability-adjusted sales forecasts

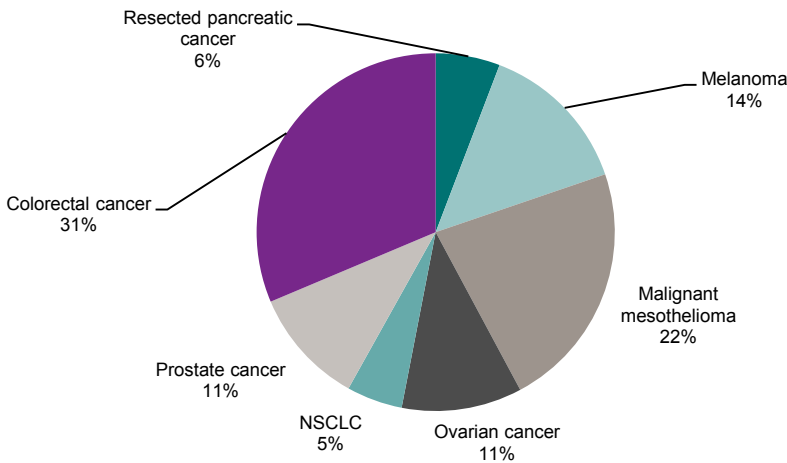
As mentioned earlier, we use probability-adjusted revenue forecasts for this type of company and the probability of success is relatively low at this early stage in the development. This can make the case seems high-risk, but compensating for this is that the company has several products in its pipeline and that the basic technologies for the oncolytic virus vaccines and the peptide vaccines are completely different and hence have uncorrelated outcomes.

Probability of success low

In the figure below, we have looked at the potential probability-adjusted sales revenues for the different indications in 2021–2031e. As shown, in our model the colorectal cancer indication is the largest followed by malignant mesothelioma.

Colorectal cancer is the largest indication

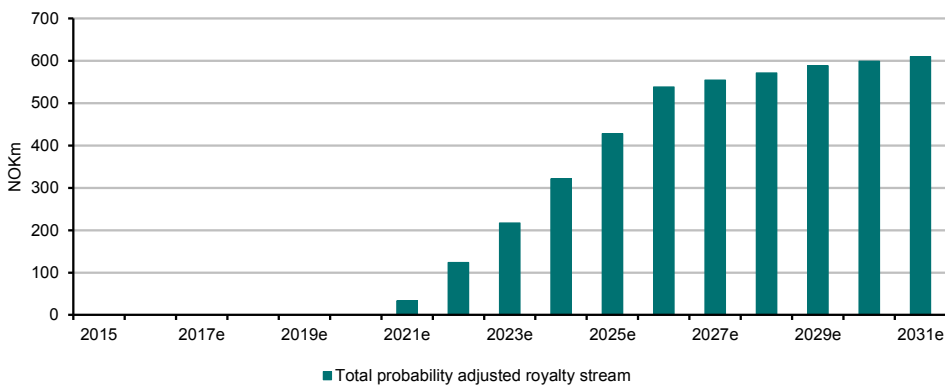
Value by indication



Source: DNB Markets

In the figure below we show the estimated probability-adjusted sales forecasts that go into the figure above and into our NPV SOTP valuation.

Total probability-adjusted royalty stream



Source: DNB Markets

Marketing strategy – upfront and royalties

We believe the most reasonable marketing strategy going forward for Targovax is to out-license the products to a big pharma partner (or to several) and get a partner that can take the costs for larger clinical trials and the market introduction of the products when the time comes. Looking at the pipeline from Targovax's perspective, we believe that two deals would be most appropriate – with the peptide vaccines out-licensed to one pharmaceutical partner and the

Out-licensing the most reasonable strategy

oncolytic virus vaccines to another. On the other hand, a potential partner might be interested in both technologies (to hedge its bet on the therapeutic cancer vaccines). We assume Targovax strikes one deal in the coming years for the two vaccine platforms.

The interesting question is how large the payments (upfront and milestones) might be. That is difficult to answer, but one can look at: 1) deal terms in the industry in recent years; or 2) more specifically the oncology or even immuno-oncology space and use these deals as a benchmark for what the company might hope to get. In the table below, we have looked at strategic alliances (all types) in the GlobalData deal analytics database. We searched for strategic alliances in 2013–2015 between big pharma and Biotech companies in the oncology space. Deals that did not have published deal values were excluded. We also excluded deals between big pharma and research institutions (in reality we only looked at public companies in the search). In total we found 53 deals classified as strategic alliances and fulfilled all other search criteria. Given the focus the industry has had on immuno-oncology for the past few years, a large proportion of the deals in the search include immuno-oncology deals.

Potential deal terms

Deal terms – oncology 2013–2015

| Total deals | Average upfront (USDm) | Average milestone payments (USDm) | Average deal value (USDm) |
|-------------|------------------------|-----------------------------------|---------------------------|
| 53 | 91.83 | 470.09 | 772.03 |

Source: GlobalData

Note that the average deal value (USD772m) is higher than the sum of the average upfront and average milestones, because in some transactions the total deal value is given but not split into what is upfront and what are milestones. Hence the average for upfront and milestones are based on fewer transactions than the total average deal values.

For transactions where the split was announced, on average the upfront payment was c16% of the total deal value. Applying this to the total average deal value implies that the upfront payment should be cUSD125m (16% of cUSD772m). We believe this is a reasonable level to assume for Targovax as well if it out-licenses the products at or around phase II.

Upfront payment c16% of the deal value

In general, the data available on the deals (from the GlobalData Deal database) do not specify royalty rates. The most common details (where financial information is available) are upfront payments, milestones, and total deal value. There are, however, a few deals where royalties were included and we have used 20% in our calculations, which is in line with the (few) deals available in GlobalData's database.

Estimated royalty rate of c20%

With all this in mind, we consider it reasonable to include at least one deal with big pharma where Targovax receives an upfront payment of cUSD125m and milestones of at least cUSD575m, in total a deal worth cUSD700m. The interesting question is how to include these upfront and expected milestones in the valuation model and at what probability. We have done the following: regarding the estimated upfront payment we believe there is a high probability of the company striking at least one deal with big pharma at the levels we highlighted above. As a result, we have included an upfront payment of USD125m in 2018e at a 30% probability. As for the expected milestones, they are most likely linked to the clinical development so we have used a probability of 5% (in line with the LOA for most projects in the valuation model). As we know nothing about the structure of a potential deal, we assume that a deal would be back-end loaded. As we have included a reasonably high royalty rate (20%) this usually goes hand in hand with a back-end loaded deal. For total milestones of USD575m, we have put cUSD325m in 2019–2021e (we estimate this is the most likely time for the first marketing approval of products) and the remaining cUSD250m as sales milestones to come after the products have been launched, hence in 2023e and 2024e. In summary the upfront and milestones should look as we highlight below according to our estimates.

Targovax could strike a deal worth cUSD700m, we believe

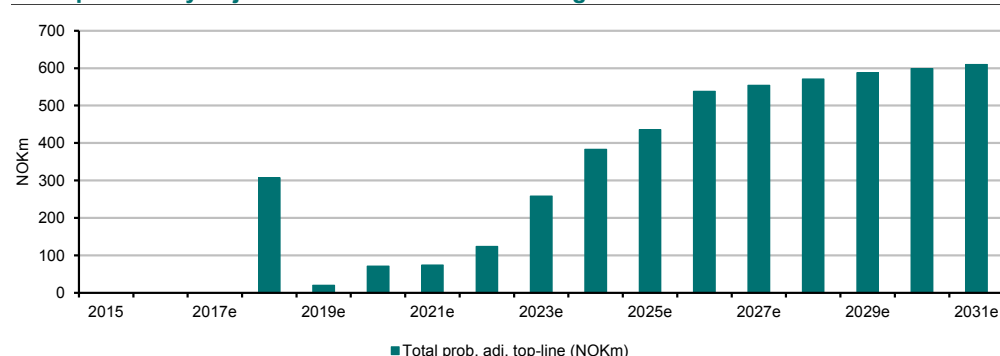
Upfront and milestones

| | 2016e | 2017e | 2018e | 2019e | 2020e | 2021e | 2022e | 2023e | 2024e |
|---------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Upfront and milestones (USDm) | 0 | 0 | 125 | 50 | 175 | 100 | 0 | 100 | 150 |
| Probability adjusted (USDm) | 0 | 0 | 37.5 | 2.5 | 8.75 | 5 | 0 | 5 | 7.5 |
| Prob. Adj upfront & milestones (NOKm) | 0 | 0 | 308 | 21 | 72 | 41 | 0 | 41 | 62 |

Source: DNB Markets

Hence, summarising the probability-adjusted revenue stream (upfront, milestone and royalties) for Targovax, gives the forecasts in the figure below.

Total probability-adjusted revenue stream for Targovax



Source: DNB Markets

Operating cost forecasts

In our calculations we have taken the operating costs forecasts in Targovax as a separate item that we deduct from revenues (royalties, upfront and milestone payments). Our forecasts for the company include mainly R&D-related expenses and expenses related to personnel.

The company is relatively small right now (c28 people) and in our view should be able to remain rather nimble. We believe it will have a large cost item called 'other operating expenses' related mainly to the CRO costs for driving forward the clinical development.

As Targovax does not quantify costs for each of the various activities, we have followed the reporting structure as it looks in Targovax. Hence we have looked at three main cost items:

- Payroll and related costs.
- External R&D costs.
- Other operating costs.

We forecast a relatively stable payroll line (at least for the next few years). The other two cost items in the P&L will most likely increase as the company is set to initiate several new clinical trials in H2 2016 and have all five trials running in H1 2017.

There are important things to keep in mind when looking at R&D costs, including the cost per patient in the trials. Some trials will be 'relatively' cheap while others might be more expensive. Trials run in collaboration with partners (ovarian cancer and prostate cancer) should be less costly as the partners take the bulk of the costs, while e.g. the colorectal trial (where Targovax might have to pay for a CPI in some cases) should be more expensive.

In general, we believe the costs for the different indications will range from USD50,000 per patient in some indications to above USD150,000 for others.

In our view, the clinical development for prostate, mesothelioma, and ovarian cancers should be at the lower end of the cost range, while colorectal should be towards the higher end (probably even above USD150,000 per patient, among other things due to the cost of CPI in the treatment regimen).

On top of this Targovax will need to spend some money on CMC for TG01 and TG02 as well as ONCOS-102. We estimate that these costs could total cNOK5m p.a. for the coming years.

Forecasts mainly include R&D-related expenses

One item that at some point in time will require high costs is the CMC for developing the GM-CSF. According to our calculations, this will require at least cNOK50m–80m. However, this is not an acute cost and Targovax should be able to postpone it until it is in a stronger financial position. Hence, we have postponed these costs in our calculations until 2018e onwards.

In the table below, we show our cost estimates for the coming years. Note that we expect an increase in Other operating expenses for 2018–2019e related to CMC.

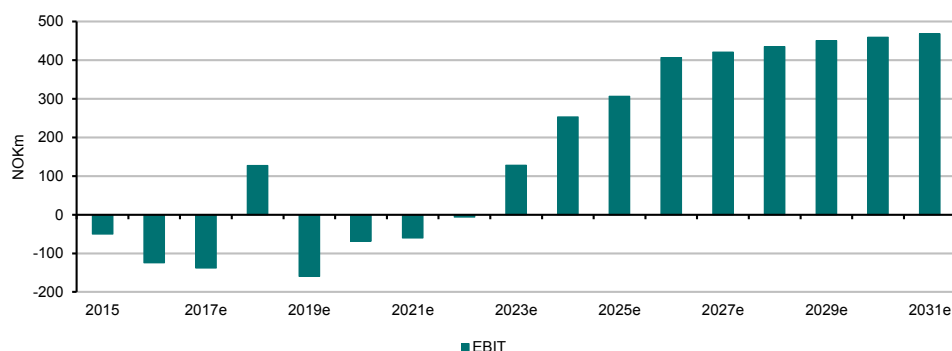
Cost base

| (NOKm) | 2015 | 2016e | 2017e | 2018e | 2019e | 2020e | 2021e | 2022e |
|---------------------------|-----------|------------|------------|------------|------------|------------|------------|------------|
| Payroll and related costs | 35 | 50 | 53 | 55 | 55 | 55 | 55 | 55 |
| External R&D costs | 10 | 45 | 45 | 50 | 55 | 50 | 50 | 45 |
| Other operating expenses | 5 | 30 | 40 | 75 | 70 | 35 | 30 | 30 |
| Sum | 50 | 125 | 138 | 180 | 180 | 140 | 135 | 130 |

Source: DNB Markets

Adding the operating cost forecast to our revenue forecast gives us our operating profit (loss) forecasts.

Targovax – operating profit (loss) forecasts



Source: DNB Markets

Sensitivity analysis

We believe that a NPV SOTP model is the most appropriate way to identify the underlying long-term value of a company like Targovax. Our target price is NOK17.

However, all DCF-based models are sensitive to the input variables and earlier we presented our base-case assumptions. Here we present some sensitivity analysis where we look at what impact changes in the discount rate (WACC at 10% in the base case) as well as drug prices (\pm USD10,000) might have on the value as well as what impact the royalty rate will have on the valuation. Remember that we estimate a 20% royalty rate in our base case.

WACC and drug price sensitivity - NOK per share

| | | WACC | | | | |
|------------------|--------|------|-----|-----|----|----|
| | | 12% | 11% | 10% | 9% | 8% |
| Drug price (USD) | 45,000 | 8 | 9 | 11 | 13 | 15 |
| | 50,000 | 10 | 12 | 14 | 16 | 19 |
| | 55,000 | 13 | 15 | 17 | 20 | 23 |
| | 60,000 | 16 | 18 | 21 | 24 | 27 |
| | 65,000 | 18 | 21 | 24 | 27 | 31 |

Source: DNB Markets

As shown, a change in the WACC has a relatively small impact on the company's value. The drug price is a more critical component in the valuation. However, the royalty rate is probably the factor in the valuation that is the most critical factor for the value (see below).

Company to wait with CMC of GM-CSF

Burn rate of cNOK140m p.a.

cNOK17 target price

Impact of changes in discount rate, drug price, and royalty rate

WACC and royalty rate sensitivity - NOK per share

| | | WACC | | | | |
|--------------|-----|------|-----|-----|----|----|
| | | 12% | 11% | 10% | 9% | 8% |
| Royalty rate | 10% | 0 | 0 | 0 | 0 | 1 |
| | 15% | 6 | 7 | 8 | 10 | 12 |
| | 20% | 13 | 15 | 17 | 20 | 23 |
| | 25% | 20 | 23 | 26 | 30 | 34 |
| | 30% | 28 | 31 | 35 | 40 | 45 |

Source: DNB Markets

We believe that our target price of NOK17 contains reasonable assumptions for the company.

Patents

The company has several patents issued and pending on the two vaccine platforms. As the development of the products have been going on for quite some time (particularly in the TG case) the first, initial patent has expired in some markets and is set to expire in the US in 2016. These patents were applied for back in the days when Norsk Hydro was developing the products and for some years not a lot of development took place; as a result the application for new and extended patents was at a minimum. Since then, there has been a lot of activity and new patents have been applied for, most with priority dates between 2008 and 2015.

Several patents issued and pending

Patent situation for Targovax

| Patent/patent application | Priority date | Status | Area covered | Geographic area | Expiry date |
|---------------------------|-------------------|-------------------|--|--|--|
| EP15172418.4 | 16 June 2015 | Pending | New peptide targeting RAS exon 4 mutations and mixtures of defined RAS-mutated peptides can be used as a vaccine against, or treatment for RAS mutated cancers. In addition, mixtures of T cells specific for RAS-mutations in individual patients can be administered to those patients, with or without RAS-mutated peptides, and RAS mutation specific T cell receptors can be used to engineer chimeric antigen receptor T cells (CART) that can be administered as treatment to patients with RAS mutated cancer. | Currently EPO, but will proceed to international | 16 June 2035 |
| WO2015/169804 | 6 May 2014 | Pending | Administration of a mixture of RAS-mutated peptides together with an anti-metabolite chemotherapeutic agent such as gemcitabine leads to a stronger immune response than the administration of the peptide mixture alone. | International | 6 May 2034 |
| WO2015/086590 (A2) | 9 December 2013 | Pending | Mixture of at least two defined RAS-mutated peptides can be used as a vaccine against, or treatment for, over 99% of all RAS mutated cancers. In addition, mixtures of T cells specific for RAS-mutations in individual patients can be administered to those patients, with or without RAS-mutated peptides. If granted, this patent application would cover TG02 and TG03. | International | 9 December 2033 |
| WO 0066153 (A1) | 30 April 1999 | Granted | Method of vaccinating humans with a mixture of RAS-mutated peptides to elicit a RAS-specific T cell immune response (therapeutic and prophylactic use). This patent covers TG01. | Norway | 30 April 2019 |
| USP 5961978 | 26 February 1991 | Granted | Peptides and method of vaccinating humans with RAS-mutated peptides to elicit a RAS mutation-specific T cell immune response (therapeutic and prophylactic use). This patent covers the TG0X technology in general. | The US | 5 October 2016 |
| WO2013076374 (A1) | 25 November 2011 | Granted / Pending | Composition of matter and method of use of oncolytic adenoviruses having several different characteristics. This patent describes ONCOS-402. | Granted in Finland. Pending in EPO and the US | 25 November 2031 |
| EP 15186798.3 | 25 November 2011 | Pending | ONCOS-402 composition of matter and method of treating patients (divisional application of WO2013076374 (A1)). This patent covers ONCOS-402. | Pending EPO and the US | 25 November 2031 |
| US 2013323205 (A1) | 24 September 2010 | Granted / Pending | Composition of matter and method of use of viral constructs in which the viral replication is under hTERT gene activated by telomerase activity found in cancer cells. Viral construct include the use of CD40L transgene. This patent covers several viral constructs containing the CD40L transgene, but not ONCOS-402. | Granted in Finland, South Africa, Australia. Allowed in China*. Pending in Canada, EPO, South Korea, Singapore, the US | 24 September 2031 |
| WO 2012038607 (A1) | | | | | |
| WO 2010072900 (A1) | 22 December 2008 | Granted / Pending | ONCOS-102 viral construct and its uses. Composition of matter for Ad5/3-D24-GMCSF. Method of treating patients suffering from various cancer indications using the virus alone or in combination with chemotherapeutics. This patent covers ONCOS-102. | Granted in Finland, Russia, Singapore, South Africa and the US. Pending in Australia, Brazil, Canada, China, EPO, Hong Kong, India, Japan, South Korea | For most territories 22 December 2029. For Finland 28 April 2029. For Russia 22 December 2034. |

Source: Company data

Note: In the "allowed" stage, meaning that the local patent office has approved that it will be granted. As formal registration is in progress and requires some admin tasks, status is not legally granted.

EPO = European Patent Office.

Hence the majority of new patents for Targovax and Oncos are valid (if approved) until 2033 and 2034 for Targovax and 2029 for Oncos. On top of the patent protection listed above, the company has orphan drug designations (ODDs) in pancreatic cancer (Targovax) and in soft tissue sarcoma (STS), ovarian cancer and in mesothelioma for Oncos.

Orphan drug designations

| Product | Indication | Granted by EMA | Granted by FDA |
|-----------|------------------------|------------------|------------------|
| TG01 | Pancreatic cancer | August 5 2011 | June 7 2011 |
| ONCOS-102 | Malignant mesothelioma | December 16 2014 | December 22 2014 |
| ONCOS-102 | Ovarian Cancer | April 29 2014 | March 17 2014 |
| ONCOS-102 | Soft Tissue Sarcoma | June 19 2013 | July 24 2013 |

Source: Company data

Extending the patent life

One can extend a drug's patent life, which is usually 20 years from filing the patent, by attaining for example a Patent Term Extension and market exclusivity, granted by the regulatory bodies in the US and Europe. Herein we will shortly review patent extension and market exclusivity; both could come to extend the patent lives of TG01 and ONCOS-102.

Patent extension

In the US the whole patent can be extended up to five years under the Drug Price Competition and Patent Restoration Act (also known as the Hatch-Waxman Act). The United States Patent and Trademark Office (PTO) determines the period of patent extension, which is calculated based on the time it has taken to develop the drug in clinical testing, divided in two, plus the time it takes to receive regulatory approval. In Europe a similar patent extension can be granted, which provides an extra five years of patent protection after the original expiry date.

An additional six months of patent extension to the five years granted for long development times can be attained if the FDA or EMA requests the company to conduct studies in paediatric patients. This is a way to incentivise studies in children, as most drugs are not labelled to use in a paediatric setting, and therefore place children at greater risk if there is a need to treat them with the drug in question.

Data and market exclusivity

Apart from patent extension, a drug can receive data and market exclusivity upon approval. Data exclusivity prevents a competitor from applying for market authorisation with supporting data referencing to the innovator drug, while market exclusivity only prevents a competitor from entering the market, and not from receiving market authorisation. In the US a new drug normally receives five years of data exclusivity, while a drug already approved but developed for a new indication receives three years of data exclusivity. In Europe a new drug receives eight years of data exclusivity plus two years of market exclusivity, and in a number of circumstances an additional one year of market exclusivity is granted, e.g. if the drug is approved in an additional indication. Hence, a generic drug cannot enter the market until 11 years post approval (as long as the patent has expired at this point).

Importantly, biologics are granted even longer exclusivity than small-molecule drugs, due to the increased difficulty in developing them. In the US biologics, products such as vaccines are granted four years of data exclusivity and eight years of market exclusivity, i.e. a biosimilar cannot enter the market until 12 years post approval. In Europe the situation is similar, and biologics have data exclusivity for 10 years, hence a biosimilar can first enter the market in Europe 11–12 years post the approval of the reference drug. Also, an orphan drug designation provides the product with additional exclusivity. In the US products granted orphan status receive seven years of market exclusivity, and in Europe it is 10 years. During this period a generic competitor cannot receive market approval for the same indication, but could be approved in another indication.

Patent life extension for Targovax

We estimate that TG01 and ONCOS-102 will be first approved in 2021, indicating about 7–8 years of clinical development, and c1 year from NDA submission to approval; hence TG01 and ONCOS-102 could get about four or five years' patent extension, respectively, in the US. This would provide patent coverage of TG01 until c2037 and of ONCOS-102 until c2034, which is longer than any form of data or market exclusivity. However, if for some reason any of the newer patents were not approved, on which we have based our estimated patent extension period, the longest period of exclusivity would be provided by the biological

Patent extension and market exclusivity extend the patent life

A patent can be extended by up to five years

Biologics are granted longer exclusivity

Four or five years patent extension likely for Targovax's products

exclusivity. The biological exclusivity would protect TG01 and ONCOS-102 until c2033 in both the US and Europe, if approved in 2021.

Risks and uncertainties

We see several risk factors associated with an investment in a company like Targovax. Below we highlight some of the more important ones – the list is not exhaustive.

Several risk factors worth considering

- **Early stage development.** The company is still in an early phase of its clinical development. The most advanced project (TG01) is in phase II.
- **Highly competitive indication areas.** As the medical need is high in several of Targovax's focus areas, there is intense competition from other companies. Several of these companies have longer track records and significantly greater financial capacity to fund clinical trials than Targovax has. Other competing projects might reach the market before Targovax's drug candidates and thus change the market dynamics for the worse.
- **A need to raise more capital.** The company will need to finance the operation through the financial markets for some time, as it has no revenues from products. This might result in dilution for current shareholders. Financing might also not be available at acceptable terms when it is needed.
- **Side effects.** Although peptide vaccines and oncolytic virus vaccines so far in general development have been considered relatively safe, there is no guarantee the company in the development programme will not experience unexpected side effects from its drug candidates either as monotherapy or as a part of a combination therapy with other drugs.
- **Lack of efficacy.** The company might experience a lack of efficacy in one or more of its drug candidates. There has historically been some disconnect between immunological efficacy and overall survival efficacy. In some clinical trials for other vaccines and immunological drugs the clinical efficacy has taken time to see; hence the follow-up time for patients will be important in order to establish clinical efficacy or not.
- **Small organisation dependent on key personnel.** As Targovax is still a small company, its dependency on key personnel is proportionately higher than for larger/more mature companies. The risk of losing a person key to the company's development is a clear risk, and it might take time to find a suitable replacement.
- **No partner for future drug development.** The company has no development partner or marketing partners yet, and there is no guarantee it will be able to strike a favourable partnership. As the cost of performing the clinical development programme for all potential indications is high, Targovax will need a partner to share the costs with. In our view, the costs of clinical development on its own would be prohibitively high for Targovax.
- **Partnering could mean loss of control of the projects.** Although the benefits of having a development partner are clear, there is also a downside to a partnering deal. The company will to some extent lose control over the development path for its projects as the partner will have at least partial control over design and execution of the clinical trials. There is a risk Targovax and its partner might have different opinions as to how certain trials should be conducted and the final decision on how the proceed might not rest with Targovax.
- **New competing therapies might raise the bar for Targovax's drug candidates.** As virtually all the company's areas of drug development are in indications with intense competition and poor clinical alternatives for patients, new competing therapies might reach the market ahead of Targovax's drugs and thus improve clinical outcomes for patients to such an extent that these new therapies rapidly become the new standard of care and hence the new benchmark for new products. If this happens during an ongoing clinical trial, it might be difficult to change the design of the trial while it is running, so the clinical outcomes might be less interesting and useful for the company.
- **Regulatory risk.** There is always a risk that the regulatory authorities have a different view from the company and the stock market on what information and what data is needed to approve a specific product. Also, demands on new products might change during the development time, so the final clinical data package might lack some information deemed critical by the authorities at the time of filing (even though the authorities had a different

view at the start of the clinical development programme). The company is considering manufacturing its own GM-CSF, which might pose an additional risk as the plan is to get the peptide vaccines and GM-CSF registered as a combined product. According to the advisors of the company, this should not pose a problem but in the end one cannot know for sure how the regulatory authorities will look on the product.

- **Price pressure in end-user market.** Modern cancer treatments that have reached the market over the past few years have, in general, commanded high prices. As a result, attention in the clinical and payer communities has focused on whether these high prices are justifiable. There is a risk that high prices of cancer drugs might come under increased pressure, making it difficult for the company and its partners to regain the investments made in clinical development. This might be a risk more pronounced in the immune-oncology market as most ongoing trials are combination trials leading to very high prices in total when several expensive drugs are combined.
- **Limited financial history.** Targovax was created by the merger between Targovax and Oncos in summer 2015. All financial data available to the stock market is pro forma and not the actual financial data for the company as it is structured right now.
- **Uncertainty regarding milestones.** We estimate that the company will strike a licensing deal with a large pharmaceutical company during 2018. It is still highly uncertain if/when the company might strike such a deal and an out-licensing deal could materialise later than we expect or not at all.
- **IP/patent risk.** The company has an extensive IP estate with patents on its drug candidates that expire in 2029–2035. There is, however, always a risk that patents can be challenged and their scope limited, and in a worst-case scenario be deemed invalid. We have no indications that this will be the case, but in highly competitive areas of the drug industry using patent infringement cases as a means of competing is not uncommon. Until a patent has been tried in court and found valid there is always a risk that the patent protection is less robust than initially thought.

Management and board of directors

Management

The background and experience of the management team in a company of Targovax's size and development stage will be key to making the right decisions in the drug development process.

- **Gunnar Gårdemyr – CEO.** Mr Gårdemyr has 30+ years of international experience from the pharma and biotech industry, including business development, M&A, global marketing and commercial strategy. Before joining Targovax, he was senior vice president, corporate development/M&A at Nycomed. He has also been senior vice president, global marketing at Takeda in Zürich, Switzerland.
- **Øystein Soug – CFO.** Mr Soug was previously CFO at Algeta, where he built up the functions of finance, IR, compliance, IT and HR. He oversaw Algeta's launch of Xofigo, capital raisings of cUSD200m, and the subsequent USD2.9bn sale of Algeta to Bayer. He has experience from positions at Orkla Group as CFO of Sladco, the Russian operations of Orkla, and project manager in Orkla's corporate development M&A team.
- **Dr Magnus Jaderberg – CMO.** Dr Jaderberg has 25+ years' experience from various positions in R&D, most recently as CMO at Bristol-Myers Squibb Europe. He has experience of all phases of clinical research, including clinical pharmacology, dose finding, registration, post launch product differentiation and surveillance. He has extensive experience of immunotherapy, including Yervoy (ipilimumab), Enbrel (etanercept), Torisel (temsirolimus), Orendia (abatacept), Rapamune (sirolimus) and Nulojix (belatacept).
- **Jon Amund Eriksen – COO.** Mr Eriksen has 35+ years of R&D experience in the pharma and biotech industry, of which c25 years in the field of immuno-oncology. He is the co-founder of Targovax and co-inventor of the Targovax technology. He has held managing positions in the development of cancer immunotherapy from early preclinical to phase III clinical development.
- **Antti Vuolanto – executive VP.** Mr Vuolanto has 10+ years of experience in biotechnology business development, product development, and commercialisation. Prior to that, he was a management team member responsible for product commercialisation, product development, and quality at Mobidiag, a company specialising in rapid nucleic acid-based infectious disease diagnostics. He was also project manager at Medice developing bioinformatics infrastructure. He is a Doctor of Science (Technology) in bioprocess engineering, Aalto University in Helsinki.
- **Peter Skorpil – VP business development.** Mr Skorpil has extensive experience of licensing, commercial assessments, business intelligence, and partnering. Previously, he was commercial director in Pronova BioPharma and business development manager for Clavis Pharma, where he was responsible for, among other things, out-licensing and managing Clavis partners. He has also worked as a venture capital analyst at NeoMed Management. He has an MBA from Brandeis University, Massachusetts, US, and a PhD in molecular biology from the University of Geneva, Switzerland.
- **Tina Madsen – VP quality assurance.** Mrs Madsen has more than 20 years of experience in research & development and commercial manufacturing in the pharmaceutical and biotech industry, including quality assurance, process development and formulation. Before joining Targovax, she was director of product quality assurance in Algeta ASA (now Bayer AS).
- **Anne Kirsti Aksner – VP Clinical development.** Mrs Aksner has more than 20 years of experience within clinical research and development in the pharmaceutical and biotech industry and 10 years of experience working in clinical physiology. Previously, she was VP Clinical Research in Algeta ASA (now Bayer AS), where she had a key role in the strategic, scientific and clinical development, as well as in medical communications.

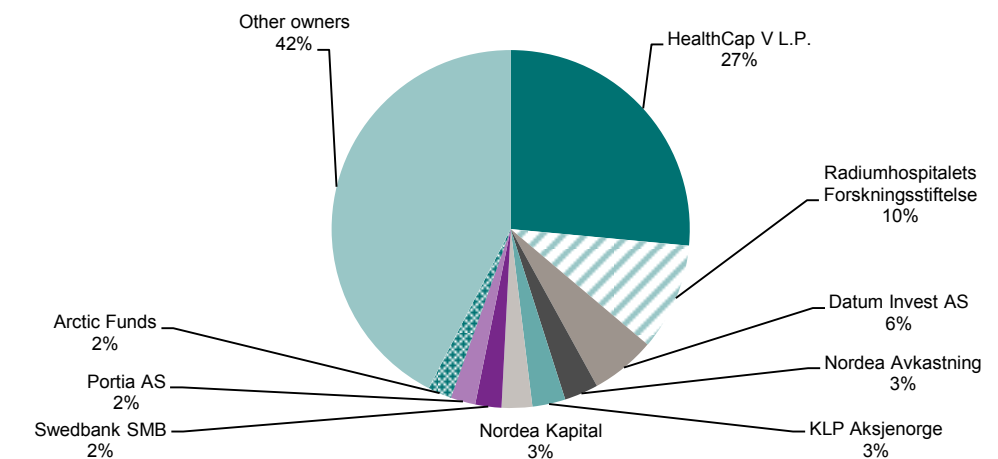
Board of directors

- **Jónas Einarsson, MD – chairman of the board.** Dr Einarsson is the CEO of Radiumhospitalets Forskningsstiftelse, and serves on the board of several Norwegian biotech companies. He was one of the initiators behind Oslo Cancer Cluster and the Oslo Cancer Cluster Innovation. He is independent of the company but not of its main owner.
- **Johan Christenson, MD, PhD – board member.** Dr Christenson is a partner at HealthCap, and previously responsible for the life science portfolio at SEB Företagsinvest. Prior to joining the financial industry, he gained senior management experience from Astra Pain Control as a project director and AstraZeneca as global product director. He has a PhD in neuroscience and (among others) is the author of 17 scientific publications. He is independent of the company but not of its main owner.
- **Per Samuelsson – board member.** Mr Samuelsson is a partner at HealthCap. Before joining the company in 2000, he gained 15 years' experience of investment banking, mainly at Aros Securities in Sweden. Prior to that, he was head of research at Aros Securities. He is independent of the company but not of its main owner.
- **Bente-Lill Bjerkelund Romøren – board member.** Mrs Romøren has considerable experience in the pharmaceutical industry and was employed in various positions at Novo Nordisk Scandinavia in 1976–2012. She was, among others, CEO of Novo Nordisk Norwegian unit (2008–2012). She holds an MSc in chemistry. She serves on several boards including Radiumhospitalets Forskningsstiftelse, Nordic Nanovector, Farmastat and Photocure. She is independent of the company and its main owner.
- **Robert Burns, PhD – board member.** Dr Burns is the CEO of 4-Antibody and chairman of Haemostatix. He has extensive experience in building biotechnology companies, previously as the CEO of Affitech and Celldex Therapeutics. Prior to Celldex, he was director of technology licensing at the Ludwig Institute for Cancer Research. He is independent of the company and its main owner.
- **Lars Lund-Roland – board member.** Mr Lund-Roland is CEO of Bringwell AB, a public Swedish healthcare company. He was previously MD of MSD Norway (Merck & Co Inc. subsidiary) for 10 years and has 25+ years' experience from various executive positions in marketing and sales. He is chairman of the board of PI Innovation and has been a board member of Infodoc and Health Tech. He is independent of the company and its main owners.
- **Eva-Lotta Allan – board member.** Mrs Allan is CBO at Immunocore Ltd, having joined the company in 2013. Mrs. Allan has over two decades of business development experience from the biotechnology and life science industry in both public and private companies. Among others, she was CBO at Ablynx in 2006–2013. Before joining Ablynx she was a senior director of business development at Vertex Pharmaceuticals. She holds a degree in microbiology from the University of Stockholm. She is independent of the company and its main owners.
- **Diane Mellett – board member.** Ms Mellett is CBO and general counsel at Affitech A/S. Prior to that, she was general counsel and a main board director of Cambridge Antibody Technology (CAT). Part of her responsibilities was establishing the strategy for enhancing CAT's intellectual property portfolio as a leading developer of phage display antibody technology. She secured numerous licensing and cross-licensing agreements for CAT. Additionally, she played a leading role in defending CAT's commercial position in a contract dispute with Abbott that eventually led to a settlement in favour of CAT. She is also a governor of the UK Medical Council's Technology group. She is independent of the company and its main owners.

Main owners

The main owners of Targovax are the Swedish venture capital firm HealthCap, followed by the research foundation associated with the radiation therapy hospital in Oslo. Following these two large owners, are a number of private investment companies in Norway.

Ownership situation in Targovax (as of 12 September 2016)



Source: Company data

Quarterly numbers

| (NOKm) | Q1 2015 | Q2 2015 | Q3 2015 | Q4 2015 | Q1 2016 | Q2 2016 | Q3 2016e | Q4 2016e | Q1 2017e | Q2 2017e | Q3 2017e |
|-------------------------------|---------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|
| Revenues | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cost of sales | 0 | -2 | -3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gross profit | 0 | -2 | -3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Operating expenses | -6 | -10 | -27 | -41 | -31 | -32 | -31 | -31 | -35 | -35 | -35 |
| EBITDA | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -35 | -35 | -35 |
| Depreciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EBITA | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -34 | -34 | -34 |
| EBIT | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -34 | -34 | -34 |
| Net interest | 0 | 0 | 0 | -1 | -1 | -1 | 0 | 0 | 0 | 0 | 0 |
| Net financial items | 0 | 0 | 0 | -1 | -1 | -1 | 0 | 0 | 0 | 0 | 0 |
| PBT | -7 | -13 | -29 | -42 | -31 | -33 | -31 | -31 | -35 | -35 | -35 |
| Taxes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Net profit | -7 | -13 | -29 | -42 | -31 | -33 | -31 | -31 | -35 | -35 | -35 |
| Adjustments to net profit | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Net profit adj | -7 | -13 | -29 | -42 | -31 | -33 | -31 | -31 | -35 | -35 | -35 |
| <i>Per share data (NOK)</i> | | | | | | | | | | | |
| EPS | -0.72 | -0.49 | -1.08 | -1.55 | -1.18 | -1.25 | -0.74 | -0.74 | -0.82 | -0.82 | -0.82 |
| <i>Growth and margins (%)</i> | | | | | | | | | | | |
| Revenues, QOQ growth | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm |
| Revenues, YOY growth | nm | nm | 694.5 | nm | nm | nm | nm | nm | nm | nm | nm |
| EPS adj, YOY growth | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm |
| Gross margin | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm |
| EBITDA adj margin | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm |
| Depreciation/revenues | nm | nm | 6.9 | nm | nm | nm | nm | nm | nm | nm | nm |
| EBIT adj margin | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm |
| Net profit margin | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm | nm |

Source: Company (historical figures), DNB Markets (estimates)

Adjustments to quarterly numbers

| (NOKm) | Q1 2015 | Q2 2015 | Q3 2015 | Q4 2015 | Q1 2016 | Q2 2016 | Q3 2016e | Q4 2016e | Q1 2017e | Q2 2017e | Q3 2017e |
|-------------------|---------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|
| EBITDA | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -35 | -35 | -35 |
| EBITDA adj | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -35 | -35 | -35 |
| EBITA | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -34 | -34 | -34 |
| EBITA adj | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -34 | -34 | -34 |
| EBIT | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -34 | -34 | -34 |
| EBIT adj | -7 | -13 | -29 | -41 | -31 | -32 | -31 | -31 | -34 | -34 | -34 |
| Net profit | -7 | -13 | -29 | -42 | -31 | -33 | -31 | -31 | -35 | -35 | -35 |
| Net profit adj | -7 | -13 | -29 | -42 | -31 | -33 | -31 | -31 | -35 | -35 | -35 |

Source: Company (historical figures), DNB Markets (estimates)

Annual P&L

| (NOKm) | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|-------------------------------|-----------|------------|------------|-------------|-------------|------------|
| Revenues | 0 | 0 | 0 | 0 | 0 | 308 |
| Cost of sales | -4 | 0 | 0 | 0 | 0 | 0 |
| Gross profit | -3 | 0 | 0 | 0 | 0 | 308 |
| Operating expenses | -4 | -18 | -90 | -125 | -138 | -180 |
| EBITDA | -7 | -18 | -90 | -125 | -138 | 128 |
| Depreciation | 0 | 0 | 0 | 0 | 0 | 0 |
| EBITA | -7 | -18 | -90 | -125 | -138 | 127 |
| EBIT | -7 | -18 | -90 | -125 | -138 | 127 |
| Net interest | 0 | 0 | 0 | -1 | -1 | 0 |
| Net financial items | 0 | 0 | 0 | -1 | -1 | 0 |
| PBT | -8 | -18 | -90 | -126 | -139 | 127 |
| Taxes | 0 | 0 | 0 | 0 | 0 | 0 |
| Effective tax rate (%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Net profit | -8 | -18 | -90 | -126 | -139 | 127 |
| Adjustments to net profit | 0 | 0 | 0 | 0 | 0 | 0 |
| Net profit adj | -8 | -18 | -90 | -126 | -139 | 127 |
| <i>Per share data (NOK)</i> | | | | | | |
| EPS | -1.81 | -1.87 | -3.42 | -2.98 | -3.30 | 3.03 |
| <i>Growth and margins (%)</i> | | | | | | |
| Revenue growth | nm | -80.1 | 101.4 | nm | nm | nm |
| EPS adj growth | nm | nm | nm | nm | nm | nm |
| Gross margin | nm | 100.0 | 100.0 | nm | nm | 100.0 |
| EBITDA margin | nm | nm | nm | nm | nm | 41.5 |
| EBITDA adj margin | nm | nm | nm | nm | nm | 41.5 |
| Depreciation/revenues | 0.0 | -15.2 | -101.4 | nm | nm | -0.1 |
| EBIT margin | nm | nm | nm | nm | nm | 41.4 |
| EBIT adj margin | nm | nm | nm | nm | nm | 41.4 |
| PBT margin | nm | nm | nm | nm | nm | 41.4 |
| Net profit margin | nm | nm | nm | nm | nm | nm |

Source: Company (historical figures), DNB Markets (estimates)

Adjustments to annual P&L

| (NOKm) | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|-----------------------------|-----------|------------|------------|-------------|-------------|------------|
| EBITDA | -7 | -18 | -90 | -125 | -138 | 128 |
| EBITDA adj | -7 | -18 | -90 | -125 | -138 | 128 |
| EBITA | -7 | -18 | -90 | -125 | -138 | 127 |
| EBITA adj | -7 | -18 | -90 | -125 | -138 | 127 |
| EBIT | -7 | -18 | -90 | -125 | -138 | 127 |
| EBIT adj | -7 | -18 | -90 | -125 | -138 | 127 |
| Net profit | -8 | -18 | -90 | -126 | -139 | 127 |
| Net profit adj | -8 | -18 | -90 | -126 | -139 | 127 |
| <i>Per share data (NOK)</i> | | | | | | |
| EPS | -1.81 | -1.87 | -3.42 | -2.98 | -3.30 | 3.03 |

Source: Company (historical figures), DNB Markets (estimates)

22 September 2016

Cash flow

| (NOKm) | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|--|-----------|------------|------------|-------------|-------------|------------|
| Net profit | -8 | -18 | -90 | -126 | -139 | 127 |
| Change in net working capital | 0 | 0 | 0 | 0 | 0 | 0 |
| Cash flow from operations (CFO) | -8 | -18 | -90 | -126 | -139 | 128 |
| Capital expenditure | 0 | 0 | 1 | -1 | -2 | -2 |
| Acquisitions/Investments | 0 | 0 | 0 | 0 | 0 | 0 |
| Cash flow from investing (CFI) | 0 | 0 | 1 | -1 | -2 | -2 |
| Free cash flow (FCF) | -8 | -18 | -89 | -127 | -141 | 126 |
| Net change in debt | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 16 | 4 | 9 | 3 | 2 | 2 |
| Cash flow from financing (CFF) | 16 | 72 | 200 | 107 | 2 | 252 |
| Total cash flow (CFO+CFI+CFF) | 8 | 54 | 111 | -20 | -139 | 378 |
| <i>FCFF calculation</i> | | | | | | |
| Free cash flow | -8 | -18 | -89 | -127 | -141 | 126 |
| Less: net interest | 0 | 0 | 0 | 1 | 1 | 0 |
| Less: acquisitions | 0 | 0 | 0 | 0 | 0 | 0 |
| <i>Growth (%)</i> | | | | | | |
| CFO | nm | -132.1 | -409.4 | -39.6 | -10.8 | 191.7 |
| CFI | nm | 46.0 | 821.9 | -186.6 | -50.0 | -33.3 |
| FCF | nm | -125.4 | -398.3 | -42.6 | -11.1 | 189.3 |
| CFF | nm | 342.4 | 177.9 | -46.5 | -98.6 | 16700.0 |
| FCFF | nm | nm | nm | nm | nm | nm |

Source: Company (historical figures), DNB Markets (estimates)

Balance sheet

| (NOKm) | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|--------------------------------------|-----------|-----------|------------|------------|------------|------------|
| Assets | 14 | 67 | 545 | 526 | 387 | 764 |
| Inventories | 0 | 0 | 0 | 0 | 0 | 0 |
| Trade receivables | 6 | 5 | 12 | 12 | 12 | 12 |
| Other receivables | 0 | 0 | 0 | 0 | 0 | 0 |
| Current financial assets | 0 | 0 | 0 | 0 | 0 | 0 |
| Cash and cash equivalents | 8 | 63 | 174 | 154 | 15 | 393 |
| Current assets | 14 | 67 | 185 | 166 | 27 | 404 |
| Property, plant and equipment | 0 | 0 | 2 | 2 | 2 | 2 |
| Goodwill | 0 | 0 | 358 | 358 | 358 | 358 |
| Other intangible assets | 0 | 0 | 0 | 0 | 0 | 0 |
| Deffered tax assets | 0 | 0 | 0 | 0 | 0 | 0 |
| Non-current financial assets | 0 | 0 | 0 | 0 | 0 | 0 |
| Non-current assets | 0 | 0 | 360 | 360 | 360 | 360 |
| Total assets | 14 | 67 | 545 | 526 | 387 | 764 |
| Equity and liabilities | 14 | 67 | 545 | 526 | 387 | 764 |
| Total equity to the parent | 0 | 61 | 423 | 401 | 262 | 640 |
| Total equity | 0 | 61 | 423 | 401 | 262 | 640 |
| Trade payables | 3 | 3 | 6 | 6 | 6 | 6 |
| Other payables and accruals | 11 | 4 | 19 | 19 | 19 | 19 |
| Short-term debt | 0 | 0 | 0 | 0 | 0 | 0 |
| Total current liabilities | 14 | 7 | 25 | 25 | 25 | 25 |
| Long-term debt | 0 | 0 | 38 | 44 | 44 | 44 |
| Deferred tax liabilities | 0 | 0 | 59 | 55 | 55 | 55 |
| Pension liabilities | 0 | 0 | 0 | 0 | 0 | 0 |
| Other non-current liabilities | 0 | 0 | 0 | 0 | 0 | 0 |
| Total non-current liabilities | 0 | 0 | 97 | 99 | 99 | 99 |
| Total liabilities | 14 | 7 | 122 | 124 | 124 | 124 |
| Total equity and liabilities | 14 | 67 | 545 | 526 | 387 | 764 |
| <i>Key metrics</i> | | | | | | |
| Net interest bearing debt | -8 | -63 | -136 | -110 | 29 | -349 |

Source: Company (historical figures), DNB Markets (estimates)

22 September 2016

Valuation ratios

| (NOKm) | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|-------------------------------|----------|---------|---------|--------|--------|-------|
| <i>Enterprise value</i> | | | | | | |
| Share price (NOK) | | 24.62 | 16.74 | 8.70 | 8.70 | 8.70 |
| Number of shares (m) | 4.20 | 9.43 | 26.86 | 42.13 | 42.13 | 42.13 |
| Market capitalisation | | 232 | 450 | 367 | 367 | 367 |
| Net interest bearing debt | -8 | -63 | -136 | -110 | 29 | -349 |
| Adjustments to NIBD | 0 | 0 | 0 | 0 | 0 | 0 |
| Net interest bearing debt adj | -8 | -63 | -136 | -110 | 29 | -349 |
| EV | | 170 | 314 | 256 | 395 | 18 |
| EV adj | | 170 | 314 | 256 | 395 | 18 |
| <i>Valuation</i> | | | | | | |
| EPS | -1.81 | -1.87 | -3.42 | -2.98 | -3.30 | 3.03 |
| P/E | | -13.2 | -4.9 | -2.9 | -2.6 | 2.9 |
| Average ROE | -5510.0% | -57.9% | -37.2% | -30.5% | -42.0% | 28.2% |
| EV/SALES | | 2339.27 | 2149.79 | | | 0.06 |
| EV/SALES adj | | 2339.27 | 2149.79 | | | 0.06 |
| EV/EBITDA | | -9.7 | -3.5 | -2.1 | -2.9 | 0.1 |
| EV/EBITDA adj | | -9.7 | -3.5 | -2.1 | -2.9 | 0.1 |
| EV/EBIT | | -9.6 | -3.5 | -2.0 | -2.9 | 0.1 |
| EV/EBIT adj | | -9.6 | -3.5 | -2.0 | -2.9 | 0.1 |
| EV/NOPLAT | | -9.6 | -3.5 | -2.0 | -2.9 | 0.1 |
| EV/OpFCF (taxed) | | -9.6 | -3.5 | -2.0 | -2.8 | 0.1 |

Source: Company (historical figures), DNB Markets (estimates)

Key accounting ratios

| | 2013 | 2014 | 2015 | 2016e | 2017e | 2018e |
|---------------------------------------|---------|----------|----------|----------|---------|--------|
| <i>Profitability (%)</i> | | | | | | |
| ROA | -107.1 | -43.3 | -29.4 | -23.5 | -30.5 | 22.1 |
| <i>Return on invested capital (%)</i> | | | | | | |
| Net PPE/revenues | 0.0 | 206.9 | 1089.0 | | | 0.5 |
| Working capital/revenues | -2220.7 | -2798.6 | -9495.2 | | | -4.5 |
| <i>Cash flow ratios (%)</i> | | | | | | |
| FCF/revenues | -2167.6 | -24560.7 | -60774.0 | | | 40.8 |
| FCF/market capitalisation | | -7.7 | -19.7 | -34.5 | -38.3 | 34.2 |
| CFO/revenues | -2086.3 | -24340.0 | -61565.1 | | | 41.5 |
| CFO/market capitalisation | | -7.6 | -20.0 | -34.2 | -37.9 | 34.8 |
| CFO/capex | -2566.6 | -11029.1 | 7782.3 | -12550.0 | -9266.7 | 6375.0 |
| CFO/current liabilities | -54.6 | -263.8 | -353.6 | -493.7 | -546.8 | 501.6 |
| Cash conversion ratio | 103.9 | 100.8 | 98.6 | 100.6 | 100.9 | 98.6 |
| Capex/revenues | 81.3 | 220.7 | -791.1 | | | 0.7 |
| Capex/depreciation | | 1454.5 | -780.4 | 357.1 | 535.7 | 714.3 |
| OpFCF margin | -2128.2 | -24454.5 | -60589.7 | | | 40.8 |
| <i>Leverage and solvency (x)</i> | | | | | | |
| Interest cover | -37.84 | -41.04 | -33.52 | -61.89 | -68.64 | nm |
| EBIT/interest payable | -38.11 | -41.86 | -34.42 | -62.64 | -69.14 | |
| EBITA adj/interest payable | -38.11 | -41.86 | -34.42 | -62.64 | -69.14 | |
| Cash coverage | -51.97 | -228.18 | -333.14 | -250.00 | -138.00 | |
| Net debt/EBITDA | 1.12 | 3.56 | 1.52 | 0.88 | -0.21 | -2.73 |
| Total debt/total capital (BV) | 0.00 | 0.00 | 0.07 | 0.08 | 0.11 | 0.06 |
| LTD / (LTD + equity (MV)) | | 0.00 | 0.08 | 0.11 | 0.11 | 0.11 |
| <i>Cash conversion cycle</i> | | | | | | |
| Inventory turnover days | 0.0 | | | | | |
| Receivables turnover days | 5834.7 | 23460.7 | 28892.5 | nm | nm | 13.7 |
| Credit period | 260.8 | nm | nm | nm | nm | nm |
| Cash conversion cycle | 5573.9 | | | | | |

Source: Company (historical figures), DNB Markets (estimates)

22 September 2016

Important Information

Company: Targovax
 Coverage by Analyst: Patrik Ling
 Date: 22/09/2016

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Recommendation structure and risk classification

DNB Markets recommendations are based on absolute performance:

Buy - indicates an expected return greater than 10% within 12 months
 Hold - indicates an expected return between 0 and 10% within 12 months
 Sell - indicates an expected negative return within 12 months

The return-requirement bands above may be applied with some degree of flexibility depending on the liquidity and volatility characteristics of the individual share.

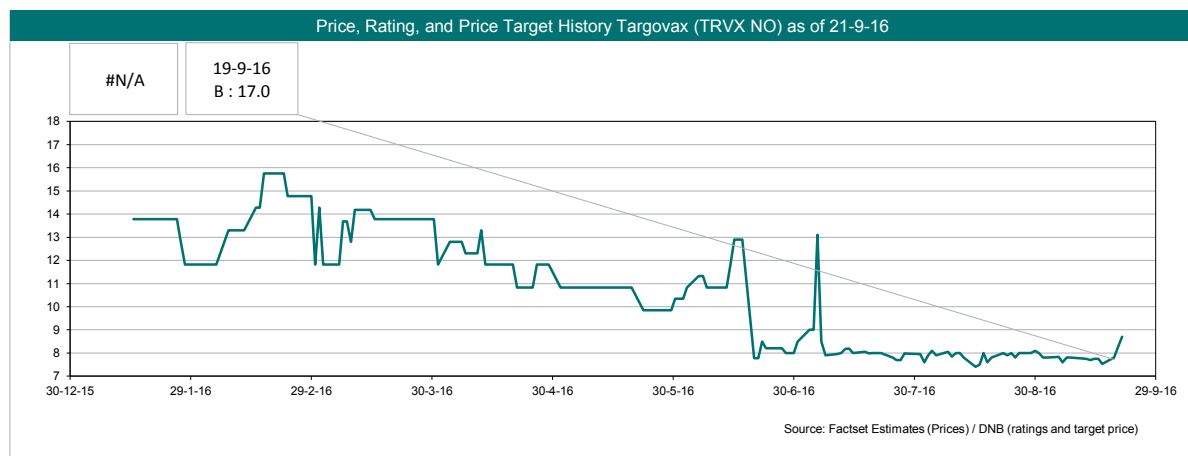
High risk - Volatility over 40 percent.
 Medium risk - Volatility from 25 percent to 40 percent.
 Low risk - Volatility under 25 percent.

Current 6 months volatility rates this security as HIGH risk.

Investing in any security is subject to substantial risk. Return on investment may vary greatly.

Careful consideration for possible financial distress should be accounted for before investing in any security.

Price targets are based on a combination of several valuation methods such as discounted cash flow, pricing based on earnings multiples, multiple on book value, net asset value and peer comparison. Substantial material sources for coverage of this company include historical financial figures and communication with the company, and relevant third party information. Recommendations and historical target prices below may not compile all recommendations by DNB Markets, for further information please contact DNB Markets.



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| Share positions in the company: | Analyst* | Employees** | DNB*** | Update |
|---------------------------------|----------|-------------|--------|------------|
| Number of shares | 0 | 0 | 0 | 22/09/2016 |

*The analyst or any close associates. **Share positions does not include administration and section FX/Treasury.

***Share positions as part of DNB Group. Holdings as part of DNB Markets investment services activity are not included.

Recommendation distribution and corporate clients for the last 12 months

| | Buy | Hold | Sell | No rec | Total |
|--------------------|------|------|------|--------|-------|
| Number | 97 | 63 | 47 | 3 | 210 |
| % of total | 46 % | 30 % | 22 % | 1 % | |
| DNB Markets client | 9 % | 3 % | 5 % | 1 % | 37 |

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