SalvaRx

PETERHOUSE RESEARCH

Immunology's Killer application

22 March, 2016

SalvaRx's (SALV) long term aim is to develop a pipeline of complementary cancer immunotherapy-focused products and technologies that can work to activate the body's immune system and down-regulate tumour progression. Prolonged patient survival is highly valued by healthcare systems and Pharma companies buying pipelines. Success in the clinic with its first investment, iOx Therapeutics, could be a valuable entry ticket to potential billion-dollar licensing deals.

iOx Therapeutics activating NKT cells

iOx Therapeutics is set to start an Oxford University-funded Phase 1/2 trial to evaluate its patented iNKT agonists in metastatic melanoma - alone and in combination with an approved PD-1 'checkpoint' immunotherapeutic.

Building a pipeline of complementary 'cancer-focused' assets

SALV's shares commenced trading on AIM on 22 March, following a £1.95m share placing. The company's model is to proactively seek out technologies which complement its cancer focus and where it can 'design in' its vast collective scientific and management experience of immuno-oncology development.

- **Substantial >$70bn market opportunity forecast by 2020**: It is estimated that in 2014, cancer immunotherapy drugs captured nearly 50% of the overall oncology drugs market (Research&Markets.com). Compared to conventional chemotherapy, this new selectively targeted product class can provide both extended patient survival and potential blockbuster status.
- **Immune checkpoints enable multi-pronged tumour attack**: Tumours have remarkable mechanisms to escape the body's immune system. However, recent research insight into tumour immunology has allowed development of novel treatments to harness and activate the immune system and prevent this 'immune escape'. SALV is aiming to build a leading cancer immunotherapy pipeline - iOx Therapeutics is an initial investment.
- **iOx brings novel agonists to activate iNKT cells**: This emerging technology aims to harness both the 'innate' (first-line defence) and 'adaptive' (memory) arms of the immune system in helping combat tumour progression.
- **Speculative, but highly attractive investment segment**. The last five years have seen investor interest in new forms of cancer treatment push new listings to record highs. Despite a recent softening in the global biotech IPO market, the cancer immunotherapy segment has become a focus of attention for industry M&A, with high-value deals (some >$1bn) - even for preclinical programmes. The opportunity for SALV investors to exit on a premium multiple should be a realistic prospect.

Company Data	
EPIC	**SALV**
Market	AIM
Placing Price	35.5p

Description

SALV is a life sciences company managing the development of novel technologies to deliver new anti-cancer therapies.

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Executive summary

SalvaRx Group plc (SALV) listed on AIM on 22 March 2016. **The SALV business model is focused on investing in and developing novel mechanism-driven immunotherapies**. **Cancer is the hottest area of drug development,** with the immunotherapy segment currently enjoying the limelight. Immuno-oncology has promoted a step-change in therapy effectiveness in the clinic, which has translated to strong share price evolution for those companies developing new cancer immunotherapy products with blockbuster commercial potential.

SALV is developing a buy & build strategy, aiming to add to its **first investment, iOx Therapeutics**, to complement the emerging 'checkpoint-enhanced' standard of cancer care with additional 'novel mechanism of action' products.

SALV's commercial opportunity is to develop an expanded and robust pipeline, acquiring novel and differentiated anti-cancer assets that are potentially complementary to existing anti-cancer therapy products and, preferably, synergistic in activity.

iOx represents a novel approach compared to the current immuno-oncology drug pipeline that predominantly targets the 'adaptive' side of immunity (for example, antibodies recognising tumour antigens and stimulating an immune response). iOx is **seeking new drug candidates that can modulate the body's 'innate' immune response** (and also link with the 'adaptive' arm) producing a unique and differentiated approach.

If iNKT cell activation potentially expands to become anywhere near as key to oncology treatments as some of its counterparts (i.e. PD-1 inhibitors), then companies with the **lead drug candidates could be set for a big payday**.

An initial Phase 1/2 study should determine iOx's lead program's activity alone, and in combination with an approved 'checkpoint inhibitor' - a positive result would suggest that this approach could work generically with a spectrum of approved and in-development 'checkpoint' inhibitors.

Cancer immunotherapy is a relatively new field but **quickly gaining clinical support** and **commercial traction**, with a **market projection of >$70bn sales by 2020** (Source: Research&Markets.com). SALV's initial immunotherapy approach is activating a specialised lymphocyte called an iNKT cell that could potentially form a first-line defence against tumour antigens and, in addition, enables constructive cellular 'crosstalk' with the adaptive or memory arm of the immune system. **iOx Therapeutics** is about to enter clinical development with its **lead product** that aims to stimulate a specific immune cell (Natural Killer T-cell or NKT cell) to potentially up-regulate its activity against tumour cells.

Positive results from this initial iOx trial are likely to attract the interest of the pharmaceutical industry's oncology strategy and business development teams. With the recent trend to underpin M&A and licensing deals with significant monetary terms (**that can reach >$1bn for even preclinical assets**), the opportunity for investors in SALV to exit on a premium multiple should be a realistic prospect.

SalvaRx's investment opportunity

SalvaRx Group plc (SALV) is a life sciences development company investing in innovative technology platforms to **deliver new anti-cancer drugs in the immunotherapy space** with novel mechanisms of action. **Cancer immunotherapy** is a relatively new field but **quickly gaining clinical support** and **commercial traction**, with a **market projection of >$70bn sales by 2020** (Source: Research&Markets.com).

An investment in SALV represents an opportunity to participate in the **exciting, fast-growing** and, importantly, **commercially viable** cancer treatment segment of **immunotherapy**. These newer cancer treatments and, **particularly in combination approaches**, suggest that harnessing the body's immune system can produce the most durable results and **improved patient survival**. SALV's **iOx Therapeutics** is about to enter clinical development with its **first product** that aims to stimulate a specific immune cell (Natural Killer T-cell or NKT cell) to potentially up-regulate its activity against tumour cells.

As this iOx, and other yet-to-be acquired, anti-cancer 'assets' are developed, the **utility of bringing (multiple) novel mechanism** approaches, in potential **(multi-)combination therapies** using cytotoxic, biological, immune response modifiers and cellular approaches is **likely to also elicit great interest from the Pharma oncology industry**. With the recent trend to underpin M&A and licensing deals with significant monetary terms (**that can reach >$1bn for even preclinical assets**), the opportunity for investors in SALV to exit on a premium multiple should be a realistic prospect.

Listing and transaction details

SalvaRx shares (ticker: SALV) commenced trading on after a share placing of £1.95m (5.49m shares at 35.5 pence/share), resulting in a total outstanding share number of 36.47m (or 39.69m fully diluted). The market cap at the placing price was £12.9m. This listing follows a share consolidation and acquisition by 3Legs Resources (see below) and a change of name to SalvaRx Group plc.

3Legs Resources, an Isle of Man registered company (ticker: 3LEG), acquired an ~11% stake in SalvaRx, a BVI registered and cancer drug development company, in September 2015. Two of 3LEG's directors, Jim Mellon and Dr Greg Bailey, founded SalvaRx in May 2015. In March 2016, 3LEGS acquired the outstanding equity in SalvaRx for £8.8m in 3LEGS shares. Concurrently, 3LEGS raised £1.95m through a Placing and changed its name to SalvaRx Group plc (SALV). SALV has put together a Board and management team with considerable operational expertise in drug discovery, development and commercialisation.

SALV's strategy is to build a diverse portfolio, or pipeline of assets, through investment in companies with **innovative development programmes**, **exceptional management** and **outstanding growth opportunities**. A key focus is on cancer and immunology, emphasised by its initial investment.

SALV's sole investment to date is in iOx Therapeutics (~60% equity stake), acquired by SalvaRx in July 2015. SalvaRx invested £510k on signing and is committed to investing a further ~£1.3m against certain milestones. Existing cash (~£1.5m) and placing monies (£1.95m) should see SALV adequately funded for an 18-month period.

Importantly, Oxford University, SALV's equity partner in iOx Therapeutics, is committed to funding the initial clinical trial.

Capital structure of SALV (post-transaction)		
Name	**Number of New Ordinary Shares**	**% of Enlarged Share Capital**
Jim Mellon	13,320,291	36.53
Dr Greg Bailey	13,320,291	36.53
Hon & Co Holdings Limited	2,122,676	5.79
Totals	**28,763,258**	**78.85**

Source: Company *Enlarged share capital following Admission – 36,466,619*

Investment portfolio

iOx Therapeutics (iOx) was founded in February 2015 by **ISIS** (Oxford University's technology transfer arm) and the **Ludwig Institute**. The aim is to develop a new type of immunotherapy against cancer, using key findings from an earlier collaboration between Professor Vincenzo Cerundolo (of Oxford University) and the Ludwig Institute.

The **Ludwig Institute for Cancer Research** is an international not-for-profit organization with a 40-year legacy of pioneering cancer discoveries. The institute combines robust translational medicine programs with potential breakthrough discoveries in order to help create attractive projects for subsequent commercial development.

iOx Therapeutics is SALV's first investment. The expert due diligence that enabled SALV to recommend a modified Phase 1/2 clinical plan for iOx's iNKT agonist candidate in metastatic melanoma, and quickly move to invest in iOx is testament to the strength of SALV's model - which is **likely to be the template for investing in complementary cancer immunotherapy products and technologies** with novel mechanism of action properties.

SALV is actively screening for further acquisitions or investments in cancer immunotherapy and other, complementary areas of oncology.

iOx Therapeutics

iOx's team **discovered a number of synthetic lipid compounds that were found to activate iNKT cells** and potentially play an important role in anti-cancer immune responses. Oxford University's Weatherall Institute of Molecular Medicine has been working on the biology of iNKT cells for >10 years.

These synthetic lipid compounds form the basis of iOx's R&D programme. iOx has an **exclusive** licence (with the right to sub-licence) from the Ludwig Institute to develop and commercialise iNKT cell agonists (including the lead candidates) for treating various human diseases, including cancer.

SalvaRx has been working informally with iOx since mid-2014, helping design and implement a series of preclinical experiments to identify the proposed mechanism of action of these novel iNKT cell agonists. The outcome of this particular collaboration has been:

- **Evidence of an effective second-generation of iNKT cell agonists** (including the rejection of cancer in mouse models),
- **Crystallising iOx's development programme and commercial strategy**. SALVs collaboration (including designing some additional preclinical work), a pre-requisite for its investment, to develop a highly commercial drug development approach should not be understated. **This is a key benefit of SALV's pro-active and highly commercial deal-making process**.

A further benefit of iOx's experienced management and scientific advisor boards is a well-connected industry network. We understand that a number of (non-dilutive) funding deals are under discussion.

Therapeutic strategy

Clinical development

iOx is aiming to carry out a ~60-patient study of its lead product in advanced melanoma. Preliminary discussions with the UK's Medical and Healthcare products Regulatory Agency (MHRA) have taken place regarding trial design, although the protocol has yet to be finalised. This study is to be fully funded by Oxford University. We understand that the combined Phase 1/2 study is likely to include:

- **A dose-finding study** in order to establish some clinical parameters for the lead product alone and in combination with a PD-1 inhibitor (includes maximum tolerated dose, MTD and any dose-limiting toxicity, DLT), followed by a
- **3-arm randomised study** of it alone, compared to the PD-1 inhibitor alone, and compared to the combination of it and the PD-1 inhibitor.

The aim is to develop an immunotherapy product that can achieve a significant long-term response (a 'functional cure') in multiple cancer types, helping improve overall survival.

Studies are also being considered in lung cancer (lead program, preclinical status) and as a vaccine adjuvant (IMM47, preclinical status). Further agonist candidates are at the discovery stage.

Cancer treatment is evolving

Significant advances have been made with newer immunotherapy agents in treating cancer and achieving better progression-free survival (PFS) outcomes.

We develop the idea (see Appendix, page 18) that **tumour growth is now understood to be the result of cells achieving 'immune escape'**, which is the **net balance of a number of molecular 'accelerators' and 'brakes'** having an effect on **tumour cell differentiation** and the **tumour's ability to avoid immune system surveillance**.

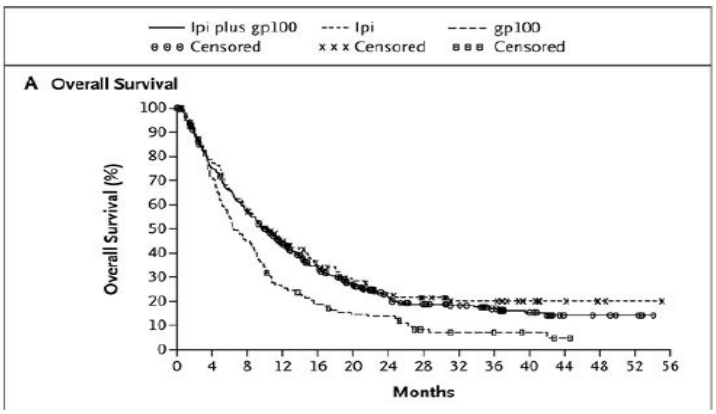
Recent immunology research has demonstrated many of these **accelerators** and **brakes** working to modulate T-cell activity. **A better understanding** of the complex **cellular interplay** during **tumour growth** and differentiation and the **body's immune system** has resulted in some **major achievements** in treating **advanced stage cancer** and **improving patient survival**.

Below, we outline some of the **results supporting Bristol-Myers Squibb (BMS) Yervoy's (ipilimumab) approval by the FDA in 2011** for the treatment of melanoma. **Ipilimumab, an antibody immunotherapy**, was the first in its drug class (CTLA-4 checkpoint inhibitor) to block these brakes; in fact, ~30 percent of patients with widespread metastatic melanoma seem to have long-term benefit with this drug.

Patients on the 'tail' of the survival curve seem to be living with their cancer for years (rather than early and inevitable death) – see table below. It should be remembered that these patients had poor prognoses right from the beginning - the altered outcome with the introduction of ipilimumab has been a significant move forward.

Ipilimumab is a monoclonal antibody that **works to activate the immune system by targeting CTLA-4**, a protein receptor that down-regulates the immune system. Cytotoxic T lymphocytes (CTLs) can recognize and destroy cancer cells (CTL is a T lymphocyte, or type of white blood cell that kills cancer cells, bacteria and viruses). However, an inhibitory tumour-directed mechanism interrupts this destruction; **ipilimumab turns off this inhibitory mechanism and allows CTLs to function normally**. As we see from the figure below, ipilimumab clearly enhances overall survival - which was **a first in metastatic melanoma** - and underscored its commercial opportunity as a monotherapy.

Ipilimumab in metastatic melanoma: Kaplan-Meier analysis of survival



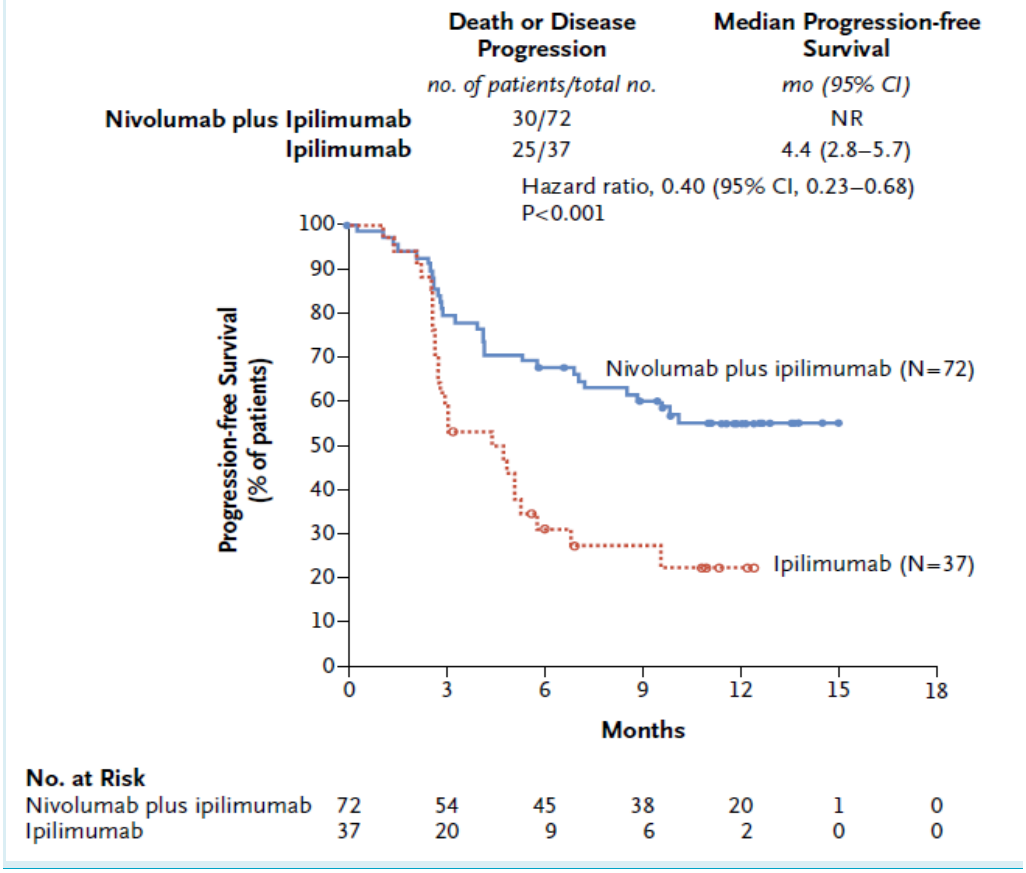
Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Source: Hodi et al NEJM (2010); ipilimumab alone or combined with gp100 (a peptide vaccine) showed a significant survival improvement with long-term effects in metastatic melanoma when compared to gp100 alone.

However, to increase response rate and reduce adverse reactions, emphasis turned to various drug combinations. In 2013 ipilimumab alone was compared to ipilimumab in combination with nivolumab (BMS's Opdivo). The response rate (tumours shrinking by at least 30%) was 58% for the combination, 44% for nivolumab alone, and 19% for ipilimumab alone. The **Yervoy/Opdivo combination was approved by the FDA for melanoma in October 2015**.

iOx's management team, Ian Walters MD and Dr Rob Kramer, are alumni of the BMS oncology group that helped bring both of these products to market.

Nivolumab plus ipilumumab combination versus ipilimumab alone (pub 2015)



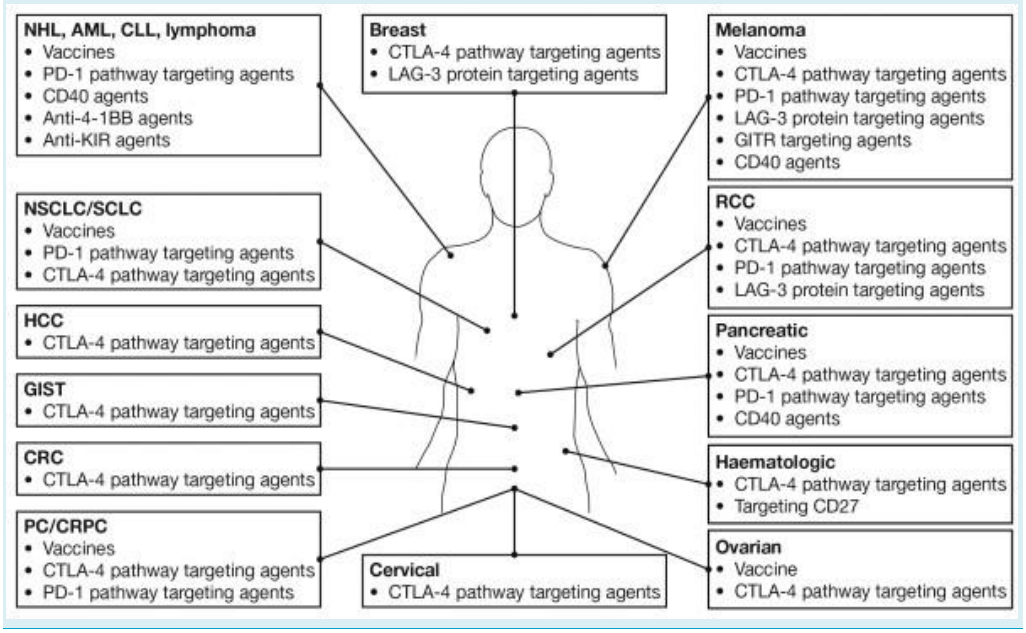
Source: Postow, Chesney et al (2015) New England Journal of Medicine; Kaplan–Meier curves for progression-free survival among patients with BRAF wild-type tumors treated with the combination regimen or ipilimumab alone.

Opdivo is an anti-PD-1 monoclonal antibody developed by Ono Pharma and Medarex (acquired by BMS). Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells.

Next steps, for clinical scientists and companies with approved products**,** underline **the importance of combinations based on ipilimumab and/or other checkpoint inhibitor molecules**, aligned with the improved understanding of cancer and pushing the (relevant) accelerators and blocking the brakes - at the molecular and cellular level.

Combinations hold potential advantages, as additional data from recent and ongoing clinical trials suggest that targeting other components of the immune system (and not just checkpoints) can provide even longer term survival benefits.

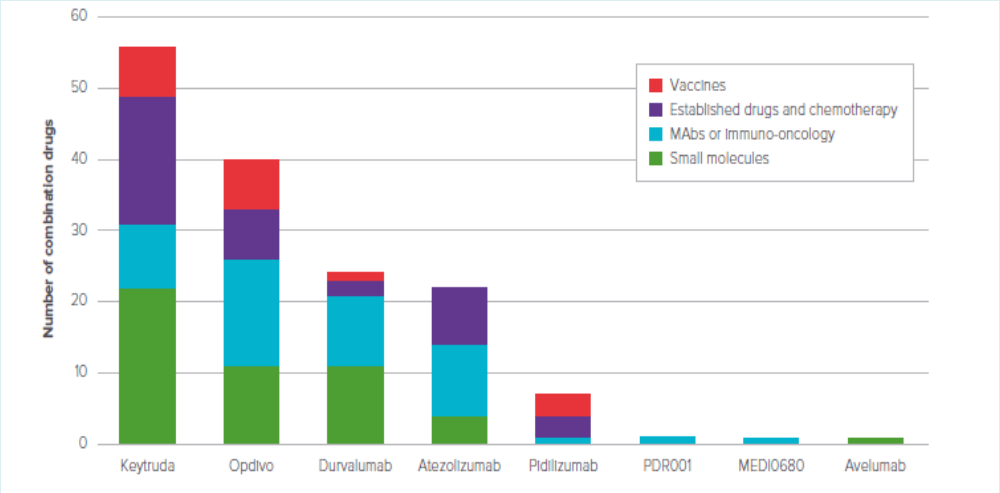
Immuno-oncology agents in clinical development across multiple tumour types



Source: J Transl Med (2014); Selected therapies and tumours - not exhaustive. Key: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukaemia; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte antigen-4; GIST, gastrointestinal stromal tumour; HCC, hepatic cell carcinoma; LAG-3, lymphocyte activation gene 3; mAb, monoclonal antibody; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PC, prostate cancer; PD1, programmed death 1; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

The rationale for combinations covers a spectrum of thinking, from additional potential efficacy to lower adverse events with lower doses of the separate agents (compared to monotherapy), to name just a couple.

Combination studies for anti-PD-1/ PD-L1 antibodies



Source: Evaluate Pharma

BMS' Yervoy is currently being investigated in >20 combination trials, many of these paired with its own PD-1 monoclonal antibody product, Opdivo. AstraZeneca is the only other company with both PD-1/PD-L1 and CTLA-4 antibodies (durvalumab and tremelimumab).

What is clear is that a diverse range of companies, **from Big Pharma to small biotech**, are developing a variety of alternative 'checkpoint' molecules as well as the panoply of alternative chemotherapy classes (and the means to investigate combinations in the clinic), from small molecules, through vaccines to cell therapies.

Activating immune cells to prevent/kill tumours

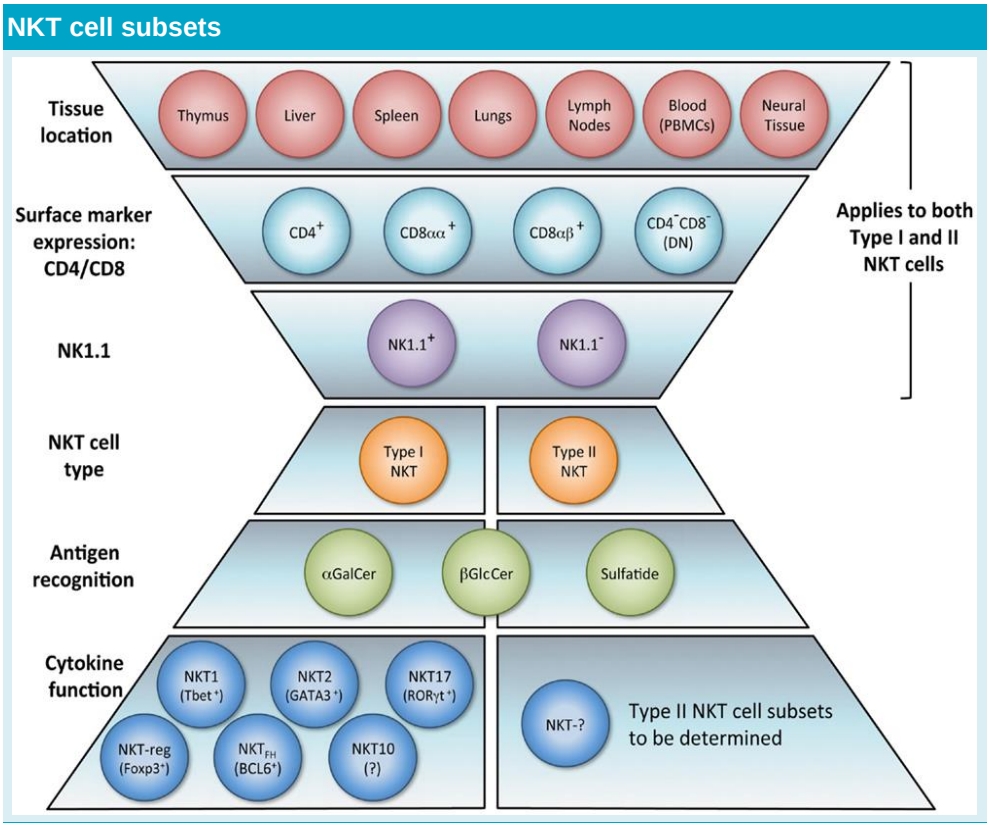
Just stepping back a moment, let's consider the important receptor and effector cells that make up the body's immune system and how it responds to 'non-self' antigens, and particularly the presence of tumour cells.

The immune system, and its activation, could be simply described as having two principal arms, that is:

- **The Innate immune response**, which is activated immediately following infection or injury, through numerous immune cells (including macrophages, neutrophils, dendritic cells and natural killer cells) can also rapidly respond to an immunological threat such as cancer; and
- **The Adaptive immune response**, which provides the basis to mediate immunity in a more precise and lasting manner, elicited through cells including T- and B-lymphocytes and provides the physical basis for an 'immunological memory'.

NKT, or Natural Killer T-cells

A special cell type involved in immunosurveillance which bridges the innate and adaptive immunity is the **'natural killer T' (NKT) cell** (not to be confused with Natural Killer, NK or T- cells!). NKT cells, in an innate fashion, can respond quickly to antigenic stimulation, producing a range of cytokines and activating antigen-presenting dendritic cells (DC). **These responses can have a lasting and powerful effect on both arms of the immune system**, and potentially help modulate the body's immune response to cancer and other diseases.



Source: Robertson et al, Frontiers in Immunology 2014; The natural killer T (NKT) cell population is made up of several different subsets - with different characteristics and functions. Tissue location and surface markers (CD4, CD8 and NK1.1) are defining and dictate functionality.

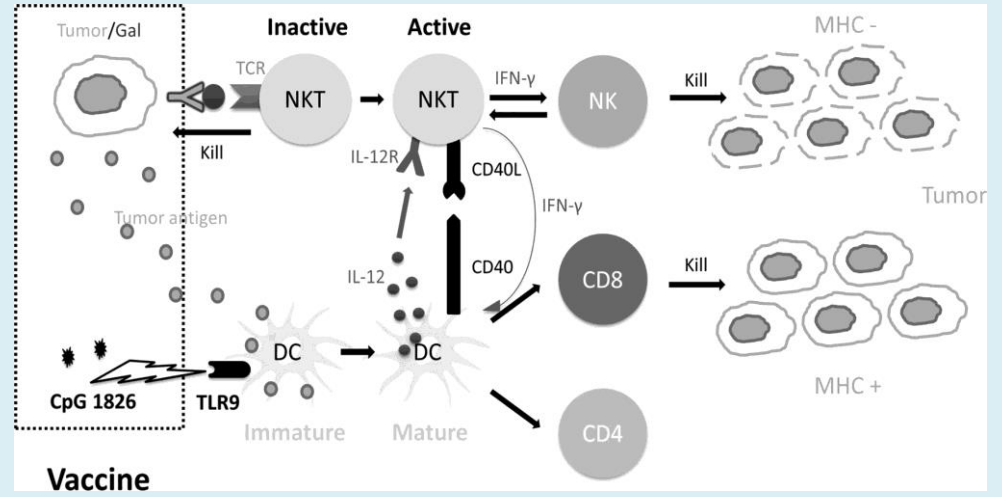
NKT cells 'punch well above their weight', with antigen recognition to both self- and non-self antigens (unlike other T-cells) and fast reaction to stimulation through producing a range of cytokines and chemokines to modulate the immune response. This modulation can have both immune-enhancing and immuno-suppressive effects.

On stimulation, NKT cells produce a range of cytokines including interferon (IF)-gamma, interleukins (ILs-2, -4, -10, -13, -17, -21 and -22), GM-CSF and TNF-alpha. These cytokines activate other immune cells (NK cells, T cells and B cells) to help recruit additional cytolytic cells for tumour surveillance. At the same time, DC maturation (through NKT activation) potentiates **CD8+ T cells**. **These are cytotoxic T-cells that can kill tumour cells**.

Of particular interest are the *invariant* NKT, or iNKT cells. Their activation can be caused by a range of stimuli, antigenic or chemical, and through interaction with other immune cells (like antigen presenting cells, APC) providing a watchdog function in the immune surveillance for 'non-self' across the body's immune system. iNKT cells can respond to these stimuli - including non-self tumour antigens - extremely fast, secreting chemicals to attack bacteria, viruses and tumour cells, as well as linking into the adaptive immune arm (to potentiate CD8+ killing).

Representation of this complex interplay and the constant new detail that is becoming apparent through research efforts (at Oxford University and other institutions) is difficult. Nevertheless, the activation of NKT cells through presentation with tumour antigens and depiction of the immediate and subsequent killing efforts directed at the tumour cells by cytokines (amongs others) or indirectly through interaction with dendritic cells to further activate more professional and long-lived killer T-cells, particularly CD8+, is simplified below.

Schematic to show NKT cell function in innate and adaptive mode



Source: Dong et al, Co-operation of α-galactosylceramide-loaded tumour cells and TLR9 agonists induce potent anti-tumour responses in a murine colon cancer model, Biochem J (2015)

iOx's iNKT programme

iOx are aiming to directly intervene through activating iNKT cells. In the previous figure, one of the interesting characteristics described for iNKT cells is their susceptibility to activation by 'Gal', shorthand for alpha-galactosylceramide (α-GalCer), a synthetic form of a chemical extracted from a marine deep sea sponge (*Agelas mauritanius*).

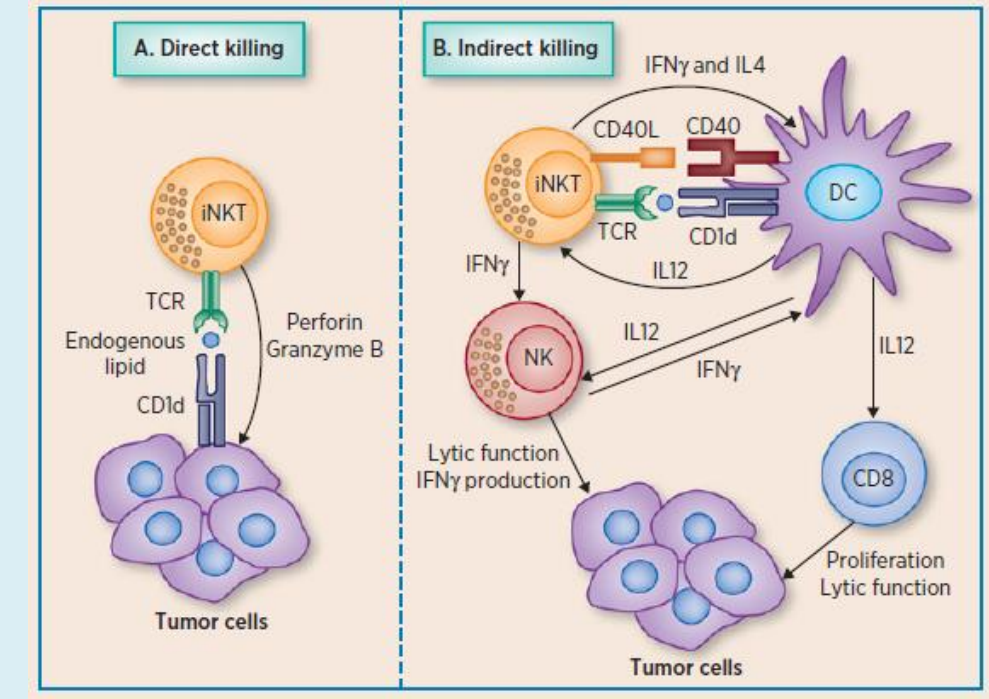
iOx (and others) are seeking to not only understand the biology of iNKT cells better, but also **introduce innovation through generating analogs of α-GalCer** that can **produce more specific** and **more durable activation of iNKT cells** - in other words to achieve a better outcome for both the immediate iNKT response and its linking into the body's adaptive response. A number of non-glycosidic agonists based on threitolceramide (ThrCer) have been described by Vincenzo Cerundolo's Oxford University team and collaborators.

Progress has been encouraging to date, with recent publications charting the optimisation of the chemical structure for iNKT performance and, at the same time, helping minimise some of the potential disadvantages, such as hyperproduction of cytokines ('cytokine storm') and anergy (a lack of responsiveness of iNKT cells). Indeed, iOx believes it has a number of relevant/new strategies to avoid anergy.

The proposed combined Phase 1/2 study is likely to focus on combining the lead program iNKT agonist with an approved PD-1 class inhibitor (which could be either nivolumab or pembrolizumab).

A potential successful outcome to this trial would establish a meaningful difference between the separate monotherapy arms and the combined arm, **suggesting activation of NKT cells and potentiation of both the target cellular networks**. Further work is likely to be needed to distinguish direct from indirect immune system effects, but the significance of such an outcome, albeit preliminary, would resonate strongly with pharmaceutical companies on the look-out for novel and effective cancer immunotherapy assets.

Anti-tumour activities of iNKT cells



Source: McEwen-Smith et al, Cancer Immunol Res, American Association for Cancer Research 2015. Direct Killing - recognition of CD1d-presented tumour antigens, followed by iNKT cell-mediated lysis, or Indirect Killing - CD1d-expressing and TLR (Toll-like receptor)-activated APC (Antigen Presenting Cell) promotes activation of NK (Natural Killer) cells and tumour-specific T-cell response leading to indirect tumour cell death.

Further research work into the potential co-administration of peptide/protein antigen(s) - to elicit a further adjuvant effect - is being evaluated.

iOx's Patents and intellectual property

iOx has rights to three patent families relating to the discoveries by Vincenzo Cerundolo with his Oxford University and other collaborators. The patent applicants are - depending on the patent family - the Ludwig Institute, Oxford University and Birmingham University, separately or combined. **iOx benefits from these granted and in-application patents** as a result of a licence from the Ludwig Institute.

iOx patent rights

Patent Family	Application	Regarding	Granted patents	IP owner
1	Based on Patent Cooperation Treaty (PCT) application , number WO2007/050668	Galactosylceramide (GalCer) derivatives and combinations	Patents are granted in Europe, China, Canada and US. Pending in Brazil, Japan and Russia. Expiry mainly October 2026 (some January 2028).	Ludwig Institute primarily (with Birmingham University or Oxford University for some IP)
2	Based on PCT, WO2012/188414	Liposome formulations comprising certain amounts of thritolceramide (ThrCer) and a number of ligands. The liposomes may also include antigen(s) and therapeutic agents. This family also relates to liposome compositions, their uses (in treatment - infections and cancer), combination therapies and liposome production methods	Patent applications are pending in Europe and US. Ultimate expiry of family in December 2031.	Ludwig Institute
3	Based on PCT, WO2012/188415	Alpha-GalCer analogs and compositions, and their use in activating iNKT cells, their use in treatig sidease associated with iNKT activation and importanly including combination therapies	Patent applications are pending in Europe and US. Ultimate expiry of family in November 2032.	Ludwig Institute (US application), Oxford & Birmingham University (European application)

Source: Company

SALV is obliged to pay licence fees for access rights to patents and (potentially) future royalties on product sales to both the Ludwig Institute and Oxford University.

SalvaRx's market and commercial opportunity

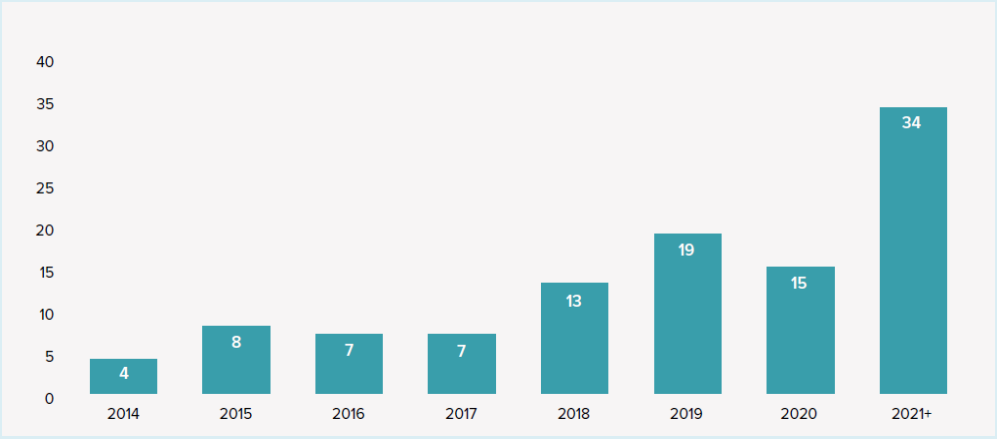
Although (some) immunotherapies have been around for years (importantly cytokines and a variety of targeted antibody therapies), **heightened commercial interest has reached a crescendo with recent ground-breaking results** from PD-1 (and other checkpoint) inhibitors, dendritic cell (DC) therapies, T-cell therapies (CAR-T) and cancer vaccines.

A wave of new concept-based immunotherapy agents hold out the promise of improved survival with lower toxicity for some patients. At the same time, combination therapies address multiple pathways in a tumour, potentially leading to substantial increases in survival.

Global spending on oncology medicines (includes therapeutic treatments and supportive care, but not discounts, rebates and patient access schemes) increased 10.3% and **reached $100bn in 2014**, up from $75bn five years earlier. That is a 5YR CAGR of 6.5% globally (constant currency basis), though only 5.3% in the U.S.

Targeted therapies now account for almost 50% of total spending and they have been growing at a compound average growth rate of 14.6% over the past five years. The immunotherapy drugs market is estimated to grow at a CAGR of 12.8% to reach >$70bn by 2020 (Markets&markets.com, 2015). **The checkpoint inhibitors, by type of drugs, are expected to witness the fastest growth during this period**.

Potential combination launches in oncology



Source: CenterWatch, FDA, clinicaltrials.gov, IMS R&D LifeCycle, IMSCG Analysis

Commercial opportunity

SALV currently has no product sales or meaningful revenues. However, the company has a number of potential technology opportunities (iOx Therapeutics, other assets to be determined) and potential future revenue streams that should, in time, allow us to develop a detailed earnings model.

As we have emphasised above, the market opportunity is a significant and rapidly growing one.

SALV's advantage, to kickstart its technology into rapidly gaining traction as a commercial venture, is the wealth of experience and expertise that its management and advisory boards bring to the development of highly technical immunotherapy approaches.

The impact of iOx's iNKT agonists (probably as part of an oncology combination therapy) on human health could be huge, allowing SALV an entry ticket into licensing discussions with pharmaceutical companies and biotech companies.

There are, nevertheless, a number of potential risks to manage and overcome - **a major challenge will be to prove that such therapies represent an improvement over current treatments**, with well-designed and controlled clinical trials that demonstrate a superior long-term efficacy and safety (to current pharmacotherapy).

The commercial goal is a deal, initially with iOx's lead product (and preferably following the planned Phase 1/2 study), which could be either a license and development agreement, product acquisition or sale of the company. The oncology immunochemotherapy segment is a highly attractive one, with recent clinical success and opportunity fueling significant transaction values - even for preclinical assets.

Recent immunotherapy deals for early phase products

Target	Acquirer	Deal value	Category	Stage (on deal signing)	Date announced	Additional
Merck KGaA	Pfizer	$850m upfront, $2bn total (50:50 costs)	anti-PD-1/ PD-L1 antibody	Phase 1	November 2014	Strategic alliance, with intent to progress 20 clinical trials, multiple indications
Juno Therapeutics	Celgene	$1bn (30:70 costs)	CAR-T/ T-cell	Phase 1	June 2015	10-year strategic alliance
cCam Biotherapeutics	Merck	$95m upfront, $605m total	Novel checkpoint monoclonal antibody (CEACAM 1)	Phase 1	July 2015	Acquisition
Flexus Biosciences	Bristol-Myers Squibb	$800m upfront, $1.25bn total	IDO inhibitor (small molecule)	Preclinical	February 2015	Acquisition (Anti-T-cell suppressor technology)
Aduro Biotech	Novartis	$200m upfront, $50m equity investments, potential $500m milestones	STING agonists (small molecule)	Preclinical	March 2015	Cyclic dinucleotides activate innate and adaptive immune responses
Cellectis	Pfizer	$80m upfront, $265m total (plus 10% equity stake)	CAR -T	Preclinical	June 2014	Strategic alliance
Five Prime	Bristol-Myers Squibb	$350m upfront, $1.7bn total	Anti-CSF1R antibody	Phase 1	October 2015	License and collaboration agreement

Source: author, various websites

Catalysts

We have identified some near-term potential events that could trigger share price moves.

Potential 'trigger' events		
Calendar		**Event**
2016	H2	Decision on drug product manufacturing plan
2016		Nominate a second product for the clinic
2016		Potential second transaction for SALV
2017		Commence human study for lead program in metastatic melanoma

Source: Analyst

Investment Risks

We believe the main uncertainties in SALV's commercial ambitions relate to:

- In the near term, a lack of efficacy and little activity differentiation with iOx NKT agonists alone or in combination with PD-1 and/or other checkpoint inhibitors;
- Material delays in eliciting interest and establishing iNKT development licences with pharmaceutical partners and other commercial partners;
- Lack of investor commitment to invest in additional funding rounds;
- In the medium term, failure to identify acquisition targets or obtain additional funding to follow a 'buy & build' model; and
- Potential product competition, new technology entrants.

Board, Senior Management and SAB

Chairman - **Jim Mellon**. Jim has a significant track record in investing. He established a listed fund management company, Charlemagne Capital and an Asian investment group, Regent Pacific Group. He is a controlling shareholder of Manx Financial Group and Webis Holdings. Jim co-founded Uramin and Red Dragon Resources. Burnbrae, his personal investment vehicle, is a substantial landlord and owns a hotel chain (Sleepwell). He is co-Chair of FastForward Innovations Ltd, a director of Portage Biotech Inc and a published author (Cracking the Code, 2012). Jim is an honorary fellow of Oriel College, Oxford University.

CEO - **Ian Walters, MD**. Previous experience at Bristol-Myers Squibb, PDL BioPharma, Millenium Pharma and Sorrento Therapeutics in managing and strategic positions leading corporate development, translation medicine projects, clinical development and medical affairs. Ian specialised in helping build drug pipelines in cancer from research stage through approval - at BMS he helped develop the international clinical experience of more than eight oncology compounds, including nivolumab (anti-PD-1), ipilimumab (anti-CTLA-4), brivanib (anti-VEGF/ FGF), anti-IGF-IR, VEGFR2 biologic inhibitor and elotuzumab (Empliciti). Previously he was a lead clinical investigator at Rockefeller University, helping initiate a number of immunology programmes. Ian has an MD from the Albert Einstein College of Medicine (NYC) and an MBA from The Wharton School, University of Pennsylvania.

Chief Financial Officer - **Kam Shah**. Previous experience working in commercial and corporate roles for some of the world's leading food companies including Birds Eye (Unilever), Walkers Snacks (Pepsico), and Premier Foods.

NED - **Dr Greg Bailey**. Previous experience as an investment banker and physician; currently an investor and entrepreneur in the biomedical sector. Experience ranges across multiple financings, M&A transactions, and taking companies public. He is a co-founder and managing partner of MediqVentures Inc. and the Executive Chairman of Portage Biotech Inc. He was a managing partner of Palantir Group merchant bank involved in a number of biotech company start-ups and financings. Dr. Bailey co-founded Ascent Healthcare Solutions, VirnetX Inc. (VHC:AMEX), Portage Biotech Inc. (PTGEF: OTCBB) and DuraMedic Inc. and was the initial financier and an independent director of Medivation, Inc. (MDVN:NASDAQ) from 2005 to December 2012.

NED - **Richard Armstrong**. Extensive experience in turnaround situations and raising capital, especially in the quoted microcap sector. Previously occupying board positions at Weatherly International plc, KP Renewables (now IGas Energy plc), Future Internet Technologies (now Artilium plc) and Mobilefuture plc.

NED - **Colin Weinberg**. Background in stockbroking sector, including Durlacher and Walker Crips Weddle Beck. A former director of Peckham Building Society and currently a director of Associated British Engineering plc.

Chief Scientific Officer - **Dr Robert Kramer**. 24 years' experience in the pharmaceutical industry. A former Head of Oncology Discovery Research at Bristol-Myers Squibb and Janssen Pharma (part of Johnson & Johnson). Responsible for transitioning >30 drugs from discovery into the clinic, and was key to BMS developing its immunotherapy interests, including the acquisition of Medarex in 2009 (gaining Yervoy/ipilimumab and Opdivo/nivolumab). He has a PhD in pharmacology and was previously an assistant Professor at Harvard Medical School.

The iOx Board (as well as Ian Walters) includes:

Scientific adviser - **Prof Vincenzo Cerundolo**. Professor of Immunology at the Weatherall Institute of Molecular Medicine, University of Oxford. He is responsible for the IP and know-how licensed to iOx Therapeutics by the Ludwig Institute. Research 'firsts' include elucidating the mechanism of ligand binding of lipids to CD1d receptors and subsequent presentation to lymphocytes; demonstrating the importance of iNKT cells in enhancing antigen-specific T- and B-cell responses in disease; developing novel iNKT agonists (now being developed by iOx Therapeutics).

NED - **Declan Doogan**. Previously SVP and Head, Worldwide Development, Pfizer for multi-billion dollar programmes, including Viagra and Lipitor.

NED - **Jonathan Skipper**. Executive Director of Technology Development at the Ludwig Institute.

NED - **Annalisa Jenkins**. CEO at Dimension Therapeutics (floated on Nasdaq in October 2015).

In addition, the Group is already working with leading academic experts to assemble an **iOx Scientific Advisory Board**

Appendix

Immunochemotherapy - the future of cancer treatment

The roots of cancer immunology can be traced back to the 1800s and include concepts linking cancer to inflammation (Virchow), new thinking on immune surveillance (Ehrlich) and the modulation of the immune system using bacterial toxins (Coley). Cancer genetics became a force for greater understanding in the 1900s using studies from animal tumour viruses (Rous), tissue culture (Eagle) and cytogenetics (Nowell), eventually leading to the significant discovery of oncogenes (1970).

Interestingly, in the 1980s, the discovery and widespread use of immunodeficient mice to support research into human tumours saw the important observation that these deficient mice don't have a higher incidence of spontaneous cancer compared to normal mice. **This led to the notion that the immune system had no part to play in the cancer proces**s, That is you could irradiate the mouse, damage its immune system to not reject human xenografts and then investigate the effect of anti-cancer drugs on the new human tumour grafts.

Cancer immunology didn't become a recognised force again until 2000 with the introduction of sophisticated 'knockout' mutant animals and the realisation that the immune system (and at that time a growing understanding of the function of interferon production) is an important suppressor mechanism for cancer - and possibly the most important one.
This was the start of a coming together of genetics and immunology over the last 10-15 years, and followed the observation that if specific tissues lacked the necessary inflammation signals then 'cancer-causing' genes were inactive.....leading to an **understanding of the immune system as a key suppressor mechanism**.

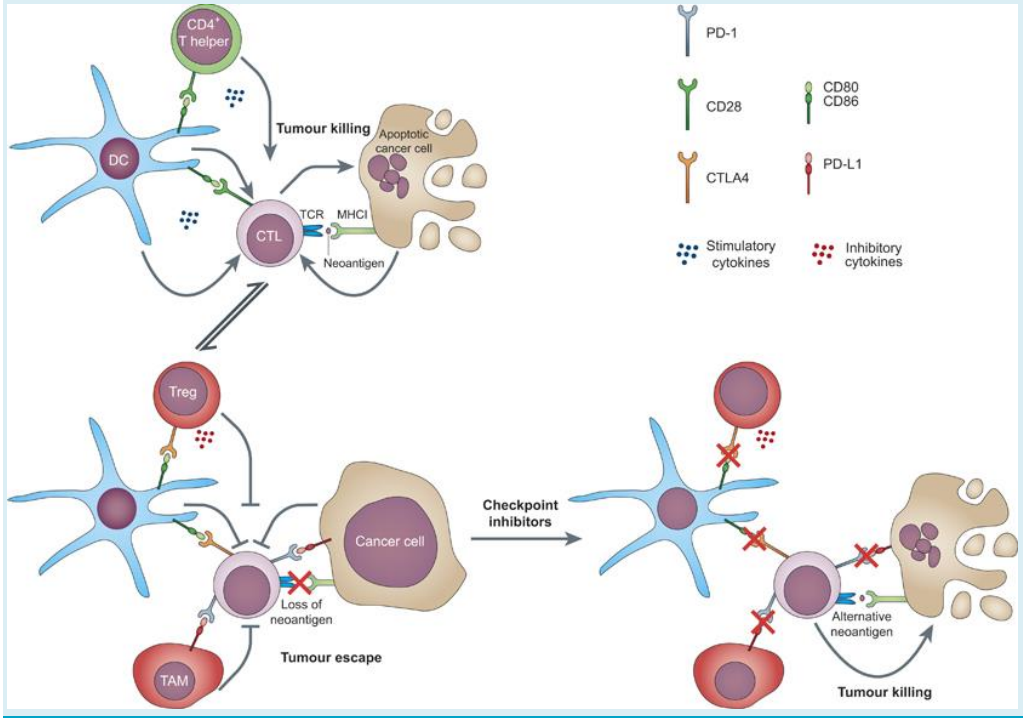
The current vogue for **immunochemotherapy** is the latest crossroads for research that has its roots in knowledge of today's cancer cell (and cancer stem cells) and how the host can modulate the development of these cells through cellular processes, like angiogenesis and immunological means. Immunochemotherapy **consists of treating the host immune system as well as applying existing treatments** of chemotherapy and traditional radiotherapy and surgery.

So can we define cancer better these days, rather than just an uncontrolled fast growth of a ball of cells in an undifferentiated manner?

Modern theory is that cancer's rogue cells are created by cancer-inducing molecules - and our modern therapies attack those molecules (for example, Erbitux attacking the EGF receptor, and Avastin, an anti-VEGF antibody, stopping angiogenesis which is the attraction of a blood supply by a tumour).

The emerging idea over the last few years is the concept of 'immune escape' - this is where rogue or cancer cells have to learn how (mutations) to escape the surveillance and actions of the immune system - in the end, [the majority?] learn. Treatments that target escape mechanisms and restore immune control can be effective. For example, Yervoy, a CTLA-4 antibody helps reset the (down-regulated) immune system, neutralising the CTLA-4 cell protein receptor and allowing cytotoxic T lymphocytes (CTLs) to function once more. Certainly, various data point to the presence of a pre-existing immune response held in check by 'adaptive immune resistance' in those who respond to checkpoint inhibition.

Overcoming adaptive immune resistance with checkpoint inhibitors



Source: Phan et al (2015) Immunol & Cell Biology; The immune system recognises neoantigens generated by somatic mutation so as to eliminate cancer cells. However, cancers have developed multiple strategies to evade and suppress this antitumour immune response (including loss of neoantigen expression and disrupting normal control mechanisms - CTLA-4-mediated suppression by regulatory T cells, and PD-1/PD-LI-mediated exhaustion of antitumour CTLs). ***Checkpoint inhibitors*** *block these inhibitory molecules to drive CTL killing of cancer cells expressing escape neoantigens.*

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