IMMUNOTHERAPY
WINNING THE FIGHT AGAINST CANCER

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Introduction

Cancer can be a devastating, life-limiting disease. According to the Global Burden of Disease study, cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 17.5 million new cases in 2015. The number of new cases is expected to rise by approximately 70% over the next 2 decades.

To put these data into context, cancer is the second leading cause of death globally, and was responsible for 8.7 million deaths in 2015. These figures equate to nearly 1 in 6 deaths being due to cancer.

Billions of pounds are spent on research into cancer treatments and over the past 5 decades survival has significantly improved for many common cancers, particularly breast and colorectal cancer. However, major breakthroughs in long term cure of patients with recurrent or metastatic disease are now being made using immunotherapy.

Immunotherapy is a revolutionary type of treatment that may turn many cancers that are currently considered terminal illnesses, into a long-term chronic condition, much like diabetes or multiple sclerosis.

This paper is a basic explanation of what immunotherapy is and how it works.

The immune system

Before we explain immunotherapy, it is important to understand the principles of the body's immune system and how it works.

The immune system is extremely complex. It can recognise and remember millions of different foreign entities (e.g. bacteria, viruses, abnormal proteins), and can produce both cellular and antibody responses to destroy and clear these from the body.

The immune system is essential to defend humans from pathogens, including bacteria and viruses such as streptococci and herpes. These defences are made up of white blood cells (leukocytes), proteins, and other tissue systems, including the lymphatic system (the lymphatic system drains tissue fluid from around the body tissues through lymph nodes as part of immune surveillance).

The bone marrow is the soft tissue inside the hollow section of certain bones and is where blood stem cells reside. The bone marrow is responsible for production of red blood cells and platelets that are important for the cardiovascular system but also makes white blood cells (leukocytes), which provide important roles in immune responses ("innate immunity").

The different types of leukocytes include:

- lymphocytes which identify and remember enemy micro-organisms to help the body destroy them,
- phagocytes, which engulf and digest micro-organisms,
- basophils, which are involved with allergic responses and inflammation.

Lymphocytes are of two main types: B cells and T cells. Prior to maturing, B cells remain in the bone marrow. By contrast, T cells travel from the bone marrow to an organ called the thymus, (located just behind the sternum) to mature.

B and T cells are the body's adaptive defence against foreign bodies such as bacteria or viruses. When antigens (e.g. abnormal or foreign proteins) are detected, B cells are stimulated to produce specific antibodies. Antibodies are proteins specifically selected to recognise and attach to foreign antigens and to form complexes called antigen-antibody complexes. Although the antibodies can bind to abnormal cells and bacteria they do not directly kill them but provide signals or markers for other cells to become involved. T cells take over. T cells can recognise antibodies that have coated abnormal cells and can also organise other cells, for instance phagocytes, to help destroy micro-organisms and remove them via the lymphatic system.

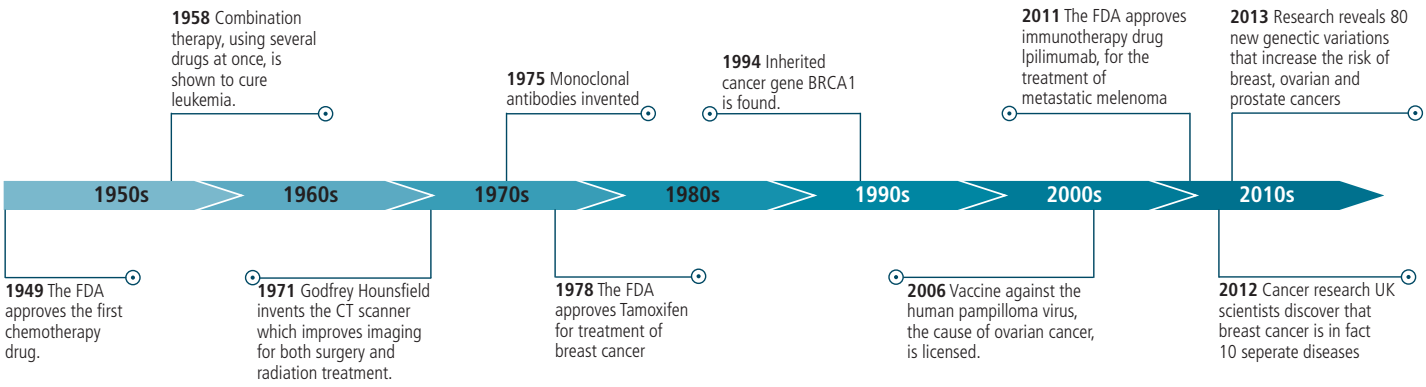
The immune system

Critically, the B cells that expand to produce antibodies against an infection remain in the body, providing a "memory" of the antigens they are specifically targeted for. If the body is re-exposed to the same antigen, these B cells recognise this and can rapidly organise an immune response. Consequently, we are able to become immune to diseases such as chicken pox and measles through this process.

The immune system is constantly scanning for mutations and malfunctions in cells that could lead to cancer and other disease. This is a process known as "immuno-surveillance".

Loss of immuno-surveillance is one factor that can contribute to cancer development. The changes that transform a normal healthy cell to a cancerous cell involves the generation of new forms of host molecules known as cancer antigens or tumour associated antigens (TAAs). These changes can distinguish cancer cells from normal cells and allow the immune system to recognise cancerous tissue.

FIGURE 1: SIGNIFICANT MILESTONES IN THE DEVELOPMENT OF ANTI-CANCER THERAPIES



Cancer is a disease arising from Deoxyribonucleic acid (DNA) damage leading to uncontrolled growth of cancer cells.

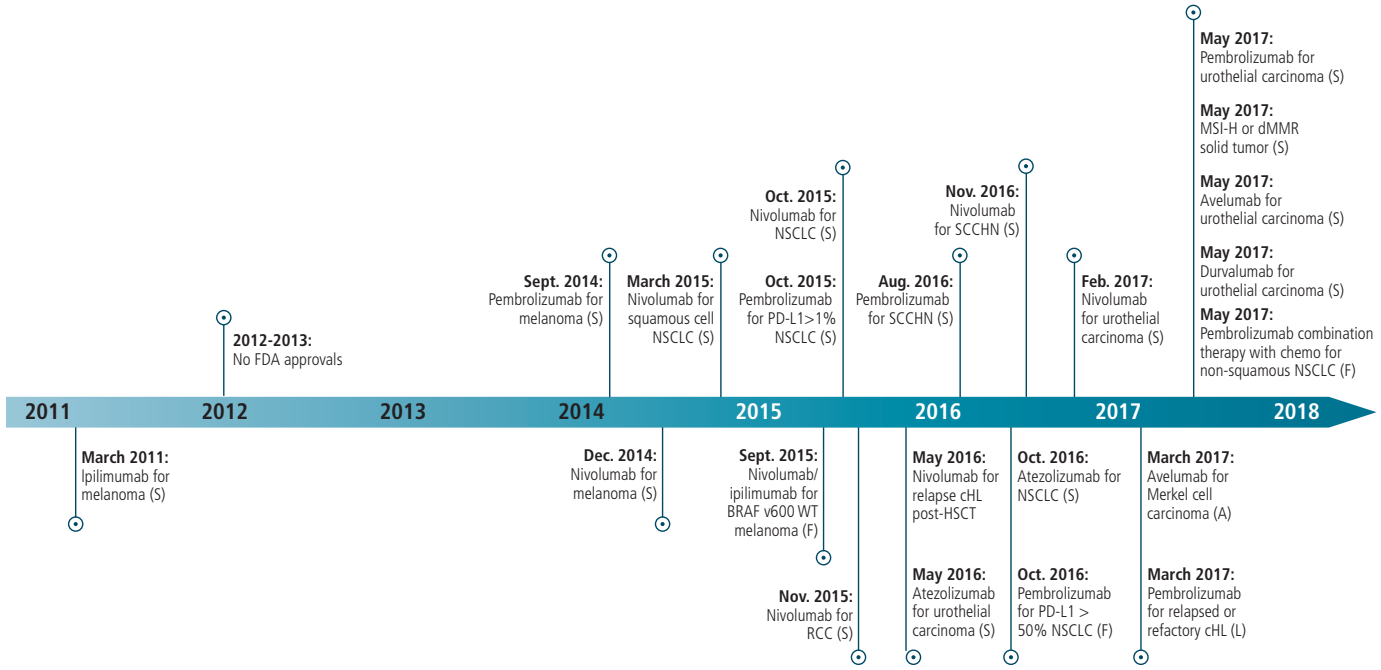
FIGURE 1, on the previous page, summarizes a timeline of significant milestones in the development of anti-cancer therapies.

Research from the early 2000s developed the first understanding of how cancer cells may evade the immune system and how specific therapy could be used to overcome this (2011 FDA approves ipiluminab). These discoveries focused on how cancer can turn off the ability of T-cells to fight cancer cells and showed that (1) cancer cells are genetically unstable and as they grow, randomly produce variants with properties that can enable the cells to hide from the immune system and (2) can prevent the expression of TAAs or secrete immunosuppressive molecules. The major step forward was to develop immune checkpoint inhibitor therapies that can turn T-cells back on, allowing T-cells to recognise cancer cells and destroy them. Current research and clinical trials are intensively focusing on how to use immunotherapy to prevent recurrence of cancer in patients that are in remission.

As can be seen in the graphic FIGURE 2 below, the US Food and Drug Administration (FDA) approved the first immunotherapy drug in 2011 to treat patients with metastatic melanoma. Since then, other immunotherapy drugs have been granted approval to treat other cancer sites such as bowel cancer, Hodgkin's lymphoma, kidney and bladder cancer. It is expected that many others will be fast-tracked in the coming years.

At present in the UK, the National Institute for Health and Care Excellence (NICE) has approved immunotherapy for the treatment of metastatic melanomas. More recently, approval was granted for Pembrolizumab as first line treatment against non-small cell lung cancer where there has been distant spread and the cancer is positive for a specific inhibitor of the immune response called PD-L1.

FIGURE 2: PROLIFERATION OF FDA APPROVED IMMUNOTHERAPY DRUGS IN RECENT YEARS



What is cancer immunotherapy?

Chemotherapy uses cytotoxic drugs to treat cancer by interfering with cellular activity during specific phases of the cells' growth cycles. Chemotherapy drugs can be poorly tolerated as they also kill healthy cells, which causes unwanted side effects such as nausea, fatigue and hair loss.

However, the aim of immunotherapy in cancer treatment is to re-awaken the body's immune system, thus reactivating the ability of T-cells to attack the tumour. As immunotherapy does not use toxic drugs or radiation, it is much more tolerable and there are fewer side effects. The most common side effect from immunotherapy is increased autoimmunity against normal tissues (e.g. colitis, arthritis) which can be severe and life-threatening.

Generally, the main types of cancer immunotherapies are as follows:

MONOCLONAL ANTIBODIES

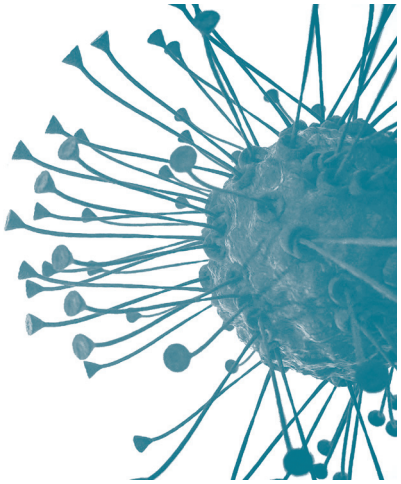
Some cancers, such as breast cancer and lymphomas, display certain molecules on their surface which can be altered by monoclonal antibodies (laboratory-generated immune proteins that target these highly expressed molecules). For example, Herceptin (trastuzumab), detects a molecule known as ERBB2 (also called HER2) on breast cancer cells. Herceptin interrupts the function of the ERBB2 molecule leading to cancer cell death. Although this is strictly not immune therapy it is a good example of how synthetic antibodies can be used as specific medicines. During claims assessment, you will often see histology/medical reports that confirm a patient's tumour expresses the HER2 molecule. These patients can then be selected for this type of therapy.

IMMUNE CHECKPOINT INHIBITORS

The immune system is designed to halt an immune response once it has been effective and prevent the immune system from damaging healthy tissue. Many cancers exploit these "stop signals" (so called immune checkpoints) and prematurely stop the immune response, thus allowing a tumour to develop and grow unchecked. Checkpoint inhibitors are currently the most promising type of immunotherapy; blocking immune checkpoints allows the immune system to attack the tumour. This type of immunotherapy has been approved by NICE for use in the treatment of metastatic melanoma and non-small cell lung cancer. Clinical trials are also under way in many other cancer types.

ADOPTIVE T CELL THERAPY

As well as targeting the tumour cells, immunotherapies also target the immune cells directly. An example of this is where a patient's T cells can be removed and those that will attack the tumour are expanded in the lab and then reintroduced into the patient (much like stem cell therapy). In addition, T cells can be genetically modified so that they find it easier to recognise the tumour. This approach includes Chimeric Antigen Receptor (CAR) T cells. CAR T cell therapies are yet to be approved by NICE but this approach has shown promise in clinical trials, particularly in leukaemia and there is considerable hope that this will be available to UK patients in the future.



CANCER VACCINES

Cancer vaccines can be used in 2 ways as cancer therapies. Prophylactic vaccines are used as a preventative measure. Girls between the ages of 12 and 18 are now offered the HPV (human papillomavirus) vaccine free from the NHS which greatly reduces the chance of having persistent HPV virus infection which is the main cause of most cervical cancers and many oral cancers.

Therapeutic vaccines work differently to prophylactic vaccines. They are designed to treat an existing cancer by enhancing the immune response against particular TAAs.

Provenge is a type of vaccine used in the treatment of aggressive prostate cancers. With this treatment, doctors take immune cells from the patient and incubate them outside the body with a fusion protein, which is made by joining the genes for two different proteins together. One of these is called Prostatic Acid Phosphatase (PAP), which is found on prostate cells, and at particularly high levels on prostatic cancer cells. The other is a protein called Granulocyte-macrophage colony-stimulating factor (GM-CSF).

When mixed with the patient's extracted immune cells GM-CSF stimulates them to respond to PAP and these hyper-responsive immune cells are then injected back into the patient, where they are primed to start attacking PAP-expressing cancer cells, including prostate cancer cells.

Unfortunately, Provenge is an extremely expensive form of treatment and so whilst it has been licensed in the UK, NICE have not approved it for routine use on the NHS as the cost/benefit does not outweigh other treatment options.

ONCOLYTIC VIRUS THERAPY

Some viruses are being used to boost immune activity in cancer. These oncolytic (cancer-bursting) viruses act in two ways; they kill some cancer cells directly and activate the immune system to destroy non-infected cells (bystander effects). A herpes virus called T-VEC has recently been approved for use in melanoma and many other viruses are being tried in laboratory and clinical studies.

Checkpoint inhibitors

As mentioned previously, checkpoint inhibitors are currently the most promising type of immunotherapy.

A key property of the immune system is its ability to tell the difference between normal cells in the body and those it sees as "foreign." This lets the immune system attack only the foreign cells without interaction with normal cells. To do this, it uses "checkpoints" – molecules on certain immune cells that need to be activated (or inactivated) to start an immune response.

Cancer cells sometimes find ways to use these checkpoints to avoid being attacked by the immune system. However, drugs that target these checkpoints are starting to prove very effective by reactivating immune responses against cancer cells.

IMMUNOTHERAPIES THAT TARGET PD-1 OR PD-L1

PD-1 is a checkpoint protein on immune T cells. It normally acts as a type of "off switch" that helps keep the T cells from attacking other healthy cells in the body. It does this when it attaches to PD-L1, a protein found on some normal, and cancerous cells. When PD-1 binds to PD-L1, it essentially tells the T cell to leave the other healthy cells alone. Some cancer cells have large amounts of PD-L1, which in turn helps them avoid an immune response FIGURE 3 on the following page.

Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune response against the cancerous cells.

PD-1 inhibitors have been shown to be helpful in treating several types of cancer, including melanoma, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin's lymphoma. Research continues to see if they are effective against other types of cancer.

PD-L1 inhibitors have also been shown to be helpful in treating different types of cancer, including bladder cancer, Non-small cell lung cancer, and Merkel cell skin carcinomas. Whilst these drugs do not have the same toxic side effects associated with chemotherapy, a concern with these drugs is that they switch off normal controls on the immune system. This can lead to autoimmunity and immune damage on normal organs in the body and serious side effects in some people. Common side effects of these drugs can include fatigue, cough, nausea, loss of appetite, skin rash, and itching. Although far less common, they can cause more serious problems in the lungs (pneumonitis), intestines (enteritis and colitis), liver (hepatitis), kidneys (renal syndrome), hormone-making glands (e.g. hypothyroidism) or other organs.

IMMUNOTHERAPIES THAT TARGET CTLA-4

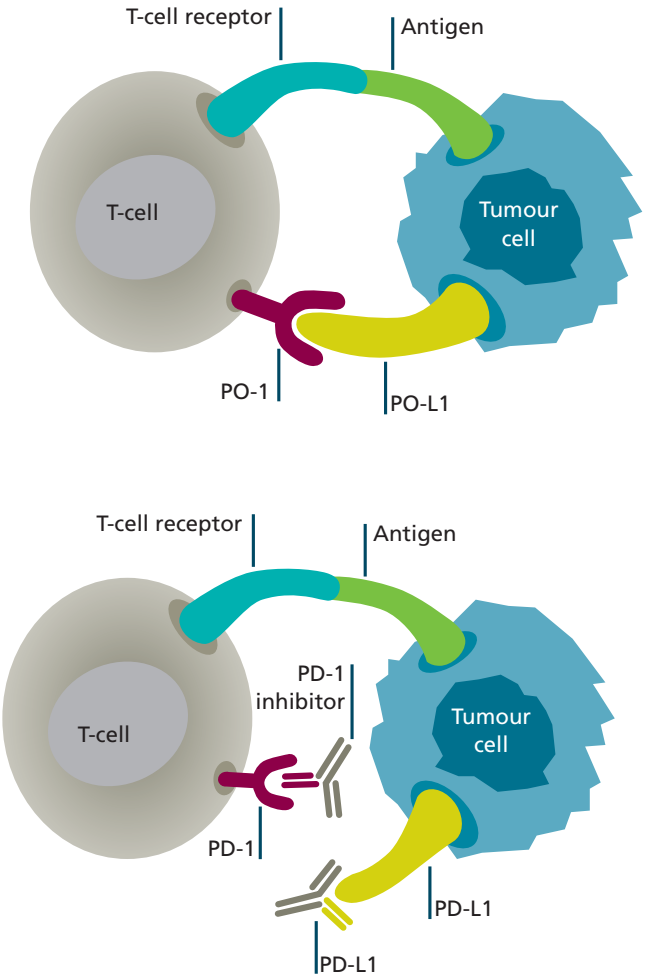
CTLA-4 is another protein on some T cells that acts as a type of "off switch" to keep the immune system from attacking healthy cells.

Ipilimumab is a monoclonal antibody that attaches to CTLA-4 and stops it from tripping the "off switch". Consequently, this boosts the body's immune response against cancer cells.

Because ipilimumab affects the immune system, serious side effects are more common with this drug compared to those that target either PD-1 or PD-L1.

> "Checkpoint inhibitors are currently the most promising type of immunotherapy"

FIGURE 3: CHECKPOINT INHIBITORS PROCESS



How do checkpoint inhibitors work?

Checkpoint inhibitors are administered intravenously, and their aim is to switch back on the body's immune system to fight cancer. When effective, T-cells can identify and attack a tumour.

Historically, doctors will judge the effectiveness of treatments for cancers that are visible on scans by looking at whether tumours have grown, shrunk, or remained the same in size, and whether any new lesions appeared after a period whilst undergoing cancer treatment.

Treatment will be considered successful if the tumour shrinks and the opposite will apply if the tumour grows or new areas of disease appear. The size of the cancer is most commonly used to indicate whether there is a response in the cancer when treating with standard chemotherapy or targeted therapies.

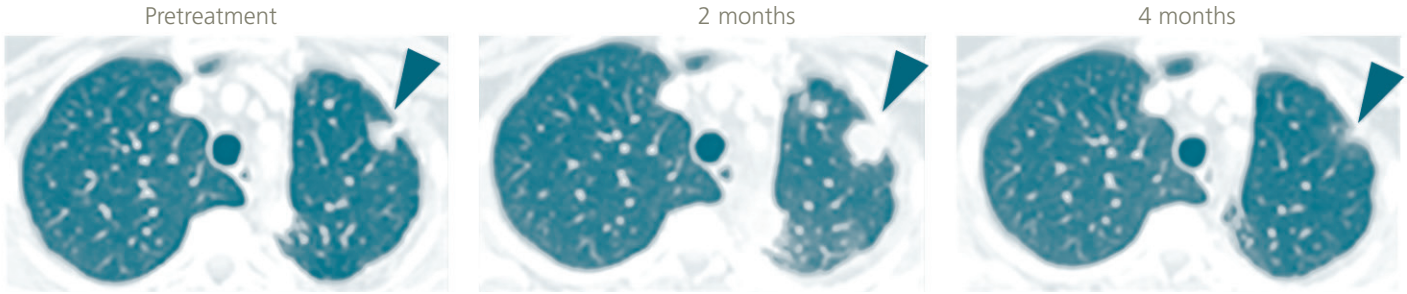
However, use of tumour size is more complex for assessing response to checkpoint inhibitors. When treatment commences, growing or even new lesions do not always signify progressing cancer.

Patients undergoing immunotherapy will be scanned at regular intervals (usually every 3 months) and in the early phases of treatment, despite tumours appearing larger on a scan, patients can report feeling well with improving symptoms. Early scans may indicate no obvious change in the size of a patient's tumour and some may appear to have grown following the first scan since treatment commenced. However, unlike chemotherapy, these changes may in fact be showing that the treatment is effective. This phenomenon is called pseudo-progression. As the name implies, it looks like progression of a cancer, but represents the effects of immune mediated damage and swelling in the cancer microenvironment. In fact, pseudoprogression often precedes strong and prolonged response to immunotherapy.

As the scans in FIGURE 4 demonstrate, the initial scan prior to treatment shows the tumour pre-treatment. The next interval scan appears to show that the tumour has grown. However, where immunotherapy is effective, it is quite possible that most of the areas of disease are shrinking, but there is one new or a growing lesion. What this suggests is an infiltration of the patients' T-cells that appear to be attacking the tumour, thus making it appear bigger at the next scan.

The additional lesion may be a collection of mostly immune cells that may have converged on an area that was a small collection of tumour cells so small it wasn't picked up on a previous scan, so it looks like a new lesion now FIGURE 5 on the following page. Due to the small size, these additional lesions may not be visible in subsequent scans.

FIGURE 4: TUMOUR TREATMENT PROGRESSION SCANS



Immunotherapy monitoring is therefore very different from standard treatment in that, if a tumour looks to have grown during chemotherapy, treatment will stop immediately as it is deemed not effective and medics will want to prevent further exposure to toxic drugs. It is therefore very important to understand the concept of pseudo-progression when handling claims. With immunotherapy, this suggests the treatment is potentially working and so treatment is likely to continue to allow an additional immune response.

The next interval scan could well show that the tumour has shrunk since the last scan which further suggests the treatment is proving to be effective.

It can be difficult to differentiate pseudo-progression from disease progression. Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudo-progression TABLE 1.

Unfortunately, doctors cannot just presume that growing lesions in most people are something other than progressing cancer. However, patients that are now undergoing immunotherapy, it makes sense to do a biopsy if the interval scans look worse than the clinical picture. As immunotherapy is far more tolerable than chemotherapy, it allows patients who seem to be doing well clinically to stay on treatment even in the face of a new or growing area of disease to maintain a long-term response.

FIGURE 5: T-CELL INFILTRATION

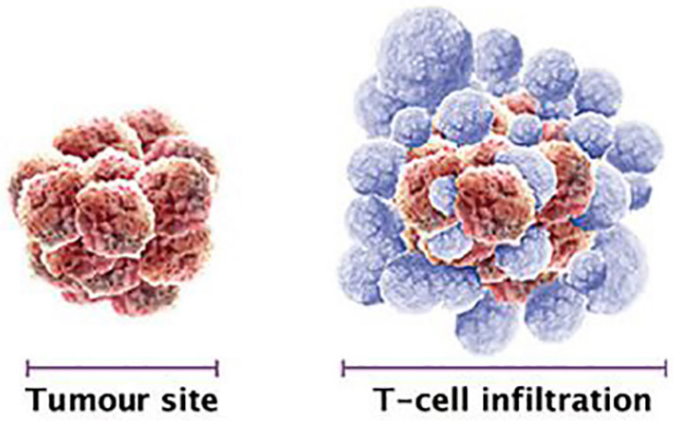


TABLE1: DISEASE AND PSEUDO-PROGRESSION MONITORING FACTORS

	DISEASE PROGRESSION	PSEUDO-PROGRESSION
PERFORMANCE STATUS	Deterioration of performance	Remains stable or improves
SYSTEMIC SYMPTOMS	Worsen	May or may not improve
SYMPTOMS OF TUMOUR ENLARGEMENT	Present	May or may not be present
TUMOUR BURDEN BASELINE	Increase	Initial increase followed by a response
NEW LESIONS	Appear and increase in size	
BIOPSY MAY REVEAL	Evidence of Tumour growth	Evidence of immune cell infiltration

Combination therapy

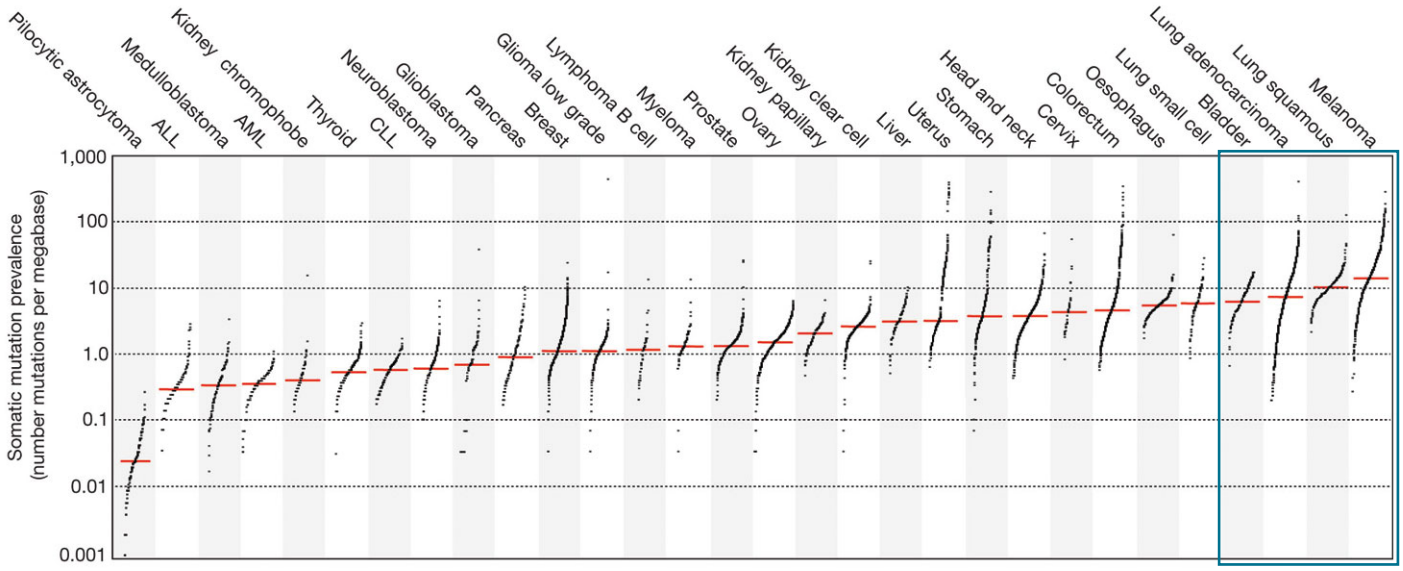
A major focus of new trials is to explore whether improved cure rates can be achieved with different combinations of immune checkpoint therapies with either different checkpoint inhibitors or with targeted therapies (e.g. PARP inhibitors). In melanoma, using both CTLA4 and PDL1 inhibition has improved response rates although the risk of autoimmune side effects is greatly increased.

WHY DO SOME CANCERS RESPOND TO IMMUNE THERAPY?

Some cancers are more responsive to immunotherapy than others. The perception is that cancers with a greater "mutational load" i.e. the number of genetic mutations in the DNA of the tumour, is associated with a greater tendency to respond to immunotherapy. The more mutations a cancer cell has, the more it appears different compared to normal tissue because of changes in cellular proteins caused by the mutations. These abnormal proteins are called neoantigens and make it easier for the immune system to recognise and target cancer cells.

The turquoise box in FIGURE 6 below shows tumours with a higher mutational load and thus are more amenable to immunotherapy.

FIGURE 6: TUMOUR MUTATIONAL LOAD AND SUITABLITY FOR IMMUNOTHERAPY



Alexandrovet al, Nature, 2103, 500: 415

Claims and Underwriting considerations

CLAIMS

In the UK at least, immunotherapy is still very much in its infancy in treating cancer. However, there is no doubt that we will see more immunotherapies approved by NICE in the years to come. Longer survival rates for patients with metastatic cancer has the potential for major impacts on us as insurers.

TERMINAL ILLNESS (TI) CLAIMS

Notoriously difficult to assess, terminal illness claims will usually pay out when a claimant's life expectancy is 12 months or less. However, many insurers will allow a degree of flexibility and consider claims where life expectancy will not exceed 18 months.

However, as treatments evolve and are proven to be more successful, the assessment of TI claims is becoming more and more complex. For cases where we see a claimant is undergoing immunotherapy or combination therapy, a more cautious approach should now be applied and CMO input is highly recommended. It would not be unreasonable to allow a period of postponement to see if there is a response to treatment, particularly if factors such as pseudo-progression are to be considered.

INCOME PROTECTION (IP) CLAIMS

Immunotherapy appears to be tolerated much better than traditional treatments such as chemotherapy and the hope is that patients will be able to maintain as normal a life as possible whilst they undergo treatment. Therefore, consideration will need to be given as to whether they will be capable of work.

The following points should be considered when reviewing an IP claimant who is undergoing immunotherapy.

- What is their occupation?
- How strenuous is their occupation?
- How well are they tolerating treatment?
- Are there any health and safety issues to consider?

Regular contact on the telephone with the claimant or maybe even a nurse visit would be ideal in understanding the considerations listed above. Naturally, some claimants will be determined to maintain a normal life and continue as normal, whilst others will be less so.

It will be important to manage the expectations of claimants during this time, but a degree of pragmatism may be warranted.

UNDERWRITING

UNDERWRITING

It is perhaps arguable that research development of new immunotherapy agents is at the cutting edge of cancer research. What is clear is that these new agents are improving the outcomes for cancer patients in clinical trials and daily practice. What is perhaps a little less certain at present is how these new agents will impact the insurance industry and to what degree overall mortality data will change over time and what pricing and protection underwriting adjustments will need to be made.

SCOR Global Life continuously monitors mortality data associated with cancer, and more recently undertook significant development when adding a Cancer Calculator to SCOR's underwriting manual (SOLEM) which looks to provide a more realistic/accurate evaluation of an individual's risk for selected types of cancer (Breast, Colon and Hodgkin's disease). In developing these calculators SCOR have designed a new underwriting model which moves away from using traditional relative survival for these cancers to a model of conditional survival. Predicted survival is then calculated on an individual basis based on survival at time of underwriting and adjusting the predicted survival going forward using multiple prognostic factors such as staging, grade of cancer, age, treatment and others.

Immunotherapy may become a factor to be incorporated in modelling to adjust underwriting to predicted risks and outcomes of cancer patients. Regrettable at present, is the fact that many of the new immunotherapies licenced under either FDA approval or more recently by NICE for use in the UK are for advanced cancers with wider metastasis where prognosis is guarded, and underwriting terms would ordinarily not be available in these settings. So, while these agents show significant potential in the improvement of prognosis and quality of life for these patients, the impact these agents may have on conditional and median survival is still developing as more trials and research are undertaken. At present, there is little impact for the pricing and underwriting guidelines for ratings of protection business for evolving immunotherapy agents. It is for this reason insurers will need to continuously monitor research and development in this field.

That said there are factors that underwriters should be aware of if they are assessing cases where a life assured is currently undergoing or have undergone immunotherapy. While standard antineoplastic therapy is associated with immunosuppression and infections, some of the recent approaches and new immunotherapy agents can induce overwhelming long-term inflammation and autoimmunity side effects.

This is particularly evident in the new rising stars in cancer treatment bispecific antibodies (BAB's), chimeric antigen receptor (CAR) T cells and checkpoint inhibitors which have been discussed earlier in this paper.

Cytokine-release syndrome (CRS) describes a complex of symptoms including fever, hypotension, and skin reactions as well as lab abnormalities. CRS may occur after the infusion of monoclonal or bispecific antibodies (MABs, BABs) targeting immune effectors and Tumour cells and is a major concern in recipients of chimeric antigen receptor (CAR) modified T lymphocytes as well. BAB and CAR T-cell treatment may also be compromised by central nervous system (CNS) toxicities such as encephalopathy, cerebellar alteration, disturbed consciousness, or seizures.

While CRS is known to be induced by exceedingly high levels of inflammatory cytokines, the pathophysiology of CNS events is still unclear. Treatment with antibodies against inhibiting immune checkpoints can lead to immune-related adverse events (IRAEs); colitis, diarrhea, and endocrine disorders are often the cause for ICU admissions. The severity of these side effects does though range from mild to fatal, so underwriters do need to be aware of the risks when assessing applicants who are currently undergoing or have undergone immunotherapy.

FIGURE 7 on the following page should assist underwriters in understanding the possible side effects these new cancer agents may produce.

FIGURE 7: DIFFERENT CLASSES OF NEW CANCER DRUGS, FREQUENTLY USED AGENTS, AND MAIN TOXICITIES

	AGENT	TARGET	INDICATIONS	TOXICITIES
MONOCLONAL ANTIBODIES				
	Rituximab Ofatumumab Obinutuzumab	CD20	B-cell lymphomas and leukaemia's	CRS Immunodeficiency
	Trastuzumab	HER2-neu	Breast cancer Gastric cancer	Cardiac disease
	Cetuximab	EGFR	Colorectal cancer Head&Neck cancer	Diarrhoea
	Bevacizumab	VEGF	Colorectal cancer Breast cancer Renal cell cancer NSCLC Ovarian cancer Glioblastoma	Hypertension GI bleeding or perforation Thromboembolism
	Ramucirumab	VEGFR	Gastric cancer Hepatocellular carcinoma	
BISPECIFIC ANTIBODIES (BAB)				
	Blinatumomab	CD3/CD19	ALL B-cell lymphomas	CRS Neurotoxicity (e.g., convulsions) Liver toxicity (transaminitis)
CHECKPOINT INHIBITORS				
	Ipilimumab	CTLA-4	Melanoma	IRAEs: Diarrhoea, colitis Hypophysitis Immuno-hepatitis Polyarthritis
	Nivolumab Pembrolizumab	PD-1	Melanoma NSCLC RCC Hodgkin's lymphoma	
CELLULAR TREATMENTS				
	CAR T cells	CD19	ALL B-cell lymphomas	CRS Neurotoxicity (e.g., convulsions, encephalopathy, or ischemia)

CRS cytokine-release syndrome, VEGF vascular endothelial growth factor receptor, VEGFR vascular endothelial growth factor receptor, HER human epidermal growth factor receptor, GI gastrointestinal, NSCLC non-small cell lung cancer, RCC renal cell cancer, LVEF left ventricular ejection fraction, CML chronic myeloid leukemia, ALL acute lymphoblastic leukemia, EGFR epidermal growth factor receptor, PI3K phosphoinositol-3 kinase, MEK MAP (mitogen-activated protein) kinase/ERK (extracellular signal-regulated kinase) kinase, PRES posterior reversible encephalopathy syndrome, GIST gastrointestinal stromal Tumours, CTLA-4 cytotoxic T-lymphocyte-associated protein 4, PD-1 programmed death receptor 1, IRAEs immune-related adverse events, CAR chimeric antigen receptor

Publisher
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