ICR The Institute of Cancer Research

Immunotherapy

Position Statement from

The Institute of Cancer Research, London

Summary

Immunotherapies are leading to spectacular responses in some cancer patients but their clinical development has outpaced our scientific understanding of how they work. We need new research programmes to identify biomarkers to pick out which patients will benefit most – which should lead to smaller, more targeted clinical trials, and potentially make immunotherapies more cost-effective for the NHS. We must also ensure that the design and regulation of clinical trials is appropriate to support the development of new immunotherapies. We need suitable clinical trial endpoints as size of tumour may not always be a good measure of whether immunotherapies are working. The Government and regulators should also incentivise drug companies to trial immunotherapies in combination with other treatments where they may be most effective. Regulators can view viral immunotherapies with excessive caution so earlier discussions between companies and regulators are needed to prevent delays in these exciting new treatments reaching patients.

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Immunotherapy

Background information

Immunotherapies harness a patient's own immune system to fight against cancer and are generating enormous excitement as new cancer treatments. They have the potential to overcome cancer's ability to evolve resistance to treatment by taking advantage of the immune system's own ability to respond dynamically, and to keep pace with cancer as it changes.

Several immunotherapies have shown spectacular responses in relatively small subsets of patients – even in people with advanced cancers that are normally lethal. These dramatic responses have led to great excitement within the scientific community and heavy investment by the pharmaceutical industry.

Various immunotherapies have already been licenced and made available on the NHS. T cell checkpoint inhibitors pembrolizumab and nivolumab block a natural signal that usually stops the immune system attacking the body's own cells – but which is hijacked by cancer cells to allow them to hide from the immune system. By blocking this signal, checkpoint inhibitors unmask the cancer, leaving the immune system free to target it.

The first viral immunotherapy, TVEC, has been approved for NHS patients. Viral immunotherapies use modified viruses – from measles to cough and cold viruses – to infect and kill cancer cells, and to spark the immune system into action against the rest of the tumour.

CAR T cell therapy is an exciting new type of treatment that involves removing a patient's immune cells, genetically engineering them in the lab, and then returning them to fight the patient's cancer.

However, immunotherapies are often extremely expensive – even by the standards of new cancer drugs – and there are concerns that this could be a barrier to their wider uptake.

While the field of immunotherapy is rapidly developing, much remains to be explored, especially in understanding the biology of how these therapies work. As a result, we don't yet know how widely effective immunotherapies will be.

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The proportion of people who benefit from immunotherapies can be quite small. We don't yet have good ways of telling who is most likely to respond to immunotherapies or to develop side effects, and how best to use them in combination with other treatments.

Side effects are a real issue with many types of cancer treatment and can limit how widely a treatment is used, or even whether it becomes available for patients at all. Immunotherapy is no different – its side effects can be severe, and even in some cases deadly. Researchers are investigating how to identify patients most likely to experience some of the more severe side effects and how to manage these.

Immunotherapies can behave differently than conventional therapies, so for example tumours may respond rather slowly to them. We haven't therefore fully worked out how to assess whether an immunotherapy is working. In addition, there is much to do to understand how best to combine immunotherapy with other conventional treatments, such as radiation, chemotherapy and surgery.

Working out how to make immunotherapies more effective, and to target their use towards patients who will benefit most, is essential if they are to become cost-effective treatments.

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Key ICR positions on immunotherapy

- We need much more biological research to understand how immunotherapies work, how to make them more effective and reduce side effects, and how to identify patients who will benefit most. The clinical development of immunotherapies has outpaced our understanding of the biology underlying them, and that means doctors are often in the dark when attempting to get them to work better or to adapt their use to new situations.

- We need to ensure that patient samples are collected in as many immunotherapy clinical trials as possible, to help us develop better tests to predict who will respond best and who will develop the most severe side effects. The pharmaceutical industry is missing opportunities to collect information that may prove useful in understanding the biology driving the successes or failures of immunotherapy. By improving sample collection, we can ensure that even negative trials yield information that contributes to our understanding of immunotherapies.

- We need to develop new and appropriate clinical trial endpoints, because immunotherapies should not necessarily be assessed by the same standards as traditional cancer treatments. Cancers that respond to immunotherapy can continue to grow at first before later shrinking, so size of tumour may not be always an appropriate measure. The gold standard should remain overall survival benefit, but this can only be demonstrated in large clinical trials which are slow and expensive to run. As we move towards smaller, adaptive clinical trials that yield valuable information quickly, drug regulators should consider novel, earlier endpoints that may predict longer-term clinical outcome or measure the effect on a patient's quality of life.

- We need to incentivise drug companies to trial immunotherapies in combination with other treatments – even those manufactured by other companies – whenever there is strong clinical data. Hundreds of clinical trials have looked at immunotherapies in combination but often only with drugs within a company's own pipeline or with limited scientific justification. Once an immunotherapy has been licensed on its own, there is currently

little commercial incentive for a company to invest in clinical trials to prove that it may work more effectively in combination with other treatments, leaving the burden of running these trials to academic institutions.

- We need drug regulators to have a better understanding of viral immunotherapies in particular, which are often viewed with excessive caution and concern over patient safety. It's important that regulators, academics and industry engage in early discussions to help clinical trials of new immunotherapies to be approved as quickly as possible, to avoid the delays we are often seeing at the moment.

- We need to find ways to make immunotherapies affordable for the NHS. As it stands, they are extremely expensive and this is a major barrier to widespread uptake. The Government should investigate new models of drug pricing – such as tying price to clinical outcomes – that allow a return on investment for businesses while providing a fair deal for healthcare providers. Better understanding of the biology behind immunotherapies should allow smaller, cheaper clinical trials targeted at those patients most likely to benefit – and these savings must be passed on by companies in the form of lower drug prices.

- We need to invest in cross-specialty training between radiotherapy and immunotherapy to take advantage of the potential synergies between these particular types of treatment. Staff are often trained only as radiotherapists or immunotherapists and so we are missing opportunities for faster progress. Collaborative networks should bring disciplines together to share best practice and highlight the challenges in current standards of care.