

Notes of Virtual Café held at 10am on 24th March 2021 via Zoom

Attendees: There were 25 attendees present

Chair: Pam Walls

Dr Mazhar Ajaz gave a presentation on immunotherapy development which is summarised below:

1. The Origin of Melanoma

Melanocytes are the cells that contain pigment giving our skin its colour. Melanocytes live in a stable relationship with skin cells unless transformed into cancer cells by a variety of types of DNA damage, including mutations.

2. The body's immune system

The body fights off infection through its lymphocytes (white blood cells) characterised as either T-cells or B-cells. Additionally, the body's innate mechanisms such as bloodborne phagocytes and physical barriers (skin, mucous membranes, saliva, stomach acid etc.) also play a part in fighting infection.

3. The Immune System and Cancer

Skin cancers spread when they become tolerant to our immune system. Specific types of lymphocytes chase them down and kill melanoma cells before they can do any harm. Some melanomas spread and then disappear; the primary tumour having been dealt with by the immune system. Immune attrition keeps moles in check. T-cells and antibodies to tumour proteins can destroy the tumour. If cancers grow and persist it is because the cancer is able to fight off our immune responses.

4. Immune checkpoint blockade

Melanoma has a deep relationship with the immune system from an early stage. The key to providing effective drugs is to ensure they are able to reverse immune tolerance by suppressing the binding sites with the cancer cell, and so effectively releasing an attack on those cells. Dr Ajaz discussed the science behind how T-cells and macrophage cells interact with tumour cells to stop them spreading.

5. Trial results

The trial results and science of how they worked were provided for the commonly used drugs: Ipilimumab, Pembrolizumab and Nivolumab. These drugs aid the T-cells in eliminating the cancer cells by immune checkpoint blockade (as above). Ipilimumab (blocks CTLA-4) and Nivolumab (blocks PDL-1) arrived in 2010 and Pembrolizumab (blocks PD-1) arrived in 2015 after being left on the shelf of a particular drug company for 20 years before it emerged! Success rates with these drugs are good and after a course of treatment:

Ipilimumab :	54% effective - 20% unlikely to survive after 3 years
Nivolumab:	Much better efficacy than Ipilimumab
Pembrolizumab:	3-5% after 5 years following complete remission unlikely to survive
A combination of Ipilimumab + Nivolumab 61% effective- bad side effects	

Standard Adjuvant treatment (after surgery) is Ipilimumab for a period of 1 year.

All new single drug trials have failed and T-Cell options have been exhausted.

The future is reviewing combinations of treatments personalised for the patient. The issue is that there are seven effective drugs on the market and trialling combinations of seven drugs is difficult as there are 5040 different combinations to consider.

The Pareto rule applies; The big win has happened and there is not one single treatment for the remaining 35%.

The good news: From what we know today, after complete remission 85% of patients will survive longer than 5 years

6. Resistance to immunotherapy and the future

Immunotherapy can fail because the T-cells become exhausted and effectively inactive; the tumour cells can adapt to hide their visibility to T cells and also find new ways of turning the T-cells off; The tumours foster an anti-inflammatory microenvironment; Some immune systems are too well behaved to attack the body; and there are immune privileged sites (e.g. the brain). Future developments will focus on: exhausted T-cells; inflaming the tumour environment; different checkpoint interventions; putting extra mutations into the cancer so there are more abnormal proteins for the immune system to recognise thus activating the T cell response; drug combinations; the microbiome (bacteria in poo).

Note: Trials have shown that taking pro-biotics are counter productive and they should be stopped. The focus should be on taking pre-biotics (30 different vegetables and nuts).

Other Points raised during the presentation and question and answer session

- Covid 19 is tested for by analysis of the B-Cells, T-cells cannot be tested for Covid 19.
- Sarah Reid recommended the following reading: "How to Live" book by Professor Robert Thomas
- The effective history of Immunotherapy is quite short.
- No more new versions of Ipilimumab, Nivolumab & Pembrolizumab will be forthcoming.
- Adjuvant treatment for one year after surgery.
- NICE has agreed that Nivolumab (adjuvant) will go back to being routinely funded, after listening to comments from Melanoma Focus, 55 oncologists and Melanoma UK.
- Delia to provide info on how to get the Tim Spector Interview on Radio 4

An interesting question and answer session followed Dr Ajaz's talk.

Our thanks go to Dr Ajaz for taking the time and trouble to present to us. I feel sure we all learned something from the event and we look forward to his next talk.

After Dr Ajaz left a general discussion took place between the group and the session closed at 11:40 hrs

SNH – 25/3/2021