The breakthrough of personalized mRNA cancer vaccines to treat Pancreatic Ductal Adenocarcinoma

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Problem

How can personalized mRNA neoantigen vaccines treat patients with Pancreatic Ductal Adenocarcinoma (PDAC) by triggering an immune response?

- What is the function and parts of the pancreas, and where does Pancreatic Ductal Adenocarcinoma occur?
- Why are traditional forms of immunotherapy such as immune checkpoint inhibitors ineffective against Pancreatic Ductal Adenocarcinoma?
- How do neoantigens stimulate the immune system of patients with Pancreatic Ductal Adenocarcinoma?

Method

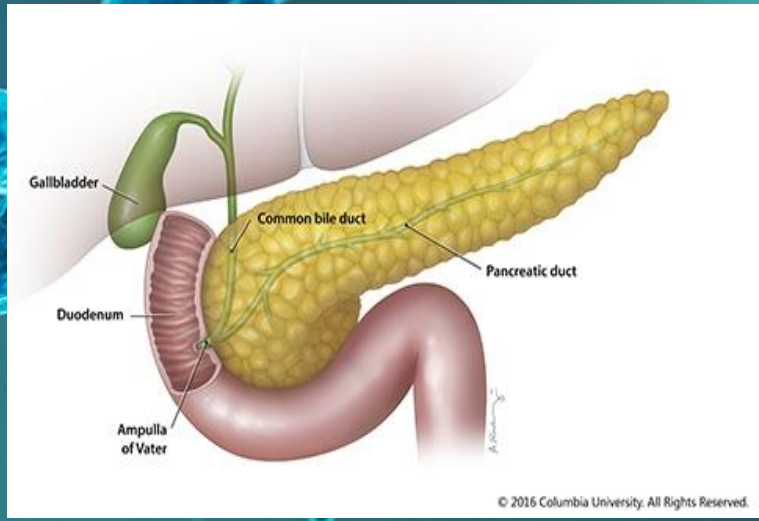
- Firstly, I will be using various online resources including videos, websites, and news articles to research and present about Pancreatic Ductal Adenocarcinoma.
- The next part of my research will be about the inefficacy of traditional forms of immunotherapy, specifically immune checkpoint inhibitors, on PDAC. I will then research how mRNA cancer vaccines work to treat PDAC.
- To support my research, I will be referring to specific data collected from a phase 1 clinical trial conducted to test mRNA vaccines against Pancreatic Ductal Adenocarcinoma.

Research - Information about the Pancreas

- The pancreas is a gland located in the abdomen which plays a key role in converting the food that we eat into fuel.

- The pancreas is located between the stomach and the spleen in the upper left abdomen, and is surrounded by other organs and blood vessels.

- It has two main functions:
  - Exocrine function.
  - Endocrine function.



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Research - The development of Pancreatic tumors

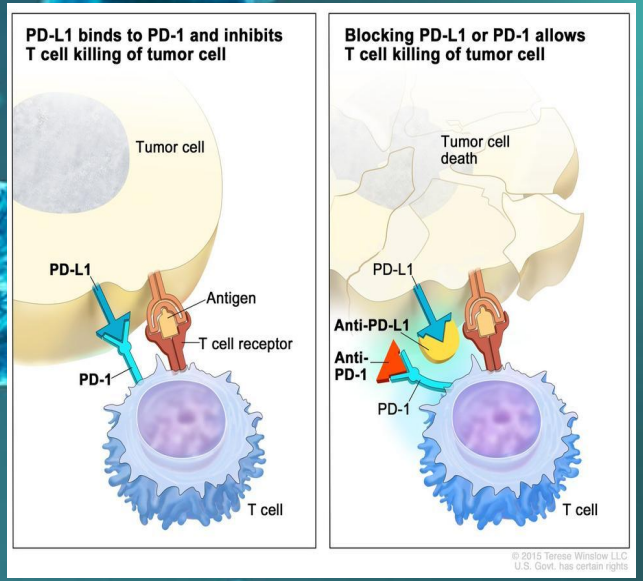
- Cancer cells outcompete the growth of healthy cells as they have mutations in their DNA which allow them to grow faster and more rapidly.

- Pancreatic tumors are malignant as they can metastasize rapidly to other parts of the body.

- 95% of pancreatic tumors occur in the exocrine glands, and the most common type is Pancreatic Ductal Adenocarcinoma (PDAC).
    - PDAC is caused when cancerous cells line the Pancreatic duct. This growth of cancerous cells compresses the common bile duct, and blocks the flow of bile out of the liver. PDAC can metastasize early to other parts of the body, such as the liver and the lungs.

Research - How do immune checkpoint inhibitors work?

- Before the breakthrough of mRNA vaccines for Pancreatic Ductal Adenocarcinoma, several clinical trials were conducted to test the efficacy of a type of immunotherapy known as immune checkpoint inhibitors on PDAC tumors.
- Immune checkpoint inhibitors:
  - Immune checkpoint inhibitors are types of drugs which “inhibit” or stop the cancer receptors from increasing the presence of checkpoint proteins on T-cells. Therefore, these checkpoint inhibitors allow for the immune system to be turned back on, and fight the immunosuppressive nature of tumors.



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Research - Inefficacy of checkpoint inhibitors on PDAC

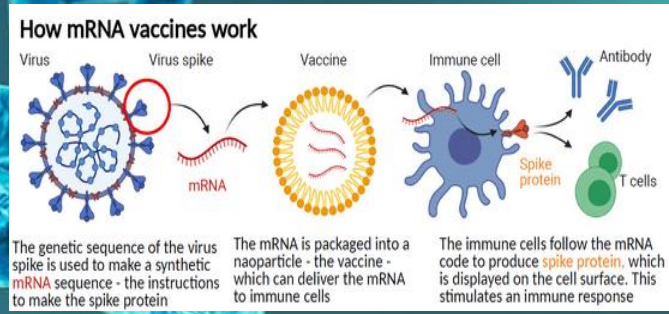
- PDAC tumors have a low mutation rate: In order for checkpoint inhibitors to be effective, they need to be able to bind to a specific mutation. Lower mutations result in a reduced sensitivity of PDAC tumors towards checkpoint inhibitors.

- To overcome this problems, mRNA neoantigen vaccines increase the presence of specific types of antigens known as tumor specific antigens, so that T-cells can effectively recognize the tumor cells as foreign and attack them.

Research - How do mRNA vaccines work?

- The reason that the immune system is ineffective against cancers is because all cancer cells are the mutations of the body's own cells. This way, the immune system has trouble recognizing them as foreign and cannot successfully suppress the growth of cancer cells.

- mRNA cancer vaccines use a special type of antigens on the surface of tumor cells, known as neoantigens. mRNA cancer vaccines identify and locate the neoantigens on the tumor cells, and then increase the expression of these neoantigens on the surface of the body's immune cells. This way, the immune system can recognize the cancer cells as foreign and can build antibodies against them.



Research - mRNA neoantigen vaccines in PDAC patients

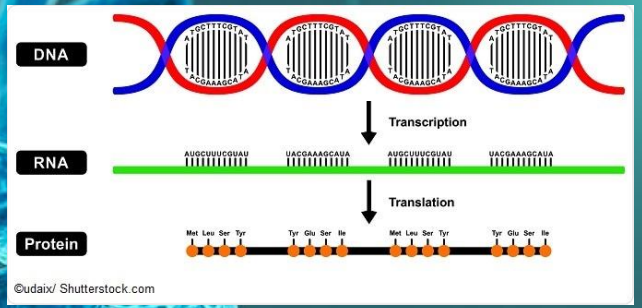
- In 2023, a pharmaceutical company named BioNtech conducted a Phase 1 clinical trial testing mRNA neoantigen vaccines on patients with PDAC.

- First, the 16 patients enrolled in the study had their PDAC tumors resected surgically using the a surgical process known as the whipple procedure.

- These tumors were then shipped within 72 hours to a manufacturing facility, where a process known as exome sequencing was conducted on them.
  - Exome sequencing is a method used to scan the exome part of the genome (protein-coding region) to look for mutations in nucleic bases (adenine, thymine, guanine, and cytosine).

Research - mRNA neoantigen vaccines in PDAC patients

- The surgically resected PDAC tumors then underwent a step known as RNA sequencing (RNA seq), in which the transcriptome (entire content of the RNA) was analyzed to determine which genes were turned on or off, and which regions of the RNA coded for mutated proteins.
- RNA sequencing was used to determine which parts of the mRNA coded for neoantigens on PDAC tumors, and computational identification of these tumors allowed for the personalized mRNA vaccines to be manufactured incorporating the neoantigens specific for each patient enrolled in the trial.
- These neoantigens were then packaged within the identified mRNA sequence, which formed the vaccine.



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Research - mRNA neoantigen vaccines in PDAC patients

- During the manufacturing process of the mRNA vaccines, the PDAC patients were given a targeted therapy drug known as atezolizumab. Atezolizumab is a type of drug which blocks a protein on tumor cells known as PDL-1 from binding with a protein on T-cells known as PD-1.

- Atezolizumab prevents the PDAC tumors from suppressing the immune system.

Research - mRNA neoantigen vaccines in PDAC patients

- 9 weeks after the surgery, the patients enrolled in the trial were given 8 consecutive priming doses of personalized vaccines, each containing 20 neoantigens per patient.

- Following this, the patients received a form of aggressive chemotherapy known as FOLFIRINOX. Using chemotherapy before mRNA vaccines is an effective way to debulk primary PDAC tumors and reduce the number of cancer cells that the immune system has to fight against.

Data - Inefficacy of immune checkpoint inhibitors

Table 1. Single-agent trials of checkpoint inhibition in PDAC to date.

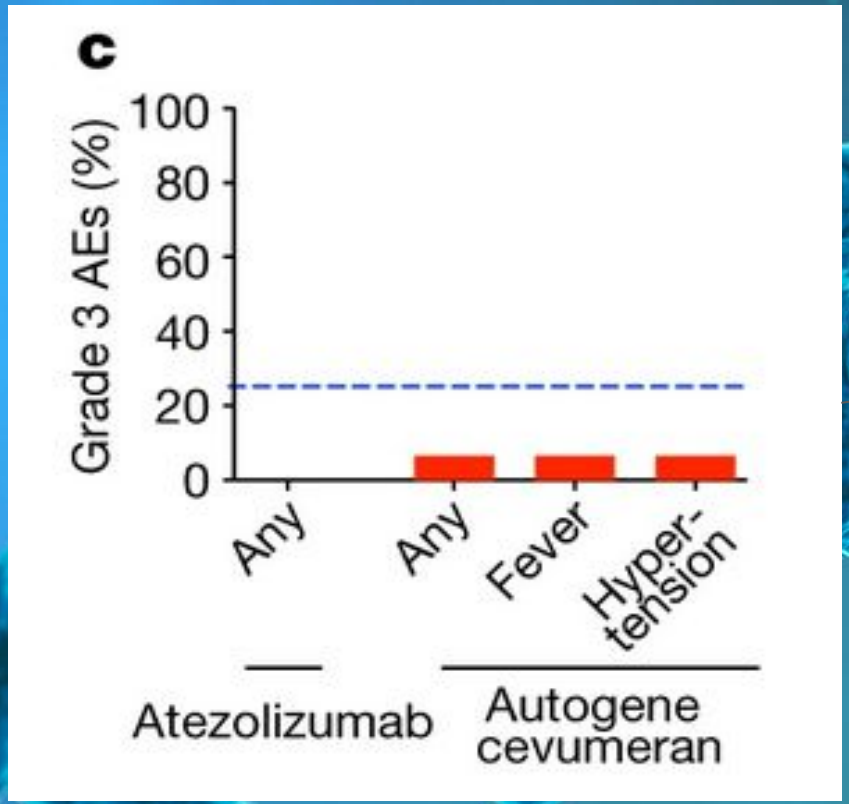
Reference	Phase	Design	*N*	Results	Toxicity
Royal and colleagues[8]	II Locally advanced/ metastatic PDAC	CTLA-4 inhibitor ipilimumab	27	One patient had a delayed objective response	11% patients experienced grade ⩾3 immune-related adverse events
Brahmer and colleagues[9]	I Multiple tumours, advanced PDAC	Anti-PD-L1 (BMS-936559)	14	0 PDAC patients had an objective response	9% patients across all tumour types had grade ⩾3 immune-related adverse events

PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death ligand 1.

Image Source

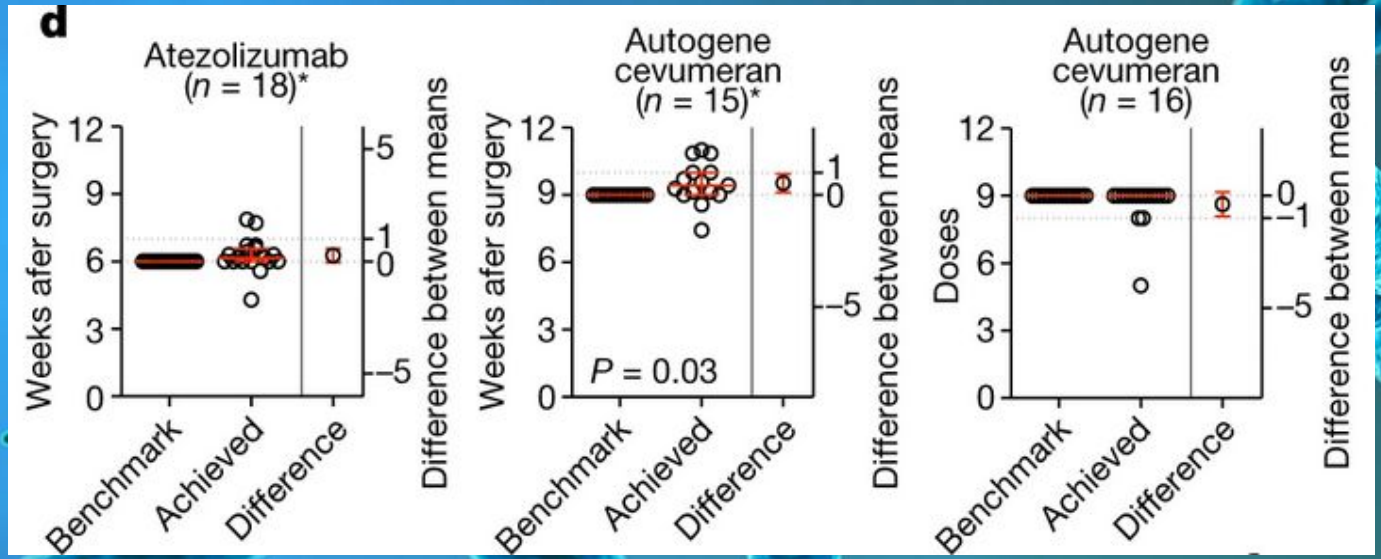
This table shows two studies conducted using different immune checkpoint inhibitors to treat PDAC. As we can see from the results, both of these checkpoint inhibitors failed to trigger a response in the immune system of the patients.

Data - Safety of mRNA neoantigen vaccines against PDAC



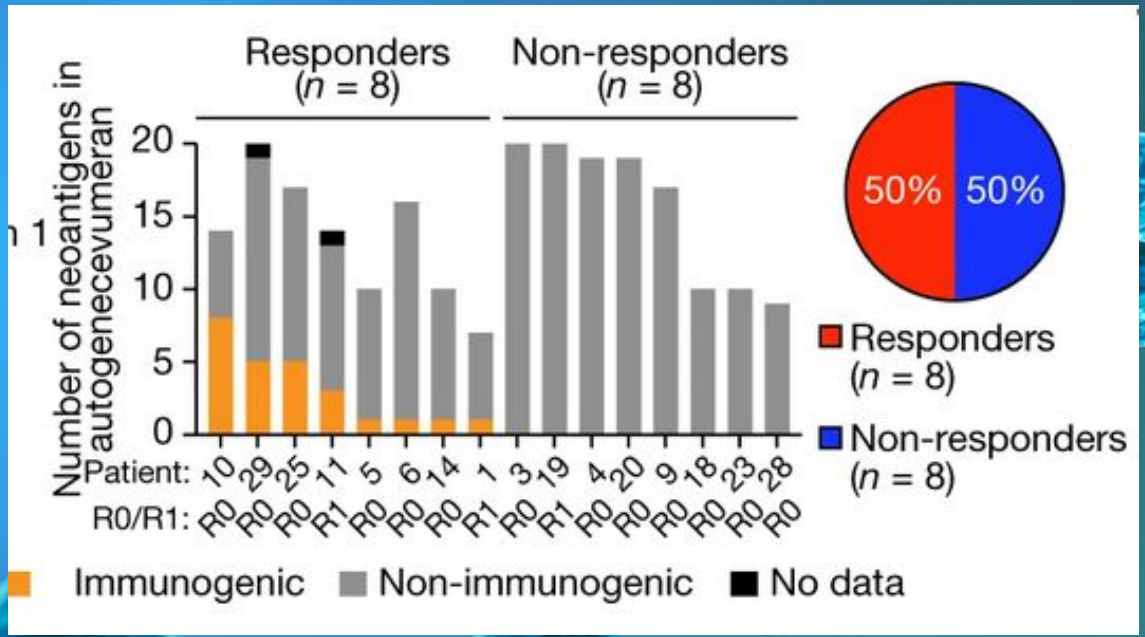
From this graph, we can see that the percentage of Grade 3 Adverse Effects in patients who received Autogene Cevumeran (mRNA vaccine) is very small. This is well within the study threshold of 25% indicated by the dotted blue line.

Data - Feasibility of mRNA neoantigen vaccines against PDAC



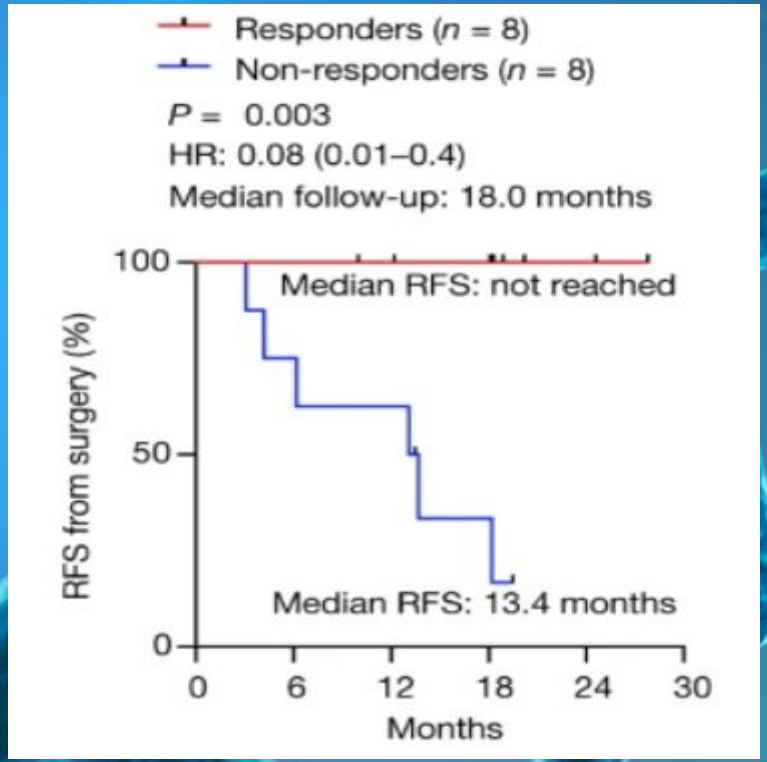
From the graph below, we can see that the benchmarked times for the administration of atezolizumab as well as Autogene Cevumeran were met. The administration of these were within 3 days of the benchmarked time.

Data - Immunogenicity of mRNA neoantigen vaccines against PDAC



From the circle graph (right), we can see that out of the 16 patients enrolled in the study, 50% of them, had an immune response to the mRNA vaccines. The graph to the left shows that responders had several neoantigens which were immunogenic (shown in yellow), whereas the non-responders did not react to any of the neoantigens.

Data - Recurrence free survival rates of patients who received mRNA vaccines



As seen from the graph, vaccine non-responders (represented by the blue line) had a recurrence free survival (RFS) of 13.4 months after the surgical resection of their tumors. However, the 8 responders (represented by the red line) continue to have an RFS of 100% even after the follow-up period of 18 months.

Conclusion

- Until recently, traditional forms of immunotherapy such as immune checkpoint inhibitors have been ineffective against Pancreatic Ductal Adenocarcinoma.

- The novel approach of mRNA neoantigen vaccines, however, is more effective as it uses a special type of tumor specific antigen known as a neoantigen to stimulate an immune response.

- From the research and data presented, it can be seen that mRNA neoantigen vaccines are safe and feasible, and can trigger an immune response in patients with PDAC by strengthening their immune system against tumors. It has also resulted in an increased recurrence free survival for PDAC patients.

Conclusion - Future Steps

- Phase 2 of the BioNtech clinical trial has recently opened, and will involve 260 patients from 80 sites around the world. This will test the benefits that mRNA cancer vaccines can offer for PDAC patients in comparison with the current therapy of surgery and chemotherapy.

- A recent clinical trial in the U.K. has been launched which uses a type of mRNA vaccines known as therapeutic mRNA vaccines to treat lung and skin cancers. With the development of mRNA cancer vaccines, these can be a reliable method to cure lethal cancers.

Acknowledgements

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