EDISON

Oncology ABCs (part 2)

Vaccines: Niche no longer

Edison themes

3 October 2022

Despite fits and starts, scientists remain fully invested in discovering curative vaccines. The complexity of the topic warrants a closer look, especially after recent events. The most notable and recent catalysts are anticipated to continue to fuel advancements and include heightened immunotherapy awareness (with the global COVID-19 pandemic), momentum in combination therapies (extending survival) and drive for personalized medicine. These recent trends and wider acceptance of complex vaccines are anticipated to reinvigorate deal activity that targets companies with the most robust and innovative technologies and possibly change perceptions.

Evolution from tried-and-true to curative

For quite some time, commercialized vaccines have proven to be reliable in preventing infectious disease. Supported by an early thesis from more than 300 years ago and the eradication of smallpox less than 50 years ago, vaccines have played an important role in preventative care. Although considered a basic scientific foundation, vaccines train the immune system to detect, attack pathogens, and forge immunological memories. Perhaps the effectiveness of traditional vaccines on less variable pathogens has staved off the urgency to materially diverge the development of alternative applications for more complex therapies. Nonetheless, we believe recent catalysts provide an impetus to change this dated perception and optimism for the discovery of therapies with improved efficacy and survival.

Numerous advanced concepts have evolved over the past decades. Most of these technologies (vaccine platforms) have not advanced outside of the clinic or materially circulated outside a small community of highly specialized scientists. The vaccines used during the COVID-19 pandemic are just a taste of a relatively more advanced technology (mRNA and DNA), which we view as a half step in the potential evolution of vaccines.

Combination therapies are the key (in oncology)

This heightened awareness of novel technologies, coupled with the notable emergency order government funding and political support, has drawn significant global interest and has started to change perceptions of vaccines. Cancer vaccines now represent an important part of many biotech pipelines. Although there is much variability in approaches, several companies are forging their own paths.

There had not been much success with proposed monotherapies so far. Significant investments (and strides) have been made in checkpoint inhibitors, but recent thinking has evolved and suggests it is not a long-term, standalone solution. Recent advancements in vaccines and the wider acceptance of combination therapies are anticipated to reinvigorate partnering and deal activity, targeting companies with the most robust and innovative technologies. We view this as pivotal for oncology vaccines, either independently (through partnerships) or as acquisition targets, where buyers contemplate the buy-versus-build decision in a segment with a significantly long investment tail.

Series recap

We expect the most robust science will remain the underpinning of biotech success and drive long-term growth. Despite the tightening financial market, oncology development will continue to blaze new trails in driving advancements, and oncology therapies are anticipated to remain front and center of healthcare. Read our first note in this series here.

Edison themes

As one of the largest issuer-sponsored research firms, we are known for our bottom-up work on individual stocks. However, our thinking does not stop at the company level. Through our regular dialogue with management teams and investors, we consider the broad themes related to the companies we follow. Edison themes aims to identify the big issues likely to shape company strategy and portfolios in the years ahead.

Companies mentioned in this report (Edison clients in bold)

Astrazeneca
BioNTech (BNTX: NASDAQ)
Bristol Myers Squibb (BMY: NYSE)
Mendus (IMMU: STO)
Merck & Co (MRK: NYSE)
Moderna (MRNA: NASDAQ)
OSE Immunotherapeutics (OSE: PA)
Pfizer (PFE: NYSE)
Roche Holding (RO: SIX)
Ultimovacs (ULTI: NO)

Analysts

Soo Romanoff	+44 (020) 3077 5700
Adam McCarter, PhD	+44 (020) 3077 5700
Harry Shrives, PhD	+44 (020) 3077 5700

healthcare@edisongroup.com

Evolution to curative vaccines

Therapeutic vaccines represent a new class of immunotherapy medicine with the opportunity to be personalized, in which the vaccine can be designed to treat a specified patient's unique tumor blueprint. The aim of curative vaccines is, by stimulating an immune response, to target a disease already present in the body (eg cancer) and forge long-lasting immunological memory against cancer cells, rather than just protect against future disease (preventative). In oncology, this approach introduces layers of variability and complexity when compared to traditional preventative vaccines addressing more static targets, as it involves targeting the body's own cells, which the immune system is naturally hardwired to avoid.

Even identifying tumor-specific antigens (proteins on the surface of tumor cells) for vaccines to target, isolating suitable neoantigens (tumor-specific proteins generated by mutations in tumor cells) and selecting vehicle of delivery is a critical decision tree, which is the basis of much dedicated research. Through various mechanisms, cancer vaccines cause the immune system to recognize antigens or neoantigens present on cancer cells (not on healthy cells). Once recognized, this triggers a targeted immune response where T cells can bind to the antigens presented on the surface of cancer cells and destroy them.

However, it is essential for a cancer to possess mechanisms by which it can avoid the immune system and multiply further. Hence, therapeutic cancer vaccine monotherapies have historically been met with limited success in the clinic, as the vaccine may cause an immune response, but (the immune system) cannot access the necessary tumor. This is highlighted by the development of many successful immune checkpoint inhibitors (ICIs) in recent decades. Cancer vaccine platforms can largely be categorized into four categories: cell-based vaccines (tumor-l or dendritic-cell derived), virus-based vaccines, peptide-based vaccines and nucleic acid-based vaccines, Exhibit 1 and Appendix A.

Exhibit 1: Classes of therapeutic cancer vaccines

Cancer vaccine type	How they work	Pros	Cons
Cell-based vaccines (tumor cells)	Vaccines that use inactivated versions of tumor cells to be injected into patients; may derive from patients (autologous) or non-patients (allogeneic)	■ Many different tumor antigens recognized ■ Allows development of vaccine without knowing specific antigen	■ May be expensive and difficult to produce ■ Production can be time consuming ■ Potentially weak antigen presentation due to downregulation of MHC class I molecules
Cell-based vaccines (DCs)	Vaccines that use patient-derived (autologous) or non-patient derived (allogeneic) DCs that are loaded with peptide antigens or antigen corresponding genes and administered to patient	■ High immunogenicity ■ Control over antigen presentation	■ May be expensive and difficult to produce ■ Production can be time consuming ■ White blood cell removal may cause problems in patients (vascular injury, electrolyte imbalance)
Virus-based vaccines	Vaccines that use viruses and viral vectors to target either tumor cells directly, triggering the breakdown of cancer cells (oncolysis) and secondary immune responses or DCs to deliver antigens and elicit an immune response	■ High immunogenicity ■ Easier to produce on large scale	■ Potentially high toxicity ■ Potential risk of undesired infections ■ May illicit an undesired immune response against the vector
Peptide/protein-based vaccines	Vaccines that are composed of known or predicted tumor antigens injected into patients, taken up and presented by APCs such as DCs	■ Lower toxicity ■ Easy to produce	■ Can elicit a less powerful immune response ■ Peptide vaccines are restricted to human leukocyte antigen (HLA) presenting subtypes ■ Protein vaccines can be expensive to produce
Nucleic acid-based vaccines	Vaccines that use DNA and RNA to produce peptides and proteins in APCs. These are then processed to produce cancer specific antigens that are displayed on the surface of the APC	■ Ease of delivery of multiple antigens ■ Not restricted to HLA patient type ■ Can induce both cellular and humoral immunity	■ RNA vaccines require specific transportation and storage conditions ■ DNA/RNA vaccines suffer from poor immunogenicity in humans ■ DNA vaccines require extra transcriptional step

Source: Journal of Experimental & Clinical Cancer Research. Note: DC, dendritic cell; MHC, major histocompatibility complex; APC, antigen presenting cell.

Right-sizing expectations

After an intensified period of research activity over the last decade, therapeutic vaccines have only seen limited clinical success as a monotherapy within the regulatory framework construct. The first therapeutic cancer vaccine approved for use by the FDA in 2010 was sipuleucel-T (Provenge), a DC-based vaccine for treating metastasized prostate cancer. However, the widespread clinical uptake of sipuleucel-T has been limited due to its cost and concerns associated with the overall patient benefits. The vaccine has been withdrawn and is no longer available in the European Union. A second therapeutic vaccine received FDA approval in 2015, Imlygic (T-VEC), an oncolytic viral-based vaccine for the treatment of advanced melanoma; however, it has only received approval in this one indication as a monotherapy. Recently, a combination study of T-VEC with pembrolizumab (Keytruda) failed to improve overall survival in unresectable melanoma; however, the combination is still under active investigation in other melanoma sub-patient groups and solid tumors. Historically, attempts to develop cancer vaccines as monotherapies have been met with disappointing results, meaning their full clinical utility is yet to materialize.

Lessons learned from past failures, however, mean cancer vaccine research is now starting to translate into positive clinical results and numerous therapies are progressing through development. The critical lessons that have helped to drive this progress lie in three key areas:

- the requirement of having multiple immunogenic antigens;
- the requirement of having highly effective and stable viral vectors and adjuvants; and
- an improved understanding of how to downregulate tumor-mediated immunosuppression.

Advancements in all three of these areas, we believe, will be critical for the long-term success and application of therapeutic cancer vaccines.

The evolving oncology competitive landscape

ICIs fall short (on their own)

A noticeable theme in therapeutic cancer vaccine development is that very few are being investigated as monotherapies. While vaccines alone may be able to elicit an immune response, it is often not strong enough to deliver a clinical benefit. This reinforces a previous point whereby scientific research has advanced and clinical investigators now have a greater understanding of how to overcome the lack of efficacy observed in earlier vaccines. With the emergence of ICIs, particularly programmed cell death 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors, cancer vaccine development has moved towards combination therapies. The first PD-1/PD-L1 ICIs (pembrolizumab, Keytruda, Merck and nivolumab, Opdivo, BMS) were approved in 2014 and have since revolutionized treatment regimens in certain cancers.

Most ICIs are monoclonal antibodies that block the receptors that tumors use to switch off T-cell responses (and therefore the whole immune system). This turns the tumor microenvironment from 'cold' (immunosuppressive) to 'hot' (vulnerable to the immune system). In this way, ICI treatments could be considered combination therapies, where the ICI represents one part of the combination and the patient's immune system the other. The success of ICIs, both pharmacologically and economically, has rapidly changed the oncology landscape. However, their use as a monotherapy has limitations characterized by low response rates in certain indications and the development of tumor resistance. Therefore, a clear synergy exists between ICIs and therapeutic cancer vaccines, with the former overcoming the tumor immunosuppression and the later upregulating the T-cell response to extend survival. This combinational approach opens a host of potential opportunities for cancer vaccines in the clinic, a number of which have been highlighted above.

Second look at oncology vaccines: Changed perceptions

While the pandemic has helped define companies such as Moderna and BioNTech as the giants of mRNA therapeutics, it is important to understand it is not the only technology that can be used in cancer vaccine development. In recent years, various vaccine technologies have caught the eyes of big pharma with multiple deals and strategic partnerships being struck, Exhibit 2. However, because of the complexity associated with oncology therapies and variables across indications, it is almost impossible to state confidently that one type of technology will be superior to another because each has its own advantages and disadvantages. It may be important to administer a vaccine quickly in the case of some advanced cancers, so those vaccines that require extended production times may not be suitable. The route of administration and frequency of vaccination may also affect the choice of vaccine selected for treating a patient. As such, we believe each cancer vaccine may bring its own unique offering to the market, providing opportunities across more than just one type of platform. However, as is the case in drug development, the key to success will lie in developing therapies with robust data combined with a clear and focused clinical strategy.

There have been several interesting collaborations and deals to date. A few are summarized below.

Exhibit 2: Big pharma collaborations and deals

Company	Deal partner	Vaccine	Indication/phase	Phase	Deal value	Technology	Checkpoint inhibitor combination	Clinical trial reference
Roche/ Genentech	Nykode Therapeutics	VB10.NEO	Locally advanced or metastatic Phase I/II	Phase II	Up to $715m	DNA vaccine	No	NCT03548467
Sanofi	BioNTech	Multiple programs	Multiple Indications	Phase I Phase II	Up to $360m	mRNA vaccine	Yes	NCT03871348 NCT04526899
Regeneron	Nykode Therapeutics	Undisclosed	Undisclosed	Preclinical	Up to $925m	DNA vaccine	Undisclosed	Preclinical
Odeon Therapeutics	OBI Pharma	OBI-833	Esophageal cancer	Phase I	Up to $200m	Peptide/protein vaccine	No	NCT05376423
Boehringer Ingelheim	Enara Bio	N/A	N/A	N/A	Up to $905m	Vaccine discovery platform	N/A	N/A
Takeda*	Turnstone Biologics	TBio-6517	Solid tumors	Phase I/II	Up to $900m	Viral vector vaccine	Yes	NCT04301011
Medigene	Roivant/ Cytovant	WT1 / PRAME vaccination	AML	Phase I/II	Strategic partnership	Cellular vaccine	No	NCT02405338
Eli Lilly*	CureVac	Multiple programs	Skin cancers	Phase I	Up to $1.7bn	mRNA vaccine	Yes	NCT03291002
Medimmune*	Inovio	Multiple programs	Multiple indications	Phase I	Up to $727m	DNA vaccine	Yes	NCT03835533
AstraZeneca	OncoPep	PVX-410	Triple negative breast cancer	Phase II	Strategic partnership	Peptide/protein vaccine	Yes	NCT02826434
BioNTech	**Neon Therapeutics	NEO-PV-01	Advanced or metastatic melanoma, smoking-associated NSCLC, or bladder cancer	Phase I	Up to $67m	Peptide/protein vaccine	Yes	NCT02897765
Regeneron	Nykode Therapeutics	Multiple programs	Multiple Indications	Preclinical	Up to $900m	Undisclosed	Undisclosed	Preclinical
Boehringer Ingelheim	Amal therapeutics	ATP-128	Colorectal cancer	Phase I/II	Up to $366m	Peptide /protein vaccine	Yes	NCT04046445
Boehringer Ingelheim	Vira Therapeutics	VSV-GP	Colorectal cancer	Phase I/II	Up to $245m	Viral vector vaccine	Yes	NCT04046445
Moderna	Merck	mRNA-4157	Melanoma	Phase II	Strategic Partnership	mRNA vaccine	Yes	NCT03897881
Bristol Myers Squibb	UbiVac	DPV-001	Triple negative breast cancer	Phase I/II	Strategic Partnership	Peptide/protein vaccine	Yes	NCT02737475
Janssen	Nouscom	VAC85135	Solid tumors	Phase I/II	Strategic Partnership	Viral vector vaccine	Yes	NCT05444530

Source: Evaluate Pharma, Edison Investment Research. Note: *Partner has exited the deal. **Neon Therapeutics was acquired by BioNTech in 2020.

Combinations are the likely answer: Vaccines boost survival

While regulatory complexities mean oncology discovery pathways are long (trial by error), we anticipate advancements will continue in shorter intervals in light of the strides made to date by many of the nimblest biotech companies (robust science/technology) and recently heightened awareness with the COVID-19 pandemic. As we continue to see clinical data for different platforms, small biotechs will inch closer to proving the robustness of their technology and science. With this progression, we anticipate an acceleration on combinations and alignments with pharma companies with deeper pockets seeking to bolster their broader solutions to maintain market share.

In this oncology vaccine series, we anticipate vaccine companies will line up best with more established checkpoint inhibitors as combination therapies to bolster efficacy and survival. We view this as the most natural extension for combinations outside of acquisitions into new (blank slate) areas that generally incur higher degrees of execution risk. Based on what we have learned so far, checkpoint inhibitors are not likely to go it alone. Plus, the required time to market (studies require significant investment in time and specialization and a pause) would likely be another deterrent and risk the decay of market share garnered to date.

Subject to the positive outcomes of randomized clinical trials, an oncology vaccine acquisition by a pharma company with a leading checkpoint inhibitor would improve the efficacy in their indication

through a one-two punch and easily support a buy-versus-build argument, especially in the light of current valuations. Vaccines would recruit T cells to kill cancer cells, create long-term immune memories and provide long-term monitoring. The combination with checkpoint inhibitors (that open pathways for the immune system or therapy) would improve survival rates. Recent studies show that oncology vaccines survive in excess of seven years.

To better visualize the most natural combinations, we have outlined large pharma with checkpoint inhibitors by indication and likeliest vaccine counterpart (with ongoing clinical trials) (Exhibit 3).

Exhibit 3: Likeliest checkpoint inhibitor and oncology vaccine combinations

	MERCK	Bristol-Myers Squibb	Bristol-Myers Squibb	Roche	Pfizer	AstraZeneca	GSK	REGENERON
Market cap	$228bn	$155bn	$155bn	CHF7bn	$266bn	$213bn	£69bn	$66bn
Cash	$10bn	$13bn	$13bn	CHF270bn	$33bn	$5bn	£7bn	$8bn
	Keytruda (pembrolizumab)	Opdivo (nivolumab)	Yervoy (ipilimumab) + Opdivo	Tecentriq (atezolizumab)	Bavencio (avelumab)	Imfinzi (durvalumab)	Jemperli (dostarlimab)	Libtayo (cemiplimab)
Malignant melanoma	ULTI	ULTI	ULTI	ULTI				
NSCLC	OSE, ULTI	OSE, ULTI	OSE, ULTI	OSE, ULTI		OSE, ULTI		OSE, ULTI
HNSCC	ULTI	ULTI						
Mesothelioma		ULTI	ULTI					
Prostate	ULTI	ULTI	ULTI	ULTI				
Ovarian	ULTI, OSE, IMMU	ULTI, OSE, IMMU		ULTI, OSE, IMMU		ULTI, OSE, IMMU	ULTI, OSE, IMMU	
AML		IMMU						
SCLC								
Renal								
Urotherial								
MSI-High								
Gastric								
Cervical								
Hepatocellular								
Merkel cell								
Hodgkin's								
Large B-cell								
Breast								
Pancreatic	OSE	OSE	OSE	OSE	OSE	OSE	OSE	OSE
Esophageal								
Endometrial								
Colon								
Cutaneous cell carcinoma								
Basal cell carcinoma								

ICI Phase II | ICI Phase III | ICI approved

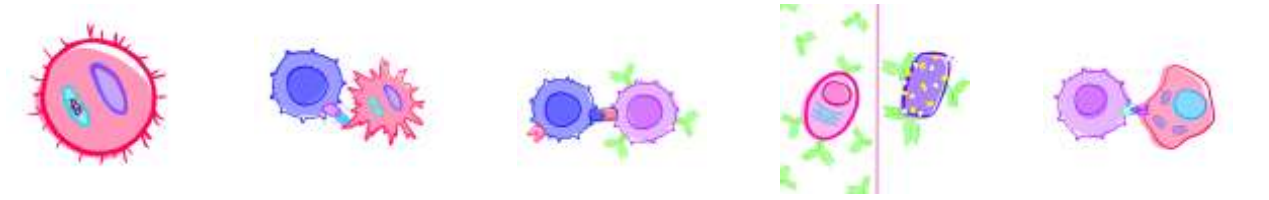
Source: SEC filings and company presentations. Note: Tickers indicate areas (indications) where the company's lead vaccine candidate is currently in active clinical trials.

Appendix A: Back to basics – preventative (traditional) vaccines

The body's immune system is highly effective at detecting altered or foreign cells and pathogens and disposing of them through the innate immune system. These responses are often non-specific, meaning they are the same despite the characteristics of the invading pathogen. Traditional vaccine platforms leverage the body's immune response by priming the immune system to protect it from future infections. The most reliable vaccines address pathogens with little or no variability such as the smallpox, polio and measles (MMR vaccine). The smallpox vaccine is based on a weakened (attenuated) version of the pathogen. The origins of the first smallpox vaccine surfaced in the 18th century and it was effective in eradicating the global outbreak in 1980.

We have simplified the mechanisms of action for preventative (traditional) vaccines below, as it is a good starting point to better understand the more complex platforms evolving in the clinic. There are a few variations in preventative vaccines, such as those that employ attenuated or live bacteria or viruses. Relatively newer subunit vaccines employ inactive portions (shells without genetic information) of the bacteria/virus (eg human papillomavirus vaccines) and activate an immune response with the addition of adjuvants. This immune response creates immunological memory, which allows the immune system to remember the initial response and mount a more efficient secondary response (monitoring).

Exhibit 4: Adaptive immune system



Source: Edison Investment Research

Curative vaccines are all the rage

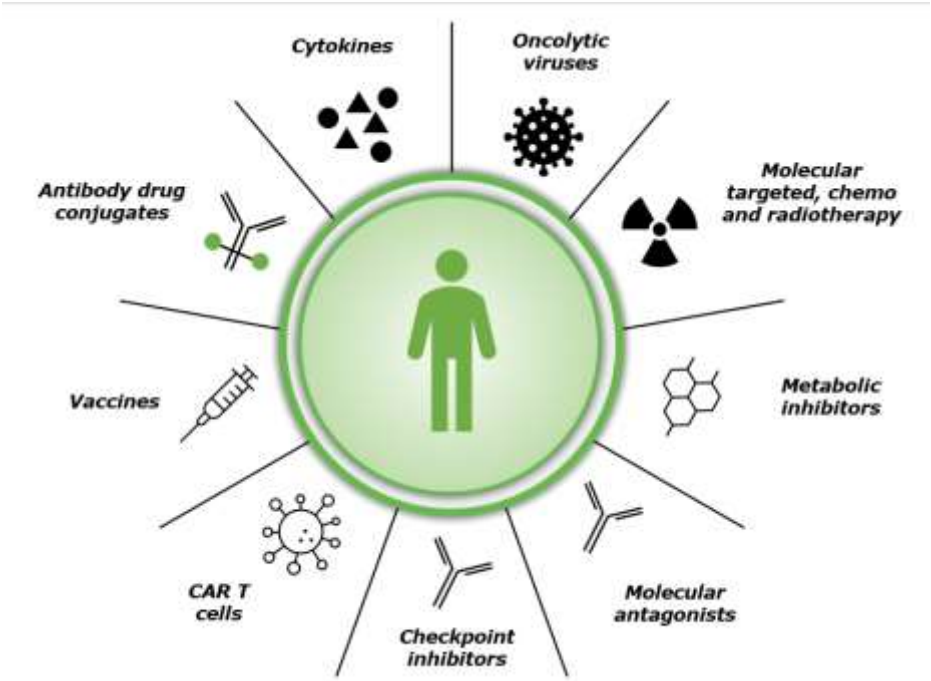
The COVID-19 pandemic has been a global catalyst for vaccine development on a few fronts. The development and deployment of viral vector vaccines during the pandemic is a notable advancement (outside of the clinic). In this approach, genetic materials (RNA and DNA) of the target pathogen are manufactured in the lab, which is much faster than replicating the whole pathogen (in a lab) as for traditional vaccines. The created genetic material of the identified pathogen is encased in a virus shell (the viral vector) to provide stability before injection with the intent of triggering an immune response (produce antigens and recruit T cells). After injection, the genetic payload of the vaccine is integrated into the patient's own cells, which then begin to manufacture the required antigen, causing an immune response and immunity to the selected pathogen. Although the scientific intent of these vaccines is still preventative, the technology employed was a notable advancement from traditional vaccines.

Pfizer, BioNTech and Moderna manufactured viral vector technology with mRNA, and the University of Oxford and AstraZeneca employed the same technology with DNA sequences (Exhibit 2). The Oxford-AstraZeneca vaccine was based around a genetically modified version of a chimpanzee adenovirus known as ChAdOx1.

Immunoncology: A wide breadth of potential therapies

The overall immunoncology (IO) market is expected to grow to c $100bn by 2026 and it is estimated that cancer vaccines will represent c 10% of this, comprised of both preventative and therapeutic cancer vaccines. IO therapies have evolved significantly over the past decade with the landscape now consisting of a variety of different types of drugs with unique mechanisms of actions (Exhibit 5).

Exhibit 5: Types of IO therapy



Source: Edison Investment Research

An emerging theme observed in the IO treatment space is that the likelihood of one specific therapeutic subtype being used as a sole treatment for cancer is unlikely. More regularly, the most effective therapies are proposed as combinations. However, because many of these therapies are discovered through trial and error, there are notable challenges in coordinating with partners, which are often considered peers in a highly competitive market. As a result, understanding the correct IO combinations to be used in patient-treatment regimens is the subject of significant clinical research. Additionally, certain indications may be more suited to IO therapies than others.

This is clearly highlighted by the NSCLC IO market, which is expected to dominate IO therapy. It is estimated that sales of NSCLC IO therapies will reach c $25bn by 2028 (EvaluatePharma), almost double the value of the second leading indication, melanoma. While it may be challenging to predict, we believe cancer vaccines have the potential to play an important role in the IO market. With market-leading ICIs such as Merck's pembrolizumab (Keytruda), Roche's atezolizumab (Tecentriq) and Bristol Myers Squibb's nivolumab (Opdivo) continuing to improve on current SoC regimens and score FDA approvals across a range of indications, we believe this provides an exciting opportunity for future cancer vaccine combinations.

IO therapies are also attempting to address one of the most significant drawbacks of classical chemotherapy agents, toxicity. IO drugs are being developed to address these safety issues by targeting cancer specific biomarkers that are absent on healthy cells. As such, IO medicines have the potential to represent the next generation of personalized medicines, each being designed on a patient-by-patient basis to treat an individual's unique cancer profile and limiting off-target side effects.

Classes of therapeutic cancer vaccines

Cell-based vaccines

Cell-based vaccines introduce whole cells to the body to induce an immune response to a patient's specific cancer. Vaccines of this type can be based on inactivated tumor cells or dendritic cells (DCs), either of which can be autologous (patient derived) or allogeneic (off-the-shelf). DCs play an important role in immune system pathways and are critical in presenting TSAs to the immune system's B and T cells. As such, DCs are a primary cellular target or component of many cancer vaccine therapies. Clinical responses to DC vaccines have so far proven to be limited, with previous trials failing potentially due to the use of only single antigen-loaded DCs. Additionally, autologous therapies have encountered challenges associated with costly and time-consuming production processes. Of interest is Mendus's DCP-001, an allogeneic vaccine that consists of DCs produced from maturation and differentiation of the company's proprietary acute myeloid leukemia (AML) cell line DCOne. The company's DCs are derived from a cancerous cell line and, therefore, DCP-001 contains a broad panel of tumor-associated antigens, increasing the probability of an immune response compared to single antigen therapies. Additionally, as the product is cell-line based it allows for scalable, centralized manufacturing, which is a major challenge faced by many cancer vaccine products during commercialization. DCP-001 can also be effectively stored frozen, allowing for immediate access to patients. Management's lead Phase II program for DCP-001 is investigating its use as a maintenance therapy in patients with AML who display measurable residual disease. Currently, the only oral chemotherapy approved for AML maintenance (azacitidine) is associated with toxicities that may not be suitable for long-term maintenance therapies, particularly in elderly patient populations.

Viral vectors

The same viral vector-based technology (discussed above) can be used in therapeutic cancer vaccines where modified viruses can deliver genes to cells. The targeted cells could either be DCs, to produce antigens that trigger a direct immune response, or tumor cells, to generate proteins that result in tumor cell death (oncolytic viruses) and release antigens to trigger an indirect immune response. A slightly altered version of ChAdOx adenovirus has been investigated in the clinic as a therapeutic vaccine. This vaccine is designed to target DCs and stimulate T-cell activity for the treatment of pancreatic cancer. In a Phase IIa study (NCT03815942) the ChAdOx vaccine was combined with ICI Opdivo. It was observed that 22% of patients had a >50% reduction in prostate-specific antigen (a prostate cancer biomarker) levels compared to 9% response rates seen in a previous ICI monotherapy study (NCT02787005). This study also represents a type of vaccine that can be successfully combined with ICIs to deliver a therapeutic response. AstraZeneca UK's COVID-19 vaccine AZD1222 also employs the viral vector technology (ChAdOx1; chimpanzee adenovirus Oxford 1).

Peptide- or protein-based vaccines

Peptide- or protein-based vaccines are the most comparable to traditional vaccines used for infectious disease prevention when considering mechanisms of action. Vaccines of this type consist of cancer-related proteins that can induce an immune response in patients. The ease of production and (relatively) lower toxicities make this form of vaccine attractive to developers.

For example, Ultimovacs is focused on the development of UV1, a potentially universal peptide-based cancer vaccine that targets human telomerase reverse transcriptase (hTERT). Telomerase is expressed in up to 90% of all cancers; however, it is not expressed in most normal human cells. Expression of telomerase plays a critical role in tumor cell lifecycles, resulting in unlimited, uncontrolled cell division. hTERT is primarily expressed in a subpopulation of cancer cells called cancer stem cells (CSCs), which are often resistant to conventional cancer treatments, leading to

metastasis and tumor resistance. As such, this makes hTERT an attractive target for cancer vaccine development. UV1 peptides are administered to patients through intradermal injection and, following uptake, processing and presentation by antigen-presenting cells (APCs), induce an hTERT specific CD4 T-cell response orchestrating immune responses against tumor-specific antigens. In the company's most advanced clinical trial, UV1 is being investigated in the Phase II INITIUM study in combination with nivolumab (Opdivo) and ipilimumab as a first-line treatment for patients with unresectable or metastatic melanoma, with top-line readouts expected in H123. The company is also developing UV1-based combinations for the treatment of mesothelioma, ovarian cancer, head and neck cancer and non-small cell lung cancer (NSCLC).

Another example of a peptide-based cancer vaccine comes from OSE Immunotherapeutics. Its lead asset, Tedopi, is targeting second-line NSCLC as its lead indication. The vaccine is composed of 10 epitopes (the part of the antigen that is recognized by the immune system) derived from two wild-type, seven chemically modified peptides and a pan-DR epitope (PADRE) to enhance cytotoxic T-cell response. These can prime the immune system to target five tumor associated antigens (CEA, p53, HER-2, MAGE-A2 and MAGE-A3) that are commonly over expressed in NSCLC. Recently announced results from the Phase III ATALANTE-1 trial demonstrate that Tedopi monotherapy caused a statistically significant survival benefit (median overall survival (OS) 11.1 months versus standard of care (SoC) 7.5 months) in patients with HLA-A2-positive NSCLC who have developed secondary resistance to ICIs.

Nucleic acid vaccines: The same but different

There is a degree of crossover between nucleic acid-based vaccines and viral vaccines as they both use either DNA or RNA to produce proteins that ultimately trigger an immune response to target cancer cells. However, differences between these vaccines arise from potentially different mechanisms of action, as well as the nucleic acid delivery platform.

BioNTech and Genentech recently announced the results of a Phase I study in pancreatic cancer (NCT04161755) that utilizes lipophilic mRNA structures (mRNA-lipoplex) to deliver the mRNA vaccine to DCs. The trial included 16 patients who had previously undergone surgery, who were then dosed with the personalized, neoantigen specific mRNA vaccine (autogene cevumeran) in combination with ICI atezolizumab. A T-cell response was observed in 50% of patients with a median recurrence-free survival of 13.4 months and demonstrated a tolerable safety profile.

Further clinical studies are also underway investigating the use of personalized cancer vaccines with dual characteristics. A recently initiated Phase II trial (NCT05456165) is dosing patients with a vaccine comprised of both a viral vaccine component (ChAdOx) and a lipid nanoparticle RNA vaccine component to provide a double immune response. The vaccine will be administered in combination with ICIs atezolizumab and ipilimumab, with the primary outcome of the study measuring the decrease in circulating tumor deoxyribonucleic acid.

Appendix B: Shining a spotlight on the clinic

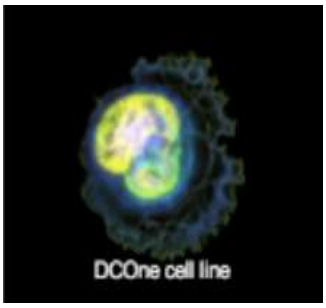
Mendus: DCP-001 cell-based vaccine

Mendus is a Swedish biotech company focused on the development of its DC-based vaccine (DCP-001). The lead Phase II program for DCP-001 is investigating its use as a maintenance therapy in AML in patients who have responded to previous treatments, but still display measurable residual disease. Oral chemotherapy agent azacitidine (Onureg, Bristol Myers Squibb) is the only therapeutic approved for AML maintenance therapy and is the existing SoC. However, due to toxicities associated with chemotherapy agents, they may not be suitable for long-term maintenance therapies, particularly in elderly patient populations.

There are seven ongoing clinical studies (NCT03697707, NCT03679650, NCT03083054, NCT03059485, NCT01096602, NCT01686334, NCT05000801) assessing the use of either allogeneic DCs or autologous DCs for the treatment of patients with AML. Clinical responses to DC vaccines have so far been limited, with previous trials failing potentially due to the use of only single antigen-loaded DCs. Autologous therapies, in particular, also have challenges associated with costly and time-consuming production processes.

Mendus's DCP-001 is an allogeneic DC vaccine that aims to address some of the historic issues associated with these therapies. DCP-001 consists of mature DCs that have been produced from maturation and differentiation of the company's proprietary AML cell line DCOne (Exhibit 6). Mendus's technology platform has been designed to allow for DC maturation during the manufacturing process. As these DCs have been derived from a cancerous cell line, DCP-001 possesses a broad panel of tumor-associated antigens. This multi-antigen design therefore increases the probability of eliciting an immune response when administered to patients compared to single-antigen therapies. Additionally, as the product is cell-line based, it allows for scalable, centralized manufacturing, which is one of the major challenges faced by many cancer vaccine products during commercialization. DCP-001 can also be effectively stored frozen, allowing for immediate access to patients (Exhibit 7).

Exhibit 6: DCOne Cell line image



Source: Mendus Corporate Presentation

Exhibit 7: DCP-001 product

Source: Mendus Corporate Presentation

In the ongoing Phase II study (ADVANCE-II), DCP-001 is being assessed as a monotherapy and has generated positive interim results. Measurable residual disease (MRD), an important risk factor in AML and the primary endpoint of the study, responses were observed in 35% (seven out of 20 patients) and a stable MRD was observed in a further 35% of patients. Median regression free survival (mRFS) and OS, both secondary endpoints, have, so far, not been reached at 14.3 months, suggesting a potentially significant benefit over Onureg (mRFS 7.1 months, median OS 14.6 months). While final datasets from the open label ADVANCE-II study are still required, these preliminary results have started to demonstrate the high immunogenicity of DCP-001. Mendus is also investigating the use of DCP-001 as a first-line monotherapy treatment for ovarian cancer (ALISON trial) with initial results expected in H222.

OSE Immunotherapeutics: Tedopi peptide cancer vaccine

Drug resistance is a major cause of therapeutic failure in NSCLC and only three drugs have been approved for the treatment of advanced NSCLC in a second-line setting (docetaxel, pemetrexed and erlotinib). This indication therefore remains an area of high unmet need.

OSE Immunotherapeutics (OSE) has developed its lead asset Tedopi, a peptide-based therapeutic vaccine targeting second-line NSCLC as its lead indication. The vaccine has been developed to target five tumor-associated antigens (CEA, p53, HER-2, MAGE-A2 and MAGE-A3), commonly over expressed in NSCLC, based on nine epitopes (the part of the antigen that is recognized by the immune system). This multi-antigen and epitope design further increases the chances of eliciting an immune response in patients while decreasing the likelihood of off-target toxicity (Exhibit 8).

Exhibit 8: Tedopi targeted design

Source: OSE corporate presentation

Tedopi is one of the most advanced therapeutic vaccines in clinical development, with OSE having recently announced the final datasets from its Phase III ATALANTE-1 trial. The trial investigated Tedopi as a monotherapy for the treatment of patients with HLA-A2-positive NSCLC who have developed secondary resistance to ICIs. In this context, secondary resistance refers to patients who failed treatment after receiving a minimum of 12 weeks ICI. The study's primary endpoint assessed OS associated with Tedopi monotherapy over SoC (docetaxel or pemetrexed) and demonstrated a statistically significant outcome (median OS 11.1 months versus SoC 7.5 months). It is anticipated that this data will support filing with the FDA's early access program, allowing the use of Tedopi outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

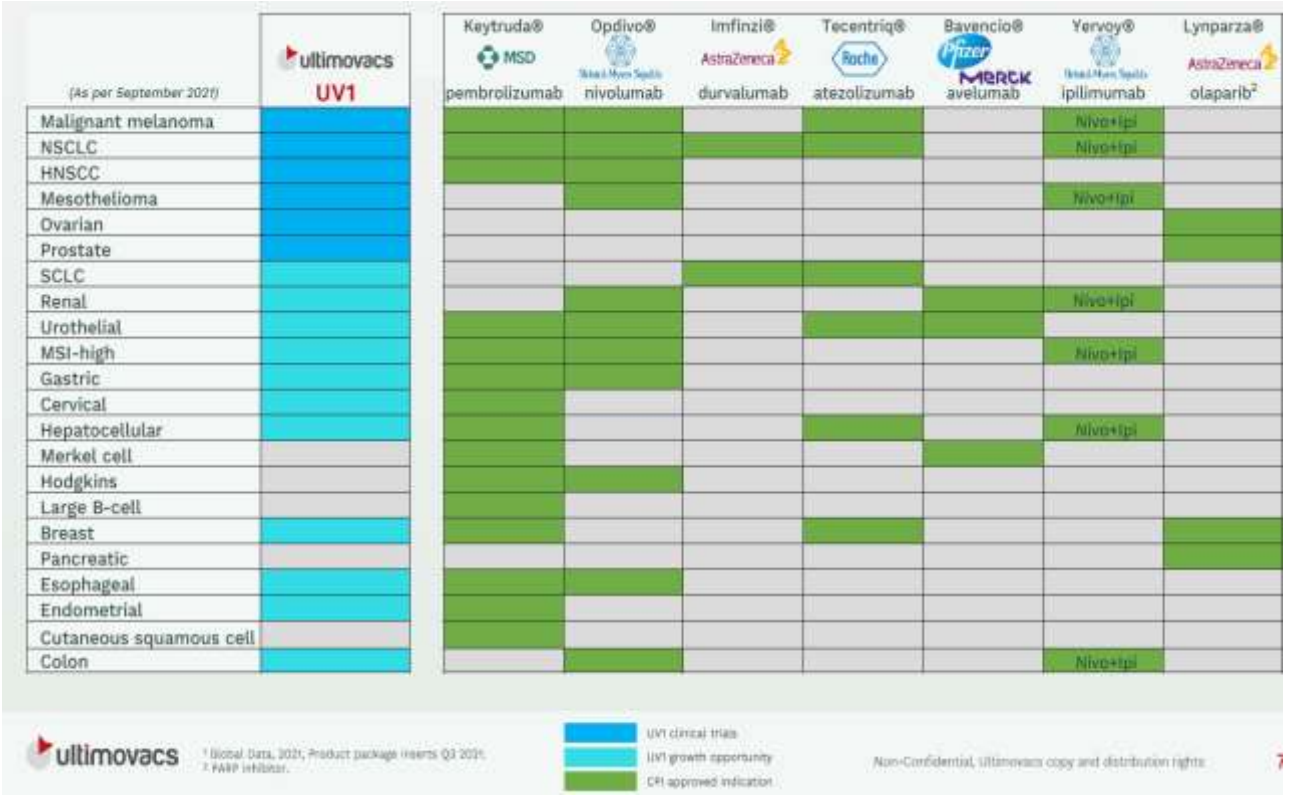
In collaboration with academic partners, OSE will supply Tedopi as part of two Phase II studies to investigate the vaccine in ICI combinations. In a further second-line NSCLC setting, the Combi-TED study will evaluate Tedopi in combination with nivolumab while the TEDOVA trial will combine Tedopi with pembrolizumab as a maintenance therapy in ovarian cancer. We believe the clinical success observed with Tedopi as a monotherapy provides encouraging signs for future clinical utility, particularly in combinational therapy settings with ICIs.

Ultimovacs: UV1 universal cancer peptide vaccine

Ultimovacs is a pharmaceutical company that is primarily focused on the development of its lead asset, UV1, a peptide-based cancer vaccine with the potential for universal application across cancer types. This pan-cancer characteristic comes from the antigens that UV1 is designed to elicit in an immune response against tumor cells. These antigens are derived from the cell replication enzyme, telomerase. Telomerase is expressed in up to 90% of all cancers; however, it is not expressed in most normal human cells. Expression of telomerase plays a critical role in tumor cell lifecycles, resulting in unlimited, uncontrolled cell division. hTERT is primarily expressed in a subpopulation of cancer cells called CSCs, which are often resistant to conventional cancer treatments, leading to metastasis and tumor resistance. As such, this makes hTERT an attractive target for cancer vaccine development. UV1 peptides are administered to patients through intradermal injection and, following uptake, processing and presentation by APCs, induce an hTERT-specific CD4 T-cell response, orchestrating immune responses against tumor-specific antigens.

Ultimovacs is investigating the use of UV1 in combination with ICIs. With this combination, the company is leveraging the mutual dependency and synergistic relationship between both the immune system and ICIs. In summary, the UV1 vaccine is designed to enhance the activity of the immune system's T cells to target cancer cells while ICIs block the cancer cells' defense mechanism against those same T cells. This clinical strategy allows Ultimovacs to explore the use of UV1 across a range of indications in which blockbuster ICIs have received approval and may provide UV1 with future growth opportunities (Exhibit 9).

Exhibit 9: UV1's ICI combination potential



Source: Ultimovacs corporate deck, May 2022

In its lead indication, malignant melanoma, UV1 has received dual fast-track designation from the FDA as an add-on therapy to pembrolizumab (Keytruda) or ipilimumab (Yervoy) for treating unresectable or metastatic melanoma. UV1 has also received orphan drug designation in the treatment of malignant melanoma. UV1 is being investigated in the Phase II INITIUM study in

combination with nivolumab (Opdivo) and ipilimumab as a first-line treatment for patients with unresectable or metastatic melanoma. Top-line readouts are expected in H123. However, the encouraging results, in year five, of a Phase I study of UV1 with ipilimumab in malignant melanoma reported a median OS in 12 patients of 66.3 months versus 17 months with ipilimumab alone. This result demonstrates proof-of-concept for clinical efficacy. This result is clinically very relevant as it shows that UV1 can affect lasting immune memory via the stimulation of CD4 lymphocytes on administration, a mechanism not demonstrated by many other cancer vaccines. In addition to positive clinical results, UV1 is easily manufactured using low-cost standard peptide synthesis techniques and possesses an extended shelf life (three years), making it an attractive off-the-shelf product.

General disclaimer and copyright

This report has been prepared and issued by Edison. Edison Investment Research standard fees are £60,000 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the research department of Edison at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Crown Wealth Group Pty Ltd who holds an Australian Financial Services Licence (Number: 494274). This research is issued in Australia by Edison AU and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

This document is prepared and provided by Edison for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document.

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

Edison relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia