CRA Insights
Life Sciences

CRA Charles River Associates

November 2023

Oncology vaccines: Are they positioned for PMS success

With combinations taking centre stage following the initial influx of immune checkpoint inhibitor monotherapies, Aaron Everitt and Cécile Matthews look ahead to the potential of mRNA vaccines in oncology and describe the pricing and market access opportunities and challenges that may await current and future competitors.

Cancer has posed a philosophical and pragmatic problem for payers since the arrival of the first biologics in the late 1990s. While payers want to provide patients with access to life-extending treatments, they must often pay large sums to do so. These problems have not abated, and despite the arrival of biosimilars, innovation with new treatments and combination-based therapeutic approaches has kept ahead of payers' and policy makers' ability to address these challenges. As we enter a new wave of innovation courtesy of mRNA technology, approaches to valuing and pricing oncology products will need to adapt yet again.

Cancer vaccines, or onco-vaccines, have been a holy grail for medicine for years, but instances of commercial success have been limited to two. First is Merck's Gardasil (human papillomavirus 9-valent vaccine), which targets HPV, a virus implicated in cervical cancer. It succeeded mainly because it targeted a virus that plays a key role in oncogenesis and had a pricing strategy in line with payers' expectations of a vaccine-type price, specifically ~€150 per dose in Germany, given up to three times every 10 years. Second is Imlygic (talimogene laherparepvec), perhaps the first example of a therapeutic vaccine, wherein an oncolytic virus is administered directly into melanoma lesions. However, issues with its clinical trial design and outcomes led to a somewhat disappointing health technology assessment (HTA) and reimbursement, with Amgen choosing to not seek reimbursement in many markets.[1] Another stark difference that may also have foiled its success was its ambitious pricing strategy. For example, in Germany, where the product was found to provide no additional benefit, Imlygic achieved prices of about €1300 per dose—over €5000 per cycle, which is repeated every two weeks.

---

[1] Ferrucci PF, Pala L, Conforti F, Cocorocchio E. Talimogene laherparepvec (T-VEC): an intralesional cancer immunotherapy for advanced melanoma. Cancers (Basel). 2021;13(6):1383. doi:10.3390/cancers13061383

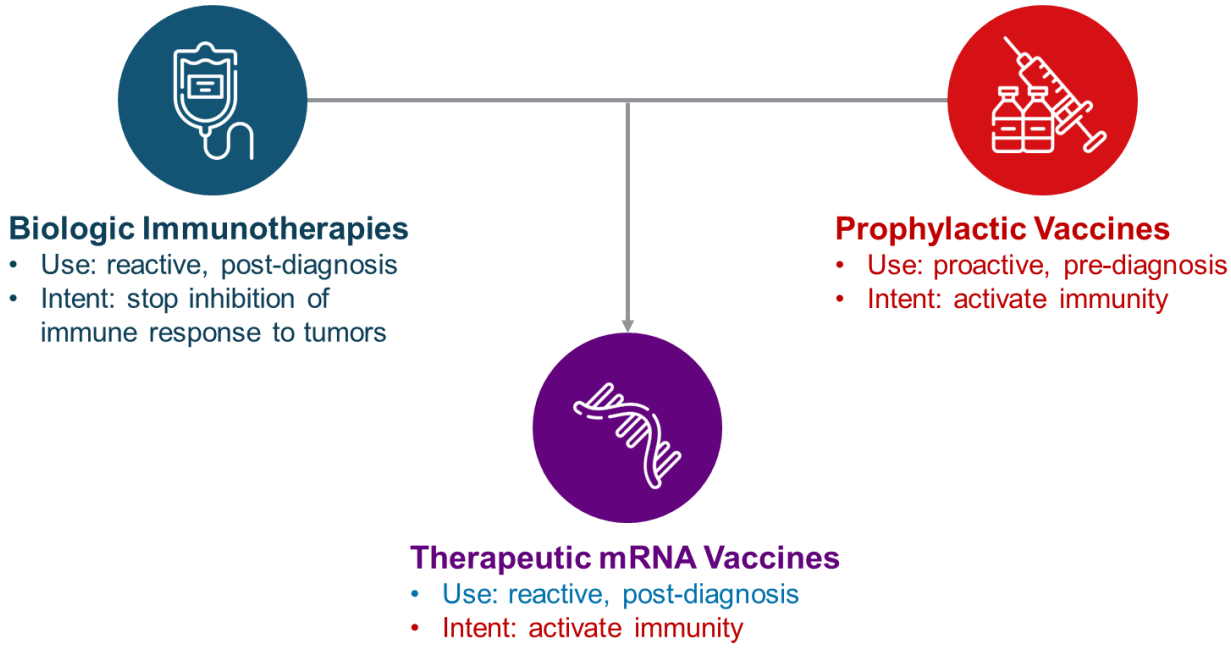
The next generation of onco-vaccines is expected to be based on mRNA technology. Having been catapulted into the spotlight by the COVID-19 pandemic, mRNA vaccines have so far fit a model of preventative vaccines that payers are familiar with. While manufacturers can still build on the acceptance of the technology's safety in humans, key questions remain for payers and the industry that can in turn impact pricing, sales, and revenue:

1. How will mRNA vaccines be positioned in cancer?

It is important to first contrast mRNA-based vaccine approaches in oncology with existing vaccines regarding their purpose or role. Gardasil, like other traditional vaccines, acts as a monotherapy prophylaxis to prime the immune system in healthy patients. Imlygic, on the other hand, is seen as a post-diagnosis therapy aimed at stimulating the body's immune response, somewhat like immunotherapies. Beyond the semantics of distinguishing "prophylactic vaccines" from "therapeutic vaccines", this could have important pricing consequences.

Figure 1 illustrates the hybrid role that novel therapeutic mRNA vaccines play in comparison with existing prophylactic vaccines and biologic immunotherapies. The biological purpose of a therapeutic vaccine is largely in line with that of prophylactic vaccines: activating immunity. However, the key difference that will have pricing implications is that therapeutic vaccines are more akin to biologic immunotherapies (IOs) in their use and positioning within the treatment paradigm as an intervention in an active disease post diagnosis. This plausibly allows clinical and pricing parallels to be drawn between the existing immunotherapies and new mRNA onco-vaccines, as they will be focused on the same populations with an overall intent of treating diagnosed cancers.

Figure 1: Illustration of the differing roles of vaccines and immunotherapies in relation to one another



Onco-vaccines' biological role of priming the immune system, as opposed to binding to cancerous cells, lends itself to treating earlier stages of cancer in combination with biologic immunotherapies, which are themselves moving into pre-metastatic stages. The synergies that exist between the two technologies could theoretically maximize clinical outcomes.

Moderna and Merck, who are leading the charge with their KEYNOTE-942 trial, have combined Moderna's vaccine candidate, V940 (mRNA-4157), with Merck's Keytruda (pembrolizumab) in patients with resected, high-risk stages IIIB, IIIC, IIID, and IV melanoma. Their recent readout of the phase 2b trial, presented at ASCO 2023[2,3], has shown a recurrence-free survival (RFS) of 78.6% for the combination (for pembrolizumab alone, at 18 months post treatment, that figure is 62.2%). This corresponds to a 44% reduction in the risk of recurrence or death attributable to the onco-vaccine. Distant metastasis-free survival (DMFS) has also been significantly improved in the combination arm.

Although the phase 2 trial has targeted both locally advanced and metastatic melanoma in its focus on stages III and IV, the recently announced phase 3 trial (V940-001) protocol includes patients in phase IIC[4]. This illustrates the likely intended direction of the fledgling approach to cancer—presumably continuing to focus on localised stages I–II cancers, which are being targeted with biologics in multiple trials.

This positioning presents pricing and access challenges that are currently being experienced by the immunotherapies in regard to how clinical efficacy is measured in stages I–III of cancer. In the metastatic stage, treatment is focused on eradicating tumours and prolonging survival. Therefore, payers have sought overall survival (OS) data as an appropriate measure of clinical impact. However, measuring OS in advanced or localised cancers not only becomes increasingly complex and time consuming, it also does not reflect patient-relevant outcomes in the earlier stages. It is for this reason that we have seen the proliferation of so-called xFS (event x–free survival) endpoints. The key challenge for manufacturers will be to convince payers that these endpoints should not be viewed as surrogates for survival, as they have in metastatic disease; rather, they are truly meaningful, patient-centric endpoints that stand alone. This is discussed further in section 3, below.

2. What price can mRNA vaccines achieve in cancer?

Negotiations between payers and manufacturers about achievable prices for mRNA onco-vaccines are likely to be protracted across markets, considering the arguments that can be made from different perspectives on the new technology.

Manufacturers will likely target immunotherapy-like prices on the basis of the high unmet need in oncology as well as the increased clinical value that the onco-vaccines bring to patients: being cancer or disease free. Further, from a scientific perspective, the synergies between mRNA onco-vaccines and immunotherapies make biological sense, perhaps even more so than combining two different inhibitors, which many current combinations do. Fundamentally, these onco-vaccines are the next generation of early-stage, interventional immunotherapy technology, and it could be argued that they should be valued at the same level as those existing biologics.

Further, manufacturers will draw attention to the fact that these onco-vaccines are not off-the-shelf solutions, as are biologic immunotherapies or prophylactic vaccines, but rather a form of personalised medicine containing up to 34 patient-specific tumour antigens within the mRNA

---

2 Moderna and Merck announce MRNA-4157 (V940) in combination with KEYTRUDA(R) (pembrolizumab) demonstrated a statistically significant and clinically meaningful improvement in distant metastasis-free survival in patients with high-risk stage III/IV melanoma following complete resection versus KEYTRUDA. News release. Moderna; June 5, 2023. https://s29.q4cdn.com/435878511/files/doc_news/Moderna-and-Merck-Announce-mRNA-4157-V940-in-Combination-With-KEYTRUDAR-pembrolizumab-Demonstrated-a-Statistically-Significant-and-CI-9DQYG.pdf

3 Khattak A, et al. Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial. J Clin Oncol. 2023;41(17 suppl): LBA9503. doi:10.1200/JCO.2023.41.17_suppl.LBA9503

4 A clinical study of V940 plus pembrolizumab in high-risk melanoma (V940-001). Clinical Trials. Accessed July 18, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05933577

payload. This inevitably has implications for scalability and a knock-on impact on cost, as economies of scale cannot be applied to personalised medicines at present. The tailored approach to manufacturing, at least superficially, bears more resemblance to the CAR-T therapies in haematology, which command significant price premiums. It remains to be seen whether Moderna has a means of addressing the scalability of the technology, given the personalised nature of the onco-vaccines and the sizeable number of cancer patients it would intend to supply, which has been an issue for some autologous CAR-T therapies. This could in turn lead to access and supply issues if not addressed.

However, it should be noted that the cost of manufacturing mRNA therapies, relative to cell therapies or antibodies, can be several levels of magnitude lower, despite the need for personalised tailoring. The COVID-19 pandemic put drug pricing under a global spotlight, with the media openly comparing the prices of the first mRNA vaccines from Moderna and Pfizer/BioNTech. Manufacturers showed their hand by revealing that the cost of goods associated with these vaccines was also low and that they made sizeable profits. So, although personalisation will indeed be a modifier that drives up costs, which should be considered in pricing, it cannot be the focal argument put forward by manufacturers.

Payers, on the other hand, are likely to be looking at the situation from a different perspective, basing their pricing rationale on affordability as well as the quality of evidence supplied by manufacturers (discussed below, in section 3), the lower costs of mRNA technologies, and the fact that these onco-vaccines are still classified as vaccines, which in several markets means that entirely different routes of assessment and value accreditation are employed. However, it is likely that the treatment focus of the onco-vaccines will see them assessed in the same manner as the established array of small molecules and biologics.

Affordability and the proportional expenditure on oncology relative to other diseases is likely to remain a key payer argument for the onco-vaccines. Although the first wave of onco-vaccines is being trialled in advanced-stage patients, it is clear that trials will progress to earlier disease states. With improved diagnosis of cancer in earlier stages and the ballooning number of patients it creates, public healthcare systems will be unable to fund access to early stage–focused mRNA onco-vaccines that are priced like current biologics. Access restrictions are therefore a means for payers to control budget impact based on their assessment of remaining unmet need. If priced at a level that payers see as unsustainable, they may limit reimbursement or coverage to patient subsets, despite the public unpopularity of such restrictions and barriers to access in cancer.

The arrival of biosimilars that can replace key immunotherapies, including Keytruda (pembrolizumab) and Opdivo (nivolumab), will further feed into payers' hesitation to reimburse onco-vaccines at high price points. They would hope to see increased use of drugs that are biosimilar to the often very effective checkpoint inhibitors to ease affordability concerns. Indeed, treatment sequencing could become a focus for payers that would seek to trial the cheaper biosimilars ahead of an immunotherapy/onco-vaccine combination.

However, the key challenge attributable to payers is their scrutiny of the perceived quality of evidence provided by onco-vaccine manufacturers. Continuing to achieve metastatic stage–like pricing in the earlier stages will require manufacturers to deliver truly paradigm-altering outcomes for cancer patients to overcome pricing and access barriers. Factoring in the current resistance to acknowledging the stand-alone value of non-survival-based trial endpoints makes this much more complicated.

3. How will mRNA vaccine manufacturers present evidence to justify their price in cancer?

Approaches to treating cancer have until recently focused on killing cancer cells in advanced and metastatic stages of disease, with the goal of prolonging survival for patients in the final, severe stages of disease. The potential for a cure is remote, so the intent is to increase the number of months a patient has left. Overall survival has therefore been seen as the gold standard for payers making their HTA and pricing decisions in oncology, as it appropriately records objective, patient-centric outcomes.

However, measuring OS is not always feasible, nor is OS always the most appropriate way to assess the patient-centric impact of an intervention in cancer. In stages I–III, when resection is possible, patients are treated with a curative intent. Although survival is clearly a means of understanding whether a patient has been cured, measuring it becomes impractical if patients survive – or do not see cancer recur – for years or even decades. Looking beyond the timescale required for such trials, the complexities of measuring the impact of the initial early-stage intervention are confounded by subsequent treatments in patients' lives, whether they are related to a recurring cancer, a new cancer, or any other disease. Therefore, it can be argued that alternative measures such as xFS outcomes, including disease-free survival (DFS), recurrence-free survival (RFS), and event-free survival (EFS), among others, are more representative measures of characterizing treatment outcomes in non-metastatic-stage cancers.

Despite this scientific and practical rationale, HTA agencies have not kept pace with the changing focus of clinical trials; they often see these non-OS endpoints as surrogates for survival. It is important to note that payers do have reasons for hesitation in accepting xFS measures. Progression-free survival, for instance, has been shown to have a variable correlation with survival in stage IIIB, IIIC, and IV disease[5]. However, more recent evidence lends support for the other xFS measures ultimately correlating with survival, especially in earlier stages of cancer. AstraZeneca has recently shown a strong correlation between disease-free survival and OS for Tagrisso (osimertinib) in stage IB to IIIA non-small cell lung cancer[6]. At the time of launch, mature OS was unavailable, so payers were forced to evaluate on the basis of disease-free survival alone.

Ultimately, HTA agencies have been shown to be largely inflexible and to have not kept pace with the rate of scientific change with respect to the value of xFS endpoints. This poses a problem for the first mRNA onco-vaccines if things do not change. KEYNOTE-942 focused on recurrence-free survival and distant metastasis-free survival but has no measure of survival in its phase 2b trial design. The proposed phase 3 V940-001 protocol does include OS as a secondary endpoint, but with a collection window of 85 months. At the time of submission, this design is unlikely to allow for meaningful OS comparisons between the treatment arms. Payers are likely to highlight the inclusion of late-stage melanoma (stage III or IV) as a rationale for supplying OS data for submission. Based on current approaches to HTA, suboptimal assessments could be likely. However, it is plausible that the situation facing the first mRNA onco-vaccines from an HTA perspective will have changed due to the sheer number of trials utilising xFS endpoints in progress for biologic immunotherapies in stages I–III of various cancers. Messaging from across the

---

[5] Merino M, Kasamon Y, Theoret M, Pazdur R, Kluetz P, Gormley N. Irreconcilable differences: the divorce between response rates, progression-free survival, and overall survival. J Clin Oncol. 2023;41(15):2706-2712. doi:10.1200/JCO.23.00225

[6] Tagrisso achieved unprecedented survival in early-stage EGFR-mutated lung cancer, with 88% of patients alive at five years in ADAURA Phase III trial. News release. AstraZeneca; June 4, 2023. https://www.astrazeneca.com/media-centre/press-releases/2023/tagrisso-achieved-unprecedented-survival-in-early-stage-egfr-mutated-lung-cancer-with-88-of-patients-alive-at-five-years-in-adaura-phase-iii-trial.html

industry and the scientific community will be focused on boosting acceptance of these endpoints so they are no longer regarded as surrogates that limit pricing potential.

Beyond what is measured, payers also will be concerned with the scale of improvement beyond the current standard of care if prices are to be justified. In this regard, the first mRNA onco-vaccines, which are used in combination with an existing "backbone" treatment, face the same issues as the imminent oncology combinations that use two biologics or small molecules. Typically, the addition of the second molecule does not double the scale of outcomes in a linear fashion. As a result, payers value the "add-on" at a lower level than the existing "backbone". KEYNOTE-942, for example, has shown an increase in recurrence-free survival from 62.2% to 78.6% when comparing Keytruda monotherapy to the combination with the onco-vaccine. Although this improvement is clinically meaningful and positive news for patients, it poses the same dilemma as other combination approaches in oncology with respect to the financial value attributed to the second product. Payers could conclude that most of the efficacy is attributable to the already available "backbone", with the onco-vaccine improving – but not revolutionising – efficacy.

A second component of the evidence package that must be considered is the relative safety of mRNA onco-vaccines, particularly when compared to biologic immunotherapies or small molecules. Here, the onco-vaccines have an almost indisputable advantage over their more toxic counterparts. One of the key considerations for the current wave of IO/IO combinations is the cumulative effect of two components that each individually can carry harsh side effect profiles, affecting patient quality of life as well as discontinuation rates and weighing into payers' risk/benefit decision-making when assessing new products.

Although safety is important to payers, it is not often rewarded vis-à-vis price potential. However, it could be an important part of the value offering for mRNA onco-vaccines, as they could provide many of the benefits of the immunotherapies but with an improved safety profile. This beneficial shift in the risk/benefit profile could be an important one for patients, payers, and manufacturers.

Concluding remarks

mRNA onco-vaccines carry high expectations and are being reported as the next important step in the clinical management of oncology, one that builds on the foundations established by the various protein inhibitors. So far, a great deal of attention has been paid to the scientific and clinical promise of these interventions, but manufacturers must look beyond these factors to consider the pricing and market access dynamics that await.

It is critical that manufacturers developing onco-vaccines – and those looking to compete with them at launch – begin to plan their evidence generation and pricing strategies early in the development process. So too must payers and regulators proactively plan and legislate to allow for timely access to cutting-edge medicines that may bring significant clinical innovation. Recent developments in certain markets indicate that payers believe a clear opportunity exists for onco-vaccines; examples are the creation of the Cancer Vaccine Launch Pad in the UK and the memorandum of understanding signed in January 2023 between NHS England and BioNTech to treat up to 10,000 patients with mRNA onco-vaccines by 2030[7]. This willingness to embrace new technologies in cancer will be an important factor if these therapeutic vaccines are to succeed.

[7] Samarasekera U. New partnership to boost UK cancer vaccine research. Lancet Oncol. 2023;24(2):132. doi:10.1016/S1470-2045(23)00011-6

About CRA's Life Sciences Practice

The CRA Life Sciences Practice works with leading biotech, medical device, and pharmaceutical companies; law firms; regulatory agencies; and national and international industry associations. We provide the analytical expertise and industry experience needed to address our clients' toughest issues. We have a reputation for rigorous and innovative analysis, careful attention to detail, and the ability to work effectively as part of a wider team of advisers. To learn more visit **www.crai.com/lifesciences**.

Contacts

Cécile Matthews
Vice President
+44 1223 783 910
cmatthews@crai.com