Disrupting oncology; the mRNA promise

Executive Summary

Treatment paradigms in oncology are constantly evolving with more precise medicine and longer duration therapies. Novel technologies are critical in unlocking improved treatment strategies; mRNA therapeutics represent a significant growth area and could significantly change the way oncology is treated. Short- to mid-term growth is expected to come from mRNA therapeutic vaccines, with phase 2 and 3 trials ongoing. The results of these trials will determine whether this technology can live up to its expectations: to reshape how cancer is being treated and provide transformational benefits.

Key Takeaways

Clinical unmet need will continue to drive growth in oncology, with worldwide annual sales expected to reach over $375 B in 2028 [1]

mRNA therapeutics have significantly expanded the potential repertoire of therapeutic agents in oncology, with >25 assets in clinical development and >55 assets in preclinical development

mRNA therapeutic vaccines are most advanced in the clinical pipeline, though oncology therapeutics and *in vivo* adoptive cell therapies are on the rise

Given the nascency of the space, several key risks on long-term safety and efficacy exist; tracking readouts from key P2 and 3 assets will be critical to continue assessing mRNA potential

Manufacturers should assess necessary clinical and commercial trade-offs in order to gain a strong foothold in the evolving mRNA oncology space

Oncology Landscape and Growth

Over 1.9 M new cancer cases and 600 K cancer-related deaths occurred in the U.S. in 2022. Worldwide annual sales of cancer treatments is expected to grow from ~$172B in 2021 to ~$375B in 2028, largely driven by cancers with high incidence and mortality. This growth will largely be funneled to leading companies and key assets. In 2030, Merck, AstraZeneca and Johnson & Johnson are expected to generate sales of ~$32B, ~$24B and ~$22B projected revenues, respectively. Currently, PD-1/PD-L1 inhibitors currently make up ~19% of worldwide sales and will likely to continue dominating the market.

Therapeutic advancements and earlier diagnosis have contributed to the increase in 5-year survival rate. However, tumor heterogeneity, immunological accessibility and resistance (primary and acquired) remain key challenges with existing therapies.

Novel technologies are urgently needed to address the unmet need of these vulnerable patient populations. mRNA therapeutics offer promising, novel solutions to overcome existing challenges in oncology.

FIGURE 1 - Cancer Epidemiology

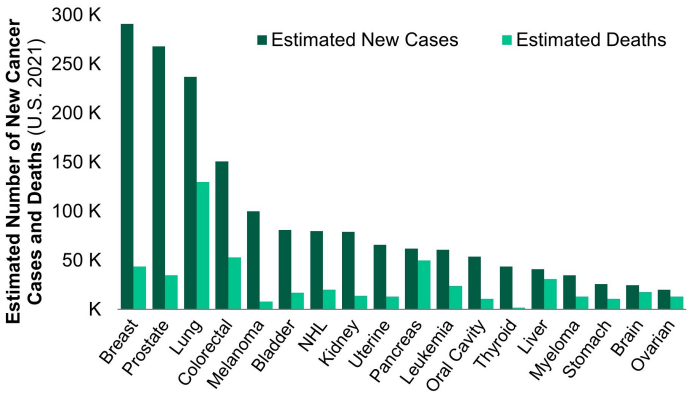
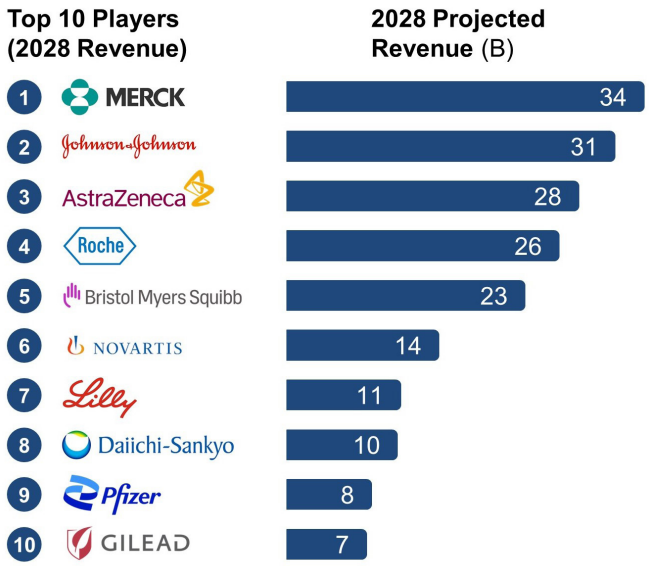


FIGURE 2 - Oncology Pharma. Market Landscape



Value of mRNA Therapeutics

mRNA therapeutics have the potential to disrupt the way cancer is treated, significantly expanding the repertoire of available therapeutic agents. mRNA is highly versatile and can encode a broad range of proteins to target multiple tumor-associated antigens simultaneously. With significant efforts underway to direct mRNA therapies to specific tissues, we are closer to unlocking the potential for a broad range of applications.

Increasing scientific understanding and clinical validation of mRNA therapeutics will further support their potential value in oncology. Approximately twenty-five assets are in Phase 1 to 3 clinical development, with another ~57 preclinical assets illustrating research and promise in this space. The mRNA space is ripe with potential to significantly change the oncology treatment paradigm. Pharma and biotech players should seek to harness this momentum as they develop their oncology pipelines.

Key Considerations for Biotech and Pharma Players

As companies consider entering the mRNA therapeutics space and/or optimizing their existing mRNA pipeline, key questions must be considered:

- How will the technology reshape the way cancer is managed?
- What technical and clinical challenges are they positioned to overcome?
- Where in the complex oncology landscape can they create transformative benefit?
- How to enter the mRNA space?

How will the technology reshape the way cancer is managed?

mRNA technologies are expanding beyond prophylactic

FIGURE 3 - Novel mRNA Technologies

Vaccines *Stimulate immune response through mRNA encoded target*	**Genentech** and **BioNTech** developing personalized mRNA cancer vaccine autogene cevumeran, an individualized mRNA neoantigen vaccine containing up to 20 major histocompatibility complex class I and class II (MHCII) restricted neoantigens in lipoplex nanoparticles
***In vivo* therapeutics** *mRNA encodes therapeutic to deliver protein in vivo*	**Moderna** is developing encoding OX40L T cell co-stimulator, IL-23 and IL-36γ pro-inflammatory cytokines for intratumoral (ITu) injection in combination with durvalumab in advanced solid tumors and lymphoma
Cell reprogramming *mRNA enabled direct lineage conversion*	Efforts to date a largely pre-clinical, **Sanofi** acquired **Tidal Therapeutics** uses mRNA to reprogram T-cell *in vivo* with mRNA to make CAR-T cells, eliminating the need for *ex vivo* manufacturing
Gene/base editing *CRISPR-Cas mRNA for ex vivo or in vivo genome editing*	Multiple tools are currently being explored (mainly pre-clinically) to improve efficacy of adoptive cell therapy, for example editing the PD1 locus or looking to target essential genes in cancer such as polo-like kinase 1

vaccines into other applications, mostly comprising therapeutic vaccines and therapeutic drugs.

Therapeutic vaccines deliver mRNA sequences encoding tumor-associated antigens to initiate an anti-tumor response. mRNA vaccines showcase multiple advantages over existing vaccines. They can be personalized based on patient-specific mutations or target common (neo) antigens without personalization. In addition, mRNA oncology vaccines are expected to have a similar safety profile to COVID-19 mRNA vaccines [2]. However, to demonstrate this favorability, long-term follow-up and head-to-head comparisons vs. immunotherapies may be necessary in pivotal trials. mRNA vaccines will need to demonstrate efficacy in the metastatic setting, where many previous therapeutic vaccines and neoantigen approaches have failed, often due to tumor heterogeneity.

Data for mRNA-4157 (V940) was recently presented by Moderna and Merck at the 2023 American Society of

FIGURE 4 - Oncology mRNA Pipeline (Illustrative Selection) [4]

	Indication	Company	mRNA Asset	Asset Type	Phase	Type
Hot	Melanoma	BIONTECH	BNT-111	Therapeutic Vaccine / Therapeutic Agent	Disc. PC P1 **P2** P3	Common Mutations (FixVac Platform)
		moderna	mRNA-4157	Therapeutic Vaccine / Therapeutic Agent	Disc. PC P1 P2 **P3**	Personalized (≤34 PSNs)
		CUREVAC	CV8102	Therapeutic Vaccine / Therapeutic Agent	Disc. PC **P1** P2 P3	Common Mutations
	Lung	REPLICATE	RBI-3000	Therapeutic Vaccine / Therapeutic Agent	**Disc.** PC P1 P2 P3	Undisclosed
		BIONTECH	BNT-116	Therapeutic Vaccine / Therapeutic Agent	Disc. PC **P1** P2 P3	Common Mutations (FixVac Platform)
Cold	Breast	REPLICATE	RBI-1000	Therapeutic Vaccine / Therapeutic Agent	Disc. **PC** P1 P2 P3	Undisclosed
	Prostate	BIONTECH	BNT-112	Therapeutic Vaccine / Therapeutic Agent	Disc. PC **P1** P2 P3	Common Mutations (FixVac Platform)
		pHion THERAPEUTICS	PTX V3	Therapeutic Vaccine / Therapeutic Agent	Disc. **PC** P1 P2 P3	Undisclosed
Mixture	Multiple Targets / Solid Tumors	BIONTECH	BNT-122	Therapeutic Vaccine / Therapeutic Agent	Disc. PC P1 **P2** P3	Personalized (iNeST Platform)
		moderna	mRNA-2752	Therapeutic Vaccine / **Therapeutic Agent**	Disc. PC **P1** P2 P3	OX40L, IL-23, IL-36γ

Clinical Oncology (ASCO) Annual Meeting, showing it lowered the risk for distant metastasis or death by 65% in stage III/IV melanoma patients with high risk of recurrence following complete resection. mRNA-4157 contains up to 34 different neoantigens and was used in combination with the checkpoint inhibitor Keytruda (pembrolizumab) [3]. A larger Phase III study has been initiated. Moreover, Moderna and Merck also plan to expand studies to include other tumor types, including lung cancer.

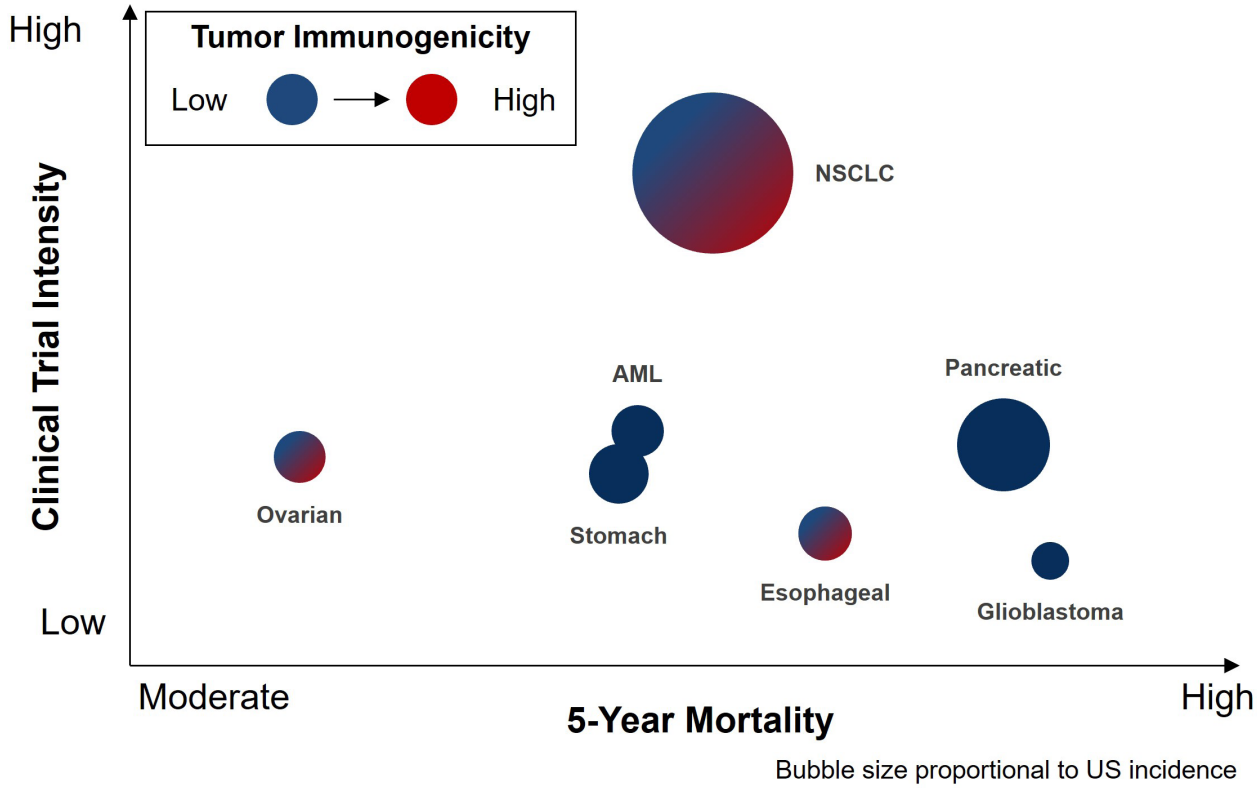
mRNA may additionally encode for a therapeutic protein that is delivered via lipid nanoparticles (LNPs) and translated only in target tumor cells. For example, BioNtech is pursuing using locally delivered cytokines (BNT131) and antibodies (BNT141) to trigger anti-tumor responses. These approaches may be able to deliver therapeutic benefits which would not be possible without highly localized delivery approaches.

mRNA therapeutic vaccines are more advanced and validated than other mRNA applications, comprising ~60% of the preclinical and clinical development pipeline. However, oncology therapeutics and novel applications such as *in vivo* adoptive cell therapies are beginning to surface as promising alternative applications. Companies must monitor development of these applications to decide which technologies they are best positioned to pursue.

What technical and clinical challenges is mRNA positioned to overcome?

Recent advances in mRNA technologies seek to address existing challenges surrounding targeted delivery, unwanted immunogenicity, and limited clinical validation, but risks remain. pH-sensitive ionizable cationic lipids have improved LNP organ delivery and functionalized lipids are being explored to further improve organ selectivity. However, the ability to target (and de-target) specific organs with mRNA technologies remains a key limitation, today. Similarly, self-amplifying RNA and circular RNA may enable lower dosing and prolonged response to avoid unwanted immunogenicity by increasing the effective amount and durability of mRNA delivered in a single dose. However, these technologies are still in preclinical stages and do not address limitations around targeted delivery. Lastly, mRNA therapeutics in oncology are relatively early stage [5]. BioNTech and Moderna have assets that have progressed to Phase 2 and 3 trials with promising early results, but long-term efficacy is still unexplored. Readouts

FIGURE 5 - Tumor Rankings Across Key Metrics



from these key Phase 2 trials in late 2023 to 2024 will be critical in understanding the impact of mRNA therapeutics. Novel entrants in the mRNA space should consider which of these remaining risks they are best positioned to address to optimize their impact in the evolving treatment paradigm.

Where in the complex oncology landscape can they create transformational benefit?

Clinical need, competitive landscape, addressable patient population and scientific rationale must be combined to identify where to play and win with mRNA technologies in oncology. While the field is still evolving, a relatively low risk opportunity would be to target tumors with some degree of clinical validation.

mRNA technologies, especially therapeutic vaccines, are believed to be more efficacious in "hot" tumors given greater response to immunotherapies. As a result, companies are developing more assets targeting "hot" tumors such as melanoma vs. "cold" tumors such as most breast cancer subtypes (TNBC may be more responsive to PD-(L)1). Trials in "hot" tumors are further along (e.g., P2) in comparison to preclinical studies of mRNA assets in "cold" tumors such as colorectal, prostate and breast. Thus, while "hot" tumors present attractive opportunities for mRNA vaccines, "cold" tumors remain largely unexplored and are therefore currently less competitive [6, 7, 8].

Beyond the consideration of "hot" vs "cold" tumors and pipeline activity, actual clinical need must also be assessed to understand where to play within oncology. NSCLC (28% 5-year overall survival), esophageal cancer (25% 5-year overall survival) or pancreatic cancer (15% 5-year overall survival) have high unmet needs and significant patient populations, yet have highly active clinical pipelines. Companies should weigh these clinical and commercial risks in addition to other portfolio-specific strategic factors when deciding where the highest potential for transformational benefit may exist in oncology.

How to enter the mRNA space?

The final key step for successful implementation of novel mRNA therapeutics is to determine how to enter and develop in this space. The current pipeline comprises of several small- to mid-sized pharma with strong in-house mRNA expertise partnering with big pharma with existing oncology portfolios. For example, BioNTech has their own proprietary mRNA vaccine platform and is partnered with Genentech to leverage their immunotherapy portfolio and co-develop novel cancer vaccines. Similarly, Moderna has a validated mRNA vaccine platform in infectious diseases and is now partnered with Merck and AstraZeneca to help commercialize in oncology. Alternatively, manufacturers may choose to enter the mRNA oncology space through acquisitions and partnerships with smaller players that can help in early stages of development. CureVac, an mRNA vaccine company, is pursuing this exact strategy with its deals with Frame and myNEO, both of which utilize genomics- or bioinformatics-based platforms to identify cancer therapeutic targets. Given the interest in mRNA technologies additional opportunities for investors, partnerships are expected to emerge as new approaches to utilize and fine-tune the mRNA continue to emerge.

Moreover, an increasing number of contract development and manufacturing organizations (CDMOs) are developing differentiated capabilities to support the development of products and were crucial for the development of the COVID-19 vaccines. Companies including Aldeveron, TriLink, Lonza, CordenPharma, Cellonic and Acuitas all played important role, plus new entrants in segments like synthetic plasmid DNA (e.g., Touchlight and Anjarium).

Conclusion

As the field of oncology evolves with the discovery of more therapeutic targets, novel mechanisms of action, and more durable and efficacious treatments, companies need to consider how their pipelines can keep up with ongoing trends. While these therapeutics are relatively early stage in oncology, pipeline activity, investments and promise from the basic science all signal significant potential, which will be further enhanced as innovations in encapsulation technology enable more precise specific delivery.

COVID-19 vaccines were only the start; how will the transformation enabled by mRNA compare to that created by biologics, in oncology and beyond? Understanding the opportunities which can be unlocked, potential challenges, risks, and relevant tumor types for mRNA therapeutics will enable companies to unlock value for many stakeholders in this rapidly evolving space.

About ClearView Healthcare Partners

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***Pipeline intensity considers the total number of clinical trials from Phase 1 to Phase 3**

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