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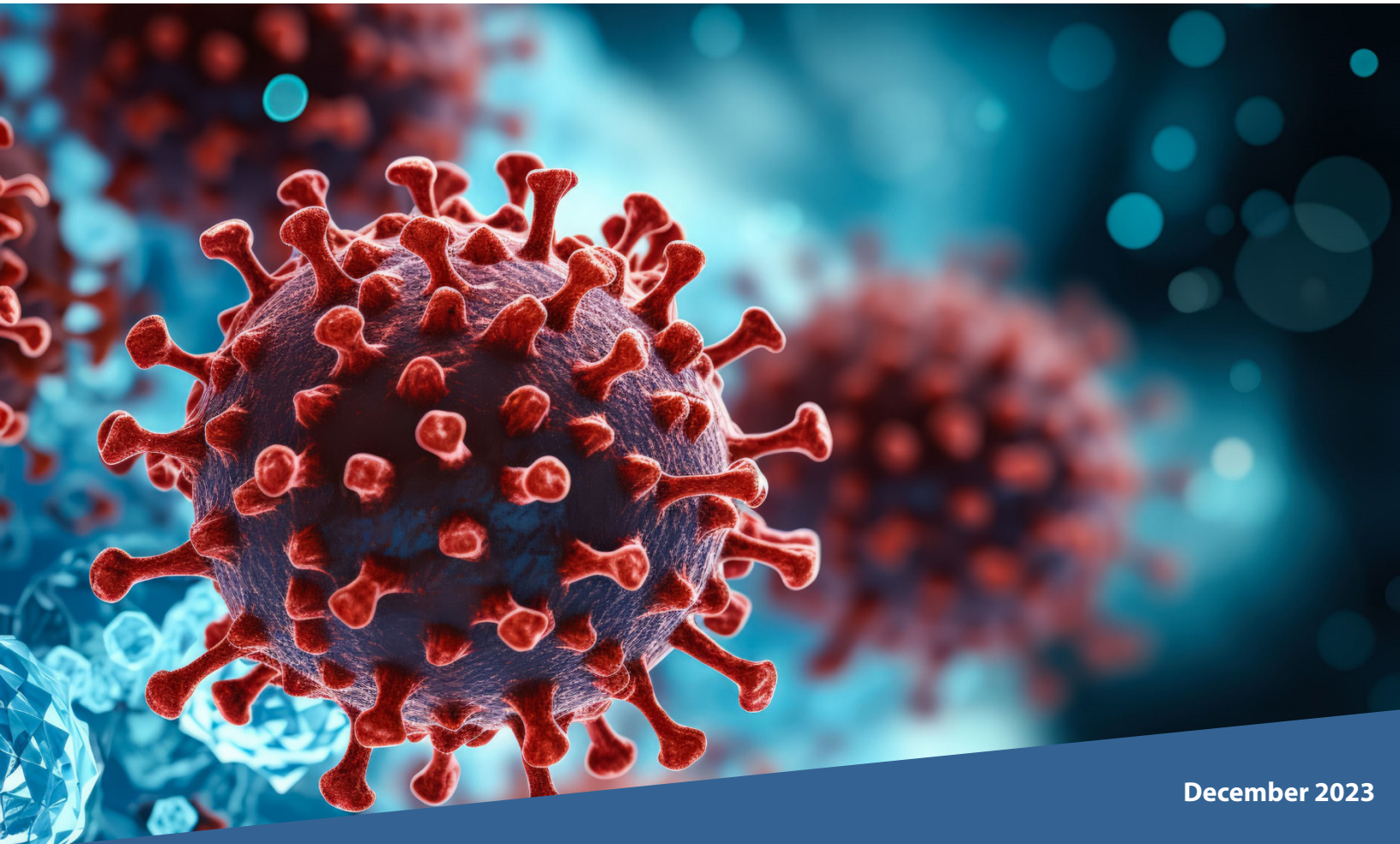
WHITE PAPER

Empowering Cancer Immunotherapy: Unleashing the Potential of NK Cell Therapies in Oncology

Nikki Aaron • James Lee • Keya Viswanathan • Jake McIntyre • Utkrisht Yadav • Jason Karas



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Introduction

Abstract

Cell therapies are becoming increasingly incorporated as late-line standards of care across relapsed/refractory oncology indications, with an expanding ability to improve outcomes for a diverse set of tumors and patient subgroups. As the next frontier of personalized and precision medicine continues to grow, **Natural Killer (NK) cell therapies offer the potential to penetrate untapped needs across a variety of cancers**. However, enthusiasm surrounding the opportunity offered by NK-based technologies has fluctuated over recent years. Several large pharma leaders have made significant early investments in the NK space, signaling potential for sizeable clinical and commercial opportunity. At the same time, emerging data from small biotechs at the forefront of NK innovation warrant a more critical perspective on the new technology. In mid-2023, Nkarta, a leading manufacturer of CAR-NK therapies, reported remission rates of acute myeloid leukemia (AML) patients treated with their lead asset that fell short of expectations based on earlier studies, resulting in an immediate drop in stock as investors became more wary of the asset's potential.[1] Today, the early development landscape of NK cell therapies is characterized by a similarly balanced sentiment of hope and skepticism. According to syndicated market research however, if clinical potential of NK cell therapies can be realized, **the future global market size of this therapeutic class is forecasted to reach heights of ~$5-6B by the 2030s**.[2]

While unlikely to evolve into frontline standard of care or displace CAR-Ts as they themselves move into earlier lines, NK cell therapies harness unique clinical value not offered by existing therapeutics to fulfill key unmet needs in cancer treatment today. Firstly, NK cell therapies have shown minimal risk of cytokine release syndrome (CRS), neurotoxicity and graft versus host disease (GvHD), which are all common severe adverse events associated with CAR-T cell therapies. Secondly, most NK cell therapies currently in development are allogeneic ("off-the-shelf"), which reduces long manufacturing time and production costs constraining broad uptake of current CAR-Ts. Lastly, while additional evidence is required, NK cell therapies and NK adjacent technologies may extend value beyond hematologic malignancies into solid tumors, assuming that adequate tumor infiltration and persistence in the solid tumor microenvironment (TME) can be demonstrated. NK cell therapy thus has the potential to transform the innate immune cell therapy landscape and find a niche in oncology that maximizes value to patients. **Biopharma leaders invested in cell therapy and/or oncology must continue to monitor the NK cell therapy space as near-term catalysts, if positive, are likely to attract heightened attention and trigger significant investments.**

Scope and Methodology

This report is designed to deliver an overarching assessment of the NK cell therapy space with a background on NK-based technology, current clinical development and ultimately, the value proposition NK cell therapies hold in order to equip readers with the necessary knowledge to drive informed decision-making and potential investment in the space. The findings in this white paper are accurate as of time of publication and based not only on secondary research of published literature but also primary market research with both key opinion leaders (hematology and medical oncologists) and industry experts. In the scope of this assessment, Trinity does not include pricing and market access (P&MA) or ex-U.S. development considerations but acknowledges the importance of such considerations in the eventual global commercialization of NK cell therapies.

[1] Halley, J. (2023, June 27). Why shares of Nkarta are slumping Tuesday. The Motley Fool. https://www.fool.com/investing/2023/06/27/why-shares-of- nkarta-are-slumping-tuesday/

[2] BCC Research. (2022). Natural Killer (NK) Cell Therapeutics Market - A Global and Regional Analysis: Focus on NK Cell Therapy Type, Indication, Country, Pipeline Analysis, and Competitive Landscape - Analysis and Forecast, 2022-2032. https://www.bccresearch.com

The Fundamentals of NK Cell Therapy

What are Natural Killer cells?

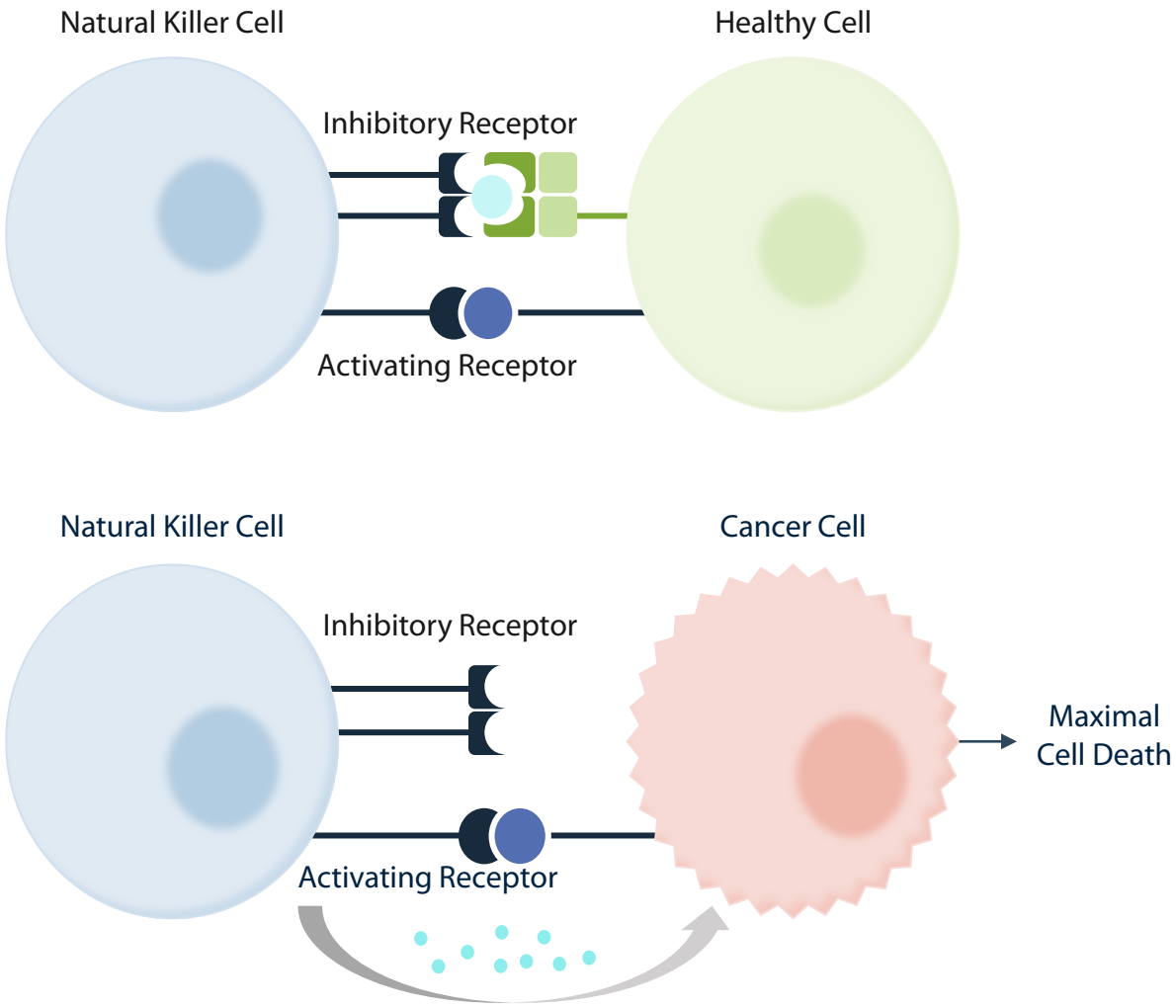


Figure 1 | Natural Killer (NK) cells play a crucial role in the immune system's defense against cancer by identifying and eliminating cancerous cells through their ability to induce apoptosis and release cytotoxic molecules.

In recent years, the development of cell therapies for oncology indications has rapidly expanded. Most notably, T cell therapies have successfully launched in hematologic malignancies, demonstrating promising efficacy and paving the way for additional cell therapies to succeed. Much like T cells, Natural Killer (NK) cells respond to the presence of pathogens to promote cell killing. However, unlike T cells, NK cells do not require previous exposure to an antigen and therefore respond through quicker mechanisms.

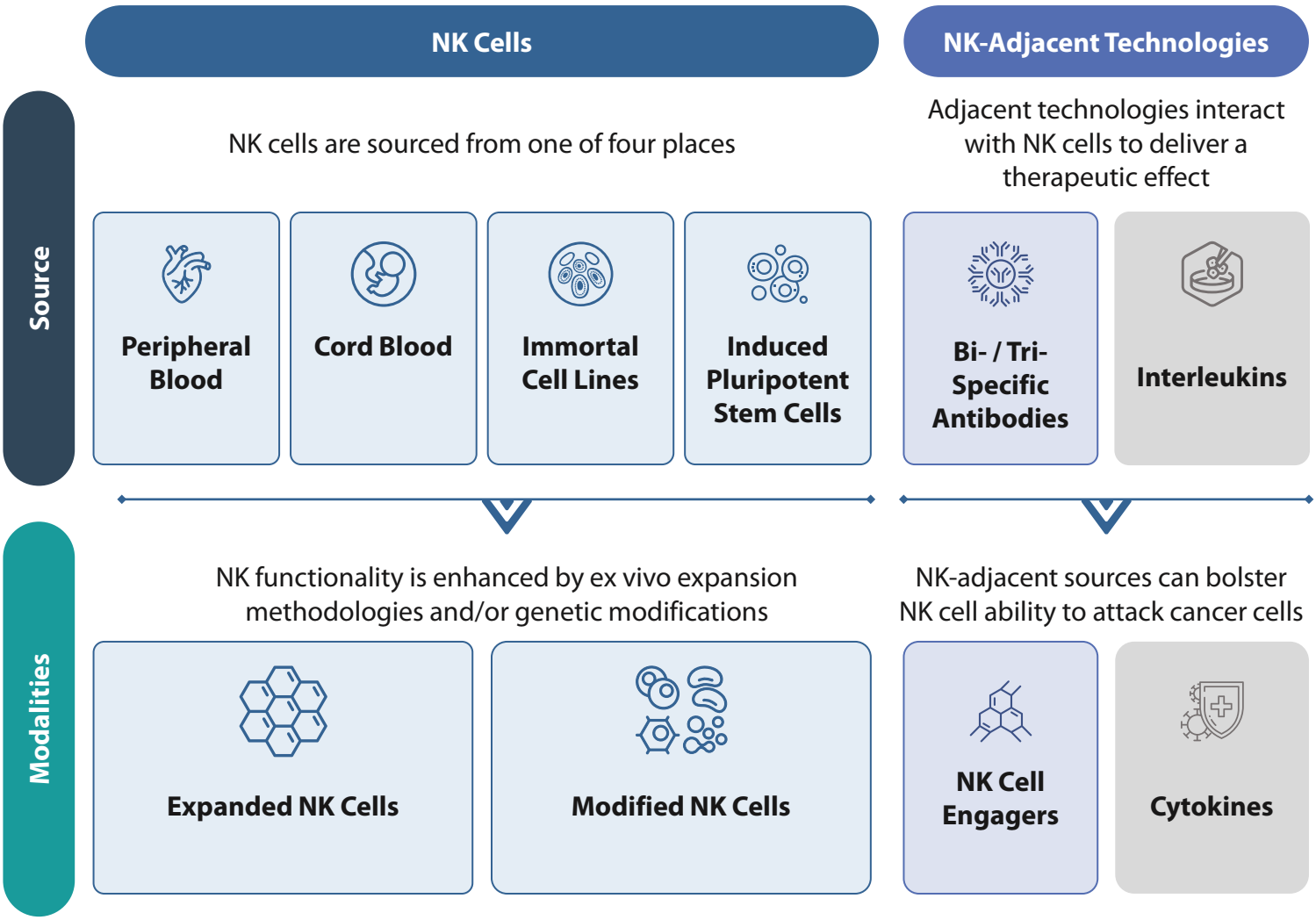


Figure 2 | NK cells can be derived from various sources, including peripheral blood, umbilical cord blood and pluripotent stem cells, and their therapeutic modalities encompass adoptive transfer, cytokine stimulation and genetic engineering to enhance their anti-cancer properties. Interleukins and cytokines are shown in gray because we are not focusing on characterizing them within this paper.

Given the nascency of NK cell therapies, researchers are still exploring how to best design this novel approach to promote safety as well as improved efficacy over existing standards of care. In doing so, NK cells have been obtained from a variety of sources for clinical use. The majority of NK cells for which we have seen early-stage data have been sourced from primary cells derived from donor peripheral blood or cord blood cells (PBNK or CBNK). Being that they originate from a smaller source, cord blood NK cells require the most amount of expansion. While large pools of peripheral blood NK cells are easier to obtain, key opinion leaders (KOLs) have noted concern that the maturity of PBNKs may make them more challenging to engineer and, ultimately, expect lower potency and more frequent re-dosing required to promote a significant response.

More recently, induced pluripotent stem cells (iPSCs) have been explored as a potential source in cell therapies, including NK cells. The process of turning a healthy donor cell into an iPSC and then transforming it into a desired NK cell requires additional time and resources during the manufacturing process. However, once formed, they provide a homogenous cell source that is relatively easy to expand without the use of feeder cells, more straightforward to engineer with modifications and can be cryopreserved. The introduction of iPSCs as a cell therapy source was initially met with resistance, as many KOLs believed that these cells would not behave the same as a proper NK cell and voiced concern over the potential for genetic drift. However, more recently, concerns have been assuaged by preclinical and early clinical data showing comparable efficacy across iPSCs, primary NK (PBNK/CBNK) cells and NK cell lines.

Though the value of NK cell therapies is largely believed to be their "off-the-shelf" potential as an allogeneic therapy, some scientists are exploring autologously sourced NK cells. The manufacturing process is longer and more costly, but KOLs believe that autologous NK cells may offer better persistence. With allogeneic NK cells, there is concern for patient rejection if the patient develops auto-antibodies from consistent re-dosing.

While the majority of cell therapies have been explored primarily in patients with hematological malignancies, NK cells are being explored as potential therapies for solid tumors, given their ability to evade heterogenous microenvironments. Furthermore, most NK cells in development have been genetically engineered to enhance anti-tumor activity and are therefore thought to improve overall efficacy. Of note, the most common modification to NK cells is the addition of a chimeric antigen receptor (CAR) that enables NK cells to recognize specific tumor-associated antigens, enhancing their ability to target cells of interest. Given the success of CAR-T and the familiarity of KOLs with the CAR modification, there are high expectations for this approach to be effective in NK cells.

NK Adjacent Technology

Researchers are simultaneously exploring alternative approaches to activate and modify NK cells for clinical use. Most notably, NK cell engagers (NKCEs), much like T cell engagers, are multifunctional antibodies that bring tumor cells and immune cells together to trigger a response. NKCEs are categorized as either bi- or tri-specific depending on the number of domains present that target specific tumor antigens (e.g., CD123 in AML) and NK cell receptors (e.g., CD16, NKp46). These molecules have the potential to be used as a monotherapy or in combination with other effective anti-cancer therapies, including NK cells. In addition, researchers have been exploring the use of cytokine administration in conjunction with existing treatment or NK cell therapy to promote NK activation. Of note, cytokines IL-2, IL-12 and IL-15 are expected to be directly involved in NK cell activity and are, therefore, the most likely candidates to boost immune response. Given recent setbacks observed in the pipeline of NK cell therapies (discussed below), these adjacent technologies may provide a more promising option to augment NK cell activity to achieve notable cytotoxicity.

Key Competitors in the NK Cell Space

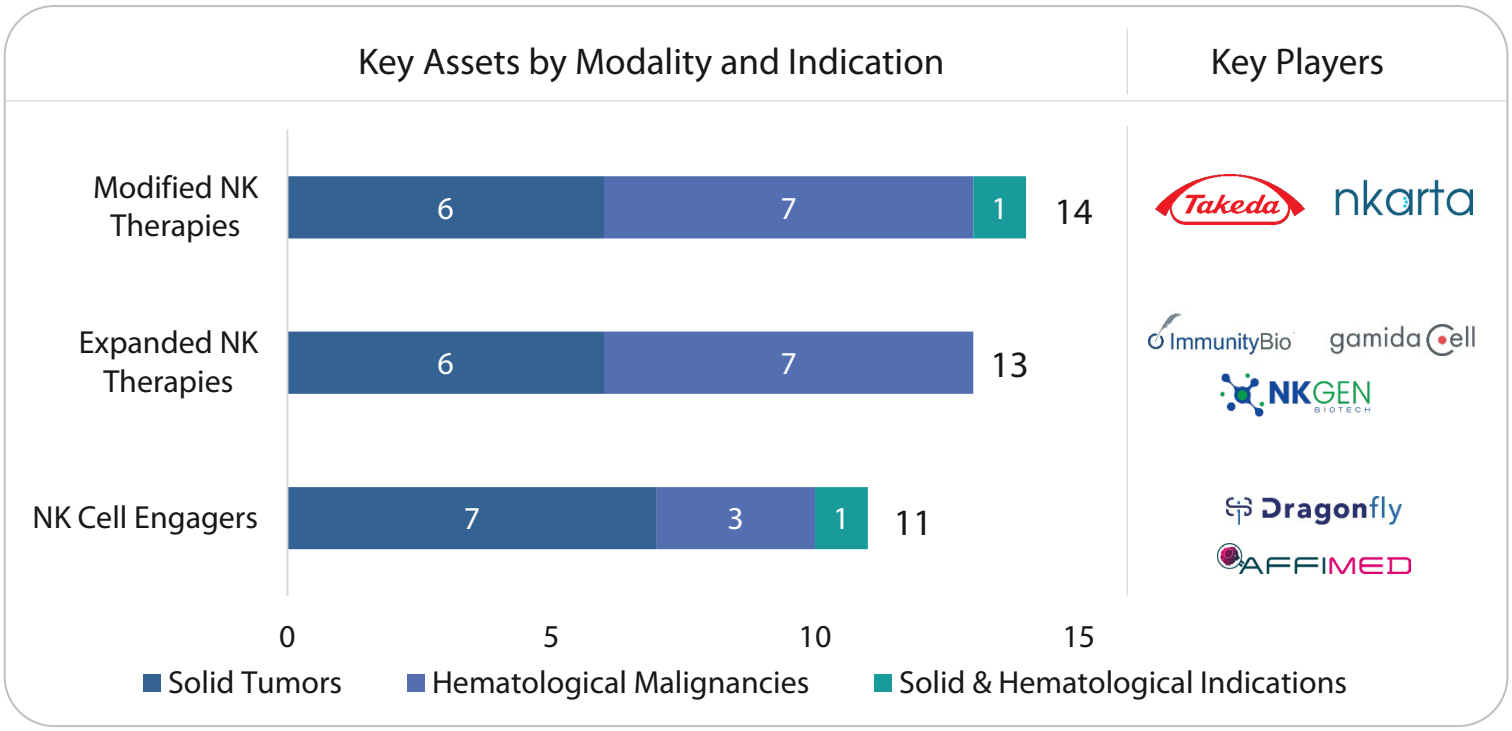


FIGURE 3 | The field of NK cell development is marked by intense competition among researchers and biotech companies striving to optimize manufacturing processes, enhance therapeutic efficacy and explore innovative genetic engineering approaches to unlock the full therapeutic potential of NK cells in cancer immunotherapy.

While the NK space is dominated by early-stage companies (Fate, Nkarta, Affimed, etc.), recent years have seen large biopharma companies take an active interest in NK-based approaches. Takeda's TAK-007, a CAR-modified NK therapy being co-developed with MD Anderson, showed impressive early clinical efficacy. Additionally, Sanofi's portfolio includes an allogeneic NK cell platform from its acquisition of Kiadis in late 2020 and numerous NK cell engagers through its partnership with Innate Pharma. Though BMS recently returned the rights to Dragonfly's IL-12 DF6002, the two continue to collaborate on six other TriNKET (NKCE) programs. Dragonfly's TriNKETs have also attracted partnerships with other large pharma players (Merck, AbbVie and Gilead).

Roughly forty percent of key assets in clinical development are modified NK therapies. Unsurprisingly, due to its success in T cell approaches, the CAR-modification strategy is employed by a majority of players. CAR-modified assets most commonly target CD-19, though other emerging targets include CD-22, HER2 and PD-1. Preliminary data from Takeda's TAK-007,[3] a CD-19 CAR-NK derived from cord-blood, in patients with NHL or CLL, and Nkarta's NKX101,[4] a CAR-NK targeting NKG2D, were both perceived to have promising results. On the other hand, Fate Therapeutics discontinued three modified NK projects (FT516, FT596, FT538) after a run of poor clinical outcomes. Other non-CAR modifications include CISH KO, as explored by Shoreline, Gamida and ONK along with CD38 KO from Fate, Gamida and ONK.

[3] Liu E, Marin D, Banerjee P, et al. (2020) Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. NEJM 382:545-553. doi: 10.1056/NEJMoa1910607

[4] https://ir.nkartatx.com/news-releases/news-release-details/nkarta-updates-clinical-progress-car-nk-cell-therapy-nkx101

Asset	TAK-007	NKX101
Manufacturer	Takeda	Nkarta
Technology	CD-19 CAR-NK	NKG2D CAR-NK
Clinical Trial	Phase I/II NHL or CLL (N = 11)	Phase I AML (N = 6)
Data	ORR 73% No CRS, neurotoxicity or GvHD	Response Rate: 67% CR/CRi

Table 1 | Key Modified NK Cell Data

A third of therapies in clinical development utilize the expanded NK cell approach. NKGen's autologous expanded NK cell treatment, SNK01, in combination with pembrolizumab showed an encouraging two-year survival rate vs. pembrolizumab monotherapy in NSCLC patients that failed prior front-line platinum therapy.[5] Recently presented at AACR and AHNS in June 2023, data from the proof-of-concept study of Immunity Bio's cytokine induced memory-like (CIML) NKs used alongside IL-15 superagonist N-803[6] showed signs of tumor regression in heavily pretreated HNSCC patients. Gamida Cell's GDA-201 demonstrated impressive efficacy in NHL patients.[7] Other key players with expanded NKs in their pipelines include Immunity Bio, Glycostem, Gaia Biosciences, Indapta and Deverra.

Asset	SNK01 + Pembrolizumab	GDA-201
Manufacturer	NKGen	Gamida Cell
Technology	Autologous NK Cells	Nam-enhanced allogeneic PB-NK Cells
Clinical Trial	Phase I/II NSCLC (N=20)	Phase I NHL (N=19)
Data	2-year survival 58% (vs.17% Pembrolizumab monotherapy)	ORR 74% (68% CR) mDOR 16 months

Table 2 | Key Expanded NK Cell Data

[5] Park HJ, Kim YM, Jung JS, et al. (2022) Two-year efficacy of SNK01 plus pembrolizumab for non-small cell lung cancer: Expanded observations from a phase I/IIa randomized controlled trial. Thorac. Cancer. 13(14):2050-2056. doi: 10.1111/1759-7714.14523

[6] https://immunitybio.com/phase-1-study-indicates-allogeneic-cytokine-induced-memory-like-natural-killer-cells-plus-n-803-may-induce-tumor-regression-in-advanced-head-and-neck-cancer-patients/

[7] https://investors.gamida-cell.com/news-releases/news-release-details/gamida-cell-reports-preliminary-data-phase-1-study-natural

Early clinical results from NK cell engagers (bi- and tri-specific) have been mixed. Affimed's EGFR-targeting NKCE, AFM24, being studied as monotherapy in EGFRm NSCLC patients, fell short of "formal continuation criteria for the cohort," leading Affimed to stop enrollment and shift focus to AFM24's trial in combination with PD-L1 inhibitor, Tecentriq. Affimed's other NKCE, AFM13, demonstrated disappointing phase 2 results as monotherapy in PTCL leaving the company to focus resources on AFM13 in combination with Artiva's allogeneic NK therapy AB-101. Prior clinical results of AFM13 complexed with cord-blood derived NK cells showed robust efficacy in heavily pre-treated CD30+ HL and NHL patients.[8] These findings are in line with NK cell KOL expectations that NKCEs will likely fare best when utilized as tools to enhance NK cell approaches.

Asset	AFM-13 + CB-NK
Manufacturer	Affimed
Technology	CD16A/CD30 Bispecific NKCE
Clinical Trial	Phase I/II CD30+ and NHL and HL (N=35)
Data	ORR 94% (CR 71%)

Table 3 | Key NKCE Data

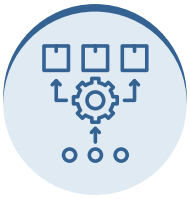
While some of the enthusiasm around NK cells has tempered given recent unimpressive data readouts, companies continue to move forward with development. KOLs believe the modified and NK cell-NKCE combination approaches could result in safer, efficacious alternatives to traditional cell therapies and expand potential utility to community settings. Upcoming catalysts from Nkarta (NKX101 AML data H1'24, NKX019 NHL data H2'24), Affimed (AB-101 + AFM13 cHL interim data H1'24), Takeda (TAK-007 updated data Q4'23-Q1'24) and others can help answer many of the questions surrounding NK cell efficacy, durability and overall potential.

[8]https://www.affimed.com/affimed-provides-updated-clinical-data-from-phase-1-2-study-of-afm13-precomplexed-with-cord-blood-derived-nk-cells-at-the-ash-2022-annual-meeting/

The Potential Value of NK Cell Therapy

What NK Cell Therapies Bring to the Table

Improved safety over CAR-Ts, enabling outpatient administration



Ease of manufacturing through off-the-shelf sourcing

Biologic potential across both hematologic and solid tumor malignancies

FIGURE 4 | Despite relatively limited late-stage clinical evidence generated to date, NK cell therapies and NK-adjacent technologies hold potential to offer value across three primary drivers.

I. Improved Safety:

NK cell therapies unleash cytotoxic power with reduced adverse events

> The field of NK cell therapies has a long way to go, but has high value in offering allogenic cell therapy options with low to no risk of CRS, no need to worry about GvHD, and minimal bridge time needed.
>
> **– Medical Oncologist, NK Cell Therapy KOL**

Potentially lethal systemic toxicities are the primary drawbacks associated with CAR-T cell therapies, in particular, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) that manifest as a result of the release of inflammatory cytokines at the time of CAR-T activation. In the pivotal trial leading to the FDA approval of the first approved CAR-T therapy, Kymriah (tisagenlecleucel), in 2017, approximately 46% and 13% of the relapsed/refractory B-cell ALL patients in the trial experienced Grade 3+ CRS and Grade 3 neurologic events, respectively. These adverse events are particularly dangerous as they lead to potential lethal manifestations, such as multiorgan failure, hypoxia, seizures or prolonged hospitalizations. On the other hand, early clinical data from current NK cell therapy trials demonstrate that risks of CRS or neurotoxicity are limited. For example, Fate Therapeutics' Phase I trial with its now-discontinued iPSC-derived NK cell therapy candidate, FT516, reported no dose-limiting toxicities, serious CRS, neurotoxicity or GvHD in B-cell lymphoma, despite minimal efficacy. Similarly, Nkarta's CAR-NK candidate, NKX101, was well-tolerated in its ongoing Phase 1 trial without any cases of Grade 3+ CRS or neurotoxicity in patients with R/R AML, although there were several cases of Grade 2 CRS/ICANs adverse events. Relative to toxicities observed with CAR-Ts however, KOLs believe that NK cell therapy is a potentially more tolerable therapeutic with a similar cytotoxic potential.

In addition to limited serious CRS and neurotoxicity, another safety-related advantage is that NK cell therapies show limited evidence of causing GvHD, in contrast to allogeneic-sourced T-cell therapies. This can be attributed to several factors, including limited major histocompatibility complex (MHC) antigen recognition by NK cells as well as lack of antigen specificity, that reduces the risk of off-target effects on healthy cells. A combination of these biological factors allows NK cell therapies to be administered with lower risk of immune rejection. Ultimately, NK cells stand out as having the potential to alleviate one of the most significant concerns associated with cell therapies today, assuming they are able to meet the otherwise high expectations set for them.

With their improved safety, patient access to NK cell therapies is expected to surpass that of CAR-Ts

> If successful, NKs would offer a cellular therapy solution that can be first, more easily administered in outpatient setting given negligible CRS and nonexistent neurotoxicity, and two, simplified access. Because of those two, they have greater potential to be adopted in the community setting.
>
> **– Medical Oncologist, KOL with prior NK trial involvement**

CAR-T therapies currently require in-patient administration in medical centers equipped to manage patients experiencing life-threatening complications. However, with their de-risked safety profile, NK cell therapies have potential to be primarily administered in outpatient settings. Enabling outpatient administration would reduce geographical and economic barriers and broaden access to patients, as the need for large-scale facilities typically required for CAR-T administration is diminished. In addition to broader physical access, patients who are currently ineligible or unfit for CAR-T therapies due to their toxicities may be suitable candidates for NK cell therapies. Assuming robust efficacy and superior safety is demonstrated in the future, NK therapies may competitively position themselves in oncology and other therapeutic areas to a broad population of patients. However, assuming success, KOLs also expect the regulatory landscape to evolve accordingly. KOLs note that "at some point, cellular therapy will be put on regulatory oversight to require certification to administer and will likely not easily be obtained … but right now, it's the wild west." Payer coverage and pricing of NK therapies, both factors critical to the successful launch and availability of these novel products, will emerge as top-of-mind for manufacturers as clinical development continues to progress.

II. Alleviating Manufacturing Complexity:

Off-the-shelf NK cells may enable broad patient access to scalable and renewable cell therapies

Current autologous T-cell therapies are costly and have a high manufacturing burden, due to the need for personalization and long bridge time from collection-to-infusion. While turnaround times are accelerating, the time-consuming process of autologous CAR-T manufacturing limits patient access to those who are often at risk of progressing beyond the point of eligibility or dying prior to infusion availability. On the other hand, NK cells are viable candidates for allogeneic expansion due to their antigen-independent tumor-killing mechanism and no need for strict human-leukocyte-antigens (HLA) matching. As an off-the-shelf option, NK cells solve the "one-donor, one-patient" limitation that plagues the current autologous cell therapy manufacturing process and enable large-scale manufacturing and distribution to patients.[9]

[9]Heipertz EL, Zynda ER, Stav-Noraas TE, Hungler AD, Boucher SE, Kaur N and Vemuri MC (2021) Current Perspectives on "Off-The-Shelf" Allogeneic NK and CAR-NK Cell Therapies. Front. Immunol. 12:732135. doi: 10.3389/fimmu.2021.732135

As one KOL mentioned, NK cell therapies would also not require the multi-week bridge time required with autologous CAR-T sourcing and manufacturing, widening access and expediting time-to-treatment for patients. The combination of these improvements to the cell therapy supply chain would downstream lead to lower COGS associated with NK cell therapies and enable manufacturing at scale. In particular, iPSC-derived NK cells could present as a renewable, scalable option that, as KOLs note, could alleviate the historical barriers associated with the development of cellular therapies like CAR-Ts. As the net cost of NK therapies decreases and manufacturing is streamlined, NK therapies could uniquely position themselves to payers and gain advantageous coverage to broad patient populations, unimpeded by many of the constraints limiting cell therapy uptake today.

III. Biologic Potential Across Both Hematologic and Solid Tumor Malignancies:

Engineered modifications of NK cells provide an opportunity for success in solid tumors and beyond

> There is potential for NK-based therapies in solid tumors because NK cells and NKCEs can penetrate the tumor microenvironment and identify cell surface receptors that T cells may not or have not been able to do so far. **– Medical Oncologist, NK Cell Therapy KOL**

Solid tumors have a complex microenvironment characterized by the presence of inhibitory immune cells that can suppress the immune system. Additionally, solid tumors can be made up of heterogeneous cancer cells, making it challenging to target through a single, directed therapy. As such, existing cell therapies have struggled for years to find success in treating solid tumors. However, KOLs believe that NK cells may have the best ability to identify tumor cells from non-tumorous cells in order to traffic to the site. However, the physical barriers of densely packed tissue and poor vascularization in solid tumors can impede infiltration of NK cells, inhibiting them from performing their proper function. Addressing these challenges requires a multifaceted approach, including strategies to improve tumor targeting.

To further improve response in both solid and hematologic tumors, modified NK cells provide an advantage over nascent NK cells by promoting antigen specificity. Furthermore, these modifications can help promote the metabolic function of NK cells and drive a downstream immune response. While the consensus seems clear that the most promising approach to NK cell therapy is likely through modifications, there is an additional challenge for scientists to select the best modification to achieve this success. In hematologic malignancies, the most common modification being explored is CAR CD-19s, while the solid tumor field is more varied in its approach. Though the existing modified NK landscape gives us an idea of what may be successful, KOLs note that it's hard to determine what the "magic bullet" will be given that NK cell therapy development is still in a nascent stage. Nonetheless, the absence of cell therapy in solid tumors highlights a gap that NK cells could potentially fill in the long-term, optimistic future.

NK cells may unlock greater potential as combination therapy

As a later addition to the cell therapy landscape, NK cells may struggle to displace existing therapies and to become adopted as standard of care, especially given the high efficacy bar set by currently approved CAR-Ts. However, there is sufficient biologic rationale for NK cells to be successful in combination therapy. In relapsed-refractory patients, later-line therapy options decline in efficacy and durability, leaving significant unmet need. NK cell therapy in combination with standard of care could help to improve overall immune response to existing treatments. Furthermore, later-line tumors are often characterized as more heterogenous and drug-resistant, making it difficult for NK cells to be effective as monotherapy. In addition to standard of care, NK cells may provide benefit as combination with NKCEs, especially in solid tumors, as NCKEs hold a greater potential to facilitate tumor penetration in a challenging microenvironment. NKCEs could initiate additional innate intrinsic NK cell activity to help override inhibitory factors present in the solid tumor environment.

Blockbuster opportunities exist in late-line hematologic oncology markets with high unmet need

NK cell therapy provides a niche opportunity, particularly among patients for which CAR-T is not a feasible option due to associated comorbidities, a low performance status, or adeno-virus antibodies that preclude its use. Additionally, as CAR-T moves into earlier lines of therapy across hematologic malignancies, NK cells could fill in as a second option for patients who still progress to later lines of therapy. As such, analysts predict that NK products could potentially achieve near-blockbuster status in relapsed/refractory hematologic cancers with high unmet need, such as Multiple Myeloma. TD Cowen analysts forecast global sales of two of Fate Therapeutics' NK assets in R/R 3L+ MM at $800M by 2035, assuming approval in the indication in the late 2020s. The analysts also highlight that the forecast is conservative, with upside potential in revenue if the Fate's products are able to move into even earlier lines of therapy.[10] These estimates resonate with other optimistic projections of the total NK cell therapy market, which forecast a $5B+ global NK cell market by the early 2030s.[11] If the biological potential and value drivers of NK cell therapies are able to be realized, successful NK cell pharma companies have the opportunity to establish themselves as emerging players in historically competitive markets.

NK Cell Therapy Headwinds and The Path Forward

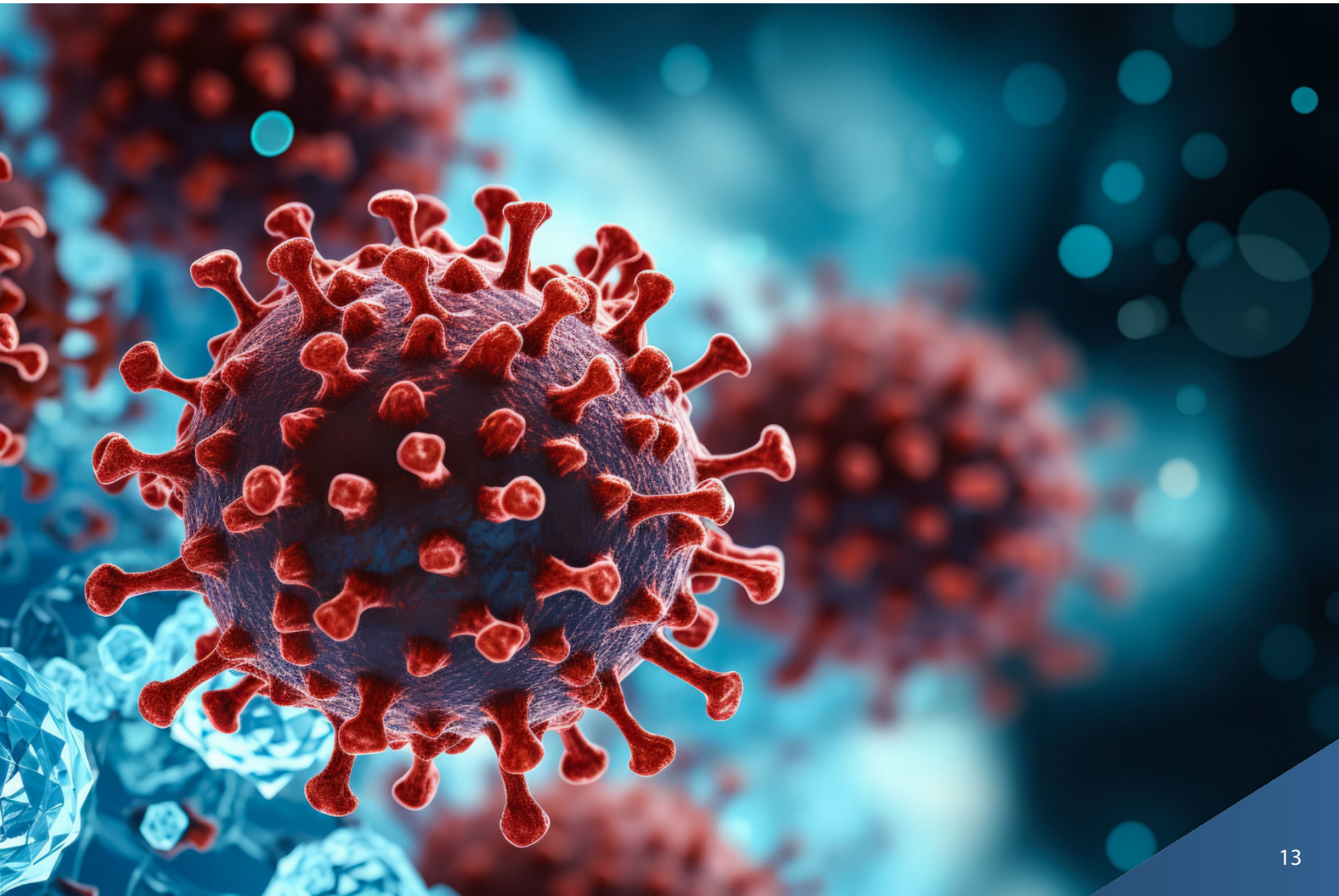
While NK-based therapies may offer a cheaper, less toxic, off-the-shelf option with broader combination applicability than existing cell-based therapies, there are a variety of barriers that have tempered commercial expectations, particularly in recent months. First of all, some of the challenges that originally plagued first-generation CAR-T launches have been at least partially surmounted, as supply infrastructure expands, manufacturing turnaround times decrease and physicians become more comfortable managing associated toxicities (e.g., CRS, neurotoxicity). NK value over CAR-T in these areas will not completely dissipate, but it is important to note that these differentiators may not be as salient as previously thought, particularly among academic centers with greater capabilities to support the administration of complex therapeutics and established familiarity with physicians.

[10]TD Cowen, "A Twist of Fate", September 22, 2023, p. 28, available from AlphaSource, accessed November 1, 2022

[11]BCC Research. (2022). Natural Killer (NK) Cell Therapeutics Market - A Global and Regional Analysis: Focus on NK Cell Therapy Type, Indication, Country, Pipeline Analysis, and Competitive Landscape - Analysis and Forecast, 2022-2032. https://www.bccresearch.com.

An additional hurdle for NK therapy entry into hematologic malignancies is the first mover advantage held by CAR-T and its corresponding entrenchment in relapsed/refractory standards of care over the course of the past four to six years. Peak share advantages for first launched therapeutics are well documented, and the perception of improved potency for autologous options over allogeneic will further bolster this advantage. While NK efficacy in large, pivotal-stage trials has not yet been released, KOLs express skepticism regarding the ability of NK to exceed CAR-T efficacy in head-to-head comparisons and harbor concerns around durability of NK response. These physicians largely regard NK data to date as promising early signals but lacking the scope necessary to fully ascertain key factors like duration of response.

It remains to be seen how impactful each of these headwinds to NK development may prove to be, with even some clinical and manufacturing experts in NK-based therapies still uncertain. However, in light of the data produced to date and perspectives from key opinion leaders, Trinity holds at this time that NK-based therapies are well-positioned to capitalize on a relapsed/refractory niche within hematologic and potential solid tumor malignancies. The greatest value of NK-based therapies will likely be in patients who are either relapsed/refractory, ineligible or have limited access to CAR-T, particularly in smaller community centers without the capabilities or infrastructure necessary to support CAR-T. Combination opportunities abound, both within oncology and across other therapeutic areas (e.g., Lupus, Alzheimer's), meaning that despite some early stage failures, NK-based technology is likely here to stay. And as additional data is released, the landscape will become increasingly clear, with a number of key catalysts anticipated in the coming months.



How Trinity Can Provide Support for Players in the NK Space

In addition to NK cell therapy, Trinity holds subject matter expertise and has led commercialization strategy development for a number of novel cell and gene-based therapies. By partnering our Cell & Gene Therapy leaders with functional centers of excellence, Trinity offers integrated, end-to-end solutions to manufacturers of complex novel therapeutics, including but not limited to the following:

Cell and Gene Therapy (CGT): Deep strategic expertise and analytical capabilities to support cell and gene therapy organizations across the value chain.

Evidence, Value, Access and Pricing (EVAP): Collaborating across functions to develop locally nuanced and comprehensively global strategies spanning evidence, value, access and pricing.

Dynamic Market Intelligence (DMI): Next-generation analytics and strategies to offer life sciences leaders an integrated approach to making informed decisions in a complex and challenging environment.

- Explore Trinity's recently launched Market Intelligence Dashboard.

Brand and Marketing Strategy (BMEx): Supporting marketing and brand strategy across all phases of the product lifecycle.

Launch Excellence (LEx): Partnering with clients to confidently develop, optimize and achieve commercialization readiness for a successful launch.

- Explore Trinity's recently launched Launch Accelerator.

Forecasting: Excellence in forecasting to elevate commercial decision-making across life sciences organizations.

Patient Centricity: Listening to the Voice of the Patient all the way from R&D through launch and beyond.

Patient Services: Data-driven insights, strategy and solutions to power patient-centric support service.

Authors

Nikki Aaron, PhD | Senior Consultant, Strategic Advisory

Nikki has experience across various therapeutic areas including oncology, immunology, metabolic diseases, and cell and gene therapy. She has partnered with clients on early-stage commercial and scientific prioritization, BD due diligence and strategic planning.

Nikki earned her PhD in Pharmacology from Columbia University.

James Lee | Senior Consultant, Strategic Advisory

James has worked with both large cap pharma and biotechs across a range of therapeutic areas, including oncology, nephrology, rare disease, and cell and gene therapy. His works spans opportunity assessments, portfolio prioritization strategy, commercial due diligence, and real-world advanced analytics.

James holds a Bachelor's Degree from Harvard University.

Keya Viswanathan | Senior Consultant, Strategic Advisory

Keya has experience across many therapeutic areas including oncology (with a key focus on cell-based therapies), vaccines, metabolic disease and rare disease. She has worked with clients on a range of projects including commercial due diligence, competitive analysis, opportunity assessments and market research.

Keya has a Bachelor's degree in Biology and Biotechnology from Tufts University.

Jake McIntyre | Senior Consultant, Strategic Advisory

Jake has over 3 years of consulting experience in the life sciences industry, focusing on all aspects of commercial strategy work from early-stage NPP (new product planning) to post-launch LCM (lifecycle management). He has led valuation/due diligence assessments, qualitative and quantitative market research, and go-to-market strategy development across both global biopharma companies and emerging biotech. His expertise spans both solid tumor and hematologic malignancies within oncology, rare/orphan diseases, inflammation/immunology, pulmonology, and genomic medicines across therapeutic areas.

Jake holds a Bachelor's Degree from Harvard University.

Utkrisht Yadav | Associate Principal, Strategic Advisory

UT has worked with global biopharmaceutical companies and emerging biopharma on projects including corporate and growth strategy, commercial opportunity assessments including forecasts and valuations, portfolio strategy, new product launch strategy, and brand and lifecycle growth strategy. His experience is spread across several therapeutic areas including, oncology, rare diseases, CNS/psychiatry, hematology, immunology, and women's health. UT also has deep experience in cell and gene therapies, including NK cell related technologies.

UT has an MSc in Biomedical Engineering from Carnegie Mellon University.

Jason Karas | Principal, Strategic Advisory

Jason has significant expertise in helping develop and execute growth strategies for biopharmaceutical companies, from portfolio management (e.g., business development strategies, therapy area expansion, R&D prioritization, and investment decisions) to clinical development strategy support (e.g., using real-world data to identify right patient segments, pipeline and competitive analysis) to commercialization (e.g., opportunity assessment and launch strategy). Jason brings over decade of corporate and product valuation experience in the life sciences, leading several global valuations across a range of technologies and therapeutic areas.

Jason holds an MBA in Entrepreneurial Studies from London Business School.

Glossary

AACR	American Association for Cancer Research
AHNS	American Head and Neck Society
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CAR	Chimeric Antigen Receptor
cHL	Classic Hodgkin's Lymphoma
CIML	Cytokine-Induced Memory Like
CLL	Chronic Lymphocytic Leukemia
COGS	Cost of Goods
CRS	Cytokine Release Syndrome
GvHD	Graft vs. Host Disease
HLA	Human Leukocyte Antigen
HNSCC	Head and Neck Squamous Cell Carcinoma
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
iPSC	Induced Pluripotent Stem Cell
KOL	Key Opinion Leader
MHC	Major Histocompatibility Complex
MM	Multiple Myeloma
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
NKCE	NK Cell Engager
NSCLC	Non-Small Cell Lung Cancer
PTCL	Peripheral T Cell Lymphoma
R/R	Relapsed/Refractory
TME	Tumor Microenvironment

About Trinity

Trinity is a trusted strategic commercialization partner, providing evidence-based solutions for the life sciences. With over 25 years of experience, Trinity is revolutionizing the commercial model by providing exceptional levels of service, powerful tools and data-driven insights. Trinity's range of products and solutions includes industry-leading benchmarking solutions, powered by TGaS Advisors. To learn more about how Trinity is elevating life sciences and driving evidence to action, visit trinitylifesciences.com.

For more information, please contact us at info@trinitylifesciences.com.