WHITE PAPER

Oncology platforms and the promise of a cure

How to cultivate your oncology pipeline

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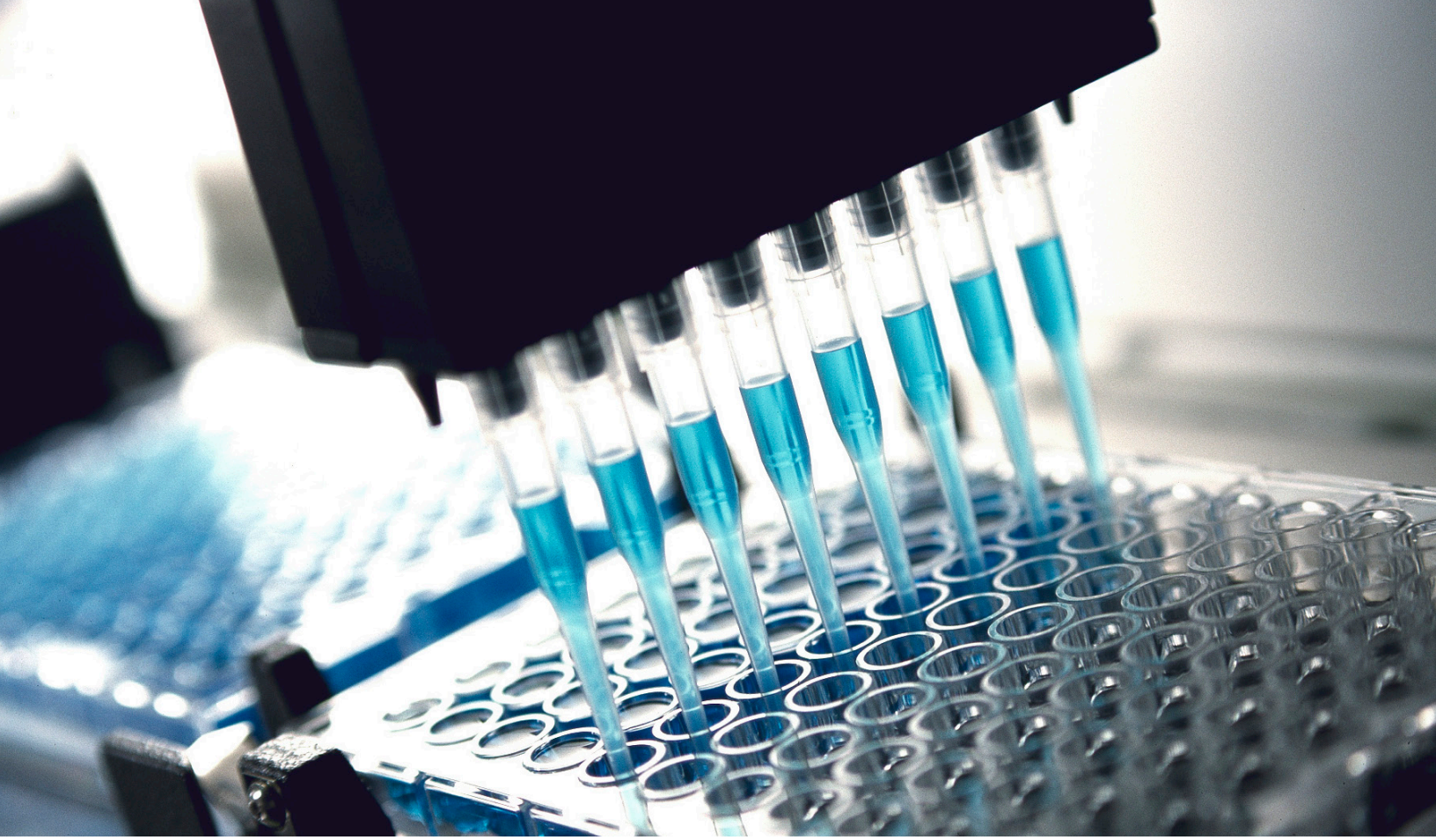


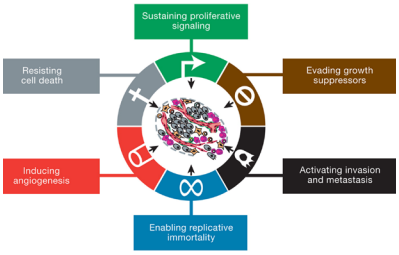
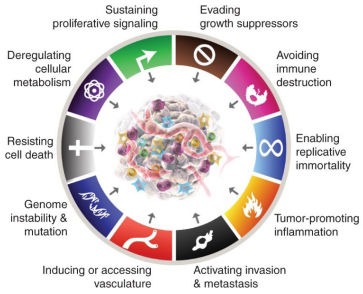
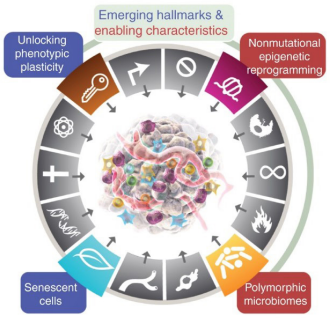
At ZS, the mantra of our oncology work is “Cure it.” Thanks to emerging therapeutic platforms, that mantra is becoming less of a mere aspiration and more of a reality, as this white paper will discuss. We will also describe implications for bringing these platforms to more patients.

Outcomes for people diagnosed with cancer have improved dramatically over the last several decades. Across cancers, five-year survival in the U.S. has increased from 50% between 1970 and 1977, to 67% in the period between 2007 and 2013, according to the National Cancer Institute’s Surveillance, Epidemiology and End Results program. Similarly, five-year survival in Europe has increased from 49% in the period between 1990 and 1999, to 56% in the period between 2010 and 2014, according to EUROCARE-3 and CONCORD-3 respectively. Despite trailing Europe and the U.S., China has also seen improvement in outcomes, moving from a 31% five-year survival rate in the period between 2003 and 2005, to 41% in the period between 2012 and 2015.

These improvements in five-year survival can be attributed to increasing awareness about causes of cancer, earlier screening leading to earlier detection and better understanding of tumor biology and pathophysiological drivers of cancer. Figure 1 below illustrates these advances in understanding through the lens of “cancer hallmarks.”

FIGURE 1

Hallmarks of cancer

2001	2011	2022
The Hallmarks of Cancer (2000)*	**Hallmarks of Cancer: New Dimensions (2022)#**	
Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57-70. doi: 10.1016/s0092-8674(00)81683-9. PMID: 10647931.	Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46. doi: 10.1158/2159-8290.CD-21-1059. PMID: 35022204.	
		
6 Hallmarks Hanahan and Weinberg outline six acquired capabilities of cancer: Self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis and evading apoptosis	**6 Hallmarks, 2 Emerging Hallmarks, 2 Enabling Characteristics** Two additional emerging hallmarks (deregulating cellular energetics, avoiding immune destruction) and two enabling characteristics (tumor-promoting inflammation, genome instability and mutation) are added to the original six hallmarks[1]	**8 Hallmarks, 2 Enabling Characteristics, additional 2 Emerging Hallmarks and 2 Enabling Characteristics** Additional proposed emerging hallmarks (unlocking phenotypic plasticity, senescent cells) and enabling characteristics (nonmutational epigenetic reprogramming, polymorphic microbiomes) join the two now validated hallmarks (deregulating cellular metabolism, avoiding immune destruction), two enabling characteristics (tumor-promoting inflammation, genome instability and mutation), and the six original hallmarks

*Reprinted from Cell, 2000, Volume 100, Issue 1, p. 57-70. Hanahahan, D and Weinberg RA., "The hallmarks of cancer", with permission from Elsevier

#Reprinted from Cancer Discovery, 2022, Volume 12,Issue 1, p. 31-46, Hanahan D., "Hallmarks of Cancer, New Dimensions", with permission from AACR.

1. Figure originally published in 2011. https://www.cell.com/cell/fulltext/S0092-8674(11)00127-9

A deeper understanding of cancer hallmarks and advances in science and engineering have set the stage for emerging therapeutic platforms that will continue to improve survival for patients diagnosed with cancer.

The rapid growth of therapeutic platforms

For the purposes of this white paper, we're defining a therapeutic platform as the confluence of scientific understanding and engineering technology. Through variations in the engineering process, a single therapeutic platform can address many different types of cancer. While the term "platform" refers to the engineering of the product itself, we will also discuss numerous "targets," which we define as the molecules involved in the growth, progression and spread of cancer that can be disrupted by a treatment. We believe the following platforms are the fastest growing in oncology:

1. **Cell and gene therapy.** The goal of cell therapies is to take a population of cells from a patient or donor and direct them to fight disease. At the time of publication in the first half of 2022, there were seven cell therapies approved in the U.S. for oncology indications: Kymriah, Yescarta, Tecartus, Breyanzi, Abecma, Carvykti and Provenge. There are more than 40 ongoing registrational trials for cell and gene therapies in oncology. Five years ago, Provenge was the only approved cell therapy and there were no approved chimeric antigen receptor T-cell (CAR-T) therapies.

2. **Tumor-agnostic development of precision medicine and immuno-oncology therapies.** As increasingly advanced diagnostic techniques identify commonalties between different tumor types, interest in developing therapies that can be applied across multiple tumor types is growing. At the time of publication, there were two precision medicine therapies, Vitrakvi and Rozlytrek, and two immuno-oncology therapies, Keytruda and Jemperli, approved in the U.S. for tumor-agnostic indications. Additionally, there were eight therapies with ongoing registrational tumor-agnostic trials. Five years ago, there were no approved tumor-agnostic therapies.

3. **Bispecific antibodies.** Building on the success of monoclonal antibodies (mAbs) directed at a single target, bispecifics can bind two molecular targets simultaneously. This can bring two target cells in close proximity, like a tumor cell and a T cell. This approach can also address multiple cell-surface targets concurrently, such as the epidermal growth factor receptor (EGFR) and MET. At the time of publication, there were three bispecific antibodies—Blincyto, Rybrevant and Kimmtrak—approved in the U.S. for oncology indications and more than 25 ongoing registrational trials. Five years ago, there were no bispecific antibodies approved in oncology.

4. **Antibody-drug conjugates (ADCs).** ADCs have actually been prescribed for patients with cancer for over a decade. The first FDA approval for an ADC was for Adcetris in August 2011. This platform utilizes a synthetic linker to join an antibody to a cytotoxic payload with the goal of delivering the cytotoxic medication directly to tumor cells, sparing normal cells. Currently there are 12 ADCs approved in the U.S. for oncology indications: Adcetris, Kadcyla, Besponsa, Mylotarg, Lumoxiti, Polivy, Padcev, Enhertu, Trodelvy, Blenrep, Zynlonta and Tivdak. Despite these approvals, only recently has the potentially transformative efficacy of ADCs begun to be realized. The DESTINY-Breast03 trial for Enhertu and POLARIX trial for Polivy have achieved outcomes capable of altering long-standing standards of care in previously treated HER2-positive metastatic breast cancer and previously untreated diffuse large B-cell lymphoma (DLBCL), respectively.

5. **Therapeutic cancer vaccines and oncolytic viruses.** This platform trains the adaptive immune system to recognize antigens unique to tumor cells as foreign and attack those cells. At the time of publication there were still only three approved therapies: Bacillus Calmette-Guerin, Provenge and Imlygic. While consistent with the state of the platform five years ago, advances in engineering technology, such as mRNA vaccine technology, have reignited development around this platform. There currently are 26 ongoing registrational trials for therapeutic cancer vaccines and oncolytic viruses.

6. **Radiopharmaceuticals.** This platform harnesses one of the long-standing cornerstones of oncology treatment. The latest generation, Lutathera and Pluvicto for example, use molecular targeting to facilitate precise delivery of radiation. To date, these molecular targets are becoming increasingly diverse in the 41 ongoing trials in radiopharmaceuticals, 12 of which are registrational.

Cell and gene therapy

Autologous CAR-T therapies have significantly advanced treatment of hematologic malignancies, achieving great depth of response and durability. Transformative efficacy is often not without side effects, however. Most CAR-T therapies have shown non-negligible rates of cytokine release syndrome (CRS) and neutropenia. Increased clinical and real-world experience with CAR-T therapies has led to mitigation strategies for key side effects. Key efficacy and tolerability data points for each FDA-approved CAR-T are summarized in Table 1 below.

TABLE 1

FDA-approved CAR-T therapy notable efficacy and tolerability endpoints

Product	Indication	Efficacy					Safety
		OS/PFS (%)	Response Rates (%)	mDOR (months)	CRS (Gr3+) (%)	NT(Gr3+) (%)	Other Gr3+
Provenge	Prostate cancer (n=341, efficacy; n=601, safety)	mOS – 25.8 mos	-	-	-	-	Back pain – 3%, Chills – 2%
Kymriah	B-cell precursor ALL in <25 years (n= 63, efficacy; n=68, safety)		CR/CRi-83%	DOR - Not reached (n=52)	49%	21%	Cytokine release syndrome – 49%, Febrile neutropenia – 37%
Yescarta	3L+ - BCL (n=101, efficacy; n=108, safety)		ORR - 72%	9.2 mos (n=73)	9%	31%	Febrile neutropenia – 31%, Encephalopathy – 29%
Kymriah	DLBCL in adults (n= 68, efficacy; n=106, safety)		ORR - 50%	Not estimable (n=34)	23%	18%	Infections – 25%, Cytokine release syndrome – 23%
Tecartus	MCL (n=60, efficacy; n=82, safety)		ORR - 87%	Not reached (n=60)	18%	37%	Hypotension - 27%, Infection - 24%, Encephalopathy – 24%
Breyanzi	B-cell lymphoma (n=192, efficacy; n=268, safety)		ORR - 73%	16.7 mos (n=141)	4%	12%	Infections – 16%, Encephalopathy – 9%
Yescarta	3L+ FL (n=81, efficacy; n=146, safety)		ORR - 91%	Not estimable (n=74)	8%	-	Febrile neutropenia – 41%, Encephalopathy – 16%
Abecma	Multiple myeloma (n=100, efficacy; n=127, safety)		ORR - 72%	11 mos (n=72)	9%	4%	Febrile neutropenia – 16%, Infections – 15%
Tecartus	B-ALL (n=54, efficacy; n=78, safety)		CR - 65%	DOR – 13.6 mos (n=54)	26%	35%	Fever – 38%, Febrile neutropenia – 35%,
Carvykti	Multiple myeloma (n=97, efficacy; n=97, safety)		ORR - 98%	21.8 mos (n=97)	5%	11%	Infections – 17%, Pneumonia – 11%
Yescarta	2L - BCL (n=180, efficacy; n=168, safety)	EFS - 60% at 8.3 mos PFS –52% at 14.9 mos	ORR - 83%	-	9%	25%	Febrile neutropenia – 31%, Encephalopathy – 18%

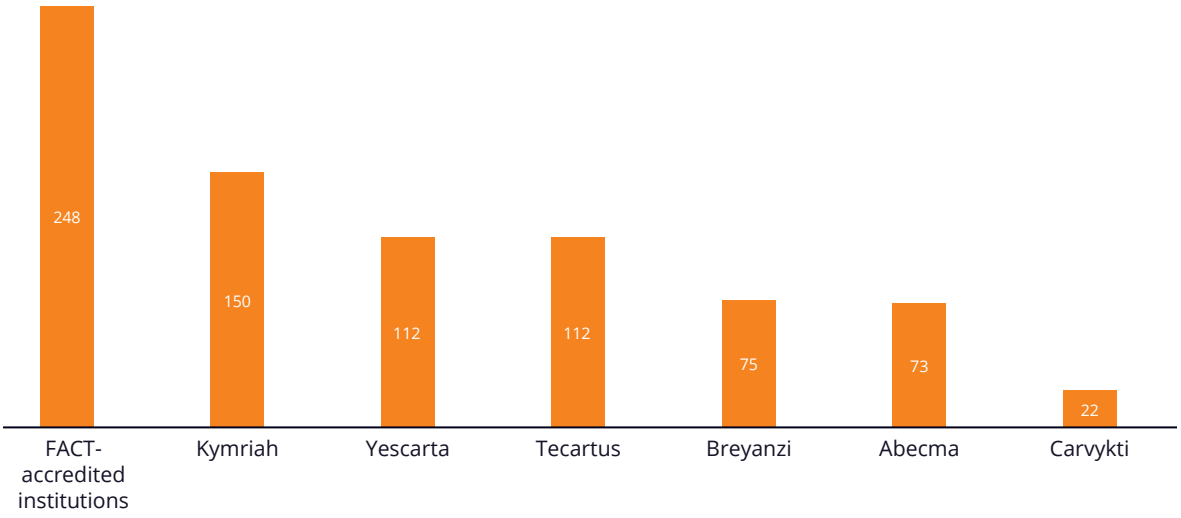
Abbreviations:
mDOR – Median duration of response OS – Overall survival, mOS – Median overall survival PFS – Progression-free survival, ORR – Overall response rate, DOR – Duration of remission, EFS – Event free survival, DRR - Durable response rate, CR – Complete response, CRS - Cytokine release syndrome, NT - Neurologic toxicities, ALL - Acute lymphoblastic leukemia, FL – Follicular lymphoma, BCL - B-cell lymphoma, LBCL - Large B-cell lymphoma, MCL – Mantle cell lymphoma, eff – Efficacy, saf – Safety, CR – Complete response, CRi - Complete remission with incomplete blood count recovery, mos - Months

Sources:
Abecma - www.fda.gov/media/147055/download
Breyanzi - www.fda.gov/media/145711/download
Carvykti - www.fda.gov/media/156560/download
Kymriah - https://www.fda.gov/media/107296/download
Tecartus - www.fda.gov/media/140409/download
Yescarta - https://www.fda.gov/media/108377/download
Provenge - www.fda.gov/media/78511/download

Of course, the complexity of CAR-T therapy currently necessitates delivery in academic hospitals and often in an inpatient setting. As collated in Figure 2 below, there are over 200 existing U.S. treatment centers accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). In addition to FACT certification, there are 20-150 centers of excellence for individual therapies.

FIGURE 2

Number of hospitals authorized to deliver FDA-approved CAR-T therapies



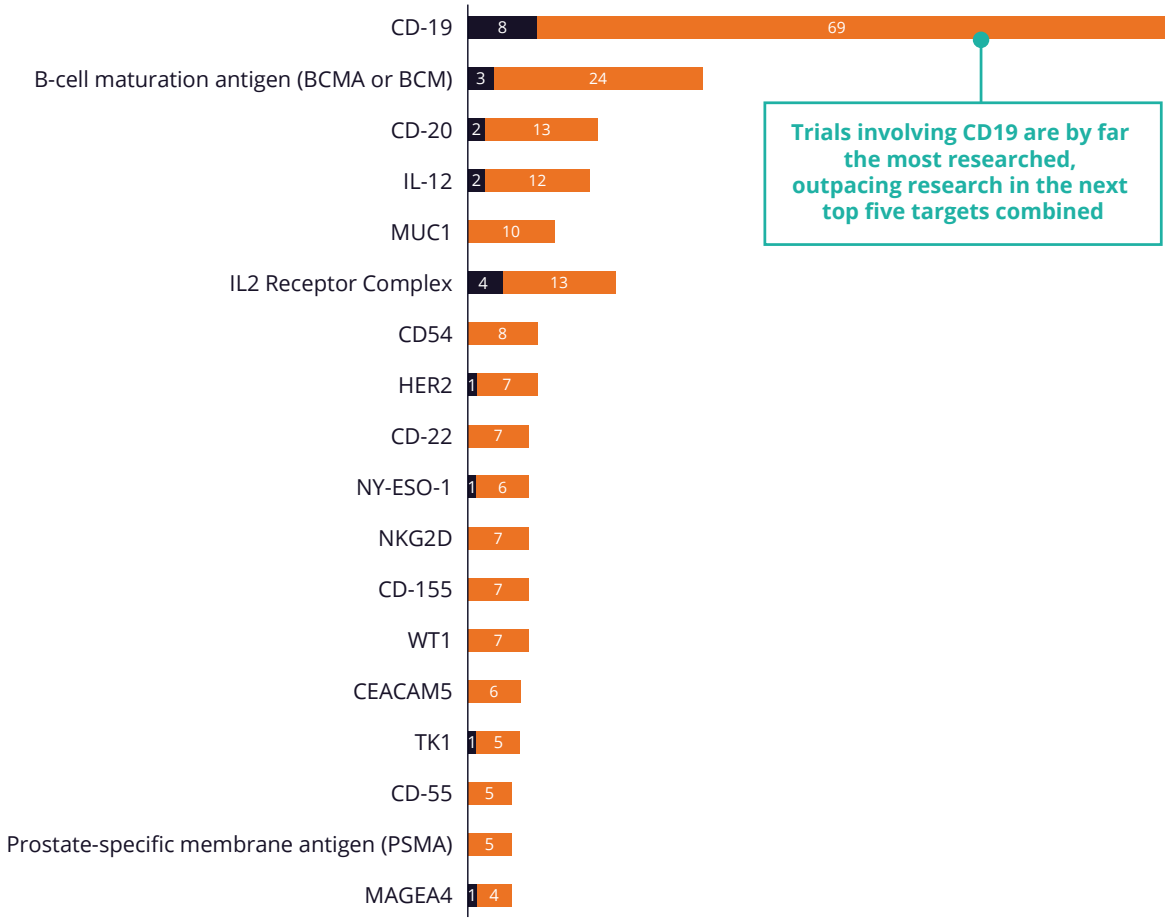
Despite those footprints, and the fact that there are 10,000 to 15,000 patients in the U.S. with relapsed or refractory (R/R) DLBCL, our estimates indicate that only about 25% of this population is treated with one of the three approved autologous therapies: Kymriah, Breyanzi and Yescarta. There are major access issues for eligible patients. Expansion into the outpatient setting and especially into community hospitals could expand the eligible CAR-T therapy patient pool to over 100,000 patients in the U.S.

One method of improving access to cell therapies and moving them to the outpatient setting would require a change in the approach to CAR-T sourcing and engineering. Shifting to allogeneic cells from healthy donors, coupled with gene editing technologies like CRISPR, can create an "off-the-shelf" CAR-T. By eliminating the need for apheresis, allogeneic cell therapies could be more accessible. Despite the promise of allogeneic cell therapies, roughly 80% of ongoing cell therapy trials are for autologous therapies, while the remaining 20% are for allogeneic therapies.

Autologous CAR-T therapies currently approved by the FDA focus on CD19 and BCMA, targets ubiquitously expressed in B-cell malignancies and multiple myeloma, respectively. As might be expected, clinical development of cell and gene therapies, summarized in Figure 3 below, indexes heavily on those targets. But common hematological targets such as CD20 and even emerging solid tumor targets like MUC1, NY-ESO-1 and MAGE-A4 are also represented.

FIGURE 3

Cell therapy trials summarized by antigen/target



As this platform evolves, we see several implications for the oncology pipeline:

- Future cell therapies will need to be better tolerated and more readily available. While processes to mitigate autologous CAR-T therapy side effects and improved turn-around times are on the horizon, allogeneic therapies may help address some of these unmet needs. While allogeneic cell therapies are purportedly easier to deliver and potentially quite tolerable, manufacturers of these therapies will still need to collaborate closely with hospitals to establish management protocols. This is even more important for hospitals without prior CAR-T experience.
- When considering how to shift cell therapies into earlier lines of treatment, manufacturers should prioritize opportunities to disrupt standards of care predicated on long, continuous durations of treatment. Treatment-naïve multiple myeloma and chronic lymphocytic leukemia are good examples currently.
- As real-world evidence emerges from patients receiving the first generation of CAR-Ts, we know that some patients will relapse after receiving them. One-year CAR-T relapse rates are reportedly as high as 57% for patients with R/R DLBCL. Characterizing the population of non-responders or short responders is necessary to identify optimal sequencing for these patients and addressing unmet need.

Tumor-agnostic development of precision medicine and immuno-oncology therapies

The understanding of commonalities in tumor biology and cancer hallmarks across tumors has enabled development of therapies with efficacy across tumors. The growing rate of next-generation sequencing (NGS) has also aided this trend by helping oncologists have a more complete and unique profile of cancer for more of their patients. For example, NGS testing in metastatic non-small cell lung cancer (NSCLC) has grown from less than 1% in 2011 to greater than 45% in 2019. Similarly, NGS testing in metastatic colorectal cancer (CRC) has grown from less than 1% to greater than 35% in the same time period. We're also seeing public entities like the National Cancer Institute investing in public-private partnerships such as the NCI-MATCH program to aid development of tumor-agnostic therapies.

Thus far, four therapies have been approved across five tumor-agnostic indications, which are summarized below in Table 2.

TABLE 2

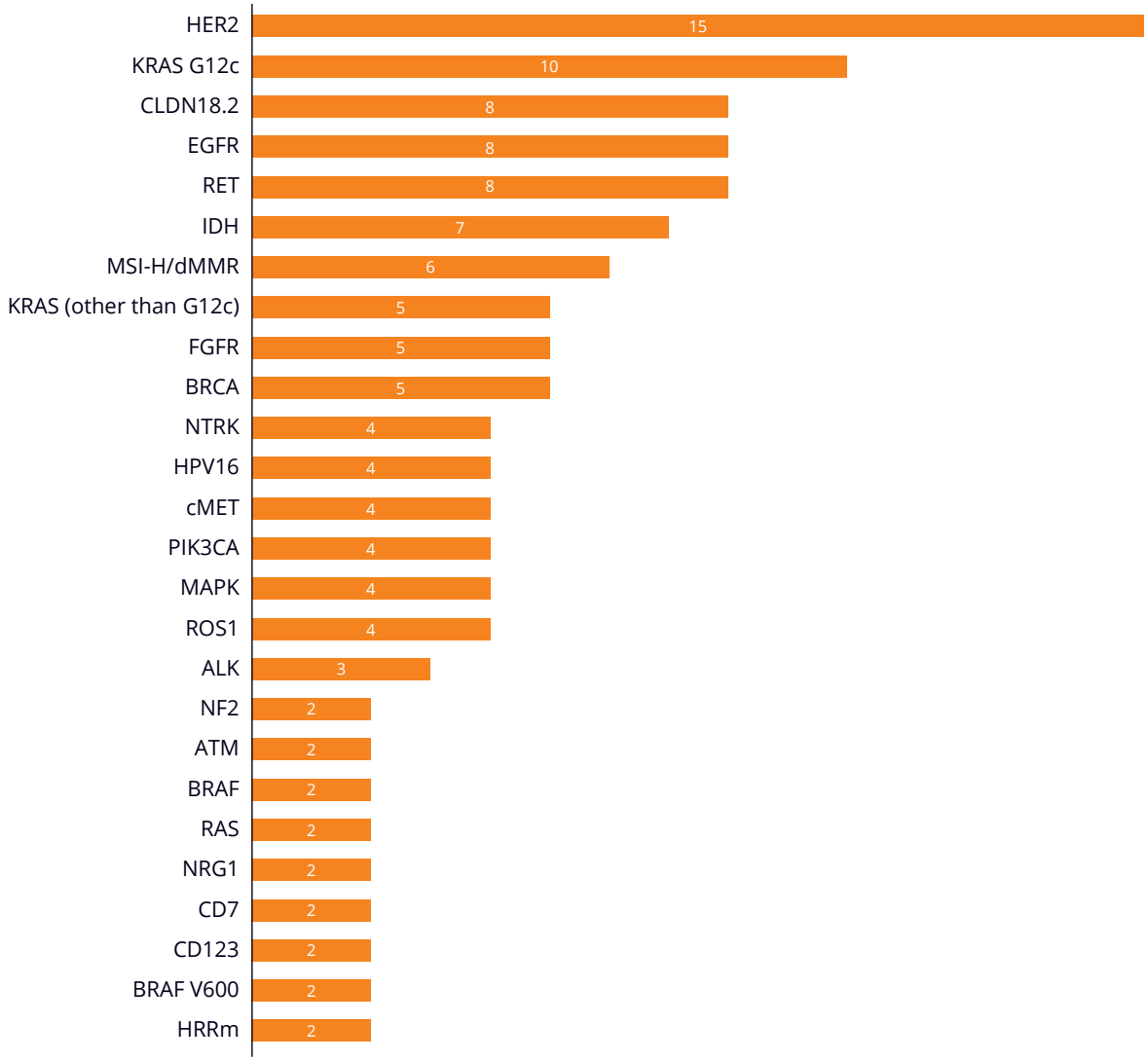
FDA-approved tumor-agnostic indications

Therapy	Indication/biomarker	NCT ID(s)	Date of FDA approval
Keytruda (pembrolizumab)	MSI-H or dMMR solid tumors	NCT01876511, NCT02460198, NCT01848834, NCT02054806, NCT02628067	5/23/2017 (Accelerated)
Vitrakvi (larotrectinib)	NTRK+ solid tumors	NCT02122913, NCT02637687, NCT02576431	11/26/2018 (Accelerated)
Rozlytrek (entrectinib)	NTRK+ solid tumors	NCT02097810, NCT02568267	8/15/2019 (Accelerated)
Keytruda (pembrolizumab)	TMB-H solid tumors	NCT02628067	6/16/2020 (Accelerated)
Jemperli (dostarlimab)	dMMR solid tumors	NCT02715284	8/18/2021 (Accelerated)

Looking to the future, this platform appears set for growth with eight therapies. Tipifarnib, envafolimab, tislelizumab, zanidatamab, serplulimab, rucaparib, seribantumab and ABI-009 are in registrational trials for tumor-agnostic indications. These therapies address eight distinct biomarkers, including HRAS, dMMR/MSI-H, HER2, HRRm, NRG1 and TSC1/TSC2, respectively. Among registrational and pre-registrational trials, there are over 100 tumor-agnostic trials across a wide range of targets summarized below in Figure 4.

FIGURE 4

Tumor-agnostic trials summarized by target or biomarker



Targets approved across multiple tumor types, or with known implications in multiple tumor types, such as HER2, KRAS G12c, EGFR, RET and IDH are not surprises. The target CLDN18.2 is interesting. There currently are no approved therapies, but there is substantial pre-registrational tumor-agnostic activity.

We see several implications for incorporating tumor-agnostic development into the oncology pipeline:

- Prior to biomarker selection for a tumor-agnostic trial, researchers should robustly interrogate the literature on a biomarker and its associated pathways to understand the full extent of applications. This approach may also yield better understanding of potential mechanisms of escape or resistance, which has implications for next-generation targeted therapies or combination regimens.
- Therapies targeted to a specific biomarker should start clinical development with basket trials to understand efficacy signals across multiple tumor types concurrently. All therapies currently approved for tumor-agnostic indications either started as a phase I evaluation with basket trials or were used in a phase I basket trial as part of the registrational evidence package.
- Manufacturers should evaluate the strategic implications of speed to market and focus within individual tumor types, versus the broad applicability of a tumor-agnostic approval.
  - Keytruda is an interesting case here, with its MSI-H tumor-agnostic indication complemented by indications specific to advanced or metastatic MSI-H colorectal cancer (CRC) and previously treated (in any setting) advanced MSI-H/dMMR endometrial cancer (EC). This approach demonstrates particular focus on tumor types with among the highest incidence of MSI-H/dMMR, and that both CRC and EC can potentially be treated earlier.
- For assets already approved for individual tumor types, manufacturers should seek public-private partnerships, such as NCI-MATCH to explore tumor-agnostic potential.

Bispecific antibodies

Bispecific antibodies approved to date have taken two different approaches:

- T-cell engagement and activation via a CD3 moiety, paired with an antibody or molecule to recognize a tumor antigen, such as Blincyto with CD19 molecule and Kimmtrak with a gp100 peptide.
- Addressing multiple mechanisms of tumor growth in a single therapy, such as with Rybrevant via concurrent antagonism of EGFR and MET receptors.

Both approaches are seeing extensive registrational clinical development, as detailed in Table 3 below.

TABLE 3

Bispecific antibodies in registrational clinical trials

Bispecifics containing CD3 or otherwise engaging immune cells	Bispecifics addressing multiple targets (not CD3)
Blincyto (CD19xCD3)	Rybrevant (EGFRxMET)
Mosunetuzumab (CD20xCD3)	Zanidatamab (HER2xHER2 – different domains)
Odronextamab (CD20xCD3)	Anbenitamab (HER2xHER2 – different domains)
Glofitamab (CD20xCD3)	Erfonrilimab (PD-L1xCTLA-4)
Epcoritamab (CD20xCD3)	Cadonilimab (PD-1xCTLA-4)
Elranatamab (BCMAxCD3)	SI-B001 (EGFRxHER3)
Teclistamab (BCMAxCD3)	Navicixizumab (DLL4xVEGF)
REGN5458 (BCMAxCD3)	AK112 (PD-1xVEGF)
Flotetuzumab (CD123xCD3)	
AFM13 (CD30xCD16A – Engages NK cells rather than T cells)	

The modular nature of engineering antibodies designed for either of these approaches affords great flexibility in addressing a wide variety of tumor types, as evidenced in Figure 5 below.

FIGURE 5

Bispecific antibody trials by tumor type

The notion of combination therapy involving bispecific antibodies is also attracting interest given the exciting potential to address three or more mechanisms with a single regimen. About 70% of bispecific registrational trials are actually combination trials. Across registrational and pre-registrational trials, that proportion drops to 40%, owing to earlier-phase and proof-of-concept trials more often testing bispecifics as monotherapies.

Trispecific antibodies push the envelope further, hypothetically enhancing efficacy relative to bispecific T-cell engagers via costimulation of T cells (for example, through CD28 engagement). Development of trispecific antibodies, such as HPN-217, CC-96191 and SAR443215, are still largely in pre-registrational phases, however.

As this platform evolves, we see several implications for the oncology pipeline:

- When developing immune cell engager bispecifics, especially T-cell engagers, it is critical to consider the amenity of the target tumor to immuno-oncology approaches. This means assessing characteristics like tumor-infiltrating lymphocyte presence and historical efficacy benchmarks for checkpoint inhibitors.
- When developing bispecifics addressing multiple cell-surface targets, those targets need to co-locate—either on a single tumor cell, as with EGFR and MET, or between an immune cell and tumor cell, as with PD-1/PD-L1 and CTLA-4—to ensure the bispecific will be able to address both targets.
- When composing combination concepts, prioritize the idea of additive efficacy through each component of the combination over synergy. Emerging research is demonstrating that efficacy of combinations—immune-oncology combinations in particular—may be predicated more on addition (i.e., 1+1=2) than synergy (i.e., 1+1>2).

ADCs

ADCs use mAbs to deliver cytotoxic payloads directly to tumors. These two components are covalently bound via a linker and administered as an infusion. To be clinically successful, ADCs must be designed with two primary factors in mind:

- The mAb must be sufficiently specific to minimize off-target delivery of the cytotoxic compound. Conversely, the target must be accessible to circulating mAbs.
- The cytotoxic payload must be stable, hydrophilic, potent and not susceptible to tumoral resistance mechanisms.

This platform has gone through several evolutions since the early 2000s, with current ADCs benefitting from advancements in joining the payload to the mAb (site-specific conjugation) and improved drug antibody ratio resulting in more homogenous molecules and consistent behavior in vivo. These advancements translated to substantial clinical benefit in the Destiny-Breast03 trial for Enhertu and POLARIX trial for Polivy.

With an eye on broadening the reach of ADCs, 234 clinical trials are currently underway, representing a diverse set of tumor types (Figure 6) and targets (Figure 7). Many trials are focused on NSCLC and breast cancer and, accordingly, HER2 and TROP2 targets.

FIGURE 6

Antibody-drug conjugate trials by tumor type

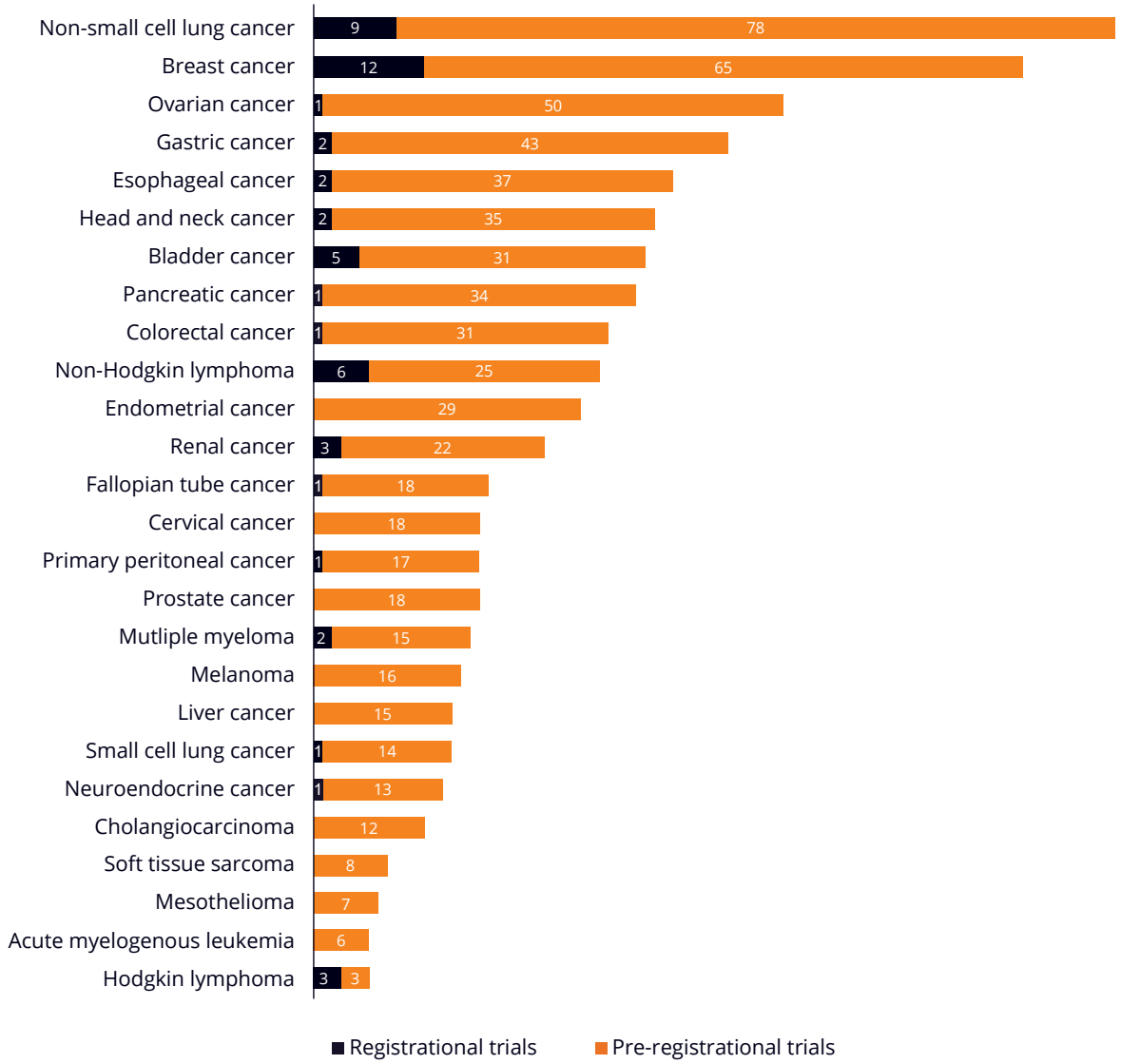
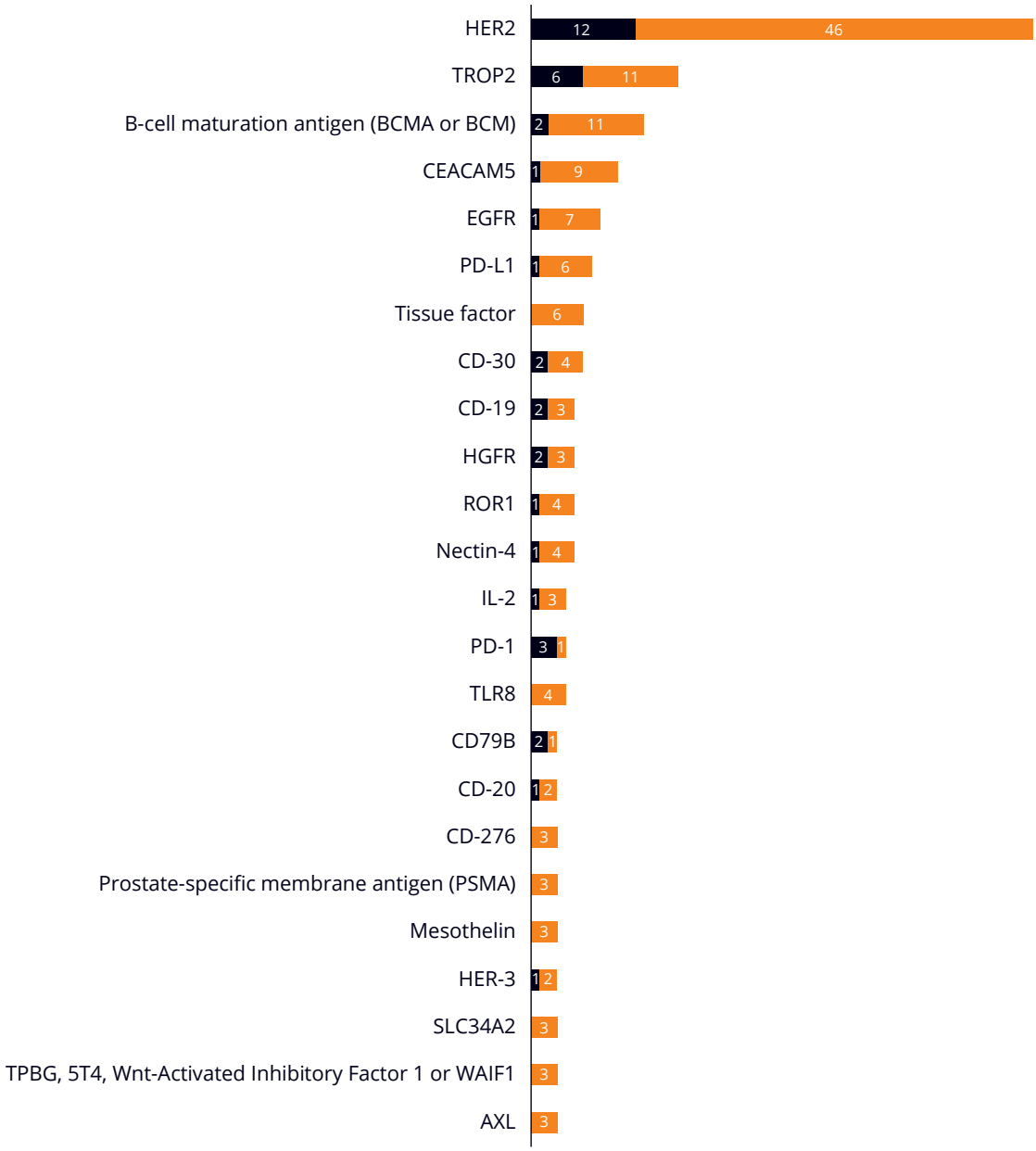


FIGURE 7

Antibody-drug conjugate trials summarized by target



Interestingly, of the 234 ADC trials, 157 are investigating the ADC as a monotherapy and 77 are studying the ADC in combination.

As this platform evolves, we see several implications for the oncology pipeline:

- ADC linker stability can still be improved. Even recently approved ADCs have non-negligible side effects, so improving linker stability can lead to more tolerable ADCs.
- ADC binding and internalization can be improved. This is an active area of pre-clinical research. For example, using a bispecific approach to bridge the prolactin and HER2 receptors has shown improved internalization of HER2 ADCs.
- Pursuing combination approaches with ADCs may help mitigate mechanisms of resistance or escape. This is the principle behind the Blenrep and gamma-secretase inhibitor combination trial NCT04126200.

Therapeutic cancer vaccines and oncolytic viruses

To date, therapeutic cancer vaccines and oncolytic viruses have seen relatively targeted clinical success and modest commercial success as detailed in Table 4 below.

TABLE 4

FDA-approved cancer vaccines/oncolytic viruses

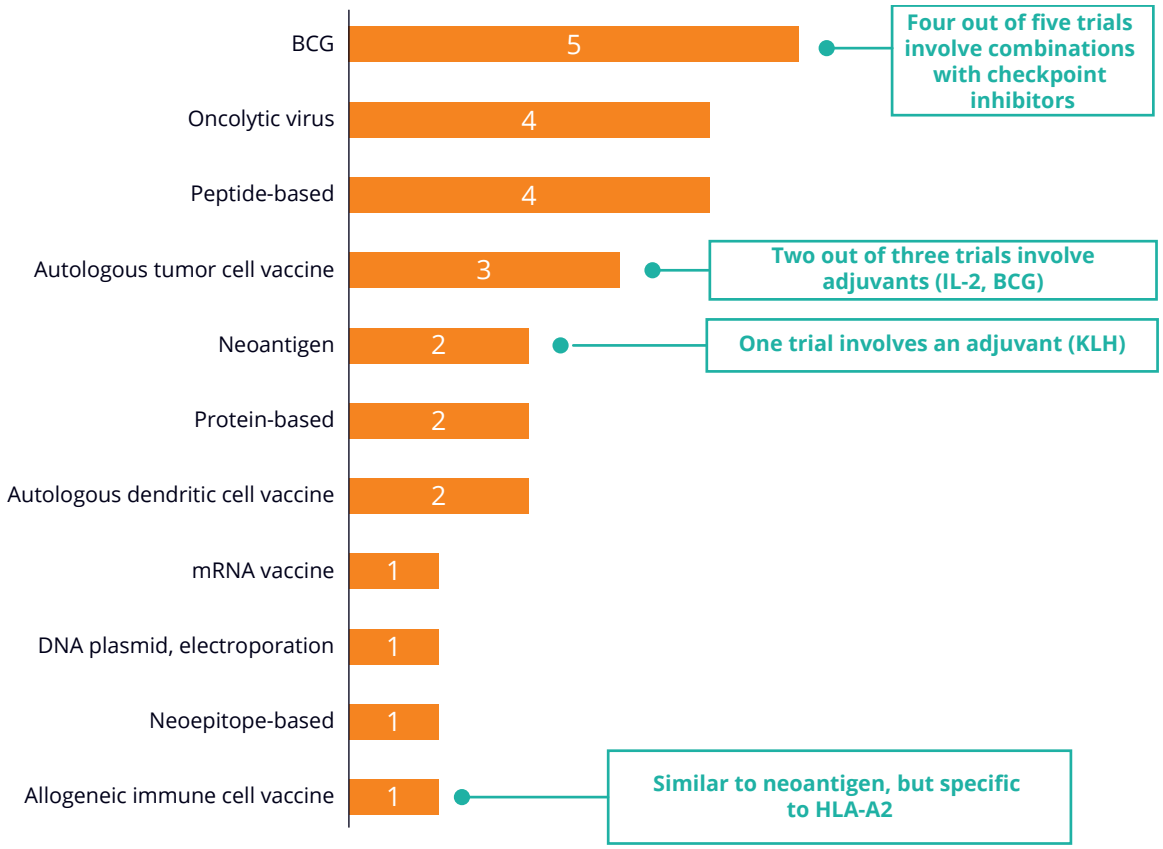
Bacille Calmette-Guérin (BCG)	Provenge	Imlygic
2020 world-wide sales: Not available	2020 world-wide sales: $200 million	2020 world-wide sales: $75 million
Indicated for treatment of non-invasive bladder cancer	Indicated for treatment of metastatic castration-resistant prostate cancer	Indicated for treatment of unresectable advanced or metastatic melanoma
Cornerstone of treatment, but limited commercial opportunity (in terms of addressable patient population and revenue per patient)	Can also be considered an autologous cell therapy. Initial launch was side-tracked by manufacturing issues, which have limited availability to specific institutions. Commercial opportunity further constrained by limited indication statement and strong competition from multiple therapeutic modalities.	Intralesional delivery limits applicability to cutaneous, subcutaneous and nodal lesions. Commercial opportunity further constrained by success of checkpoint inhibition and TKIs.

New technologies may expand the utility of this platform, however. The success of mRNA vaccine technology in addressing COVID-19 has crossed over to cancer, with 39 mRNA therapeutic vaccine candidates in pre-clinical development, nine assets in phase I trials and 12 assets in phase II trials. Novel adjuvants are also being tested to target specific components of the immune system to generate a more robust and longer lasting immune response, such as TLR agonists, CD40 agonists, STING agonists and cytokines like IL-2. Improved delivery technology like electroporation and lipid complexing, as well as improved neoantigen identification and selection (which leads to the development of bespoke therapeutic vaccines based on unique patient neoantigen profiles) may further evolve this platform.

We see these new technologies, as well as older modalities, diversely represented in the current set of 26 registrational cancer vaccine and oncolytic virus trials. They are summarized by modality in Figure 8 below.

FIGURE 8

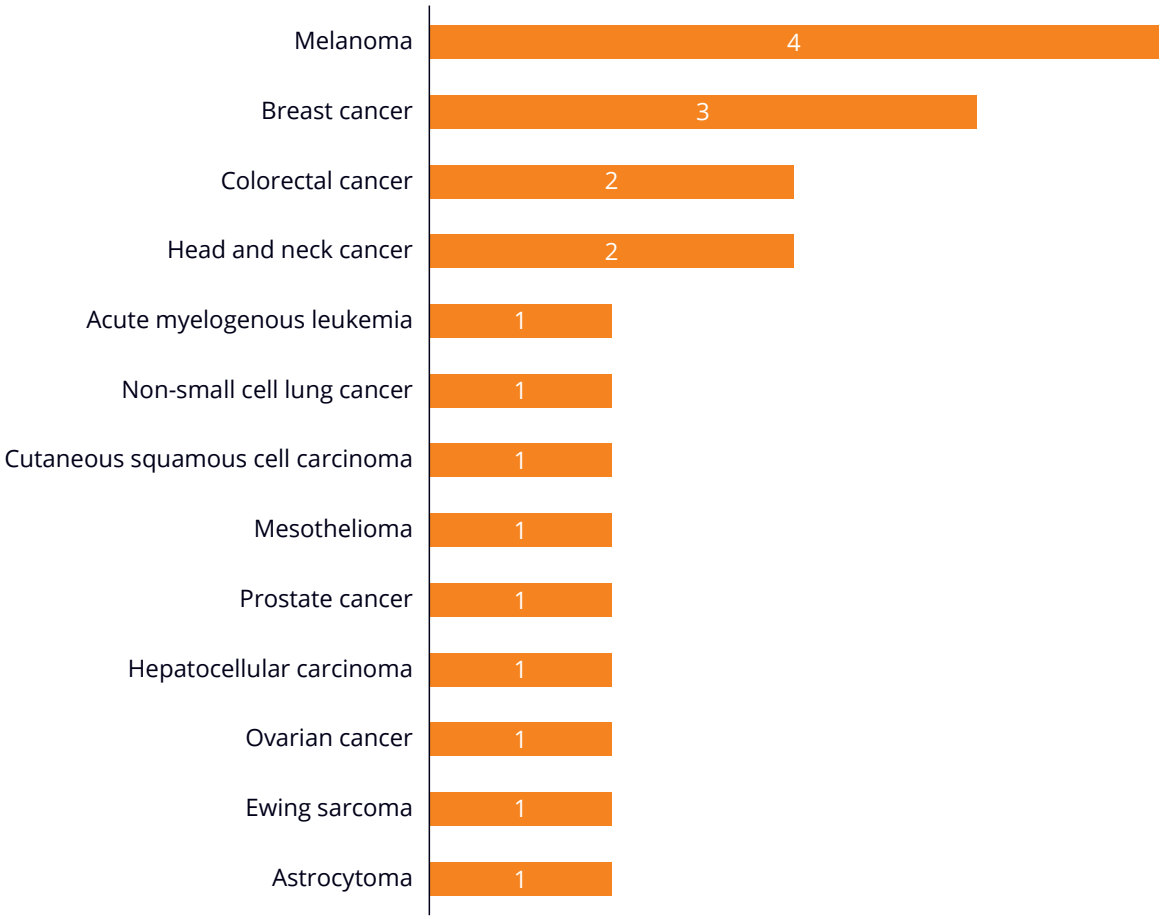
Registrational cancer vaccine and oncolytic virus trials by modality



Interestingly, all but one of the current registrational cancer vaccine and oncolytic virus trials are focused on solid tumors, detailed in Figure 9 below.

FIGURE 9

Registrational cancer vaccine and oncolytic virus trials by tumor type

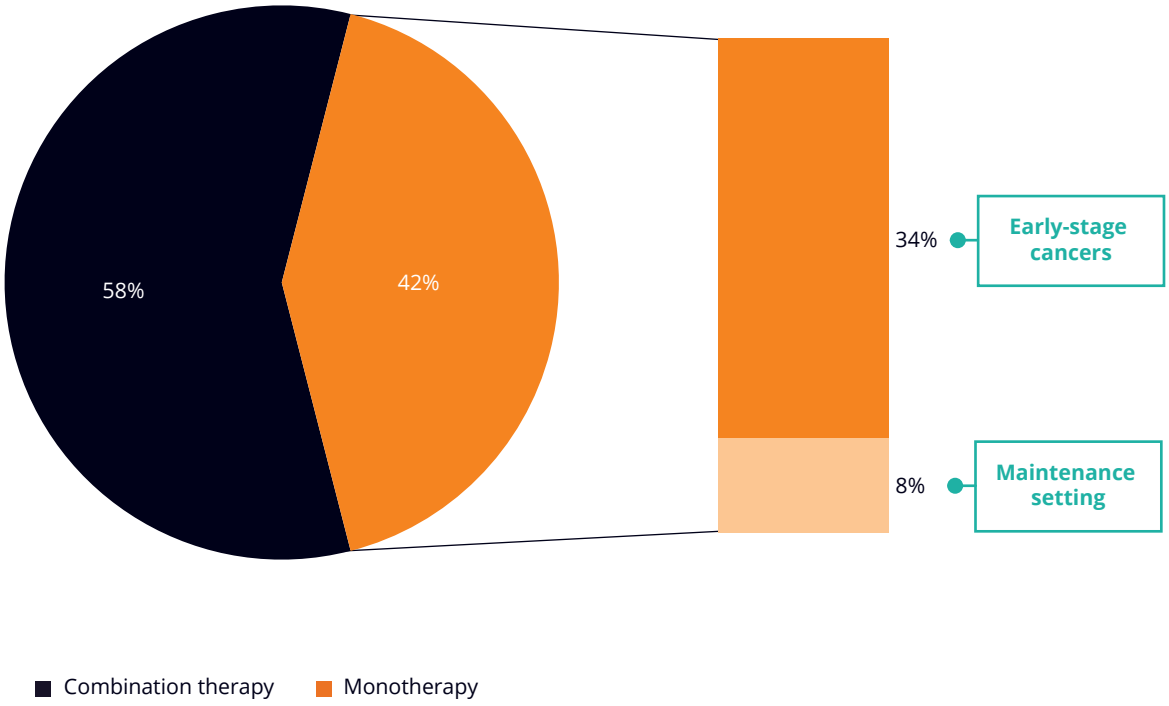


Past research has shown that monotherapy efficacy of cancer vaccines and oncolytic viruses may be limited to low tumor burden or early-stage cancers due to immune evasion mechanisms and immunosuppressive elements of the tumor microenvironment. Accordingly, greater efficacy could be realized through combination therapy, such as with other immuno-oncology modalities.

This research appears to be borne out in the current set of registrational cancer vaccine and oncolytic virus trials summarized in Figure 10 below. While about 40% of registrational trials test a monotherapy, all those trials are in early-stage or low tumor burden settings, such as maintenance following chemotherapy.

FIGURE 10

Registrational cancer vaccine and oncolytic virus trials by combination therapy versus monotherapy



As this platform evolves, we see two implications for the oncology pipeline:

- When considering monotherapy applications for cancer vaccines or oncolytic viruses, researchers should prioritize—from a feasibility perspective—early-stage and other low tumor burden settings.
- For treatment of metastatic cancers, cancer vaccines and oncolytic viruses are likely to see greatest feasibility when used in combination with other immuno-oncology modalities.

Radiopharmaceuticals

The undesirable effects of external beam radiation therapy have led to numerous attempts to limit collateral damage while retaining efficacy. This has contributed to two major evolutions in the past 50 years: radiation localization and systemic delivery optimization. Localization of radiation can occur by external or internal delivery of targeted radiation.

Stereotactic body radiotherapy increases specificity of external radiation by focusing individual beams of radiation on the tumor tissue from different directions, summating only on the tumor. Internal delivery of radiation is accomplished by selective internal radiation therapy. In this process, ^{90}yttrium microspheres are delivered to primary tumors or metastatic lesions located in the liver parenchyma. Optimizing systemic delivery of radiation has been explored via delivery of mimetic molecules. For example, Xofigo has a molecular structure that mimics calcium. Accordingly, it can selectively deliver radiation to bone metastases associated with prostate cancer.

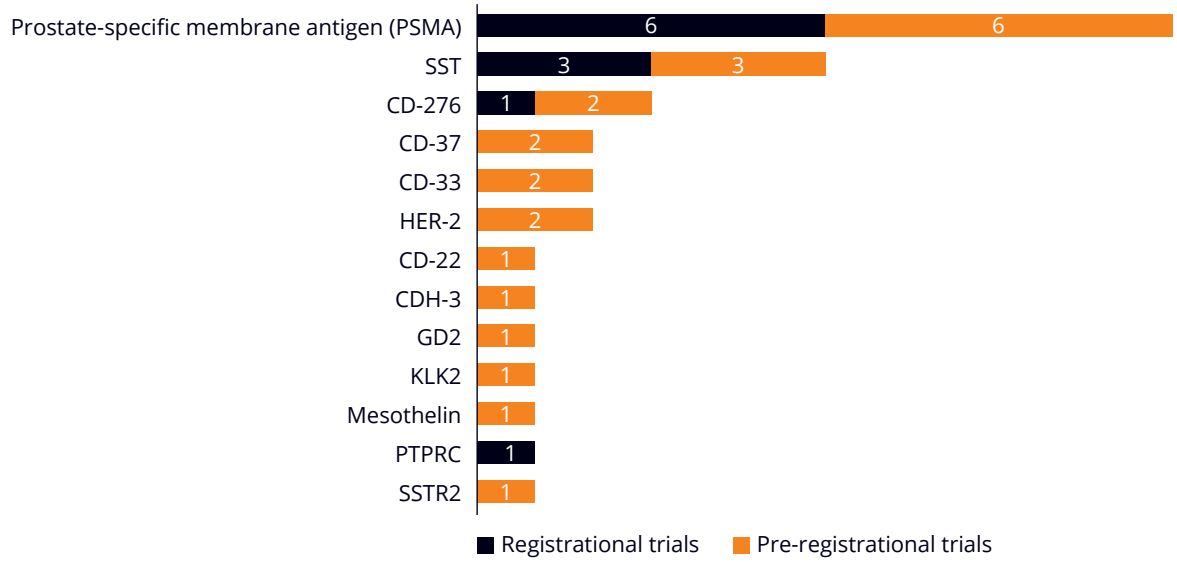
More recent radiopharmaceuticals refine further by molecular targeting—attaching the radioactive molecule to a targeting molecule via a linker. This is like the approach used by ADCs. The targeting molecule is highly sensitive toward specific tumor cells and is internalized, allowing the radioactive molecule to kill tumor cells in the area. These "targeting molecules" may be mAbs or engineered peptides that target tumor tissue.

For example, Lutathera, approved in 2018, targets neuroendocrine tumors by using a peptide, DOTA-TATE, which can bind the somatostatin receptor, facilitating entry into the cell and delivering the isotope Lu-177. Similarly, Pluvicto, approved in 2022, links a peptide that targets prostate-specific membrane antigen (PSMA) to Lu-177.

This approach has yielded renewed interest in investigating radiopharmaceuticals. There are currently 41 studies underway, 14 of which are registrational. As summarized in Figure 11 below, most of these trials are addressing similar targets to Pluvicto (PSMA) and Lutathera (somatostatin receptor). However, there are several targets that are new to radiopharmaceuticals, which indicates interest in expanding the set of addressable tumor types.

FIGURE 11

Radiopharmaceutical trials by target



Telix's acquisition of olaratumab, after it was shelved by Lilly when it failed to show overall survival benefit in soft tissue sarcoma, exemplifies this renewed interest in radiopharmaceuticals. Olaratumab is a mAb that targets platelet-derived growth factor. The intention for Telix is to add a radioactive tag to this molecule to enhance efficacy.

In addition to increasing the variety of tumor targets, Novartis has indicated that they will aim to grow their radiopharmaceuticals treatment center network to 550 centers in the near future to increase access to radiopharmaceuticals. Also notable, earlier this year the Society for Nuclear Medicine and Molecular Imaging launched a center of excellence certification process.

As this platform evolves, we see several implications for the oncology pipeline:

- The ability to address a broader range of tumors. Radiopharmaceuticals may adopt a similar approach to ADCs by diversifying molecular targets. The platform may provide an arena for targeting assets that previously underperformed in vivo, as was the case with olaratumab.
- An extension of the scope of benefit for radiopharmaceuticals by exploring combinations, including with therapies that can capitalize on DNA damage, such as poly (ADP-ribose) polymerase (PARP) inhibitors.

- A need to mitigate the impact of a limited treating universe, which currently is made up of a small set of nuclear medicine physicians. Accordingly, it will be important to facilitate collaboration between nuclear medicine physicians and oncologists in a multidisciplinary team setting.

Market trends and predictions

We see several themes for companies investing in these platforms:

- Many biotech companies appear to be organizing primarily around a particular platform, such as Adaptimmune with SPEAR-T TCR T-cell therapies, SELLAS Life Sciences with the GPS cancer vaccine and Seagen with ADCs.
- Larger pharmaceutical companies with more diverse portfolios are starting to organize their portfolios around these platforms. AstraZeneca, Novartis and Bayer are good examples of this approach.
- The platform approach is influencing deal-making as well:
  - In February 2022, ImmunoGen and Lilly agreed on a licensing deal to develop and commercialize ADCs using ImmunoGen's Camptothecin platform.
  - In January 2022, AstraZeneca signed a collaboration agreement with Scorpion Therapeutics around discovery, development and commercialization of precision medicines against previously hard-to-target cancer proteins.
  - In January 2021, Merck licensed two off-the-shelf CAR-NK cell therapy programs for solid tumors from Artiva Biotherapeutics.
  - Additionally, the bispecific antibody Rybrevant was actually developed based on a licensed bispecific development platform, Genmab's DuoBody.

Because platforms have potentially broad applicability across tumor types, identifying and prioritizing targets is critical to realizing the full potential of a platform. The platforms we have discussed are all proven to some extent, with many approvals in hand and tens of registrational trials ongoing for each platform. However, there will always be a need to look for the next platform that may not be as proven. Based on substantial deal activity, protein degraders may be the next platform. Of note, Arvinas and Pfizer expect to initiate multiple registrational trials for ARV-471 in 2022. BMS and Merck KGaA have both recently initiated partnerships with British biotech Amphista. Amgen, Lilly and Novartis have also all entered into agreements to access this platform.

About the authors

Matt Furlow is a manager in ZS's Philadelphia office and is a lead within the ZS oncology vertical. He has been with ZS for seven years, leading oncology engagements in pipeline strategy, commercial strategy, market research, forecasting and secondary data analytics. Matt's expertise spans solid tumors and hematological malignancies, with a special interest in rare and difficult-to-treat tumor types. In addition to advising his clients on development and commercialization of novel oncology therapeutics, Matt has attended oncology medical congresses on behalf of ZS for the past seven years. Matt holds a PhD in bioengineering from the University of Pennsylvania. He also holds a BSE in biomedical engineering from Duke University.

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About ZS

ZS is a professional services firm that works side by side with companies to help develop and deliver products that drive customer value and company results. We leverage our deep industry expertise, leading-edge analytics, technology and strategy to create solutions that work in the real world. With more than 35 years of experience and 12,000-plus ZSers in more than 30 offices worldwide, we are passionately committed to helping companies and their customers thrive.

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