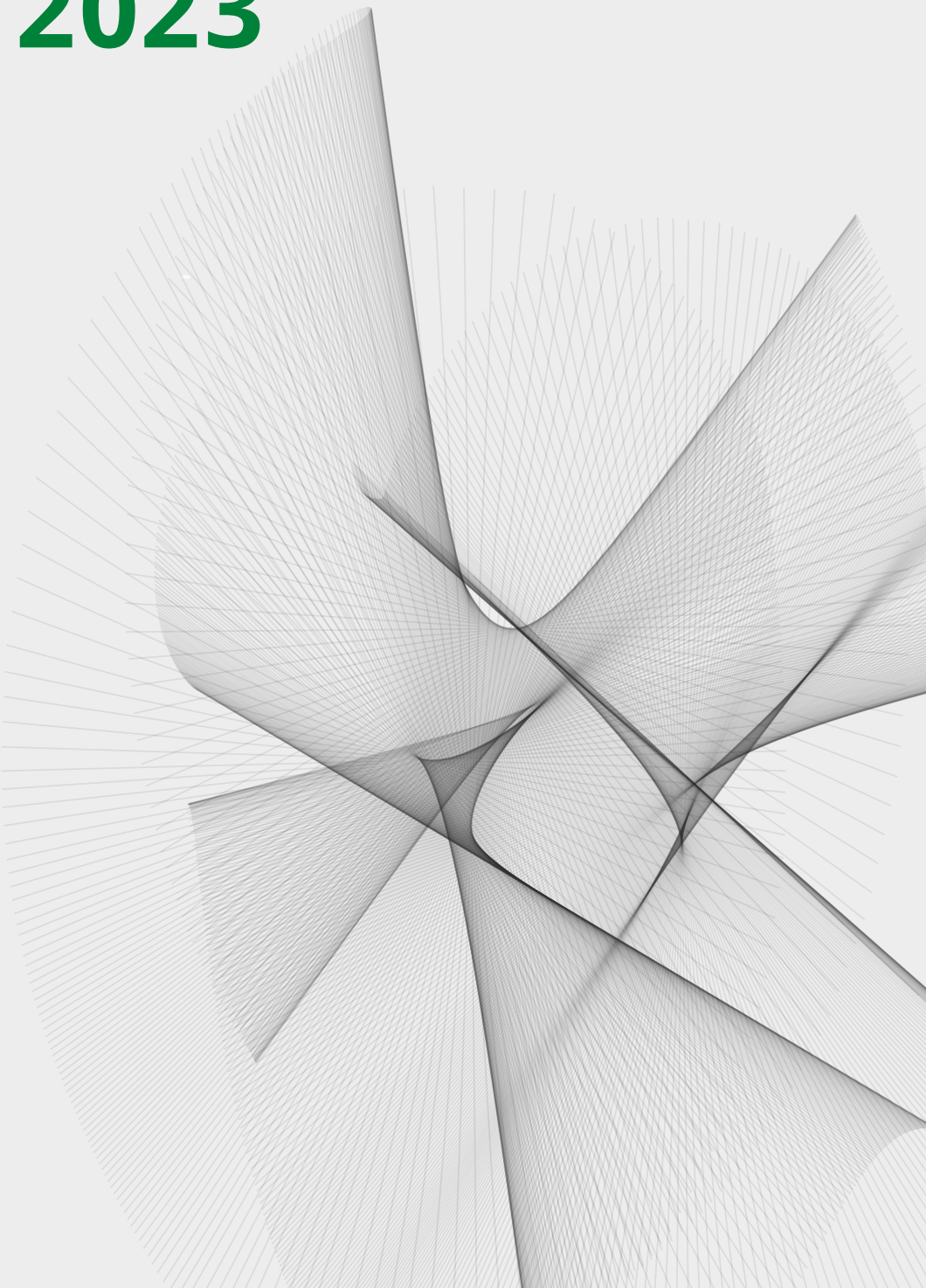
IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

Global Oncology Trends 2023

OUTLOOK TO 2027



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Introduction

The global oncology ecosystem continues to discover, develop, and deliver important novel treatments that are intended to bring improved outcomes for an increasing number of patients. While this is a strong testament to the ingenuity and innovative power of the stakeholders involved, at the same time global oncology is facing complex challenges reflected in the trends highlighted in this report.

Our research profiles the current state of research and development in oncology, including key mechanisms, targets and cancer types being investigated as well as pointing to some novel areas which are only just emerging. We also look at metrics of clinical development productivity and the progress being made to improve representativeness of race and ethnicity in clinical trial populations.

As more novel cancer medicines are launched, patient access and use of those drugs vary widely around the world. Trends in the use of novel mechanisms in specific cancer types are reported here and intended to provide an evidence base that encourages stakeholder discussion.

Finally, the costs associated with treating more patients for longer and with more advanced therapies is bringing stress to healthcare budgets, even as the broader adoption of biosimilars provides some relief. How these spending dynamics will play out over the next five years globally is also examined in this report.

This study was produced independently by the IQVIA Institute for Human Data Science as a public service, without industry or government funding.
The contributions to this report of Julia Kern, Penelope Price, Khushboo Rastogi, Tizita Zeleke and many others at IQVIA are gratefully acknowledged.

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MURRAY AITKEN
Executive Director
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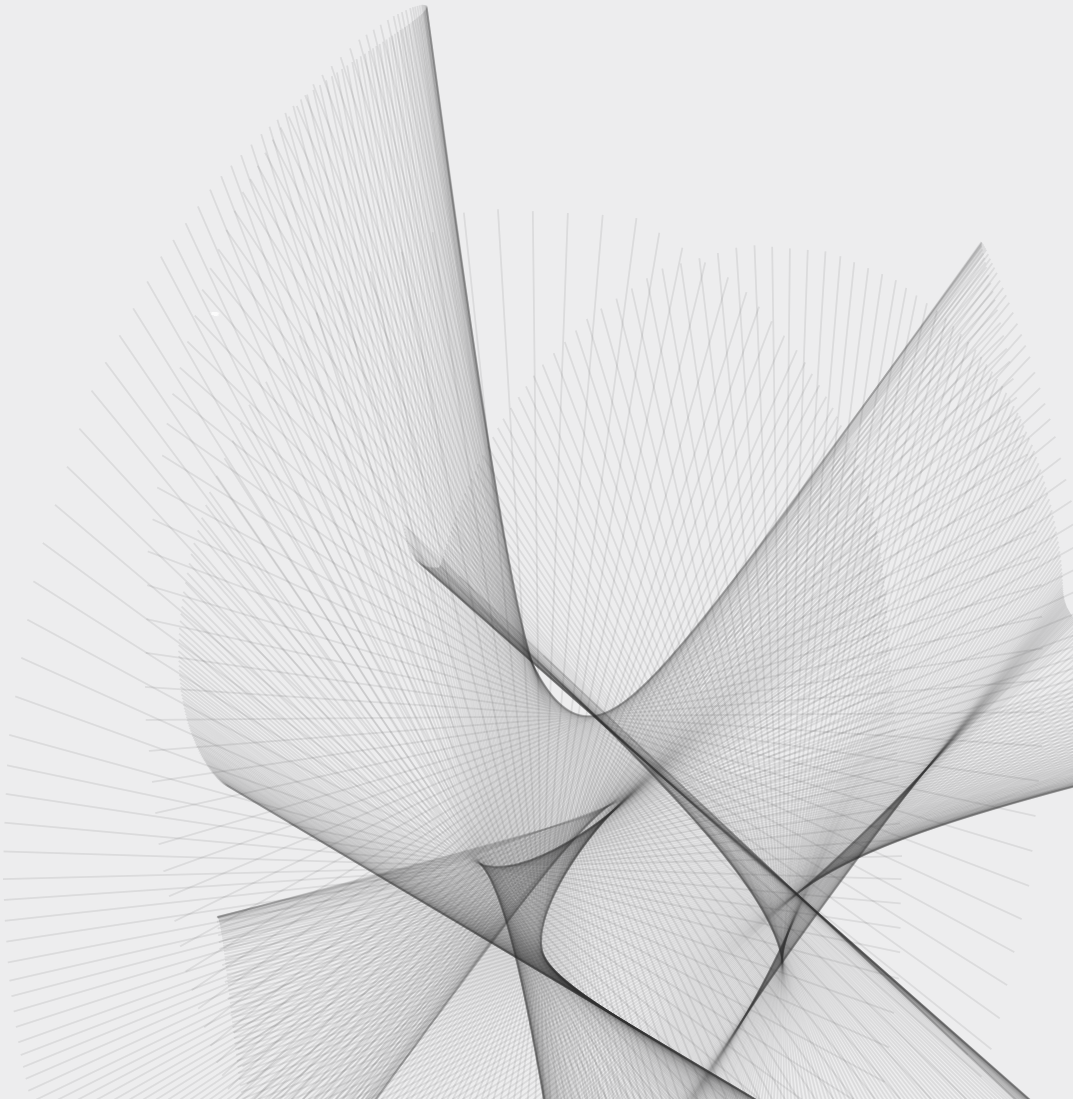


Overview

Global oncology R&D and innovation continue to expand, bringing forward new therapies for advanced cancers and some of the most advanced novel science in pharmaceutical development. These therapies represent the largest area of collective research and the largest overall area by drug spending. Despite significant advances in treatment, the global oncology community and patients continue to struggle with disparities in access and care. The outlook for the next five years includes important continuation of some of these trends and shifts in others.

ONCOLOGY RESEARCH AND DEVELOPMENT ACTIVITIES

Oncology trial starts remained at historically high levels in 2022, up 22% from 2018 and primarily focused on rare cancers. In terms of the sponsors of research, emerging biopharma companies were responsible for 71% of the oncology pipeline in 2022, up from 45% a decade ago and increasingly involved without larger pharma company partners until later in the development of an asset, or even after it has launched. Drugs from China-headquartered companies have risen to 23% of the oncology pipeline from only 5% a decade ago, and many of these companies will likely partner with multinationals to reach developed markets.

Oncology research and development has seen an increasing focus on targeted drugs, with innovative mechanisms of action for treatment of cancers over the last decade. PD-1/PD-L1 inhibitor trial starts grew 54% over the last five years, with most ongoing PD-1/PD-L1 late-stage trials in single countries and a majority in China, reflecting that the drugs being tested in these trials may not be bound for international markets. Antibody-drug conjugates are emerging with significant efficacy across a broad range of targets with 15 approved globally to date. Six bispecific antibodies are marketed globally for oncology with more than 130 in development. The next-generation biotherapeutic pipeline has expanded, with significant growth in CAR T-cell therapy and mRNA vaccine research.

ONCOLOGY CLINICAL DEVELOPMENT PRODUCTIVITY

Composite success rates in oncology have been trending down since 2015, falling to 3.5% in 2022. Oncology trials are substantially more complex than other disease areas when measured by number of eligibility criteria, endpoints, trial sites, countries, and clinical subjects. Oncology trials have significantly less "white space" — the difference between the duration of clinical trials and the duration of time between trial phases when administrative activities often take place — than other therapy areas but longer trial duration. Combining probability of success with complexity and duration, overall productivity of oncology research is among the lowest of all therapy areas, though rare cancer productivity is higher.

DIVERSITY AND INCLUSIVITY IN ONCOLOGY

Disparities exist across demographic groups in both socioeconomic status and cancer outcomes, with 12% higher mortality in Black/African American populations than other demographic groups. Despite these disparities in disease outcomes, Black/African American and Hispanic inclusion in oncology clinical trials is among the lowest of all major therapeutic areas with only 2.8% Black/African American and 5.9% Hispanic patients in trials completed 2020–2022, 80% and 61% below their 2019 U.S. cancer incidences of 13.8% and 15.3%, respectively. Key operational decisions can impact trial inclusivity, including inclusion/exclusion criteria, number of subjects, and trial sites. Planning across the entire trial lifecycle can improve patient inclusivity.

NOVEL ACTIVE SUBSTANCES IN ONCOLOGY

In 2022, 21 novel active substances (NASs) for oncology launched globally, down from the record 35 in 2021 and bringing the average annual new launches from 2018–2022 to 23. In the past five years, 115 NASs have launched globally and a total of 237 since 2003. While not all of these drugs have become available in every

country, most have access to some key breakthroughs in immuno-oncology and the use of precision biomarkers have become the standard of care in dozens of tumors.

In the U.S., 134 unique new cancer medicines have launched in the past 10 years, with many approved for more than one indication. There have been important concentrations of new therapies in solid tumors of the lung, breast, and skin, as well as hematological malignancies such as non-Hodgkin lymphoma and multiple myeloma. Many of these drugs have received orphan designations and are increasingly using novel mechanisms. Emerging biopharma companies originated 70% of new U.S. oncology drugs in 2022 and launched 71% of their own products.

CANCER PATIENT ACCESS AND USE OF SCIENTIFIC ADVANCES

The number of treated cancer patients globally grew at an average of 5% over the past five years and is expected to accelerate in the next five years as access to novel medicines further expands. Despite this growth, the pace of bringing novel cancer therapies to patients is uneven across countries, with differences in biomarker testing rates, adoption of novel therapies, and the presence of infrastructure capacity to deliver some of the most advanced therapies. A range of novel oncology medicines have demonstrated significant clinical value in the last decade, but access and use can vary greatly across countries.

Non-small cell lung cancer treatment has shifted to include PD-1/PD-L1 inhibitors and kinase inhibitors as the standard of care in the past three years, contributing to the extension of the median duration of first-line therapy by nearly a year. Treatment of women's cancers and multiple myeloma has advanced in recent years as novel modalities become more widely adopted and improve outcomes for patients. Next-generation biotherapeutics, including cell and gene therapies, continue to grow in cancer treatment, and while the number of CAR T centers is increasing, their location and availability of products can potentially result in lack of access to patients without the resources to travel long distances.

Despite continued discovery, development, and delivery of novel treatments for cancer patients, the global oncology community and patients continue to struggle with disparities in access and care.

SPENDING ON ONCOLOGY MEDICINES

Cancer medicine spending rose to $196Bn globally in 2022 and is expected to reach $375Bn by 2027, driven by continued innovation and offset by continued uptake of biosimilars in major markets. Growth in major markets is driven by new products and brand volume and offset by losses of exclusivity, including biosimilar impact. The U.S. remains the largest market globally followed by major countries in Europe. China oncology spending grew $6.8Bn over the last five years, driven by expanded access to new therapies and brand volume and offset by lower prices. Globally, seven of the top ten tumors had double-digit spending growth over the last five years from new medicines and as novel therapies move to earlier lines of therapy, including PD-1/PD-L1 inhibitors. The robust pipeline of next-generation biotherapeutics in oncology includes significant potential as well as a wide range of uncertainty both clinically and commercially, with a potential to lift the current $3Bn global spending to $19Bn by 2027. If usage of these therapies expands including novel therapies across new indications, movement of existing CAR T-cell therapies into earlier lines of therapy, and continued improvement of safety and efficacy, spending could reach as high as $50Bn.

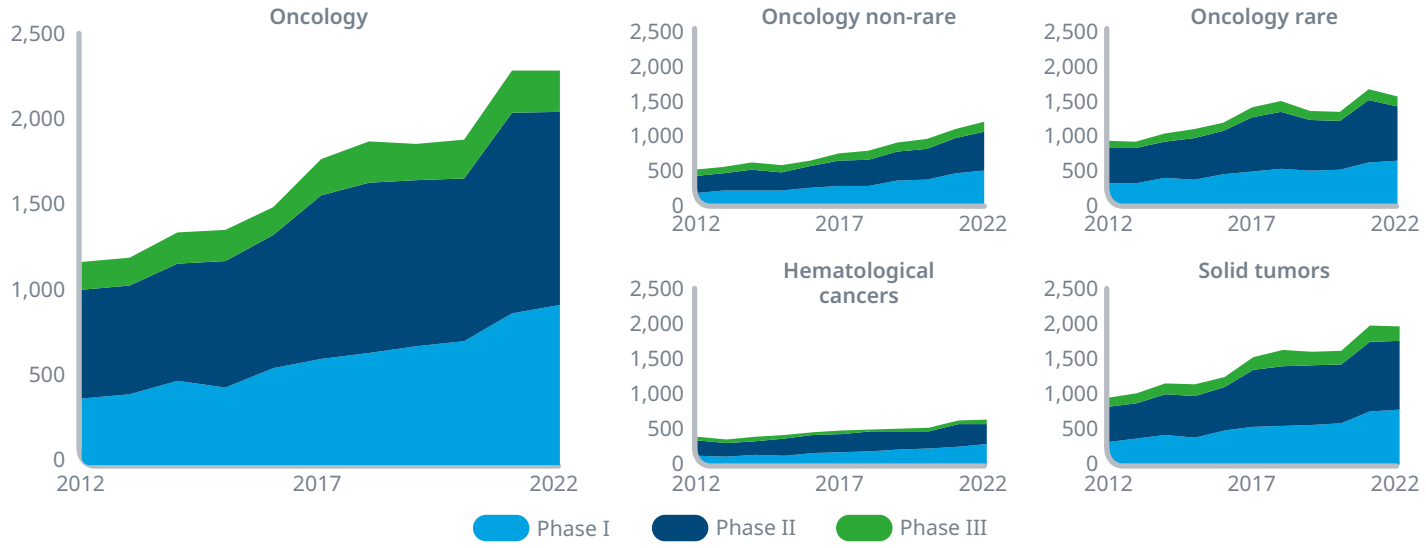
Oncology research & development activities

- Oncology trial starts remained at historically high levels in 2022, up 22% from 2018 and primarily focused on rare cancers and solid tumors.
- Emerging biopharma companies are leading innovation in oncology and were responsible for 71% of the oncology pipeline in 2022, up from 45% a decade ago.
- China-headquartered companies are playing an increasing role in the oncology pipeline accounting for 23% in 2022, up from only 5% a decade ago.
- Oncology development is focused on solid tumors with next-generation biotherapeutics and other novel modalities, such as antibody-drug conjugates and bispecific antibodies, growing across all cancers.
- PD-1/PD-L1 inhibitor trial starts grew 54% over the last five years, with 81% of ongoing late-stage trials in single countries. Trials taking place only in China represent 1,287 of the over 3,000 ongoing late-state PD-1/PD-L1 trials, reflecting that the drugs being tested in these trials may not be bound for international markets.
- Antibody-drug conjugates are emerging with significant efficacy across a broad range of targets, including HER2, CLDN18, and Trop-2, with some setbacks as some research is discontinued.
- Six bispecific antibodies are marketed globally for oncology with many in development for rare hematological cancers.
- The next-generation biotherapeutic pipeline is focused on cell therapies, particularly CAR T in hematological cancers.
- Nearly 250 trials testing CAR T-cell therapies in oncology started in 2022 with a growing number across a range of solid tumors.
- Driven by the success of COVID-19 vaccines, development of mRNA vaccines for cancer has more than doubled since 2017, with focus on solid tumors.
- Several ongoing and new trends in oncology will continue, including use of novel modalities in earlier lines of therapy and ctDNA use in clinical care across the patient journey.

Oncology clinical activity represents the largest portion of industry R&D activity with significant innovation across many novel modalities.

Oncology trial starts remained at historically high levels in 2022, up 22% from 2018 and primarily focused on rare cancers

Exhibit 1: Clinical trial starts by year, 2012–2022



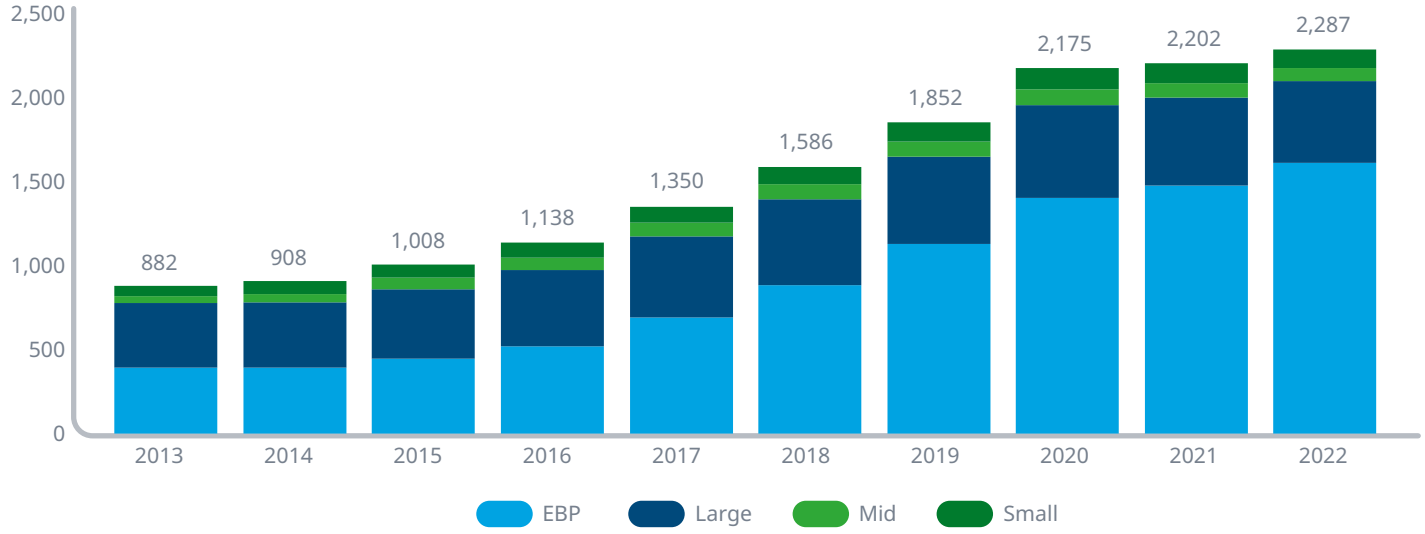
Source: Citeline Trialtrove, IQVIA Institute, Jan 2023.

- Oncology trials represent a significant portion of all clinical trials and after reaching historic levels in 2021, remained flat in 2022 but are still up 29% from the number of trials started in 2017.
- Phase II trials, including Phase I/II, IIa and IIb, represent the largest share of trials, with 49% of oncology trials started in 2022 being Phase II compared to 41% Phase I and 10% Phase III.
- Most oncology trials are focused on rare cancers, with 56% of trial starts in 2022 evaluating medicines for rare cancers, however rare oncology trial starts fell 6% in 2022 after a 25% jump in 2021.
- Seventy-five percent of oncology trials started in 2022 are testing drugs against solid tumors, though growth was flat in 2022 compared to 2021.
- Although a small share of trials are addressing hematological cancers, the number of trials rose 30% from 2017 to 2022, with more than 550 trials investigating drugs for treatment of hematological cancers started in 2022.

Notes: Phase II includes phases I/II, II, Iia, IIb. Phase III includes phase II/III and III. Terminated trials are included to track the activity involved with their initiation, partial execution and termination. Trials were industry sponsored, interventional trials and device trials were excluded.

Emerging biopharma companies were responsible for 71% of the oncology pipeline in 2022, up from 45% a decade ago

Exhibit 2: Number of Phase I to regulatory submission oncology pipeline products by company segment, 2013–2022



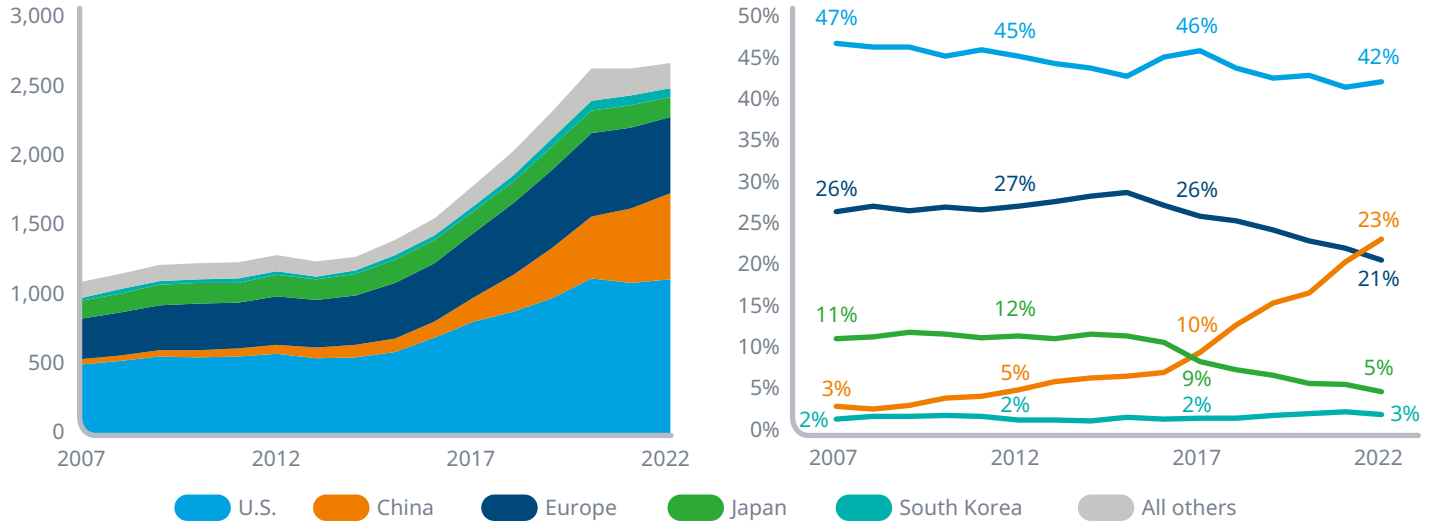
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Apr 2023.

- The number of products under development in oncology has grown significantly over the last decade, with more than 2,000 products currently under development.
- Emerging biopharma companies — defined as those with less than $500Mn in annual sales and R&D spending less than $200Mn per year — are responsible for 71% of products currently under development for cancers, an increase from 51% in 2017.
- Large pharma companies — those with greater than $10Bn in annual sales — have seen a declining share of the oncology pipeline, responsible for 21% of products currently under development, down from 36% in 2017.
- Since 2020, oncology pipeline growth has slowed growing just 5% over the last two years, with 15% growth in the emerging biopharma pipeline compared to a 13% decline across larger companies.
- Of the emerging biopharma companies working in oncology, 77% are solely focused on oncology drug research and development and of those focused solely on oncology, 72% are only developing a single drug.

Notes: Analysis includes medicines in active research with a focus on cancer therapeutics and does not include supportive care. Company segment when two or more companies are involved is determined by the larger sales segment. Emerging biopharma companies (EBP) are those with either R&D spend less than $200Mn or global sales up to $500Mn per year. Small companies have global sales between $500 million and $5Bn per year. Mid-sized companies have global sales between $5Bn and $10Bn per year. Large companies have global sales exceeding $10Bn per year.

Drugs from China-headquartered companies have risen to 23% of the oncology pipeline from only 5% a decade ago

Exhibit 3: Number of oncology drugs over time and country share of pipeline Phase I to regulatory submission based on company headquarters location, 2007–2022



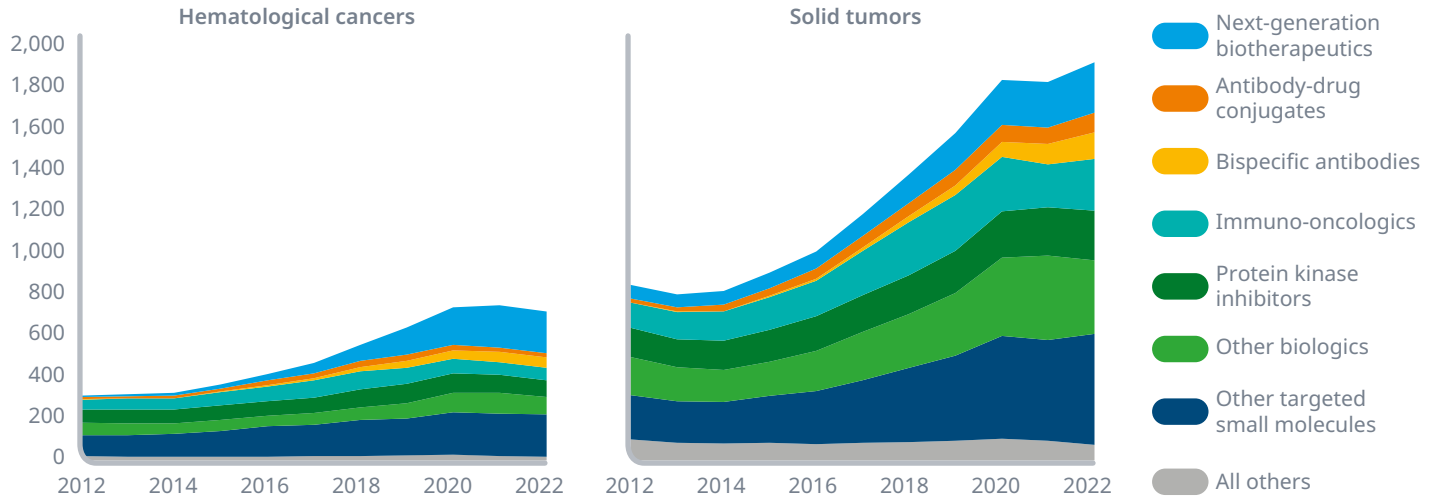
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Apr 2023.

- Currently, more than 1,000 companies and nearly 50 academic or research groups around the world are involved in the oncology pipeline.
- The U.S. share of the oncology pipeline has fallen 5% over the past 15 years but remains above 40%.
- Europe's share declined to 21% in 2022, down from 26% five years ago, while the absolute number of active oncology programs grew by 19% — from 458 to 546.
- Companies headquartered in Japan have seen a declining share of the oncology pipeline, dropping to 5% in 2022, down from 9% five years ago, and an 11% drop in absolute number of active oncology programs since 2017.
- Products from China-headquartered companies now represent 23% of the oncology pipeline, up from 10% five years ago and 3% in 2007 and passing Europe for the first time in 2022. The active oncology pipeline from China-headquartered companies has more than tripled in the last five years, highlighting the important role that companies headquartered there will play in the development of new products globally.
- South Korea's share of the oncology pipeline has remained low and relatively stable despite 82% growth in the absolute number of active programs over the last five years.

Notes: Analysis includes medicines in active research with a focus on cancer therapeutics and does not include supportive care, with phase determined by the highest phase of research in each year regardless of indication. Each company involved in a drug's development is counted individually, so products with more than one company involved are counted more than once and may be included in more than one region. Europe is defined as any country in continental Europe.

Oncology development is focused on solid tumors with next-generation biotherapeutics growing across all cancers

Exhibit 4: Oncology R&D pipeline Phase I to regulatory submission by type, 2012–2022



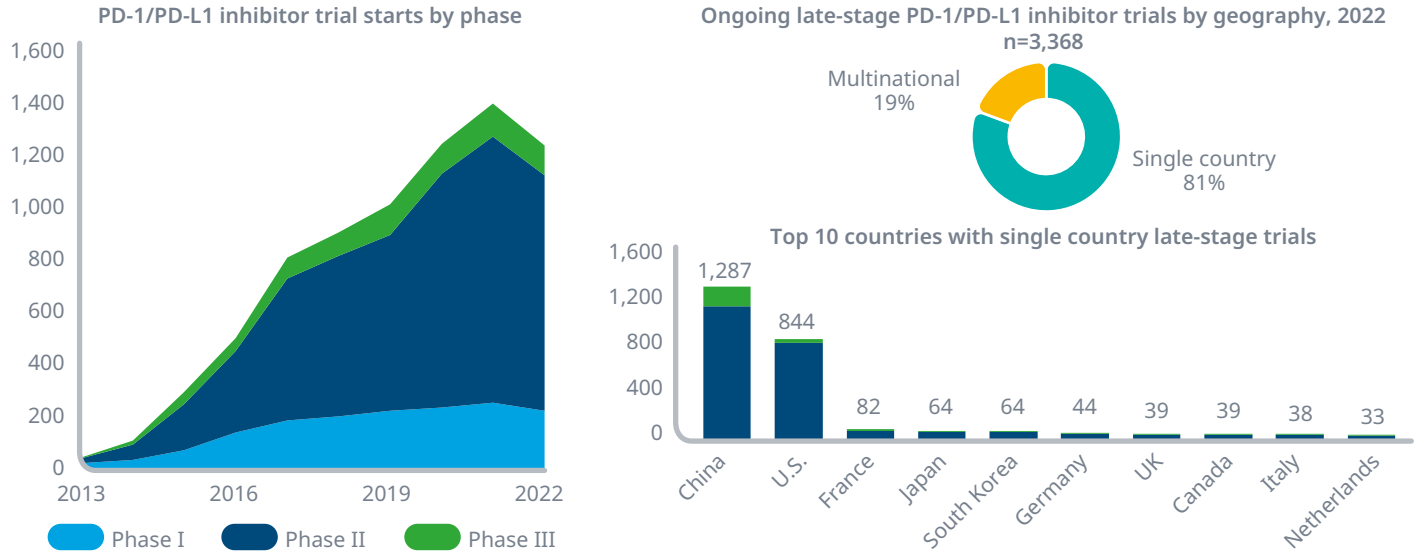
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

- Oncology research and development has seen an increasing focus on targeted drugs, with innovative mechanisms of action for treatment of cancers over the last decade.
- While development of drugs for hematological cancers declined 4% in 2022, clinical development for solid tumor cancers grew 5% following a slight contraction in the pipeline in 2021.
- Immuno-oncologics, including PD-1/PD-L1 checkpoint inhibitors, which saw significant growth over the last decade, have begun to taper off in recent years, with declines beginning in 2018, indicating a crowded market and switch to even newer targeted molecules.
- Bispecific antibody development for cancer treatment has grown significantly, now representing 7% of both the hematological cancer and solid tumor pipelines, indicating an increasing focus on the ability of these molecules to act on multiple targets or through different mechanisms of action.
- Antibody-drug conjugates, which allow for targeting cytotoxic agents directly to cancer cells reducing the non-specificity of older chemotherapeutics, are primarily focused on solid tumors, with 65% growth over the last five years in solid tumor development.
- Next-generation biotherapeutics are increasingly under investigation for hematological cancers, with the number of products currently in active research more than four times what it was in 2017 and accounting for 28% of the hematological cancer pipeline.

Notes: Analysis includes medicines in active research with a focus on cancer therapeutics and does not include supportive care, with phase determined by the highest phase of research in each year regardless of indication. Other includes non-targeted mechanisms within categories of cytotoxics, hormonal, and radiotherapeutics. Products being investigated for more than one type of cancer may be included in both hematological and solid tumor cancers.

PD-1/PD-L1 inhibitor trial starts grew 54% over the last 5 years with 81% of ongoing late-stage trials in single countries

Exhibit 5: PD-1/PD-L1 inhibitor trial starts by phase and ongoing trials by geography



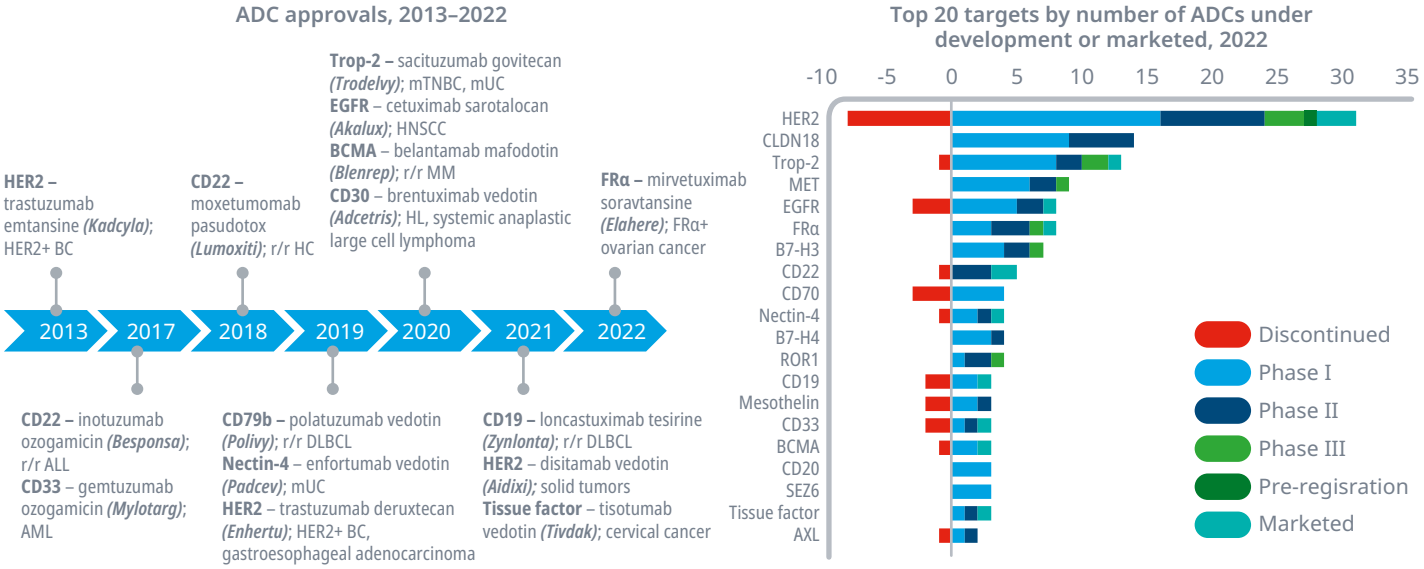
Source: Citeline Trialtrove, IQVIA Institute, Apr 2023.

- The FDA approved the first PD-1/PD-L1 checkpoint inhibitor, pembrolizumab (Keytruda), for patients with melanoma in 2014, and since then six additional PD-1/PD-L1 inhibitors have been approved across a range of hematological cancers and solid tumors.
- In 2022, 1,236 trials started globally testing PD-1/PD-L1 inhibitors, down 11% from 2021 but up 54% from the 804 started in 2017.
- Of the more than 3,000 late-stage PD-1/PD-L1 trials that were ongoing in 2022, 81% were being conducted in a single country.
- China has 1,287 ongoing late-state PD-1/PD-L1 trials that are only being conducted domestically and reflect that the drugs being tested in these trials may not be bound for international markets.
- More than 80% of clinical trials with PD-1/PD-L1 inhibitors are investigating their use in combination with other drugs, with PD-1/PD-L1 inhibitors being tested in combination with therapies targeting nearly 300 different targets and pathways.[1]

Notes: Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry and non-industry sponsored, interventional trials and device trials were excluded. Ongoing trials in 2022 are those that are recruiting patients or those where patient recruitment has completed but final dosing, follow-up, data collection and/or analysis continues.

Antibody-drug conjugates are emerging with significant efficacy across a broad range of targets with varying success

Exhibit 6: Antibody-drug conjugates approved and under development by target



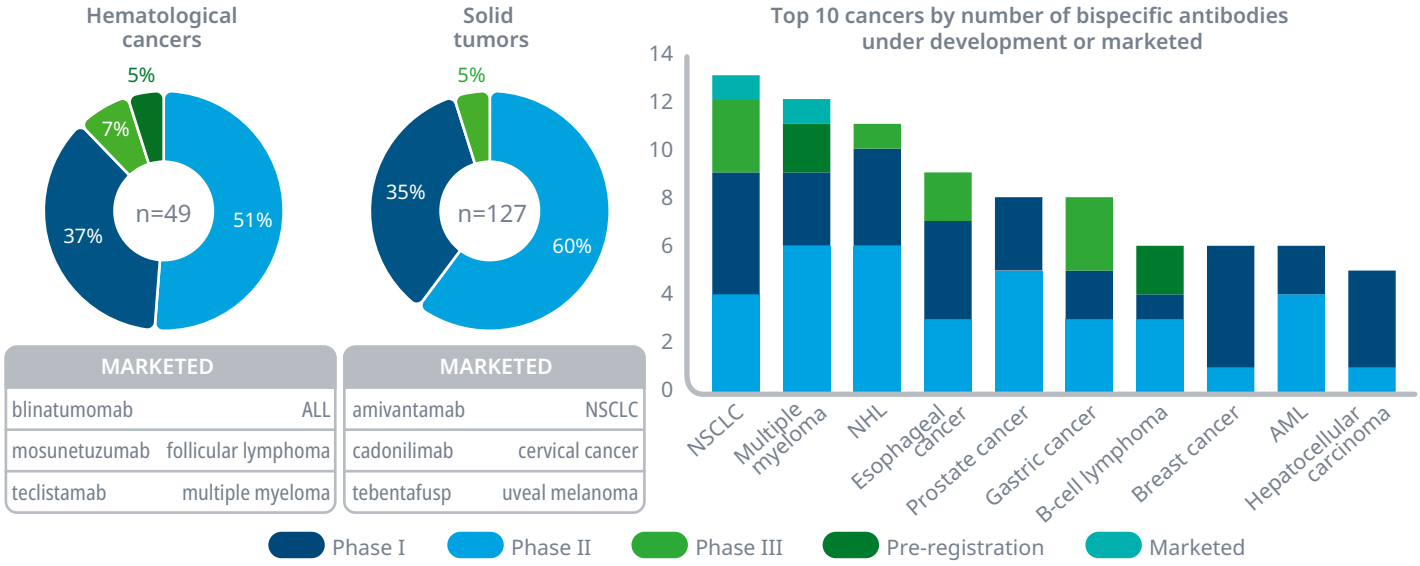
Source: Citeline Trialtrove, IQVIA Pipeline Intelligence, IQVIA Institute, May 2023.

- Antibody-drug conjugates are becoming more widely studied for cancer treatment and consist of a monoclonal antibody linked to a cytotoxic agent, allowing for a targeted chemotherapy.
- The first antibody-drug conjugate approved for cancer, gemtuzumab ozogamicin (Mylotarg), received accelerated approval in 2000 but was later withdrawn from the market following serious safety concerns and then re-approved in 2017. Since 2000, 15 antibody-drug conjugates have been approved across 12 different targets and across a range of hematological cancers and solid tumors.
- Despite setbacks from discontinued research, there are 76 biomarker targets with ongoing antibody-drug conjugate research, with 28 products currently under development targeting HER2, 14 for CLDN18, and 12 for Trop-2, common antigens expressed on solid tumors.
- Thirty-six targets that were once thought to be promising for antibody-drug conjugates no longer have any active research, highlighting the difficulty of developing compounds that will provide significant benefits for cancer patients.
- Significant progress has been made in the development of antibody-drug conjugates and future research will focus on new targets, different cytotoxic agents, varying molecular structures, and different indications to improve treatment for patients over traditional chemotherapy.[2]

Notes: Mylotarg initially received accelerated approval in 2000 but was later withdrawn and re-approved in 2017. ALL=acute lymphocytic leukemia; AML=acute myeloid leukemia; BC=breast cancer; BCMA=B-cell maturation antigen; DLBCL=diffuse large B-cell lymphoma; FRα: Folate receptor alpha; HCL=Hairy cell leukemia; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinomas; MM=multiple myeloma; mUC=metastatic urothelial cancer; r/r=relapsed or refractory; TNBC=triple negative breast cancer.

6 bispecific antibodies are marketed globally for oncology with many in development for rare hematological cancers

Exhibit 7: Bispecific antibody pipeline by tumor and phase, 2022



MARKETED	
blinatumomab	ALL
mosunetuzumab	follicular lymphoma
teclistamab	multiple myeloma

MARKETED	
amivantamab	NSCLC
cadonilimab	cervical cancer
tebentafusp	uveal melanoma

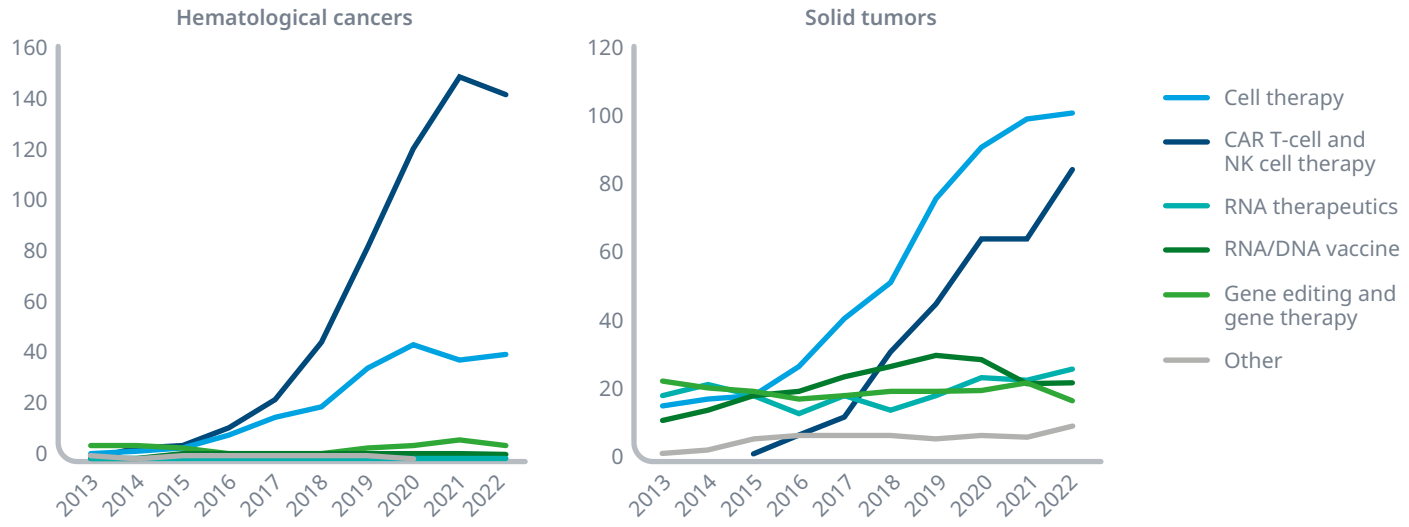
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Apr 2023.

- Bispecific antibodies can bind multiple targets and act by bringing immune cells to cancer cells or through inhibition or activation of two separate targets.[3]
- There are currently six bispecific antibodies on the market for treatment of cancer — three for hematological cancers and three for solid tumors — including the bi-specific T-cell engagers (BiTEs) blinatumomab and tebentafusp.
- More than 130 bispecific antibodies are currently under development for cancer treatment, with 67% being investigated to treat solid tumor cancers, 24% for hematological cancers, and nearly 9% being investigated for both.
- More than 50% of bispecific antibodies are in early clinical development, with only 7% of those under investigation for hematological cancers and 5% of those for solid tumors currently in Phase III trials.
- Bispecific antibodies are being tested across a range of cancers, with multiple myeloma and non-Hodgkin lymphoma having significant development in hematological cancers and non-small cell lung cancer and esophageal cancer, with a number of drugs under development in solid tumors.
- As bispecific antibody development has progressed, novel multispecific antibody modalities, such as trispecific antibodies, have emerged.[4]

Notes: Analysis includes drugs in active research with a focus on cancer therapeutics and does not include supportive care. Products being investigated for more than one indication may be included in more than one disease area. Phase is determined by highest phase within each indication. ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; NHL = non-Hodgkin lymphoma; NSCLC = non-small cell lung cancer.

The next-generation biotherapeutic pipeline is focused on cell therapies, particularly CAR T in hematological cancers

Exhibit 8: Oncology next-generation biotherapeutics Phase I to regulatory submission by mechanism, 2013–2022



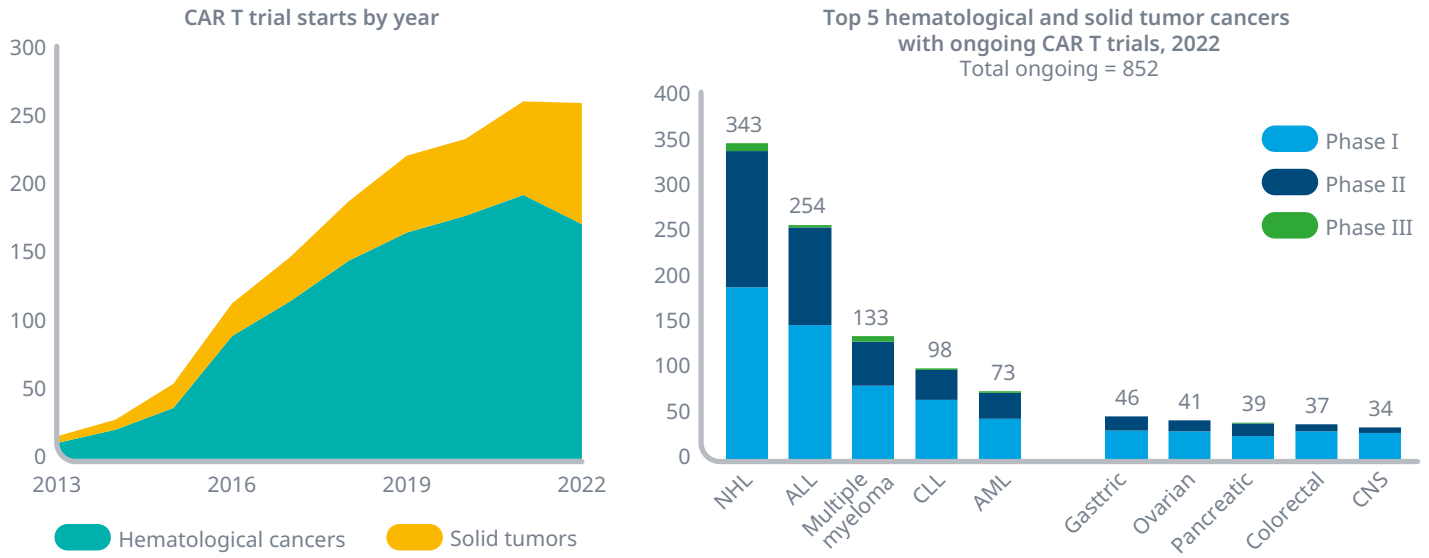
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Apr 2023.

- In 2022, 194 next-generation biotherapeutics were under development for hematological cancers, up from 14 a decade ago, and 254 for solid tumors, up from 73.
- Across all therapy areas, oncology accounts for 42% of the next-generation biotherapeutic pipeline, highlighting a significant amount of research and promise for using these products to improve care for cancer patients.
- Chimeric antigen receptor (CAR) T-cell and natural killer (NK) cell therapies represent 74% of the next-generation biotherapeutic pipeline for hematological cancers and are increasingly being investigated for solid tumors, with a number of CAR T therapies under development for gastric cancer, non-small cell lung cancer, and liver cancer.
- RNA and DNA vaccines which have long been investigated in oncology have received new attention since the rapid development and marketing of mRNA vaccines to prevent COVID-19 (Exhibit 10).
- Although gene therapies, including gene editing technologies such as CRISPR, in the past made up a larger share of oncology next-generation biotherapeutics under development, research has slowed in recent years due to a significant number of adverse events in clinical trials; however, this has led to the implementation of proactive safety plans to ensure patient safety while investigating these products, which still may offer significant promise.

Notes: Analysis includes medicines in active research with a focus on cancer therapeutics and does not include supportive care, with phase determined by the highest phase of research regardless of indication. Other includes oligonucleotides and other less common next-generation biotherapeutics.

Nearly 250 trials testing CAR T-cell therapies in oncology started in 2022 with a growing number across a range of solid tumors

Exhibit 9: Oncology CAR T-cell therapy clinical trial starts and ongoing trials by top tumors



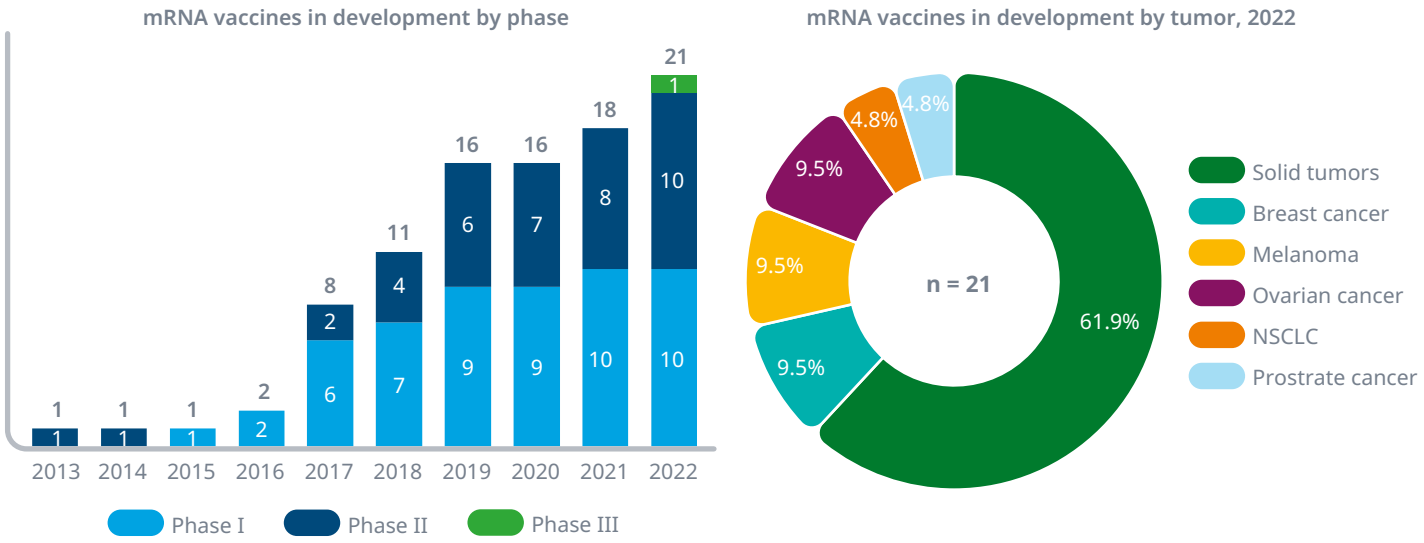
Source: Citeline Trialtrove, IQVIA Institute, Apr 2023.

- The first CAR T-cell therapy, tisagenlecleucel, was approved and launched for treatment of acute lymphoblastic leukemia (ALL) in 2017; since then, six other CAR T-cell therapies have launched globally for treatment of a range of relapsed or refractory hematological cancers.
- In 2022, 264 trials were started investigating the use of CAR Ts in oncology similar to the number started in 2021, however solid tumor trial starts grew 30% while hematological cancer trial starts declined 11%.
- Historically, more than 70% of trials have been for hematological cancers, however a rising share of CAR T trials are looking at treatment of solid tumors, which accounted for 34% of trial starts in 2022, up from 22% in 2017.
- Of the 852 ongoing CAR T trials in 2022, 72% are evaluating CAR Ts for treatment of hematological cancers, with 343 looking at patients with non-Hodgkin lymphoma. While only accounting for 28% of ongoing trials, CAR T-cell therapies for solid tumors are being investigated across a range of difficult to treat cancers, including gastric and pancreatic cancer.
- Though 98% of ongoing trials are in Phase I or II, all the currently marketed CAR Ts in the U.S. were approved based on data from Phase I or II trials.

Notes: Phase I, II, III. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry and non-industry sponsored, interventional trials and device trials were excluded. Ongoing trials in 2022 are those that are recruiting patients or those where patient recruitment has completed but final dosing, follow-up, data collection and/or analysis continues. ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CLL=chronic lymphocytic leukemia; NHL = non-Hodgkin lymphoma.

Development of mRNA vaccines for cancer has more than doubled since 2017 with focus on solid tumors

Exhibit 10: Oncology mRNA vaccines in development by phase and tumor



Source: IQVIA Pipeline Intelligence, IQVIA Institute, Apr 2023.

- The COVID-19 pandemic brought increased interest in mRNA vaccines and the speed with which these vaccines were developed was largely due to decades of research on mRNA vaccines in oncology.[5]
- While oncology made up the largest proportion of the pre-COVID-19 mRNA vaccine pipeline, oncology focused mRNA vaccines have not drastically increased since then and make up 8% of the pipeline in 2022.[6]
- Development of mRNA vaccines for cancer treatment is wholly focused on treating solid tumors, with less than 40% targeting specific solid tumor indications and most targeting a range of advanced solid tumors.
- While mRNA vaccines are being tested alone for treatment of cancer, many are also being tested in conjunction with immuno-oncologics, such as PD-1 checkpoint inhibitors, to enhance the bodies immune response against tumors.
- Merck and Moderna recently announced positive Phase II results for mRNA-4157 in combination with pembrolizumab, a PD-1 checkpoint inhibitor, which cut the risk of recurrence or death by 44% in patients with high-risk melanoma compared to pembrolizumab alone.[7]

Notes: Includes mRNA vaccines with an active research program with phase determined by the highest phase of research globally in each year.

Several ongoing and new trends in oncology will continue, including use of novel modalities in earlier lines and ctDNA use

Exhibit 11: Key R&D trends in oncology

Novel modalities and emerging targets	• Extensive pipeline of multi-specifc antibodies (e.g., TrAb, quad-specific) are being engineered to enhance antitumor effect by redirecting immune cells such as T and NK-cells to specific tumor antigens. While targeting multiple antigens results in significant immune response against tumors, optimization is still needed to overcome challenges such as in vivo durability and off-target effects. • Non-coding RNAs are being explored as potential targets (e.g., piRNA in lung and breast cancer) and as diagnostic markers to guide risk stratification (e.g., in endometrial and lung cancer) which may open new RNA-related therapeutic opportunities once optimal drug delivery, tolerability, and specificity are realized.
Novel modalities, targeted therapies and their use in earlier LoT	• ADCs, BsAbs, and CAR Ts have enjoyed success in late-stage disease and anticipated to continue advancing into earlier LoT (e.g., CAR T approval in 2L DLBCL; CAR T expansion into 1L DLBCL). • PD-1/PD-L1 inhibitors and targeted therapy are also moving to earlier LoT (e.g., nivolumab + chemo in resectable NSCLC; osimertinib in EGFR+ adjuvant NSCLC), additional immunotherapies anticipated to enter earlier lines to become SOC. • Recently announced regulatory programs such as Project Frontrunner — an initiative to enable drug approval in earlier LoT to help accelerate innovation in oncology — is anticipated to encourage stakeholders to reimagine oncology R&D.
Novel combinations to target drug resistance	• Given eventual leapfrogging of novel modalities into earlier lines, a wide pool of treatment resistant populations are anticipated to emerge and will require creative therapeutic combinations to provide patients with therapy options with durable response. Mixed progress to date in successfully combining therapies (e.g., failure of pembrolizumab + lenvatinib in melanoma; pembrolizumab + mRNA-4157/V940 demonstrated successful signal in melanoma).
Next wave of IO targets beyond PD-1/PD-L1	• Immune checkpoint targets such as LAG-3 and TIM-3 have emerged with positive results in melanoma and others, paving the way for innovation in immunotherapy beyond PD-1/PD-L1. This will also enable potential combination therapies with existing PD-1/PD-L1 to provide enhanced immunomodulating effects.
Clinical progress of mRNA cancer vaccines	• COVID-19 mRNA vaccine success accelerated interest in the potential of mRNA vaccines to target tumors enabling exciting combination studies (e.g., BNT 122 + atezolizumab (PDAC), BNT 111 + cemiplimab (melanoma)) that are anticipated to advance to late-stage clinical trials.
Disease/patient segmentation based on biomarkers identification	• There will be continued disease fragmentation based on novel biomarkers (e.g., Trop-2, CEACAM5) supporting innovation in targeted therapy. • Technologies that enable sequencing accuracy from solid and liquid biopsies to identify biomarkers will drive biomarker use for predictive, and prognostic purposes.
Integration of ctDNA use in clinical care	• ctDNA will increasingly be used at different steps of the patient journey from early disease detection, targeted treatment identification, and MRD assessment during treatment to understanding resistance mechanisms of disease. • Advancement of sequencing accuracy will ensure multitude of ctDNA/MRD usage including potential to be used as a surrogate endpoint in clinical trials.
MTD optimization in clinical trials	• Sponsors are exploring optimizing doses, usually after approval while using MTD during trials. This may result in unnecessary toxicity without clinical benefit and missed opportunity for patients to receive beneficial therapies for an extended duration. • There is a need to steward available trial subjects to optimally dosed therapies that are safe and efficacious for as many patients as possible. FDA's Project Optimus is an initiative for manufacturers to establish an optimal dose before progressing to registrational trials.

Source: IQVIA Institute, Apr 2023.

Notes: ADC = antibody-drug conjugate; BsAb = bispecific antibody; DLBCL = diffuse large B-cell lymphoma; LoT = line of therapy; MRD = minimal residual disease; MTD = maximally tolerated dose; SOC = standard of care; TrAb = trispecific antibodies.

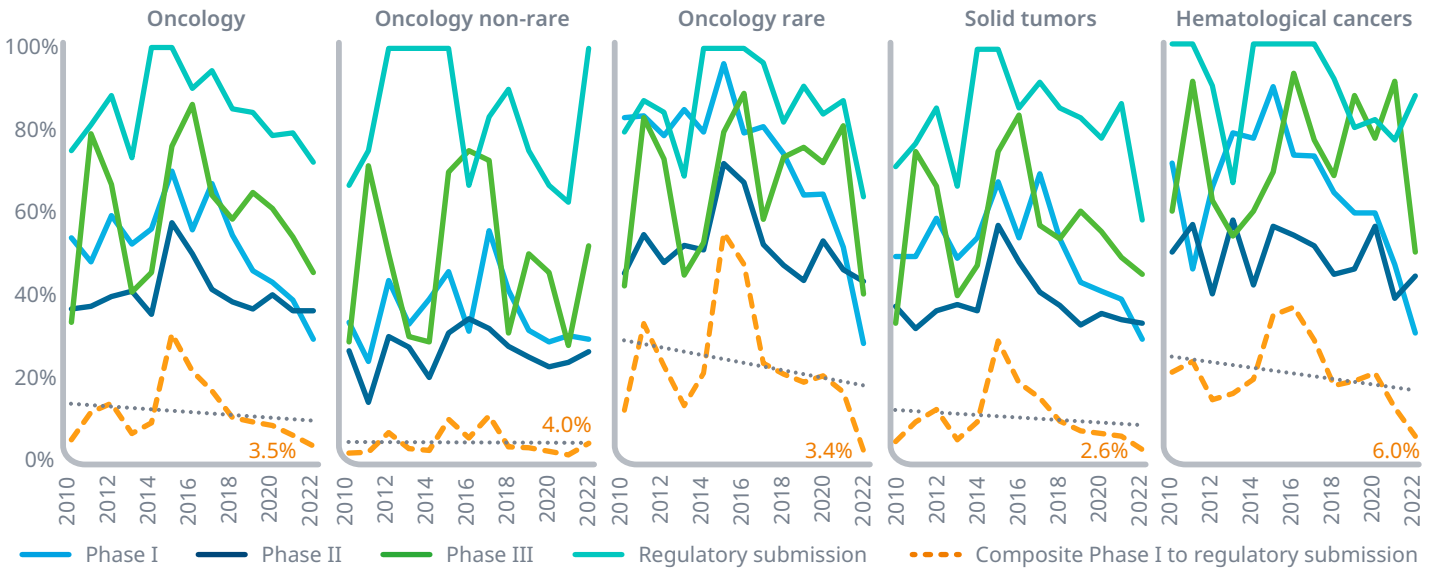
Oncology clinical development productivity

- Composite success rates in oncology have been trending down since 2015, falling to 3.5% in 2022, while hematological cancers remain the highest.
- Oncology trials are substantially more complex than other disease areas when measured across trial attributes but are often able to accommodate fewer subjects.
- A larger share of clinical trials are being conducted ex-U.S., driven by increasing activity in China, with fewer sites on average across geographies but increasing numbers of subjects per site.
- The number of subjects in oncology clinical trials globally fell 3% in 2022 to just under 290,000, while accelerated approvals tend to be based on fewer subjects in pivotal trials.
- Oncology trials have significantly less "white space" — the difference between the duration of clinical trials and the duration of time between trial phases when administrative activities often take place — than other therapy areas but longer trial duration.
- Clinical development productivity indices for oncology extends a decade-long trend as lowest of all diseases.
- Oncology trials more frequently use novel trial designs than trials for other diseases, often consolidating phases and providing program efficiencies that can potentially bring treatments to patients faster.

Novel trial designs in oncology — including adaptive, basket, umbrella, and master protocols — have more than tripled in the last decade and were used in more than 630 trials started in 2022.

Composite success rates in oncology have been trending down since 2015 while hematological cancers remain the highest

Exhibit 12: R&D phase and composite success rates by therapy area, 2010–2022



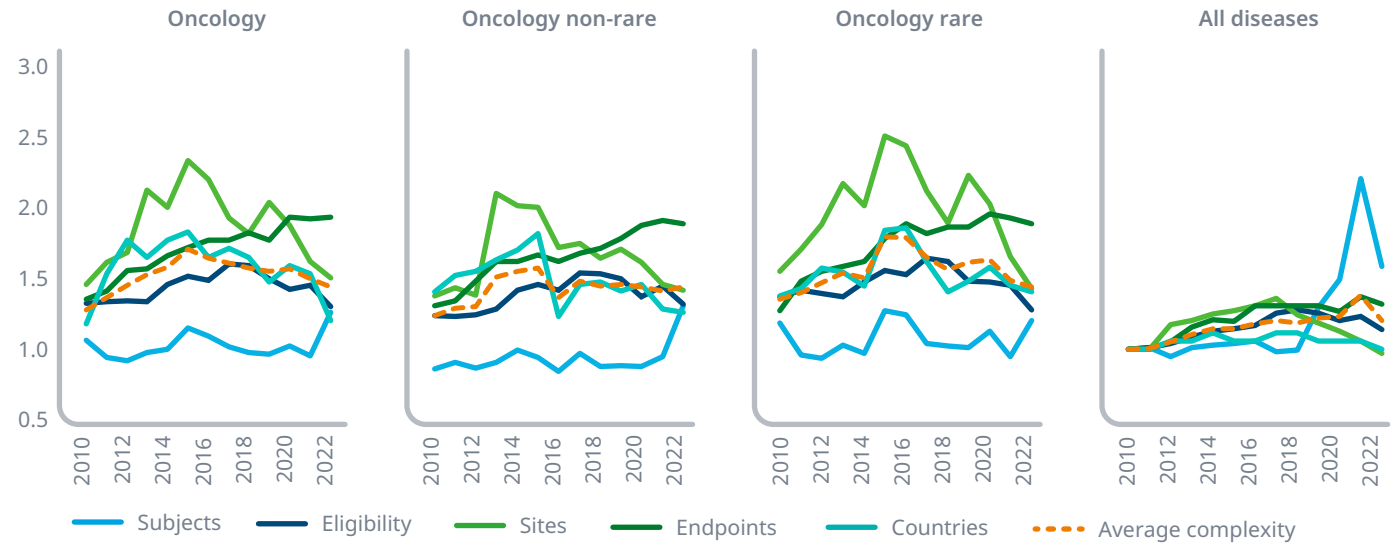
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Apr 2023.

- Oncology had one of the lowest composite success rates among all therapy areas in 2022, falling to 3.5%, which has been trending down since 2015.
- There is significant variability in success across oncology products, with those addressing rare and hematological cancers seeing higher success, on average, since 2010 compared to those for non-rare cancers and solid tumors.
- Drugs being investigated for rare cancers saw sharp declines in success in 2022 across all phases, with the largest declines in Phase I and III success, resulting in a composite success rate across all phases that fell from 17% in 2021 to 3% in 2022. This highlights a more difficult clinical journey for rare cancer drugs to reach the market.
- Drugs under investigation for non-rare cancers face a higher degree of uncertainty, with only 4.0% success across all phases, which is slightly higher than previous years due to an increase and Phase III and regulatory success but remains low.
- Drugs targeting hematological cancers tend to be more successful than those addressing solid tumors, with hematological cancer drugs two times more likely to reach the market than those for solid tumors.
- Composite success is based on success rates in each phase, which are based on progressing to subsequent phases anywhere in the world for any indication. In this way, a multi-indication cancer drug may be deemed a success when one indication is successful despite multiple indication failures.

Notes: Phase success rates are calculated as the percentage of products reaching a subsequent phase in the year out of the total products with an outcome including those which are discontinued, suspended or withdrawn as well as those which have been inactive for three years. The date three years after the last update determines which year the drug is considered to have gone inactive and become included in the denominator of the success rate, except when desk research has concluded the drug is still in active research. See methodology for more details.

Oncology trials are substantially more complex than other disease areas but are often able to have fewer subjects

Exhibit 13: Trial complexity by element and therapy area, 2010–2022



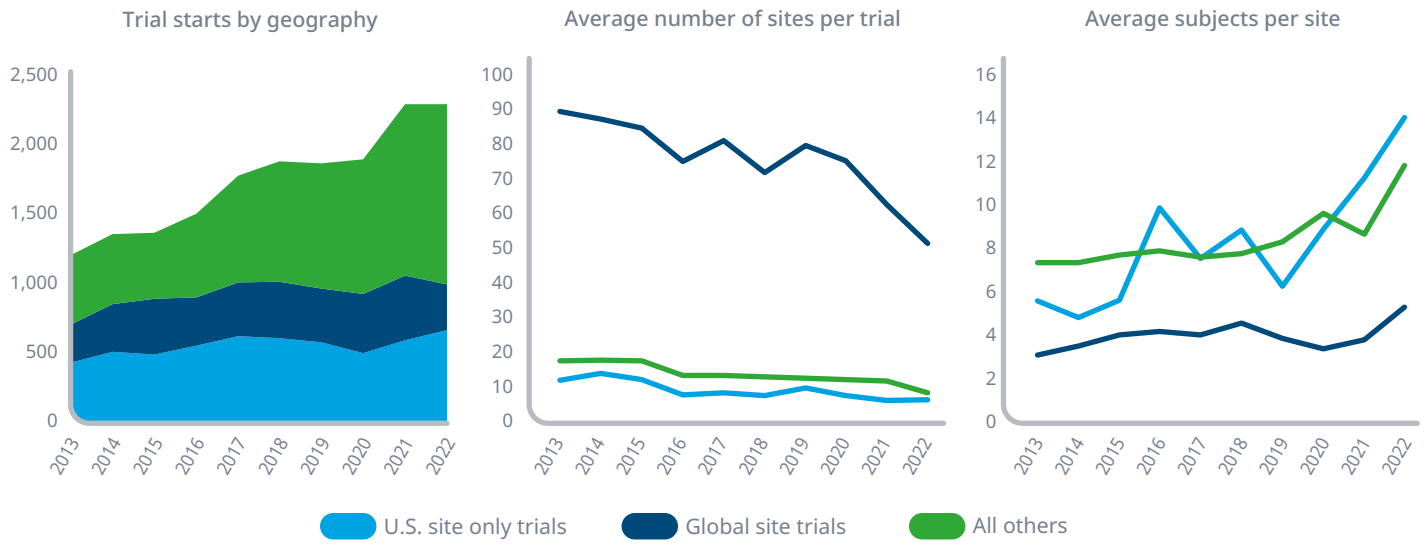
Source: Citeline Trialtrove, Jan 2023; IQVIA Institute, Apr 2023.

- Oncology trials are among the most complex using the index, though this has been declining since 2015 and declined 4% in the last year compared to complexity across all diseases, which declined 13%.
- Declines in oncology complexity can be attributed to significant drops in 2022 in the number of sites and countries as a result of the COVID-19 pandemic and offset by a 30% increase in subjects, driven primarily by non-rare cancer trials.
- Oncology trials overall have included an increasing number of endpoints since 2010, with rare oncology having the highest index indicating increasing evaluation of treatment outcomes, although endpoints in non-rare oncology trials have risen to similar levels.
- Rare oncology has seen declining complexity indices since 2015, mostly due to fewer sites, but with countries and eligibility criteria also contributing, signaling a focus on even smaller rare disease populations.
- These measures, while not definitive in determining the complexity of operating a trial, provide a useful guide for the ongoing effort associated with trials.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, devices, and medical procedures were excluded.

A larger share of clinical trials are being conducted ex-U.S. with fewer sites on average and more subjects per site

Exhibit 14: Clinical trials by site geography, average number of sites per trial, and average subjects per site, 2013–2022



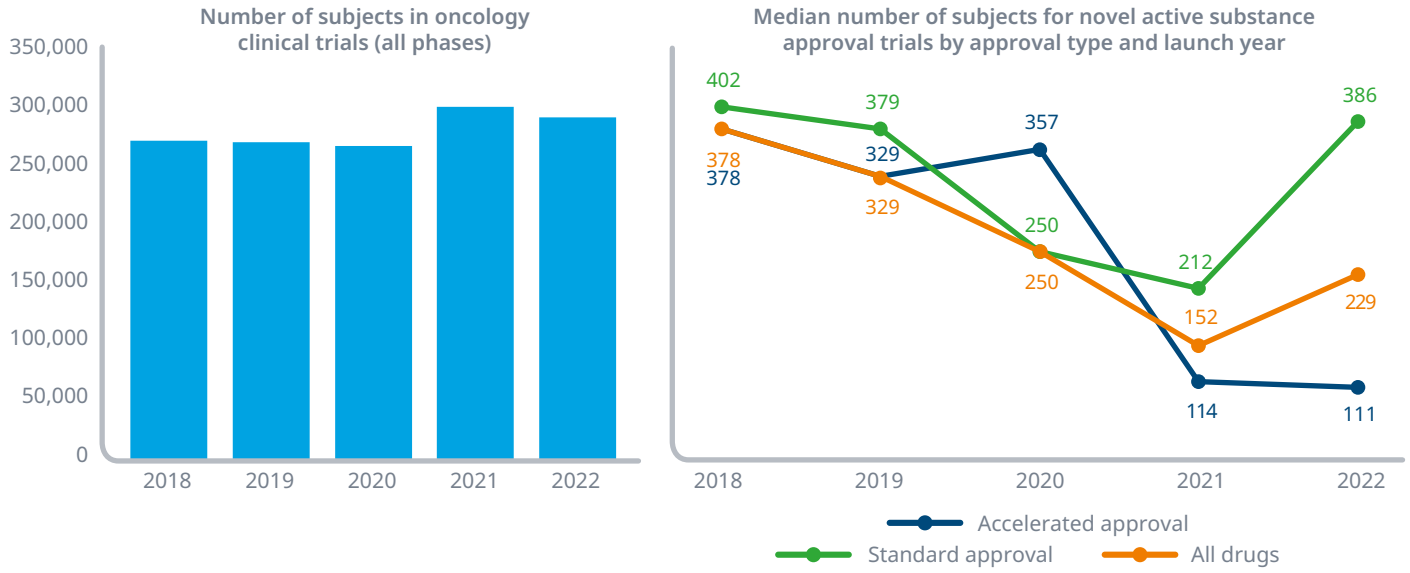
Source: Citeline Trialtrove, Jan 2023; IQVIA Institute, May 2023.

- Clinical trials take place across a range of geographies and while historically most have included sites in the U.S., this has shifted in recent years.
- Of trials started in 2022, 29% had sites only in the U.S. while an additional 14% were recruiting patients at sites both in the U.S. and globally ("global trials").
- Trials that include no U.S. sites accounted for 57% of trials in 2022, up from 42% a decade ago and primarily reflecting the rise of trial activity in China, with trials only being conducted domestically in China accounting for 57% of trials outside the U.S in 2022, up from 12% in 2013.
- The average number of sites per trial varies by geography, with global trials tending to have more five to ten times the number of sites as U.S. only or all other trials. All geographies, except U.S. only, saw declines in the average sites per trial in 2022.
- While the number of sites per trial has declined, the average number of subjects per site has increased, leading to the overall trend of more subjects (Exhibit 15).
- Subjects are spread across more sites in global trials compared to those in the U.S. only and those not including U.S. sites, which have two to three times as many subjects per site as global trials.

Notes: Phase I, I/II, II, IIa, Iib, III and II/III trials only. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry sponsored, interventional trials and device trials were excluded. Trials are plotted based on start date. Global trials are those with a mix of U.S. and ex-U.S. sites. All other trials are trials with no U.S. sites. Subjects are the reported target or actual patients reported for trials with planned or actual start dates in each year.

Number of subjects in oncology clinical trials fell 3% in 2022 while accelerated approvals tend to be based on fewer subjects

Exhibit 15: Oncology clinical trial subjects and number of subjects in novel active substance (NAS) approval trials by approval type



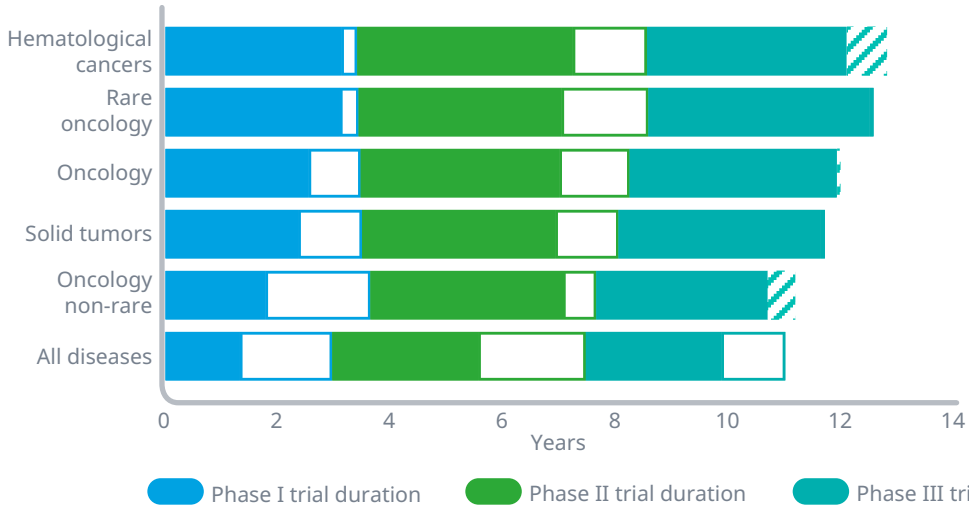
Source: Citeline Trialtrove, Jan 2023; IQVIA Institute, Apr 2023.

- The number of patients enrolled in oncology clinical trials globally has grown by over 36,000 in the last five years as the number of oncology clinical trials has grown.
- The number of subjects declined by 3% from 2021 to 2022 and grew 62% over the last decade, with oncology accounting for 16% of the industry's clinical trial subjects in 2022.[6]
- Of the 78 NASs launched in the U.S. in the last five years, only 22% have had more than 500 patients in their approval trials.
- NASs receiving accelerated approval tend to have a lower median number of subjects, with the four NASs launched in 2022 with accelerated approval having 106–311 patients in their approval trials.
- The median number of subjects for NAS approval trials was declining through 2021 but increased in 2022 driven by 2 NAS receiving standard approvals having pivotal trials with more than 700 subjects; however, the median remains below historic levels and reflects an increasing focus in recent years on targeted medicines for patients with specific tumor profiles and small population cancers with large unmet needs, with fewer focused on large patient populations.

Notes: Subjects are the reported target or actual patients reported for trials with planned or actual start dates in each year.

Oncology trials have significantly less "white space" than other therapy areas but longer trial durations

Exhibit 16: Comparison of trial duration to phase-change duration (years), 2013–2022



TRIALS	WHITE SPACE	TOTAL DURATION
11.1	0.9	12.7
10.5	1.9	12.5
9.8	2.1	11.9
9.3	2.3	11.6
8.7	1.9	11.1
6.3	4.7	10.9

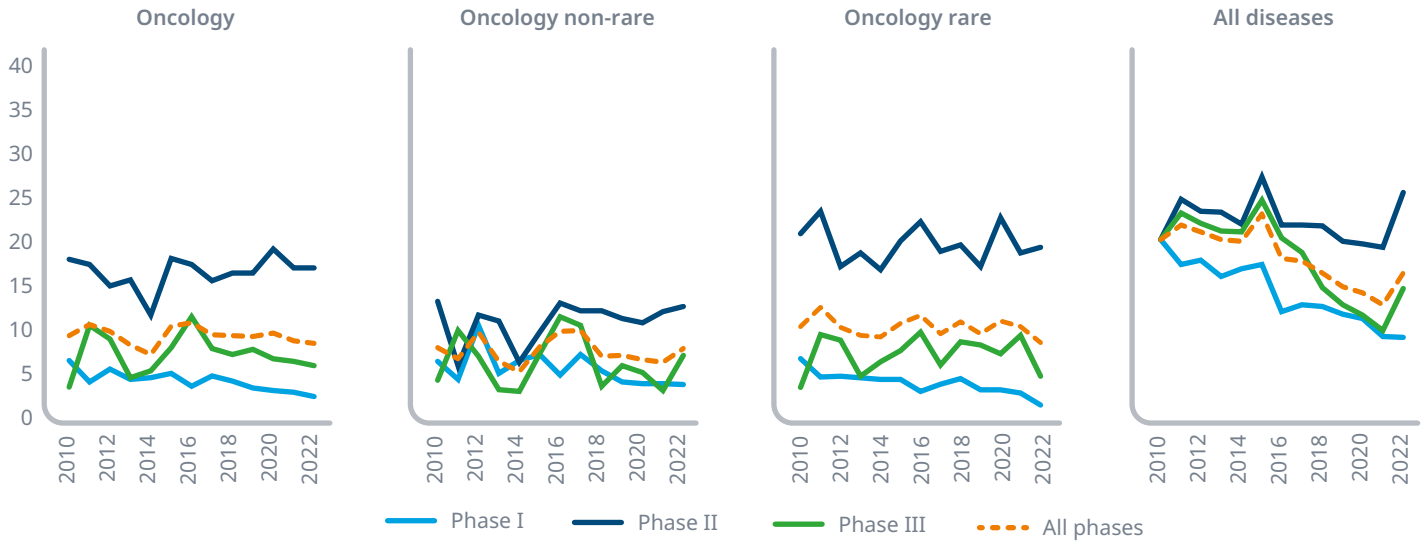
Source: IQVIA Pipeline Intelligence, Dec 2022; Citeline Trialtrove, Jan 2023; IQVIA Institute, Apr 2023.

- Reducing "white space" — the difference between the time a molecule takes to progress through clinical development and its clinical trial duration — is a major area of focus for sponsors who still must balance clinical and commercial risk carefully.
- On average, new drugs spend 43% of their development time in white space on the way to the patient, with this dropping to 18% for oncology drugs.
- The proportion of white space is significantly different for hematological cancer and solid tumor drugs, with hematological cancer drugs only spending, on average, 7% of total program duration in white space compared to 20% for solid tumor drugs.
- While oncology has the shortest average white space in the industry, it has the longest trial durations, and the trade-off of treatment and white space timing is likely partially driven by a high percentage of adaptive trials. Taking trial and white space time together, the total average program duration for oncology trials is nearly 12 years, one year longer than the average across all diseases.
- Oncology drugs are frequently submitted for regulatory review prior to final completion of their Phase III trials, allowing for earlier review of topline results in order to bring treatments to patients in an efficient manner.
- These results speak to a complex interplay between white space, trial timing and total program timing, with ongoing opportunities to optimize across all three.

Notes: Trial duration is counted from trial start to primary completion using Citeline Trialtrove. Phase duration is counted from phase start to subsequent phase start using IQVIA Pipeline Intelligence. The difference between these durations includes a variety of sponsor activities summarized in this analysis as "white space." Oncology trials demonstrate substantial diversity in trial and phase duration and as a result, the average trial duration is longer than the average phase duration, illustrated with mixed chart series.

Clinical development productivity indices for oncology extends a decade-long trend as lowest of all diseases

Exhibit 17: Clinical development productivity across all phases by therapy area, 2010–2022



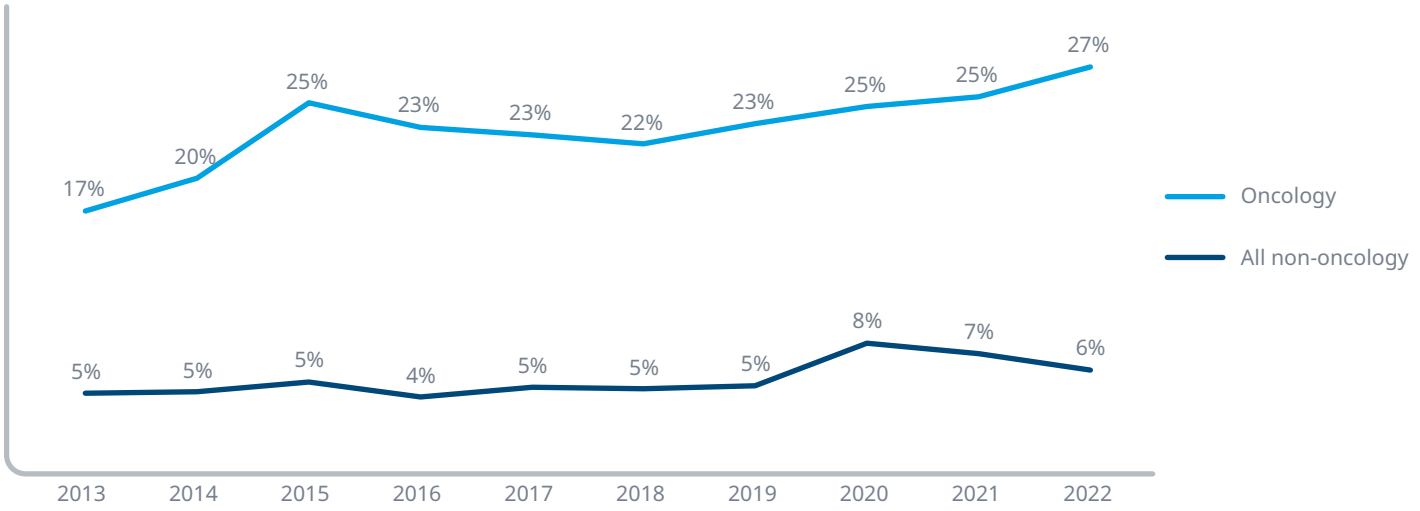
Source: IQVIA Pipeline Intelligence, Dec 2022; Citeline Trialtrove, Jan 2023; IQVIA Institute, Apr 2023.

- Oncology clinical development productivity — defined as the complexity factored by duration and then divided by the probability of success — has consistently been one of the lowest rates across the last decade.
- While productivity has generally declined across other disease areas, believed to be a result of increasing trial durations and decreasing probability of success, oncology productivity has remained relatively stable.
- Oncology productivity has been maintained due to higher productivity in rare oncology, driven by high productivity in Phase II.
- Non-rare oncology productivity was declining through 2021 but had a slight uptick in 2022 from increasing productivity in Phase II and Phase III due to higher success rates; however, non-rare oncology productivity remains 15% below productivity seen in rare oncology, driven by lower success and similar levels of complexity.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, devices, and medical procedures were excluded. Trial duration is based on trial dates reported in clinical trial databases. Trial start date is the date on which the enrollment of participants for a clinical study began. Trial end date corresponds to when the trial ended or is expected to end. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III.

Oncology trials more frequently use novel trial designs than trials for other diseases

Exhibit 18: Percent of industry-sponsored trials with novel trial design by start date, 2013–2022



Source: Citeline Trialtrove, Jan 2023; IQVIA Institute, Apr 2023.

- Novel trial designs in oncology — including adaptive, basket, umbrella, and master protocols — have more than tripled in the last decade and were used in more than 630 industry-sponsored trials started in 2022.
- Much of the growth in the use of novel trial designs in oncology occurred prior to 2015, with the share of oncology trials utilizing novel trial designs remaining stable since 2015.
- Oncology trials more frequently utilize novel trial designs than trials for other disease areas, with 27% of oncology trials utilizing these mechanisms compared to just 6% in all other disease areas in 2022.
- While there were more than 1,700 non-industry sponsored oncology trials started in 2022, which were not included in this analysis, only 7% of these used novel trials designs.
- Guidance for the Food and Drug Administration's Project Optimus, a new initiative to encourage sponsors to design trials to select an optimal treatment dose as opposed to maximum tolerated dose, recommends the use of adaptive design as a tool for better comparing multiple dosages.[8]
- Novel trial designs are often more complex, but they can consolidate phases, provide program efficiencies, and identify responding patients more effectively across a range of options, potentially bringing treatments to patients on a shorter timeline.

Notes: Phase I, I/II, II, IIa, Iib, III and II/III trials only. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry sponsored, interventional trials and device trials were excluded. Novel trial designs include umbrella, basket, adaptive, master protocol, dose escalation + dose expansion studies using a range of keyword strings.

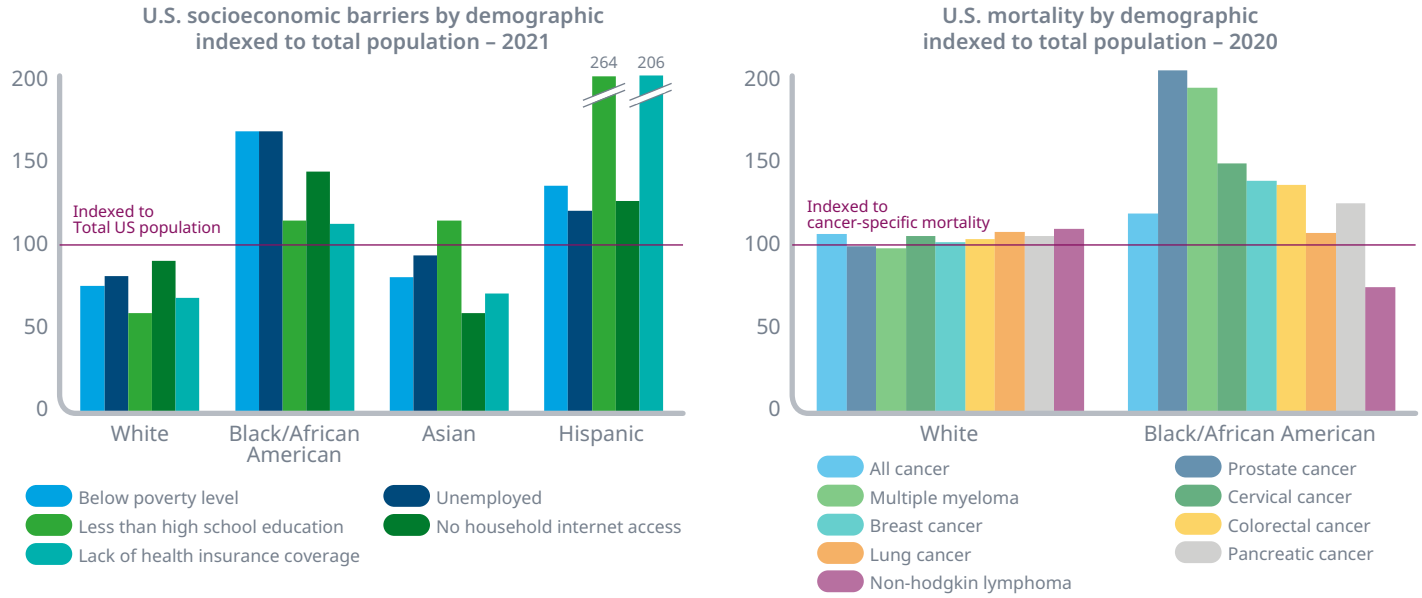
Diversity and inclusivity in oncology

- Socioeconomic and cancer outcome disparities are evident across racial and ethnic dimensions with Black/African American patients facing 20% higher likelihood of poverty and 12% higher mortality rates over the full population.
- Black/African American and Hispanic patient inclusion in oncology trials is among the lowest of all major therapeutic areas at 80% and 61% below their 2019 U.S. cancer incidence of 13.8% and 15.3%, respectively.
- Black/African American and Hispanic inclusivity is lower than expected when compared to cancer incidence and mortality is higher than average mortality across multiple cancers.
- Trial inclusivity differs with key operational decisions, most notably inclusion/exclusion criteria where trials with less than 21 selection criteria were nearly twice as inclusive of Black/African American patients versus those with more than 40 criteria.
- Black/African American, and to a lesser extent, Hispanic trial inclusion is higher in trials run entirely in U.S. sites, yet participation is still far below levels of cancer incidence for these populations.
- Planning and focus across the entire trial lifecycle can improve patient inclusivity.

Correlation of oncology trial inclusivity with number of patient selection criteria, trial subjects, and trial sites suggest strategic and operational opportunities to improve trial diversity.

Socioeconomic and cancer outcome disparities are evident across racial and ethnic dimensions

Exhibit 19: U.S. socioeconomic barriers and mortality by demographic indexed to total population



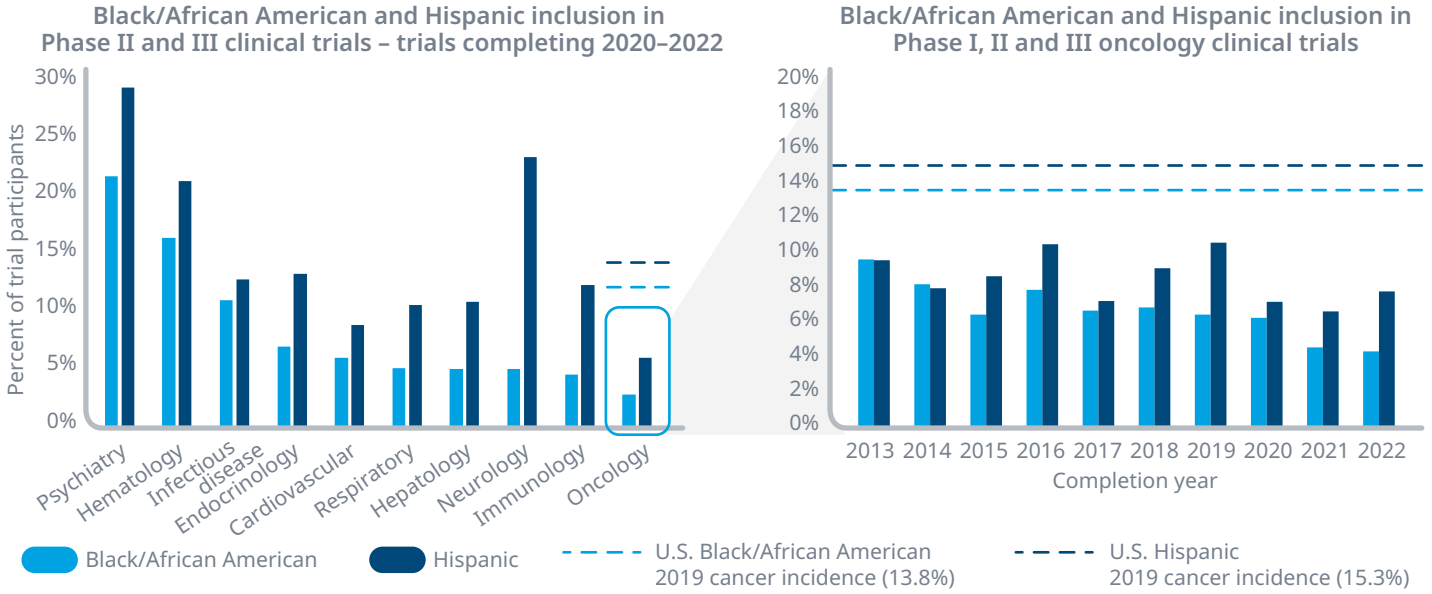
Source: U.S. Census Bureau, 2021; National Cancer Institute, IQVIA Institute, Apr 2023.

- Disparities in socioeconomic barriers persist across many patient sub-populations and are evident across racial and ethnic groups, with Black/African American and Hispanic populations more severely impacted on several key socioeconomic dimensions.
- Black/African American populations were 67% more likely than the average United States resident to be below the poverty line and face unemployment and are 12% less likely to have health care coverage, while Hispanic populations were nearly 20% more likely to be below the poverty line and were twice as likely to lack health care coverage.
- These socioeconomic barriers correlate to poorer health outcomes, which include cancer outcomes, with Black/African American populations in the U.S. experiencing 12% higher all cancer mortality rates in 2020 versus the rest of the U.S. population.
- Particularly acute disparities in U.S. mortality rates are evident in prostate cancer and multiple myeloma, where Black/African American patients experience nearly double the mortality as the rest of the population (95% and 83% higher mortality rates respectively) and breast cancer and colorectal with a nearly 30% higher mortality rate each.

Notes: U.S. socioeconomic analysis is based on 2021 American Community Survey 1-Year Estimates; National Center for Health Statistics. Health, United States, 2021: Table Age-adjusted death rates for selected causes of death, by sex, race, and Hispanic origin: United States, selected years 1950–2019. Hyattsville, MD. 2023 Apr 19, while mortality data is based on the latest data available (2020) from NCI SEER*Explorer.

Black/African American and Hispanic patient inclusion in oncology trials is among the lowest of all major therapeutic areas

Exhibit 20: Black/African American and Hispanic inclusion in Phase I, II, and III clinical trials



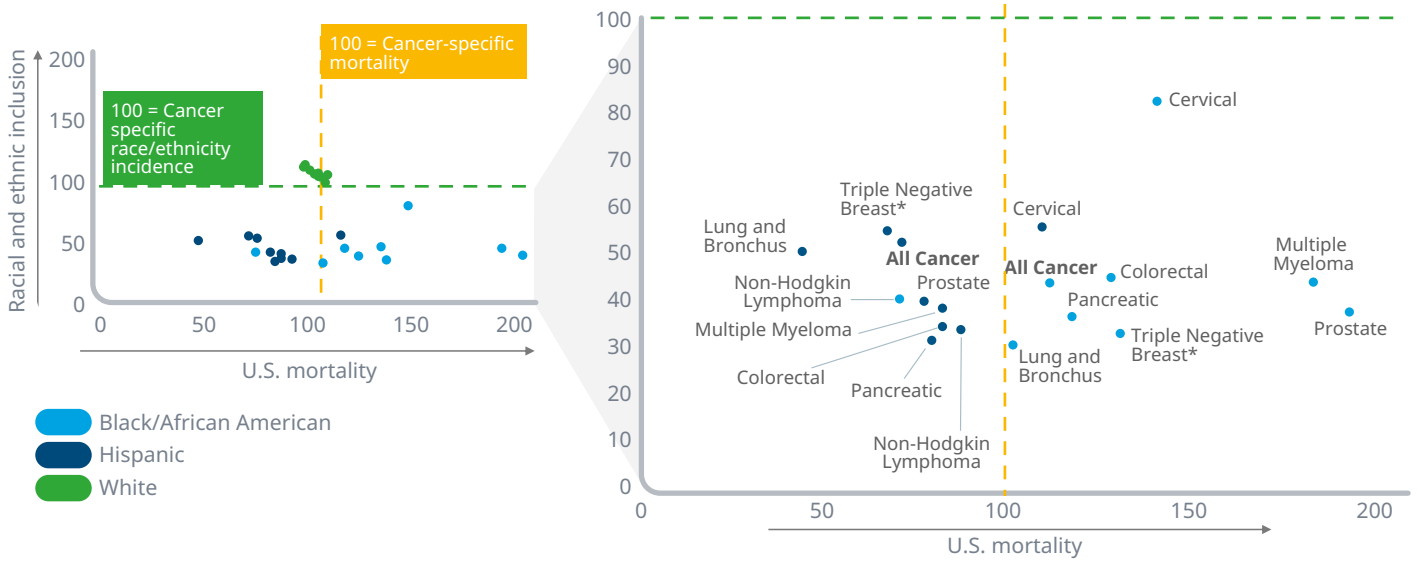
Source: U.S. Census Bureau, 2021; ClinicalTrials.gov, Citeline Trialtrove, National Cancer Institute, IQVIA Institute, Apr 2023.

- Focus on Black/African American and Hispanic representation in clinical trials across therapeutic areas reveals a wide range of inclusiveness with oncology phase II and III trial inclusion being the lowest, with only 2.8% Black/African American and 5.9% Hispanic patients in trials run 2020–2022, 80% and 61% below their 2019 U.S. cancer incidence of 13.8% and 15.3%, respectively.
- Despite increased focus on the importance of diversity in clinical trials as part of overcoming socioeconomic and healthcare disparities to improve health outcomes for all sub-populations in the past decade, this analysis demonstrates that oncology racial and ethnic sub-population clinical trial inclusion has not improved in the past decade.
- Specifically, clinical trial inclusion has declined by 45% for Black/African American and 26% for Hispanic patients in 2022 since 2016.
- Given the growing prominence of oncology trials in the industry clinical trial pipeline in the past decade (Exhibit 1), the low levels of racial and ethnic inclusivity in oncology trials is a driving factor in overall trial diversity.

Notes: Includes only interventional trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009. Only trials with racial or ethnic data collected were included in calculation of Black/African American or Hispanic patient inclusion, respectively. Analysis includes 1,494 trials over the time period. Latest available pre-COVID19 year (2019) data is used for U.S. cancer epidemiology and is based on NCI SEER*Explorer. See Methodology for additional details.

Black/African American and Hispanic inclusivity is lower and mortality is higher across multiple cancers

Exhibit 21: Racial and ethnic inclusion in Phase I, II, and III clinical trials completing 2013–2022 versus 2020 mortality, indexed to cancer specific epidemiology and all race/ethnicity mortality



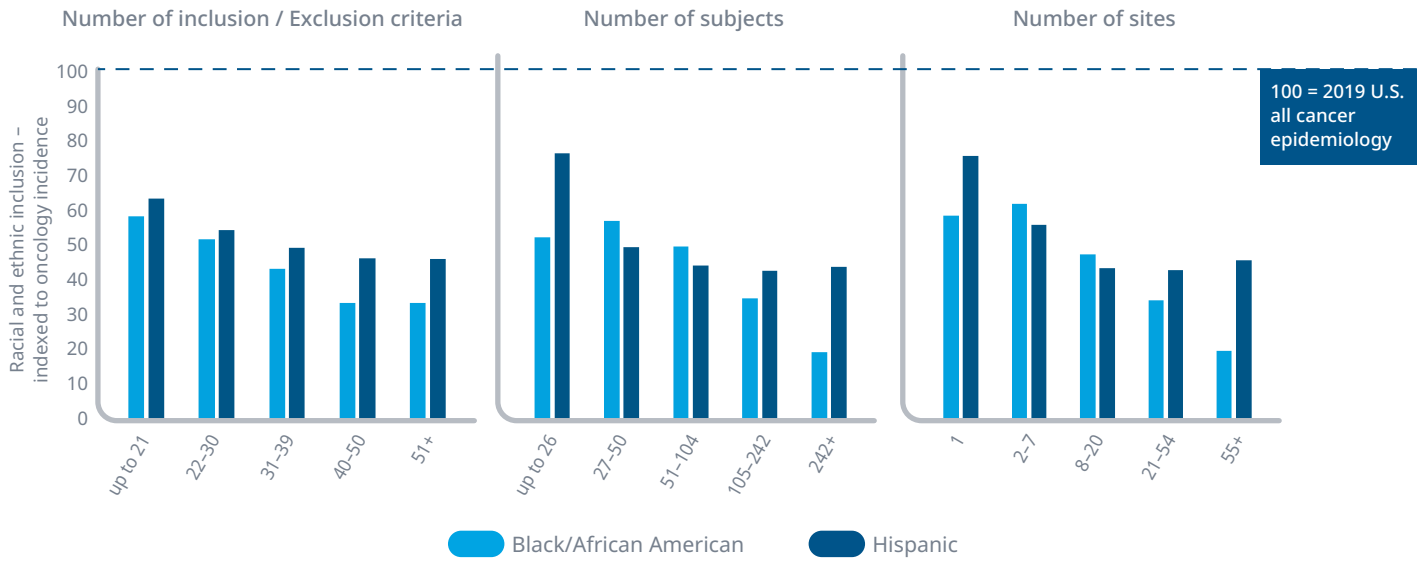
Source: ClinicalTrials.gov, Citeline Trialtrove, National Cancer Institute, IQVIA Institute, Apr 2023.

- White patients are included in oncology trials at rates close to their U.S. cancer incidence and are experiencing cancer mortality at rates that are consistently close to the average mortality across all cancers and a selection of eight specific cancers.
- In contrast, Black/African American patients have been included in clinical trials at only 45% the level of the average incidence across all cancers, and in only one of the cancer-specific cases analyzed are Black/African American patients included in clinical trials at more than 50% the expected rate based on cancer-specific incidence.
- Hispanic trial inclusion across all oncology trials is only 53% of the U.S. Hispanic cancer incidence rate, and no individual specific cancer type analyzed had more than 60% of the incidence predicted Hispanic patients included in trials completing between 2013 and 2022.
- At the same time, in all analyzed cancers but non-Hodgkin lymphoma, Black/African American patients experience higher than the U.S. mortality rate. In the cases of multiple myeloma and prostate cancer, Black/African American patients experience mortality at nearly twice the cross-population rate at 84% and 92%, respectively, above cancer-specific U.S. mortality rates.

Notes: Includes only interventional trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009. Only trials with racial or ethnic data collected were included in calculation of Black/African American or Hispanic patient inclusion, respectively. Analysis includes 1,494 trials over the time period. Latest available pre-COVID19 year (2019) data is used for U.S. cancer epidemiology and is based on NCI SEER*Explorer. See Methodology for additional details. *Triple-negative breast cancer uses total breast cancer mortality rate.

Trial inclusivity differs with key operational decisions, including inclusion/exclusion criteria, number of subjects, and trial sites

Exhibit 22: Black/African American and Hispanic inclusion in Phase I, II, and III oncology clinical trials by trial attribute – indexed to oncology epidemiology, 2013–2022



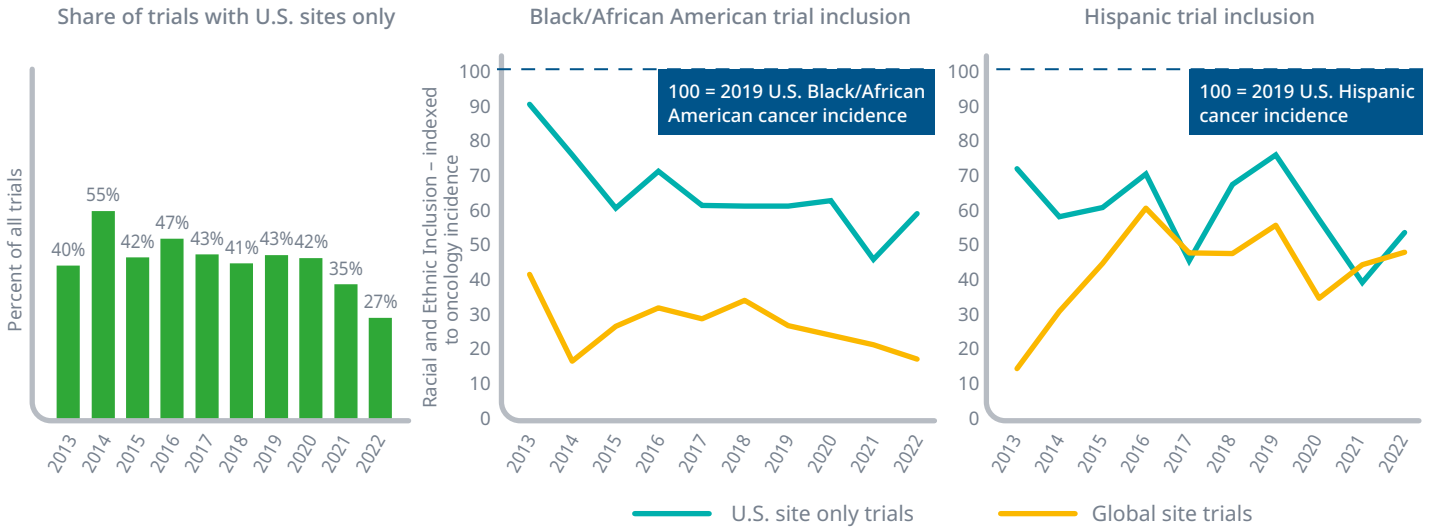
Source: ClinicalTrials.gov, Citeline Trialtrove, National Cancer Institute, IQVIA Institute, Apr 2023.

- Analysis of key clinical trial attributes showed a correlation of Black/African American and Hispanic oncology trial inclusivity with number of patient selection criteria, total number of trial subjects, and total number of trial sites suggesting key considerations for clinical planning to help improve inclusivity.
- Black/African American and Hispanic inclusion on oncology clinical trials decreased with increasing number of trial inclusion and exclusion criteria, with nearly a linear correlation for Black/African American inclusivity where trials with less than 21 selection criteria were nearly twice as inclusive versus those with more than 40 criteria.
- Similarly, inclusion of Black/African American and Hispanic patients was higher in trials with fewer patients, though Black/African American inclusion was slightly higher in the second quintile than the first, suggesting that achieving inclusivity may be more challenging in trials with very small numbers of patients (e.g., rare disease).
- Black/African American inclusivity drops to one-third its peak when patient numbers exceed 242, suggesting that it is also difficult to achieve a more diverse patient population in large trials.
- Single site trials and trials with between two to seven sites were most inclusive for both Black/African American and Hispanic patients, with diversity dropping for each in trials with more sites.

Notes: Includes only interventional trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009. Only trials with racial or ethnic data collected were included in calculation of Black/African American or Hispanic patient inclusion, respectively. Analysis includes 1,494 trials over the time period. Latest available pre-COVID19 year (2019) data is used for U.S. cancer epidemiology and is based on NCI SEER*Explorer. See Methodology for additional details. Number of inclusion/exclusion criteria, subjects, and sites are analyzed as quintiles.

Black/African American, and to a lesser extent, Hispanic trial inclusion is higher in trials run entirely in U.S. sites

Exhibit 23: Trial geography and Black/African American and Hispanic inclusion in Phase I, II, and III oncology clinical trials indexed to oncology epidemiology, 2013–2022



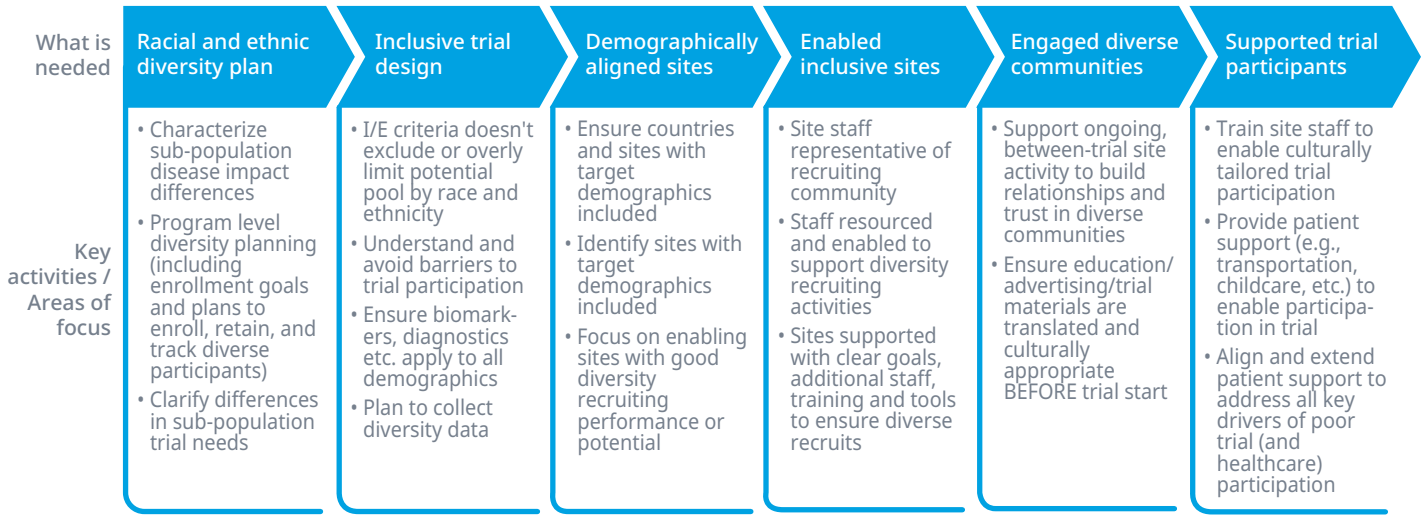
Source: ClinicalTrials.gov, Citeline Trialtrove, National Cancer Institute, IQVIA Institute, Apr 2023.

- Over the past decade, an average of 42% of all completed interventional, industry-involved, Phase I, II, and III trials, which collected diversity data, were conducted entirely in the U.S., peaking at 55% of the trials in 2014 and dropping to 27% of the trials in 2022.
- While Black/African American and to a lesser extent, Hispanic inclusion in trials remains the lowest in oncology among other therapy areas, both are higher in trials which were recruited exclusively in U.S. sites versus those run at a mix of U.S. and ex-U.S. (e.g., "global") sites.
- This observation suggests that inclusion of U.S. sites in oncology clinical trials is an important driver of better inclusivity of key racial and ethnic sub-groups.
- Despite this, even in U.S.-only trials, Black/African American and Hispanic patient inclusion has failed to reach oncology incidence levels across interventional Phase I, II, and III trials, and Black/African American and Hispanic subjects continue to be critically under-represented in trials being conducted at both U.S. only and global sites.
- Although both Black/African American and Hispanic inclusion are higher in oncology trials recruited exclusively in the U.S., their general under-representation in trials is indicative of a continued need for combined operational efforts to address clinical trial inclusivity as part of the solution to ongoing healthcare disparities.

Notes: Includes only interventional trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009. Only trials with racial or ethnic data collected were included in calculation of Black/African American or Hispanic patient inclusion, respectively. Analysis includes 1,494 trials over the time period. Latest available pre-COVID19 year (2019) data is used for U.S. cancer epidemiology and is based on NCI SEER*Explorer. See Methodology for additional details. Number of inclusion/exclusion criteria, subjects and sites are analyzed as quintiles. "Global" trials are those with a mix of U.S. and ex-U.S. sites. "All" trials include trials with no U.S. sites.

Planning and focus across the entire trial lifecycle can improve patient inclusivity

Exhibit 24: Focus areas for building diversity into confirmatory clinical trials



Source: Advancing Diversity in Clinical Development through Cross-Stakeholder Commitment and Action: An Update on Progress and Results. November 2022. Report by the IQVIA Institute for Human Data Science.

- As FDA guidance and U.S. legislation framing and required clinical trial diversity planning continue to be refined and take effect,[9,10] sponsors have an opportunity to be more proactive in researching and building inclusiveness into trials from program start.
- Understanding the impact of key design decisions, including number and type of inclusion/exclusion criteria for trial participation and use of biomarkers to target sub-populations to optimize drug efficacy, will need to be balanced with impacts on trial diversity.
- Likewise, considering country selection and number and types of sites through the lens of improving diversity as well as optimizing timelines are critical decisions for building inclusive trials.
- Investment in existing clinical development sites, and trial-naïve site capabilities and capacity to enable diverse patient participation, remains a rich area of opportunity to deliver more inclusive trials.
- Finally, focus on patient needs across all communities to ensure equal access to clinical trials through patient and healthcare professional education, advocacy, and specific patient support investments is also critical to ensuring optimized patient diversity in clinical trials.

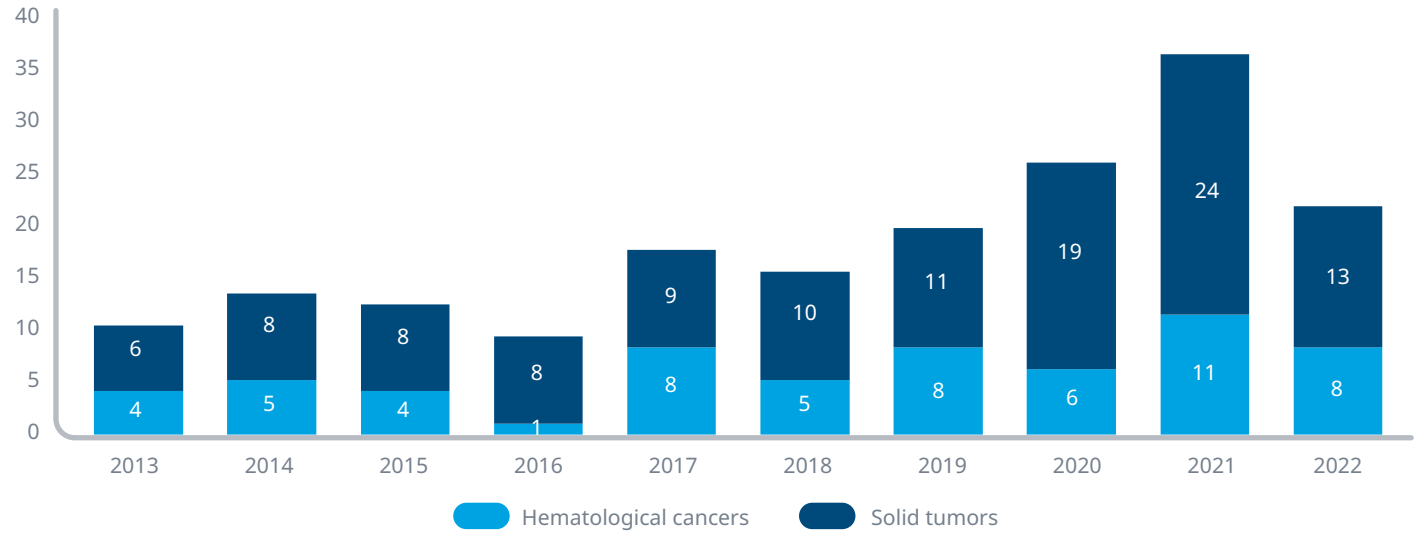
Novel active substances in oncology

- Twenty-one oncology novel active substances (NASs) were initially launched globally in 2022, with 176 total since 2013.
- A total of 115 oncology NASs have launched globally in the past five years and 237 over 20 years, with new medicines not reaching all major markets.
- There were 10 new cancer medicines launched in the U.S. in 2022 across a variety of solid tumors and hematological cancers, with nine that were orphan designated.
- Oncology drugs used increasingly for rare cancers, recombinant, and approved based on a single trial and the share of new oncologics administered orally have been declining over the last five years.
- Since 2013, 89 NASs were launched in the U.S. to treat solid tumors with some approved for multiple indications.
- In the U.S., 53 unique new hematological cancer medicines have been launched since 2013 with concentrations of innovation in non-Hodgkin lymphoma and multiple myeloma.
- New launches in the U.S. in 2022 provide significant clinical benefits to patients across a range of tumors and mechanisms.
- Time from patent to launch increased by two years for oncology NASs launched in 2022 even as two launched in less than five years.
- Emerging biopharma companies originated 70% of new oncology drugs in 2022 and launched 71% of their own products.
- The EMA approved six small molecule and eight biologic NASs for oncology in 2022, more than the 10 total approved in 2021.
- Since 2013, 27% of U.S. oncology NASs haven't launched in Europe, while 2% of Europe launches haven't reached the U.S., reflecting variations in launch strategies by companies as NASs tend to launch in the U.S. first.

Twenty-one oncology novel active substances (NASs) launched globally in 2022, a decline from the record 35 launched in 2021, and a total of 115 in the past five years.

21 oncology novel active substances (NASs) were initially launched globally in 2022 with 176 total since 2013

Exhibit 25: Global oncology launches of novel active substances (NAS), 2013–2022



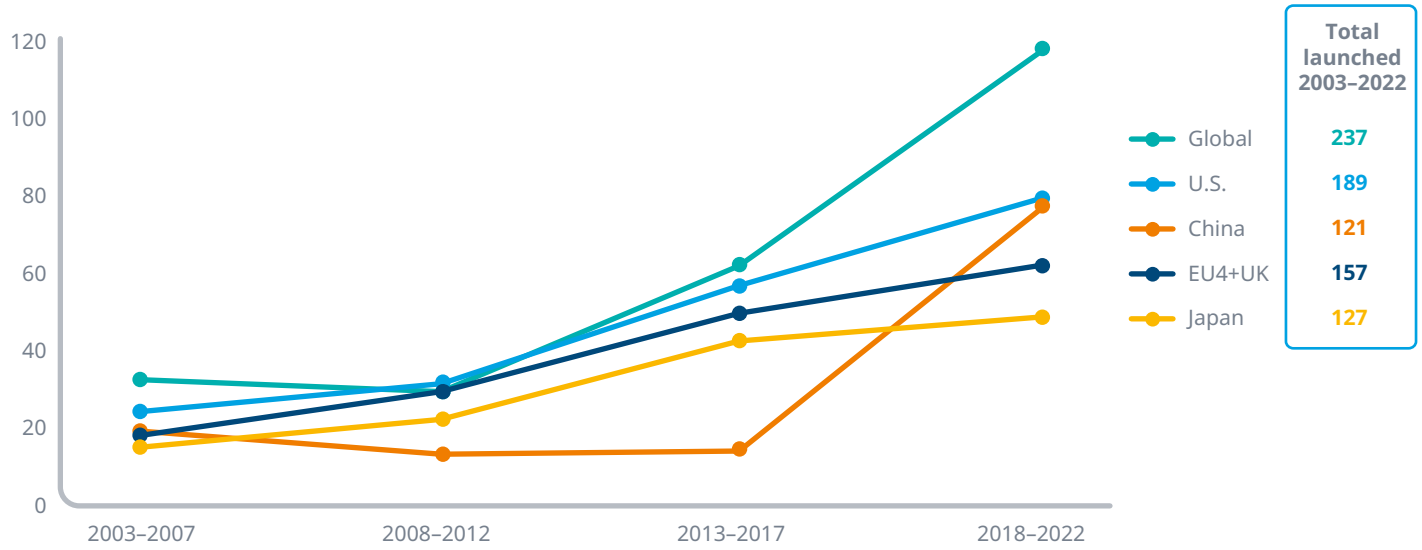
Source: IQVIA Institute, Apr 2023.

- In 2022, 21 novel active substances (NASs) for oncology launched globally, bringing the average annual new launches from 2018–2022 to 23 compared to an average of 12 annually in the five years prior.
- Following a record number of NASs for oncology launched in 2021, NAS launches fell in 2022 due to seven fewer launched only domestically in China compared to 2021 and seven fewer oncology NASs approved in the U.S. via accelerated approval.
- Two-thirds of oncology NAS launches have been for solid tumors in recent years, with 77 launches for solid tumors in the last five years, up from 39 in the five years prior.
- While a majority of innovation has been in solid tumors, hematological cancers continue to see increased innovation, with 38 NASs launched for hematological cancers in the last five years, up from 22 in the five years prior.
- Many of the NAS launched have multiple indications, further increasing the number of patients who may benefit from these novel compounds.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; includes NASs launched anywhere in the world by year of first global launch. Oncology includes diagnostics.

A total of 115 oncology NASs have launched globally in the past 5 years and 237 over 20 years with large geographic variations

Exhibit 26: Number of oncology novel active substances launched globally and in selected countries



Source: IQVIA Institute, Apr 2023.

- Globally, 237 NASs have launched to treat cancers in the last 20 years, with nearly half of these (115) in the last five years.
- The U.S. has seen 78 NAS launches for oncology in the last five years, with 189 over the last 20 years, and has consistently been first to launch the majority of new cancer medicines worldwide.
- Notably, 40 global NASs launched in the last five years have not launched in the U.S., and all but four were first launched in China or Japan, suggesting the emergence of divergent sources and destinations of innovation.
- EU4+UK has had 61 oncology NASs launched in the last five years and 157 over the 20-year period.
- China had 75 oncology NASs launched in the most recent five-year period compared to 46 from 2003–2017. This is likely driven by regulatory acceleration mechanisms from the National Medical Products Administration (NMPA) to bring both domestic and foreign developed drugs to Chinese citizens faster.
- Of the 75 NASs launched in China during 2018–2022, 28 have only been launched in China, with few having no development activity outside of China.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new and is noted in the year it launched for the first time in the relevant geography. Oncology includes diagnostics.

There were 10 new cancer medicines launched in the U.S. in 2022, with 9 that were orphan designated

Exhibit 27: Oncology novel active substances launched in the U.S. in 2022

*ATTRIBUTES KEY: 1 = Oral 2 = Biologic 3 = Specialty 4 = Next-gen biotherapeutic 5 = Orphan 6 = First-in-class 7 = Expedited review 8 = U.S. patent to launch ≤5 years 9 = EBP originated 10 = EBP launched

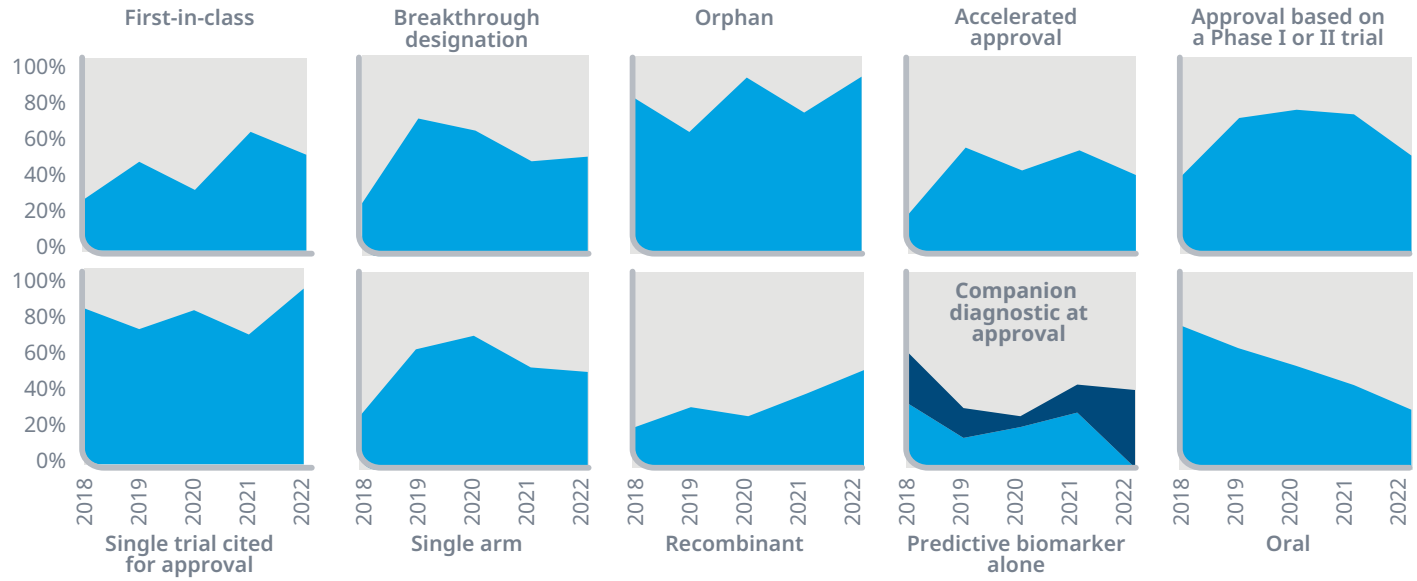
THERAPY AREA	INDICATION	MOLECULE	BRAND	ATTRIBUTES									
				1	2	3	4	5	6	7	8	9	10
Oncology	Acute myeloid leukemia	olutasidenib	Rezlidhia	●		●		●			●	●	●
	FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	mirvetuximab soravtansine	Elahere		●	●		●	●	●		●	●
	Hepatocellular carcinoma	tremelimumab	Imjudo		●	●		●		●			
	Myelofibrosis	pacritinib	Vonjo	●		●		●		●		●	●
	Non-small cell lung cancer (NSCLC)	adagrasib	Krazati	●		●		●		●	●	●	●
	Prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC)	lutetium (177Lu) vipivotide tetraxetan	Pluvicto			●			●	●		●	
	Relapsed or refractory multiple myeloma	ciltacabtagene autoleucel	Carvykti		●	●	●	●		●		●	
		teclistamab	Tecvayli		●	●		●	●	●			
	Unresectable or metastatic melanoma	nivolumab + relatlimab	Opdualag		●	●		●	●	●			
	Unresectable or metastatic uveal melanoma	tebentafusp	Kimmtrak		●	●		●	●	●		●	●
Totals				3	6	10	1	9	5	9	2	7	5

Source: IQVIA Institute, Apr 2023.

- Ten oncology novel active substances were launched in the U.S. in 2022 across a variety of solid tumors and hematological cancers.
- Nine of these NASs launched with orphan drug designations and half were first-in-class, indicating a focus on new mechanisms of action to treat rare cancers.
- Two of the oncology NASs launched in 2022 were for relapsed or refractory multiple myeloma and included a CAR T-cell therapy and the first bispecific antibody approved for multiple myeloma, which is a BCMA-directed CD3 T-cell engager.
- New launches in 2022 also included tebentafusp, a gp100 peptide-HLA-directed bispecific T-cell engager, for the treatment of patients with unresectable or metastatic uveal melanoma, becoming the first and only FDA-approved therapy for this rare and often fatal form of cancer.

Oncology drugs increasingly for rare cancers, recombinant, and approved based on a single trial

Exhibit 28: U.S. oncology NAS launches by characteristics of approval, 2018–2022



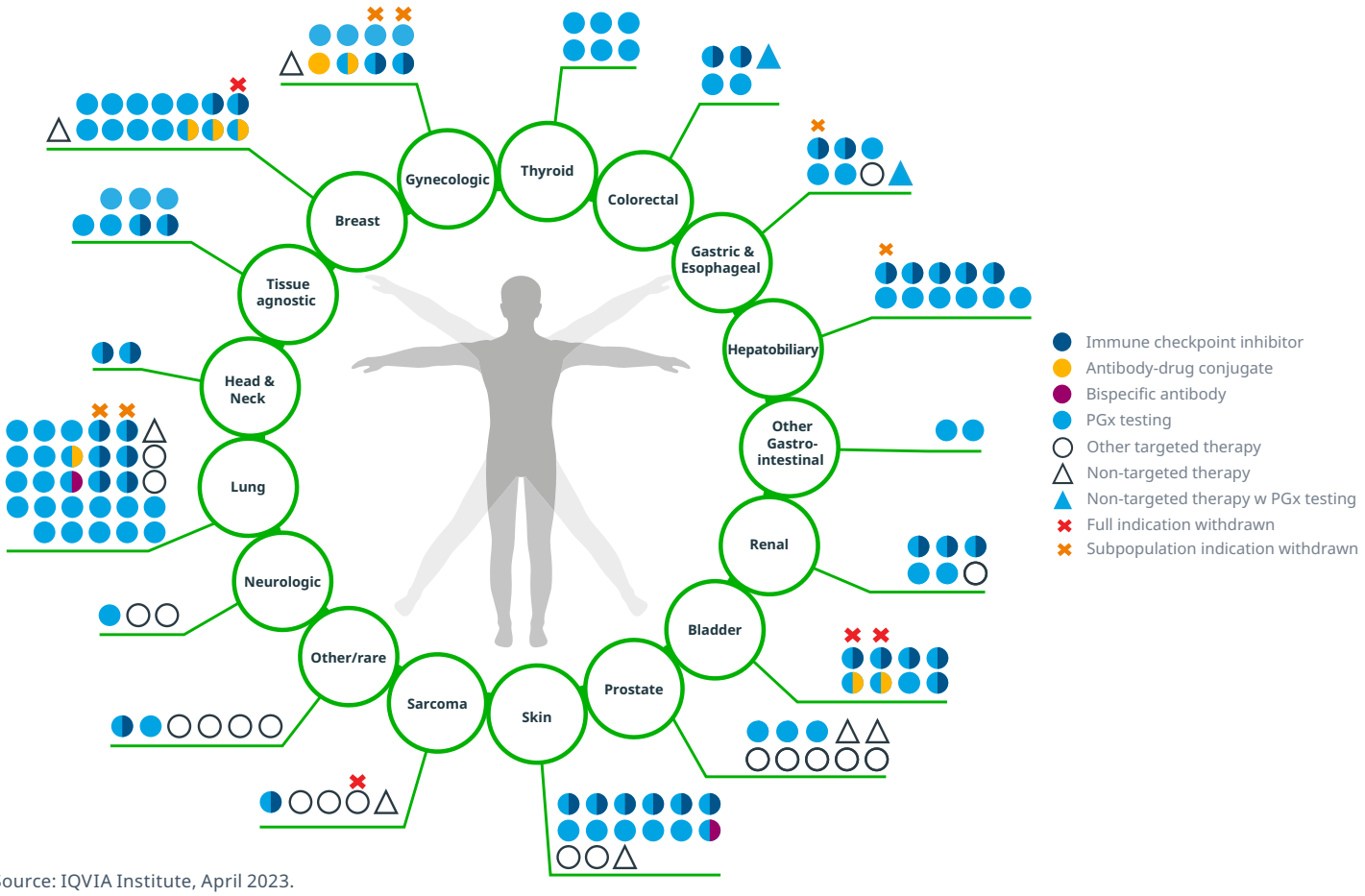
Source: IQVIA Institute, Apr 2023.

- Most of the discovery and development of new oncology medicines in recent years has focused on patients with rare cancers where few, if any, treatments may already exist, and 78% of NAS launches in the last five years received one or more orphan designations.
- Drugs that were first-in-class using a novel mechanism represent an increasing share of NAS launches in oncology, with 50% in 2022 and 44% in the last five years.
- Though there were 11 (52%) oncology NASs launched in 2021 with accelerated approvals, only four (40%) of the new oncology drugs launched in 2022 received accelerated approvals. This follows the notable withdrawal of nine accelerated approval indications in 2021, and the FDA released draft guidance in March 2023 for clinical trials to support accelerated approvals.[11]
- Many of the medicines over the past five years have been approved based on relatively limited trial evidence, in single trials with a single study arm, and based on their demonstrated evidence in earlier phase trials.
- The share of new oncologics administered orally has been declining over the last five years, with 30% of the launches in 2022 administered orally compared to 73% in 2018. This comes as there is a shift back to biologics following a wave of small molecule kinase inhibitors.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; includes NASs launched in the U.S. 2018–2022 regardless of the timing of FDA approval. Oncology includes diagnostics. Orphans include drugs with one or more orphan indications approved by the FDA at product launch. Products are not reclassified in this analysis as orphan if they subsequently receive an approval for an orphan designated indication after the launch year.

Since 2013, 89 NASs were launched in the U.S. to treat solid tumors with some approved for multiple indications

Exhibit 29: U.S. NASs in solid tumors launched 2013–2022 with indications, including those granted after initial launch



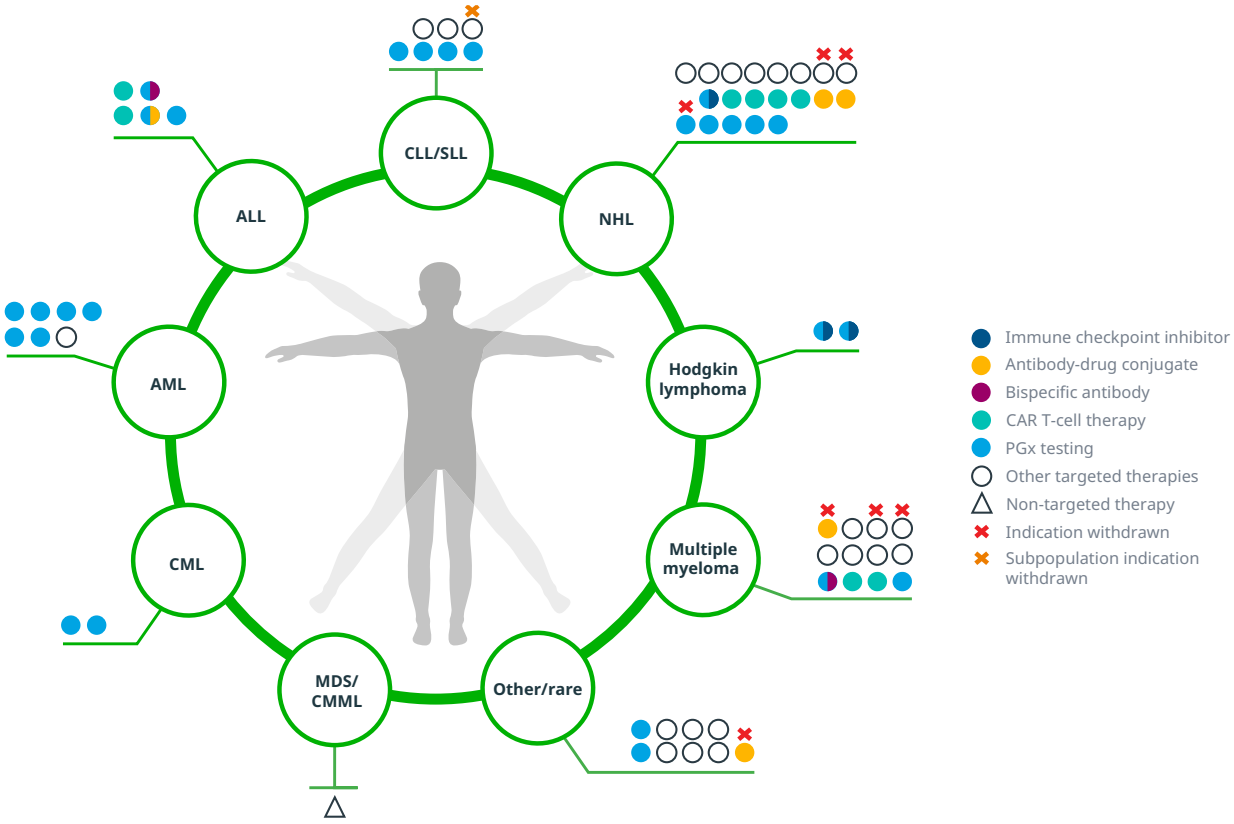
Source: IQVIA Institute, April 2023.

- Eighty-nine novel cancer drugs have launched in the U.S. since 2013 to treat solid tumors, with 22 approved for multiple indications since launch.
- Significant innovation has occurred in lung cancer, with 29 products launched and nearly all targeted therapies for a variety of biomarker subtypes, including eight checkpoint inhibitors (two of which have been withdrawn for small cell lung cancer), one bispecific antibody, and one antibody-drug conjugate.
- Breast cancer has had 15 new medicines launched for treatment since 2011, including two antibody-drug conjugates targeting HER2-positive breast cancer and one targeting triple-negative breast cancer.
- Fifteen new medicines have launched for skin cancers in the last decade, with 12 indicated for the treatment of melanoma. This includes six checkpoint inhibitors and one bispecific antibody.

Notes: Oncology includes diagnostics. Targeted therapies are cancer treatments that target specific genes and proteins that are involved in the growth and survival of cancer cells. PGx testing is a type of genetic test that assesses a patient's risk of an adverse response or likelihood to respond to a given drug, informing drug selection and dosing. Gynecologic cancers include cervical cancer, endometrial cancer, and ovarian cancer. Neurologic cancers include neuroblastoma and neurofibromatosis. Other gastrointestinal includes gastroenteropancreatic neuroendocrine tumors and pancreatic cancer. Other/rare includes cancers associated with von Hippel-Lindau disease, pleural mesothelioma, tenosynovial giant cell tumor, and neuroendocrine and adrenal tumors. Skin includes basal cell carcinoma, melanoma, merkel cell carcinoma, and squamous cell carcinoma. Products with multiple attributes are represented with more than one color. Products may be approved for more than one indication within each type of cancer (e.g., small cell lung cancer and non-small cell lung cancer) but are only represented once. Withdrawals are indicated as full indiciation withdrawn if the product had all approvals within that group of cancers withdrawn or revoked and subpopulation indication withdrawn if the product had an indication withdrawn but is still approved for at least one cancer within that group.

In the U.S., 53 unique new hematological cancer medicines have been launched since 2013

Exhibit 30: U.S. NASs in hematological cancers launched 2013–2022 with indications, including those granted after initial launch



Source: IQVIA Institute, April 2023.

- Fifty-three novel hematological cancer drugs have launched in the U.S. since 2013, with 16 approved for multiple indications since launch.
- Non-Hodgkin lymphoma has seen the most innovation in hematological cancers, with 20 new drugs launched since 2013. This includes four CAR T-cell therapies and two antibody-drug conjugates predominantly for the treatment of relapsed or refractory large B-cell lymphoma or follicular lymphoma.
- Twelve new drugs have been launched since 2013 to treat multiple myeloma, including two CAR T-cell therapies, one antibody-drug conjugate, and one bispecific antibody. Notably three products for the treatment of multiple myeloma have been withdrawn, including an antibody-drug conjugate receiving accelerated approval where the confirmatory trial failed to meet its primary endpoint.[12]

Notes: Oncology includes diagnostics. ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CLL=chronic lymphocytic leukemia; CML=chronic myeloid leukemia; CMML=chronic myelomonocytic leukemia; MDS=myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; SLL=small lymphocytic lymphoma. Targeted therapies are cancer treatments that use drugs to target specific genes and proteins that are involved in the growth and survival of cancer cells. PGx testing is a type of genetic test that assesses a patient's risk of an adverse response or likelihood to respond to a given drug, informing drug selection and dosing. Other/rare includes advanced systemic mastocytosis, blastic plasmacytoid dendritic cell neoplasms, Castleman's disease, Erdheim-Chester disease, myelofibrosis, hairy cell leukemia, and polycythemia vera. Products may be approved for more than one indication within each type of cancer (e.g., diffuse large B-cell lymphoma and follicular lymphoma) but are only represented once. Withdrawals are indicated as full indiciation withdrawn if the product had all approvals within that group of cancers withdrawn or revoked and subpopulation indication withdrawn if the product had an indication withdrawn but is still approved for at least one cancer within that group.

New launches in the U.S. in 2022 provide significant clinical benefits to patients across a range of tumors and mechanisms

Exhibit 31: U.S. oncology NASs launched in 2022 and summary of clinical benefits

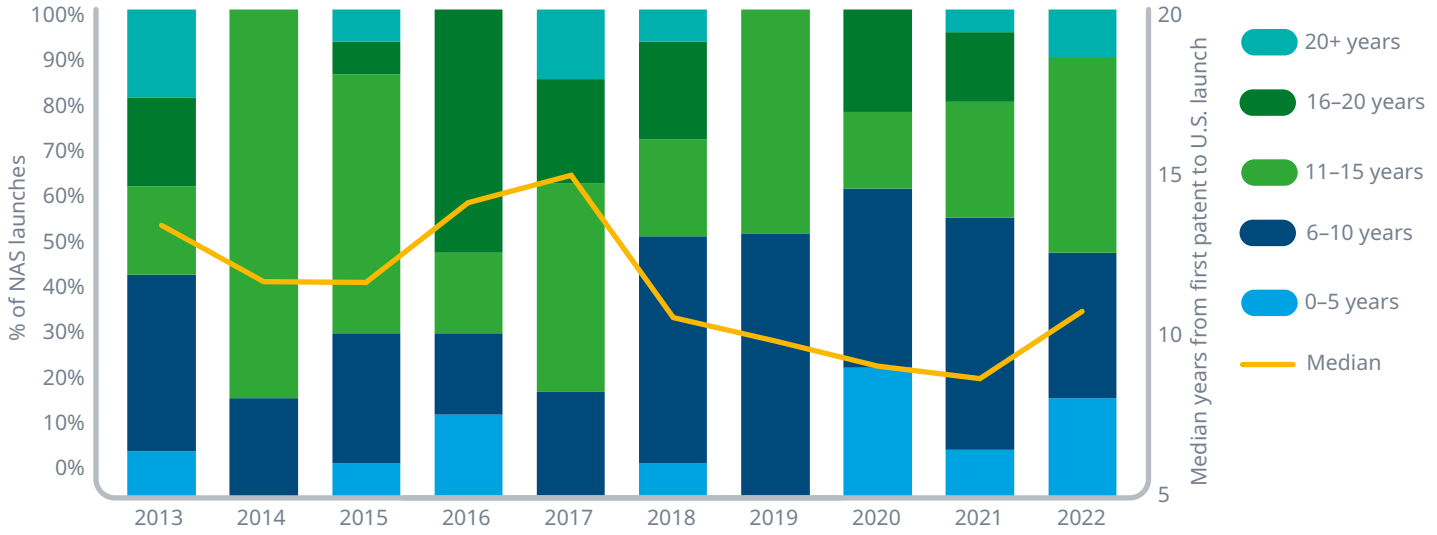
INDICATION	MOLECULE	TARGET	PROFILE
Melanoma	nivolumab + relatlimab	PD-1 + LAG-3	The review used the Real-Time Oncology Review (RTOR) pilot program. This application was granted priority review, fast track designation, and orphan drug designation. Median PFS was 10.1 months with nivolumab + relatlimab vs. 4.6 months for nivolumab alone.
Multiple myeloma	ciltacabtagene autoleucel	BCMA	FDA approved ciltacabtagene autoleucel CAR T for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy. The ORR was 97.9%. The median DOR was 21.8 months.
Primary or secondary myelofibrosis	pacritinib	JAK2 and FLT3 I	Received accelerated approval to treat adults who have a rare form of a bone marrow disorder known as intermediate or high-risk primary or secondary myelofibrosis and a platelet count below 50,000/μL. Effectiveness was measured by proportion of patients who had a 35% or greater spleen volume reduction: 29% of patients treated with pacritinib had a 35% or greater reduction compared to 3% receiving SOC.
Uveal melanoma	tebentafusp	gp100 peptide-HLA x CD3	FDA approved the first T-cell receptor therapeutic, first bispecific T-cell engager for solid tumors, and first therapy for the treatment of unresectable or metastatic uveal melanoma. This review was conducted under Project Orbis and used the Real-Time Oncology Review (RTOR) pilot program. The median OS was 21.7 months for tebentafusp treated patients vs. 16 months in the comparator group.
Prostate cancer	lutetium (177Lu) vipivotide tetraxetan	PSMA	FDA approved lutetium (177Lu) vipivotide tetraxetan as the first therapeutic radioligand for metastatic castration-resistant prostate cancer. The radioligand delivers radiation to PSMA-expressing cells. Median OS was 15.3 months for patients treated with Pluvicto + SOC vs. 11.3 months with SOC alone. The FDA also approved Locametz (gallium Ga 68 gozetotide), a radioactive diagnostic agent for PET of PSMA-positive lesions, to select patients for lutetium (177Lu) vipivotide tetraxetan.
Multiple myeloma	teclistamab	BCMA x CD3	The first bispecific BCMA-directed CD3 T-cell engager received an accelerated approval from FDA for adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy. The review was conducted under Project Orbis. The ORR was 61.8%. The estimated DOR was 90.6% at 6 months and 66.5% at 9 months.
Hepatocellular carcinoma	tremelimumab	CTLA-4	FDA approved tremelimumab in combination with durvalumab for adult patients with unresectable hepatocellular carcinoma. The median OS was 16.4 months vs. 13.8 months in those treated with sorafenib. The ORR was 20.1% vs. 5.1% in the comparator.
Epithelial ovarian, fallopian tube, or primary peritoneal cancer	mirvetuximab soravtansine	Folate receptor alpha (FRα)	FDA granted accelerated approval to mirvetuximab soravtansine, first-in-class ADC directed against FRα and is the first ADC approved for platinum-resistant disease. The FDA also approved the VENTANA FOLR1 RxDx Assay as a companion diagnostic. The ORR was 31.7% and median DOR was 6.9 months.
Acute myeloid leukemia	olutasidenib	IDH1	FDA approved olutasidenib for adult patients with relapsed or refractory acute myeloid leukemia with a susceptible IDH1 mutation. The CR+CRh rate was 35%, median time to CR+CRh was 1.9 months, and median duration of CR+CRh was 25.9 months. The FDA also approved the Abbott Real-time IDH1 Assay to select patients for olutasidenib.
Non-small cell lung cancer	adagrasib	KRAS G12C	Received accelerated approval from FDA for adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer. FDA also approved the QIAGEN therascreen KRAS RGQ PCR kit (tissue) and the Agilent Resolution ctDx FIRST Assay (plasma) as companion diagnostics. The ORR was 43% and median DOR was 8.5 months.

Source: IQVIA Institute, Apr 2023.

Notes: Summary of trials used as the basis for FDA approval of relevant drugs. PFS = progression-free survival; ORR = overall response rate; DOR = duration of response; SOC = standard of care; OS = overall survival; ADC = antibody-drug conjugate; CR+CRh = complete remission (CR) plus complete remission with partial hematologic recovery (CRh).

Time from patent to launch increased by 2 years for oncology NASs launched in 2022 even as 2 launched in less than 5 years

Exhibit 32: Time from first patent filing and U.S. launch for oncology novel active substances (NASs), 2013–2022



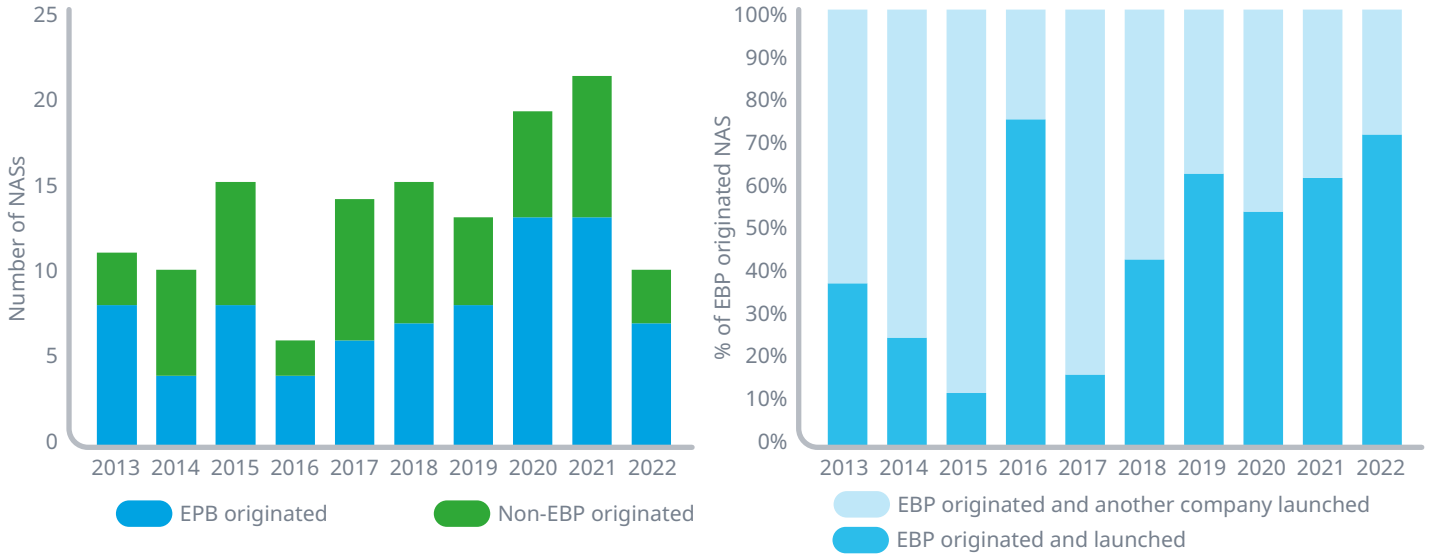
Source: IQVIA ARK Patent Intelligence, IQVIA Institute, Apr 2023.

- The time between the first patent filing for a drug and the launch into the market represents an important assessment of the amount of protected life remaining when a product launches.
- The median patent to launch for the 2022 oncology NAS cohort was 10.7 years, a two-year increase from the 2021 cohort and reversing a four-year trend of declining time to launch.
- Despite this increase in median time to launch, 50% of oncology NASs launched in 2022 had patent to launch times less than 10 years, with 20% less than five years.
- When looking at the time from initiation of the first clinical trial for a new medicine to launch, the median time from the initiation of trials to launch has fluctuated between six and eight years since 2016 and declined by one year in the 2022 cohort to 6.6 years, more than four years less than time from patent to launch.
- Tremelimumab, a CTLA-4 inhibitor launched in 2022, was first patented in 1998 and began clinical trials six years later. Nearly 90 trials had been completed or terminated for tremelimumab before it was approved by the FDA in late 2022 in combination with durvalumab for the treatment of hepatocellular carcinoma. This highlights the sometimes lengthy journey new medicines can take before reaching patients, with setbacks along the way.

Notes: For each novel active substance (NAS) launched, the first patent filing was researched to determine the time difference. The patent is not necessarily the binding patent that determines loss of exclusivity but represents the first time the sponsor deemed the innovation worthy of filing. Oncology includes diagnostics. Time from first patent filing to launch relates to the first indication(s) regardless of the future withdrawal or revocation of those indications.

Emerging biopharma companies originated 70% of new oncology drugs in 2022 and launched 71% of their own products

Exhibit 33: Companies originating and filing FDA regulatory submissions for oncology NASs and percent of launches by NAS launch year



Source: IQVIA Institute, Apr 2023.

- Seven oncology NASs launched in 2022 were originated by emerging biopharma (EBP) companies, representing a larger share of new medicines in 2022 than prior years.
- Although the share of NASs launched that are EBP originated varies significantly from year-to-year, EBP companies have originated 62% of U.S. NAS launches over the past five years, up from 54% over the previous five years and indicating increased EBP innovation reaching the market.
- Oncology products originated by EBPs are increasingly launched by an EBP company, indicating more independence on the part of EBP companies in taking products from innovation to market.
- EBP companies launched 71% of their own products in 2022, with five EBP originated and launched NASs. This was the largest share of total NASs that were EBP originated and launched (50%) over the last decade (average = 28%), except for a similar share in 2016 when there were only six new oncology medicines launched in the U.S.

Notes: Oncology includes diagnostics. NAS Launches in the U.S. have been segmented by the originator, which is based on the company which filed the first patent. Emerging biopharma companies (EBP) are those with either R&D spend less than $200Mn or global sales up to $500Mn per year. All companies with sales more than $500Mn per year are considered non-EBP. Launch company segmentation has been assessed by the FDA filing company, further verified by the status of that company in relation to acquisitions by other companies as often filing company does not change retroactively to reflect new ownership.

The EMA approved 6 small molecule and 8 biologic NASs for oncology in 2022, more than the 10 total approved in 2021

Exhibit 34: EMA approval trends for oncologic NASs approved for the first time in 2022

***ATTRIBUTES KEY:** 1 = Oral therapy 2 = Predictive biomarker 3 = Approval based on a Phase I or II trial 4 = Single arm 5 = Multi-indication at approval 6 = Orphan 7 = Conditional marketing authorization

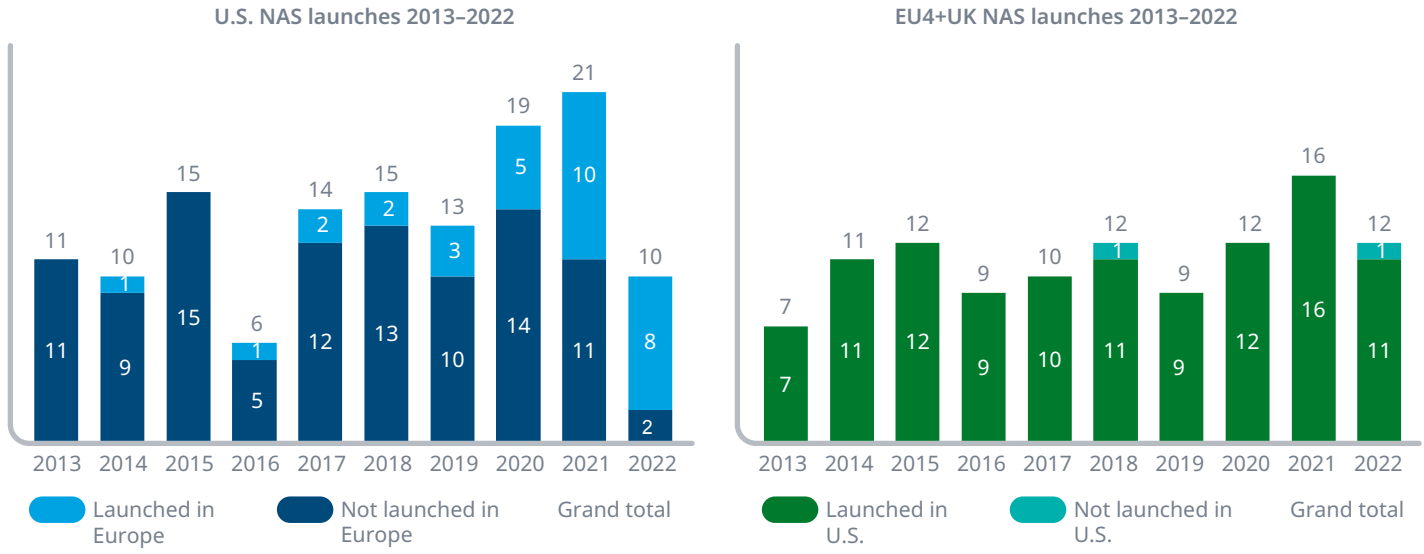
TYPE	INDICATION	BRAND	MOLECULE	ATTRIBUTES						
				1	2	3	4	5	6	7
Small molecules	Chronic myeloid leukemia (CML)	Scemblix	asciminib	●					●	
	Multiple myeloma	Pepaxti	melphalan flufenamide			●	●			
	Non-small cell lung cancer	Tabrecta	capmatinib	●	●	●				
	Non-small cell lung cancer	Lumykras	sotorasib	●	●	●	●			●
	Non-small cell lung cancer	Tepmetko	tepotinib	●	●	●	●			
	Prostate cancer	Orgovyx	relugolix	●						
Biologics	Follicular lymphoma	Lunsumio	mosunetuzumab			●	●		●	●
	Lymphoma (Diffuse large B-Cell & B-Cell)	Zynlonta	loncastuximab tesirine		●	●	●	●		●
	Lymphoma (Diffuse large B-cell, Mediastinal & Follicular)	Breyanzi	lisocabtagene maraleucel			●	●	●		
	Melanoma	Opdualag	nivolumab + relatlimab						●	
	Multiple myeloma	Carvykti	ciltacabtagene autoleucel			●	●			●
	Multiple myeloma	Tecvayli	teclistamab			●	●			●
	Urothelial cancer	Padcev	enfortumab vedotin							
	Uveal melanoma	Kimmtrak	tebentafusp			●			●	
Totals				5	4	10	8	2	4	5

Source: IQVIA Institute, Apr 2023.

- There were 14 new oncology drugs approved by the EMA in 2022, more than the 10 approved in 2021.
- Only four were associated with predictive biomarkers, including three small molecules for the treatment of non-small cell lung cancer with specific mutations and loncastuximab tesirine (Zynlonta), an antibody-drug conjugate targeting CD19 in B-cell lymphomas.
- Five out of fourteen approvals are small molecules administered orally, reducing the need for specialty visits for IV infusions.
- Only four were developed to address rare cancers, notably different from the U.S. launches where nearly all received orphan designation.
- Over 70% (10 of 14) were approved based on earlier phase trials, and five are conditional marketing authorizations. EMA has noted that these authorizations require further data post-approval to convert to full approvals and have balanced the unmet need of patients with the benefit to patients of the immediate availability of the new treatments.
- With the robust numbers of ongoing clinical trials, along with rising numbers of approved treatments essentially competing for patients, the scarcity of eligible patients is becoming a factor for sponsors and regulators to balance in determining the risks and benefits of novel drugs.

Since 2013, 27% of U.S. oncology NAS haven't launched in Europe, while 2% of Europe launches haven't reached the U.S.

Exhibit 35: Oncology NAS Launches in the U.S. and EU4+UK, 2013–2022



Source: IQVIA Institute, Apr 2023.

- The timing of regulatory submission for new medicines varies according to company strategies, and the significant numbers of oncology NAS approved and launched in the U.S. which are not in Europe reflects those patterns.
- In older periods the gap is less, suggesting these are delays, but over the past three years, 23 NASs have launched in the U.S. which are not yet available in Europe: seven are pending or approved but not yet launched, one had the application with the EMA withdrawn, and the remaining 15 are not yet filed in Europe.
- Almost all NASs launching in Europe have reached the U.S, with only two new oncology medicines launched in Europe in the last decade not yet available in the U.S.; one of these is approved but had not yet been launched in the U.S. by the end of 2022.
- For those oncology NASs which have launched in Europe in the last decade, it is notable that 31% have been launched by a larger company in order to reach the European market, when they were launched by an EBP in the U.S.

Notes: Oncology includes diagnostics. NAS launched in the U.S. in the period 2013-2022 have been assessed relative to whether they have launched in Europe in any period including years prior to the periods shown. NAS launched in EU4+UK in the period have been assessed relative to whether they have launched in the U.S. in any period including the years prior to the periods shown.

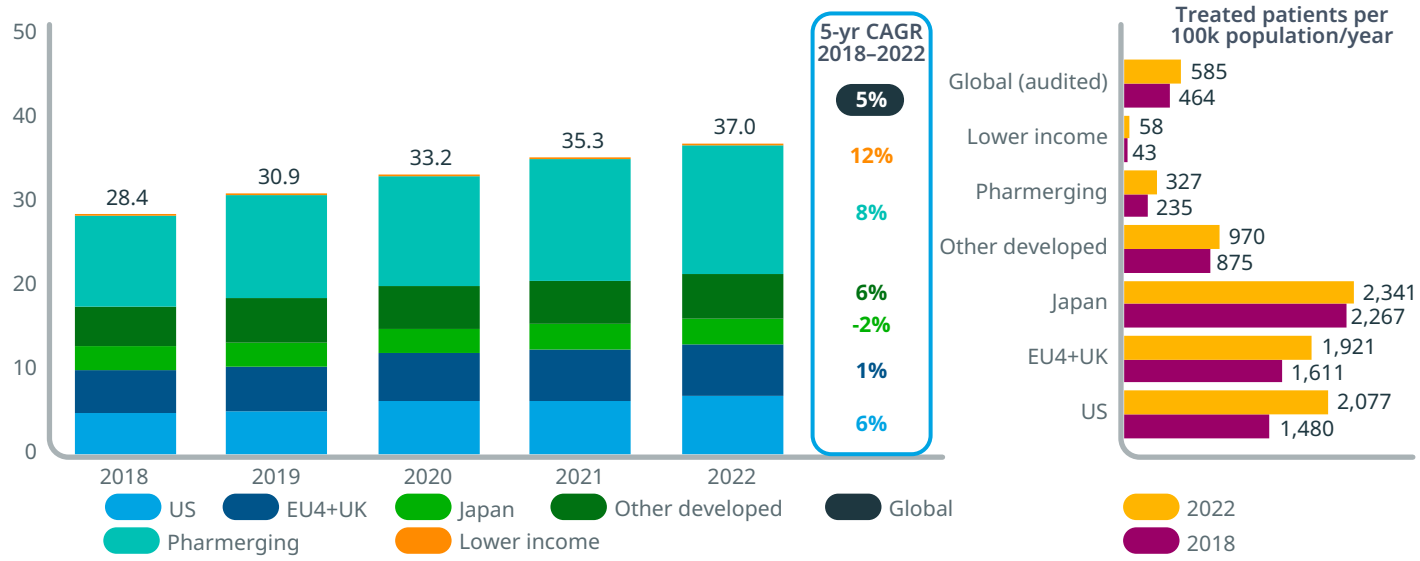
Cancer patient access and use of scientific advances

- Global numbers of treated patients have increased at an average 5% over the past 5 years as populations age and access to care increases.
- In the past decade, a range of oncology medicines have demonstrated significant clinical value and been widely adopted.
- Per capita use of oncology Essential Innovative Medicines across Europe is generally correlated with GDP, however multiple factors may be contributing to differences in use.
- Country-specific differences exist in molecular testing across different tumor types and biomarkers, which can lead to differences in use of targeted medicines.
- Use of checkpoint inhibitors has risen rapidly in major markets, with variations on a per capita basis and some lagging.
- Non-small cell lung cancer treatment declined in the past three years, driven by declines in PD-1/PD-L1 monotherapies and chemotherapies, while use of kinase inhibitors and PD-1/PD-L1 combo therapies grew.
- Significant advances in immunotherapy and kinase inhibitors have the potential to extend duration and response of first-line therapy in non-small cell lung cancer.
- Immunotherapies and PARP inhibitors have shifted treatment patterns in cancers affecting women, especially in the last 2 years.
- Multiple myeloma treatment has advanced in the U.S. driven by novel anti-CD38 monoclonal antibodies and expansion of CAR T-cell therapies.
- There are 532 hospitals accredited with international standards for administering CAR T-cell therapies globally, up 38% from 2020.
- While the number of CAR T-cell centers is growing, not all centers have all approved products available, potentially requiring patients to travel long distances to receive therapies and leading to inequities in care.
- Diagnostic tests for cancer and new patients presenting to oncologists were impacted throughout the pandemic.

Novel treatments have improved patient outcomes across a range of cancers, but differences in access may lead to variability in care.

Global numbers of treated patients have increased at an average 5% over the past 5 years

Exhibit 36: Global oncology patient treatment regimens (millions), 2018–2022



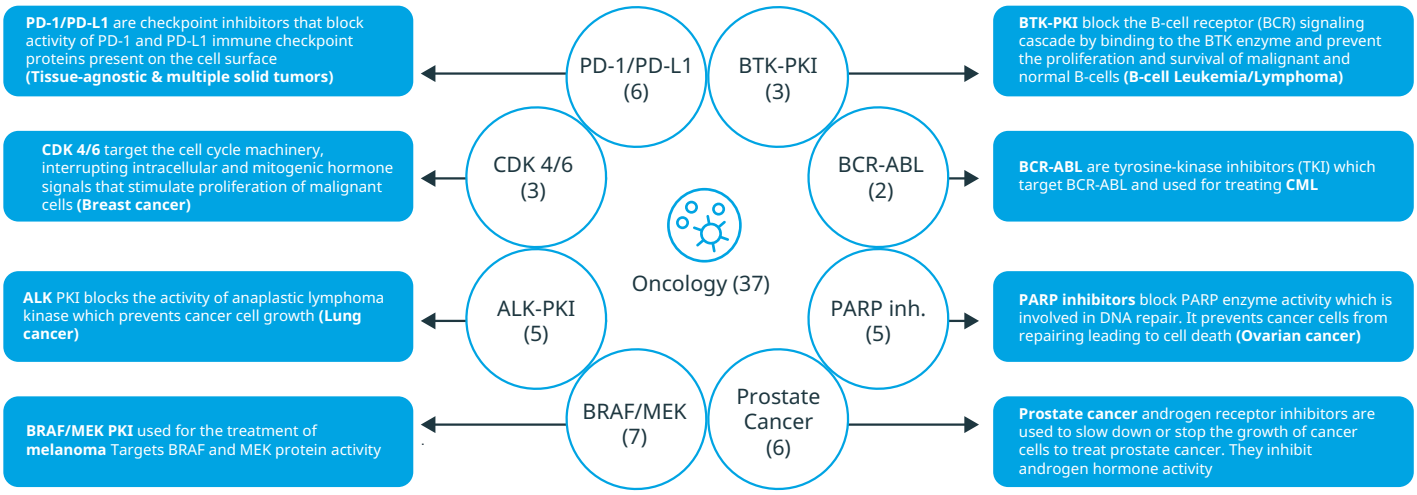
Source: IQVIA Oncology Link, The World Bank Population Estimates, Dec 2022.

- Aging populations and robust access to care are driving steady levels of cancer treatment in developed markets.
- Widening access to care in lower income markets, along with longer treatment durations, are resulting in higher numbers of patients receiving treatment each year, with treatment regimens growing globally an average of 5% annually over the last five years.
- Per capita rates of treatment remain highest in developed countries, averaging more than five times the level in lower income and pharmerging countries.
- Over the past five years, the overall number of patient treatment regimens declined in Japan while rising in the U.S., EU4+UK, and other developed countries.
- Pharmerging and lower income markets have seen the highest level of growth in the last five years, at 8% and 12% CAGR, respectively. This reflects the expanded access to cancer medicines in these geographies.

Notes: Patient treatment regimens reflect a specific combination of drugs used for a patient and counts each regimen and cycle received based on the estimation methods in Oncology Link. Pharmerging countries are defined as those with lower than $30,000 per capita income and 5-year forecast growth of the total pharmaceutical market of >$1Bn. Other developed countries are those countries with incomes above $30,000 which are not otherwise named. Lower income are a limited group of audited countries with lower incomes and not meeting the pharmerging 5-year growth criteria. Pharmerging and lower income countries often do not have audits covering all channels and may understate oncology usage and spending.

In the past decade, a range of oncology medicines have demonstrated significant clinical value and been widely adopted

Exhibit 37: Oncology Essential Innovative Medicine groups analyzed (# molecules)



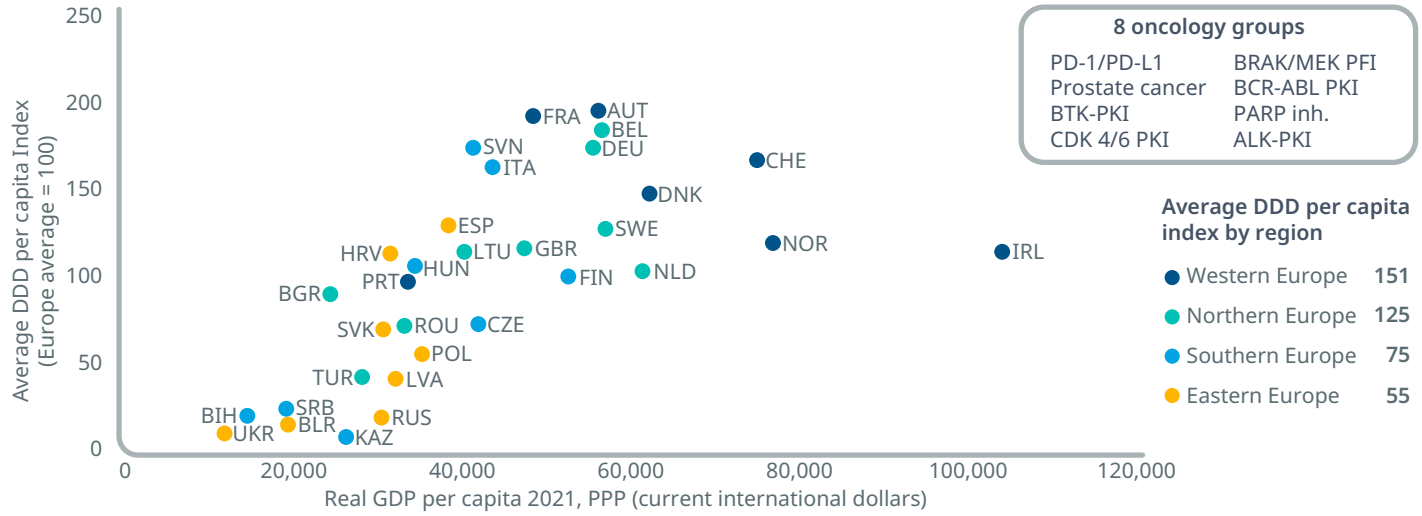
Source: Defining Essential Innovative Medicines and Measuring their Use in Europe, Sep 2022. Report by the IQVIA Institute for Human Data Science.

- There has been a surge of research and development activity over recent decades in oncology with eight groups of Essential Innovative Medicines launched 2011–2020, which are widely reimbursed across European countries (i.e., at least one drug in the group has been reviewed and received public reimbursement in at least half of the European countries assessed) and representing significant advances in treatment for patients.
- Measuring the per capita use of these Essential Innovative Medicine groups across countries can highlight differences in access to novel medicines.
- Within oncology, six PD-1/PD-L1 checkpoint inhibitors launched across Europe in the period, which have transformed and become foundational to most solid tumor treatments in the past decade.
- Six novel treatments in prostate cancer include small molecule androgen receptor blockers as well as androgen hormone inhibitors, generally thought to be more effective and less toxic than previous chemotherapy- or radiation-based therapies.
- The other six oncology EIM groups are composed of 25 small molecule kinase inhibitors linked to specific biomarkers and targeting a range of targets to disrupt cell processes and slow or stop tumor growth in leukemias, lymphomas, breast, lung, and ovarian cancer.

Notes: (#) = number of NAS launched in each group. Essential Innovative Medicines are NAS launched globally 2011-202 for which at least one similar drug in a therapeutic group has been reviewed and received public reimbursement in at least half of the European countries assessed. For additional details on the methodology refer to the IQVIA Institute report Defining Essential Innovative Medicines and Measuring their Use in Europe available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/defining-essential-innovative-medicines-and-measuring-their-use-in-europe.

Per capita use of Essential Innovative Medicines is generally correlated with GDP, but there are notable outliers

Exhibit 38: Index of volume use of 8 oncology groups compared to GDP per capita 2021, PPP, current international dollars



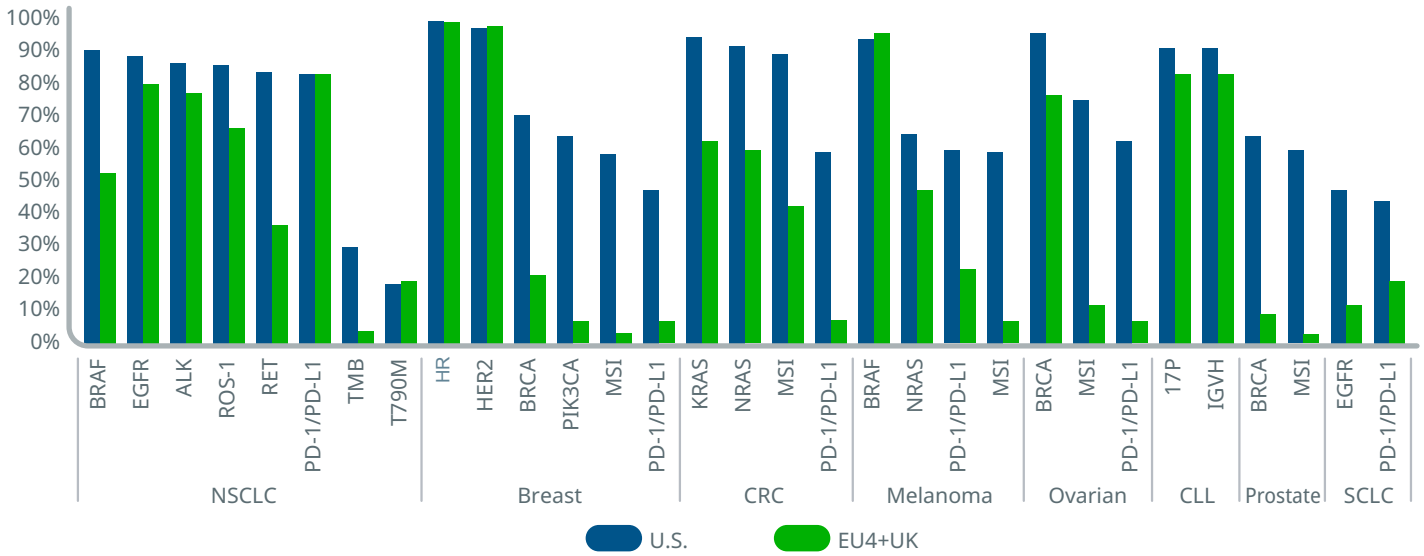
Source: Defining Essential Innovative Medicines and Measuring their Use in Europe, Sep 2022. Report by the IQVIA Institute for Human Data Science.

- Per capita use of oncology Essential Innovative Medicines is generally correlated with GDP, but there are notable outliers.
- Wealthier countries such as Ireland (IRL) and Norway (NOR) have lower per capita DDD indices across oncology groups than other high-income countries.
- Among countries with similar GDP, the use of these EIM groups in France (FRA) is 65% higher than the level in the UK (GBR), even as both have average indices above the European average.
- There are also situations where usage is highly similar even as GDP per capita varies significantly, such as in Spain (ESP) and Sweden (SWE).
- These differences in utilization are also apparent across different geographic regions of Europe: Western Europe, which generally has higher GDP per capita, has an average utilization 51% higher than the European average, while Eastern Europe has utilization of EIMs nearly half of the European average and 36% of the average utilization in Western Europe.
- Taken in isolation, differences in the level of use of these Essential Innovative Medicines may indicate gaps in access, however multiple factors may be contributing to those differences, including epidemiology, reimbursement decision methodologies, patient and provider preferences, and disease management strategies.[13]

Notes: European average excludes null values for non-covered non-retail in select classes.

Country-specific differences exist in molecular testing across different tumor types and biomarkers

Exhibit 39: 2022 testing rates by tumor, biomarker and geography



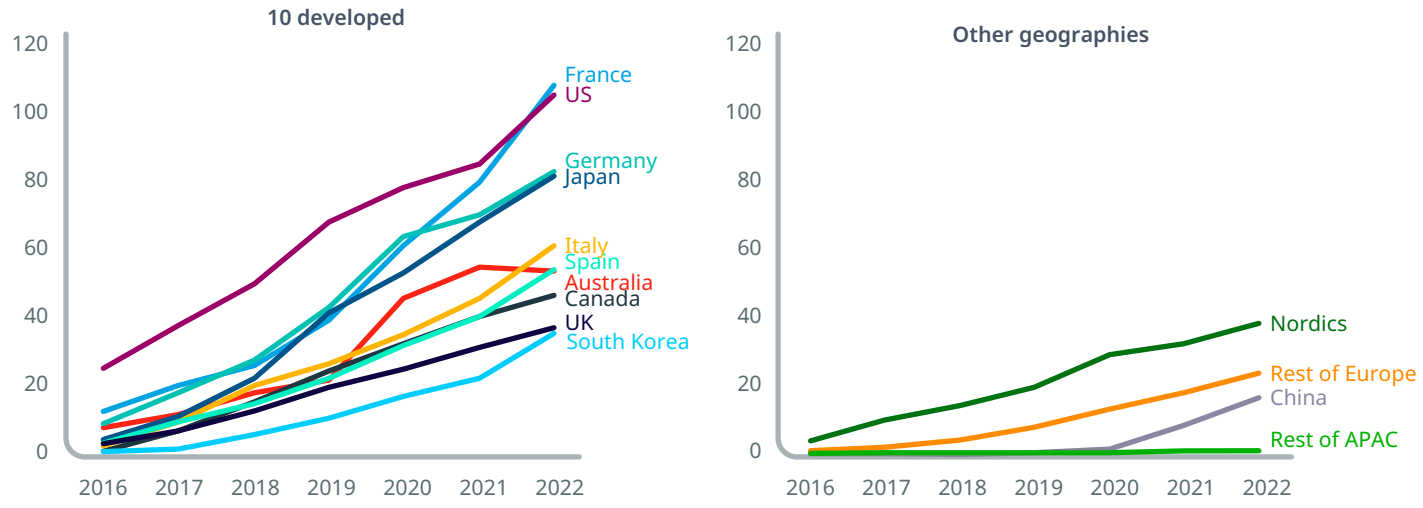
Source: IQVIA Oncology Dynamics, Dec 2022.

- Large geographic variations in testing rates suggest that patients may not yet have full access to diagnostics or the novel medicines a positive test would support for treatment.
- Guidelines recommend testing NSCLC patients for EGFR, ALK biomarkers, and PD-L1. More than 75% of patients are being tested in both the U.S. and EU4+UK, consistent with patterns relating to more established biomarkers, but with higher testing rates in the U.S for EGFR and ALK.
- While nearly all breast cancer patients are tested for HER2, the FDA approval of trastuzumab deruxtecan (Enhertu) for unresectable or metastatic HER2-low breast cancer opens up a new patient population to treatments targeting HER2 that had previously been classified as HER2-negative. However, current standard assays for determining HER2 levels may be imperfect at characterizing HER2-low.[14]
- Colorectal cancer (CRC) biomarker testing differs significantly across countries, likely owing to differences in guidelines where National Comprehensive Cancer Network (NCCN) guidelines recommend MSI testing in all patients and KRAS and NRAS testing in all patients with metastatic disease.[15]
- Testing rates in EU4+UK for TMB and MSI, which often suggest the applicability of tissue agnostic checkpoint inhibitors, have lagged behind the rates in the U.S. as there have not been guidelines, and drugs have received tissue-agnostic indication approvals later than in the U.S.

Notes: NSCLC= non-small cell lung cancer; CRC = colorectal cancer; CLL= chronic lymphocytic leukemia; SCLC = small cell lung cancer.

Use of checkpoint inhibitors has risen rapidly in major markets with variations on a per capita basis and some lagging

Exhibit 40: PD-1/PD-L1 checkpoint inhibitor treated patients per 100k population, 2016–2022

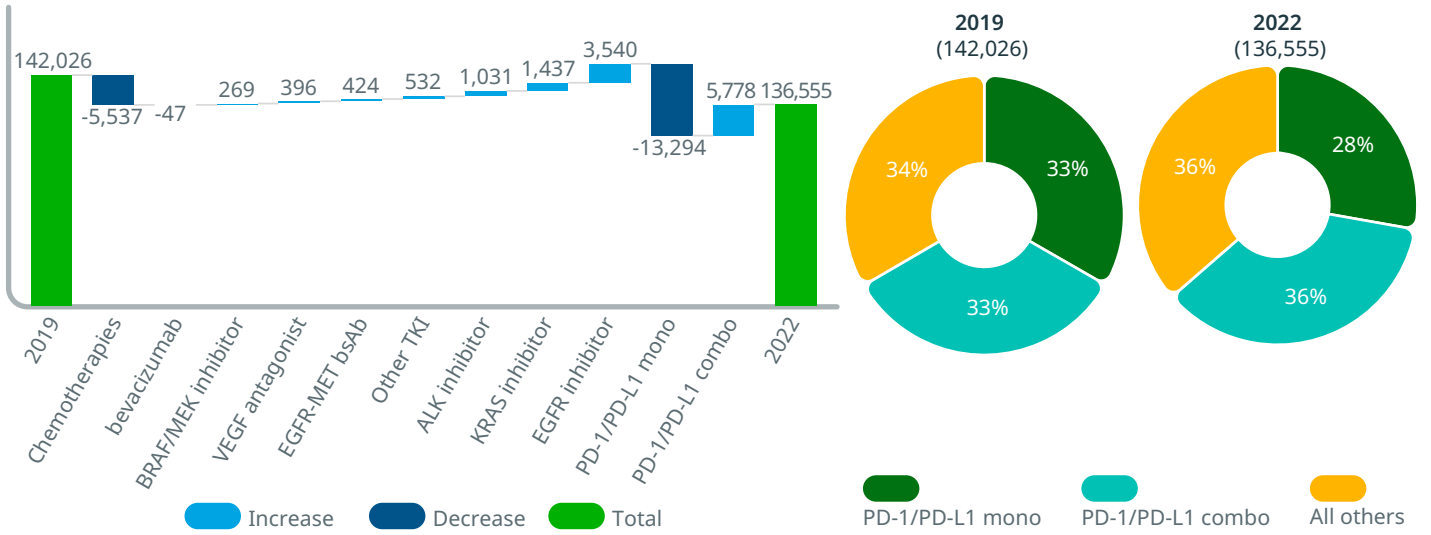


Source: IQVIA Oncology Link, Apr 2023; World Bank Population Estimates, Dec 2022.

- The wide adoption of PD-1/PD-L1 checkpoint inhibitors reflects their strong efficacy across a range of solid tumors, including several with tissue-agnostic approvals, triggering their use with biomarker testing results.
- Usage has varied considerably across countries, with the U.S. and France using almost three times more of these drugs per capita than the UK and South Korea.
- Many of the major European countries have highly similar rates of usage to other developed markets, including the Nordic countries.
- China, which had limited use of these medicines until 2021, has pulled away in per capita use from other Asian markets and is now only half the level of use seen in the UK.
- Use of these medicines is influenced by the use of biomarker testing as well as the position in protocols, where the drugs are progressively moving to earlier lines of therapy with longer treatment durations.

Non-small cell lung cancer treatment declined in the past 3 years, while use of kinase inhibitors and PD-1/PD-L1 combos grew

Exhibit 41: U.S. stage IV non-small cell lung cancer treatment regimens, 2019–2022



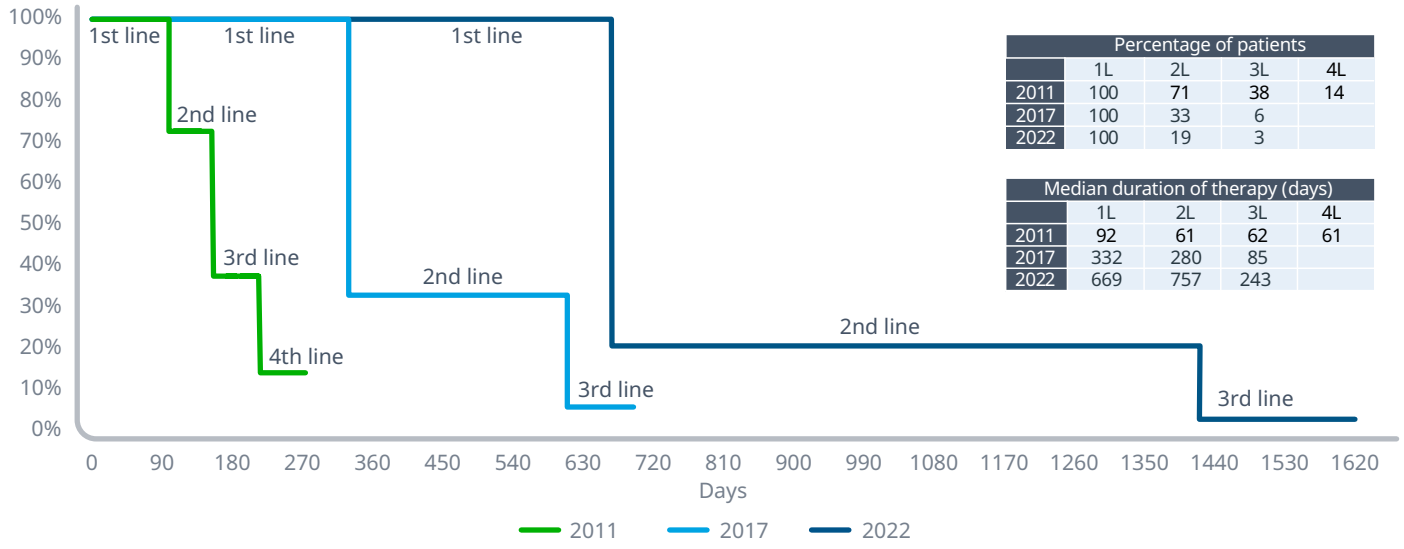
Source: IQVIA Anonymized Patient Claims Data, projected, Dec 2022.

- There have been significant changes in treatment regimens for stage IV non-small cell lung cancer in the past three years as more novel therapies have entered the market.
- The total number of patient treatment regimens has declined 4% since 2019, likely driven by improved response of patients to novel therapies and longer durations of response (Exhibit 42) even while new metastatic patients generally grew throughout the pandemic (Exhibit 46).
- Significant declines have been seen in monotherapy PD-1/PD-L1 regimens as patients are switched to combination therapies having greater efficacy, with 28% of treatment regimens for monotherapy PD-1/PD-L1 in 2022 (down from 33%) compared to 36% for combination PD-1/PD-L1 therapies in 2022 (up from 33%).
- As PD-1/PD-L1 checkpoint inhibitors have become more standard of care for patients with advanced non-small cell lung cancer, older non-targeted chemotherapies have seen a significant decline in the last three years, with more than 5,500 fewer treatments in 2022.
- Other targeted therapies are also seeing a rise in usage, with significant growth in EGFR inhibitors as well as ALK and KRAS inhibitors, highlighting the availability of a variety of targeted therapies for those with non-small cell lung cancer.

Notes: Estimated patients are based on projected medical claims and regimen clusters have been defined to be non-overlapping. Where a regimen includes multiple elements shown on the chart, a sequence has been used to report regimens containing PD-1/PD-L1 before considering others.

Significant advances in immunotherapy and kinase inhibitors have the potential to extend duration of first-line therapy

Exhibit 42: Non-small cell lung cancer duration of therapy by line of therapy



Percentage of patients	1L	2L	3L	4L
2011	100	71	38	14
2017	100	33	6	
2022	100	19	3	

Median duration of therapy (days)	1L	2L	3L	4L
2011	92	61	62	61
2017	332	280	85	
2022	669	757	243	

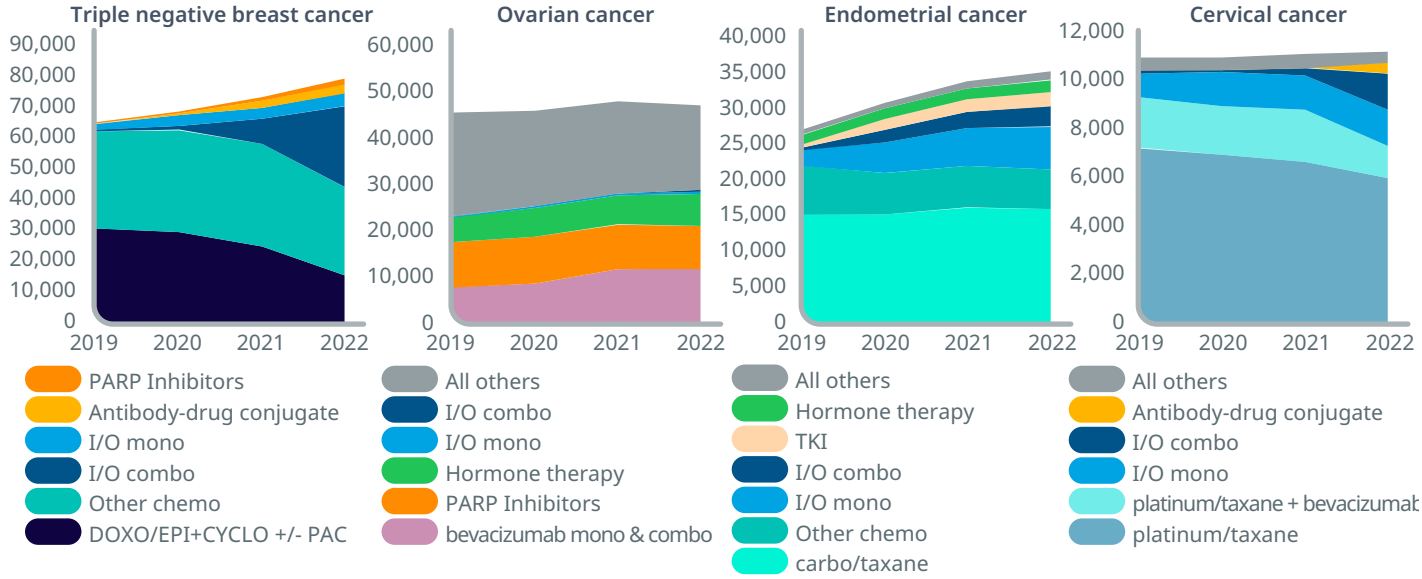
Source: IQVIA Oncology Dynamics, IQVIA Institute, Apr 2023.

- Significant improvements in therapies for non-small cell lung cancer have increased the effectiveness of first-line therapy in patients over the last decade.
- The median duration of first-line therapy in 2022 was more than seven times what it was in 2011 and now first-line therapy duration is at nearly two years compared to just three months in 2011.
- In addition to longer durations of therapy for first-, second- and third-line therapies, the percentage of patients responding to each line of therapy has dramatically increased, with only 19% of patients progressing to second-line therapy in 2022 compared to 71% in 2011.
- These improvements can also be seen in those responding to second-line therapies, with only 3% progression to third-line therapies compared to 38% in 2011 and a significant number of patients historically requiring fourth-line therapy.
- This highlights significant improvements in the standard of care and prognosis for patients living with non-small cell lung cancer, driven by innovative targeted therapies such as kinase inhibitors and immunotherapies.

Notes: Vertical axis of the chart represents the percentage of patients on the noted line of therapy based on Oncology Dynamics data. Horizontal axis represents days duration of the relevant line of therapy based on median progression-free survival for products approved within each line of therapy.

Immunotherapies and PARP inhibitors have shifted treatment patterns in cancers affecting women, especially in the last 2 years

Exhibit 43: Number of patient treatment regimens in the U.S., 2019–2022



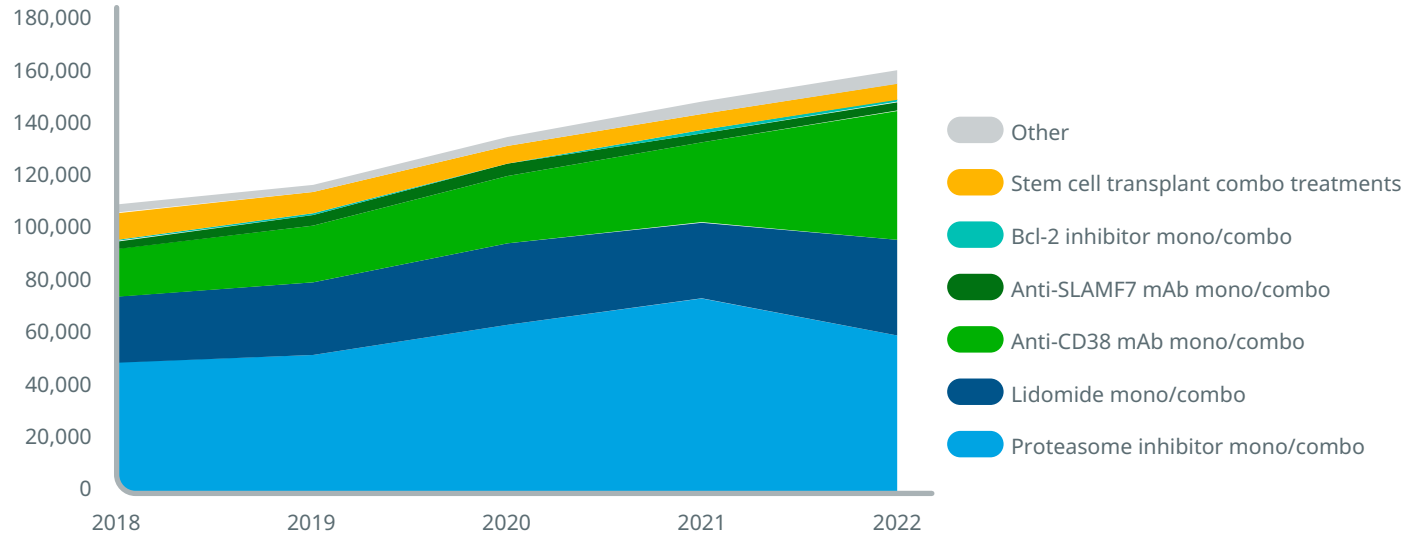
Source: IQVIA Anonymized Patient Claims Data, projected, Dec 2022.

- The overall number of patient treatment regimens has been growing strongly across a range of tumors affecting women.
- Much of the growth in treatment in the past four years has been driven by adoption of newer medicines with notably better clinical outcomes.
- Triple-negative breast cancer, a version of the disease with few options just a few years ago, has seen wider use of checkpoint inhibitors in combination regimens and much less traditional chemotherapy.
- Ovarian cancers have been relatively hard to treat but cost reductions from biosimilar bevacizumab, which is a component of the most widely used regimen, have benefited some patients.
- PARP inhibitors launched in the last decade have become a backbone of treatment in ovarian cancer, while checkpoint inhibitors are rarely used.
- Endometrial cancer has seen a dramatic rise in the use of checkpoint inhibitors both alone and in combination regimens along with small molecule tyrosine kinase inhibitors (TKI).
- Cervical cancer treatment has seen a dramatic uptake of checkpoint inhibitors in the last few years, which, like other tumors, is benefiting from their substantial efficacy and tolerability and the use of antibody-drug conjugates, while the use of platinum-based chemotherapy regimens has declined.

Notes: Regimens are non-overlapping and have been defined with the named medicines or clusters of drugs in a sequence, thus regimens that include other medicines are included but shown in the 'other' categories.

Multiple myeloma treatment has increased in the U.S. driven by novel anti-CD38 monoclonal antibodies

Exhibit 44: U.S. multiple myeloma patient treatment regimens, 2018–2022



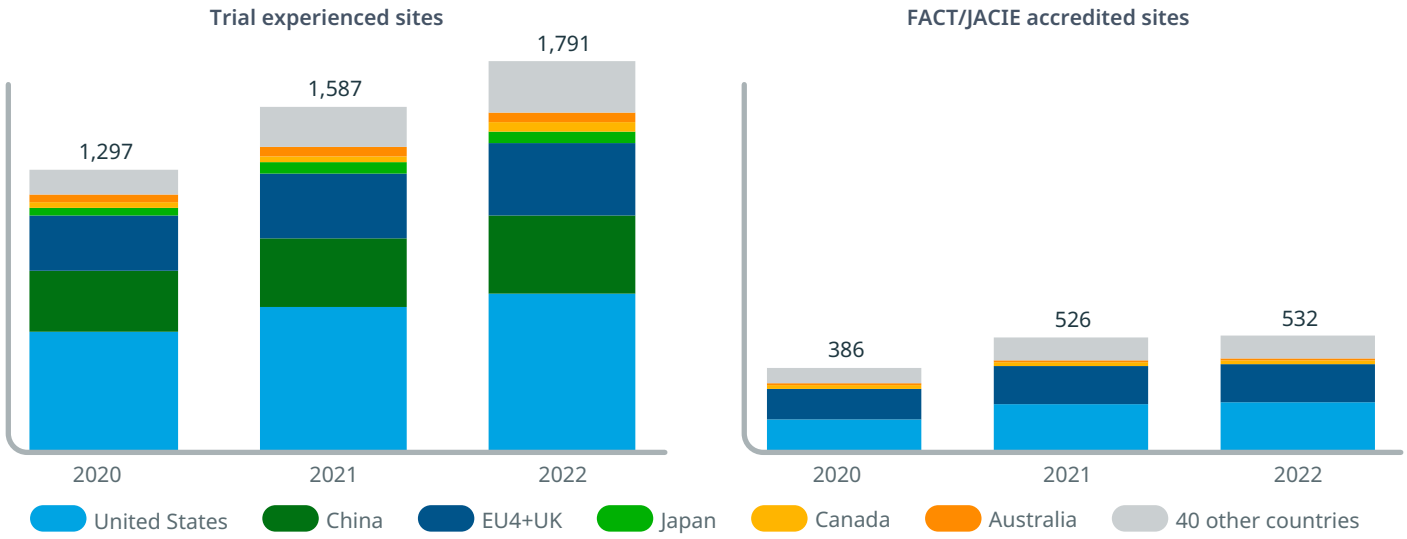
Source: IQVIA Oncology Link, Dec 2022.

- Multiple myeloma treatment has advanced significantly in recent years with the introduction of novel modalities for treating a cancer with a five-year relative survival rate of 59.8%.[16]
- Treatment in the U.S. often consists of a combination of medicines — including lidomides, proteasome inhibitors, and monoclonal antibodies — and stem cell transplantation.
- An anti-CD38 monoclonal antibody (daratumumab) launched in 2015 and is frequently used in combination with other therapies. Regimens containing daratumumab have seen significant growth in recent years, particularly since the introduction of a subcutaneous form in 2020, and now represent 31% of treatment regimens in multiple myeloma.
- Based on sales data, an estimated 1,000 patients have been treated with CAR T-cell therapies approved for multiple myeloma, reflecting an additional treatment option for these patients whose disease has progressed beyond other lines of therapy.
- Recently leaked results from a Phase III trial for ciltacabtagene autolecuel (Carvykti) showed significant improvements for patients with multiple myeloma, cutting the risk of progression or death by 74% and a median progression-free survival of greater than 23 months compared to 12 months in the comparator group.[17]
- Other novel medicines have launched, such as a Bcl-2 inhibitor, an anti-SLAMF7 monoclonal antibody, and an XPO1 inhibitor, but have seen limited use.

Notes: Regimens are grouped based on novelty of mechanism. Where mAbs are contained in regimens with other mechansims (e.g., proteasome inhibitors) these regimens are classified with the respective mAb mono/combo group. Stem cell transplant treatment combo regimens are those drugs typically used in conjunction with stem cell transplants (i.e., plerixafor and melphalan). Other includes regimens less frequently used but often novel mechanisms such as a BCMA-targeted antibody-drug conjugate and XPO-1 inhibitor.

There are 532 hospitals accredited with international standards for administering CAR T therapies globally, up 38% from 2020

Exhibit 45: Number of research sites or treatment hospitals with CAR T capabilities by country, 2020–2022



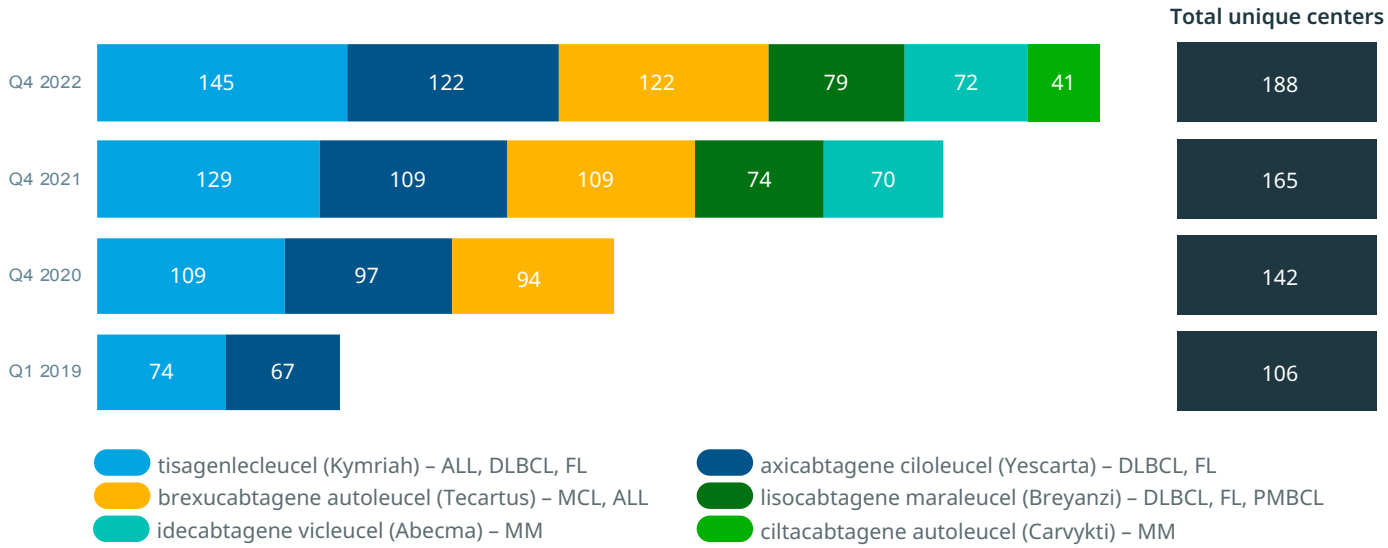
Source: Citeline Trialtrove, European Society for Blood and Marrow Transplantation, Foundation for the Accreditation of Cellular Therapy, IQVIA Institute, Apr 2023.

- Administering CAR T-cell therapies is relatively complex such that only a subset of cancer centers are trial-experienced or accredited to deliver these treatments.
- There were 1,791 trial experienced sites globally in 2022, an increase of nearly 500 since 2020, which includes 360 trial experienced sites in China, where a large amount of innovation in CAR T-cell research is taking place.
- There are many more hospitals that have participated in clinical trials for CAR T-cell therapies than have accreditation to deliver them, suggesting that in the future these therapies can become much more accessible and widely used.
- The number of accredited sites grew from 386 in 2020 to 532 in 2022, indicating the increase in approved CAR T-cell therapies and increased access for patients. More than 40% of the accredited sites are in the U.S. and none are accredited in China.
- While accreditation is not required to administer these therapies in developed countries, it is a widely accepted standard, and all of the actively administering sites in the U.S. are accredited.

Notes: Sites accredited in 2022 are based on accreditation lists downloaded in April 2023. Prior years are based on previous editions of the IQVIA Institute's Global Oncology Trends report.

While the number of CAR T-cell centers is growing, not all centers have all approved products available

Exhibit 46: Certified CAR T-cell centers by product



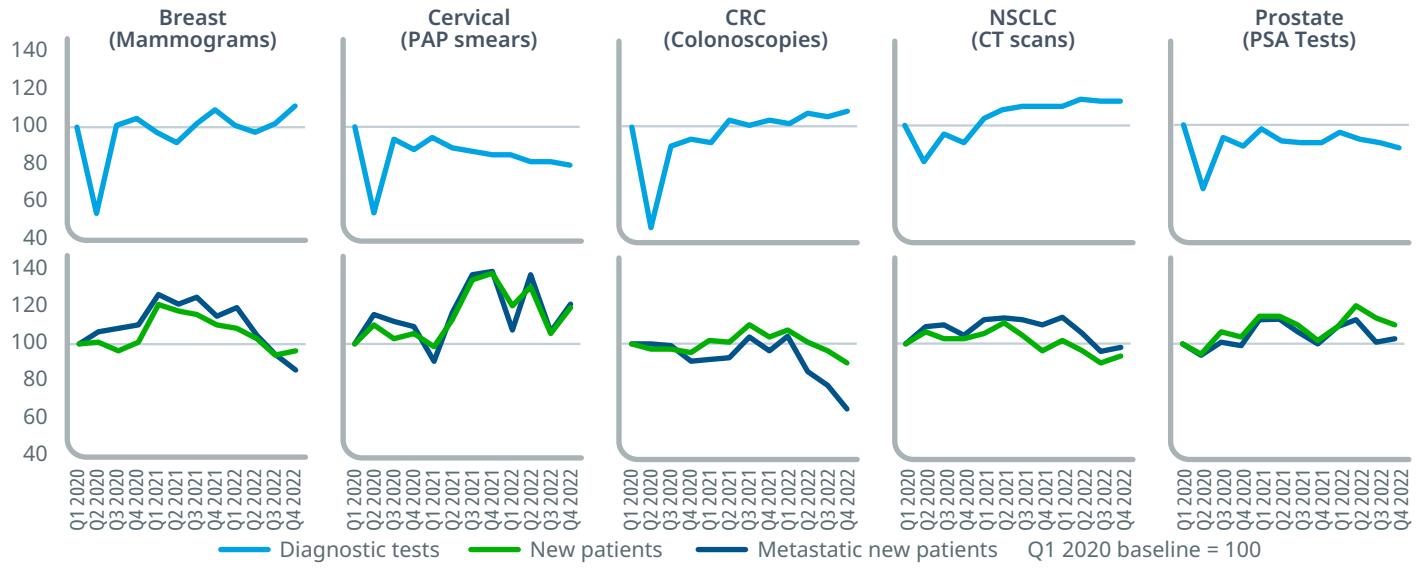
Source: IQVIA CAR T-Cell Monitor, updated Dec. 14, 2022.

- Despite significant growth in the number of centers providing CAR T-cell therapies to patients, not all centers are currently offering each approved therapy.
- The total number of unique centers in the U.S. offering at least one CAR T-cell therapy was 188 at the end of 2022, increasing by roughly 20 centers over the last two years.
- Lisocabtagene maraleucel (Breyanzi) and idecabtagene maraleucel (Abecma), both approved in 2021, were rapidly offered in roughly 40% of centers by the end of 2021 but have seen little expansion over 2022, highlighting rapid uptake at centers after launch that slows dramatically over time as expansion to new centers declines.
- Idecabtagene maraleucel (Abecma) and ciltacabtagene autoleucel (Carvykti) are both approved for the treatment of multiple myeloma, with ciltacabtagene autoleucel launching in 2022 and quickly being picked up by CAR T centers, reaching 41 by the end of the year. Despite this growth, there are only 80 centers in the U.S. carrying these multiple myeloma products, which could create difficulties for patients with advanced disease who may not live near a center.
- Given the difference in products and indications, certain products only being offered at select centers could create challenges requiring patients to travel long distances to receive therapies and creating inequities for those who may not have the resources to travel.

Notes: ALL = acute lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; MM = multiple myeloma.

Diagnostic tests for cancer and new patients presenting to oncologists were impacted throughout the pandemic

Exhibit 47: Diagnostic tests, new patients, and metastatic new patients indexed to pre-pandemic values



Source: IQVIA Real World Claims, Dec 2022; IQVIA BrandImpact, IQVIA Institute, Apr 2023.

- In the past three years, the COVID-19 pandemic has disrupted cancer screening and diagnosis of new cancer patients.
- Mammogram screenings for breast cancer have largely recovered to previous levels, even as more women have been newly diagnosed and a slightly higher rate of those new patients have been metastatic at diagnosis, suggesting there may have been an impact of early pandemic disruptions to care.
- Cervical cancer screenings have declined over the last few years, with more accurate testing and understanding of the impact of human papillomavirus and related shifting of screening recommendations potentially contributing to lower rates of testing. In the last two years of the pandemic, the numbers of new and metastatic patients have been elevated, which should be cause for concern as there have been relatively few novel therapies targeting these tumors.
- Colonoscopies have largely returned to baseline levels, not including home testing, suggesting that there may actually be higher levels of screening than shown. This coincides with guidelines lowering the age for screening to 45 years old in 2021.[18] The numbers of patients and those with advanced disease at diagnosis have not been rising.
- Low-dose CT scans for lung cancer have been rising, while new patient flows have generally not risen, and have dropped in the last two quarters.
- The frequency of prostate cancer screenings using PSA testing have been reduced, and while new patient numbers have been elevated, the degree has been less than in breast and cervical cancers.

Notes: Diagnostic weekly claims compared to the average of weeks in the baseline period Jan 3, 2020 to Feb 28, 2020 and aggregated to an average quarterly index. Quarterly new patients compared to Q1 2020 numbers.

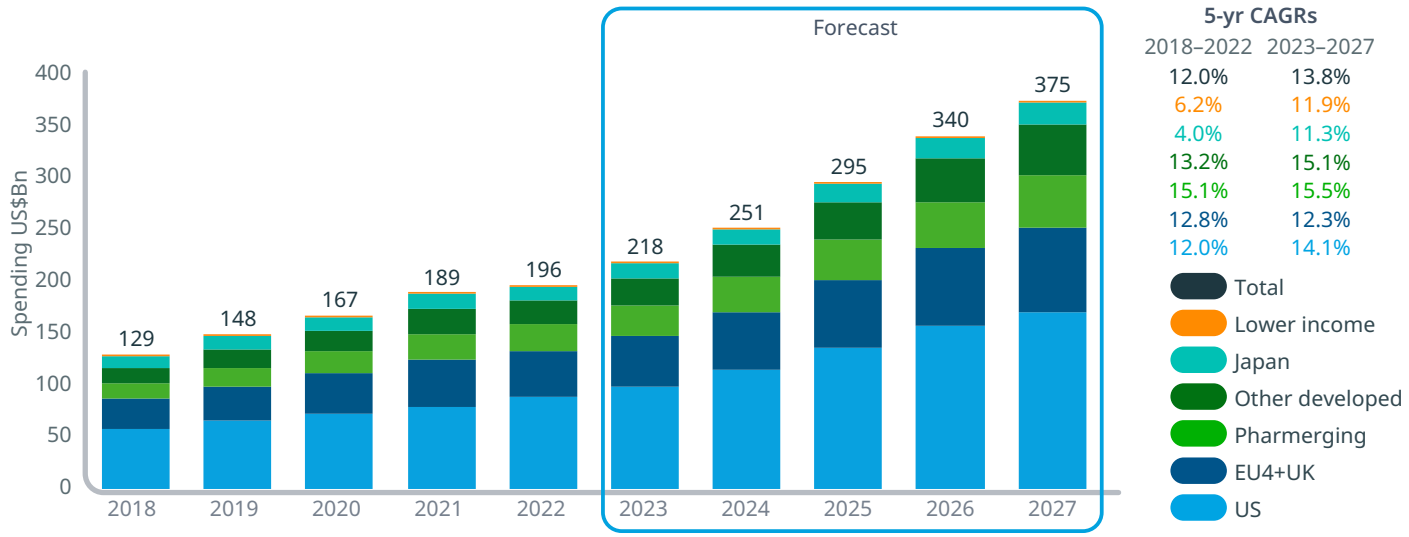
Spending on oncology medicines

- Cancer medicine spending rose to $196Bn globally in 2022 and is expected to reach $375Bn by 2027.
- Growth in major markets was driven by new products and brand volume and offset by losses of exclusivity, including the impacts of biosimilars and generics.
- China oncology spending grew $6.8Bn over the last five years, driven by new therapies, brand volume and generics.
- Oncology biosimilar uptake has been greater than 50% across major markets, and biosimilars saved $5.5Bn in 2022 and $12Bn over the last five years.
- Seven of the top 10 tumors had double-digit spending growth over the last five years, all areas of significant numbers of breakthrough new medicines.
- In the past five years, 79% of oncology launches had annual costs above $100K, up from 52% in the prior five years, and high-cost therapies totaled $48Bn of spending in 2022.
- PD-1/PD-L1 inhibitors are used across most solid tumors reaching $41Bn in spending globally in 2022, with nearly 50% of for lung and kidney cancer.
- The outlook for next-generation biotherapeutics in oncology includes significantly uncertain clinical and commercial success, with the potential to grow from the current $3Bn in global spending to $19Bn by 2027.

Cancer medicine spending rose 4% to $196Bn globally in 2022, driven by new medicines and increases in access but offset by savings from biosimilars and generics.

Cancer medicine spending rose to $196Bn globally in 2022 and is expected to reach $375Bn by 2027

Exhibit 48: Oncology spending by region, US$Bn



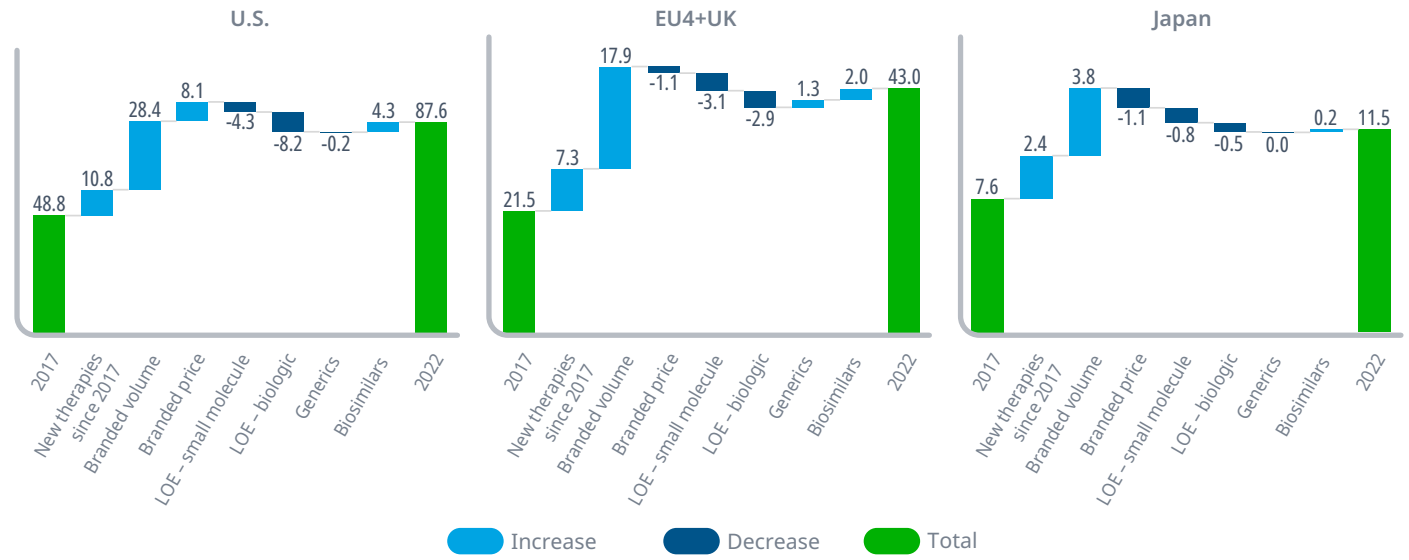
Source: IQVIA Oncology Link, Apr 2023.

- Cancer medicine spending rose to $196Bn globally in 2022, with 75% focused in the major developed markets (the U.S., EU4+UK and Japan), down from 77% in 2018.
- Spending growth in these major developed markets is expected to be similar in the next five years to the last five, with the exception of Japan, which is expected to accelerate to 11.3% CAGR over the next five years compared to 4.0% CAGR in the last five.
- The U.S. spending has risen from $58Bn in 2018 to $88Bn in 2022, representing 45% of global spending.
- Growth in the U.S. is expected to increase to the 12-15% range as more than 100 new drugs are anticipated to launch across novel modalities and frequently moving to earlier lines of therapy; increases in spending will be offset by patent expiries for small molecules and biologics.[19]
- Wider healthcare access in pharmerging and lower-income countries in the rest of the world lifted spending there, with total spending across these countries of $25Bn in 2022, representing 13% of global spending, up from 11% in 2018.
- Other developed countries accounted for $24Bn of spending in 2022, expected to grow at a rate of 13–16% through 2027, similar to the 13.2% five-year growth through 2022, as increasing access to new medicines is offset by biosimilars.

Notes: Spending is for oncology medicines only and does not include medical costs or supportive care. Notes: Pharmerging are defined as countries with less than $30,000 per capita income and more than $1Bn in five-year market growth (covering all drugs, not solely oncology). Other developed countries are those with per capita incomes above $30,000. Lower income are those with per capita incomes below $30,000 but without substantial pharmaceutical market growth.

Growth in major markets driven by new products, brand volume and offset by losses of exclusivity, including biosimilar impact

Exhibit 49: Spending and growth drivers constant US$Bn, 2017–2022



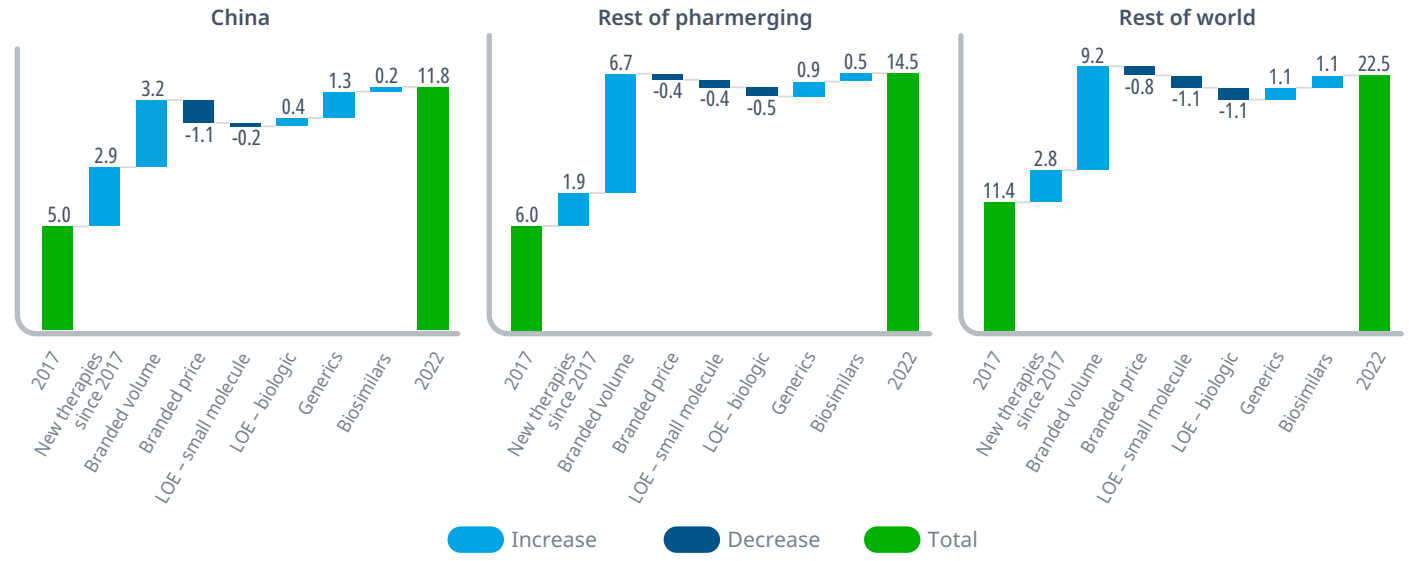
Source: IQVIA MIDAS, Dec 2022.

- Growth in constant dollars in the last five years in the global oncology market totaled $92Bn, with $39Bn of growth from the U.S.
- Growth in the U.S. was driven by new products and the wider use of earlier-launched drugs, especially immuno-oncology checkpoint inhibitors, some of which launched in 2017 or earlier.
- Price growth, long a unique feature of the U.S. market, has reduced dramatically in recent years, while biosimilar impact has begun to impact the market substantially since 2019 and new policies such as the Inflation Reduction Act will likely impact prices into the future.
- Europe has experienced very similar growth trends, while notably the oncology biosimilar uptake measured at list prices likely masks the degree of lower negotiated contract and tender prices in these countries.
- Japan's biennial price cut system, which now includes annual "on-year" and "off-year" price cuts, has dampened the sales growth from newer drugs, including checkpoint inhibitors, which initially outperformed expectations.
- In total, these leading markets have grown by $64Bn over the past five years, accounting for 70% of global growth in that period.

Notes: Product segments are mutually exclusive in each period. New brands since 2017 show the total 2022 spending for all new branded products launched since the end of 2017. New brands include both novel active substances and other brands which may be reformulations or line extensions of earlier NAS launches. Branded volume and branded price are based on protected brands, which are defined as those products with patent protection still in force, and in this analysis excluded all branded products that are new since 2017. Price growth is the impact on growth of changes to invoice prices tracked in IQVIA audits if volume is held constant. Volume growth is the impact on growth if prices are held constant. Loss of exclusivity (LOE) is defined as the growth for branded products after they lose exclusivity, typically after patent expiry. Generics include all non-original products including unbranded generics and non-original branded products such as branded generics or company branded products.

China oncology spending grew $6.8Bn over the last 5 years, driven by new therapies, brand volume and generics

Exhibit 50: Spending and growth drivers constant US$Bn, 2017–2022



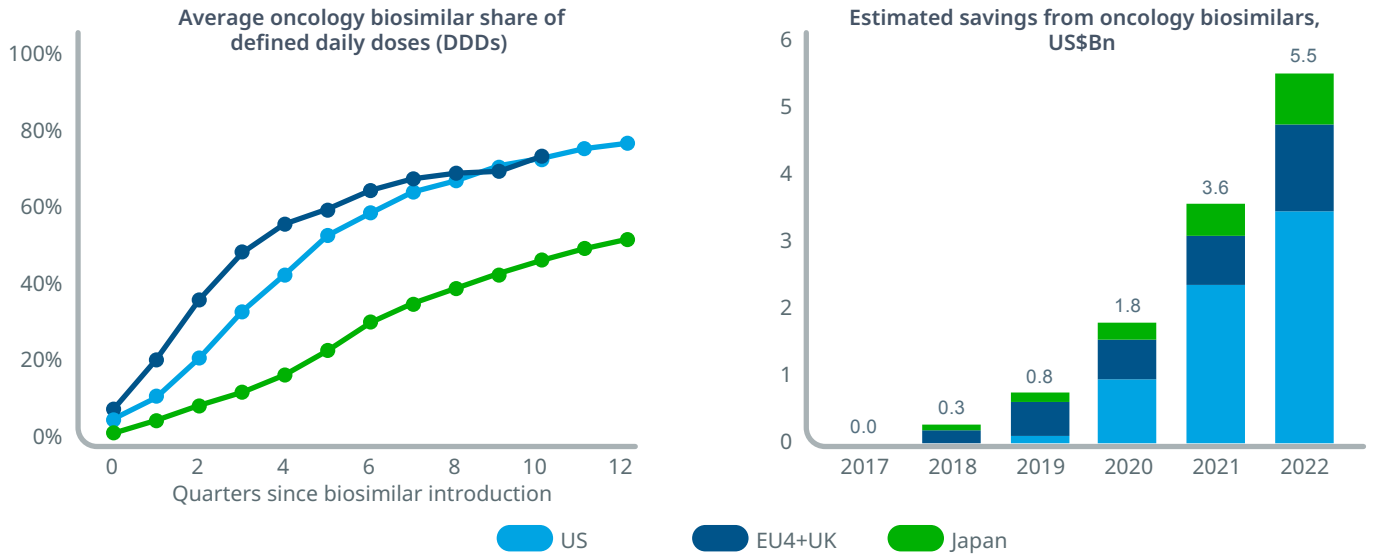
Source: IQVIA MIDAS, Dec 2022.

- China oncology spending grew by $6.8Bn since 2017, with wider access to novel global medicines, a burgeoning home-grown research-based sector, and wider use of existing medicines including generics.
- The other 21 pharmerging countries in total grew by $8.5Bn over five years, with positive growth from new drugs and more volume from existing protected brands. These drivers were offset minimally by price declines and the impact of patent expiries.
- In the remaining countries in the world, a mix of developed and lower income markets, most of the growth has been driven by new drugs and wider use of slightly older medicines, most often the checkpoint inhibitors and therapies launched just prior to 2017.

Notes: Product segments are mutually exclusive in each period. New brands since 2017 show the total 2022 spending for all new branded products launched since the end of 2017. New brands include both novel active substances and other brands which may be reformulations or line extensions of earlier NAS launches. Branded volume and branded price are based on protected brands, which are defined as those products with patent protection still in force, and in this analysis excluded all branded products that are new since 2017. Price growth is the impact on growth of changes to invoice prices tracked in IQVIA audits if volume is held constant. Volume growth is the impact on growth if prices are held constant. Loss of exclusivity (LOE) is defined as the growth for branded products after they lose exclusivity, typically after patent expiry. Generics include all non-original products including unbranded generics and non-original branded products such as branded generics or company branded products. Rest of World includes all audited countries outside pharmerging, U.S., EU4+UK and Japan.

Oncology biosimilar uptake has been greater than 50% across major markets and biosimilars saved $5.5Bn in 2022

Exhibit 51: Average oncology biosimilar uptake and estimated biosimilar savings in U.S., EU4+UK, and Japan, US$Bn



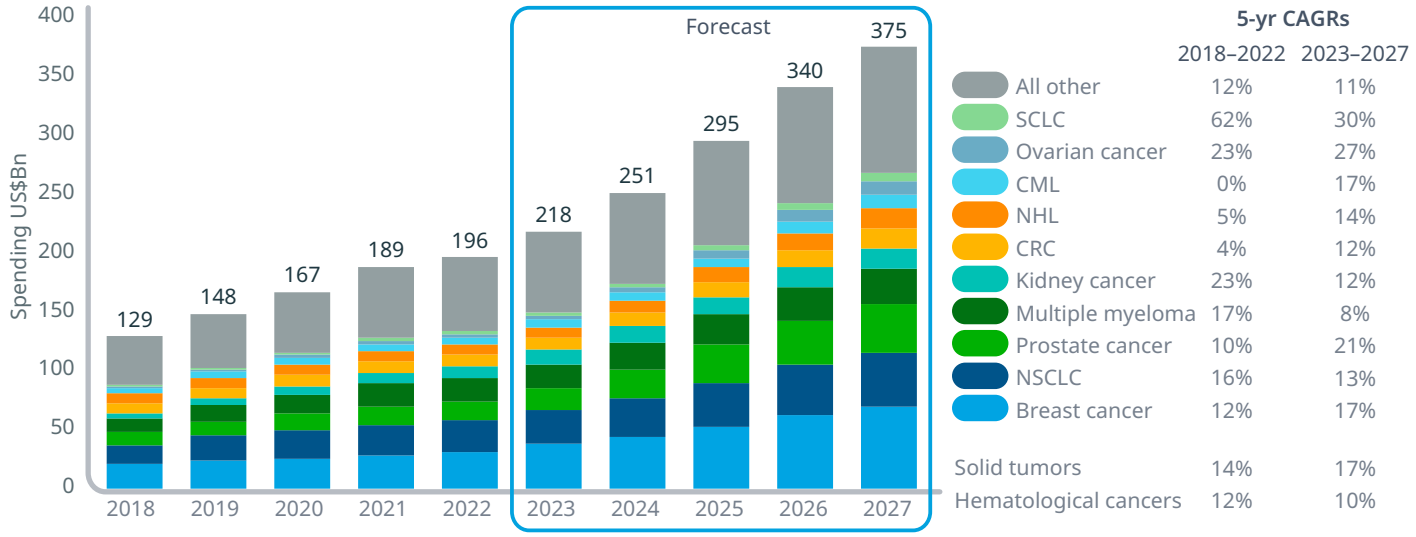
Source: IQVIA MIDAS, Dec 2022; IQVIA Institute, Apr 2023.

- Biosimilars can provide significant cost savings for both patients and health systems, with a range of factors influencing uptake across geographies.
- In major markets, three oncology molecules have had biosimilars launch: bevacizumab, rituximab, and trastuzumab. The first of these biosimilars launched in 2017 in the EU4+UK, 2018 in Japan, and 2019 in the U.S.
- Average biosimilar uptake across these three molecules reached 77% after three years in the U.S. Oncology biosimilars have seen the highest uptake across therapy areas in the U.S. where biosimilars are available.[20]
- Uptake in EU4+UK was more rapid than the U.S. but slowed after reaching 70% 2.5 years after launch, and significant variation in uptake exists among these countries, with 47% average uptake in the UK compared to 79% in Germany.
- Uptake of biosimilars in Japan, where drug pricing and reimbursement is tightly controlled, has been lower than other geographies, reaching 52% after three years.
- Oncology biosimilars have saved $12Bn over the last five years in major markets, with more than half of the savings in the U.S., reducing costs for patients and health systems and expanding access to medicines.
- Significant biosimilar events in the next few years will provide additional savings as the first immuno-oncologic, ipilimumab, is expected to face biosimilar competition as early as 2025 in the U.S.

Notes: Biosimilar share only calculated for periods in each geography when all three oncology biosimilars (bevacizumab, rituximab, and trastuzumab) were available in that geography. Savings is calculated by comparing actual molecule spending to projected spending if total molecule volume had been at originator pre-expiry prices.

7 of the top 10 tumors have double-digit spending growth, all areas of significant numbers of breakthrough new medicines

Exhibit 52: Global oncology spending by tumor US$Bn, 2018–2027



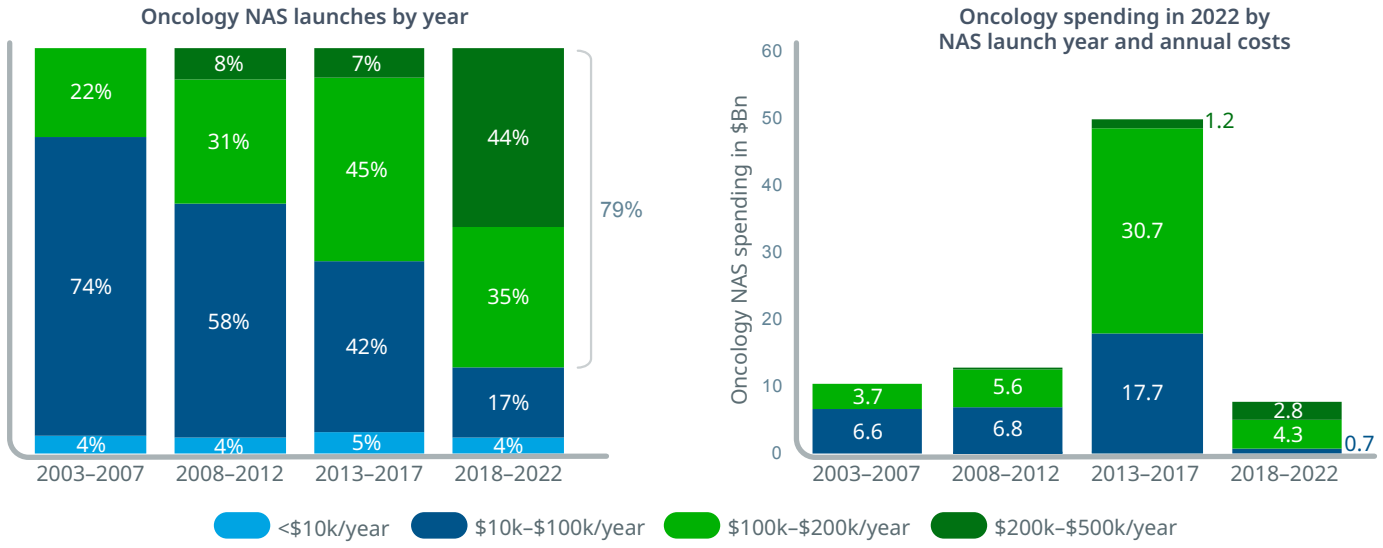
Source: IQVIA Oncology Link, Apr 2023.

- Collectively, the top five tumor types (breast cancer, non-small cell lung cancer, prostate cancer, multiple myeloma, prostate cancer, and kidney cancer), account for 53% of all oncology sales.
- The continued launch of innovative medicines is one of the key drivers fueling the growth across different tumors (Exhibits 29 and 30).
- The high value growth observed in NSCLC, kidney cancer and SCLC can be attributed to the expansion of PD-1/PD-L1 Inhibitors in these patient groups. Prior to the launch of this class of products, targeted therapy options were limited in a few of these cancer types.
- Growth in multiple myeloma has contributed significantly to the overall spending growth for hematological cancers and is driven by the increased use of novel therapies, which have shown improved efficacy over older treatments in this difficult to treat condition.
- Slower value growth is observed in colorectal cancer, where the proportion from recent novel active substance contribution is also lower.
- Growth is expected to slow in some tumors as growth shifts from newly treatable patients to earlier lines of therapy and adjuvant settings in some cases.
- Longer treatment durations and more cycles of therapy per patient contribute to spending growth directly as well as through the continued spending on medicines, which are included in regimens with more novel therapies.

Notes: Spending is for medicines only and does not include medical costs or supportive care.

In the past 5 years 79% of oncology launches had annual costs above $100K, up from 52% in the prior 5 years

Exhibit 53: Oncology NAS launches in U.S. 2003–2022 by annual costs and sales



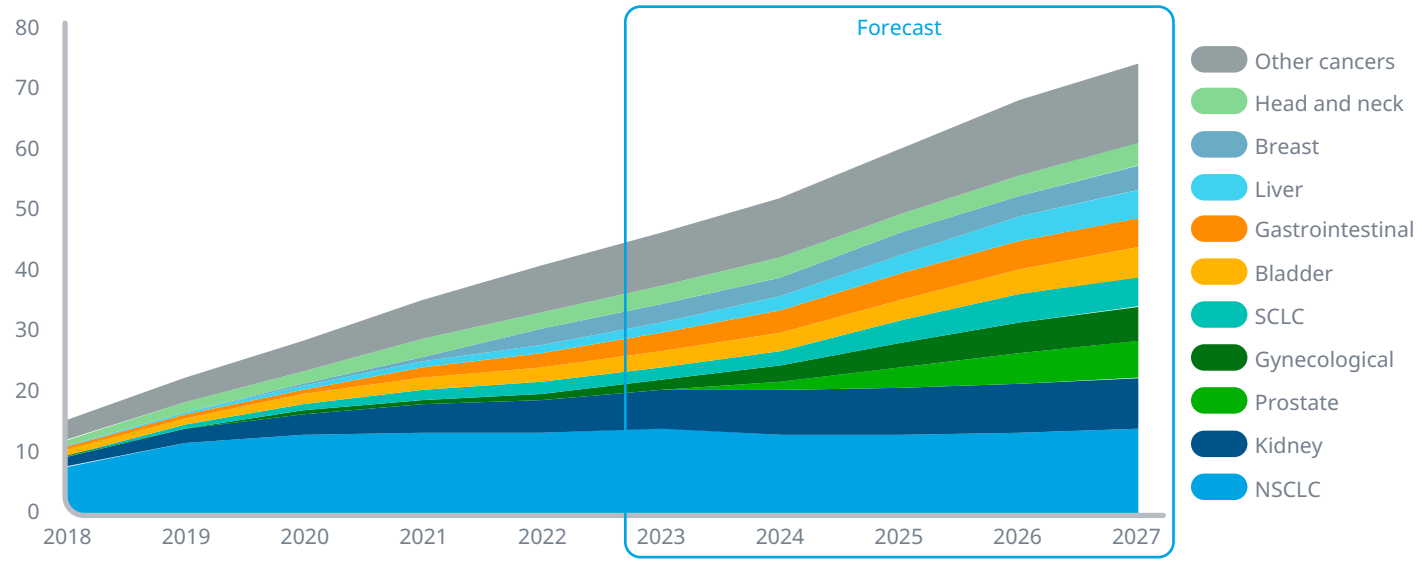
Source: IQVIA MIDAS, Dec 2022; IQVIA Institute, Apr 2023.

- The number of new cancer drugs with costs to the U.S. health system exceeding $200,000 per year has been increasing, accounting for 44% of launches in the past five years, up from 7% in the prior five years.
- Novel cancer drugs with costs above $100,000 were 79% of launches in the past five years, up from 52% in the prior five years.
- The median annual cost for new oncology medicines launched in 2022 was $260,000, up from $63,534 a decade ago as novel modalities typically for smaller patient populations have accounted for many of the launches in recent years.
- High-cost therapies totaled $48Bn of spending in 2022, with $39Bn from launches in the past 10 years.
- While individual drugs can have a high cost, the cost of a patient's treatment continues to vary based on the overall regimens they receive and non-drug components of their care, and can especially be influenced by their insurance type.

Notes: Oncology NAS include diagnostics. Spending includes company reported sales for cell therapies not otherwise captured.

PD-1/PD-L1 inhibitors are used across most solid tumors with nearly 50% of spending for lung and kidney cancer in 2022

Exhibit 54: Global PD-1/PD-L1 inhibitor sales by tumor US$Bn, 2018–2027

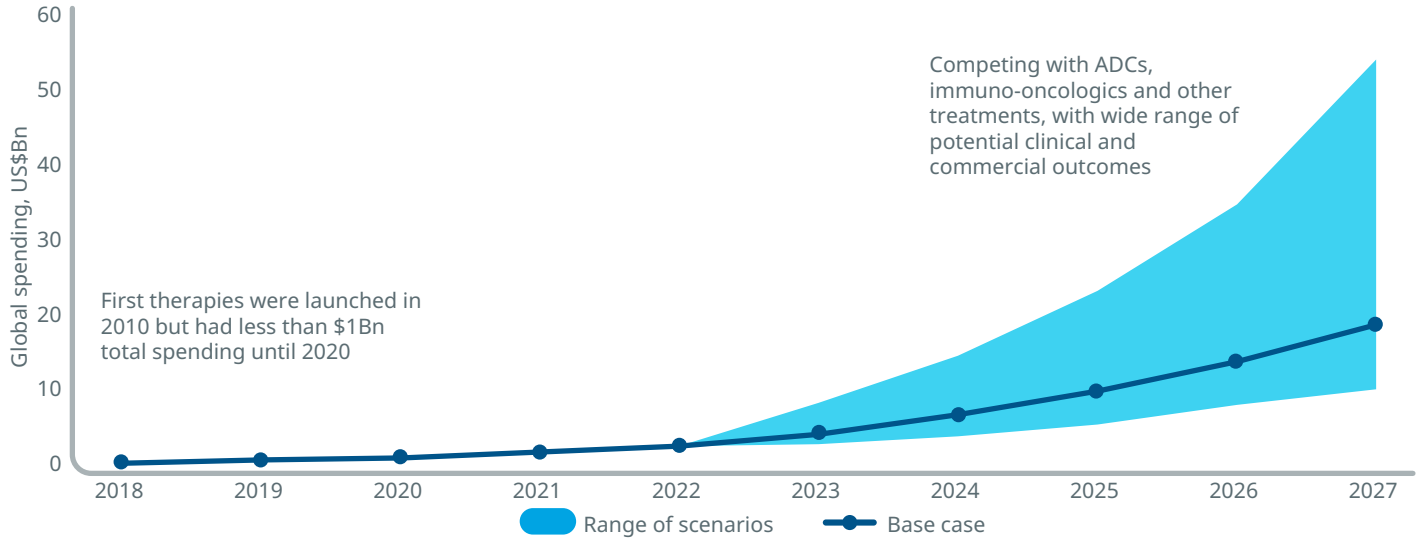


Source: IQVIA Oncology Link, Apr 2023.

- Immuno-oncology products represent a key class that has revolutionized cancer treatment across a spectrum of indications.
- Checkpoint inhibitors, mainly the PD-1/PD-L1 checkpoint inhibitors, have impacted clinical practice the most to date and account for $41Bn in global spending in 2022, up from $9.6Bn in 2017.
- The largest PD-1/PD-L1 segments today are NSCLC and kidney cancers and including dozens more as key PD-1/PD-L1s have been approved as "tissue-agnostic," where a biomarker test result indicates use, regardless of the specific solid tumor.
- Some of the fastest growing indications are small cell lung cancer (SCLC) and breast cancer, where usage is shifting to earlier lines of therapy.
- Looking ahead, many PD-1/PD-L1 inhibitors are being used as combination therapies with other molecules, as they're becoming backbone treatments in certain tumor types. This trend is expected to continue with PD-1/PD-L1 inhibitor global spending expected to exceed $70Bn in 2027.

The outlook for next-generation biotherapeutics in oncology includes significantly uncertain clinical and commercial success

Exhibit 55: Cell, gene and RNA therapeutics



Source: Company Financials, IQVIA Institute, Apr 2023.

- A range of therapies have been grouped together as next-generation biotherapeutics, reflecting a variety of cell therapies, gene therapies, gene editing and RNA interference or modification technologies, most of which had no marketed drugs a decade ago.
- Cancer cell therapies have had significant approvals in the last three years with five new launches since 2020, mostly CAR T-cell therapies, and in 2022 totaled nearly $2Bn in spending.
- The outlook for these therapies is complex, with significant uncertainties related to clinical issues such as efficacy, durability of response, and safety.
- Scenarios with higher overall spending could result if concerns are unwarranted and expected numbers of these drugs reach the market, receiving relatively wide reimbursement and usage. This could result in a large spending contribution driving a high-end scenario of over $50Bn in spending a year.
- These next-generation therapies will compete with other novel agents, where selection of a treatment for a patient may include decisions about efficacy, tolerability, and cost.
- The combination of these factors contribute to the base-case outlook for growth to $19Bn in global spending by 2027, substantially below the high-end scenario but reflecting the range of unknowns surrounding this groundbreaking research.

Notes: Historic values derived from company financials for marketed therapies. Estimates of future spending based on IQVIA estimates of numbers of future launches and expected continued uptake of existing therapies.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

IQVIA™ PIPELINE INTELLIGENCE is a drug pipeline database containing up-to-date R&D information on over 40,000 drugs, and over 9,000 in active development worldwide. The database captures the full process of R&D, covering activity from discovery stage through preclinical and clinical development, to approval and launch.

ARK PATENT INTELLIGENCE is a database of biopharmaceutical patents or equivalents worldwide and including over 3,000 molecules. Research covers approved patent extensions in 52 countries, and covers all types of patents including product, process, method of use and others.

IQVIA MIDAS™ is a unique platform for assessing worldwide healthcare markets. It integrates IQVIA's national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and provides estimated product volumes, trends and market share through retail and non-retail channels. MIDAS data is updated monthly and retains 12 years of history.

ONCOLOGY DYNAMICS is a syndicated cross-sectional survey that collects patient-level data from a representative panel of physicians and provides quick access to real-world data to unravel dynamics in subpopulations and treatment patterns. Oncology Dynamics has geographic coverage across 17 countries including key European, Middle Eastern, Asian, and Latin American markets and covers more than 180,000 cases per year and over 4,000 specialists.

BRANDIMPACT™ uses a proprietary mobile research model and longitudinal network of more than 400 internet-enabled oncologists and is the only source of continuously-captured physician treatment decisions for the biopharmaceutical industry. The real-time data generated by its information panel of oncologists enables unique insights into physician behavior and the influences on that behavior.

ONCOLOGY LINK includes 10-year drug spending and treated patient forecasts by tumor, country, target and treatment regimens. Analyses are projected to cover the total oncology market in 75 audited countries globally. Projections are based on total drug spending and volume data from IQVIA MIDAS, adjusted with detailed data in 9 key countries where patient treatment data is collected, accounting for 84% of global oncology market value. Projections are based on treatment regimens including over 300 drugs and 25 tumors.

Notes on sources

THIRD-PARTY INFORMATION

CITELINE'S TRIALTROVE provides intelligence about the drug development pipeline and information on clinical trials globally. Citeline reports that Trialtrove uses over 58,000 sources including ones in the public domain and is supported by experienced industry analysts. The database includes extracted information including protocol details, as well as additional industry-relevant search terms such as its proprietary patient segments, trial outcomes and biomarker tags. It includes information on trial design, eligibility criteria, endpoints, sites, sponsors as well as anticipated and actual start and end dates as available. For more information on Trialtrove, see https://pharmaintelligence.informa.com/products-and-services/clinical-planning/trialtrove

NATIONAL CANCER INSTITUTE SEER (SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS) PROGRAM provides detailed incidence, survival, U.S. mortality, U.S. prevalence, and lifetime risk statistics by cancer site and gender, race, and age. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48.0% of the U.S. population. SEER coverage includes 42.0% of Whites, 44.7% of African Americans, 66.3% of Hispanics, 59.9% of American Indians and Alaska Natives, 70.7% of Asians, and 70.3% Hawaiian/Pacific Islanders. For more information, see the SEER*Explorer: https://seer.cancer.gov/statistics-network/explorer/.

AGGREGATE ANALYSIS OF CLINICALTRIALS.GOV (AACT) DATABASE is a publicly available cloud-based relational database that contains all information (protocol and result data elements) about every study registered in ClinicalTrials.gov. Content is downloaded from ClinicalTrials.gov daily and loaded into AACT. The AACT database is maintained by the Clinical Trials Transformation Initiative (CTTI). CTTI was formed as a public-private partnership in 2007 between the United States Food and Drug Administration (FDA) and Duke University and now brings together stakeholders from more than 500 organizations and approximately 80 member organizations with the mission to improve the quality and efficiency of clinical trials. For more information on the AACT database, see https://aact.ctti-clinicaltrials.org/.

Methodologies

SUCCESS RATES

Using IQVIA Pipeline Intelligence, which includes event dates for a comprehensive range of drug development stages where disclosed or able to be determined by editorial staff, phase start dates were tracked for each product. A phase was considered successful if any subsequent phase has a later phase start date. In the absence of a subsequent phase start, the highest date for a negative event such as discontinuation, suspension, withdrawn by applicant, or inactive for greater than three years was examined. Analysis was conducted across all indications and considers success or failure at the drug level and so did not track a specific indication for each drug but rather measured the success of the overall program.

Overall, 32,300 distinct drugs were examined, for 129,200 potential phase transitions for events from 1977 to present. We then limited to products where the phase transitions completed between 2010 and 2022, with valid information regarding phase transitions, either successful or failed, which includes 9,625 distinct drugs and 13,926 phase transitions.

We consider the earliest date a drug entered each phase. We consider the latest date for negative event outcomes. Negative outcomes include discontinued, suspended and withdrawn which are noted in the data collection when the sponsor discloses it. Negative events also include inactivity which is determined when there is no verified activity for three years. Inactive records are assigned to the year inactivity was determined (last time record was active plus three years).

TRIAL DIVERSITY

Diversity analysis is based on data sets which include all interventional Phase I, II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009 and completing between the start of 2012 and the end of 2022 unless otherwise noted. Only trials with racial or ethnic data collected and reported on clinicaltrials.gov were included in the calculation of percent Black/African American or Hispanic patient inclusion, respectively. Analysis includes 1,494 trials over the time period.

Diversity indexes were created for each record with racial and/or ethnic data collected by comparing the percent of each race in the trial to the expected percent based on the U.S. incidence rate for that race and/or ethnicity across all cancer sites combined as well as for specific cancer type for our focus set of cancers. Analysis comparing cancer-specific U.S. mortality by race and ethnicity uses indexing to average total cancer mortality for each specific cancer.

The U.S. incidence and mortality rates are based on 2019 using the NCI SEER data. While 2020 data is available in the SEER data set, it is noted that the reported incidence rate for cancer in 2020 is lower due to the impact of COVID-19 and may not be a representative of cancer incidence trends.

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About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry, and payers.

Research agenda

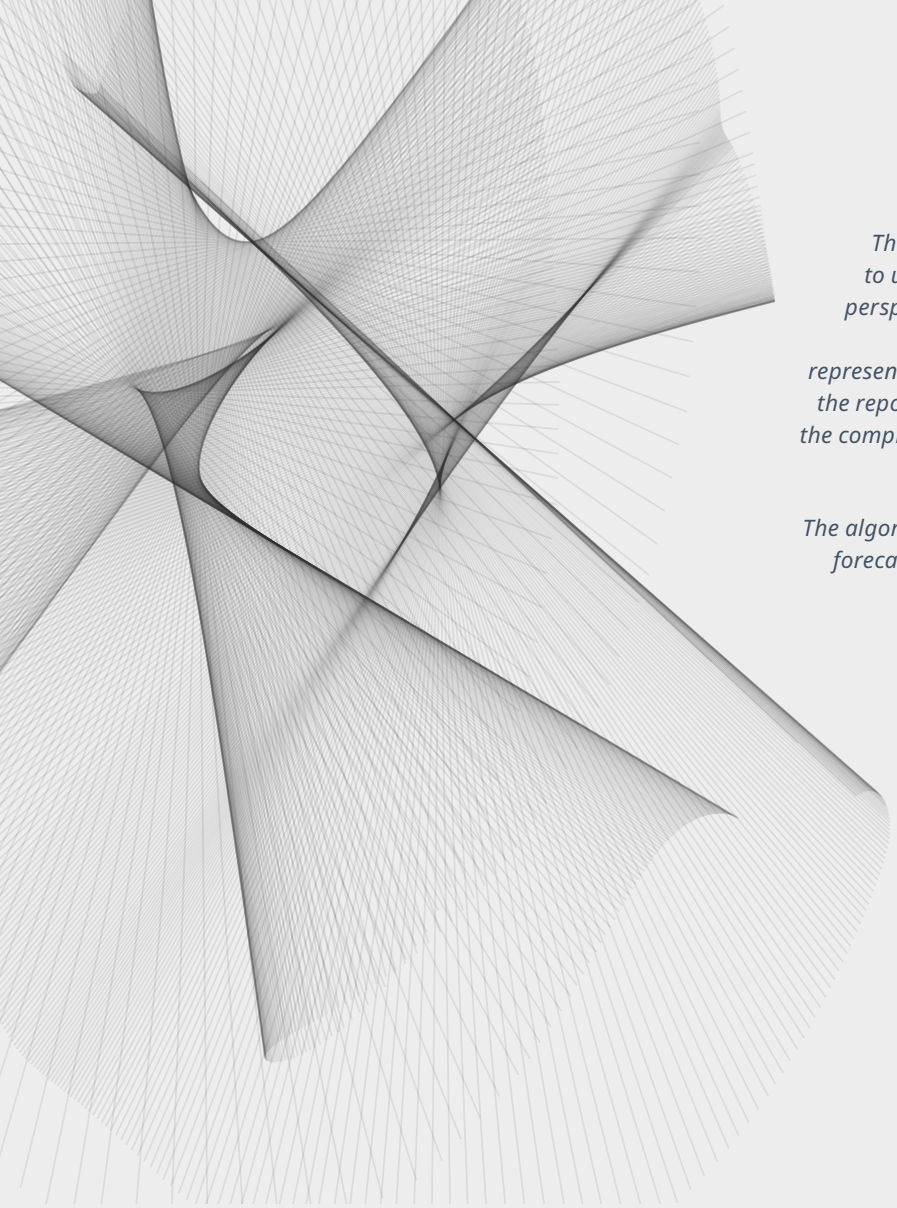
The research agenda for the Institute centers on five areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.



The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The algorithmic art on this report cover is based on historic and forecasted oncology sales and treated patients for the top 10 tumors in the U.S., EU4+UK, and Japan for 2018–2027.

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