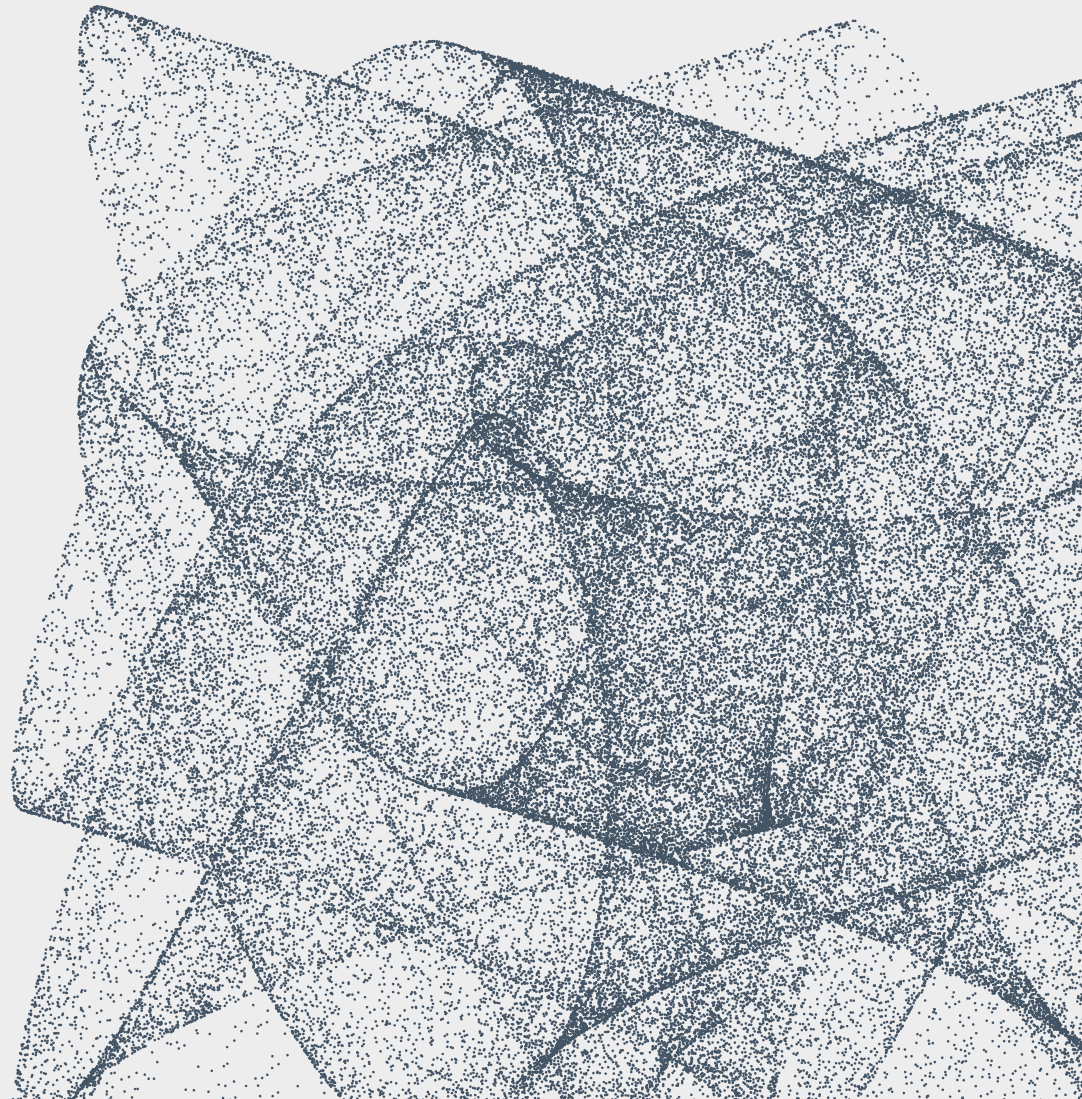




Global Oncology Trends 2019

THERAPEUTICS, CLINICAL DEVELOPMENT
AND HEALTH SYSTEM IMPLICATIONS



MAY
2019

Introduction

In recent years, record numbers of new oncology drugs have been approved, bringing new treatment options to patients. Treatment guidelines have also transformed to maximize the benefit of those treatments. However, despite high levels of pipeline activity, oncology still remains the most challenging area for research and development, facing significant risk of failure and long duration. Barriers to adoption of new drugs also remain, delaying patient benefit from treatment advances. As treatment options increase, the impact on spending levels has become a focus across most parts of the world – a trend that is expected to continue over the next five years as growth continues.

This report examines the productivity and output of the oncology pipeline and the prospect of further advances over the next five years. It takes a close look at the number of medicines under development in 2018, new mechanisms, and which patients will likely benefit from new therapies. The notable successes – and failures – that have occurred are also reviewed, each of which has furthered our understanding of the underlying causes of certain cancers, disease progression and the potential for novel treatments.

This year's report brings into focus novel advances in cancer therapeutics, the use of these drugs and the amount spent on them globally, associated clinical trial activity, complexity and success, and the outlook through 2023. The report also addresses shifts in therapy use, as new immunotherapies are adopted as first-line treatments, Next-Generation Therapeutics such as CAR-T therapies come available, and biosimilars are developed and introduced.

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 Patrick Angelastro, Caroline Anger, Paul Cariola, Onil Ghotkar, Graham Lewis, Melissa Marth, Arth Mathur, Kim Mehle, Shelia Mpima, Elyse Muñoz, Max Newton, Urvashi Porwal, Sam Riches, Chris Schulze-Solce, Adam Sohn, Durgesh Soni, Dan Winkelman, Terri Wallace, Andy Wong, and dozens of others at IQVIA are gratefully acknowledged.

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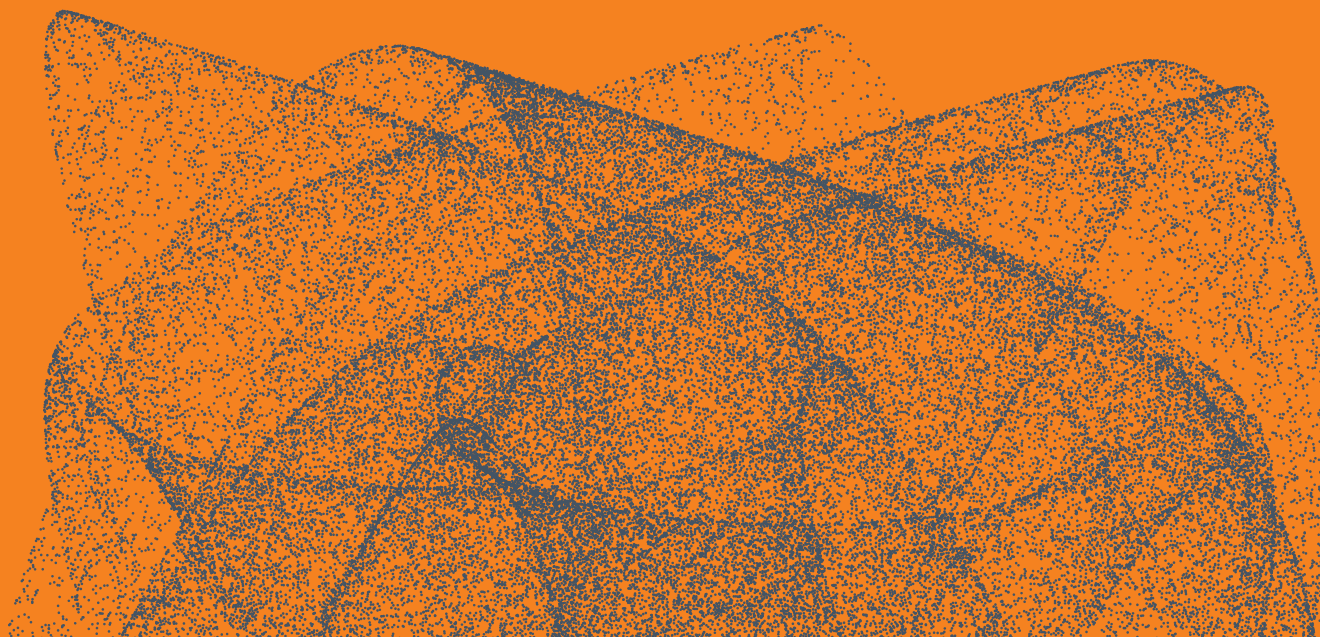
Executive Director

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Table of contents



| | |
|---|----|
| Executive summary | 2 |
| Innovation in patient therapies | 4 |
| Research and development activities | 14 |
| Bringing scientific advances to cancer patients | 29 |
| Spending on oncology medicines | 36 |
| Notes on sources | 48 |
| References | 49 |
| About the authors | 51 |
| About the IQVIA Institute | 53 |



Executive summary

INNOVATION IN PATIENT THERAPIES

A record 15 new oncology therapeutics were launched in 2018 for 17 indications. Over half of the new therapies are delivered as an oral formulation, have an orphan indication or include a predictive biomarker on their label. The 57 drugs launched between 2014–2018 have now gained 89 indications across 23 different cancer types. Thirty-one percent of the approved indications over the past five years have been for non-solid cancers – leukemia, lymphoma and multiple myeloma – while lung cancer leads the solid tumors with 12 indications, followed by breast cancer and melanoma with seven and six, respectively.

Through the course of 2018, several notable successes – and failures – have contributed to breakthroughs in the understanding of disease, including its underlying causes, progression and potential opportunities for treatment. Among notable oncology NASs in 2018, duvelisib demonstrated an overall response rate of 42% in follicular lymphoma and 74% in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), while larotrectinib demonstrated an overall response rate of 75% across solid tumors with an *NTRK* gene fusion and became the second tissue-agnostic therapeutic approved. Other notables included a first-in-class approval of a biomarker-linked treatment for ovarian cancer, positive early results in difficult-to-treat breast cancer subtypes, approvals in several leukemias, and trial failures in melanoma and lung cancers related to once-promising mechanisms.

Recently introduced therapies are being used more broadly across varied tumor populations and in earlier lines of therapy. Immunotherapies were used in over 200,000 patients in 2018 in the United States, more than double the level two years prior. Treatment with novel CDK 4/6 inhibitors for HER-2 negative breast cancer has increased dramatically in both the United States and Europe.

RESEARCH AND DEVELOPMENT ACTIVITIES

Clinical development activities are being undertaken by more than 700 companies and are at record high levels. However, despite some improvement in trial productivity and the prospect of further advances over the next five

years, development remains high-risk and of long duration. The pipeline of drugs in late-stage development expanded 19% in 2018 alone, and 63% since 2013. Within the pipeline, across all phases of clinical development, the most intense activity is focused on nearly 450 immunotherapies with more than 60 different mechanisms of action. Ninety-eight next-generation biotherapeutics – defined as cell, gene and nucleotide therapies – are also under clinical investigation and leverage 18 different approaches. The combined immunotherapies and next-generation biotherapeutics are targeting almost all cancer tumor types with over 80 mechanisms of action.

Of the 711 companies participating in oncology late-stage development, almost 500 are entirely focused on oncology and 463 of these are emerging biopharma. Of the 33 large pharma companies with global pharmaceutical sales over \$5 billion in 2018, 28 have large and active oncology pipelines.

Clinical trial activity remains high-risk with the oncology composite success rate falling to 8.0% in 2018 from 11.7% in 2017, but similar to the average level of the past decade. Clinical trial duration remains higher for oncology trials than other disease areas but has generally declined over the past five years, dropping seven months in Phase I trials, 11 months in Phase II trials and over a year in Phase III trials. Clinical trial complexity – measured as a combination of endpoints, eligibility criteria, and numbers of subjects, trial sites and countries – has increased sharply for phase I trials over the past five years. The overall productivity of oncology trials – measured as success rates relative to trial effort (complexity and duration) – has improved by 22% since 2010, but remains far lower than trials for other therapy areas.

Biomarkers that stratify patients likely to respond to therapy are now included in 39% of oncology trials, up from 25% in 2010, reflecting that precision medicine approaches are becoming more commonplace.

Modelling the impact of current clinical development trends on future productivity, the availability of pools of pre-screened patients and biomarker tests could yield productivity improvements of as much as 104% and 71%, respectively, by 2023.

BRINGING SCIENTIFIC ADVANCES TO CANCER PATIENTS

Progress is being made in accelerating the time it takes for scientific advances to reach cancer patients but barriers remain in the areas of registration, diagnostics, infrastructure and reimbursement, resulting in variability in care and delays in patients benefiting from treatment advances. New oncology drugs launched in 2018 took a median of 10.5 years from the time of first patent filing to regulatory approval and launch, down over four years from the 2017 level. After a drug's first global launch, reaching patients in other countries can be a complicated and time-consuming process, and in 2018 fewer than half of new cancer medicines launched in the prior five years are available to patients beyond nine countries.

The use of biomarker tests is increasingly associated with novel therapies, and while the use of predictive biomarker tests is increasing across relevant tumor types, the use of the tests by country, by provider or institution and the timing of their use is highly variable. The biomarkers BRCA, KRAS, NRAS, ROS-1 and MSI – all associated with new treatments approved later by the European Medicines Agency than in the United States – have between 20-36% lower testing rates in the top five European markets than in the United States.

With more complex novel therapies such as CAR-Ts, the infrastructure to extract T cells and reinfuse them after they have been engineered to fight a patient's cancer are necessary, is not widely present in oncology centers in many countries. Patients and their families may additionally face logistical and financial burdens in order to relocate temporarily to a location that can provide these treatments.

Many European markets use health technology assessments (HTAs) to inform reimbursement decisions, but the results have been highly variable, and positive decisions are trending downward as a percentage of total decisions, limiting access under insurance schemes.

SPENDING ON ONCOLOGY MEDICINES

Spending on all medicines used in the treatment of patients with cancer reached nearly \$150 billion in 2018 up 12.9% for the year and marking the fifth consecutive year of double-digit growth. This growth was driven entirely by

therapeutic drugs, which grew 15.9%, as supportive care drugs declined 1.5% in 2018. New brands launched in the past two years and protected brand volume contributed nearly all the positive growth in major developed markets, where spending growth exceeded 13% in each market with the exception of Japan.

Japan's adoption of novel therapies is significant but overall spending growth is lower in part due to efforts to drive savings with price cuts – which affect older chemotherapy brands and generics – while newer brands contributed half of positive spending growth.

LOE impact, including the effect of biosimilars, has begun to impact spending in the EU5 countries, driven by the availability of biosimilars of trastuzumab (Herceptin), as well as small molecule patent expiries, such as imatinib (Glivec/Gleevec).

The average annual cost of new medicines continues to trend upward, although the median cost dropped \$13,000 in 2018 to \$149,000, and cost per product ranged between \$90,000 and over \$300,000. The mean cost for new brands in 2018 was \$175,578, down from \$209,406 in 2017, but was above the \$143,574 mean from 2012 to 2018.

Spending on cancer medicines is heavily concentrated, with the top 38 drugs accounting for 80% of total spending. Over half of cancer drugs earn more than \$143.6 million in annual sales and in aggregate account for only 2.2% of oncology spending.

China led pharmerging markets in spending and growth and grew a remarkable 24% in 2018 to \$9 billion in total spending, even as supportive care treatments in China declined by 10%.

Over the next five years, growth in therapeutics spending of 11–14% is expected on a CAGR basis, bringing the total market to \$200–230 billion. Including supportive care, which is expected to decline by -3 to -6%, overall oncology spending will reach \$220–250 billion, growing 9–12% through 2023.

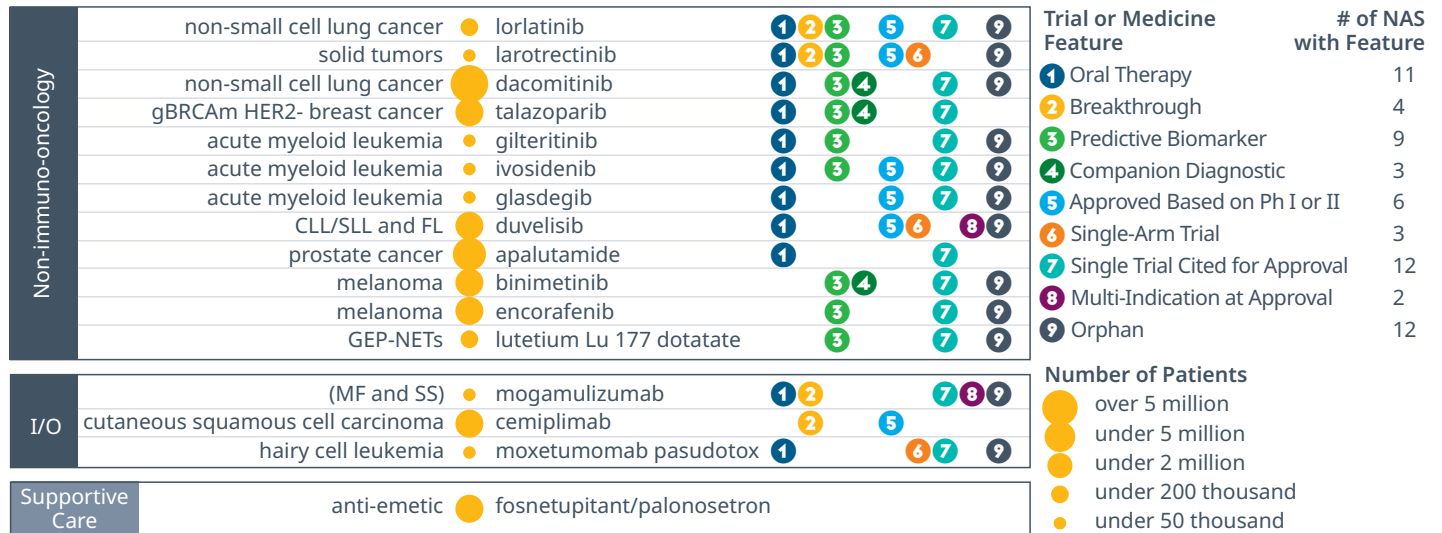
Innovation in patient therapies

- A record number of new oncology drugs was launched in 2018, bringing new treatment options to patients, and continuing the transformation of treatment patterns occurring from the introduction of immunotherapies less than five years ago.
- These new drugs use diverse mechanisms to treat cancer and include three immuno-oncology therapies. Over half of the new therapies are delivered as an oral formulation, have an orphan indication or include a predictive biomarker on their label.
- Among oncology NASs in 2018, duvelisib and larotrectinib stand out as the most pivotal, with duvelisib demonstrating an overall response rate of 42% in follicular lymphoma and 74% in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and larotrectinib demonstrating an overall response rate of 75% across solid tumors that have an *NTRK* gene fusion. Larotrectinib is the second tissue-agnostic therapy approved in the United States, a paradigm shift occurring in oncology to treat tumors based on genetic profile rather than site of origin in the body.
- Between 2014 and 2018, 57 oncology NASs launched and collectively are approved for 89 indications.
- Almost one-third of the approved indications over the past five years have been for non-solid cancers - leukemia, lymphoma and multiple myeloma - while lung cancer leads the solid tumors with 12 indications, followed by melanoma and breast cancer.
- Through the course of 2018, several notable successes – and failures – have contributed to breakthroughs in the understanding of disease, including its underlying causes, progression and potential opportunities for treatment. These include the approval of the second tissue-agnostic therapeutic.
- The immune checkpoint inhibitors have seen growing uptake by oncologists, who treated over 200,000 patients with these therapies in 2018, up from fewer than 100,000 in 2016.
- Immunotherapies – particularly anti-PD-1/PD-L1s – are rapidly becoming the primary first-line treatments in the United States for patients with metastatic non-small cell lung cancer, metastatic melanoma and metastatic renal cell carcinoma.
- Treatment with novel CDK 4/6 inhibitors for breast cancer has increased dramatically in both the United States and Europe.



A record of 15 new oncology therapeutics and one supportive care therapy were launched in 2018

Exhibit 1: Oncologic New Actives Substances (NAS) Launched for the First Time in the United States in 2018



Source: IQVIA Institute, Apr 2019

- There were 15 therapeutic oncology new active substances (NASs) and one supportive care NAS launched in the United States in 2018.
- Predictive biomarkers were associated with 60% of therapeutic oncology NASs, and three were approved with a companion diagnostic. Precision medicines are having a significant impact on the treatment of cancer by stratifying patients into specific groups of patients likely to respond to therapy (or not) via predictive biomarkers.
- Three NASs were immuno-oncology (I/O) therapies: Cemiplimab is a PD-1 inhibitor, while mogamulizumab is a chemokine receptor inhibitor (CCR4) and moxetumomab modulates a tumor-associated antigen (CD22). Mogamulizumab and moxetumomab represent new strategies in I/O therapy that historically has focused on checkpoint inhibitors and less targeted immunomodulatory mechanisms, such as interferons.
- Ten of the 16 therapies are delivered in an oral formulation, decreasing the patient burden of receiving care at an infusion center or hospital.
- Although there were only four breakthrough oncology therapies, down from historical high of 11 in 2017, 12 of the NASs were approved based on a single trial and six cited Phase I or Phase II trials as part of their approvals, indicating that innovative oncology therapies are moving quickly through R&D and regulatory filing.
- Fosnetupitant/palonosetron (Akynzeo) fills an unmet need to treat acute and delayed nausea and vomiting up to 120 hours after chemotherapy, as an infusion rather than an oral formulation.

Chart notes: NAS includes all medicines approved by FDA regardless of review division, if one or more of their ingredients are novel. Patient estimates are based where possible on disease prevalence. SLL = small lymphocytic lymphoma; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; gBRCAm = BRCA 1/2 germline mutation; GEP-NET = Gastroenteropancreatic neuroendocrine tumors; Duvelisib and mogamulizumab were each approved for multiple indications simultaneously (duvelisib for CLL/SLL and FL and mogamulizumab for mycosis fungoides (MF) and Sézary syndrome (SS), both rare forms of cutaneous T-cell lymphoma). Immno-oncology therapies are those therapies which induce the immune system to specifically target cancer cells and include the immune checkpoint inhibitors (PD-1, PD-L1, CTLA4), other T-cell mediated immunomodulators and bispecific T-cell engagers (BiTEs), immunomodulators that target specific tumor antigens and modulate immune response via other immune cells (such as B-cells), vaccines, oncolytic viruses and cell therapies, such as CAR-T therapies.

There was a surge of innovation in cancer treatments in 2018

Exhibit 2: New Active Substances Launched in 2018 and Summary of Clinical Benefits

| MOLECULE | INDICATION | TRIAL | APPROVAL TRIAL PHASES | SUMMARY |
|----------------------------|---------------------------|-----------------------------|------------------------------------|---|
| apalutamide | Prostate cancer | SPARTAN | Phase III | For patients with non-metastatic castration-resistant prostate cancer (NM-CRPC) there was a decreased risk of distant metastasis or death by 72% compared to placebo and an improved median metastasis-free survival by more than two years. This is the first FDA approved treatment for NM-CRPC, and metastasis-free survival is a novel end point in prostate cancer trials. |
| binimetinib encorafenib | Melanoma (in combination) | COLUMBUS | Phase III | In patients with unresectable or metastatic melanoma with a BRAF V600E or 600K mutation, the combination of binimetinib and encorafenib doubled the mPFS at 14.9 months compared to 7.3 months in the vemurafenib group. |
| cemiplimab | CSCC | NCT02383212; NCT02760498 | Phase I Phase II | There was an overall response rate of 47% across two, open-label studies of patients with advanced metastatic CSCC. |
| dacomitinib | NSCLC | ARCHER 1050 | Phase III | Median progression-free survival was significantly higher for patients with advanced EGFR+ NSCLC at 14.7 months compared to gefitinib at 9.2 months. This represents a new second generation EGFR TKI for NSCLC patients. |
| duvelisib | CLL/SLL; FL | DYNAMO; DUO DYNAMO-R | Phase II Phase III Phase III | Adult patients with relapsed or refractory CLL or SLL had a median PFS of 16.4 months. Duvelisib also showed an 42% overall response rate in FL patients and a 74% rate in CL/SLL patients. This therapy is another medicine for patients with limited options. |
| gilteritinib | AML | ADMIRAL | Phase III | Interim trial analysis demonstrated a CR/CRh rate of 21% with a median duration of 4.6 months. Gilteritinib is approved for use in relapsed or AML patients with a FLT3 mutation, typically associated with a poorer prognosis. |
| glasdegib | AML | BRIGHT AML 1003 | Phase II | Glasdegib was approved in combination with low-dose cytarabine (LDAC) in newly diagnosed AML patients 75 years or older or who have comorbidities that preclude standard chemotherapy. Glasdegib plus LDAC demonstrated a median survival time of 8.3 months. |
| ivosidenib | AML | NCT02074839 | Phase I | In patients with relapsed or refractory AML, the rate of complete remission was 21.6% and the overall response rate was 41.6%, and the median durations of these responses were 9.3 months and 6.5 months, respectively. Ivosidenib is approved for patients who have a specific IDH1 genetic mutation found in 6-10% of AML patients. |

INNOVATION IN PATIENT THERAPIES

Exhibit 2: New Active Substances Launched in 2018 and Summary of Clinical Benefits continued

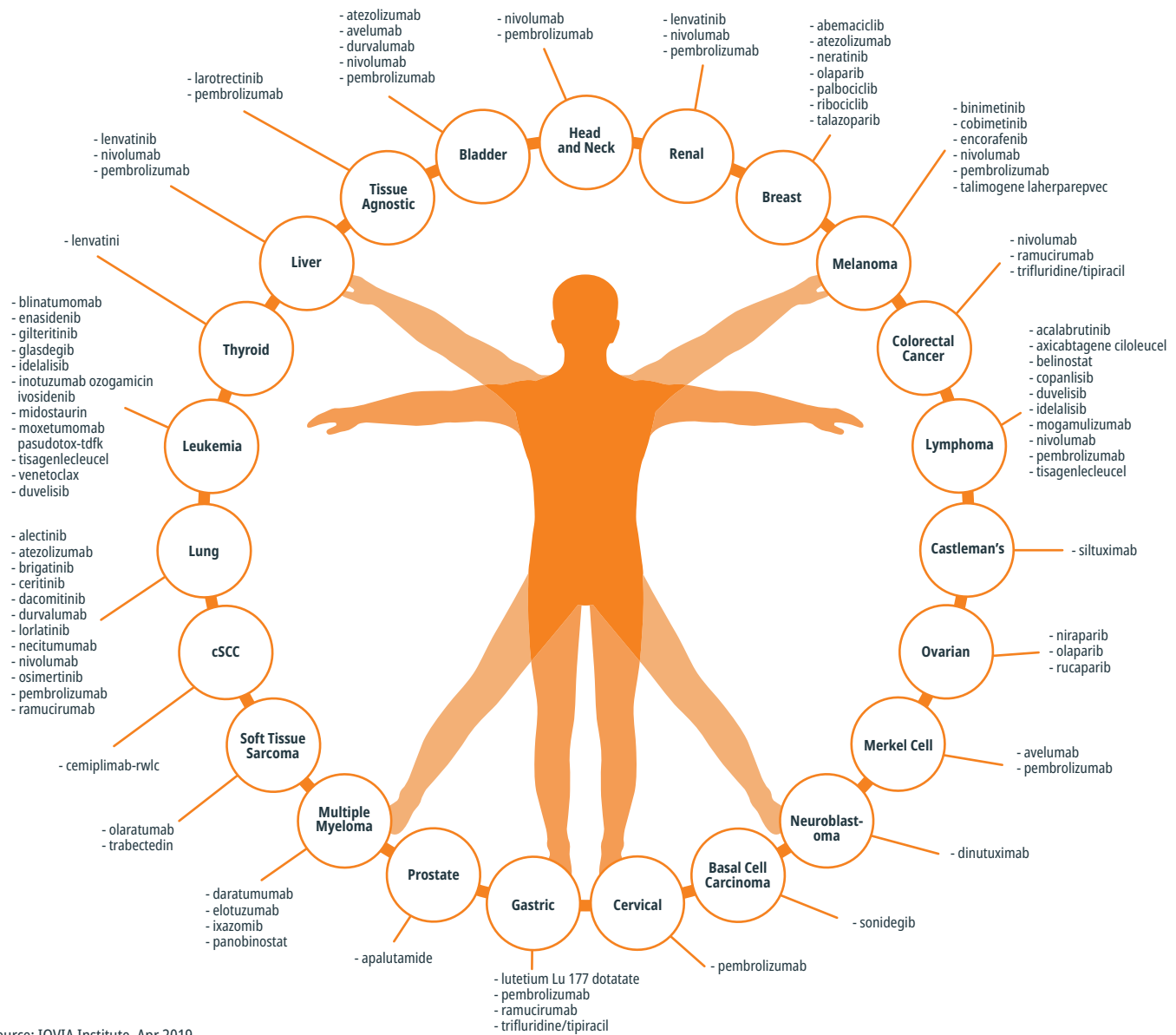
| MOLECULE | INDICATION | TRIAL | APPROVAL TRIAL PHASES | SUMMARY |
|--------------------------|--------------------------------------|---------------------------------|-----------------------------------|---|
| larotrectinib | Tumor-Agnostic | LOXO-TRK-14001; SCOUT; NAVIGATE | Phase I Phase I/II Phase II | Larotrectinib is approved for patients with solid tumors that have a <i>NTRK</i> gene fusion without a known acquired resistance mutation. Approval was based on the results of three studies that demonstrated an ORR of 75%, including a complete response rate of 22%. This is the second FDA-approved tissue-agnostic oncology agent. |
| lorlatinib | NSCLC | Study B7461001 | Phase II | Trial results demonstrated that for ALK positive NSCLC patients treated with lorlatinib, the ORR was 48% with 4% complete and 44% partial responses, respectively. |
| lutetium Lu 177 dotatate | GEP-NETs | NETTER-1 | Phase III | For patients with somatostatin positive GEP-NETs progression-free survival at 20 months was 65.2% and response rate was 18%. This is the first radiopharmaceutical approved for GEP-NETs. |
| mogamulizumab | Mycosis fungoides or Sézary syndrome | MAVORIC | Phase III | Patients with relapsed or refractory mycosis fungoides or Sézary syndrome (SS) experienced a median of 7.7 months of progression free survival compared to those receiving a standard of care who experienced 3.1 months progression free survival. This is the first FDA-approved therapy for SS. |
| Moxetumomab pasudotox | HCL | NCT01829711 | Phase III | For patients with relapsed/refractory HCL, the durable complete response rate was 30%, and 80% of patients achieved hematologic remission. The durable complete response rate was significantly higher than the historical control value of rituximab at 13%. |
| talizumab | Breast cancer | EMBRACA | Phase III | Talazoparib is a PARP inhibitor for treatment in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2 negative breast cancer, a type of breast cancer with historically fewer targeted therapy options. Talazoparib demonstrated greater PFS than standard of care at 8.6 months. |

Source: IQVIA Institute analysis of trials used as the basis for FDA-approval of relevant drugs, see References for details of the trials used: references 1-15.

Chart notes: Does not include supportive care; median progression-free survival (mPFS); CSCC = metastatic cutaneous squamous cell carcinoma; GEP-NETs = gastroenteropancreatic neuroendocrine tumors; HCL = hairy cell leukemia; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; FL = follicular lymphoma; AML = acute myeloid leukemia; *NTRK* = neurotrophic receptor tyrosine kinase; ALK = anaplastic lymphoma kinase; PARP = poly(adenosine diphosphate-ribose) polymerase; PFS = progression free survival. CR/CRh = complete remission/complete remission with partial hematologic recovery.

Over the past five years oncology NASs received 89 new indication approvals, with some drugs treating multiple tumor types

Exhibit 3: New Active Substance Approvals in Oncology by Tumor Type, 2014–2018



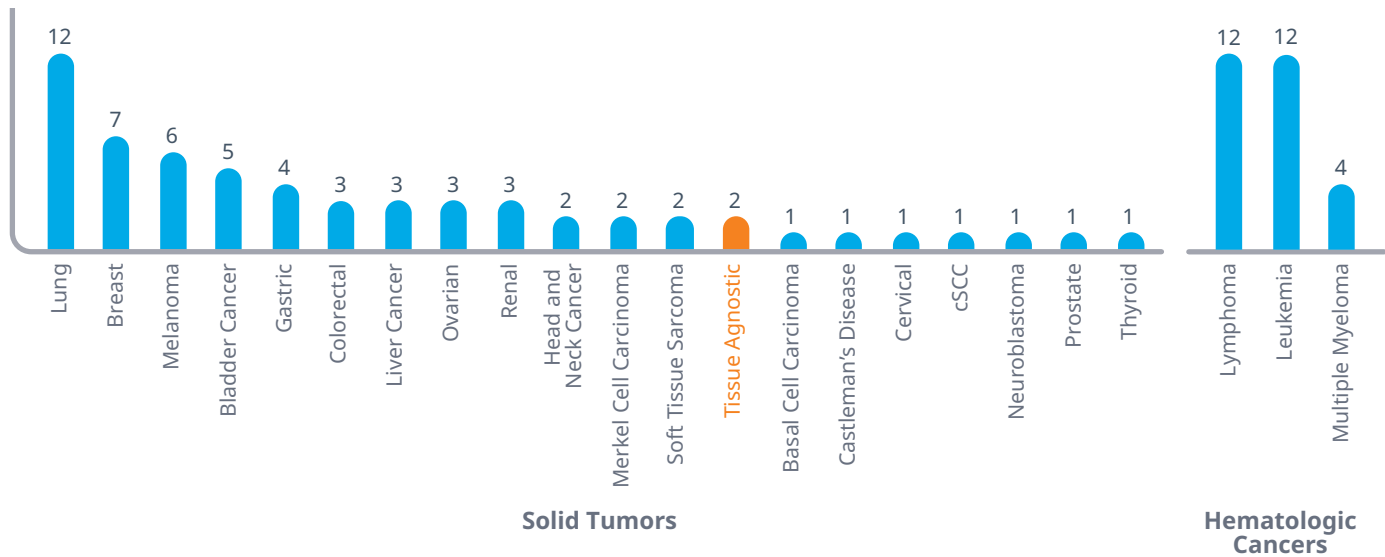
Source: IQVIA Institute, Apr 2019

- The cancer treatment landscape has continued to evolve since 2014, and now includes new medicines targeting 23 different cancer types.
- From 2014 to 2018, there were 57 unique NAS molecules with 89 indications approved, with many of these drug approved for more than one indication.

Chart notes: Excludes supportive care. cSCC = Cutaneous squamous cell carcinoma; mogamulizumab is approved for multiple lymphoma indications: Mucormycosis and Sézary syndrome. Pembrolizumab is approved for multiple lymphoma indications: classical Hodgkin lymphoma (cHL) and primary mediastinal large b-cell lymphoma (PMBCL). Chart includes three indication approvals that occurred for NAS candidates within the time frame of launch within 2014 to 2018 that had subsequent indication approvals as of May 2019: pembrolizumab, trifluridine/tipiracil and atezolizumab for renal, gastric and breast, respectively.

Thirty-one percent of the approved indications over the past five years have been for hematologic cancers

Exhibit 4: Number of New Active Substance Approvals in Oncology by Indication



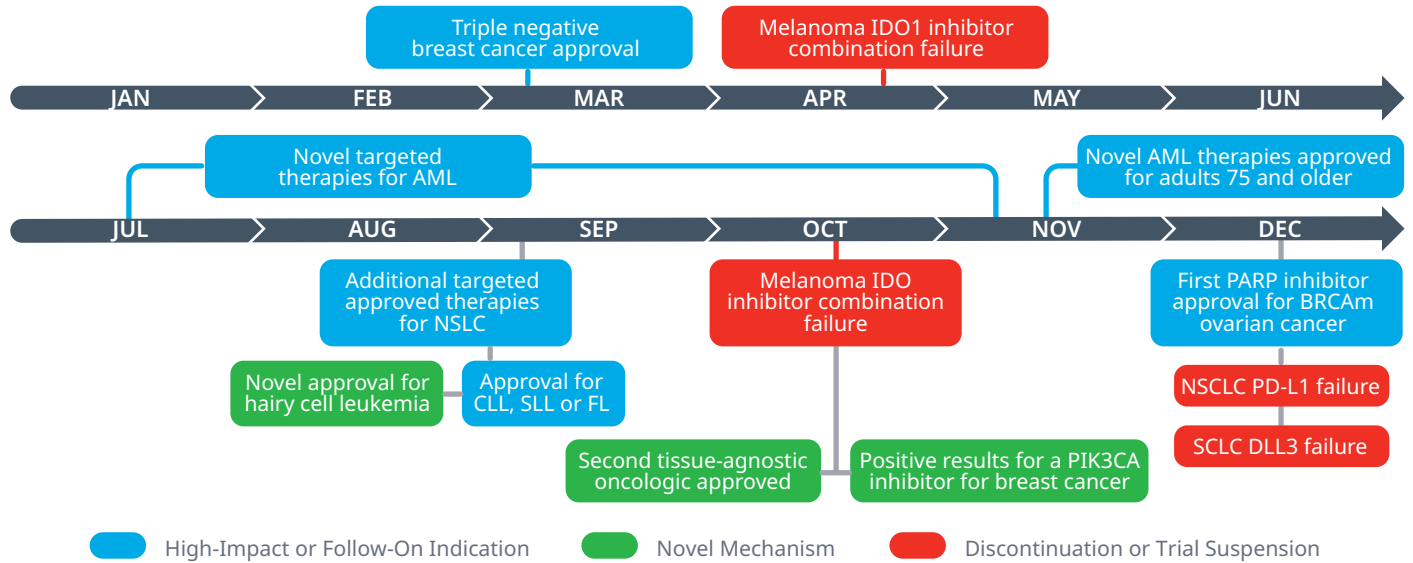
Source: IQVIA Institute, Apr 2019

- Thirty-one percent of the indications approved over the past five years have been for non-solid cancers, with 10 drugs receiving 12 indication approvals for lymphoma within this time period.
- Lung cancer had the highest number of new indications approved for NASs in 2014-2018, with 12 new indications, followed by breast cancer with seven approvals.
- Many approvals for drugs in cancers such as lung, breast and the leukemias received subsequent approvals for mutation-specific types of these tumors, such as receiving a subsequent approval for ALK positive non-small cell lung cancer (NSCLC) after a primary approval for NSCLC.
- In 2018, larotrectinib became the second tissue-agnostic oncology therapy to be approved, following the subsequent approval of pembrolizumab for this indication in 2017.

Chart notes: Excludes supportive care. cSCC = Cutaneous squamous cell carcinoma; mogamulizumab is approved for multiple lymphoma indications: Mycosis fungoides and Sézary syndrome. Pembrolizumab is approved for multiple lymphoma indications: classical Hodgkin lymphoma (cHL) and primary mediastinal large b-cell lymphoma (PMBCL). Chart includes three indication approvals that occurred for NAS candidates within the time frame of launch within 2014 to 2018 that had subsequent indication approvals as of May 2019: pembrolizumab, trifluridine/tipiracil and atezolizumab for renal, gastric and breast, respectively.

Notable successes in 2018 include drug approvals for leukemia, breast and ovarian cancers

Exhibit 5: Select Positive and Negative Registration and Clinical Events in 2018



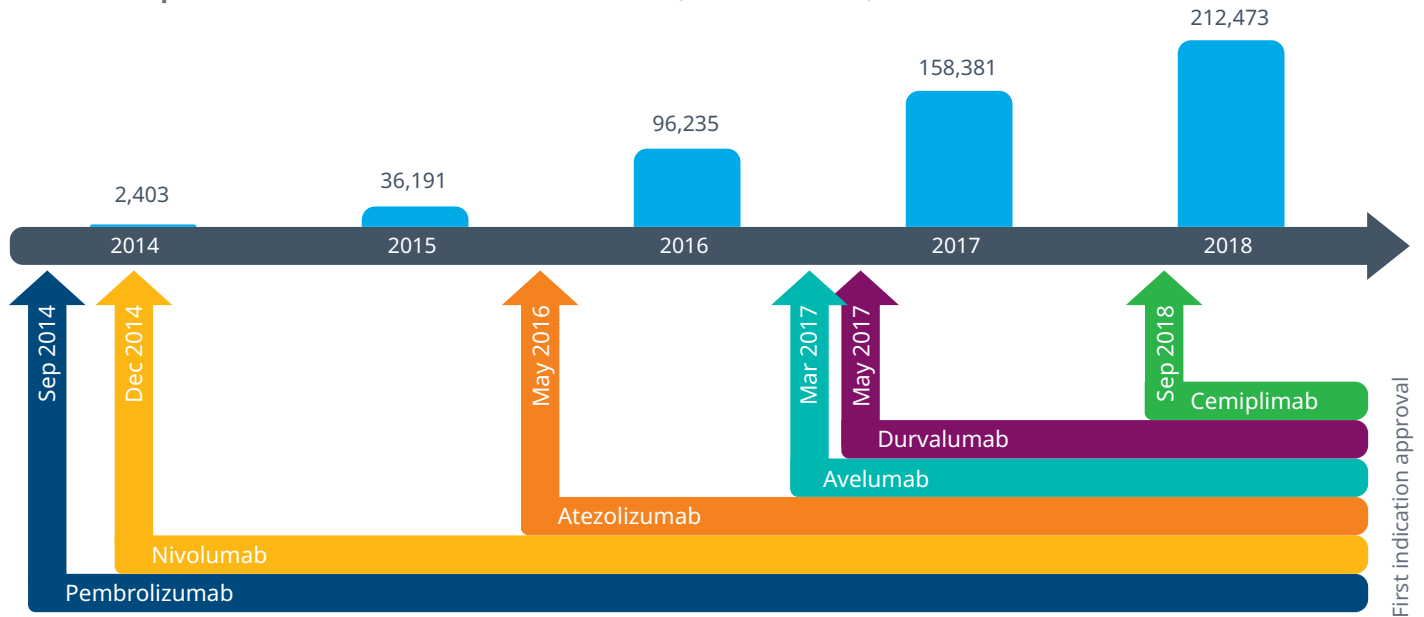
Source: Multiple public sources including 2018 FDA Drug Approvals, Nature Reviews Drug Discovery, Jan 2019; IQVIA Institute, Mar 2019

- Oncology had a number of successes in 2018. In AML – an area with few recent approvals – three targeted therapies were approved and approvals included patients age 75 and older.
- In breast and ovarian cancer, the PARP inhibitor olaparib became the first targeted therapy to receive approval for triple-negative breast cancer – a difficult to treat cancer with a poor prognosis – and the first PARP inhibitor for ovarian cancer with a BRCA mutation. In addition, the Phase III therapy alpelisib nearly doubled progression-free survival in PIK3CA-mutant breast cancer.
- Additional targeted treatments were approved for cancers including EGFR-positive or ALK-positive NSCLC, BRAF-positive melanoma and FLT3-positive and IDH1-positive AML.
- The approval of larotrectinib as the second tissue-agnostic medicine was a significant advance for precision therapies in oncology. It was approved for solid tumors with a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion and lacking a known acquired resistance mutation.
- The CAR-T therapy tisagenlecleucel (Kymriah) also received a second FDA approval in 2018 for the treatment of adult patients with relapsed/refractory DLBCL, bringing the total indications approved for the two CAR-T therapies up to three.
- There were also setbacks in oncology in 2018, including a DLL3 targeted treatment failure in SCLC and the unexpected failure of the PD-L1 inhibitors in NSCLC. In melanoma, IDO inhibitor products performed poorly, both as monotherapy and in combination.

Chart notes: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; IDO = indoleamine 2,3-dioxygenase; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; FL = follicular lymphoma; PARP = poly ADP ribose polymerase; BRCAm = mutation in either of the BRCA1 or BRCA2; PD-L1 = Programmed death-ligand 1; DLL3 = delta-like protein 3; PIK3CA = alpha subunit of phosphatidylinositol 3-kinase; FLT3 = FMS-like tyrosine kinase 3; IDH1 = isocitrate dehydrogenase-1; DLBCL = diffuse large B-cell lymphoma. Venetoclax received an additional approval in 2018; the drug was previously approved in 2016.

The number of patients being treated with PD-1 and PD-L1 inhibitors has risen dramatically since their introduction in 2014

Exhibit 6: Unique Patients Treated with PD-1 and PD-L1, United States, 2014–2018



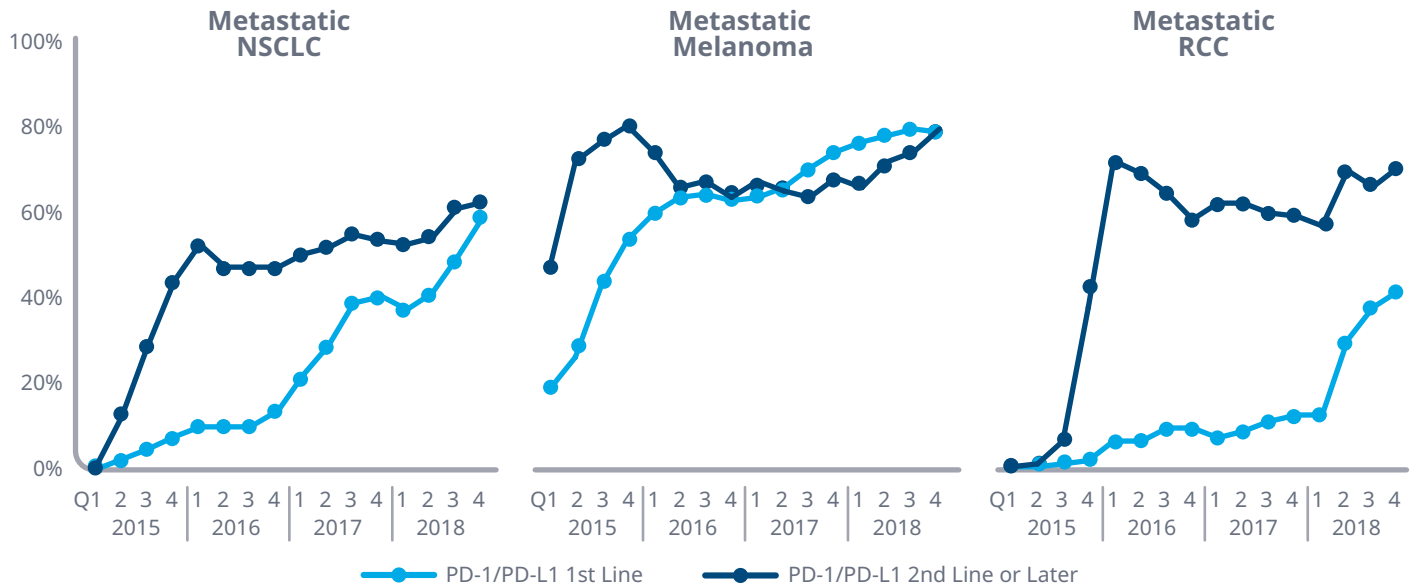
Source: IQVIA Real World Evidence, Medical Claims, Dec 2018

- The introduction of PD-1 and PD-L1 checkpoint inhibitors over the past five years has dramatically improved outcomes for patients with a wide range of solid tumors.
- These drugs work by using the patient’s own immune system that is otherwise inhibited or impaired in its ability to identify and target cancer cells.
- The number of treated patients using one of these agents has more than doubled in the past two years, largely focused on the two earliest approved agents, which have the widest range of approved uses and together account for more than 90% of the treated patients.
- There were more than 200,000 patients treated during 2018, up from 2,403 in 2014, when pembrolizumab became the first approved drug of this type to launch in in September 2014.
- There have been dozens of indications approved for these medicines since that time, but together they represent the some of the most advanced types of treatments available to patients with cancer.

Chart notes: Patients are identified as unique patients receiving at least one infusion in that year and do not reflect patients who completed a course of treatment. PD-1 = Programmed cell death protein 1; PD-L1 = Programmed cell death protein ligand 1.

Immuno-oncology therapies, particularly PD-1/PD-L1s, are used increasingly as first-line treatments

Exhibit 7: Share of Line of Therapy for Selected Tumors



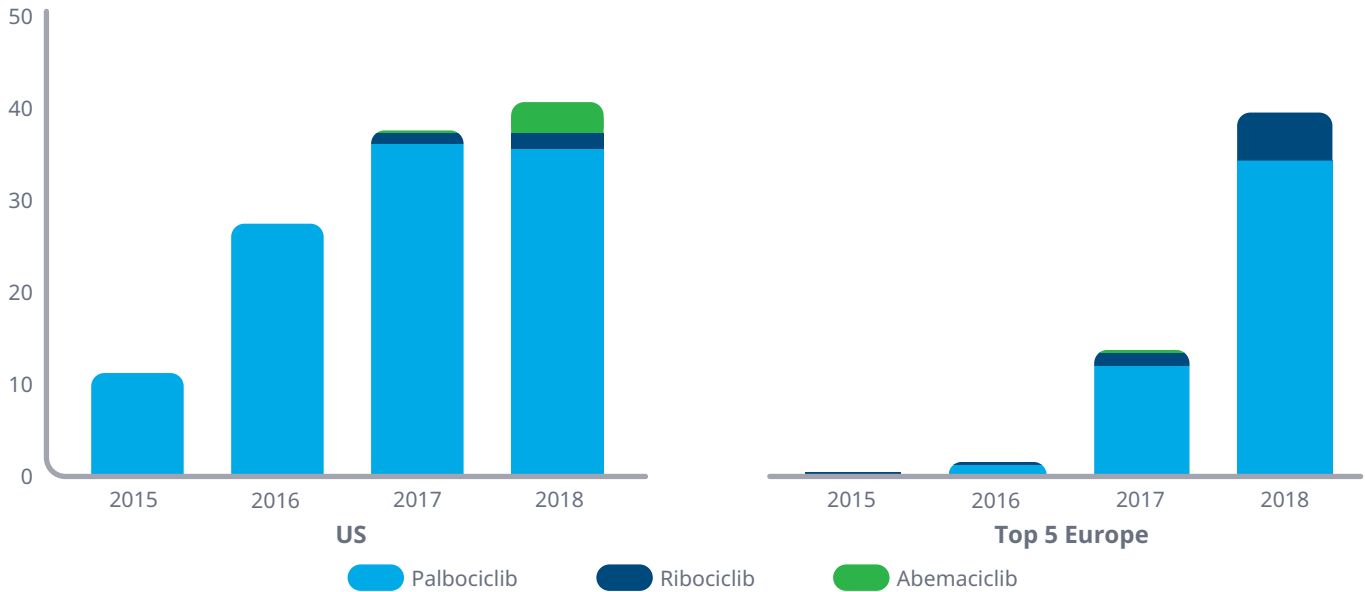
Source: IQVIA Real World Evidence, Medical Claims, Dec 2018

- As immune checkpoint inhibitors became available in the United States, use was initially focused in later lines of therapy, in a pattern typical for the adoption of new cancer treatments.
- These drugs together now account for 77% of all lines of therapy in metastatic melanoma.
- By the end of 2018, 55% of first-line treatments for newly diagnosed patients, and 59% of later lines of therapy for metastatic non-small cell lung cancer, were using one of the approved PD-1/PD-L1 drugs.
- It is notable that the movement to first-line treatment has occurred very quickly, within just 2–3 years, largely driven by the significantly better outcomes for these patients than older options.
- The shift to earlier lines of therapy has been slower in metastatic renal cell carcinoma due to the timing of approval for earlier use of the treatments.
- There are over 20 approved uses of PD-1/PD-L1 treatments in a variety of tumors, and they are progressively being adopted earlier in treatment.

Chart notes: RCC=renal cell carcinoma; NSCLC = non-small cell lung. Chart based on all patients treated with first line therapy or subsequent therapies. PD-1 = Programmed cell death protein 1; PD-L1 = Programmed cell death protein ligand 1.

Treatment with newer CDK 4/6 targeted breast cancer therapies has increased dramatically in both the United States and Europe

Exhibit 8: Metastatic Breast Cancer Patients Treated with Regimens Containing CDK 4/6 Agents in Thousands



Source: IQVIA Real World Evidence, Medical Claims, Dec 2018; IQVIA Oncology Analyzer, Dec 2016; Oncology Dynamics, Dec 2018

- Treatments for breast cancer, the most prevalent cancer among women, have evolved over the past five years with the introduction/rapid uptake of new options, particularly CDK4/6 inhibitors.
- CDK4/6 inhibitors are a class of drugs that target the enzymes CDK4 and CDK6, which are important in cell division, and by interrupting these enzymes, the drugs inhibit cancer cell growth.
- They are used in combination with hormone therapy to treat cancers that are hormone receptor-positive, but which test negative for the HER2-negative biomarker and thus, make patients ineligible for HER-2 treatments like trastuzumab.
- Hormone receptor positive breast cancer represents about 70% of breast cancers, while elevated HER-2 status is present in 20%. While HER-2 positive cancers are understood to generally be more aggressive, there have been fewer novel and targeted treatments for HER-2 negative tumors, and the new CDK4/6 inhibitors represent an important advance for these patients with aggressive metastatic diseases.
- While these treatments were approved earlier in the United States, the EU5 has now reached similar rates of use, with 14.5 patients per 100,000 in EU5 and 14.2 in the United States.
- Patients treated with these drugs nearly tripled in the top 5 European countries compared to 2017, while increasing by only 7% in the U.S in 2018, where usage increased earlier.

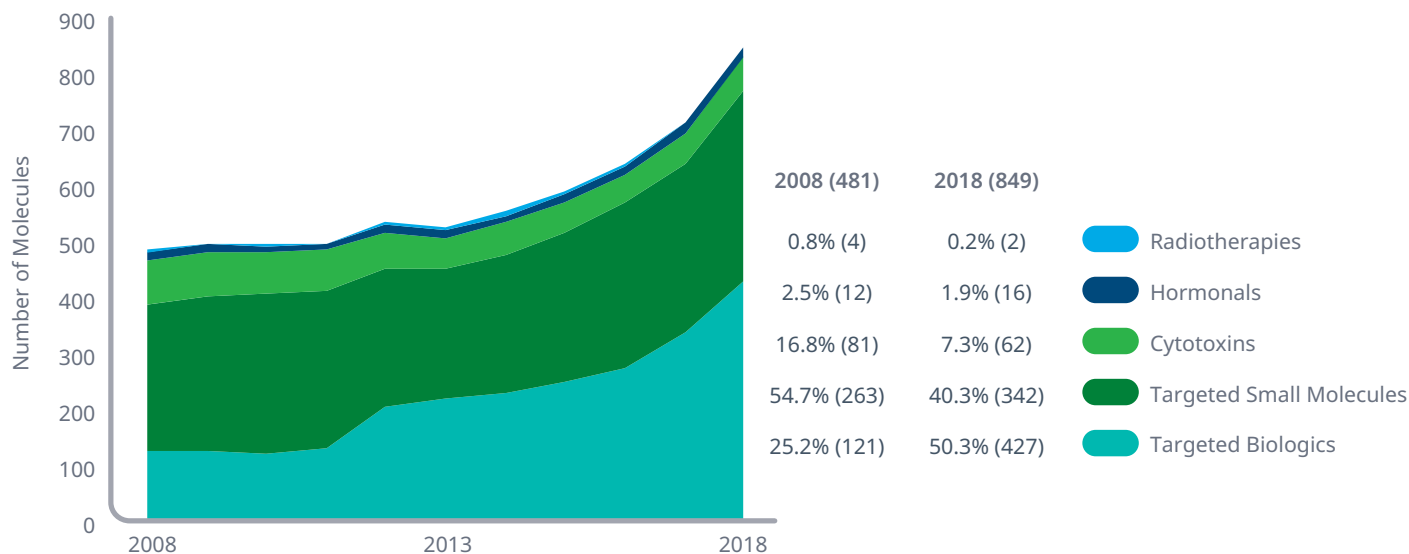
Chart notes: Rates of breast cancer and distribution of biomarkers in breast cancer were accessed from publicly available sources.^{16,17} Country population Economist Intelligence Unit estimates as of 11/7/2018. Oncology Dynamics is IQVIA's European oncology patient database including data for 2017 and 2018, while Oncology Analyzer was a similar database which was discontinued after 2016 and used a differing survey methodology. Trends are valid across the two databases despite methodology and data collection differences.

Research and development activities

- The pipeline of drugs in late-stage development expanded 19% in 2018, mostly due to a large increase in the number of targeted biologics, which now represent just over 90% of the total oncology pipeline for the first time.
- Across all phases of clinical development, the most intense pipeline activity is currently focused on nearly 450 immunotherapies with more than 60 different mechanisms of action.
- There are 98 next-generation biotherapeutics – defined as cell, gene and nucleotide therapies – under clinical investigation for oncology and these pipeline products leverage 18 different approaches.
- The combined immunotherapies and next-generation biotherapeutics are targeting most tumor types with over 80 mechanisms.
- In late-stage oncology R&D, 711 companies are active, with a significant contribution from emerging biopharma companies.
- The number of oncology clinical trials initiated in 2018 increased 27% over the prior year to 1,170, and is up 68% over the past five years, but these trials have high risk of failure, with the composite success rate falling to 8.0% in 2018 from 11.7% in 2017.
- Clinical trial duration remains higher for oncology trials than other disease areas and has generally declined over the past five years, dropping nine months in Phase I trials, 11 months in Phase II trials and over a year in Phase III trials.
- Clinical trial complexity – measured as a combination of endpoints, eligibility criteria, number of subjects, trial sites and countries – has increased 20% for phase I trials over the past five years, driven by increases in endpoints and eligibility criteria, while phase II trials have remained steady and phase III have become slightly lower in complexity.
- Overall productivity of oncology trials – measured as success rates relative to trial complexity and duration – has improved since 2010 by 22%, but remains far lower than trials for other therapy areas.
- Trial program designs for molecules are incorporating larger number of indications per molecule, especially in Phase I, with an average of 2.8 indications per molecule in 2018, up from 1.6 indications per molecule in 2010.
- Biomarkers that stratify patients likely to respond to therapy are now included in 39% of oncology trials, up from 25% in 2010, reflecting that precision medicine approaches are becoming more commonplace.
- Based on modelling future productivity against the current baseline, the availability of pools of pre-screened patients and biomarker tests could yield productivity improvements of as much as 104% and 71%, respectively, by 2023.

The late-stage oncology pipeline included 849 molecules in 2018, up 77% since 2008, due to the increasing number of targeted therapies

Exhibit 9: The Pipeline of Late Phase Oncology Molecules, 2008–2018



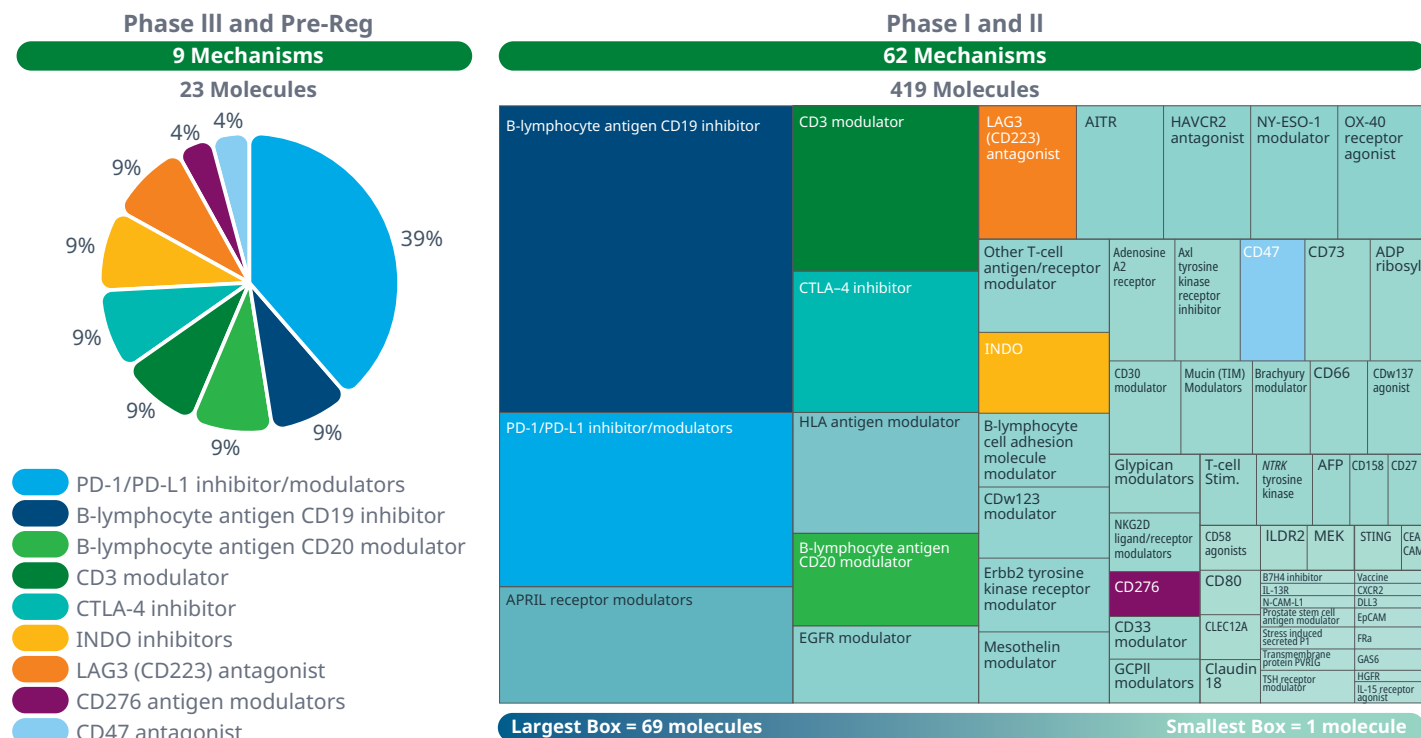
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, May 2019

- The number of late-stage pipeline therapies grew from 711 in 2017 to 849 in 2018, an expansion of 19%. This is compared to a total increase of 77% from 2008 to 2018, and a 63% increase since 2013, due to the growing number of targeted therapies in the oncology pipeline.
- Combined, 91% of late-stage oncology pipeline in 2018 were targeted small molecule therapies and targeted biologic treatments, as opposed to other non-specific therapies, such as cytotoxic agents.
- Targeted biologics increased almost 30% from 2017 to 2018, while targeted small molecules increased 14%. The number of radiotherapies and hormonal therapies in the late phase pipeline has decreased since 2017, by 33% and 6%, respectively.
- The increasing number of medicines in the pipeline is particularly notable because of the range of mechanisms being explored, the numbers of companies involved and the rate at which the research is progressing.
- Of note, Next-Generation Biotherapeutics (NGB) – defined as cell, gene and nucleotide therapies – make up less than 10% of the total late-stage R&D pipeline in 2018,¹⁸ but of these, 36% were in oncology. NGB’s technologies include the widely noted CAR-T therapies, which are associated with significant rates of remission for some blood cancers.

Chart notes: Late phase pipeline includes trials in Phase II or higher for the most advanced indication. Phase I/II trials are included as Phase II.

Immunotherapies in development have over 60 mechanisms of action

Exhibit 10: The Late-Stage and Early-Stage Immunotherapy Pipeline by Mechanisms of Action



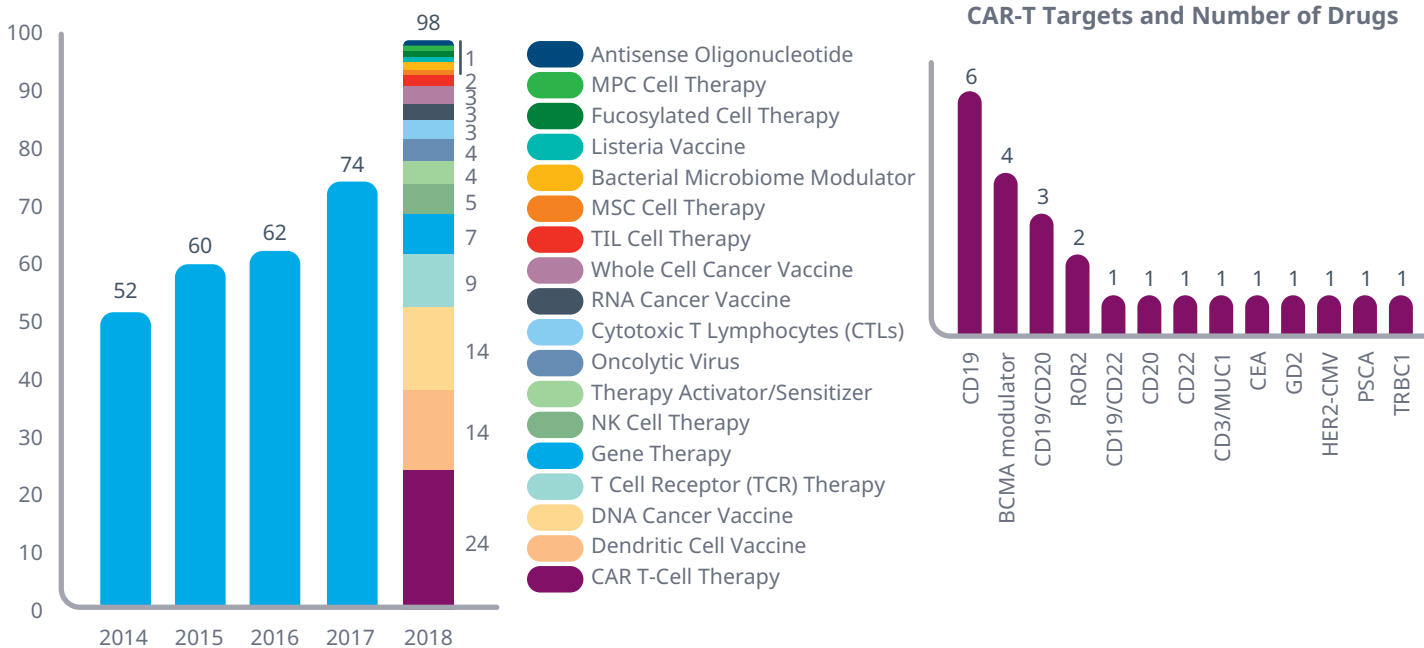
Source: Clarivate Analytics Cortellis, Feb 2019; IQVIA Institute, Mar 2019

- Nearly 450 immuno-oncology therapies are currently in development across all phases, with the Phase III and pre-registration pipeline containing only nine mechanisms for immuno-oncology and the early-stage pipeline containing 62 mechanisms.
- Combined, anti-PD-1/anti-PD-L1, B-lymphocyte CD19 antigen inhibitors (target of approved CAR-T therapies) and B-lymphocyte CD20 antigen inhibitors (a next-generation CAR-T target) made up more than half of the Phase III and pre-registration pipeline and 27% of the Phase I and Phase II pipeline.
- CD3 modulators (such as the already launched CD19/CD3-targeted bispecific antibody therapy, blinatumomab) made up 9% of Phase III and pre-registration products.
- Indoleamine-pyrrole-2,3-dioxygenase (INDO/IDO) inhibitors made up 9% of Phase III/Pre-registration products. These therapies, though initially promising, have recently demonstrated failures in late-stage trials (see Exhibit 5).
- The pipeline also includes next-generation checkpoint inhibitors, such as anti-CD223 (LAG-3) therapies, that accounted for 9% of the of Phase III and pre-registration products, anti-CD276 (B7-H3) and anti-CD47.
- PD1/PD-L1 checkpoint inhibitors remain the most efficacious immuno-oncology therapies, and improvements in formulation (e.g., oral) or combinations with targeted therapies (e.g., TKIs) may lead to breakthroughs.

Chart notes: Chart depicts the highest phase of development for drugs across phases I, II, III or pre-registration. Therapies were identified with a primary mechanism of action, although many molecules have combined mechanisms. Products flagged as immuno-oncology include immune checkpoints inhibitors, BiTEs (Bi-specific T-cell engagers), costimulators or CAR T-Cells; AITR = activation-inducible TNFR family receptor; Inducible T-cell co-stimulator has been abbreviated as T-cell Stim in the chart above; GCP11 = Glutamate carboxypeptidase II; AFP = alpha-Fetoprotein modulator; GAS6 = Growth arrest specific protein 6 ligand; HGF = hepatocyte growth factor receptor modulator; FRα = folate receptor alpha; CXCR2 = CXCR2 chemokine antagonist; B7H4 = Immune costimulatory protein B7H4 inhibitor; IL-13R Interleukin 13 receptor alpha 2; N-CAM-L1 = Neural cell adhesion molecule L1; TKI = tyrosine kinase inhibitor.

Almost 100 Next-Generation Biotherapeutics are now in late-stage development

Exhibit 11: Number of Next-Generation Biotherapeutic Pipeline Products in Late-Stage Pipeline, 2014–2018



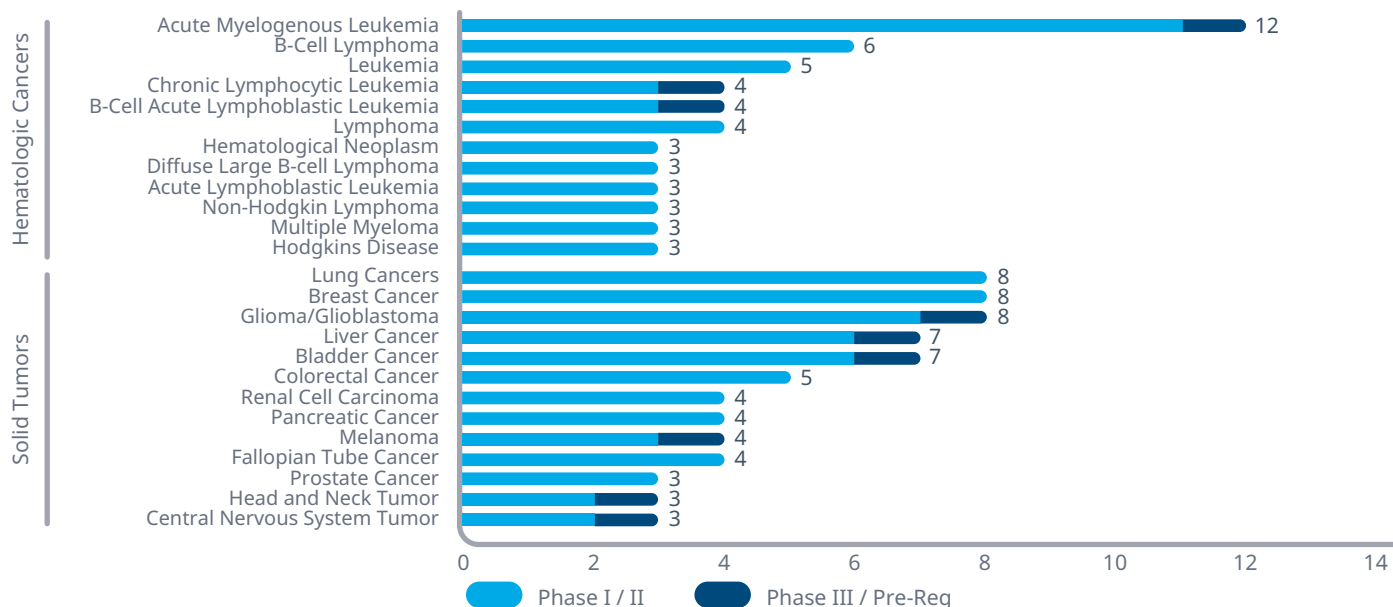
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Mar 2019

- The number of Next-Generation Biotherapeutics in development for oncology has more than doubled since 2013 and has grown 32% from 2017 to 2018, as new pathways for disease treatment and cure command growing attention and investment.
- NGB drugs launched to date have in some cases provided substantial benefits to patients, but have notably high-costs and have limited patient populations.
- In 2018, 36% of the oncology NGB pipeline candidates were vaccines designed to help treat cancer. Novel cancer vaccine treatments include plasmid DNA vaccination or taking advantage of other immune cells, such as dendritic cells, to modify the immune response to the cancer. These technologies will likely benefit from being combined with immuno-oncology therapies, such as the PD1/PD-L1 inhibitors.
- Approximately 25% of the 2018 oncology NGB pipeline was made up of CAR-T therapies. While clinical efficacy in solid tumors remains unrealized, new antigen constructs in the CAR-T therapy domain are being explored to address this challenge. Like cancer vaccines, CAR-T therapies in combination with immuno-oncology drugs could prove to be breakthrough products.

Chart notes: Next-Generation Biotherapeutics are defined as cell, gene and nucleotide therapies. Late-stage pipeline is defined as active programs (activity in past three years) in Phase II through Registered. Defined as cell and gene therapies or nucleotide therapies with mechanisms including: cell therapy; dendritic cell therapy; NK cell therapy; T-cell therapy; CAR T-Cell therapy; T-cell receptor therapy; stem cell therapy; bacterial cell therapy; CIK cell therapy; CIK-CAR therapy; whole cell vaccine; dendritic cell vaccine; bacterial cell vaccine; DNA vaccine; RNA vaccine; exon skipping; nucleic acid based; gene therapy; oligonucleotide; antisense; RNAi; microRNA mimic; gene editing; CRISPR-Cas9; zinc finger nuclease; RNA therapy; mRNA therapy.

Immuno-oncology pipeline therapeutics are targeting more than 40 different tumor types and have over 60 mechanisms of action

Exhibit 12: Top 25 Cancers and the Number of Mechanisms Targeting Each, Phase I Through Pre-Registration



Source: Clarivate Analytics Cortellis, Feb 2019; IQVIA Institute, Mar 2019

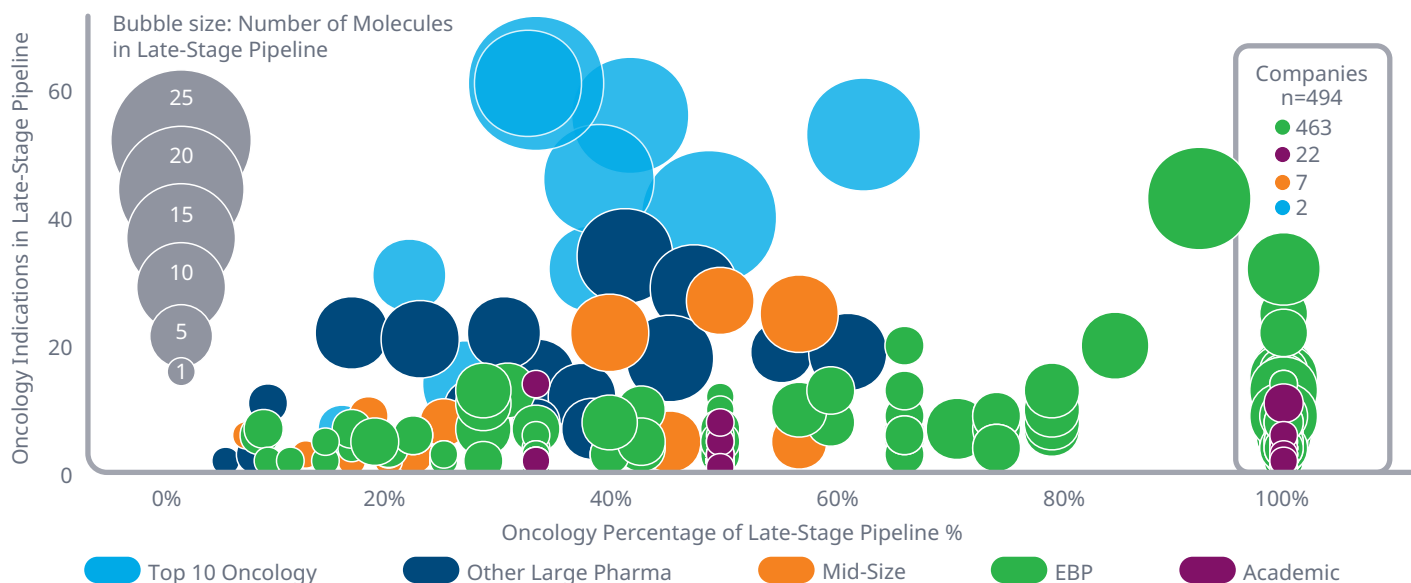
- In total, the immuno-oncology pipeline in 2018 included 43 cancer types, including solid tumor, metastasis and general cancer. The subset of the top 25 cancer types includes 52 separate mechanisms of action.
- The PD-1/PD-L1 drug class accounted for 14 different tumor types, across hematologic and solid cancers. This drug class remains the mainstay of the immune checkpoint inhibitors. B-lymphocyte antigen CD19 inhibitors account for 12 different types of tumors, with CD19 being the antigen construct in the currently available CAR-T therapies.
- Within the top 25 tumor types, almost half are hematological cancers, with acute myelogenous leukemia accounting for products with 12 separate, next-generation mechanisms, such as INDO inhibitors, OX-40 receptor agonists and CD33 modulators.
- Immuno-oncology mechanisms are demonstrating benefits across both solid tumors and hematologic cancers, which has generally been more rare in earlier generations of oncologic treatments.

Chart notes: Top 25 tumor types were selected based on the number of mechanisms for products under development. For molecules with multiple mechanisms and disease, the first listed mechanism or disease was chosen. Data query included immuno-oncology products sorted by highest status. Diagnostic molecules were not included. Sponsors include industry and non-industry. PD-1 = Programmed cell death protein 1; PD-L1 = Programmed cell death protein ligand 1.

RESEARCH AND DEVELOPMENT ACTIVITIES

711 companies are active in late-stage oncology R&D, with a significant contribution from emerging biopharma companies

Exhibit 13: Company Late-Stage Pipelines, Number of Oncology Indications and Oncology Percent of Pipeline



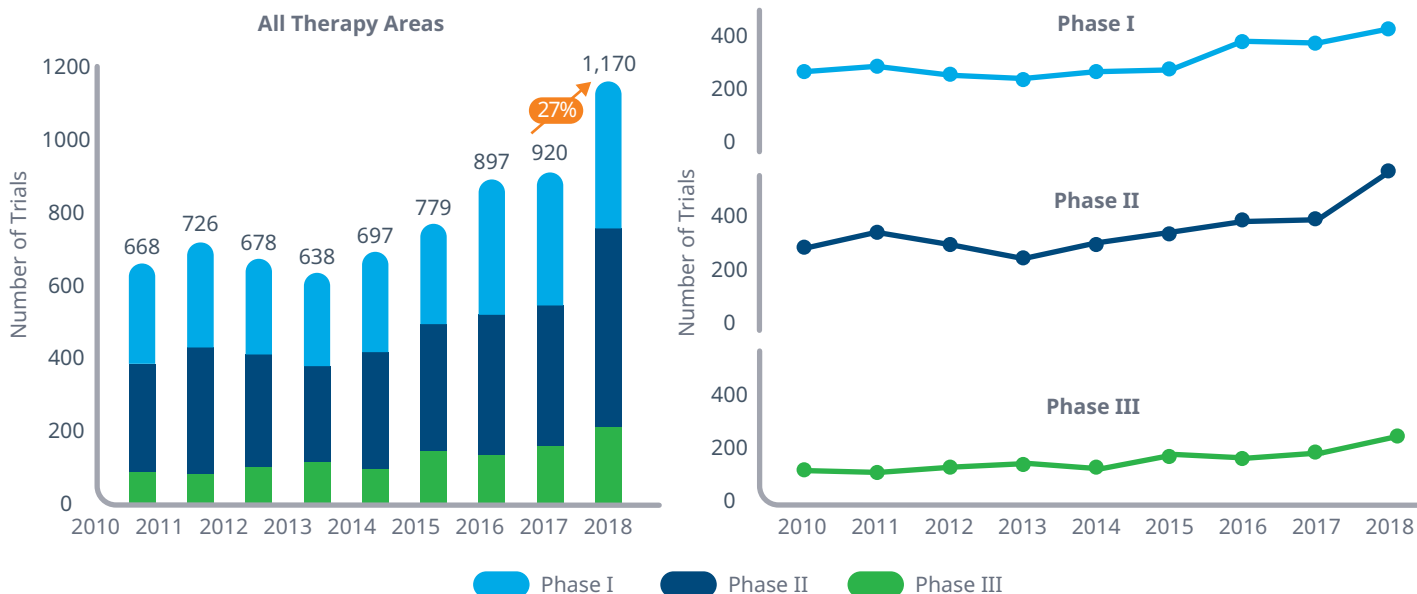
Source: IQVIA R&D Intelligence, Dec 2018; IQVIA Institute, Jan 2019

- There are currently 711 companies active in late-stage oncology R&D, working on a total of 849 products. These include 29 academic institutions, 626 emerging biopharma (EBP) companies, 28 large companies with global revenues over \$5 billion, including the top 10 in oncology, and 28 mid-sized companies.
- Of these, there are 494 companies whose entire late-stage pipeline is oncology, comprised of 463 EBP companies, 22 academic institutions, seven mid-sized companies, and two large pharma companies.
- The Top 10 oncology companies are pursuing on average 39 oncology indications, approximately triple the 13 being pursued by other large companies. Likewise, the Top 10 average 14 products, while other large companies average 6 products.
- Mid-sized companies have 2.3 products, EBP companies average 1.4 products and three indications in their cancer research.
- Twenty-eight of the 33 large pharma companies (with global pharmaceutical sales over \$5 billion) have active late-stage research in oncology.

Chart notes: EBP = Emerging biopharma is defined as companies having global revenue from \$50 million to \$400 million or having R&D spending below \$200 million including having observed R&D activity if spending has not been estimated. Large companies are defined as greater than \$5Bn in sales. Mid-size defined as \$400 million to \$5 billion in sales. The top 10 Oncology companies determined by global oncology and supportive care sales.

The number of oncology clinical trials initiated in 2018 increased by 27% over 2017

Exhibit 14: Number of Oncology Clinical Trials and by Phase, 2010–2018



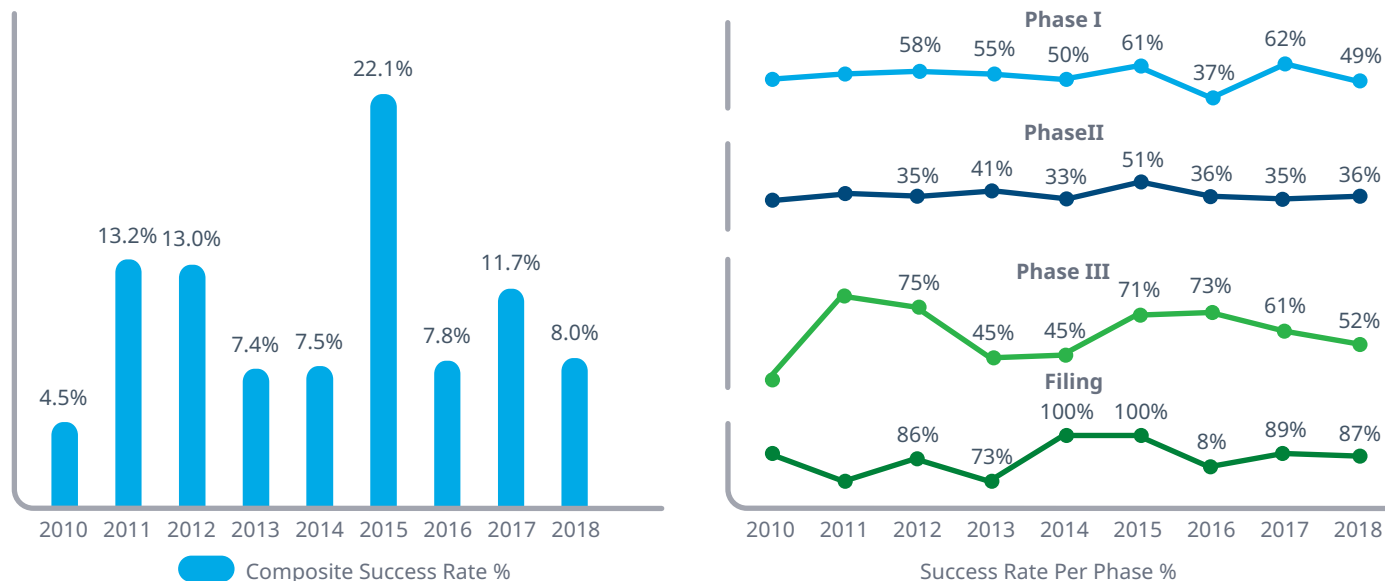
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- The total number of oncology clinical trials started in 2018 was 1,170, reflecting an increase of 27% over the prior year and growth of 68% over the level five years ago.
- Out of a total of nine key therapy areas, oncology represented 47% of Phase I trials in 2018, suggesting a large focus by manufacturers on oncology.
- The number of Phase I oncology trials have increased substantially in the past three years, from 280 in 2015 to 410 in 2018, an 46% increase.
- The number of Phase II and Phase III trials has risen steadily since 2013. Phase II trials have increased over 100% from 2013–2018 and Phase III trials have shown an increase of 83%.

Chart notes: Average reported is the mean. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Therapy areas included in % of therapy area include: oncology, immune system, cardiovascular, endocrinology, GI/NASH, infectious disease, vaccine, neurology and respiratory. Vaccine trials are infectious disease only. Totals for 2018 may be reflecting delayed filing of those trials into trial databases. *Hematology trials not shown.

Oncology clinical trials have high risk of failure with a composite success rate of 8% in 2018, slightly lower than average since 2010

Exhibit 15: Oncology Trial Phase Transition Success Rate by Phase, 2010–2018



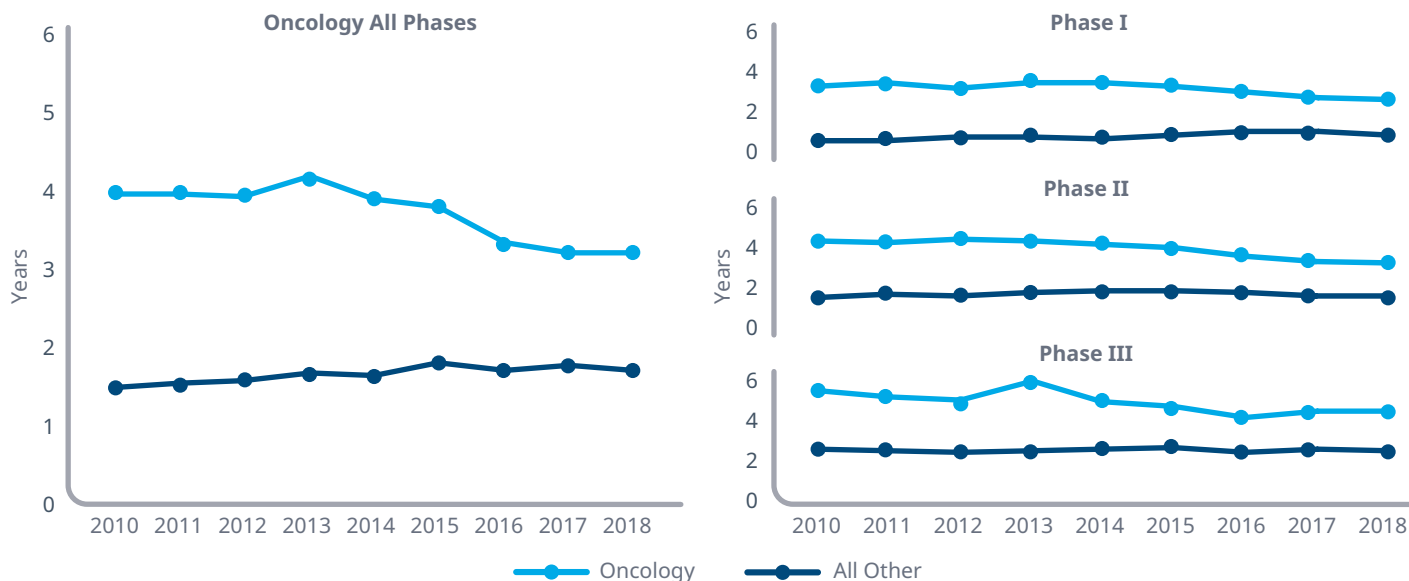
Source: IQVIA ARK R&D Intelligence; IQVIA Institute, Apr 2019

- Overall, the rate of successful phase transitions in oncology across all phases is roughly the same since 2013, and varies between 7–8%, with 2015 and 2017 remaining higher than average. The overall average from 2010–2018 was 10.6%.
- Although 2018 had 15 oncology NAS launches (not including supportive care), the composite success rate was tempered by a drop in successful Phase I and Phase III transitions. This is part due to increasing trial complexity in Phase I, as well as Phase II proof of concept/dosing trials imperfectly promoting candidates to Phase III.
- The median success rate for Phase I oncology trials was 55% from 2010–2018. From 2012–2014, success rates were relatively stable but began to become more dynamic starting in 2015, swinging between 59–63% through 2018.
- While the Phase II success rates were relatively stable between 2016–2018, this is a decline from the period of 2010–2015, which averaged approximately 39%.
- For Phase III trials, success rates have varied since 2010, from a low of 31% to a high of 82%. Overall, from 2015 to 2018, values were above 2013, 2014 and 2010, however, success rates have declined 29% from 2016 to 2018.

Chart notes: Composite Success Rate = Phase I x Phase II x Phase III x Regulatory Submission.

Oncology trials have seen a decrease in average duration across all three phases

Exhibit 16: Mean Trial Duration, 2010–2018



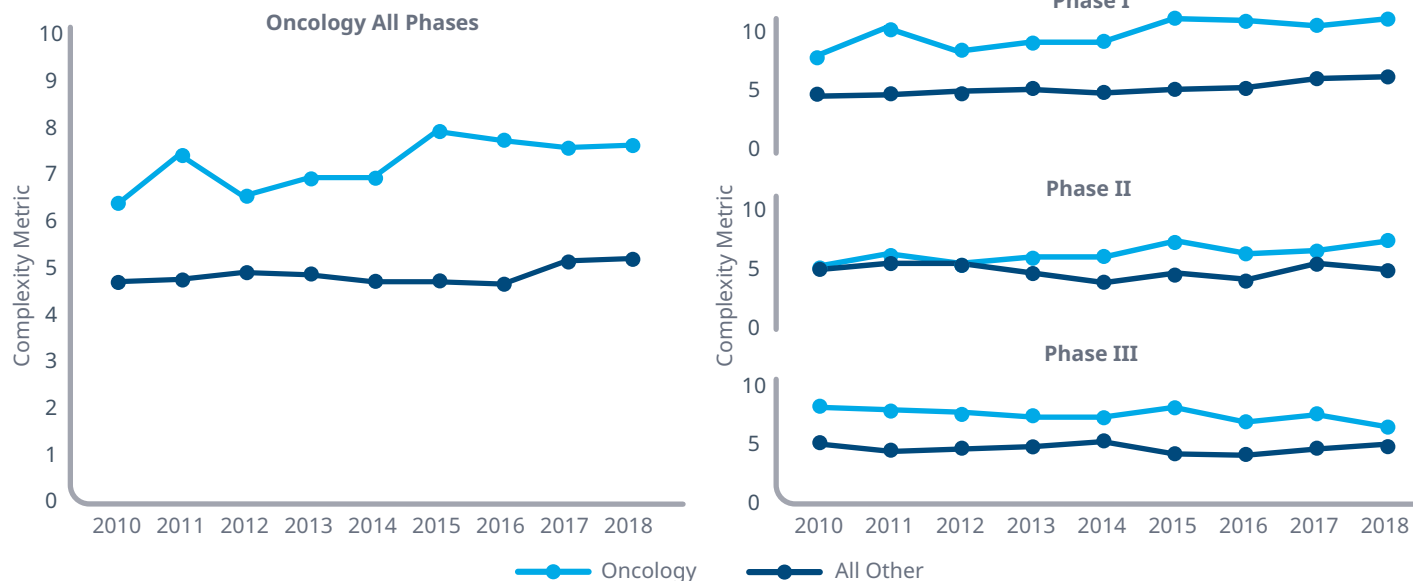
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Clinical trials in oncology remain longer than the average of other trials, when compared across nine key therapy areas, with trial duration defined from the start of the trial to end of the trial. The average duration of an oncology trial in 2018 was 3.2 years compared to 1.8 years across all other therapy areas, a difference of over 40%.
- Within the past five years, trial duration has declined in oncology, but risen slightly across other therapy areas.
- Phase I trial duration in oncology declined 23% since 2014, the sharpest among the three phases, with trials being completed on average nine months sooner in 2018.
- Oncology shows a significant change in average Phase II trial duration since 2010, dropping an average 11 months through 2018.
- Phase III trials showed the greatest difference in trial duration since 2010, completing almost a year faster in 2018 at an average of 4.4 years compared to 5.5 years in 2010.

Chart notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. All others = immune system, cardiovascular, endocrinology, GI/NASH, infectious disease, vaccine (infectious disease only), neurology, and respiratory and displays a weighted average. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III.

Complexity of oncology trials has increased 22% since 2010 in part due to increased complexity of Phase I trials

Exhibit 17: Trial Complexity, 2010–2018



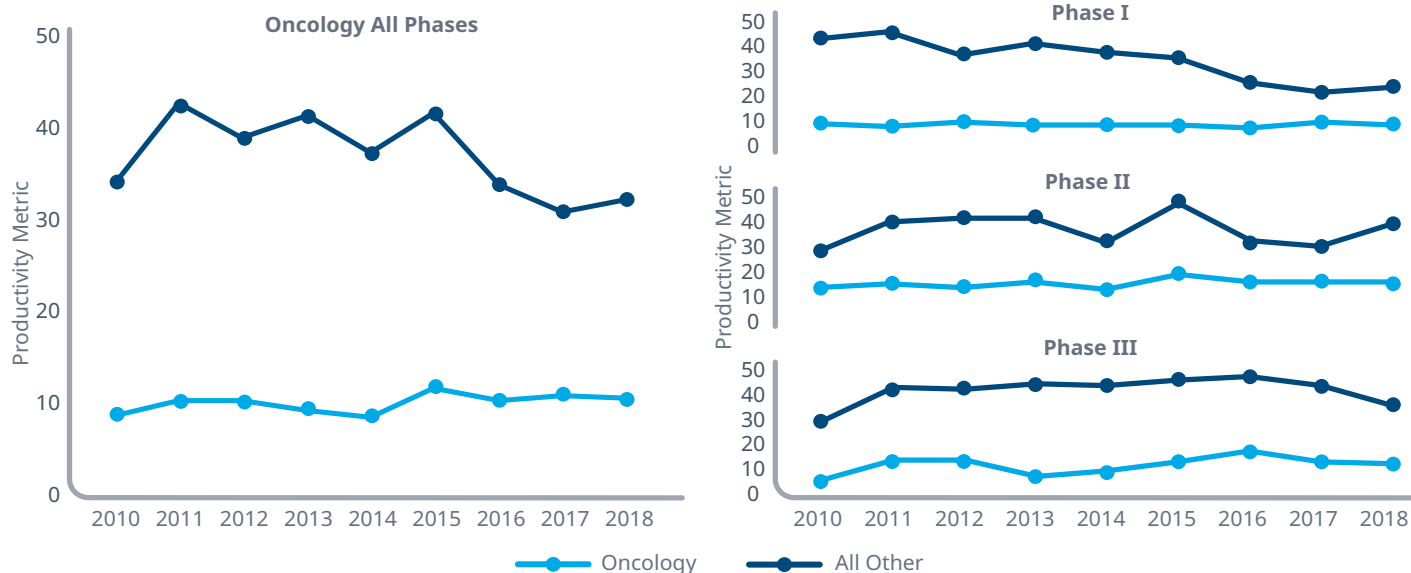
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Trial attributes that can be considered measures of clinical development complexity include five key areas: number of eligibility criteria, endpoints, trial sites, countries and patients participating in the trial.
- These attributes were measured and indexed across therapy areas to create an overall complexity metric to allow comparison across therapy areas and years.
- Clinical trial complexity in oncology has risen 11% from 2014 to 2018 and 22% from 2010 to 2018, while complexity across other therapy areas has remained relatively stable. Complexity in oncology is being driven by increases in endpoints and eligibility criteria, and offset by declines in the number of countries and number of sites.
- Phase I trial complexity has increased 5.3% since 2017 and 20% since 2014, while Phase II and Phase III trials have changed more slowly since 2014. Complexity of Phase I trials are increasingly complex in oncology due to an increase in studies using biomarkers to stratify patients susceptible to response (three times higher than 2010, data not shown), which is contributing to a jump in eligibility requirements and endpoints.
- Phase II trial complexity has been stable over for the past several years for other therapy areas, although there has been a 23% growth in the complexity of oncology trials since 2010.
- Phase III trial complexity has dropped 16% in oncology from 2010, in large part due to a sharp decline in the average number of sites for these trials.

Chart notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. All others = immune system, cardiovascular, endocrinology, GI/NASH, infectious disease, vaccine (infectious disease only), neurology, and respiratory and displays a weighted average. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III.

The productivity of oncology trials has grown by 21.7% since 2010 on average

Exhibit 18: Trial Productivity, 2010–2018



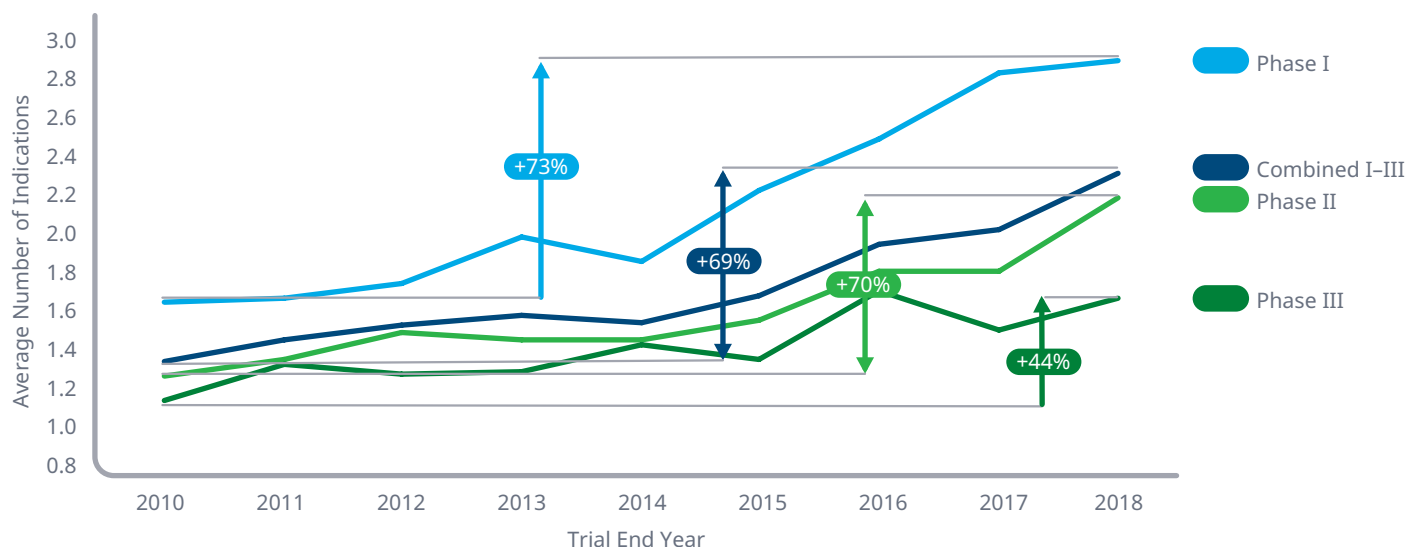
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Overall productivity of oncology trials – measured as success rates relative to trial complexity and duration – has improved since 2010 by 22%.
- The productivity of oncology trials is well below most other therapy areas and has shown only modest CAGR of 2% since 2010.
- From 2010–2018, there was a 16% decline in Phase I trials, which is due to a significant increase in complexity in this phase and a modest decline in success rates.
- Productivity for Phase II oncology trials has increased 16% from 2010 to 2018, and productivity for Phase III oncology trials has also increased, although the growth was more dynamic.

Chart notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. All others = immune system, cardiovascular, endocrinology, GI/NASH, infectious disease, vaccine (infectious disease only), neurology, and respiratory and displays a weighted average. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III.

Phase I trials have seen a 73% increase in the number of indications studied, and now average 2.8 indications per drug in 2018

Exhibit 19: Average Number of Indications per Phase of Development, 2010–2018



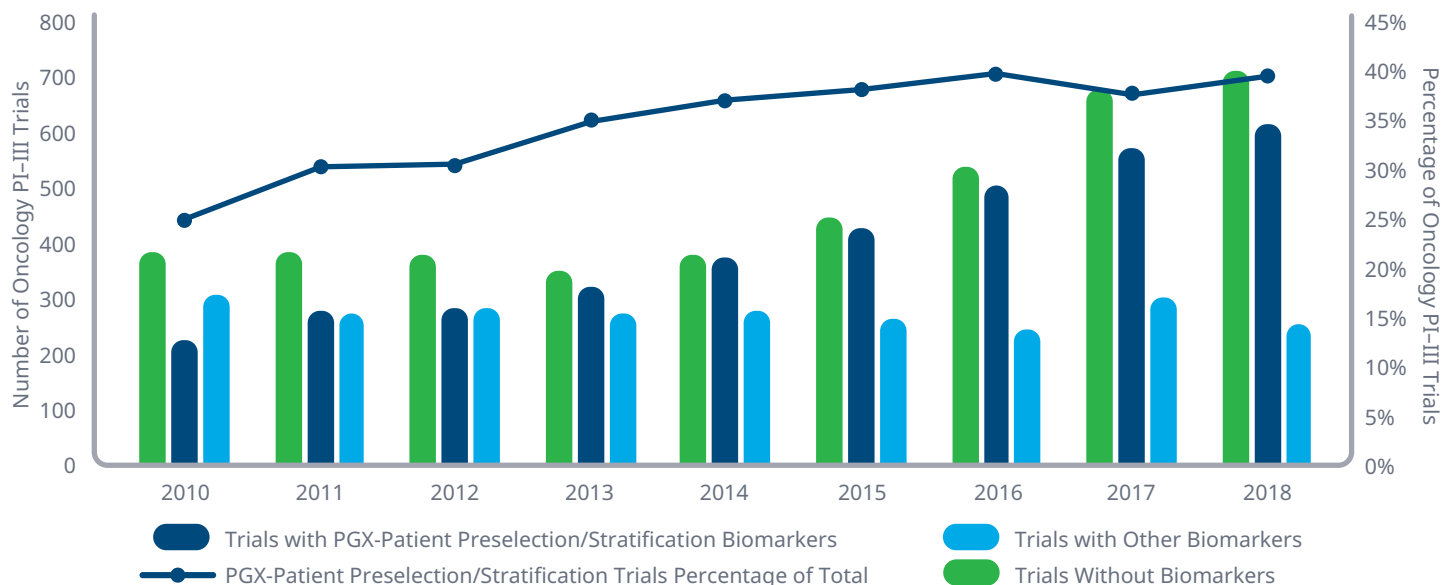
Source: Clarivate Analytics Cortellis, Aug 2018; IQVIA Institute, May 2019

- Program designs for molecules are incorporating larger number of indications per drug, especially in Phase I, with an average of 2.8 indications in 2018, up from 1.6 indications per drug in 2010.
- Phase II development programs also now are more complex, with the number of indications growing by 70% since 2010 and jumping 20% from 2017 to 2018.
- Increases in the number of indications explored in a single clinical trial reflect trends seen in currently launched therapies, where precision medicines are sometimes used across multiple indications and tumor histologies, and these indications may be included in early development.
- Unlike Phase I and Phase II, Phase III oncology programs have displayed a more modest increase in the number of indications being studied per drug, growing 44% over the past nine years. This could reflect manufacturers narrowing down tumor type for an investigational therapy after results of Phase II trials.

Chart notes: 2018 data as of August 2018. Chart displays a view of trials globally. Trials were limited to industry-sponsored, active trials and those with efficacy end points. Phase I trials not investigating efficacy were excluded.

Trials using biomarkers to stratify patients susceptible to response made up 39% of oncology trials in 2018

Exhibit 20: Number and Percentage of Oncology Phase I-III Trials by Biomarker Type, 2010-2018



Source: Trialtrove, Pharma Intelligence, Apr 2019; IQVIA Institute, Apr 2019

- A total of 858 trials included biomarkers in 2018 and use has been trending upwards since 2010, driven by the use of patient stratification biomarkers to apply personalized medicine strategies.
- The number of trials tagged as having pharmacogenomic (PGX) patient preselection/stratification, i.e., those trials incorporating pharmacogenomic and/or pharmacogenetic analysis, has increased almost three times since 2010 and represents 39% of oncology trials in 2018.
- Such PGX-patient stratification trials select patients for a trial (or a cohort in a trial) based on shared molecular profiling/genetic marking, and most tightly tie to trends in precision medicine.
- However, the percentage of patient stratification trials has not increased substantially in the past five years and has averaged around 38% of total oncology trials. This stagnation in the percentage of trials with PGX patient stratification may reflect a large increase in checkpoint inhibitor trials that include unselected patients due to the lack of data to indicate whether efficacy is related to any biomarker.
- Across the three phases, only Phase I trials have shown a notable increase in the number of patient stratification trials, with these growing as a percent of all trials by 67% since 2010. Patient stratification trials made up 35% of total Phase I trials in 2018, up from 21% in 2010.

Chart notes: Citeline’s Trialtrove’s dataset was used to create a year-over-year analysis for the number of biomarkers in oncology trials. Biomarker trials were identified using the following trial tags: biomarker/efficacy, biomarker/toxicity, PGX-biomarker identification/evaluation, PGX-pathogen, PGX-patient preselection/stratification. PGX trials are those that incorporate pharmacogenomic and/or pharmacogenetic analysis. Trials were industry only and interventional. Terminated and planned trials were excluded. Trials with healthy volunteers were excluded. Phase I through Phase III included.

Eight key trends are driving change in oncology clinical development:

Exhibit 21: Trends Driving Change in Oncology Clinical Development



Digital health technologies are expected to enable trial participants to receive rapid physician support for adverse events thus improving patient safety, decreasing attrition, and extending life. Supporting the collection of PROs and other data, they could also enable virtual trial formats, ease site work burden, and help end trials with poor outcomes earlier. They also support development of novel “functional” endpoints or digital biomarkers that measure clinical benefits.



Increased focus on PROs will shed new light on patient outcomes (PROMs) and experience (PREMs) outside the clinical setting or at home, as well as track Performance Status, to inform ongoing clinical decisions, serve as secondary endpoints, influence labeling, and accelerate trial times.



Real-world data is expected to speed trials by aiding in investigator/site selection, help optimize trial design including right-sizing trials for treatment effect, and enable new trial designs. Such designs include leveraging RWD as synthetic controls or comparators for new approvals and using RWE or registry data to conduct virtual trials post-approval for label expansions and provide supporting evidence of patient outcomes and overall survival in the real world.



Predictive analytics and AI will identify new clinical hypotheses to test, reduce trial design risks, speed enrollment by identifying protocol-ready patients, and help narrow trial patient populations to pre-defined subgroups (i.e., precision medicine). It will also enable adaptive designs that lead to earlier approval with smaller patient samples, and increase the probability of success and approval.



Shifts in drug types include the development of targeted therapies, immunotherapies, cancer vaccines, oncolytic viruses, bispecific monoclonal antibodies, next-generation biotherapeutics, and combinations, that will improve efficacy and success rates overall and lead to trials for new indications lacking current options. Shifts will also yield accelerated development timelines and approvals based on fewer patients in many cases, but will require development of new measures of response and may increase the size of Phase I targeted therapy trials and Phase III preventative trials.



Increased availability and ease of biomarker testing will help narrow enrollment to patient populations that will benefit most, increasing study efficiency and enable tissue agnostic approvals such as anti-PD-1 for Microsatellite Instability-high tumors. Informing machine learning and AI, genomic profiling data will guide trial enrollment for targeted therapies and redefine diseases as genetically- rather than histology-defined indications. However, trial complexity may increase, as novel trial designs are enabled (i.e. large basket trials with multiple arms) and sponsors become reliant on molecular profiling companies for data.



Availability of pools of pre-screened patients and direct-to-patient recruitment will facilitate trial recruitment and help sites/trials hit accrual targets. As providers/vendors conduct more diagnostic tests and record demographics and prior treatment, trials targeting defined patient subsets will find it easier to recruit. Where biomarker and genetic information is available, it may increase the number of patients available for early clinical studies. Although this is a significant part of the “future of oncology”, building and accessing such data may require significant investment.

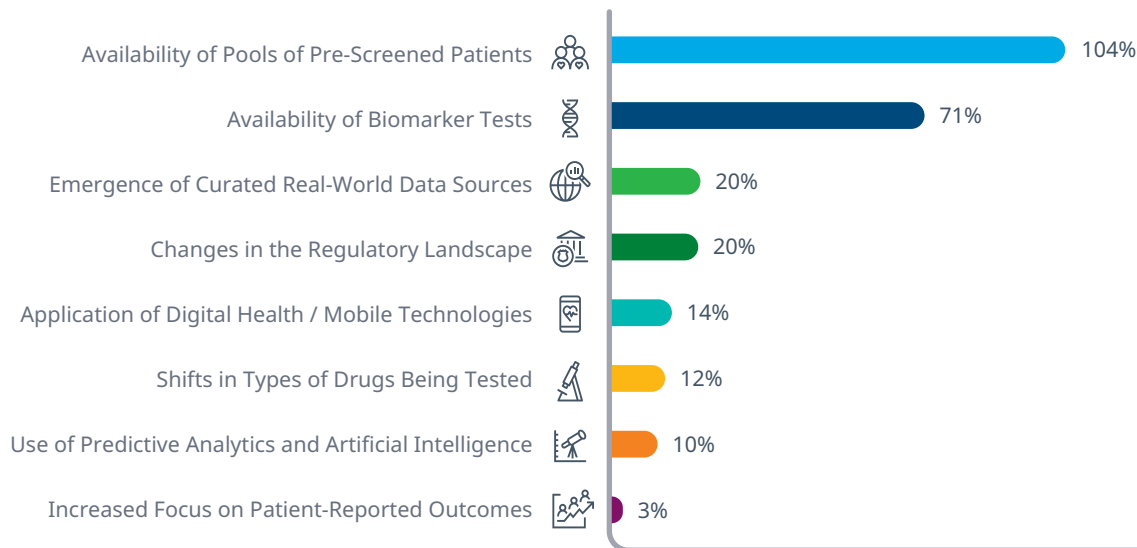


Changes in the regulatory landscape will encourage the use of biomarkers and further precision medicine, drive use of novel trial designs and endpoints, and may minimize work burden through the use of risk-based monitoring, electronic records, and electronic signatures. It will also speed drug approvals in oncology by increasing the use of real-world data to expedite drug development, especially for drugs pursuing an unmet medical need indication. However, some innovations like adaptive designs and precision dosing may increase the size of early clinical studies that run several parallel subgroups, while later trials may be impacted by regulatory allowance of virtual trial elements including mobile and wearable technologies. Recent changes in China CFDA will also dramatically increase the number oncology trials that include China.

RESEARCH AND DEVELOPMENT ACTIVITIES

Pools of pre-screened patients and biomarkers may yield productivity improvements as high as 104% and 71%, respectively, in oncology

Exhibit 22: Predicted Percentage Change in Productivity per Trend in Oncology from 2018 to 2023



Source: IQVIA Institute, The Changing Landscape of Research and Development - Innovation, Drives of Change, and Evolution of Clinical Trial Productivity ~ Report by the IQVIA Institute for Human Data Science; Apr 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- The most impactful trend in oncology development is expected to be the availability of pre-screened patients, to assess eligibility for trials and enhance the speed and efficiency of trials.
- Biomarkers continue to be discovered, both, as a result of drug discovery and through other research, and the wider range of tests and the wider availability of those tests will significantly enhance all aspects of drug development (see Exhibit 21).
- Modelling the impact of current clinical development trends on future productivity, the availability of pools of pre-screened patients and biomarker tests could yield productivity improvements of as much as 104% and 71%, respectively, by 2023.
- In addition to biomarkers, a number of other factors are reshaping approaches to clinical development with the potential to improve productivity – defined as success rates divided by trial complexity and duration – from current levels.
- The impact of these other factors is expected to be of lower magnitude, as the productivity of oncology research will continue to be heavily impacted by the significant challenges and risks in cancer drug development.

Chart notes: Displays the percentage improvement in productivity values over 2016–2018 average productivity values across all phases and the eight trends included in the analysis. Absolute values were weighted by the number of trials per phase. Exhibit X displays the weight-averaged impact across all trial phases. Rare disease category represents rare diseases across therapy areas and therefore is not mutually exclusive with the other nine therapy areas analyzed.

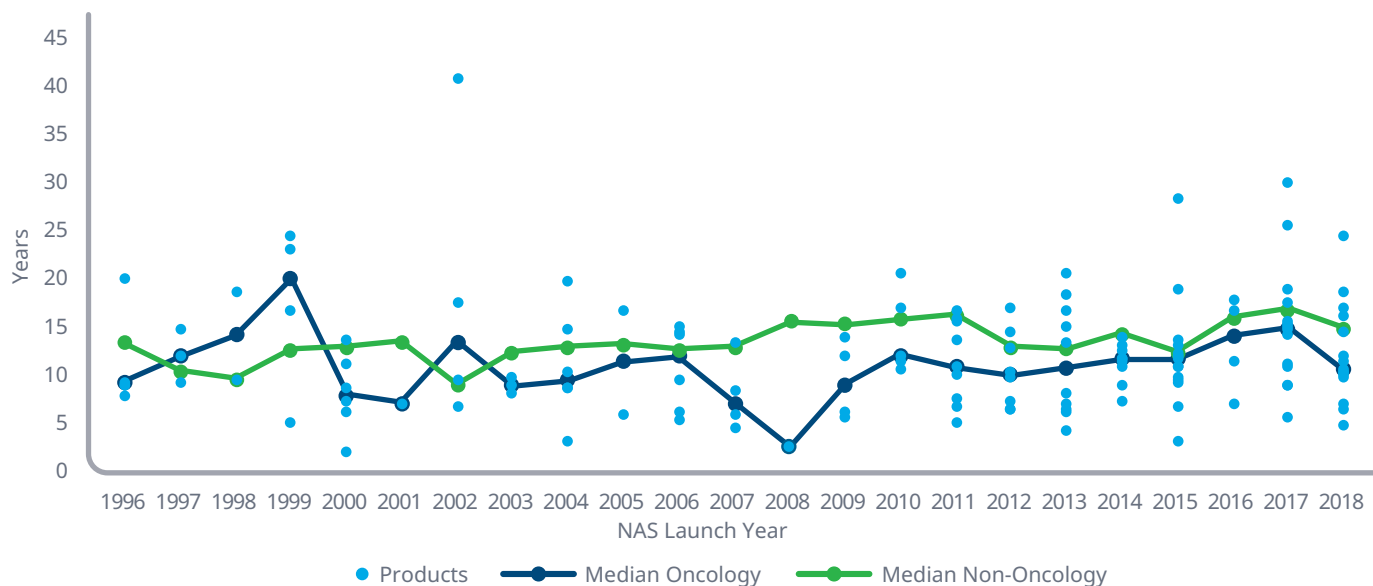
Bringing scientific advances to cancer patients

- New oncology drugs launched in 2018 took a median of 10.5 years from the time of first patent filing to regulatory approval and launch, down over four years from the 2017 level.
 - In 2018, the average number of years from first patent filing to launch of an oncology therapy with breakthrough status was 10.1 years compared to the average of all other therapy areas of 18 years.
 - Access to recently launched oncology medicines by patients living outside large developed countries remains low, with fewer than half of new cancer medicines available to patients beyond nine countries
 - Use of predictive biomarker tests is increasing across relevant tumor types, but is significantly lower in EU5 countries than in the United States, with the biomarkers BRCA, KRAS, NRAS, ROS-1 and MSI having 20–36% lower testing rates in the top five European markets than in the United States.
- Biomarker testing for patients with lung cancer and melanoma is closely associated with patients receiving a targeted treatment once tested positive. For example, 77% of patients receiving an EGFR test for non-small cell lung cancer, and 80% of those patients received an EGFR specific oncology medicine.
 - Novel therapies, such as CAR-Ts, require specific infrastructure capabilities which are not widely present in cancer centers in many countries.
 - Health technology assessments performed to inform reimbursement decisions in many countries are yielding variable results across countries, but France, Germany and the United Kingdom are trending toward fewer positive decisions, and therefore, more oncology drugs are unlikely to be widely available under current insurance schemes.



New oncology drugs launched in 2018 took a median of 10.5 years to reach patients from the time of first patent filing

Exhibit 23: Median Time from First Patent Filing to Launch by NAS Launch Year, United States



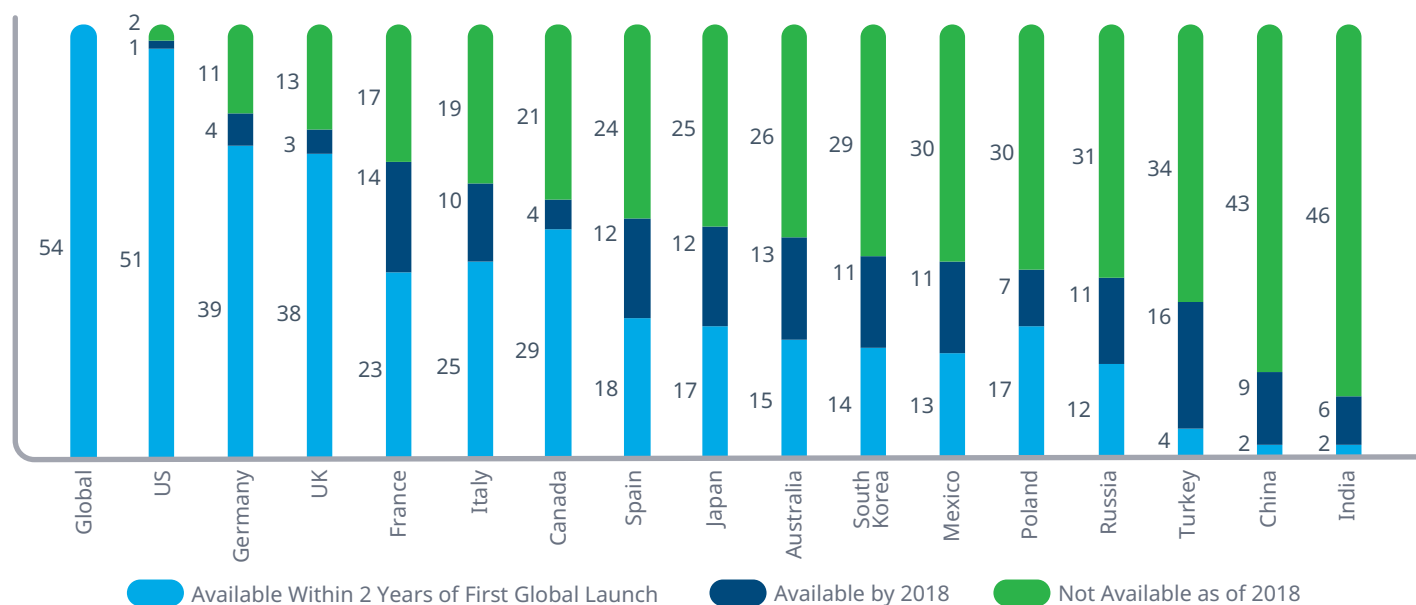
Source: IQVIA Ark Patent Intelligence; IQVIA Institute, Mar 2019

- The development of new drugs remains a slow process. In the United States in 2018, NASs across all therapy areas took a median of 13.7 years to launch from the time of their patent filing.¹⁸
- New oncology drugs launched in 2018 took a median of 10.5 years from the time of their first patent filing to regulatory approval and launch, down over four years from 2017 and down one year from the median of 2007. Non-oncology therapies launched in 2018 took an average time of 15 years.
- From 1996–2018, nine drugs were launched in five years or less from first patent filing, including dinutuximab (3.0 years), dabrafenib (4.1 years) and nilotinib (4.2 years).
- From 1996–2018, ten drugs were launched 20 years or more after their first patent filing, reflecting, in some cases, older mechanisms of action being repurposed or drugs that had previously launched globally.
- While median durations declined by about 9% in oncology, some drugs with breakthrough therapy designations have been approved after conducting only phase I or Phase II or combined Phase I/II trials.
- Oncology therapies are benefiting from special regulatory designations such as breakthrough status. In 2018, the average number of years from first patent filing to the launch for an oncology therapy with breakthrough status was 10.1 years, 44% faster than the average of 18 years for drugs with breakthrough status from other therapy areas.
- Non-breakthrough oncology therapies had an average time from patent filing to launch of 12.7 years in 2018, similar to values in 2017 and 2015.

Chart notes: NAS = new active substance and includes all medicines approved by FDA regardless of review division, if one or more of their ingredients are novel. First patent filing for a medicine compared to FDA approval for a specific indication, some medicines have multiple indications included in the analysis. Oncology does not include supportive care.

Patients in only nine countries have access to more than half of recently launched global cancer medicines

Exhibit 24: Availability in 2018 of Oncology Medicines Launched in 2013–2017



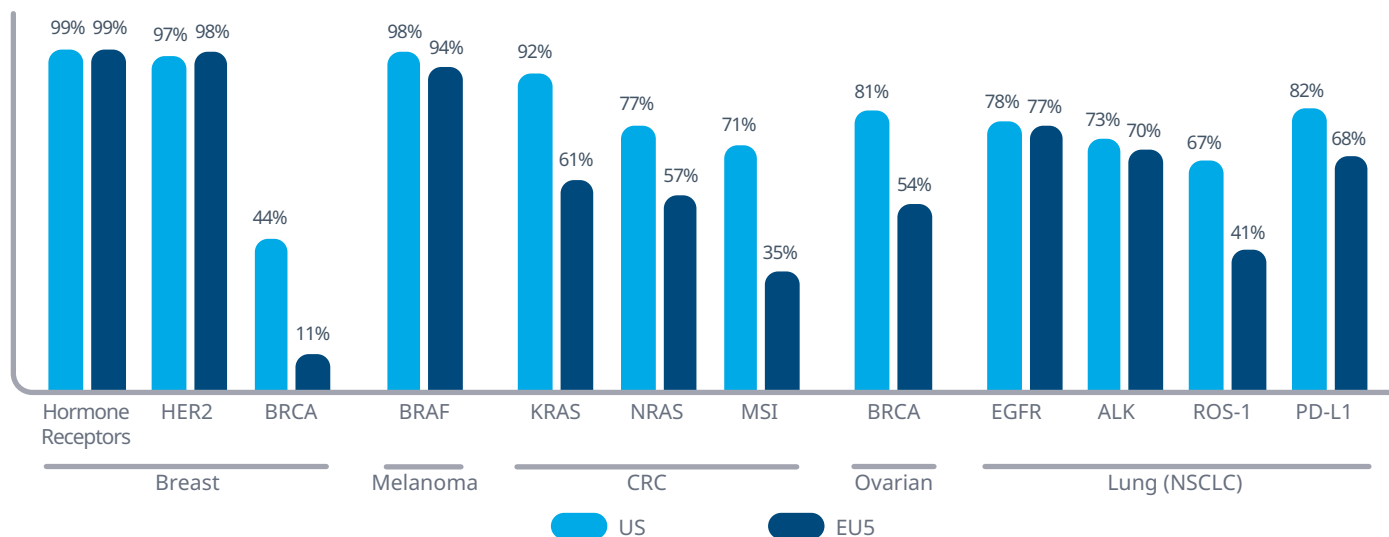
Source: IQVIA MIDAS, Dec 2018; ARK New Product Intelligence, IQVIA Institute, Apr 2019

- Only patients in the United States, Germany and United Kingdom have access to more than 40 of the 54 oncology medicines initially launched between 2013 and 2017, due to manufacturers not filing for regulatory approval, delays or denials of approval, or manufacturers awaiting the results of reimbursement negotiations prior to launching the drug in the country.
- For those countries under the European Medicines Agency (EMA), that have fewer than 43 NASs available, these differences are due to either pending reimbursement reviews and negotiations or a company’s decision not to market an approved drug in that country.
- Germany has the most medicines available under EMA, with 43, in part, because of ‘free pricing’ from launch, where a company can set their price, and then, after a year a reimbursed price is determined through a health technology assessment (HTA).
- There are distinct national-level processes for reviewing and negotiating reimbursement, often with varying HTA results by country. In single-payer countries, lack of reimbursement can influence whether a company chooses to launch.

Chart notes: Oncology global NAS launches identified and then observed for launch. Information current as of April 15, 2019.

Use of predictive biomarkers varies between the United States and Europe, particularly around BRCA testing in breast cancer

Exhibit 25: Percentage of United States and EU5 Patients Tested for Biomarker by Cancer Type



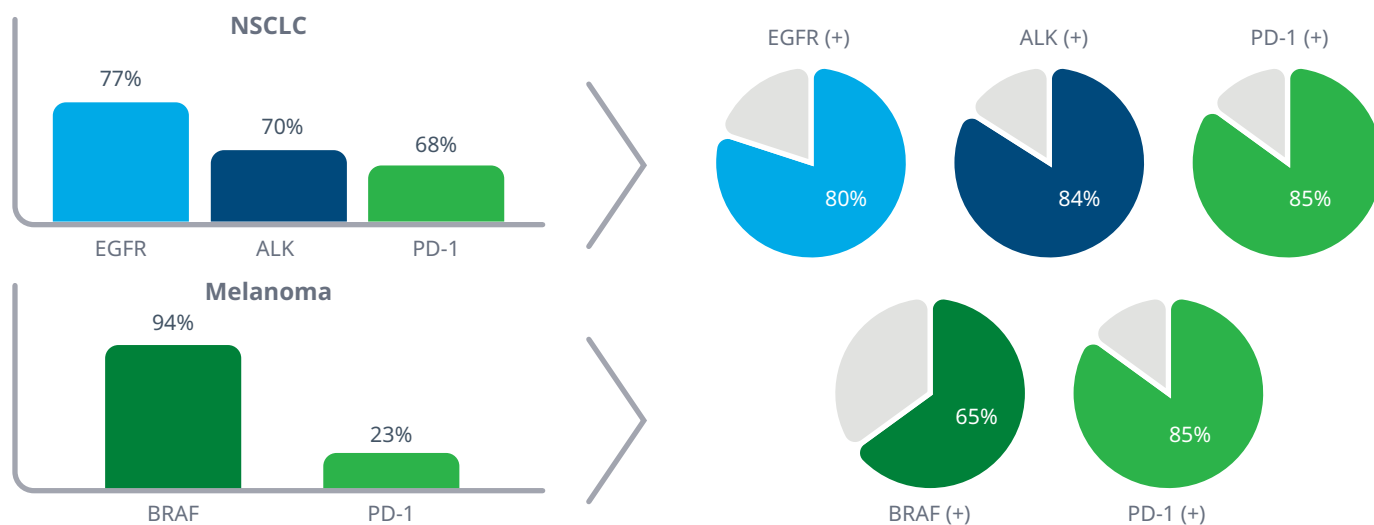
Source: IQVIA BrandImpact, IQVIA Oncology Dynamics, Mar 2019; IQVIA Institute, Apr 2019

- While many of the same drugs are approved in both the United States and top five European markets, the timing of those approvals, as well as the decisions about reimbursement in each EU member country has resulted in some notable differences in the use of biomarker tests.
- The biomarkers BRCA, KRAS, NRAS, ROS-1 and MSI 20-36% have lower testing rates in the top five European markets than in the United States.
- For tumors with multiple potential treatment modalities, the use of biomarker testing can help select appropriate treatments and avoid wasteful use of drugs that would be less appropriate for a patient than other options.
- Another driver of differences between the United States and Europe could be the timing of the approval of drugs with these various biomarkers.
- Some providers may also test patients at diagnosis, whereas others may wait to test until the current standard first-line treatments have failed, according to the protocols in practice in their countries or institutions.

Chart notes: Reported as a percentage of knowledgeable respondents; *denotes percentage of metastatic; BrandImpact number of patients covered in the survey: Lung = 13,000–20,000; Breast = 40,000–45,000; Melanoma = 2,726; Colorectal = 11,800–12,500; Ovarian = 7,365. Number of patients covered in the survey: Lung = 12,757; Breast = 16,175; Melanoma = 3,668; Colorectal = 10,167; Ovarian 3,675. PD-L1 = programmed cell death receptor and its ligand; KRAS = gene coding K-Ras protein; ROS-1 = a tyrosine kinase inhibitor encoded by ROS1; NRAS = gene coding N-Ras protein; ALK = gene coding ALK receptor tyrosine kinase; EGFR = gene coding epidermal growth factor receptor protein; BRAF = gene coding B-Raf; Hormone includes PR and ER, which are progesterone and estrogen receptors, respectively.

Most patients are receiving targeted therapies based on biomarkers when they test positive for them

Exhibit 26: Percentage of Patients Tested by Biomarker and Cancer in Europe and Patients Receiving Drug Targeting Once Tested Positive



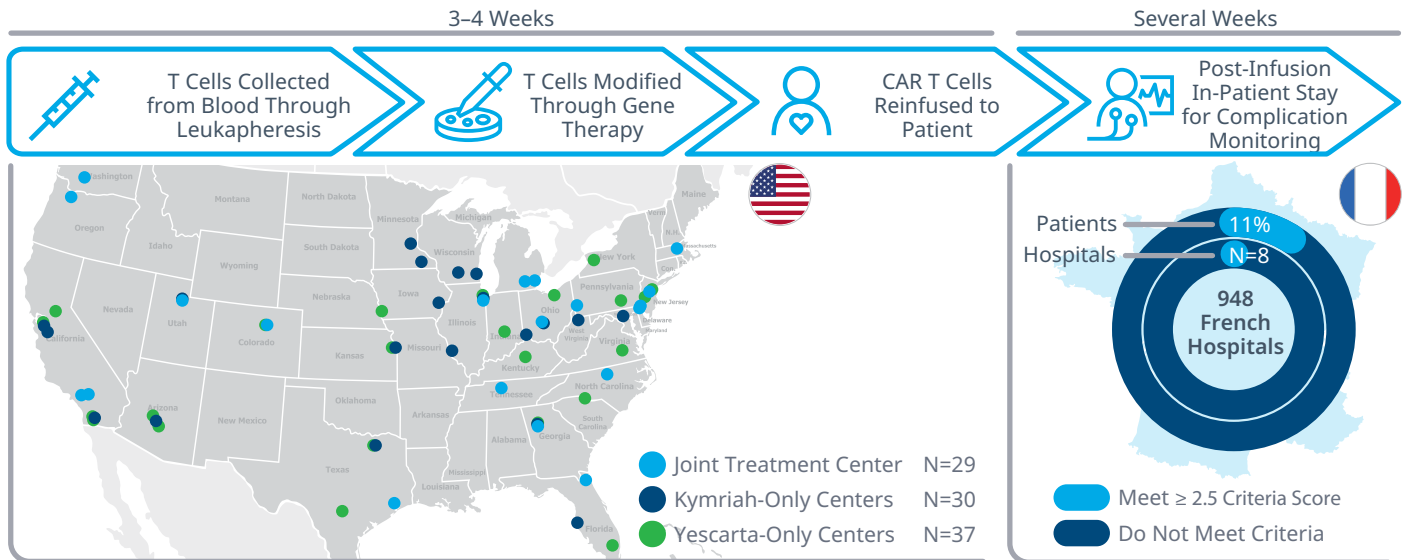
Source: IQVIA Oncology Dynamics, Patient Level Oncology Survey Data, MAT Q4 2018

- Biomarker testing for patients with lung cancer and melanoma is closely associated with patients receiving a targeted treatment once tested positive
- Despite some testing rates that are lower than in the United States, once patients in the top five European countries test positive for a specific biomarker, the majority of the patients receive a drug targeting it.
- In some cases, providers consider any expression of a biomarker to support a treatment choice, particularly in a metastatic patient.
- Other providers or protocols only consider higher thresholds such as >50% as appropriate.
- Results for the same biomarker can vary significantly across tests, and in some cases, there is not a consensus on the appropriate assays.
- Faced with varying results, and clinical options with different expected results, providers are often making treatment choices aided by biomarkers but remaining far from a binary yes or no decision based on a test result.

Chart notes: PD-1 Positive defined as >50% expression; Countries included in analysis: France, Germany, Italy, Spain, UK. NSCLC projected patients = ~150,100, Melanoma projected patients = ~30,200.

Novel therapies require significant technical capabilities that are not widely present in oncology centers in many countries

Exhibit 27: United States CAR-T Centers and Number of Centers in France Achieving Administration Eligibility Requirements and Percentage of NHL Patients Able to Be Treated by Those Centers



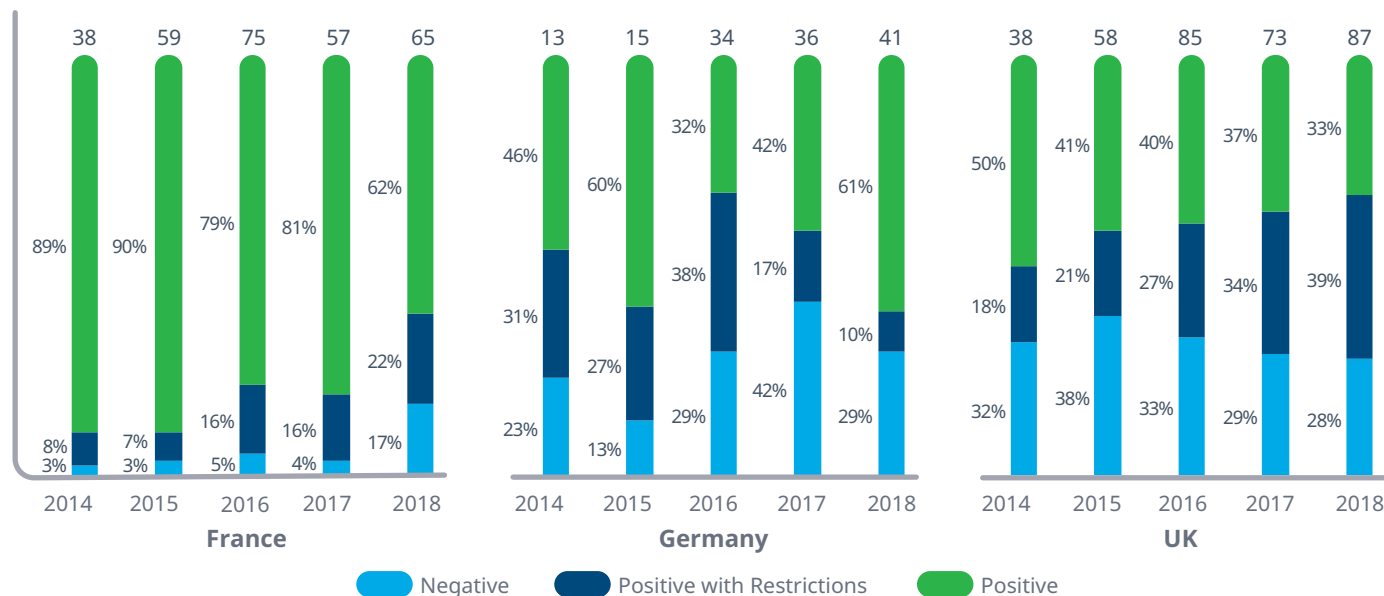
Source: Yescarta Center Location finder <https://www.yescarta.com/treatment-centers>; Kymriah Center Location finder; <https://www.us.kymriah.com/treatment-center-locator/>; IQVIA Primary Intelligence Oncology Center of Excellence, Sep 2018; France IQVIA hospital access 2016 https://academic.oup.com/annonc/article/29/suppl_10/mdy486.018/5237944

- The process of treating patients with CAR-T treatments requires that centers be competent to collect the patient’s T-cells, and reintroduce them to the patient via leukapheresis.
- In addition, the risk of complications such as cytokine release syndrome require that a patient remain on an in-patient basis for some weeks after administration for observation, effectively excluding outpatient infusion centers from these treatments.
- As of September 2018 only a limited number of cancer centers have achieved accreditation with the two manufacturers in the United States, and for patients in some geographies, these centers are thousands of miles away.
- The requirement for a post-treatment hospital stay and these distances could place a significant financial burden on family or caregivers separate from the direct medical costs for these treatments.
- In France, a study in 2016 found that only eight hospitals, treating 11% of NHL patients were found to meet criteria understood to make them eligible to provide CAR-T treatments to patients.
- As more CAR-T and other Next-Generation Biotherapeutic treatments are launched, it is likely that more treatment centers will adapt and enhance their capabilities to deliver these treatments, and other adaptations may be required to address non-medical disruptions if treatment availability remains in a relatively limited group of centers.

Chart notes: France chart displays centers that meet a score ≥ 2.5 , considered as the minimum to be able to integrate CAR-T technology within the next two years. Patients are the calculated CAR T-Cells-eligible population. Thirty-three out of 948 hospitals with NHL patients have at least one of the eligibility criteria.

More health technology assessments are being conducted in oncology, while the results remain highly variable

Exhibit 28: Five-Year Trend of Health Technology Assessments and Their Outcomes in Oncology for EU3



Source: IQVIA HTA Accelerator; Dec 2018; Pink Sheet, Aug 2018; Scrip, Dec 2018

- Over the past five years, HTA numbers have been increasing and assessments with positive results have made up a lower share of all decisions in the top three European markets.
- Germany, France and the UK are among the most influential countries with their assessments informing those of other countries around the world.
- A number of smaller countries with more limited resources are pooling their resources to conduct joint assessments or manage tendering and purchasing, including twelve cross-border initiatives across 30 European countries.
- In France, 39% of all assessments in 2018 have limited benefit ratings that curtail price flexibility, meaning manufacturers would have to offer a specifically lower price, and in some cases, these also include restrictions that specify when treatment regimens on the drug would stop.
- In Germany, G-BA, the body that negotiates reimbursed prices, generally does not restrict access, however mixed benefit ratings among patient subgroups can inform price negotiations, and this in turn, can be referenced by other countries.
- In the UK, challenges in demonstrating cost-effectiveness generally leads to no coverage, access conditional on evidence development, or ultimately requires significant discounts.

Chart notes: Health Technology Assessment (HTA) are evaluations of the clinical value of a medicine, most often relative to a cost, and in many countries using a cost per quality-adjusted life-year (QALY). Restricted recommendations include those which are negative for some indications and positive for others, or where specific indications are conditional or restricted in certain ways. Numbers may not sum to total due to rounding.

Spending on oncology medicines

- The recent surge of new treatment options, and the resulting increasing numbers of cancer being treated with available medicines and for longer, is driving spending levels and growth rates higher across most parts of the world, and this is expected to continue for at least the next five years.
 - Spending on all medicines used in the treatment of patients with cancer reached nearly \$150 billion in 2018 up 12.9% for the year and marking the fifth consecutive year of double-digit growth, entirely driven by therapeutic drugs, as supportive care drugs declined 1.5% in 2018.
 - New brands and protected brand volume contribute nearly all positive growth in major developed markets.
 - In the United States, spending on cancer drugs has doubled since 2013 and exceeded \$56 billion in 2018, with over \$9 billion in growth coming from the use of PD-1/PD-L1 inhibitors.
 - Outside the United States, oncology costs exceeded \$66 billion in 2018 and is driven by new and existing brand volume.
 - The average annual cost of new medicines continues to trend up, although the median cost dropped \$13,000 in 2018 to \$149,000.
- Spending on cancer medicines is heavily concentrated with the top 38 drugs accounting for 80% of total spending.
 - In China, oncology therapeutics grew a remarkable 24% in 2018, while supportive care treatments declined by 10% and total spending reached \$9 billion.
 - Oncology spending in China has more than doubled in the past five years, mostly coming from increased use of existing branded medicines, and very little from newly launched medicines and per capita spending in China amounts to \$4.50 per person, compared to \$173 in the United States.
 - New drug approvals in China have increased dramatically in line with global trends and with more approvals of drugs brought to China by multi-national companies.
 - Over the next five years, growth in total oncology therapeutics spending of 11–14% is expected on a CAGR basis and bringing the total market to \$200–230 billion.
 - Growth in spending on therapeutics through 2023 is forecast at double-digit levels in the United States, pharmerging markets and rest-of-world, and will reach the high single digits in the EU5 and 5–8% in Japan.

SPENDING ON ONCOLOGY MEDICINES

Oncology spending reached nearly \$150 billion in 2018 as cancer medicines grew by 15.9% offset by a decline in supportive care

Exhibit 29: Total Spending on Oncology Medicine and Supportive Care and Growth US\$Bn



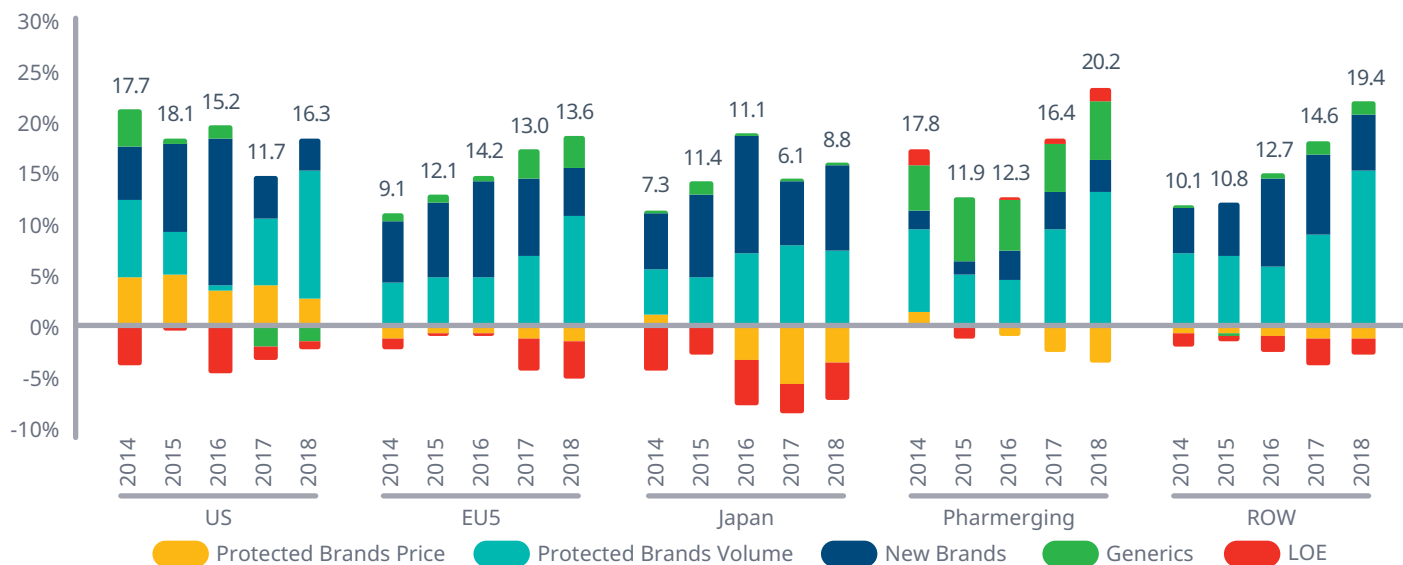
Source: IQVIA Ark Patent Intelligence, IQVIA Institute, Mar 2019

- Spending on all medicines used in the treatment of patients with cancer reached nearly \$150 billion in 2018 up 12.9% for the year and marking the fifth consecutive year of double-digit growth, entirely driven by therapeutic drugs, as supportive care drugs declined 1.5% in 2018.
- Spending continued to be focused in the major developed markets, with the United States, EU5 and Japan accounting for 75% of spending, up from 73% in 2014.
- Supportive-care spending declined by \$300 million primarily from the impact of biosimilars for the granulocyte-macrophage colony-stimulating factor (GM-CSF) treatments (e.g., filgrastim and pegfilgrastim) that help patients make more white blood cells and tolerate more cycles of treatments, which otherwise suppress their immune systems.
- Biosimilars of erythropoietin (e.g., epoetin alfa) and GM-CSF drugs are already widely available, especially in Europe and the United States.

Chart notes: Therapeutic oncologics include those classified by EphMRA (European Pharmaceutical Market Research Association) as cytotoxics in the L1 or L2 classes, as well as radiotherapeutics (V3C) and specific molecules classified elsewhere but used primarily in cancer (lenalidomide, aldesleukin, pomalidomide). Supportive care includes anti-nauseants and cancer detox agents (A4A and V3D), erythropoietins (B3C), GM-CSF white blood cell boosters (L3A), other interferon therapies used in cancer (L3B excluding multiple sclerosis drugs), and bisphosphonates used to prevent bone metastases (M5B4).

New brands and protected brand volume contribute nearly all positive growth in major developed markets

Exhibit 30: Oncology Therapeutic Spending Growth by Product Segment, 2014–2018



Source: IQVIA, MIDAS, Apr 2019; IQVIA Institute, Apr 2019

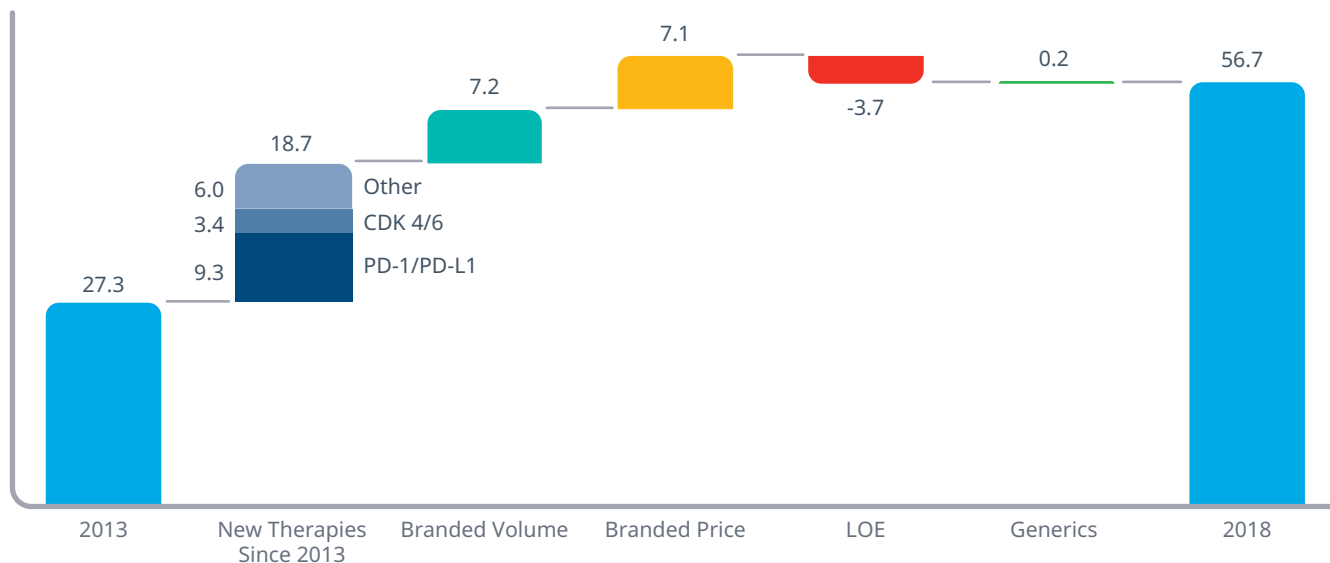
- Oncology spending growth in major developed and pharmerging markets exceeds 13% with the exception of Japan.
- Newer brands continue to drive spending growth primarily through continued volume growth for launches from 3–5 years ago and a continued flow of newer brands.
- Japan’s relative lower overall growth is partly a result of policies that encourage shifts to generics from older off-patent brands, and due to the focus of biennial price cuts on older protected brands, while insulating newer brands from those price cuts.
- Together, these dynamics in Japan contribute to a greater impact from losses of exclusivity and brand price declines and highlight significant growth drivers from newer products.
- Pharmerging markets are showing significant growth from brand volume, 20.2% in 2018, often as newer drugs are not launched or used in large numbers of patients.
- LOE impact, which reflects biosimilars, has begun to impact spending in EU5 countries with the availability of biosimilars of trastuzumab (Herceptin), as well as small molecule patent expiries, such as imatinib (Glivec/Gleevec).

Chart notes: LOE = loss of exclusivity. Protected brands are those with active patent protection in the geography and in the period charted, growth is calculated based on the products that are included in the segment in each period compared to the same cohort of products in the prior period. New brands are those launched less than two years prior. Generics includes non-original brands. LOE is defined as the growth impact on original branded products in the periods after they lose exclusivity.

SPENDING ON ONCOLOGY MEDICINES

Spending on cancer drugs in the United States has more than doubled since 2013, reaching nearly \$57 billion in 2018

Exhibit 31: United States Oncology Therapeutic Market Spending and Growth by Segment, Const US\$Bn



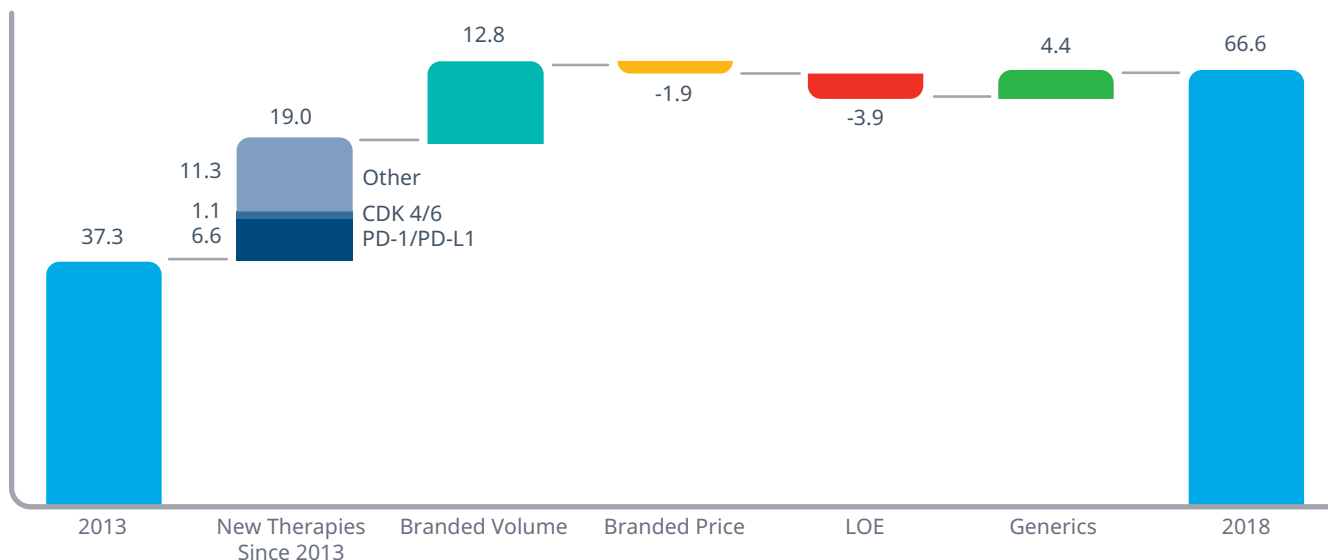
Source: IQVIA MIDAS; IQVIA Institute, Dec 2018

- Spending on cancer drugs in the United States has more than doubled since 2013 and reached almost \$57 billion in 2018, with 64% of the growth from the use of drugs launched within the past five years.
- The total cost of oncology medicines rose by \$29.4 billion to \$56.7 billion in the United States between 2013 and 2018.
- With nearly \$19 billion of growth in United States, oncology costs can be attributed to the uptake of innovative medicines launched since 2013, with the largest amount from PD-1 and PD-L1 inhibitors. These therapies accounted for \$9.3 billion while the CDK4/6 inhibitors for breast cancer contributed another \$3.4 billion.
- The costs for older protected brands increased due to both wider use and increasing prices on an invoice basis.
- Branded price growth added \$7.1 billion but is estimated to be \$5.7 billion on a net basis, as overall net spending in the United States in oncology averages 10% lower than invoice prices.
- The loss of patent exclusivity for some older brands contributed to \$3.7 billion in lower brand costs.
- Generics grew by \$200 million over five years, as the combination of relatively limited patent expiries and offsetting price deflation offset volume growth.

Chart notes: Product segments are mutually exclusive in each period. New brands since 2013 show the total 2018 spending for all new branded products launched since the end of 2013. 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 exclude all branded products that are new since 2013. New PD-1 and PD-L1, and CDK4/6 products have been shown separately. 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. LOE (loss of exclusivity) 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, as well as biosimilars if present.

Outside the United States, oncology spending exceeded \$66 billion in 2018, driven by new and existing brand volume

Exhibit 32: Oncology Therapeutic Market Spending and Growth by Segment Outside the United States, Constant US\$Bn



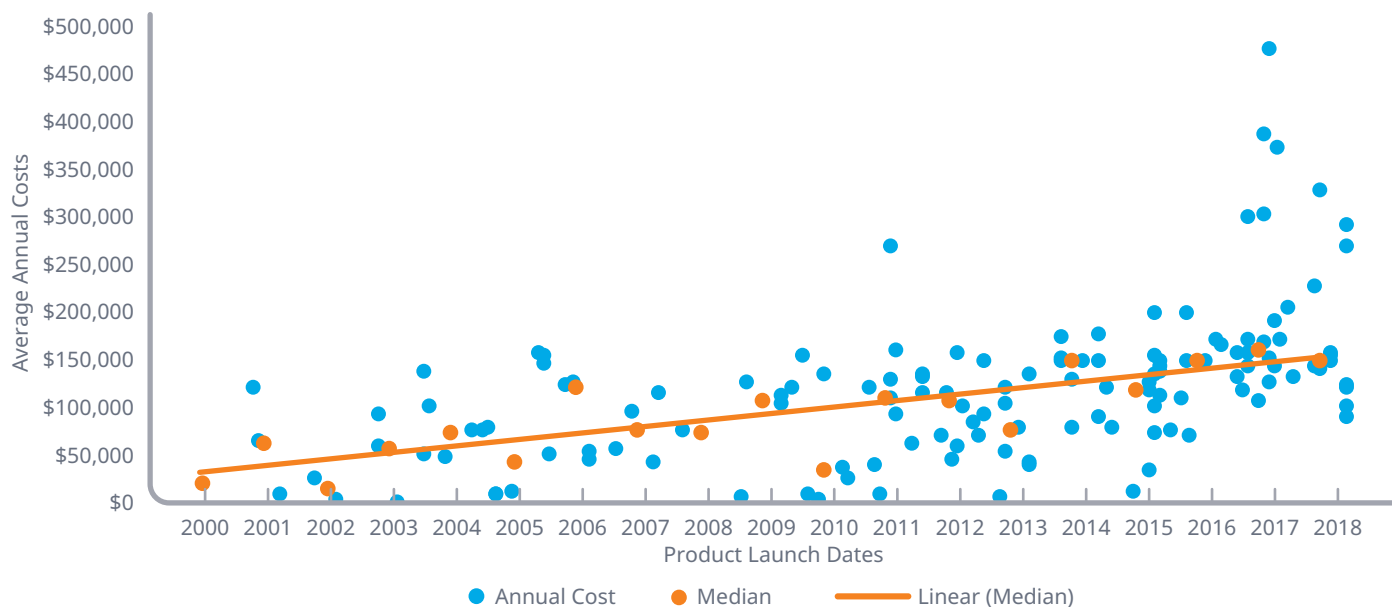
Source: IQVIA MIDAS; IQVIA Institute, Dec 2018

- Outside the United States, oncology costs exceeded \$66 billion in 2018, driven by new product launches and increased volume use of existing brands.
- The uptake of new brands resulted in \$19 billion in increased costs in other countries with more than one-third from PD-1 and PD-L1 inhibitors.
- Greater use of older brands, due to increasing numbers of patients receiving treatments, as well as lengthening treatment durations, led to \$12.8 billion in cost growth in the past five years.
- Prices declined on average for older protected brands outside the United States and contributed to a loss of \$1.9 billion of lower brand costs over five years.
- Loss of exclusivity for brands including biologics resulted in \$3.9 billion in lower costs of cancer medicines outside the United States.
- The \$4.4 billion increase in generic costs includes both small molecules and biosimilars.

Chart notes: Product segments are mutually exclusive in each period. New brands since 2013 show the total 2018 spending for all new branded products launched since the end of 2013. 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 exclude all branded products that are new since 2013. New PD-1 and PD-L1 products have been shown separately. 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. LOE (loss of exclusivity) 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.

The cost of new medicines continues to trend up, while the median dropped in 2018 to \$149,000 per average patient treatment year

Exhibit 33: Average Annual Costs for Oncology Products by Launch Year in the United States



Source: IQVIA Institute, Dec 2018

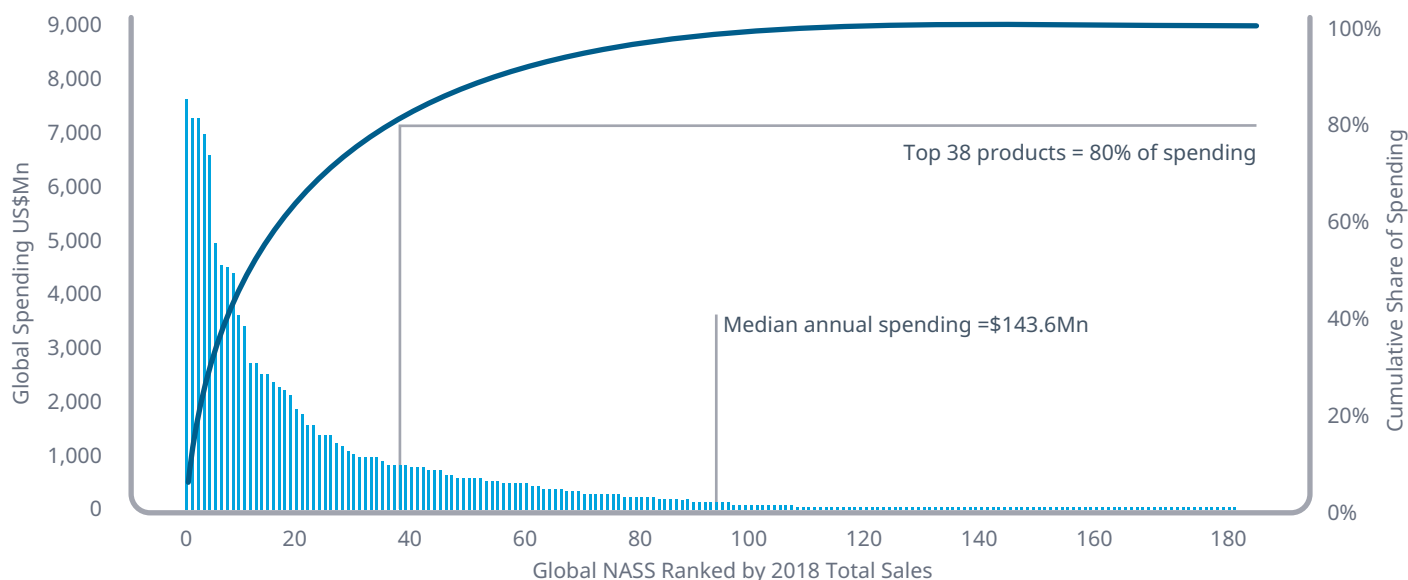
- New oncology brands in the United States include some medicines with costs above \$100,000 per year. The median annual cost for new brand launches in 2018 dropped to approximately \$148,800 from \$162,150 in 2017, and almost unchanged from \$150,000 in 2014.
- The introduction of some products with costs exceeding the median cost of that year has become more common, and this does not reflect the potential for regimen costs to be even higher if two or three agents are used in combination.
- The mean cost for the new brands in 2018 (data not shown) was \$175,578, down from \$209,406 in 2017, but above the \$143,574 mean from 2012 to 2018.
- The overall trend to more expensive treatments includes both an emphasis on smaller, more-focused sub-populations and the significant clinical benefits brought by many new treatments.

Chart notes: If published annual costs are available they have been included, and if not, annual costs were estimated based on IQVIA Institute interpretation of the most-common dosing in the approved label and available product unit pricing information.

SPENDING ON ONCOLOGY MEDICINES

Spending on cancer medicines is heavily concentrated with the top 38 drugs accounting for 80% of total spending

Exhibit 34: Global Markets Number of Oncologic Medicines Available and Average Spending per Product



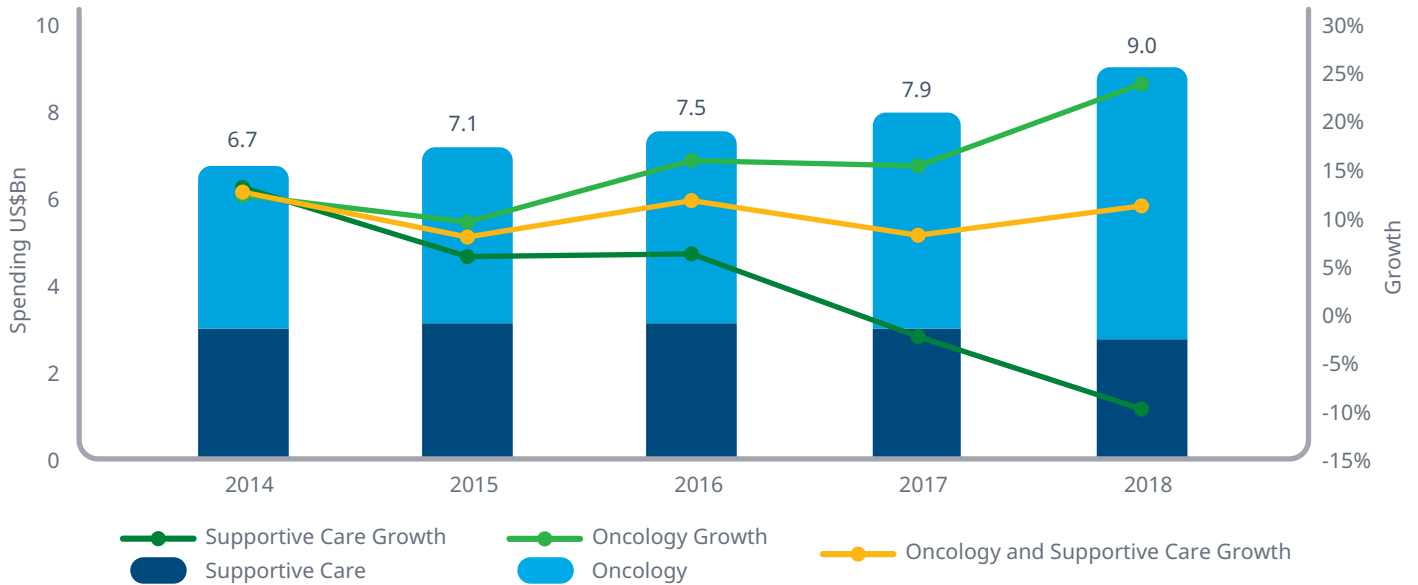
Source: IQVIA MIDAS, Dec 2018

- Spending on cancer medicines is heavily concentrated with the top 38 drugs accounting for 80% of total spending, while over half of cancer drugs have less than \$143.6 million in annual sales.
- Those products with less than \$143.6 million in sales account, in aggregate, for only 2.2% of oncology spending, as they are often older and available as generics at lower costs.
- Those medicines with the highest spending are used widely across countries, are generally newer brands, and often have multiple approved indications.
- Of cancer medicines in use around the world, 84% generated less than \$1 billion per year for the companies that produce them, and 70% made less than \$500 million in 2018.

Chart notes: Medicines aggregated based on active ingredients or fixed-dose combinations of ingredients and include spending for all manufacturers, including generics or biosimilars.

Oncology therapeutics in China grew by 24% in 2018, while supportive care treatments declined by 10%

Exhibit 35: Total Spending on Medicines and Growth in China, US\$Bn



Source: IQVIA MIDAS, Dec 2018

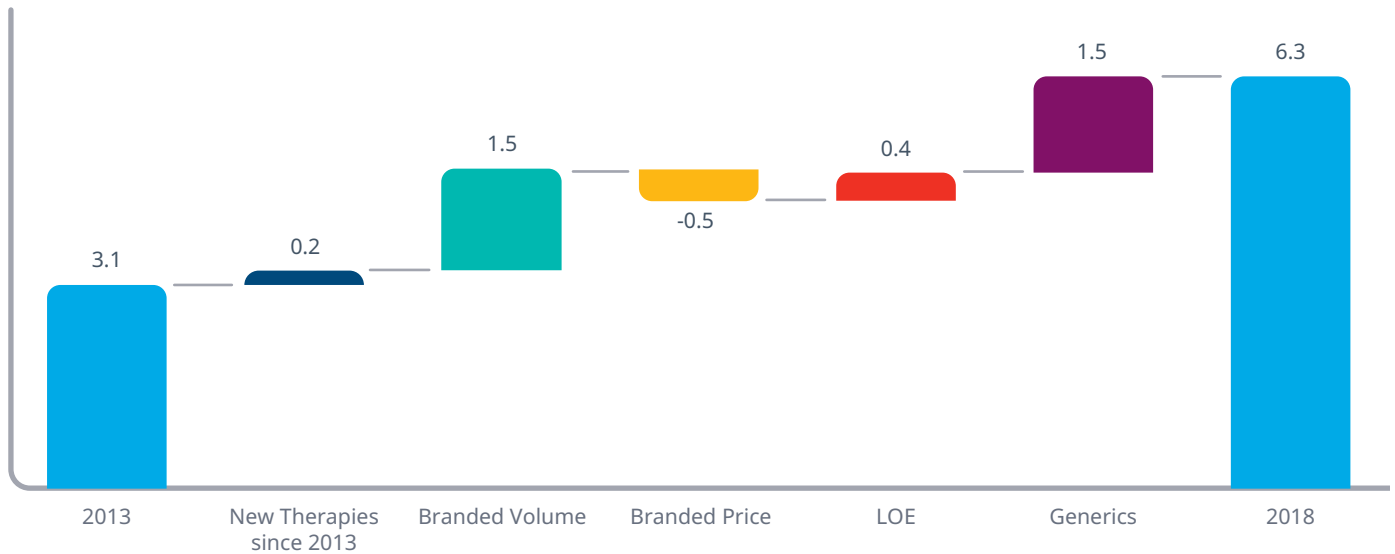
- Oncology spending in China reached nearly \$9 billion in 2018, increasing 11.1% in 2018.
- Therapeutic oncology treatments grew by 23.6% to \$6.3 billion, while supportive care treatments declined 10% to \$2.7 billion, as China generally has wide availability of non-original versions of supportive care biologics, such as filgrastim or erythropoietin.
- Therapeutic spending accounts for 70% of spending in China compared to 85% globally, as some products have much lower costs in China than other markets.
- Recent reforms in China, including the update to the National Reimbursement Drug List (NRDL) in December 2018, mean additional novel medicines will be more widely reimbursed in the future, but this has had little impact on 2018 spending.

Chart notes: Therapeutic oncologics include those classified by EphMRA (European Pharmaceutical Market Research Association) as cytotoxics in the L1 or L2 classes, as well as radiotherapeutics (V3C) and specific molecules classified elsewhere but used primarily in cancer (lenalidomide, aldesleukin, pomalidomide). Supportive care includes anti-nauseants and cancer detox agents (A4A and V3D), erythropoietins (B3C), GM-CSF white blood cell boosters (L3A), other interferon therapies used in cancer (L3B excluding multiple sclerosis drugs), and bisphosphonates used to prevent bone metastases (M5B4).

SPENDING ON ONCOLOGY MEDICINES

Oncology spending in China has doubled in the past five years, due to older brands and generics, with little growth from new therapies

Exhibit 36: Oncology Therapeutic Market Spending and Growth by Segment in China, Constant US\$Bn



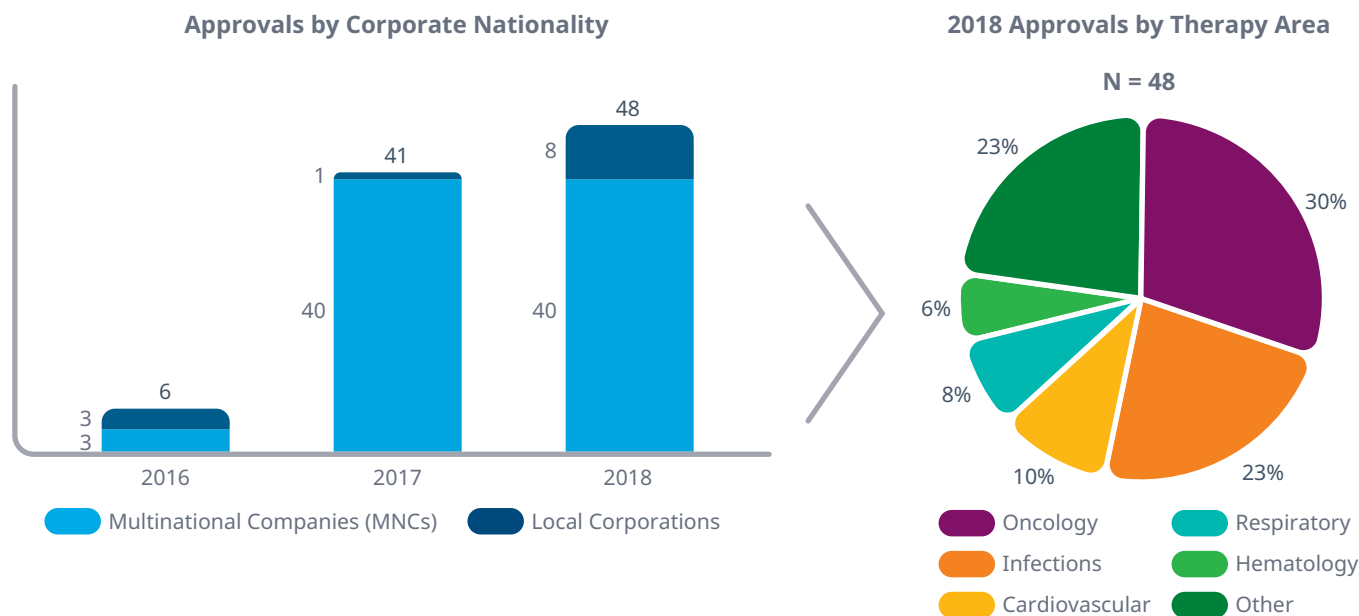
Source: IQVIA MIDAS; IQVIA Institute, Dec 2018

- Therapeutic oncology spending has more than doubled since 2013, driven mostly by increases in older-brand volume and generics.
- New medicines launched since 2013 generated \$218 million in spending in 2018.
- Only three of the six available PD-1/PD-L1 drugs (i.e., pembrolizumab, nivolumab and atezolizumab), and only one of the three CDK4/6 inhibitors for breast cancer (i.e., palbociclib) have launched in China, with the three becoming available between June and August of 2018.
- The largest contributors to new brand spending in other markets were the PD-1/PD-L1 checkpoint inhibitors, which in aggregate had \$6.4 million in sales in 2018, but these therapies have not contributed significantly to spending in China, as they were not available nor widely reimbursed until the middle of 2018.

Chart notes: Product segments are mutually exclusive in each period. New brands since 2013 show the total 2018 spending for all new branded products launched since the end of 2013. 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 exclude all branded products that are new since 2013. 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. LOE (loss of exclusivity) 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.

New drug approvals in China have increased dramatically, in line with global trends and with more multinational approvals

Exhibit 37: Progress in Approving Novel Compounds is Improving in China



Source: IQVIA Consulting, Jan 2019

- There has been a significant increase in the number of approved drugs in China in the past two years. Although this is in line with global trends since 2016, it is notable because in 2016 the number of approved drugs in China was much lower than the number approved globally.
- The large number of multinationals gaining these approvals also marks a significant reversal of a trend where drugs would be approved in China from local manufacturers even if they were originated and remained patented in other markets.
- Drugs are increasingly reaching the market faster in China as a result of expedited reviews and 35 approvals (~73%) benefited from review and approval acceleration policies in 2018.
- Lenvatinib (Lenvima) received approval for thyroid cancer only nine days after NDA acceptance.
- In 2018, there were eight NDA approvals for locally developed innovative drugs, the highest total since 2006.
- In 2018, China approved 14 new oncology drugs, very similar to the numbers in developed markets.
- Altogether, drugs launched in the past five years totaled only \$218 million in spending in 2018, though these medicines will likely contribute to growth in future years.

SPENDING ON ONCOLOGY MEDICINES

Oncology spending will reach nearly \$240 billion, growing 9–12% through 2023

Exhibit 38: Total Spending on Oncology Medicines and Supportive Care and Growth US\$Bn



Source: IQVIA Institute, Apr 2019

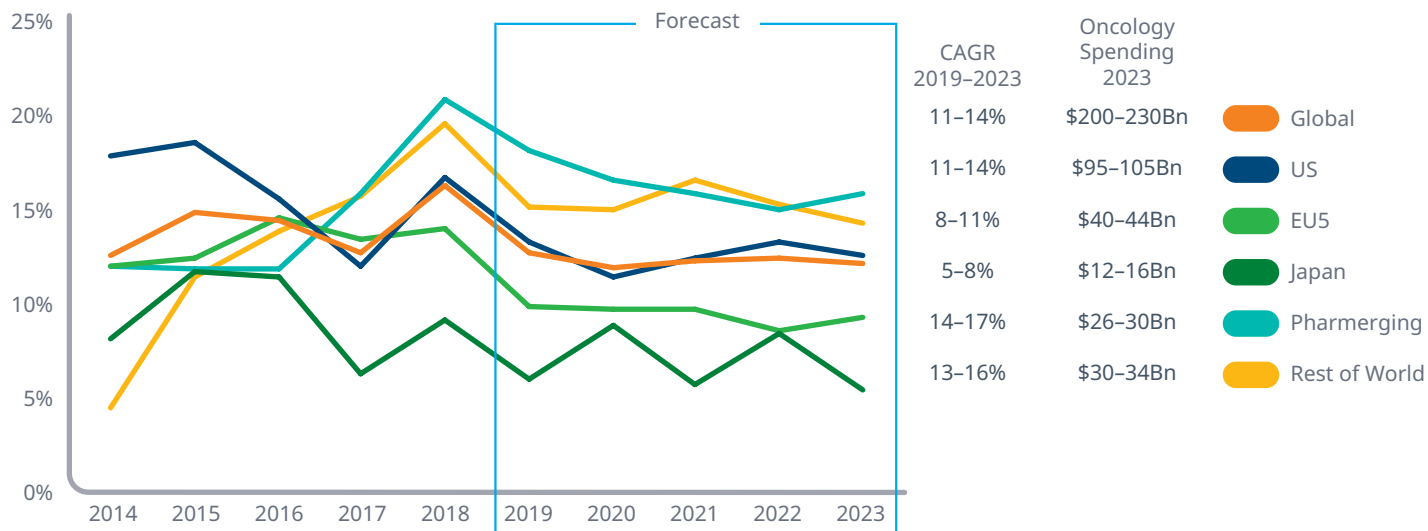
- Over the next five years, growth in oncology therapeutics spending of 11–14% is expected on a CAGR basis, bringing the total market to more than \$200 billion.
- Supportive-care spending is expected to decline by 3–6% globally, as many treatments become available as generics or small molecules, and very few novel supportive care drugs are in research or are expected to launch.
- Leading novel therapeutic drugs will grow primarily from the major developed markets, including the United States, EU5, Japan, and will also contribute significant growth, as they are now available in leading pharmerging markets.
- Overall oncology drug spending is expected to grow from 9–12% and reach \$220–250 billion in 2023.

Chart notes: Therapeutic oncologics include those classified by EphMRA (European Pharmaceutical Market Research Association) as cytotoxics in the L1 or L2 classes, as well as radiotherapeutics (V3C) and specific molecules classified elsewhere but used primarily in cancer (lenalidomide, aldesleukin, pomalidomide). Supportive care includes anti-nauseants and cancer detox agents (A4A and V3D), erythropoietins (B3C), GM-CSF white blood cell boosters (L3A), other interferon therapies used in cancer (L3B excluding multiple sclerosis drugs), and bisphosphonates used to prevent bone metastases (M5B4).

SPENDING ON ONCOLOGY MEDICINES

Global oncology therapeutic medicines will grow by 11–14% tempered by slowing growth in some geographies after highs in 2018

Exhibit 39: Growth Rates for Global Oncology Therapeutic Medicines, Constant US\$, 2014–2023



Source: IQVIA Institute, Dec 2018

- Global spending on therapeutic oncology drugs will exceed \$200 billion by 2023 with average growth of 11–14%.
- Growth will be led by the United States with an 11–14% CAGR and absolute spending reaching \$95–105 billion, driven by the continued early adoption of new treatments and the significant number and clinical value of new pipeline products expected to launch in the next four years.
- The top five European markets are expected to see slower growth, as budget pressures and the wider use of health technology assessments (HTA) limit cancer drug spending.
- Growth in the rest of the world has been driven generally by volume and increased use of medicines, which often occur a few years later than when new drugs are first adopted in developed markets.
- Japan is expected to actively slow oncology spending growth with price control mechanisms currently in place, and further reforms to pricing rules to address complexities of multi-indication cancer products.
- Pharmerging markets have significantly less use of cancer medicines than developed markets but are expected to grow by 14–17% to \$26–30 billion by 2023.

Chart notes: Spending Growth in Constant US\$; therapeutic oncology only.

Notes on sources

NATIONAL SALES PERSPECTIVES (NSP)[™] measures revenue within the U.S. pharmaceutical market by pharmacies, clinics, hospitals and other healthcare providers. NSP reports 100% coverage of the retail and non-retail channels for national pharmaceutical sales at actual transaction prices. The prices do not reflect off-invoice price concessions that reduce the net amount received by manufacturers.

NATIONAL PRESCRIPTION AUDIT (NPA)[™] is a suite of services that provides the industry standard source of national prescription activity for all products and markets across the retail, mail, and long term care channels.

REAL WORLD EVIDENCE is a suite of services that provides clinical evidence regarding the usage and potential benefits or risks of medical products or procedures derived from analysis of IQVIA Real World Data (RWD). IQVIA's RWD are a variety of information assets that represent the healthcare experiences of the patient. IQVIA's RWD provides near census-level coverage of dispensed prescription information at a prescriber and insurance plan level and tracks de-identified anonymous patient records over time to analyze distinct use patterns. Additionally, IQVIA's RWD captures information about the patient's medical, hospital, EMR, consumer, and laboratory experiences, among other details.

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.

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 sub-populations and treatment patterns. Oncology Dynamics has geographic coverage across the EU5, APAC, Romania, Saudi Arabia, Mexico and Brazil and covers more than 150,000 cases per year and over 1,500 specialists.

IQVIA NEW PRODUCT INTELLIGENCE is a database of over 500,000 products with distinct trade names, from launches dating back over 30 years covering over 60 major markets. The database reports on over 1,500 new launches every month, and the service provides insights on which companies are successful at launching products quickly, whether releasing a brand new chemical entity or the generic version of a drug that has lost patent protection.

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.

HTA ACCELERATOR[™] provides strategic insights into payer decision-making based on 25,000+ health technology assessments from 100 agencies and 40 countries. With additional clinical, regulatory and price information it sets the foundation for evidence-based insight generation.

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Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.



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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 5 areas considered vital to contributing to the advancement of human health globally:

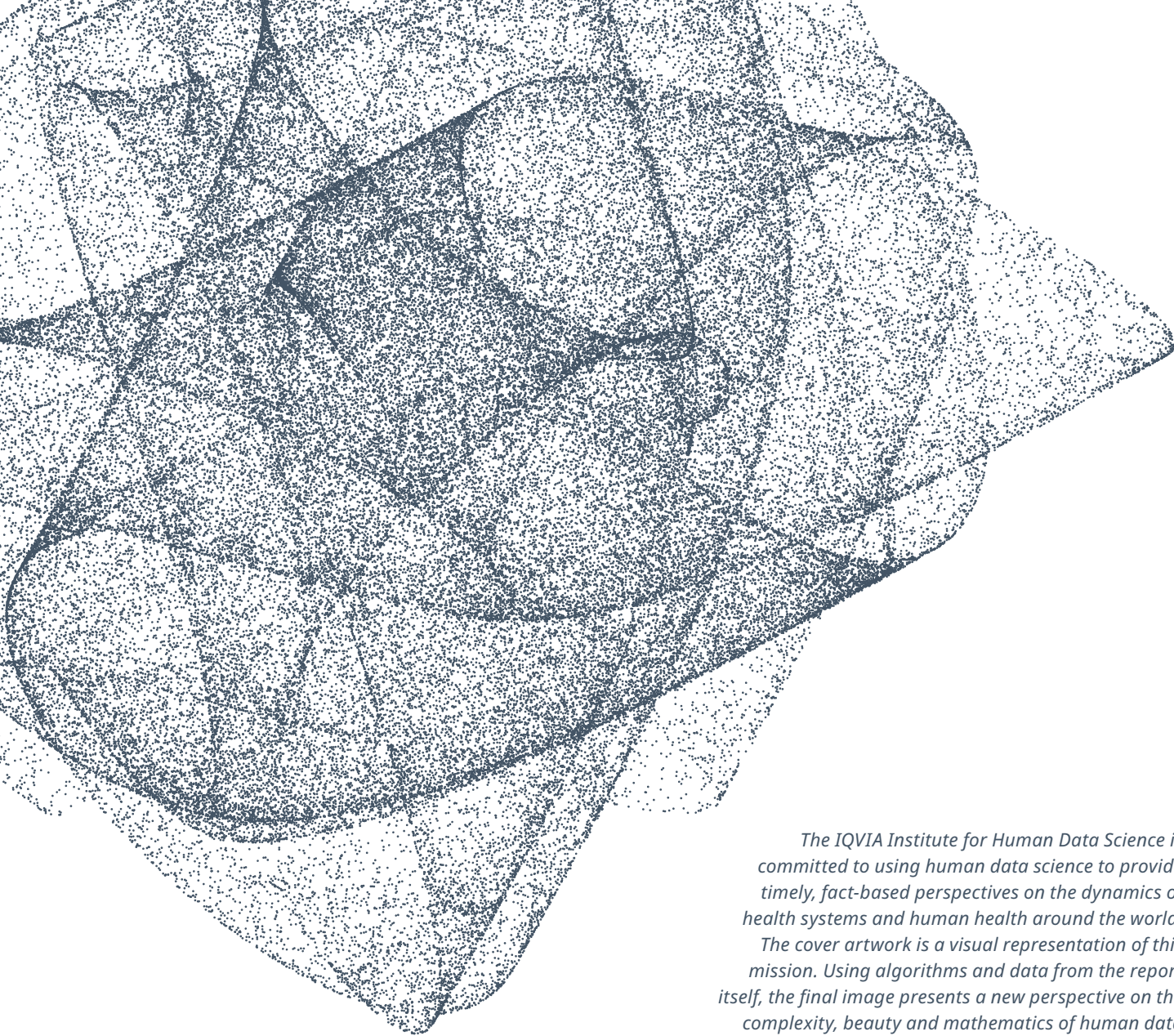
- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing 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.

Artwork on the cover of the Global Oncology Trends 2019 report was generated using data sets from IQVIA MIDAS™ that show annual product cost, number of patients, doses received and overall product sales of oncology branded drugs that have launched in the United States in the past 25 years.

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