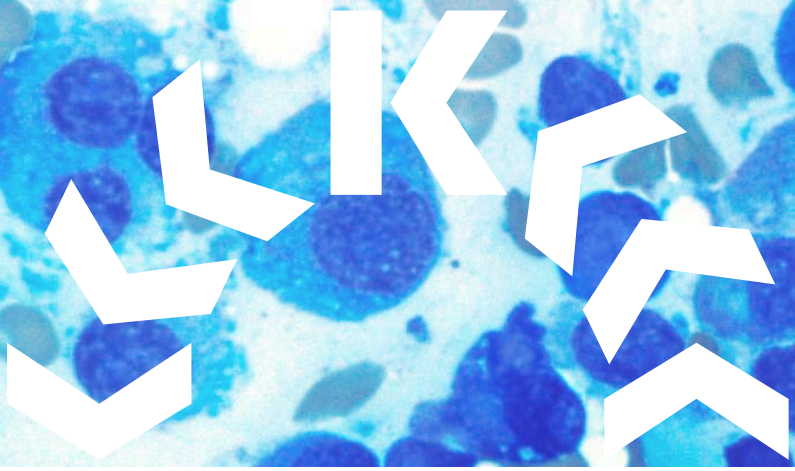
KAISER ASSOCIATES

HOT INDICATIONS LIST

ONCOLOGY DEEP DIVE

Top Indications for Global Pharma R&D Investment Intensity in Oncology

Published October 2016



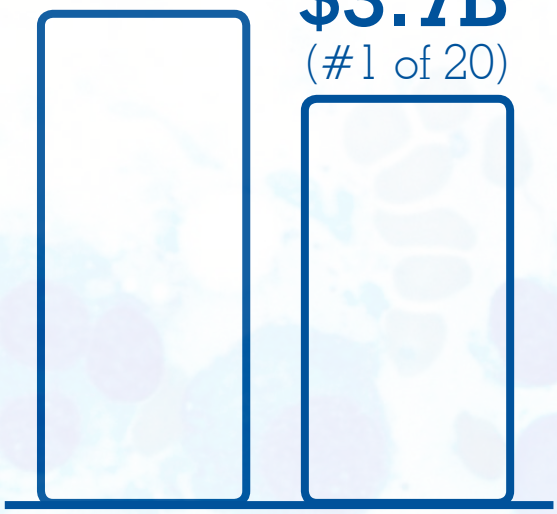
HOT INDICATIONS LIST

ONCOLOGY DEEP DIVE

(# OF 20) INDICATES TA RANK

$4.5B
(#1 of 20)

$3.7B
(#1 of 20)



2015 Cumulative VC Funding

2015 Cumulative IPO Amount

1,095
COMPANIES
(#1 of 20)

340,618
PUBLICATIONS
(#1 of 20)

1,394
PHASE II &III PROGRAMS
(#1 of 20)

INDICATIONS IN TOP 100:

Breast cancer (#2)
Non-small cell lung cancer(#3)
Brain cancer (#6)
Acute myelogenous leukemia (#7)
Ovarian cancer (#8)
Melanoma (#9)
Prostate cancer (#10)
Pancreatic cancer (#11)
Non-Hodgkin's lymphoma (#14)
Multiple myeloma (#16)
B cell lymphoma (#17)
Colorectal cancer (#21)
Chronic lymphocytic leukemia (#26)
Renal cancer (#39)
Head and neck cancer (#42)
Bladder cancer (#52)
Mesothelioma (#55)
Cervical cancer (#61)
Sarcoma (#62)
Neuroendocrine tumors (#63)
Small cell lung cancer (#65)
Epithelial cancer (#66)
Gastrointestinal cancer (#69)
Myelodysplastic syndrome (#73)
Biliary cancer (#80)
Hodgkin's disease (#99)

SOURCE: KAISER ASSOCIATES ANALYSIS

KAISER ASSOCIATES

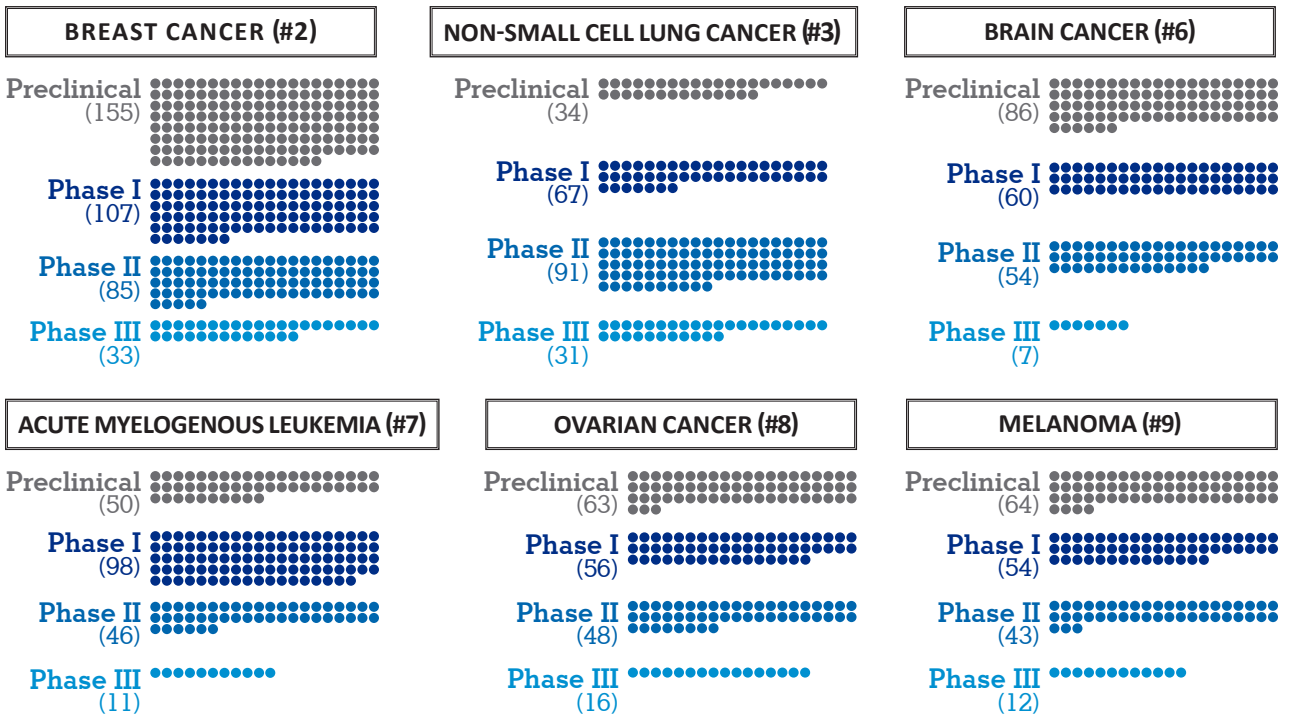
ONCOLOGY DEEP DIVE

In 2015, Oncology continued its run as a hot focus for drug development. Major indications within Oncology, such as **breast cancer (#2), non-small cell lung cancer (NSCLC, #3), brain cancer (#6)**, and **acute myelogenous leukemia (#7)**, are not new to the scene, but rather have been focuses of intense pipeline activity for many years.

However, these top indications are not the whole story: major movers and shakers in the oncology indication rankings from 2014 to 2015 include **sarcoma** (**#62** in 2015, compared to #125 in 2014) and **biliary cancer/ cholangiocarcinoma** (**#80** in 2015, compared to #176 in 2014). Biliary cancer is a rare, aggressive form of liver cancer with few current treatment options. In 2015, the FDA granted Orphan Drug designations for biliary cancer to 3 compounds from ArQule, ASLAN Pharmaceuticals, and Delcath Systems. Delcath used a $156M IPO to fund further development of their unique drug-device combination of melphalan delivered via Delcath's Chemosat system. These signs indicate that rare cancers are getting more attention that will hopefully translate into an improved treatment landscape in the years to come.

In 2015, BMS's Opdivo and Merck's Keytruda were the first immunotherapies to gain FDA and EMA approval for

Number of Programs by Stage of Development

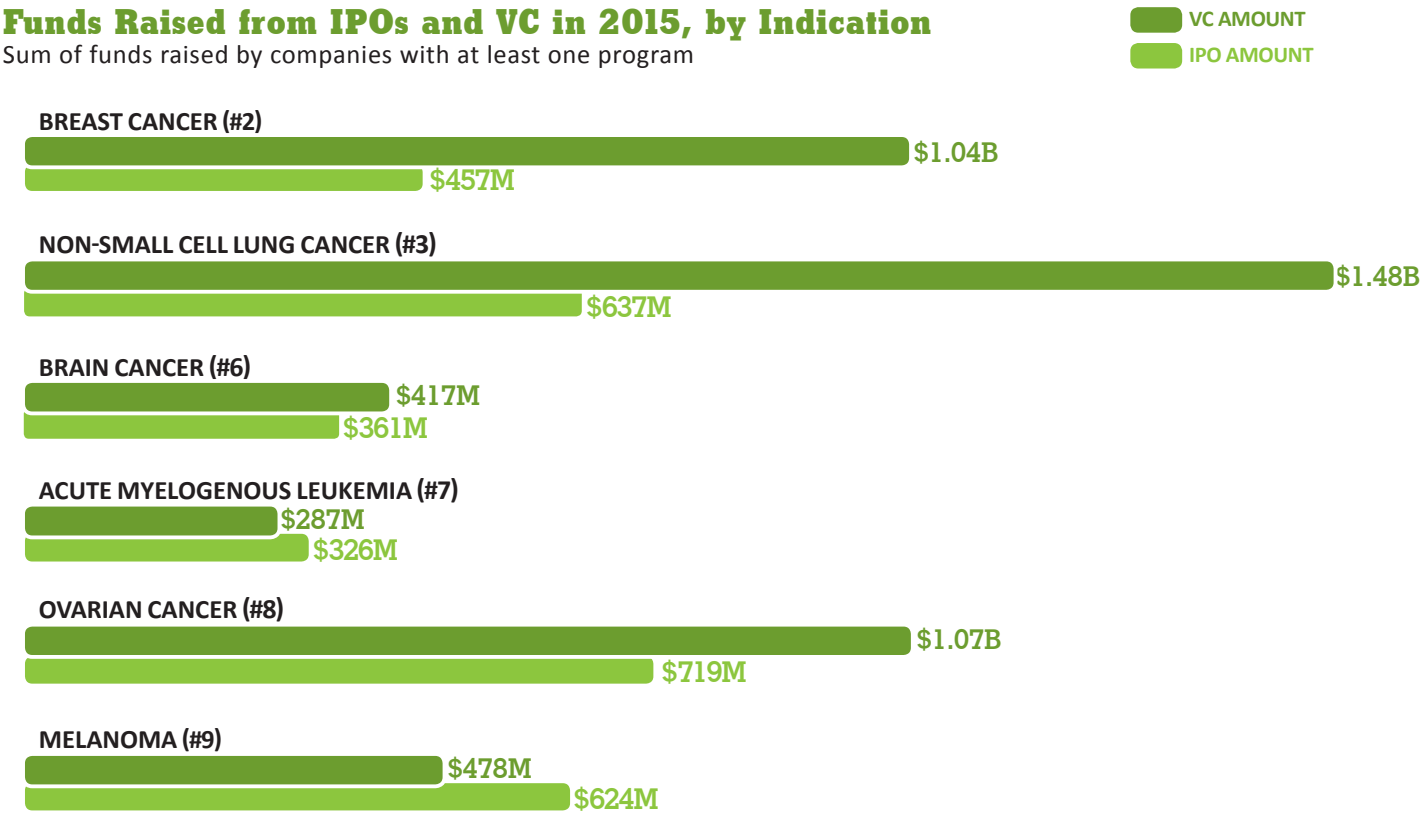


SOURCE: KAISER/BCIQ DATABASE

ONCOLOGY DEEP DIVE

Funds Raised from IPOs and VC in 2015, by Indication

Sum of funds raised by companies with at least one program



SOURCE: KAISER/BCIQ DATABASE

melanoma (#9) and **NSCLC**. These approvals paved the way for other immunotherapies currently in late stage development from major players including Roche (atezolizumab) and EMD Serono/Pfizer (avelumab). The impact of immunotherapies on development activity is still being observed, as there is a rush to capture additional indications that is reflected in cancers including **breast, colorectal (#21), renal (#39), bladder (#52)**, and **gastric cancer (#126)**. Clearly, immunotherapies are revolutionary and have changed the treatment paradigm for many cancer types — but where does the industry go from here?

Back to Basics

Alongside immunotherapy development, both large and small companies have been discovering and developing small molecule kinase inhibitors. This activity has been based on well-established knowledge:

Mutations in kinases regulating cellular growth signaling and division underlie all cancers.

Building on many years of basic research identifying key cross-tumor site mutations, and following on the success of kinase inhibitors such as Gleevec (Novartis) for **chronic myelogenous leukemia (#223)** and Zelboraf (Genentech/Roche) in **melanoma**, many other kinase inhibitors are now reaching late-stage development. Inhibiting growth signaling kinases allows companies, in theory, to target a variety of indications, from large indications such as **breast** and

prostate (#10) cancers to rare tumors such as soft tissue **sarcomas**. However, in practice, developing growth signaling kinase inhibitors requires a number of strategic choices. Among these are:

In early stage development, which mutations to target? Some kinases, such as p53 or K-Ras, are very commonly mutated but notoriously difficult to target specifically — is it worthwhile to enter clinical development with a compound that may later display an unfavorable side effect profile?

Which tumor sites to target? Is it better to choose a more common cancer, where patient populations are large but there is more intense competition, or a rare cancer, where obtaining orphan drug status may be a possibility?

Should trials include only patients confirmed to have the relevant kinase mutation, or does the potential payoff from targeting a larger patient population outweigh the risk of failure to meet endpoints?

Should candidate compounds enter trials as monotherapies, or in combination? If in combination, with what drugs (e.g. standard of care chemotherapy, immunotherapy)?

Once a kinase inhibitor has been approved, what would be the best label expansions — e.g. earlier in the same cancer treatment pathway, or is this the best opportunity to capture some rare indications?

There are a number of different ways to address the challenges of optimizing development of growth signaling kinase inhibitors, with their seemingly endless possibilities. We are now seeing some of these decisions affecting late-stage development activity.

For instance, Merck is approaching development of their AKT inhibitor MK-2206 very differently than Otsuka and AstraZeneca are advancing their candidate, AZD5363.Merck is going for multiple indications, with trials for breast, prostate, pancreatic, colorectal, and non-small cell lung cancers as well as B-cell lymphoma, while AZD5363 is only in trials for breast cancer.

As growth signaling kinase inhibitors in development approach these challenges, we can be sure that we will see the effects of their decisions, from development in 2016 to the landscape of the future oncology market — and while the mechanism of action of these compounds is well-known, their future may not be what we predict.

HOT INDICATIONS LIST

METHODOLOGY

Kaiser Associates' methodology is designed to assess investment intensity of drug development for each indication through a comprehensive and balanced analysis of the key drivers and metrics.

Our Hot Indications analysis framework considers the volume of ongoing scientific investigation, as well as the types of companies and level of funding supporting these trials. Kaiser's analysis evaluated 13,182 drug programs ongoing in 2015, categorized them into 577 unique indications, and compared available data for these indications across three main criteria:

1. PIPELINE SCORE

The Pipeline Score measures the overall level of drug development activity for an indication. The score gives greater value to later-stage programs, higher volumes of programs overall, and indications with greater numbers of companies with programs.

2. R&D FUNDING

R&D Funding estimates the availability of financing to support the development of each drug program to its reasonable endpoint. For some programs, this endpoint will be FDA approval, while for others it will be discontinuation in preclinicals or Phase I.

The score measures availability of funds and willingness to invest based on two main inputs for each indication. First, the R&D Funding Score quantifies the historical track record of sponsor companies, based on the number of drugs each company has successfully developed. Second, the score measures initial public offering and venture capital investment fundraising activity in 2014 for each indication, with the expectation that the financing from such events will be major contributors in supporting ongoing R&D programs.

3. ACADEMIC FOCUS

Academic Focus measures the overall publication activity for each indication, based on the absolute number and the one-year change in publications citing the indication for the evaluation period.

Hot Indications Ranking

For each of the 577 indications, the overall ranking score is calculated by a weighted average of Pipeline Score (50%), R&D Funding (40%) and Academic Focus (10%). Throughout this analysis, the rank number from the final Hot Indications List is denoted in parentheses immediately following first mention of the indication in each section.

Therapeutic Areas & Ranking

The Therapeutic Area Ranking is an index of R&D investment intensity that synthesizes and normalizes the Hot Indications Ranking scores for all indications within a Therapeutic Area.

Each indication is categorized into one of 21 TAs, which include 20 major fields of medicine and an "Other" group. The assignment of indications into TA plays a meaningful role in the Therapeutic Area Ranking. In general, indications are categorized based on the medical specialty most likely to treat patients with a disease or disorder.

Systemic diseases, such as automimmune disorders, or TAs representing a variety of medical specialties, such as Musculoskeletal, are grouped on a case-by-case basis. For example, Crohn's disease and ulcerative colitis are included in Gastroenterology rather than Autoimmune, whereas Multiple Sclerosis is included in Autoimmune due to the variety of symptoms it presents.

To see the full list, go to
info.kaiserassociates.com/2016-hot-indications

ABOUT KAISER ASSOCIATES

ABOUT KAISER

Founded in 1981, Kaiser Associates is an international strategy consulting firm that serves as a key advisor to the world's leading companies. We provide our clients with the unique insight to drive critical decision-making and solve their most pressing problems.

Kaiser's Global Healthcare Practice engages with executives at leading Life Sciences companies, including pharmaceutical, medical device, clinical diagnostics, consumer health, and health IT. We work with our clients to identify new growth markets, develop long-term portfolio strategies, and maximize commercial success.

The foundation of Kaiser's service offering is its world-class "outside-in" methodology, which involves delivering critical facts and insights from the complex external environment to drive strategic decision making. Kaiser possesses the unique ability to generate insights across physicians, thought leaders, patients, competitors, partners, regulators, suppliers, and payers. Kaiser uses its deep industry experience and analytical tools to synthesize this diverse set of insights and develop high-impact solutions.

ABOUT THE AUTHORS

Jenna Riffell
Jenna is a Manager in Kaiser Associates' Global Healthcare Practice based in London, UK.

You may contact her by email at jriffell@kaiserassociates.com

Bob Serrano
Bob is a Vice President in Kaiser Associates' Global Healthcare Practice based in Washington, D.C.

You may contact him by email at bserrano@kaiserassociates.com

Dan O'Neill
Dan is a Senior Vice President in Kaiser Associates' Global Healthcare Practice based in Washington, D.C.

You may contact him by email at doneill@kaiserassociates.com

Special thanks to Grey Im for his contributions to this analysis.

Design and Graphics by Kelly Martin Design