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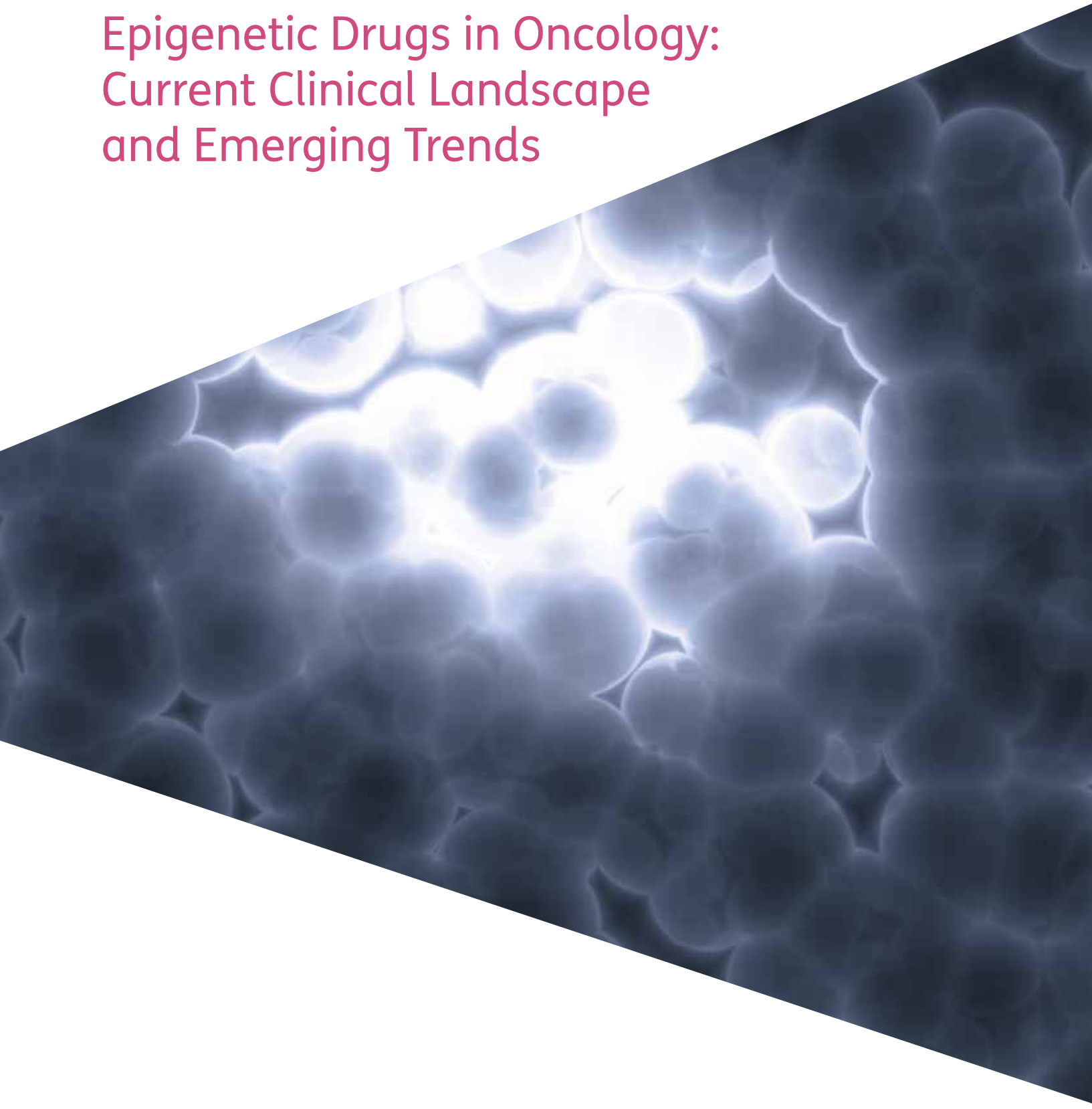
Epigenetic Drugs in Oncology: Current Clinical Landscape and Emerging Trends



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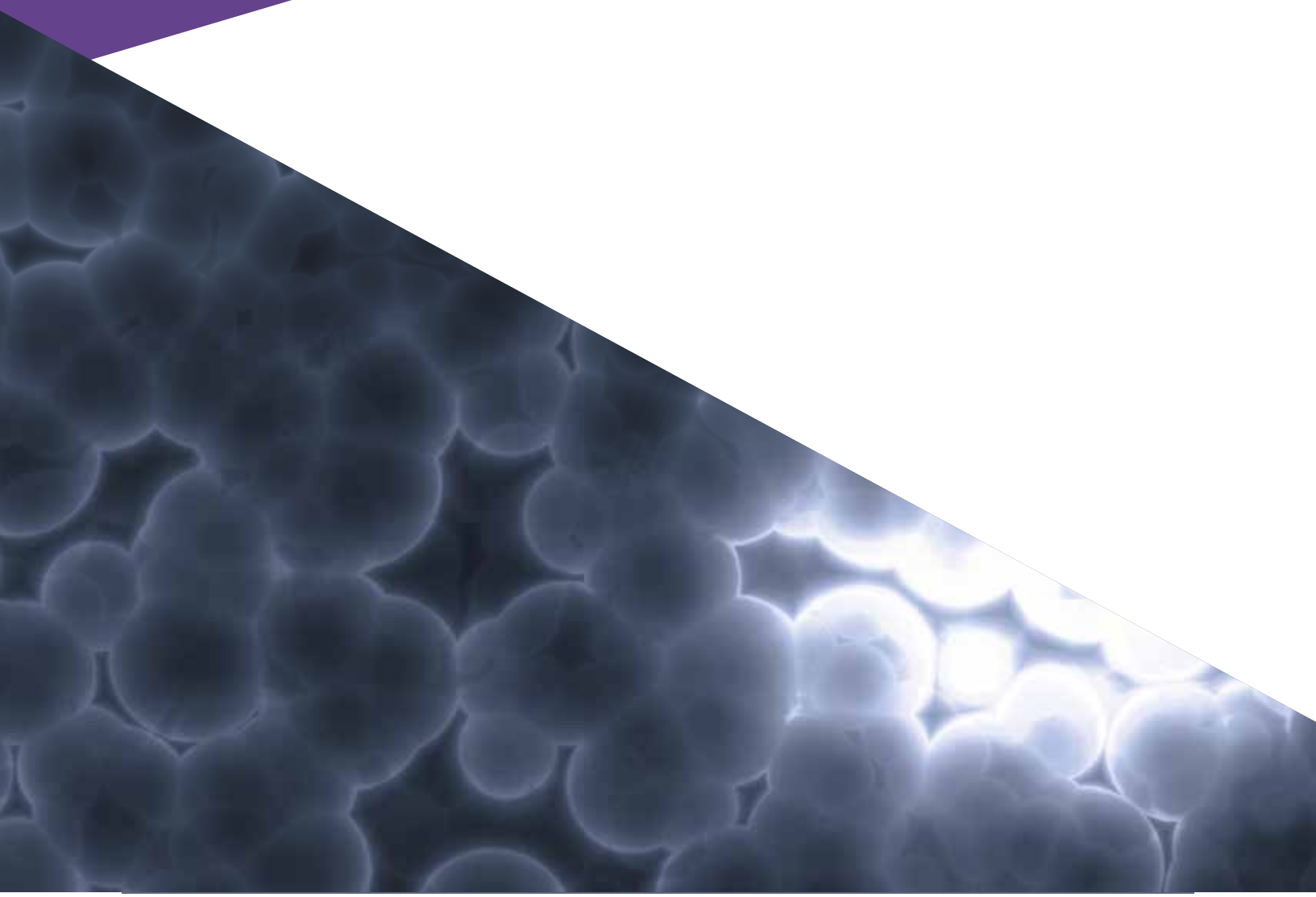


Rachel Meighan-Mantha
PhD, Principal Oncology,
Pharma Intelligence, Informa

Introduction

"Epigenetics is the study of heritable, reversible forms of gene regulation that are not dependent on the DNA sequence. This regulation includes DNA methylation and histone methylation, acetylation, ubiquitination, and phosphorylation."1 While epigenetic modifications are crucial for normal functioning in all stages in life, from embryonic development through adulthood, these events are also associated with many cardiovascular, metabolic and neurological diseases as well as cancer.1 Epigenetics has become an area of extensive interest in the years since the Human Genome Project was completed in 2003 judging by the epigenetic international initiatives launched since then, including GWAS, ENCODE, TCGA, AHEAD, ICGC, Roadmap Epigenomics and IHEC among others2. Preclinical and clinical research over the past 30 years point to the therapeutic potential of epigenetic drugs, both alone and combination, in correcting epigenetic dysregulation associated with various types of malignancies. This report analyzes the current clinical landscape and some emerging trends for epigenetic drugs in oncology.

Methodology

Data was retrieved from Informa's Pharma Intelligence services in mid to late October as follows.

Biomedtracker – a drug search with the epigenetic-associated targets: BET Proteins/ Bromodomains, Isocitrate Dehydrogenase (IDH), Histone Methyltransferase (HMT), Lysine-Specific Demethylase-1 (LSD1)/KDM1A or SIRT1

Pharmaprojects – a drug search of pipeline and approved cancer drugs (global status of preclinical to launched) with the epigenetic-associated mechanisms of action: BET protein inhibitor, demethylase inhibitor, DNA methylase inhibitor, histone acetyltransferase inhibitor, histone deacetylase inhibitor, histone deacetylase stimulant, histone methyltransferase inhibitor, isocitrate dehydrogenase inhibitor, methyltransferase inhibitor or methyltransferase stimulant

Strategic Transactions – a search of deal records (acquisitions, alliances and mergers) using keywords or phrases related to epigenetics (e.g. bromodomain, "DNA methylation", "epigenetic", HDAC, "isocitrate dehydrogenase" or "lysine-specific demethylase")

Trialtrove – an oncology trials search of primary drugs with the epigenetic-associated mechanisms of action: BET protein inhibitor, demethylase inhibitor, DNA methylase inhibitor, histone acetyltransferase inhibitor, histone deacetylase inhibitor, histone deacetylase stimulant, histone methyltransferase inhibitor, isocitrate dehydrogenase inhibitor or methyltransferase inhibitor

1 Heerboth S, Lapinska K, Snyder N, Leary M, Rollinson S, Sarkar S. Use of Epigenetic Drugs in Disease: An Overview. Genetics & Epigenetics. 2014;6:9-19.
2 Bae, JB. Perspectives of International Human Epigenome Consortium. Genomics & Informatics. 2013;11(1):7-14.

Approved Drugs

Seven epigenetic drugs, two DNA methyltransferase (DNMT) inhibitors and five histone deacetylase (HDAC) inhibitors have been approved in several different hematological malignancies as shown in Table 1. While approvals date back to 2004, three drugs were approved just in the past three years. Most of these drugs have been approved in multiple countries with the exception of belinostat and romidepsin (only approved in the USA) and chidamide (only approved in China). Not shown in this table is a HDAC inhibitor, valproic acid/valproate, which has been approved for decades to treat epilepsy, bipolar disorder and migraines. It continues to be evaluated in oncology clinical trials as a repurposed drug.

Table 1: Approved Epigenetic Drugs in Oncology

Drug Name	Epigenetic Mechanism of Action	Originator	Earliest Approval Date	Approved Indications
azacitidine (Vidaza)	DNMT inhibitor	Celgene	May 2004	AML, CML and MDS*
decitabine (Dacogen)	DNMT inhibitor	Astex Pharmaceuticals (Otsuka)	May 2006	AML, CML and MDS
vorinostat (Zolinza)	HDAC inhibitor	Merck & Co.	Oct 2006	Cutaneous T-cell Lymphoma
romidepsin (Chromadax)	HDAC inhibitor	Astellas Pharma/Celgene	Nov 2009	Cutaneous/Peripheral T-cell Lymphoma
belinostat (Beleodaq)	HDAC inhibitor	TopoTarget	Jul 2014	Peripheral T-cell Lymphoma
chidamide (Epidaza)	HDAC inhibitor	Shenzhen Chipscreen Biosciences	Dec 2014	Peripheral T-cell Lymphoma
panobinostat (Farydak)	HDAC inhibitor	Novartis	Feb 2015	Multiple Myeloma

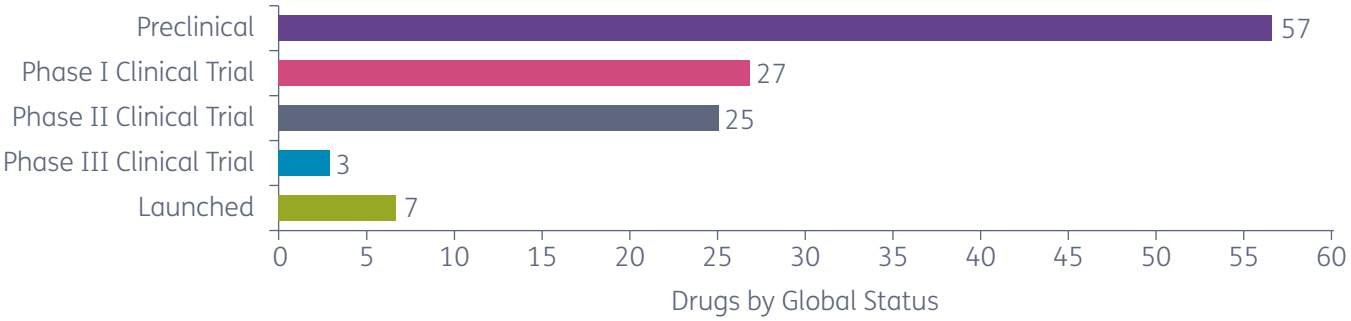
**Acute Myelogenous Leukemia (AML), Chronic Myelogenous Leukemia (CML) and Myelodysplastic Syndromes (MDS)*

Source: Pharmaprojects®, October 2016

Current Clinical Landscape

In addition to the seven approved drugs described above, the current clinical landscape, as of October 2016, included 112 active drugs. Approximately 48% of the active drugs were in preclinical development while approximately 46% were in clinical (phase I-III) development (Figure 1). Almost all of drugs in clinical development were still in early-to mid-stage trials (phase I and II). Not shown are the inactive drugs (suspended, no development reported, discontinued or withdrawn).

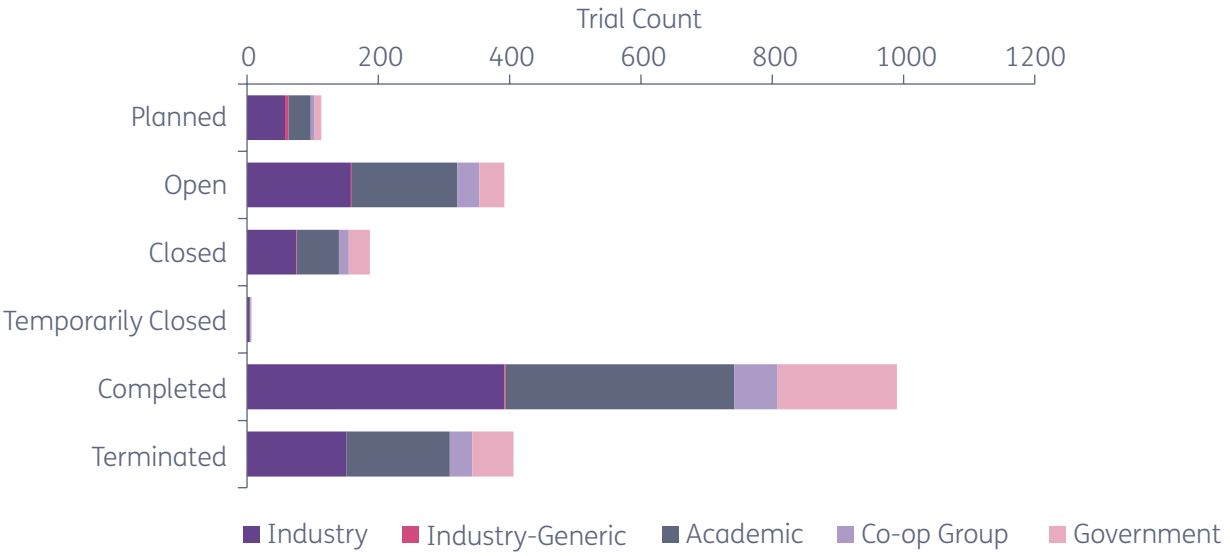
Figure 1: Global Status of Active Epigenetic Drugs in Oncology



Source: Pharmaprojects®, October 2016

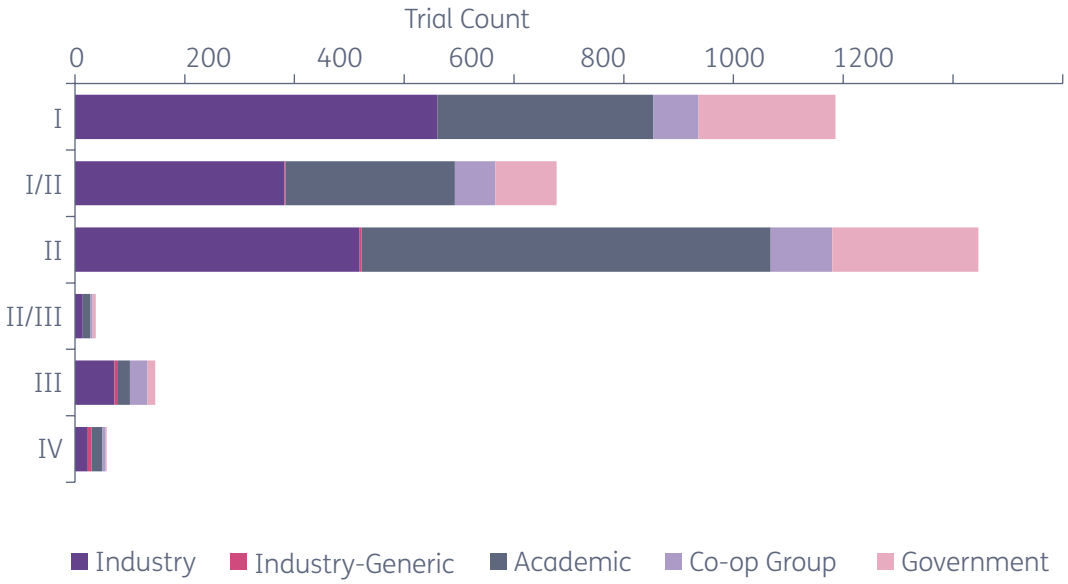
Epigenetic drugs, active and currently inactive, were evaluated in 1418 oncology clinical trials. Of these, 35% were ongoing (open, closed or temporarily closed) and planned while 65% were completed or terminated. Approximately 93% of the trials were early- to mid-stage (phases I, I/II and II) while just over 6% were late-stage (phases II/III, III and IV). The remainder of the trials were not assigned a specific phase by the sponsor (data not shown). Sponsors/collaborators of these trials were classified by type (Industry, Industry-Generic, Academic, Co-op Group and Government) and examined by trial status and phase. The ratios of sponsor/collaborator involvement relative to other types for each trial status remained relatively constant with slight increases in Industry and Industry-Generic involvement for planned trials and slight decreases in Government involvement for planned and open trials (Figure 2). Relative to the other types for each phase, Industry involvement was highest in phases I and III and lowest in phase II (Figure 3). In contrast, Academic involvement was highest in phase II and lowest in phase III. Both Co-op Group and Government involvement were similar in phases I to II/III, yet in phase III, Co-op Group involvement was highest while Government involvement dropped off.

Figure 2: Sponsor/Collaborator Type by Trial Status



Source: Trialtrove®, October 2016

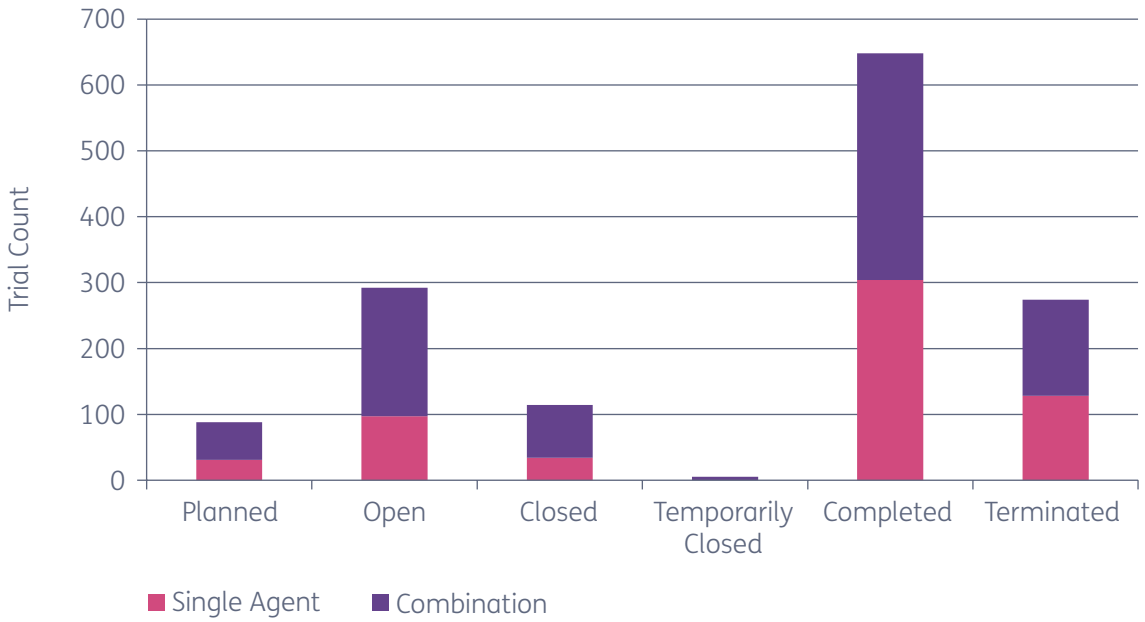
Figure 3: Sponsor/Collaborator Type by Trial Phase



Source: Trialtrove®, October 2016

By overall trial design, 42% of epigenetic drug trials in oncology evaluated single agents while 58% evaluated combinations. In completed and terminated trials, these two study designs were approximately equivalent in their use. However in ongoing and planned trials, single agents were evaluated in only 33% of trials and combinations increased to 67% from the overall trial design ratio.

Figure 4: Overall Trial Design by Trial Status



Source: Trialtrove®, October 2016

These trials were also assessed for attributes related to regulatory approvals, investigator involvement and biomarkers. Like oncology trials in general, epigenetic drug trials supported the trend towards personalized medicine, especially in ongoing and planned trials. Trials that preselected or stratified patients based on a pharmacogenomic (PGX) biomarker were more likely to be ongoing or planned rather than completed or terminated (Figure 5). Additional differences between these two trial status groups included increases in investigator-initiated and registration trials for ongoing and planned versus completed and terminated trials. Trial statuses with the highest attribute percentage are boxed, and five temporarily closed trials are not shown.

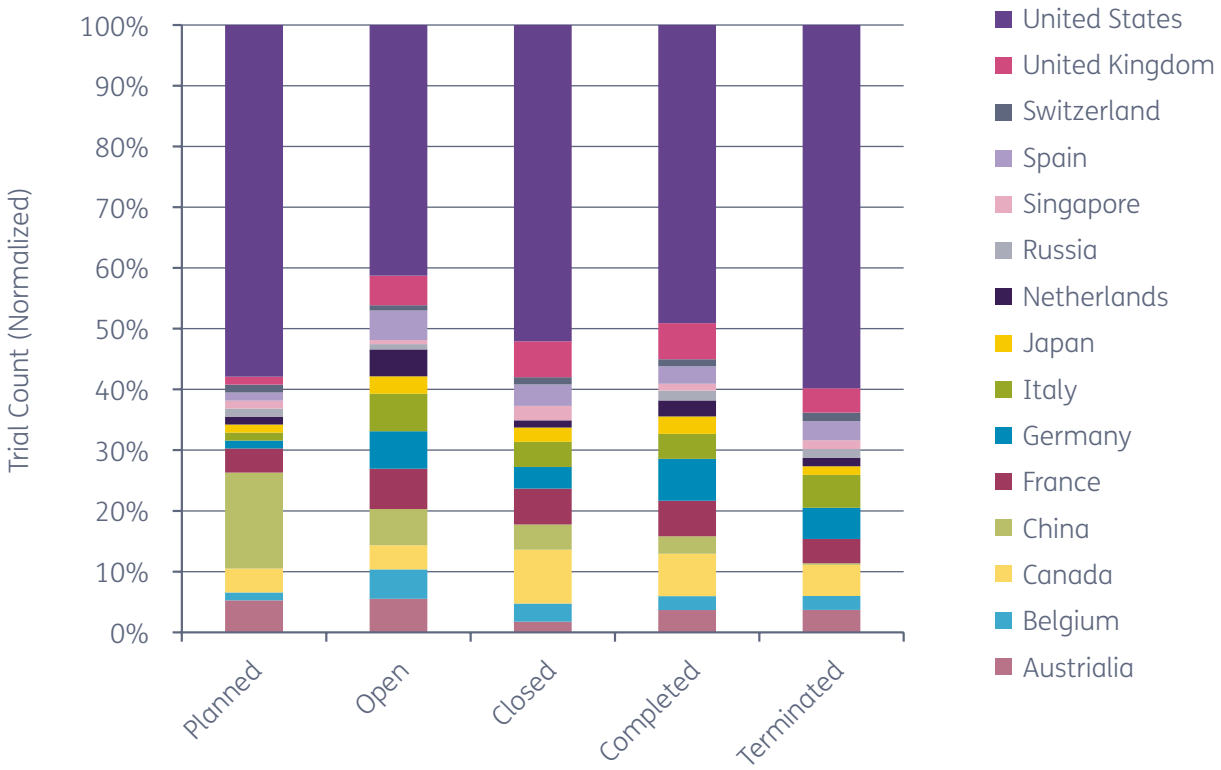
Figure 5: Trial Tags by Trial Status

Trial Tags	Planned	Open	Closed	Completed	Terminated
Biomarker/Efficacy	14%	38%	50%	43%	44%
Investigator-initiated	8%	12%	16%	5%	3%
PGX – Biomarker Identification/Evaluation	7%	22%	37%	28%	26%
PGX – Patient Preselection/Stratification	10%	22%	13%	4%	9%
Registration	7%	3%	1%	2%	0%

Source: Trialtrove®, October 2016

Locations for epigenetic drug trials in oncology encompass several different geographical regions. Overall, 70% of the trials were conducted at sites in North America, 27% in Europe (eastern and western), 15% in Asia, 5% in Australia/New Zealand, 2% in both South America and the Middle East and 1% in Africa (data not shown). The geographical representation of the top countries in each region did not change much from one status to the next, except for an increase in ongoing and planned trials conducted in China (Figure 6).

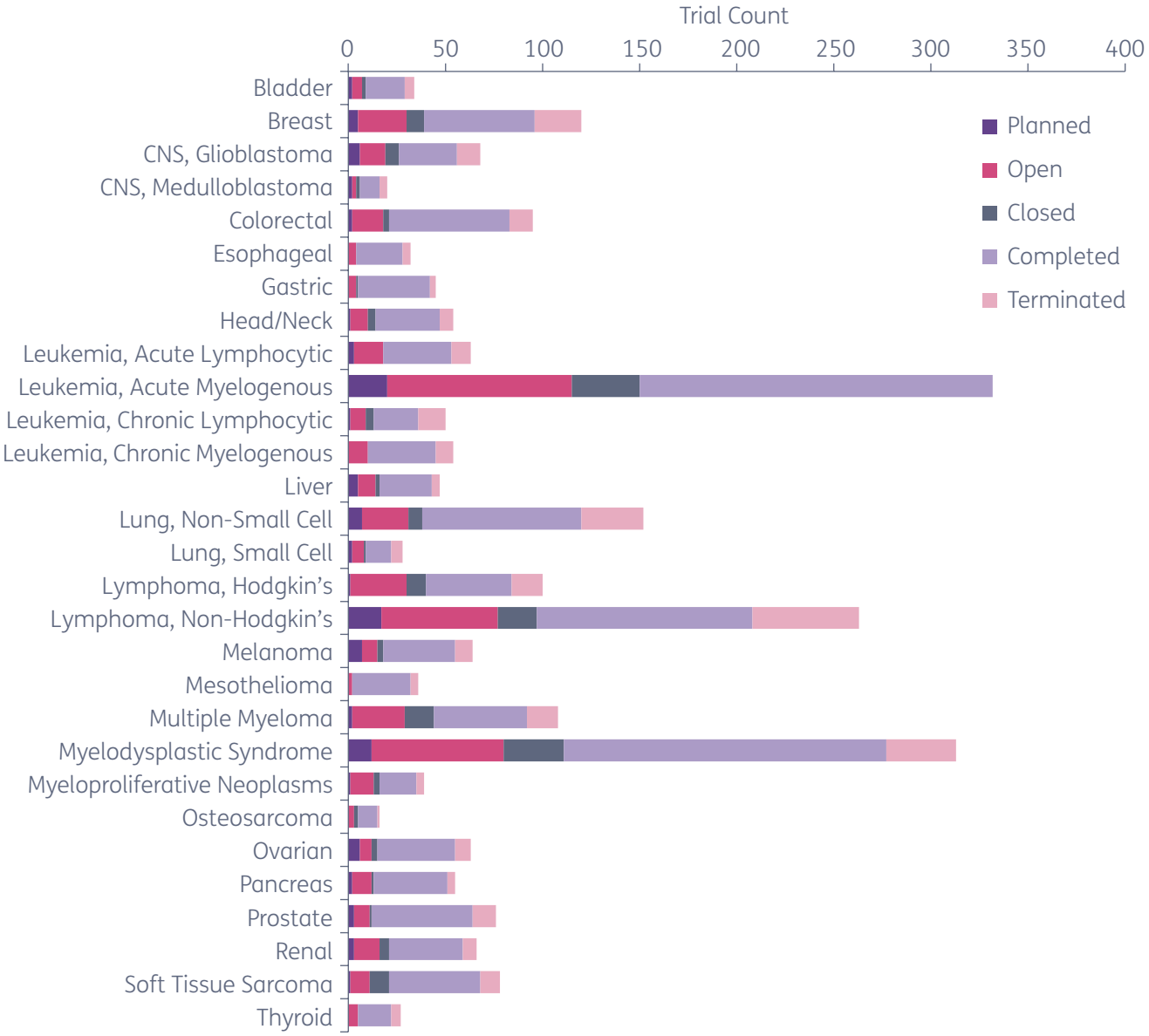
Figure 6: Top Trial Locations by Country



Source: Trialtrove®, October 2016

Epigenetic drug trials in oncology span a wide variety of malignancies, both solid and hematological (Figure 7). Diseases that included more than 100 trials were acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), non-Hodgkin's lymphoma (NHL), non-small cell lung cancer (NSCLC) and breast cancer. These same indications also contained the most ongoing and planned trials. Relative to the total number of trials within each indication, glioblastoma, AML, Hodgkin's lymphoma, multiple myeloma and myelproliferative neoplasms (MPN) had the most ongoing and planned trials.

Figure 7: Diseases with Ten or More Trials by Trial Status



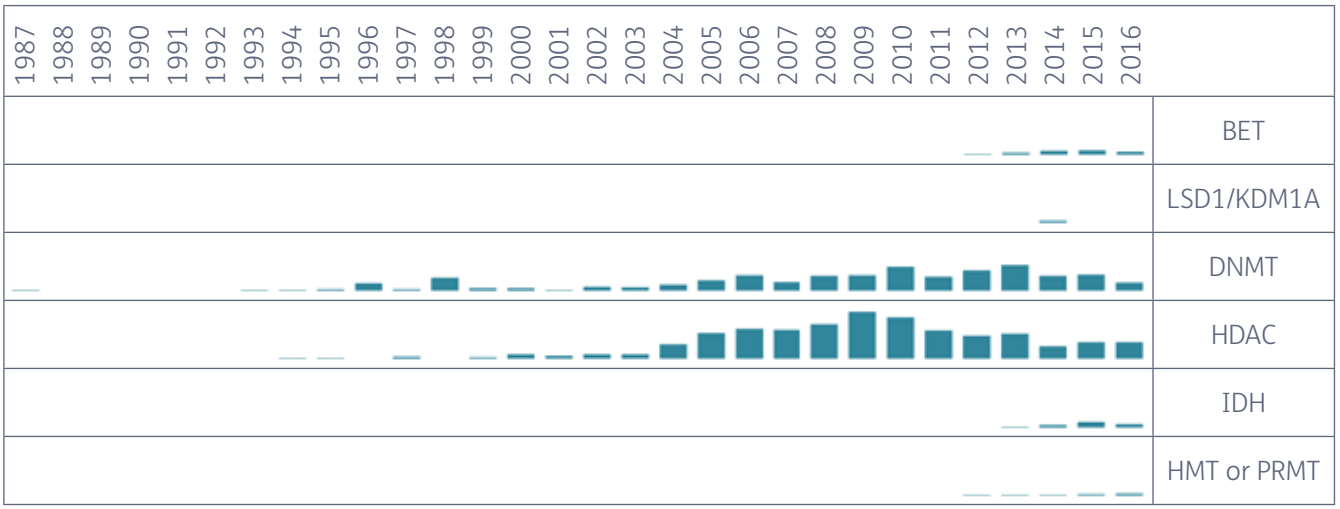
Source: Trialtrove®, October 2016

Emerging Trends

A few emerging trends should be noted for the clinical development of epigenetic drugs in oncology. Already discussed was the use of PGX biomarkers to preselect or stratify patients in ongoing and planned trials (Figure 5). Other trends to be examined include historical changes in the clinical evaluation of epigenetic drug targets, the types of combinations in ongoing and planned trials and sponsor/collaborator involvement in ongoing and planned trials.

Clinical trial activity of epigenetic drugs in oncology as determined by start year over the past three decades is shown in Figure 8. Trial activity of the DNMT inhibitors and histone HDAC inhibitors dated back to 1987 while trial activity for epigenetic drugs acting via more newly-recognized epigenetic mechanisms only dated back five years. These newer mechanisms include bromodomain and extraterminal protein (BET) inhibitors, lysine-specific demethylase 1A (LSD1/KDM1A) inhibitors, isocitrate dehydrogenase (IDH) mutant inhibitors, histone methyltransferase (HMT) and protein arginine methyltransferase (PRMT) inhibitors. The total number of trials evaluating DNMT inhibitors and HDAC inhibitors were 552 and 839 trials, respectively. The total number of trials evaluating epigenetic drugs acting via these newer mechanisms constituted just a small percentage of these totals. Only 32 trials with BET inhibitors, six with LSD1A/KDM1A inhibitors, 26 with IDH mutant inhibitors and 12 with HMT/PRMT inhibitors have been conducted (data not shown).

Figure 8: Clinical Trial Starts for Epigenetic Inhibitors

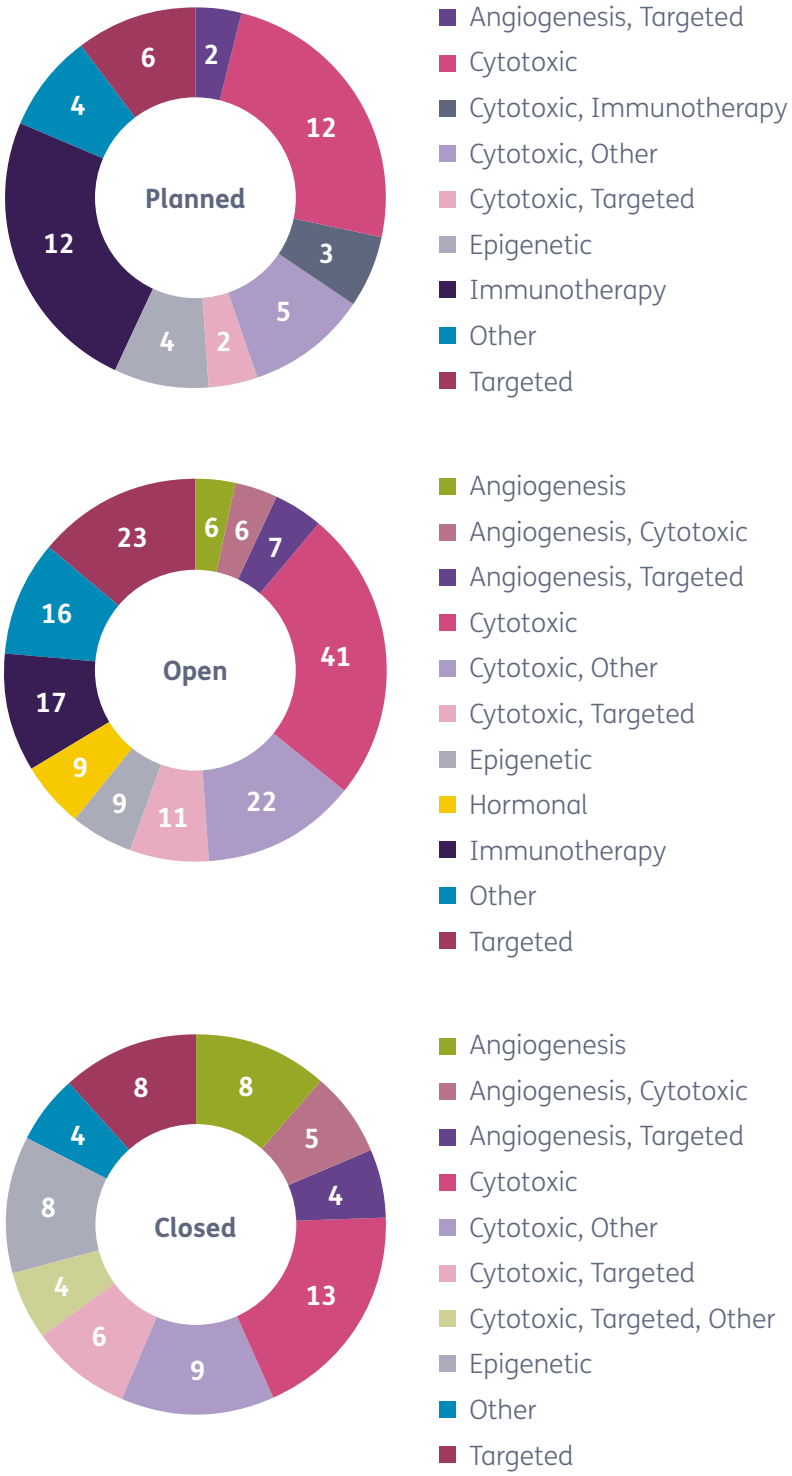


**BET – bromodomain and extraterminal protein; LSD1/KDM1A – lysine-specific demethylase 1A; DNMT – DNA methyltransferase; HDAC – histone deacetylase; IDH – isocitrate dehydrogenase mutant; HMT – histone methyltransferase; PRMT – protein arginine methyltransferase*

Source: Trialtrove®, October 2016

Another emerging trend in the clinical development of epigenetic drugs in oncology is the prevalence of combination trials in ongoing and planned trials (Figure 4). To aid in the analysis of the types of epigenetic drug combinations, drugs were categorized as Angiogenesis, Cytotoxic, Epigenetic, Hormonal, Immunotherapy, Targeted or Other. Combinations of up to seven types were evaluated in 332 ongoing and planned trials, although the majority was combinations of two or three drug types (62% and 30%, respectively). The top combinations with epigenetic drugs for 56 planned, 193 open and 80 closed trials are shown in Figure 9. Relatively consistent between trials in these three trial statuses was the use of cytotoxic and targeted drugs, alone in combination with epigenetic drugs, together in combination with epigenetic drugs or in combination with another drug type and epigenetic drugs. Notable differences include the increasing use from closed to planned of Immunotherapy combinations, the decreasing use from closed to planned of Angiogenesis combinations and inclusion of Hormonal combinations as a top drug type only in open trials.

Figure 9: Top Drug Types in Epigenetic Drug Combinations by Trial Counts

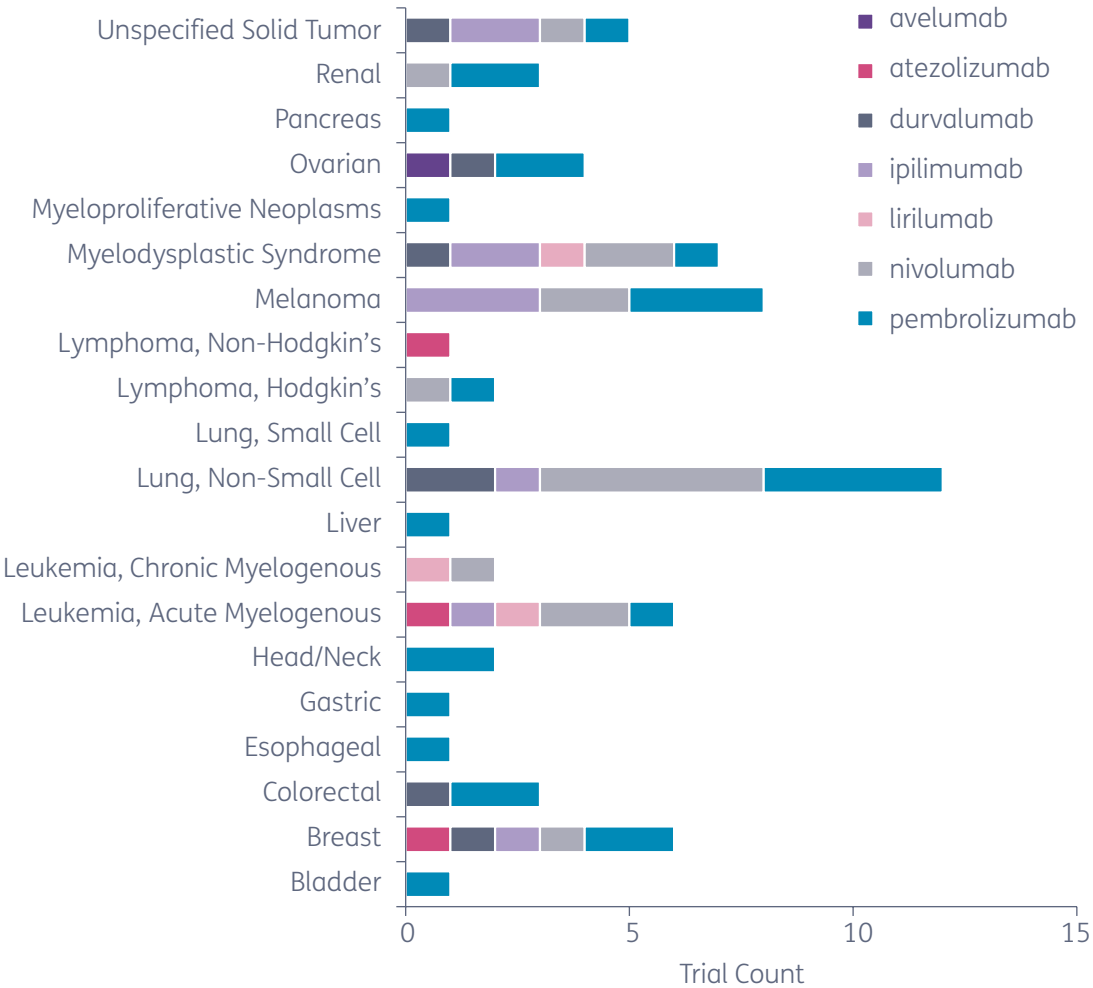


Source: Trialtrove®, October 2016

Immense interest and investment has been devoted to the clinical development of immunotherapy drugs within the past several years. Combination trials with immunotherapy drugs, both approved and unapproved for any disease, are being explored as a means to extract benefit for patients that did not/will not benefit from single agent therapy in diseases in which immunotherapy drugs are already approved or for patients in diseases that are historically difficult to treat successfully. Since epigenetic and immunotherapy combinations are an emerging trend in ongoing and planned trials, these combinations were examined more thoroughly.

Trials with the more popular immunotherapy drugs are represented by disease in Figure 10. Not shown are eight trials evaluating epigenetic drugs and peptide vaccines, peptide-pulsed cellular therapies or general immunostimulants. Epigenetic and immunotherapy combination trials occurred most frequently in diseases with approved immunotherapy drugs (e.g. NSCLC and melanoma) but also in diseases without any approved immunotherapy drugs (e.g. MDS, AML and breast cancer). Most widespread was the combination of pembrolizumab and an epigenetic drug in 18 different diseases, followed by nivolumab in nine and ipilimumab and durvalumab in six each.

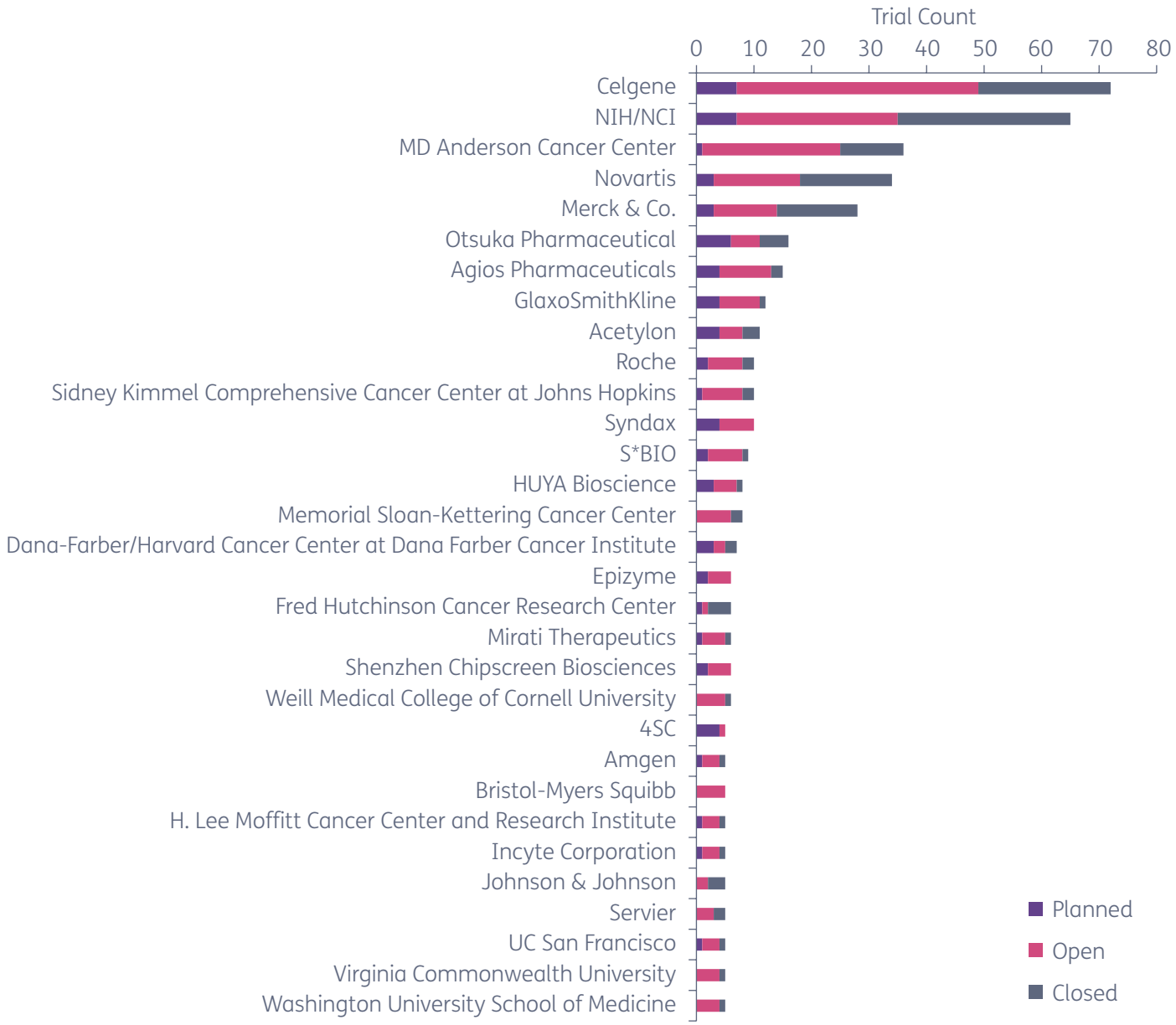
Figure 10: Epigenetic and Immunotherapy Combination Trials by Disease and Immunotherapy Drug



Source: Trialtrove®, October 2016

Sponsors/collaborators for ongoing and planned trials included a wide mix of large pharmaceutical companies, small pharmaceutical/biotech companies, university-affiliated medical centers and the National Cancer Institute at the National Institutes of Health. Industry and non-industry players that were involved with five or more trials are shown in Figure 11. The top five sponsors/collaborators by trial count included Celgene, NIH/NCI, MD Anderson Cancer Center, Novartis and Merck & Co. Among these top sponsors/collaborators, all had trials that were recruiting patients (open), while five had no trials that were ongoing but not recruiting patients (closed) and seven had no planned trials.

Figure 11: Ongoing and Planned Trials by Sponsor/Collaborator*



**Any collaborative trials were counted once for each sponsor/collaborator.*

Source: Trialtrove®, October 2016

Epigenetic Drugs and Companies to Watch

Drugs acting on newly-recognized epigenetic targets have only been in clinical development since 2012 (Figure 8). One method to predict their progress is to follow their likelihood of approval (LOA) relative to competing drugs during their clinical development. Shown in Table 2 are epigenetic drugs acting on newly-recognized epigenetic targets that have progressed beyond phase I in clinical development. Notable among these drugs are two IDH mutant inhibitors, in clinical development by Agios Pharmaceuticals in collaboration with Celgene, that have a higher LOA than other drugs in their respective phases of clinical development. Enasidenib (AG-221) and AG-120 have a 7% and 3% above average LOA for AML, respectively.

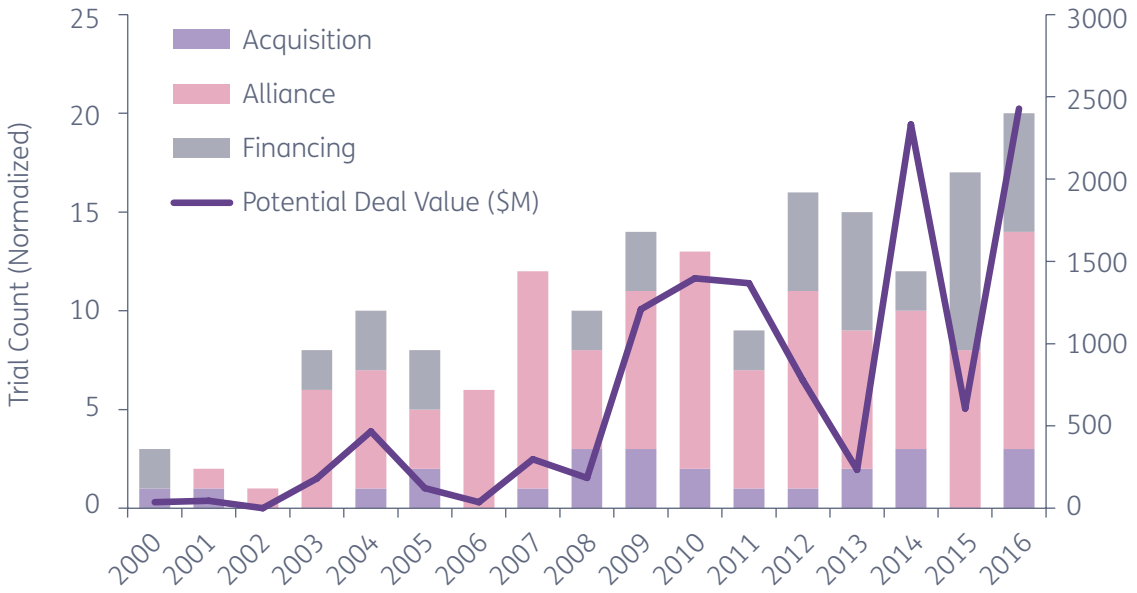
Table 2: Likelihood of Approval for Epigenetic Drugs in Oncology

Drug Name	Lead Company	Sub Disease Group	Indication Name	Current Phase	Likelihood of Approval	Target
enasidenib	Celgene Corporation	Hematologic	Acute Myelogenous Leukemia (AML)	III	42% (7% Above Avg.)	Isocitrate Dehydrogenase (IDH)
birabresib	Merck & Co.	Hematologic	Acute Myelogenous Leukemia (AML)	II	10% (Same As Avg.)	BET Proteins/ Bromodomains
birabresib	Merck & Co.	Solid	Solid Tumors	II	10% (Same As Avg.)	BET Proteins/ Bromodomains
birabresib	Merck & Co.	Solid	Brain Cancer (Malignant Glioma; AA and GBM)	II	10% (Same As Avg.)	BET Proteins/ Bromodomains
AG-120	Agios Pharmaceuticals	Hematologic	Acute Myelogenous Leukemia (AML)	I/II	13% (3% Above Avg.)	Isocitrate Dehydrogenase (IDH)
enasidenib	Celgene Corporation	Solid	Solid Tumors	I/II	10% (Same As Avg.)	Isocitrate Dehydrogenase (IDH)
BMS-986158	Bristol-Myers Squibb	Solid	Solid Tumors	I/II	10% (Same As Avg.)	BET Proteins/ Bromodomains
GSK-525762	GlaxoSmithKline	Solid	Solid Tumors	I/II	10% (Same As Avg.)	BET Proteins/ Bromodomains
INCB-54329	Incyte Corporation	Hematologic	Hematologic Cancer	I/II	10% (Same As Avg.)	BET Proteins/ Bromodomains
INCB-59872	Incyte Corporation	Solid	Solid Tumors	I/II	10% (Same As Avg.)	Lysine-specific demethylase-1 (LSD1)/KDM1A

Source: Biomedtracker®, October 2016

Companies that are pursuing clinical development of epigenetic drugs with newly-recognized targets are part of an upswing in interest and investment in this area. Evidence of this upswing is the escalating number of deals (acquisitions, alliances and financing) as well as the potential deal value from 2000-2016 (Figure 12). The top ten companies in deal activity include companies of various sizes and those with approved or just pipeline epigenetic drugs. These include Epigenomics, Syndax, Roche, Onxeo/TopoTarget, MDxHealth, Mirati Therapeutics, Celgene, GlaxoSmithKline, Epizyme and Merck & Co. (data not shown).

Figure 12: Epigenetic Deal Activity and Potential Value



Source: Strategic Transactions®, October 2016

Conclusions

Investment and interest in epigenetic drugs has dramatically increased since 2000, but only in the past several years has clinical development begun for drugs of newly-recognized epigenetic targets. Overall, only seven epigenetic drugs have been approved in oncology, and the vast majority of clinical development is still considered early to mid-stage. Clinical trials have been conducted all geographic regions, but 70% of these trials occurred in North America. Epigenetic drugs are being clinically evaluated in both solid and hematological malignancies, especially in AML, NHL, MDS, NSCLC and breast cancer. Emerging trends in ongoing and planned trials include the use of pharmacogenomic biomarkers to preselect and stratify patients, the prevalence of combinations, especially with immunotherapy drugs and the wide mix of sponsors/collaborators that are pursuing clinical development.

Pharma intelligence
informa

pharma@informa.com

United States
52 Vanderbilt Avenue
11th Floor
New York
NY 10017
USA
+1 646 957 8919
+1 888 436 3012

United Kingdom
Christchurch Court
10-15 Newgate Street
London
EC1A 7HD
United Kingdom
+44 20 7017 5000

Japan
Kotakudo Ginza
Building, 7th Floor
5-14-5 Ginza
Chuo-ku
Tokyo
104-0061
+81 351 487 670

China
23rd Floor
China Online Centre
333 Lockhart Road
Wanchai
Hong Kong
+85 239 667 222

Australia
Level 7
120 Sussex Street
Sydney
NSW 2000
+61 2 8705 6900

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