termsheet

July 2020
Issue 30

Heads of Terms

Getting better

Dr Fintan Walton
Founder & Chief Executive

Our industry is so dependent on innovation, and success is only really achieved by accessing it. The challenge has always been to find it and then back it with the minimum of risk. That, of course, is the biggest challenge and why collaborative R&D and licensing is one of the key factors in managing both access to innovation and its associated risk.

Having observed and worked in this industry for over 30 years, it is clear that we have evolved considerably and improved our ability to get efficacious and safe products more quickly to the patient. The evolution has been through a more extensive use of the partnership and coordination by the various key stakeholders. These include the innovators, the regulatory bodies, government, the financial risk takers and the pharma companies themselves. We are now better interfaced and coordinated than ever before, and this is seen through the growth of corporate venture funds, improved government grants and tax incentives (such as R&D tax credits) all working to mitigate risk and reward the risk takers. Our industry has simply got better at discovering and developing drugs.

The current coronavirus pandemic has highlighted how effective cooperation and partnership can be in our race to find a vaccine. Without our advances over the past 30 years in partnership and cooperation, I think the concept of developing a vaccine in months rather than years would not have been possible.

Industry Insight

Evolving Therapeutic Landscape of Haematological Malignancies

What Is Next?

Jisoo Choi, Associate

Haematological malignancies are types of cancers affecting blood, bone marrow and lymph nodes. Broadly speaking, there are three major types of blood cancers: leukaemia, lymphoma and myeloma. Of these, the most common blood cancer types include non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and multiple myeloma (MM). In the US, a newly diagnosed blood cancer patient is reported every three minutes, and new cases of blood cancers account for approximately 10% of all new cancer diagnoses. Also, an estimated 1.3 million people in the US are either living with or are in remission from a blood cancer. Scientific and technological advances have led to a significant improvement in five-year relative survival rates for blood cancers, having more than doubled for lymphoma and more than quadrupled for myeloma and leukaemia.

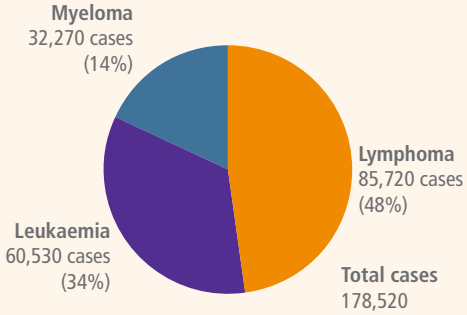

Figure 1
Estimated New Cases of Leukaemia, Lymphoma and Myeloma in 2020
Source: https://www.lls.org/facts-and-statistics/facts-and-statistics-overview/facts-and-statistics#Leukemia

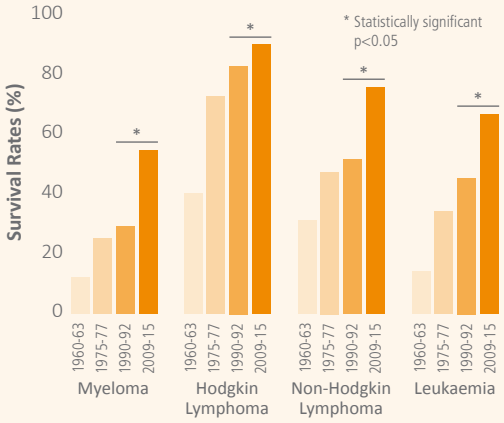

Figure 2
Five-Year Relative Survival Rates by Year of Diagnosis
Source: SEER, Cancer Statistics Review, 1975-2016. National Cancer Institute, 2019.
***Note**: 1960-63 data is for whites only*

Common treatment options for blood cancers are stem cell transplant, chemotherapy, radiation therapy and targeted therapy. Many targeted therapies (i.e. monoclonal antibodies, small molecule inhibitors, etc.) have been approved for blood cancers and some of them have established as the standard of care in specific indications. For instance, rituximab (CD20 mAb) has been widely used as part of chemoimmunotherapy for the treatment of NHL and CLL, while daratumumab (CD38 mAb) doublet/triplet combinations have rapidly established as the standard of care across all lines of therapy in MM. Ibrutinib (BTKi), an oral targeted therapy, has proven to be an effective treatment option both as a monotherapy and as combinations in CLL. However, unmet needs remain due to limitations of targeted therapies, including resistance and undruggable targets; various approaches have been adopted to overcome these limitations and develop more efficacious therapies in blood cancers.

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Emerging Therapeutic Options and Treatment Paradigm Shift

CLL

Since the approvals of two new targeted therapies, ibrutinib (BTKi) and idelalisib (PI3Ki), for the treatment of CLL in 2014, targeted therapies have provided effective treatment options as a single agent or in combination with either chemotherapy or other novel agents for CLL patients. While PI3K inhibitors remained as the choice of treatment for relapsed or refractory (r/r) CLL, BTK and BCL2 inhibitors were game-changers, expanding their use in the treat-naïve (TN) setting.

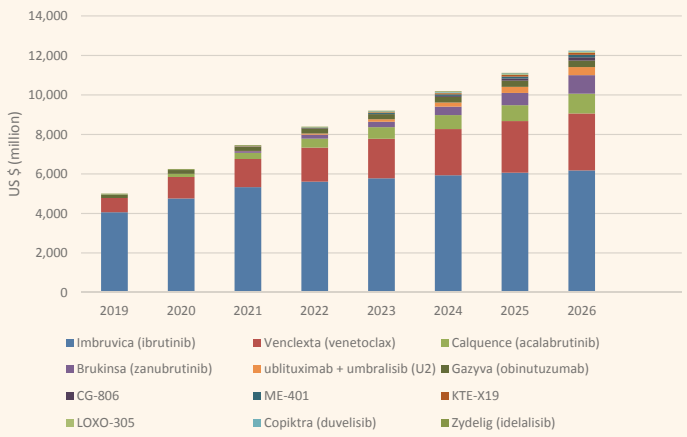

Figure 3

Annual global sales of key products in CLL (2019 – 2026).

Source: Evaluate Pharma, July 2020.

A notable trend in CLL treatment is a paradigm shift towards chemotherapy-free regimens, especially in treatment-naïve CLL (TN CLL), in which chemotherapy has been a treatment option for a long time. BTKi and BCL2i have shown superiority over chemotherapy in P3 randomised trials either as a monotherapy or in combination with CD20 mAbs, supporting the use of chemo-free regimens in CLL.

One can expect the next waves in CLL treatment to be fixed-duration (time-limited) chemo-free regimens and therapies targeting BTK-resistant or-intolerant patients. One of the first examples of this was when the FDA approved a 12-month fixed-duration treatment of venetoclax in combination with obinutuzumab for TN CLL in 2019. In addition, there are many ongoing trials evaluating the use of time-limited treatments in CLL, including BTKi + BCL2i combinations with or without CD20 mAb, with pivotal data expected from 2H 2020 onwards. Meanwhile, resistance and intolerance to BTKi has arisen from the wider use of BTKi (irreversible, covalent) in CLL. Reversible, non-covalent BTKi and PI3Ki in clinical development may have the potential to address these patient populations, positioning themselves in the post-BTKi setting.

NHL

NHL has a lot of different subtypes but can be categorised as being either indolent or aggressive, based on how the disease progresses, with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) being the most common subtypes of these two categories, respectively. Treatment and management of the two subtypes of NHL are different, however; one commonality remains in that the initial treatment for newly diagnosed patients has not changed much for a long time. Intensive chemotherapy is usually given to patients with fast-growing NHLs, whereas a highly individual approach, from watch-and-wait to chemotherapy, is adopted for indolent lymphoma, depending on various factors (e.g. stage of the disease, prognostic factors, age, or comorbidities). On the other hand, new therapeutic options, such as CAR-T or PI3K inhibitors, have become available for patients with relapsed or refractory NHL (R/R NHL).

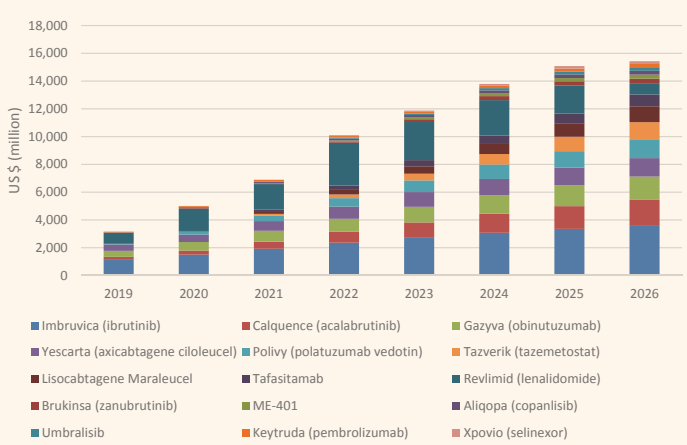

Figure 4

Annual global sales of key products in NHL (2019 – 2026).

Source: Evaluate Pharma, July 2020.

Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy specifically developed for each patient, representing a new approach to cancer treatment. Two CD19-directed CAR-T therapies (Yescarta® and Kymriah®) have been approved for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the US with the third CAR-T (lisocabtagene maraleucel) product currently under review by the FDA. Although CAR-T therapy has limitations, such as toxicities (cytokine release syndrome and neurotoxicity), complex logistics and high prices, CAR-Ts have shown encouraging efficacy in difficult-to-treat patients and are now being evaluated in earlier lines of therapy as well as in indolent lymphomas.

Polatuzumab vedotin (CD79b ADC) and selinexor (XPO1i) were also approved for r/r DLBCL after at least two prior therapies, whilst a Biologics License Application (BLA) for tafasitamab (CD19 mAb) in combination with lenalidomide is under review by the FDA. Despite these new treatment options being available in the R/R setting, rituximab-based chemotherapy remains as the standard of care in front-line (1L) DLBCL treatment. There has been an effort to improve the results of the 1L therapy by adding a targeted therapy (i.e. ibrutinib or lenalidomide) to rituximab-based chemotherapy in 1L DLBCL, however, none of them has shown superior efficacy to change the standard of care. It remains to be seen whether chemotherapy continues to be the gold standard or whether it will be challenged by potentially more efficacious therapeutic options.

For indolent NHL, three PI3K inhibitors (idelalisib, copanlisib and duvelisib) are already on the market with all of them approved for R/R FL after 2 prior therapies in the US, and the fourth one (umbralisib) is currently under the regulatory review. PI3Ki has safety concerns, including two of them carrying black box warnings on their labels, and these would likely limit wide use in NHL treatment. There have been high levels of activity across other MOAs for indolent NHL, with the FDA approving the so-called "R2" (lenalidomide and rituximab) regimen in 2019, marking the first chemotherapy-free combination in R/R indolent NHL. Also, tazemetostat, the first and only FDA-approved EZH2 inhibitor, has been recently approved for R/R FL. Data from ongoing trials evaluating the efficacy of targeted therapy (i.e. BTKi or PI3Ki) in combination with chemoimmunotherapy are expected from 2021, which if positive, may offer additional treatment options for indolent NHL. In addition, bispecific

antibodies have shown encouraging preliminary efficacy in NHL, though most of them are still in early clinical development and more data are expected in the near future.

MM

Stem cell transplant (SCT) is commonly used to treat multiple myeloma and eligibility for SCT would be considered when making a treatment decision. The other common option is drug therapy, and this is also used before the transplant to reduce the tumour burden. Many different classes of drugs are available for the treatment of MM, including chemotherapy, immunomodulating agents (lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), CD38 mAb (daratumumab, isatuximab), SLAMF7 mAb (elotuzumab), histone deacetylase (HDAC) inhibitors (panobinostat), and XPO1i (Selinexor). Use of at least two or three different kinds of drugs in combination is preferred to increase the efficacy of the treatment compared to monotherapy. Of the above drugs, daratumumab has been a huge success in MM recently, with seven approvals across all lines of therapy and the recent FDA approval of its subcutaneous formulation.

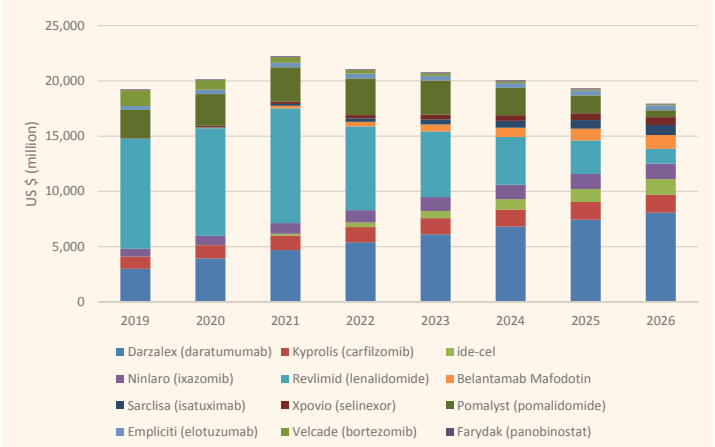

Figure 5
Annual global sales of key products in MM (2019 – 2026).
Source: Evaluate Pharma, July 2020.

B-cell maturation antigen (BCMA), a cell surface protein highly expressed on malignant plasma cells, is another therapeutic target for MM. The three most common treatment modalities used to target BCMA are CAR T-cells, antibody-drug conjugates (ADCs), and bispecific antibodies. BCMA CAR-Ts have shown impressive data in heavily pre-treated MM patients and competition is intensifying, with the first BCMA CAR-T approval expected around the end of 2020 or early 2021. BMS/Bluebird Bio plan to re-submit a BLA for idecabtagene vicleucel (ide-cel) by the end of July 2020, after receiving a Refusal to File letter from the FDA due to the insufficient Chemistry, Manufacturing and Control (CMC) data, while Janssen guides a regulatory submission for JNJ-4528 in 2020. Meanwhile, GSK's Belantamab mafodotin (GSK2857916), a BCMA ADC, would potentially be the first anti-BCMA treatment, pending results from the FDA's Oncologic Drugs Advisory Committee (ODAC) scheduled in July 2020 to review data supporting its BLA. Amgen, Janssen, Regeneron, etc. are currently developing BCMA x CD3 bispecific antibodies, mostly in early clinical development. The next couple of years would be an exciting time to see BCMA-targeted therapies entering the market, and this space is expected to continue getting more crowded, with additional drug candidates and robust clinical development plan entering the pipeline.

AML

For forty years, until 2017, standard induction chemotherapy was used for newly diagnosed AML patients eligible for an intensive chemotherapy combination of cytarabine and anthracycline, known as "7+3" (seven days of cytarabine and three days of anthracycline). Since then, the AML treatment landscape has significantly changed with the emergence of new targeted therapies, including FLT3i (midostaurin, gilteritinib), IDH1/2i (ivosidenib, enasidenib), BCL2i (venetoclax), CD33 mAb (gemtuzumab ozogamicin), hedgehog pathway inhibitor (glasdegib), and CPX-351 (a liposomal cytarabine and daunorubicin). Despite the entry of these new treatment options, 7+3 induction remains a standard of care for patients who are eligible for intensive chemotherapy, as the new treatment options have only shown a modest improvement in overall survival (OS). However, results from the Phase 3 VIALE-A trial evaluating venetoclax in combination with azacitidine, in treatment-naïve AML patients who are not eligible for intensive therapy, have shown a clear survival benefit with data recently presented at a medical conference.

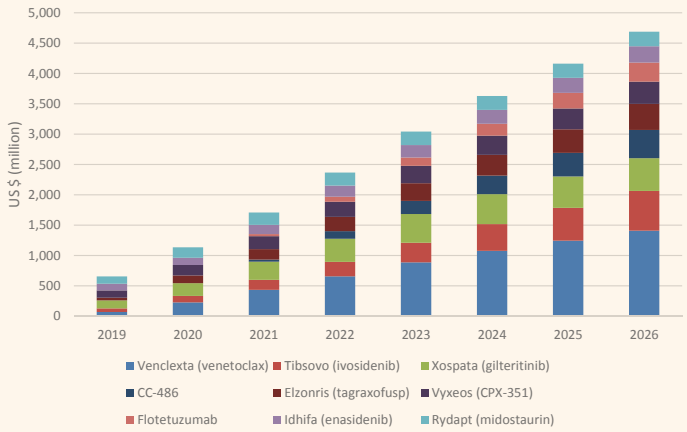

Figure 6
Annual global sales of key products in AML (2019 – 2026).
Source: Evaluate Pharma, July 2020.

CC-486 (oral hypomethylating agent) is another drug likely to be approved in the second half of 2020, and is expected to address an unmet need for maintenance treatment in AML. With a number of treatment options already available for AML, identifying actionable mutations at diagnosis and upon relapse is important when deciding the most suitable therapy for each patient. The Beat AML Master trial is using a precision medicine approach for patients with newly diagnosed AML by incorporating upfront molecular profiling at the time of diagnosis. Furthermore, combinations of novel agents or immunotherapies may provide treatments showing improved and potentially mutation agnostic efficacy in AML. Five years ago, the AML treatment landscape was frozen in time, and now it makes everyone wonder how it will look five years from now.

Deals Behind the Key Success Stories

The global haematological malignancies market is expected to grow with a CAGR of 9% between 2019 and 2026. By 2026, nearly 20 products would likely be blockbuster drugs and the estimated sales of the top three products (Imbruvica, Darzalex and Venclexta) may exceed $20 billion, accounting for almost a quarter of the global haematological malignancies market, which is forecast to be valued at ~$82 billion by 2026 . Deals play a crucial part in the development, commercialisation and success of any given drug, and these so-called mega-blockbusters in the haematological malignancies sphere are not an exception. In 2011, Pharmacyclics signed a collaboration agreement with Janssen to develop and commercialise Imbruvica, and then was acquired

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by AbbVie later in 2015. Janssen's other blockbuster, Darzalex, is also a result of its global license and development agreement with Genmab back in 2012. Venclexta is co-developed by AbbVie and Roche and jointly commercialised by AbbVie and Genentech (a subsidiary of Roche) in the US and by AbbVie outside of the US, reiterating the importance of deals and collaborations for the success of a drug.

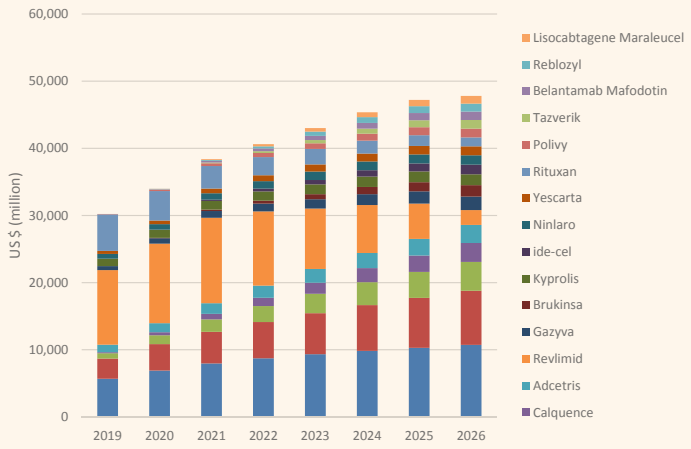

Figure 7
Annual global sales of the top 15 products in haematological malignancies (2019 – 2026). *Source: Evaluate Pharma, July 2020.*

Another area that has seen a high level of deal activity is the CAR-T cell therapy space for both CD19-targeted CAR-T cells in NHL, and BCMA-targeted CAR-T cells in MM. Three CD19 CAR-T cell therapies are currently on the market or under regulatory review by the FDA. The development pipeline is also looking robust, with Gilead and Celgene/BMS having added CAR-T cell therapies to their pipelines by acquiring Kite Pharma (Yescarta; axi-cel) in August 2017 and Juno Therapeutics (liso-cel) in January 2018, respectively. Novartis also collaborated with University of Pennsylvania to develop CAR-T cell therapies, including Kymriah (tisagenlecleucel) in 2012. Similarly, the development of the two most advanced BCMA CAR-T therapies in MM involves deals as well. Bluebird Bio and Celgene/BMS are collaborating on Ide-cel (bb2121), while Janssen has a worldwide collaboration and license agreement with Legend Biotech to develop JNJ-4528 (LCAR-B38M). Historically, innovative therapies- particularly those with first-in-class or best-in-class potential- have often been brought to the market by collaborations, on the back of license agreements and/or acquisitions. Past experience tells us that some of these recent deals and collaborations in haematological malignancies may well turn out to be another success story in the future (*Table 1*).

The total number of deals in haematological malignancies have more than doubled in the past five years, compared to the 332 deals between 2010 and 2014. Licensing agreements account for almost 60% of the total number of the deals in both timelines, representing the most popular type of deal transactions in this space. Among these deals, the proportion of research-only collaboration has increased from 19% to 27%, whereas the M&A has decreased from 13% to 6%, indicating that licensees or buyers may have become more risk-averse in their strategies to acquire the rights to the next big thing in blood cancers. The number of deals in haematological malignancies would likely further grow over time, considering the fast-evolving landscape with newly emerging therapeutic options.

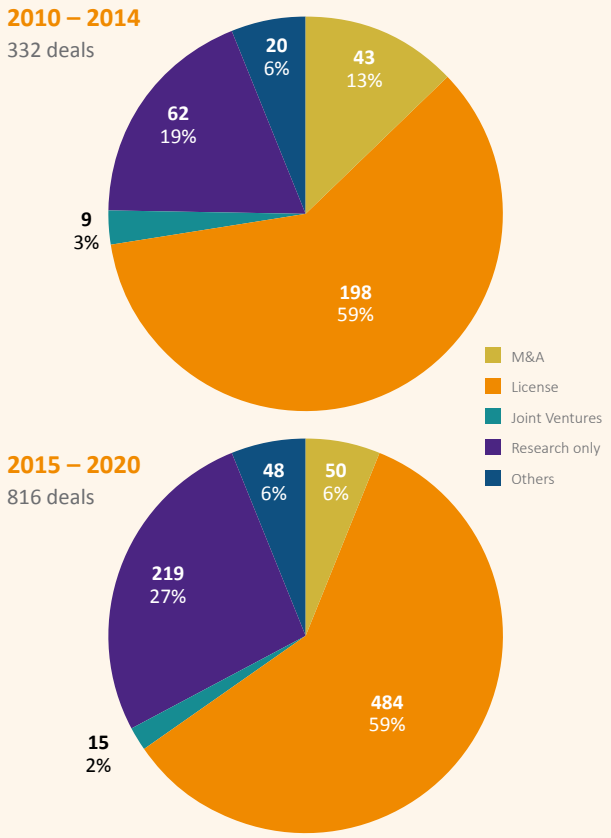

Figure 8
A breakdown of the deal types involving haematological malignancy treatments.
Source: Cortellis Deals Intelligence, July 2020.

Date	Licensor/ Seller	Licensee/ Buyer	(Lead) Product	Main Indication	Transaction Type	Total Deal Value ($M)
Dec 2011	Pharmacyclics	Janssen	Imbruvica (ibrutinib)	CLL, NHL	Strategic collaboration	975
Aug 2012	Genmab	Janssen	Darzalex (daratumumab)	MM	License	1,135
Mar 2015	Pharmacyclics	AbbVie	Imbruvica (ibrutinib)	CLL, NHL	Acquisition	21,000 ($261.25/sh)
Jun 2015	Bluebird bio	Celgene/BMS	Ide-cel (bb2121)	MM	Strategic collaboration	450
Aug 2017	Kite Pharma	Gilead	Yescarta (axi-cel)	NHL	Acquisition	11,900 ($180/sh)
Dec 2017	Legend Biotech	Janssen	JNJ-4528 (LCAR-B38M)	MM	Strategic collaboration / License	1,700
Jan 2018	Juno Therapeutics	Celgene/BMS	Liso-cel (JCAR017)	NHL	Acquisition	9,000 ($87/sh)
Jan 2020	MorphoSys	Incyte	Tafasitamab	NHL, CLL	Strategic collaboration / License	1,965
Apr 2020	MEI Pharma	Kyowa Kirin	ME-401	NHL	Strategic collaboration / License	682.5
Jun 2020	Genmab	AbbVie	Epcoritamab (CD3 x CD20 bispecific Ab)	NHL	Strategic collaboration	3,900

Table 1 *Major deals in haematologic malignancies*

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What Next?

For biotech or smaller pharmaceutical companies, partnering with big pharma companies, that already have established commercial operations and footprint in specific geographies and therapy areas, can be an effective means to minimise potential investment on the expansion of their commercial operations and allows them to focus on the further development of their pipeline.

Another notable trend is the increasing number of clinical collaborations, as shown in Figures 8 and 9. One of the main drivers behind this is the evaluating the combinations of novel therapies, which had demonstrated synergistic or promising activity in preclinical models or clinical trials with a small number of patients. On the other hand, some pharma companies have various drug candidates in their pipeline that can be used as "in-house" combination therapies, enabling them to investigate these combos without relying on striking the "right" deals or external drug sources. This is often achieved by licensing in early-stage molecules, another area in which we have seen a recent increase of deal volume.

Many novel therapies are initially approved in the US, followed by other territories (i.e. EU, Japan, or China). This can be attributed to the higher pricing that new drugs can command in the US compared to other jurisdictions, a more flexible regulatory environment in the US and additional regulatory processes, such as bridging studies, being required by the regulatory authorities of other territories. Finding local partners, especially in Japan or China, can be a good strategy for smaller companies that have limited geographical presence or development and commercialisation capabilities in these territories. Conversely, this can be an opportunity for local companies to establish partnerships with companies to add novel drugs to their pipeline and access the expertise of firms that may have more drug development and/or global commercial experience. PharmaVentures has current and recent experience in working with several leading therapeutics and precision diagnostic technologies for haematological malignancies, and as a reflection of the above points, we have recently observed an increasing number of licensing deals between big pharma and biotech companies in countries such as China and South Korea.

As science and technology take bigger leaps and the healthcare industry expands its learnings on cancer biology and the mechanisms of disease progression in haematological malignancies, one can expect to see further enrichment of the drug development pipeline and an ever-more robust global deal activity. The hope is that this explosion of research and deal activity will allow the delivery of efficacious, affordable and accessible care for the patients in need, ultimately leading to an increased quality of life and prolonged survival.

Meet the Team

Lisa Holloway
Senior Marketing Manager

Lisa Holloway joins PharmaVentures as Senior Marketing Manager, bringing over 25 years' experience across a range of marketing management roles.

Lisa began her career in the life science and healthcare industry at PharmaVentures. Her marketing experience expands across various industries such as food, automotive, nuclear, oil and gas, motorsport and defence for companies involved in performance engineering, aerodynamics and thermodynamics.

Lisa holds qualifications from the Chartered Institute of Marketing (CIM) and a certificate in Legal Practice from OCFE/Coventry University.

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Jisoo Choi
Associate

Jisoo is an Associate who brings deep pharma market knowledge across multiple indications and territories. Prior to joining PharmaVentures, Jisoo worked as an Engagement Manager for Prescient Healthcare Group, focusing on competitive intelligence and market analysis in oncology. Jisoo has worked with global pharma companies supporting their commercial and clinical development of products in various therapeutic areas.

Jisoo holds a MSc in Global Health from King's College London and BPharm from Chung-Ang University. Jisoo is a native Korean speaker and a qualified pharmacist in South Korea.

jisoo@pharmaventures.com

Kegan McColgan-Bannon
Business Analyst

Kegan joins PharmaVentures as a Business Analyst, bringing with him experience in pharmaceuticals, bioengineering and M&A.

Kegan holds a Master's in Medicinal Chemistry at Queen's University Belfast and is currently in the final stages of completing a PhD in Bioengineering and Additive Manufacturing at Newcastle University and the University of Nottingham.

During his PhD, Kegan spent three months working in M&A, gaining experience across corporate finance and strategy for mid- to large-cap companies in the chemicals industry.

In addition to undertaking a range of courses in intellectual property, entrepreneurship and business finance, Kegan attended a summer school at Durham University's Business School for Commercialising Early-Stage Technologies and is a winner of a start-up proposal competition. Kegan also has experience founding and running a commercial drinks venture.

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Team News

PharmaVentures in Action

Bio International Convention – Digital

During this convention, PharmaVentures' Senior Business Development Director, **Summer Park** met with a number of pharma and biotech companies who are aiming to achieve their strategic goals, especially at a time when connectivity is more difficult.

With more than 900 successful M&A, licensing, strategy and valuation assignments across 40+ countries over 28 years, PharmaVentures has the network, skills and experience to help companies achieve their business goals.

Conference Update

Due to the cancellation of many of the major conferences over the next few months, we hope to meet with new and existing clients via the virtual platforms that many are now offering in place of their conferences. Please look out for our future announcements.

Connect with PharmaVentures today and start maximising your reach to potential partners.

To book a telephone or video conference, please email:
enquiries@pharmaventures.com

N-Site Expert Advice Clinic

Managing Director **Adrian Dawkes** represented PharmaVentures at this first N-Site Expert Advice Clinic of the year. The clinic hosted industries such as:

- Dealmaking and Strategic Planning, PharmaVentures
- Tax Advisory, FTI Consulting
- Insurance and Risk Management, Gallagher Life Sciences Practice
- IP Strategy, Gill Jennings & Every
- Legal Advice, Taylor Wessing

About N-Site

The N-Site portal for Life Sciences companies offers a range of technical guidance on matters such as tax, legal and patent & trademark, all free to access. The portal was established by FTI Consulting in 2016 and developed with the support of MedCity and the BioIndustry Association (BIA).

N-Site was established by FTI Consulting in 2016 and developed in association with MedCity and the BioIndustry Association (BIA), the vision is that N-Site will become a primary resource for Expert Guidance for Life Sciences.
We encourage you to sign up for free to access the 100 guidance notes currently available from leading industry experts; as well as the directory of free workshops that you can register your interest in and find sector news updated on a daily basis.

For more information please visit **https://n-site.co.uk/**

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