MEDIUS DEAL WATCH

January -February 2019

A flying start to the year

It seems appropriate for our 100th issue of Deal Watch that 2019 should get off to such a flying start, namely with BMS's proposed acquisition of Celgene for a massive $74bn. For each share Celgene shareholders will receive $50 cash plus 1 BMS share (~51% premium based on the 30-day volume weighted average Celgene share price; ~54% premium on Celgene's share price on the previous day) and one tradeable CVR at $9 per share for future FDA approval of three Celgene product candidates.

BMS and Celgene certainly have complementary portfolios and combined will have nine products with annual sales over $1bn in the areas of oncology, immunology, inflammation and cardiovascular disease. The deal also brings to BMS an array of late stage product candidates; the combined company will have six near term product launches in haematology, immunology and inflammation representing potential revenue of more than $15bn. This is a very fitting acquisition given that BMS built its original oncology portfolio on in-licensed candidates.

Bristol-Myers Squibb

Celgene

Through its very active and creative deal making over the last few years Celgene also has many drug discovery, early and mid-stage partnerships to feed its pipeline. Our Annual Deal Watch reviews in previous years frequently saw Celgene featuring in the top 20 companies for deal making - both acquisition and licensing transactions. Indeed during 2016 to 2018 it agreed 24 deals with headline figures ranging up to $3.3bn, with four deals over $1bn in potential value. In 2018 alone Celgene closed deals worth over $18bn in headline value and at the end of January it entered into a $980m collaboration and option agreement with Triphase Accelerator. The deal covers TRPH-395, a preclinical stage therapeutic targeting the WDR5 protein for the treatment of haematological cancers including leukaemia. Paying $40m upfront, Celgene has the option to acquire TRPH-395 in which case it will pay up to $940m in development, regulatory and sales milestones with the potential for royalties as well. Presumably this transaction was well advanced prior to the BMS bid.

Meanwhile a few weeks are a long time in the transactional world and in recent days there has been dissent amongst two of BMS investors who say they will oppose the deal when it comes up for a vote on 12 April. One of these investors, Wellington Management which owns nearly 8% of BMS shares, stated three reasons for its decision: that the deal undervalues BMS, is risky to execute, and ignores alternative options to create value for BMS's shareholders that could be more attractive. It remains to be seen whether this shareholder revolt will be able to derail the transaction. Certainly BMS appears to be working hard to win over its investors and recent press reports citing various analysts suggest that the majority of BMS shareholders will still support the deal on 12 April.

While 2019 opened with the BMS-Celgene transaction, the rest of January seemed much more sedate in terms of deal activity, with the number of actual deals down compared to previous years. This issue's Deal Watch table notes three further $bn company acquisitions during the combined January-February period, albeit dwarfed by the size of the BMS-Celgene deal.

$bn acquisitions with a rare disease twist

Eli Lilly / Loxo Oncology

Lilly is strengthening its oncology offering via its $235 per share in cash (~68% price premium), $8bn acquisition of Loxo Oncology to access a pipeline of approved and developmental targeted medicines focused on cancers resulting from rare single gene abnormalities that can be detected by genomic testing. The Loxo portfolio includes inhibitors of molecular targets such as RET, BTK and TRK and covers a wide range of cancer types.

The oral TRK inhibitor Vitrakvi (larotrectinib), which was developed in collaboration with Bayer was approved by the FDA last November. Both Vitrakvi and LOXO-195, another TRK inhibitor, were the subject of a $1.55bn licensing and US co-promotion deal with Bayer in November 2017. Bayer has now exercised its option to obtain full licensing rights for the two TRK inhibitors under a change in control provision in its agreement with Loxo. Consequently Bayer will be solely responsible for the global development and commercialisation of both Vitrakvi and LOXO-195 (now called BAY 2731954). The co-promotion of Vitrakvi in the US will be converted into exclusive commercialisation by Bayer and Loxo will receive royalties on sales of the two products.

Despite the divestment of the two therapeutics Loxo has a number of other assets that are clearly attractive to Lilly. LOXO-292 is an oral RET inhibitor with FDA Breakthrough Therapy designation for three indications, with a potential launch in 2020. Analysts forecast annual sales for LOXO-292 of over $1bn.

Roche / Spark Therapeutics

Meanwhile and following some of its competitors, Roche is entering the gene therapy arena by buying into a portfolio of assets for rare diseases through its $4.8bn acquisition of Spark Therapeutics. The all cash transaction at $114.50 per share represents approximately 122% premium on Sparks' closing share price prior to the deal announcement.

Spark's Luxturna, a one-time adeno-associated virus (AAV) vector-based gene therapy for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, was approved in the US in December 2017 (the first FDA approval of a gene therapy product) and in the EU in November last year. While Spark markets Luxturna itself in the US, the company licensed the rights outside the US to Novartis in January 2018 for $105m upfront and $68m in milestones. Luxturna comes with a high price tag in the US, i.e. $425,000 per injection, so $850,000 for both eyes (Novartis has not yet disclosed a price for Europe). Spark reported $27m in Luxturna net product sales in the year ended 31 December 2018.

Aside from Luxturna, Spark has a pipeline of AAV-based gene therapy candidates for rare diseases at various stage of development. The most advanced are SPK-8011, a gene therapy for haemophilia A (Factor VIII deficiency) and fidanacogene elaparvovec (previously SPK-9001) for haemophilia B (Factor IX deficiency), which was partnered with Pfizer in 2014 for $20m upfront, $260m in milestones and low teen percentage royalties. In addition to rare eye and blood diseases, Spark also has early stage assets in development for Pompe disease and neurogenerative disorders, such as Huntington's disease.

Licensor Acquired/ Licensee Acquirer	Deal Type	Product / Technology	Headline ($m)
Celgene/ BMS	Acquisition - company	Portfolio includes oncology, inflammation, immunology assets	74,000
Loxo Oncology/ Eli Lilly	Acquisition - company	Pipeline of targeted cancer therapeutics	8,000
Spark Therapeutics/ Roche	Acquisition - company	Gene therapy company - has LUXTURNA™ (voretigene neparvovec) marketed in the EU by Novartis	4,800
Merck KGaA/ GSK	Development/ commercialisation alliance	M7824 (bintrafusp alfa), bifunctional fusion protein immunotherapy	4,193
Abpro/ NJCTTQ	* Licence, collaboration	Multiple bispecific antibodies based on DiversImmune™ antibody discovery platform	4,000
Adaptive Biotechnologies/ Genentech	Licence, collaboration	Neoantigen directed T-cell therapies for a broad range of cancers	2,300
Voyager Therapeutics/ Neurocrine Biosciences	Licence, collaboration	VY-AADC for Parkinson's disease, VY-FXN01 for Friedreich's ataxia, plus rights to 2 programmes	1,865
Clementia Pharmaceuticals/ Ipsen	Acquisition - company	Lead asset palovarotene (RARγ) selective agonist for fibrodysplasia ossificans progressiva (FOP), multiple osteochondromas (MO) and other diseases	1,310
Voyager Therapeutics/ AbbVie	Collaboration, option	Vectorised antibodies against tau for Alzheimer's disease, other neurodegenerative diseases	1,119
Triphase Accelerator/ Celgene	Collaboration, option to acquire programme	TRPH-395 targeting WDR5 protein for blood cancers inc leukaemia	980
Yuhan Corporation/ Gilead	** Licence, collaboration	Small molecules vs 2 undisclosed targets	785
Morphic Therapeutic/ J&J	Collaboration, option	Oral small molecule integrin inhibitors	725
Caelum Biosciences/ Alexion Pharmaceuticals	Option to acquire	Amyloid fibril-targeted therapy CAEL-101 to treat light chain amyloidosis	560
Xencor/ Genentech	Research agreement, licence	IL-15 cytokine therapeutics, inc XmAb24306 in immuno-oncology	460
MeiraGTx/ Janssen|J&J	Licence, collaboration	Gene therapies for inherited retinal diseases	440
C4/ Biogen	Collaboration	Protein degradation platform to discover treatments for neurological conditions, e.g. Alzheimer's disease, Parkinson's disease	415
Rigel Pharmaceuticals/ Grifols	† Licence, collaboration	Fostamatinib (TAVALISSE®) in chronic immune thrombocytopenia (ITP) and other indications	327.5
Spectrum Pharmaceuticals/ Acrotech Biopharma	Acquisition - assets	Portfolio of 7 FDA-approved haematology/oncology products	300
Immune Design/ Merck & Co	Acquisition - company	Vaccine-based IO and immunotherapy pipelines	300
TetraGenetics/ Imbrium Therapeutics | Purdue	Licence	To develop new, non-opioid-based biologics for treating chronic pain	273

All deals are for worldwide rights unless stated otherwise:
* China
** Excl Korea
† Europe, Turkey

RARγ, retinoic acid receptor gamma

Ipsen / Clementia Pharmaceuticals

The other billion dollar acquisition announced during the January-February period was Ipsen's $1.31bn purchase of Clementia Pharmaceuticals to bolster its rare disease portfolio. The acquisition brings a phase 3 stage asset palovarotene, a retinoic acid receptor gamma (RARγ) selective agonist for the ultra-rare/rare bone disorders fibrodysplasia ossificans progressiva (FOP), multiple osteochondromas (MO) and other diseases. Paying $25 per share in cash upfront ($1.04bn) and a CVR of $6 per share upon FDA acceptance of the NDA filing for palovarotene for the treatment of MO ($263m), this transaction brings to Ipsen an asset for which an NDA is expected to be submitted to the FDA in H2 2019 with potential approval in mid-2020. The upfront cash consideration represents a 77% premium to Clementia's 30-day volume-weighted average share price.

Gene therapy - deal frenzy in the making?

The concept of gene therapy has been discussed since the 1970s but it's only over the last few years that pharma companies have really engaged with this area. During 2018 big pharma including Pfizer, AbbVie, Astellas, J&J and Novartis entered into licence/ collaboration agreements with an array of gene therapy innovators, and Novartis acquired AveXis for $8.7bn. There were also deals amongst some smaller gene therapy players.

During January-February there were four gene therapy deals, including Roche's purchase of Spark Therapeutics. At the end of January and maintaining the retinal disease theme, Janssen signed a second deal with MeiraGTx. In this collaboration the parties will develop and commercialise gene therapies for the treatment of inherited retinal diseases (IRDs), such as achromatopsia (ACHM) caused by mutations in either CNGB3 or CNGA3 and X-linked retinitis pigmentosa (XLRP) with options to additional programmes. Janssen will pay $100m upfront and MeiraGTx could receive $340m in development and sales milestones related to the CNGB3, CNGA3 and XLRP programmes plus 20% royalties on product sales.

Under the agreement MeiraGTx and Janssen will also research potential gene therapies for other IRDs and Janssen will have opt-in rights to the programmes on IND clearance by the FDA. In the event of Janssen's opt-in, MeiraGTx will receive an opt-in payment, future potential development milestones and a high teens royalty on sales of any products.

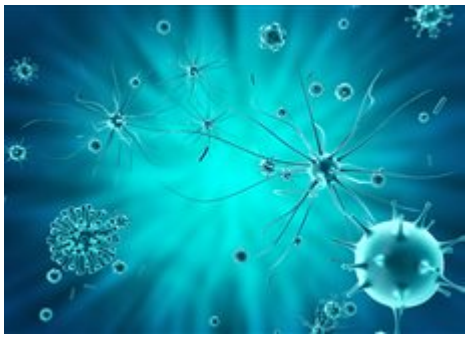
In the other gene therapy deals during the period, Voyager Therapeutics and Neurocrine Biosciences have entered into a $1.87bn collaboration on programmes for Parkinson's disease, Friedreich's ataxia and two additional programmes to be determined, and Sarepta Therapeutics has exercised its option to acquire Myonexus Therapeutics and its muscular dystrophy programmes for $165m.

And although this issue of Deal Watch focuses on January-February, it's interesting to note that on 4 March Biogen announced it was buying Nightstar Therapeutics and its pipeline of IRD gene therapy programmes for approximately $877m ($25.50 per share).

Immuno-oncology - the multi-programme approach

January-February saw a typical range of transactions scooping up multiple immuno-oncology assets with big headline values. In the largest of these, US biotech Abpro has entered into a collaboration with Chinese company NJCTTQ to discover new immuno-oncology bispecific therapeutics based on Abpro's DiversImmune antibody discovery platform for T-cell engagement. The overall deal headline of up to $4bn includes $60m in near-term R&D funding. Rather unusually for an early stage partnership, NJCTTQ only gets rights to any products generated in China. There is no information on how many programmes are included in the transaction.

Also focusing on immuno-oncology the $2bn partnership between Adaptive Biotechnologies and Genentech will utilise Adaptive's T-cell receptor (TCR) discovery and immune profiling platform (TruTCR™) to create personalised cellular therapies for patients. In return for $300m upfront, plus milestones and royalties, Genentech will receive worldwide rights.



In its second immuno-oncology alliance for the period, Genentech has entered into a research and licence agreement with Xencor paying $120m upfront to co-develop IL-15 cytokine therapeutics under a cost and profit share arrangement. The deal covers the preclinical stage XmAb24306, an engineered IL-15/IL-15Rα cytokine complex, and includes a two year discovery programme for additional IL-15 therapies. Development milestones for the XmAb24306 programme amount to $160m and Xencor could receive an additional $180m in development milestones for each new IL-15 drug candidate (including a $20m milestone on the initiation of each phase 1 trial for a new IL-15 candidate). As is typical for a US biotech, Xencor has a co-promotion option for the US.

Immuno-oncology - the pharma:pharma alliance

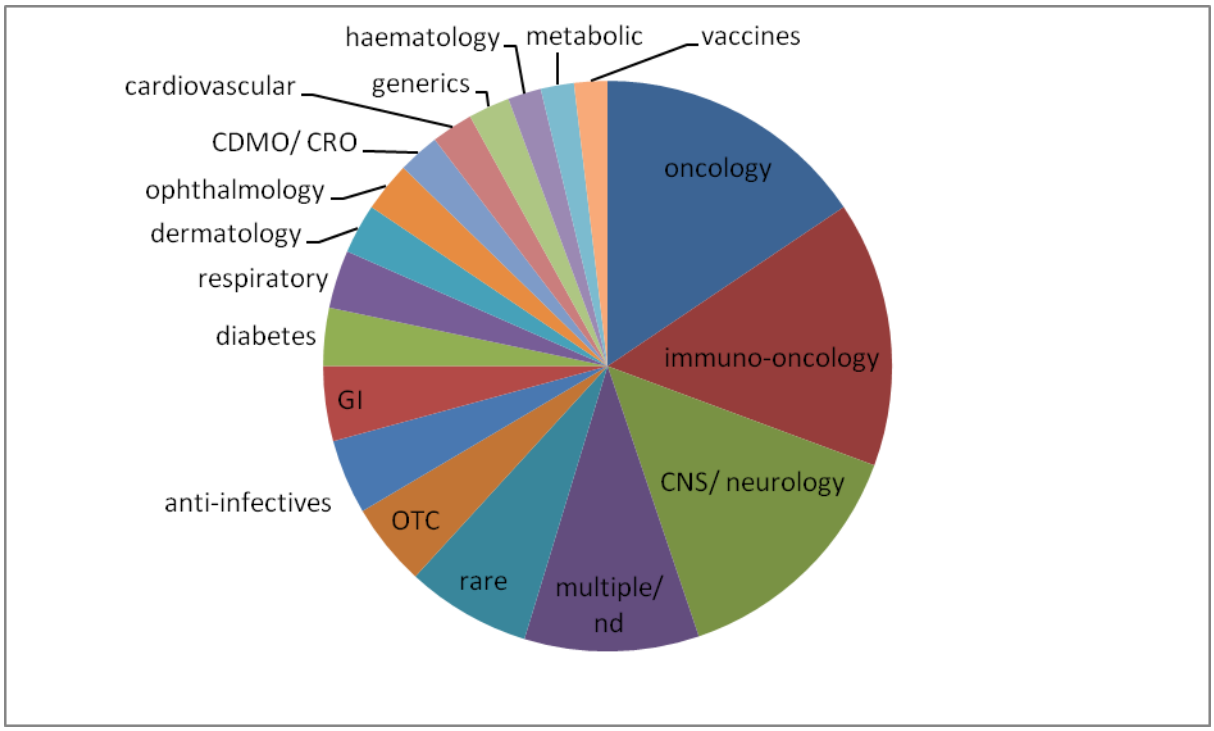
Roughly two weeks after completing its $5.1bn acquisition of Tesaro, GSK entered into a strategic collaboration with Merck KGaA to jointly develop and commercialise M7824 (bintrafusp alfa), a phase 2 stage immunotherapy with potential in difficult to treat cancers. M7824 is a bifunctional antibody that combines a transforming growth factor-β (TGF-β) trap and anti-PD-L1 mechanism in one fusion protein. In addition to ongoing clinical trials, under the alliance further studies will be initiated during 2019 covering cancers such as non-small cell lung cancer and biliary tract cancers. Both monotherapy and combination studies are being contemplated.

The financial terms of the transaction include $340m upfront payable by GSK to Merck KGaA with potential development milestones of up to $567m triggered by results from the M7824 lung cancer programme. In addition there are approval and commercial milestones of up to approximately $3.3bn. Both companies will jointly conduct development and commercialisation with all profits and costs from the collaboration being shared equally on a global basis. Merck will book US sales from the product, while GSK will account for sales outside the US.

A note on therapeutic areas

Over the last few years there has been a consistent trend with the most popular therapeutic areas for deal making being oncology, immuno-oncology and neurosciences. In our review of 236 deals announced in 2018 this trend continued with these top three areas representing ~40% of deals.

Top 18 therapeutic areas for deal making in 2018



Haematology (including rare haematology diseases) is one of those areas that does not see many deals. During 2018, only ~2.5% we reviewed were in haematology, and in 2017 ~2.7% of deals were in haematology.

In January Grifols signed an exclusive licence with Rigel Pharmaceuticals for rights to fostamatinib in Europe and Turkey for the rare blood disease chronic immune thrombocytopenia (ITP) and other indications. Marketed in the US as TAVALISSE®, fostamatinib is a SYK (spleen tyrosine kinase) inhibitor for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. Approved by the FDA in April 2018, TAVALISSE was launched by Rigel in May and had $13.9m in net product sales in the year ended 31 December 2018; the total US ITP market is estimated to be over $1bn per annum.

Rigel has already submitted a MAA for fostamatinib in chronic ITP to the EMA and anticipates potential European approval by the end of 2019. The terms of the deal include $30m upfront with regulatory and commercial milestones up to $297.5m, including a $20m payment upon EMA approval, and tiered double digit royalties on net sales, which could reach 30%.

Also under the agreement, if fostamatinib has not been approved by the EMA for the treatment of ITP in Europe in 2021, after the second anniversary of the agreement, Grifols will have the option to terminate the agreement during a six month period. Under these circumstances, Rigel will pay Grifols $25m to regain all rights to fostamatinib in Europe and Turkey. So put another way, while this is a licensing deal, the structure looks like a $5m option to fostamatinib.

Rigel is pursuing an ex-US regional licensing strategy and has already granted rights to fostamatinib in Japan, China, Taiwan and South Korea to Kissei Pharmaceuticals. Under an October 2018 licence Kissei paid $33m upfront with a potential $147m in development, regulatory and commercial milestones. Kissei will pay a product transfer price in the mid to upper 20% range based on tiered net sales.

Jill Ogden has over 30 years of commercial and R&D experience in the biopharmaceuticals and healthcare industries and provides our biologics, early stage deals and platform technologies expertise. She has worked for a number of mid-caps and biotech companies, both public and private. Jill has led and been involved in a wide range of product and technology deals, including corporate M&A.

medius associates

Signing off

With our 100th issue of Deal Watch, spanning a period of almost ten years, the Deal Watch team will be hanging up their pens. The review and analysis work will be continuing here at Medius, however finding time for publishing regular reports is proving quite challenging. We would like to thank all of our readers for their support and positive feedback over the years, it has been great fun.