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In this edition

Has the SARS-CoV-2 pandemic run its course? Low and declining deaths and hospitalisations in many regions indicate the pandemic is waning. This has implications for drug developers.

A spate of acquisitions have implications for oncology-focused biotechs.

Companies covered: **PAB, Grail, Cancer Deals, COVID-19 Clinical Trials?**

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-35.8%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 - May '15)	23.0%
Year 15 (May '15 - May '16)	33.0%
Year 16 (May '16 - May '17)	16.8%
Year 17 (May '17 - May '18)	-7.1%
Year 18 (May '18 - May '19)	-2.3%
Year 19 (May '19 - May '20)	39.5%
Year 20 (May '20 - Current)	51.9%
Cumulative Gain	1554%
Av. Annual gain (19 yrs)	17.3%

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Bioshares

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Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

Extract from Bioshares –

Major Cancer Deals in DNA Damage Repair

There is a connection between Grail's ambition (see next page) and the approach of cancer drug treatment companies which focus on tumours with damaged DNA repair systems, an area which has seen some major deals conducted recently. The two fields are linked through the provision of information about specific genetic mutations of cancers which enables new therapies to target cancers with damaged DNA repair mechanisms.

In cancer cells, DNA damage repair processes can be dysfunctional which makes those cells more dependent on the remaining repair mechanisms available. In triple negative breast cancer, 60%-69% of patients have a form with defects in DNA repair. Causing additional assault through DNA damage with chemotherapy into the cancer cell, or by interrupting additional repair mechanisms, as with PARP inhibitors in combination therapy, has become a major new and highly sought after approach to treating cancer.

Gilead Sciences Acquires Immunomedics for US$21 Billion

In April this year Immunomedics gained FDA approval for its cancer drug Trodelvy as a third line treatment for metastatic triple-negative breast cancer (TNBC). Trodelvy combines an antibody that targets the surface protein TROP-2 which is found on 90% on TNBC tumours, with a cytotoxic payload. Once attached to the cancer cell, the drug delivers a payload of SN-38 (the active metabolite of irinotecan) which the company says prevents the repair of DNA damage and causes cell death.

In a Phase III study with the drug, patients with TNBC lived for a median 5.6 months without disease progression compared to just 1.7 months for chemotherapy. The drug has already been adopted by 80% of the top 150 cancer centres in the US.

Earlier this month Gilead announced it would pay US$21 billion for the company. Market expectations are that drug sales will peak at US$4 billion for breast cancer treatment. However, Gilead is expecting additional sales in other cancer indications, with the TROP-2 protein also over expressed in the lung, prostate and pancreas.

AstraZeneca to Pay US$1 Billion for Access to TROP-2 Drug Candidate

In July, AstraZeneca announced it would pay Daiichi Sankyo US$1 billion over two years to access its TROP-2 cancer drug which is still in clinical development. Similar to the Immunomedics drug, it combines an antibody to the protein TROP-2 with an internal payload (also a topoisomerase inhibitor).

Merck to Pay Seattle Genetics US$1.6 Billion for Antibody Drug Conjugate Drug Candidate

The day after the Immunomedics deal, Merck announced that it would pay US$1.6 billion to access a Seattle Genetics antibody drug candidate (US$600 million upfront and US$1 billion in equity).

Merck and Seattle Genetics had previously combined Keytruda with the Seattle Genetics drug in metastatic or locally advanced TNBC with a 35% (mostly partial) response rate.

Cont'd over

Seattle Genetics' drug uses an antibody that targets the LIV-1 zinc transporter that is up-regulated in TNBC (as well as present in ovarian, prostate and cervical cancers). It is attached to a payload, a microtubule disrupting agent, that causes cell death once inside the cancer cell.

It is believed that the effectiveness of checkpoint inhibitors, such as Keytruda, can be enhanced when combined with drugs that cause DNA damage or inhibit repair mechanisms. Checkpoint inhibitors such as Keytruda are also known to be more effective in tumours with defects in DNA damage response pathways due to greater immune system infiltration and PD-L1 expression.

Implications for Patrys

The strong commercial activity of companies working in oncology, focusing on defects in DNA damage repair, and in conjugated drug delivery confirms the direction Patrys is taking in oncology.

Patrys' lead drug candidate, PAT-DX1, is a humanised form and fragment of the mouse lupus antibody 3E10. This antibody is attracted to cancer cells, binds to cancer cells, and infects the nucleus of cancer cells interrupting DNA damage repair.

It is also working on antibody drug candidates to use the cancer drug targeting of its antibody and cell penetration capabilities to delivery additional payloads to destroy cancer cells.

This week Patrys announced that it was expanding its portfolio with the initial production of a full sized antibody version of the fragment PAT-DX1 candidate, named PAT-DX3, which is likely to have a different half-life, as well as different tissue penetration.

Patrys expects its lead compound to enter clinical studies towards the end of next year. A transaction for its lead program may occur before then.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Grail To Be Acquired For US$8 Billion

Early this month, cancer detection company Grail Inc announced that it was set to list in the US, after having raised over US$2.0 billion since it was spun out by Illumina in 2016. Then less than two weeks later, Illumina announced that it would acquire Grail for around US$8 billion.

This announcement follows several recent blockbuster deals in the oncology space (see below) and together, give an indication of the next steps in oncology following the very successfully development of immunotherapies, including checkpoint inhibitors, which have become the backbone of the treatment of an increasing number of different cancers. These transactions have implications for locally listed biotechs specialising in oncology.

Grail's approach is to assist in the early identification of cancers in the body from blood samples, using a combination of human genomics with what it calls 'machine-learning data science." In March this year, Grail published details from its CCGA study (*Circulating Cell-free Genome Atlas*) which followed over 15,000 people, both with and without diagnosed cancer.

In a sub-group of just under 2,000 subjects, the company's test platform detected 67% of the 12 most deadly cancers at stages I-III (not the advanced stage IV). Overall it was able to detect 44% of all cancers, and remarkably, its false positive rate was just 0.7%. This is just under half of 50 different cancer types from a simple blood test, for which there is currently no screening program for 45 of those cancer types.

When a cancer signal was identified, the tissue of origin could be provided in 96% of cases with 93% accuracy.

The company believes that if all cancers at stage IV were picked up earlier, then it would result in 24% less cancer deaths. The overall five year survival rate for cancers when detected early and still localised is 89%, compared to just 21% if detected late.

The company's CMO stated that this data suggests that Grail's test could be the first example of applying the advances from the Human Genome Project to the broader population.

Grail Clinical Results to Date

Date	№ patients	Types of cancer	Results
June 2017	124	Breast. Lung, prostate	73% of all tumour mutations also detected in bloodstream
May 2018	333	Breast	21% overall with max 2% false positive rate, 56% for TNBC
June 2018	127	Lung	38%-51% detection with max 2% false positive rate
May 2019	166	Breast, lung. Liver pancreatic	87% accurate tumour of origin detection
October 2019	1264	12 cancers	76% detection (stages I-IV) at 0.7% false positive. Tissue of origin found in 97% with 93% accuracy.
March 2020	1969	50 cancers	Validation set: Detected 44% of all cancers, 0.7% false positive, tissue of origin identified in 96% of cases with 93% accuracy.
April 2020	90	Patients with suspected cancer	Validation set: 46.7% of cancers detected, 0% false positive. 79% success and 0% false positive when Stage I cancers excluded. Tissue of origin detected in 100% of cases with 97% accuracy.

Grail's CEO is Hans Bishop, who was founder and CEO of Juno Therapeutics which was sold to Celgene in 2018 for US$9 billion. Investors in Grail include Amazon and Bezos Expeditions.

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Some Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Cogstate, LBT Innovations, Opthea, ResApp Health, Pharmaxis, Dimerix, Adalta, Actinogen Medical, Patrys, Cyclopharm, Antisense Therapeutics, Imugene, Exopharm, Immutep, Neuroscientific Biopharmaceuticals, Invex Therapeutics, Anteris Technologies