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Bioshares

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

Companies covered: AVR, CHM

	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 - May '21)	86.8%
Year 21 (May '21 - Current)	9.1%
Cumulative Gain	2119%
Av. Annual gain (20 yrs)	20.7%

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Extract from Bioshares –

Chimeric Therapeutics Releases Early Phase I Data & Acquires Additional Technology

CAR T company Chimeric Therapeutics (CMP: $0.27) has released some encouraging data from its Phase I study in patients with recurrent glioblastoma, although it should be noted that it is very early data.

Of the four patients treated, at the lowest dose of 44 million cells, three of the four patients achieved disease control for up to eight weeks from a single infusion of the treatment.

There are five approved CAR T therapies on the market (see table). However, all of these are for blood-based cancers. They all target the CD19 protein on cancer cells except for Abecma which targets BCMA.

The core intellectual property behind Chimeric Therapeutics is that it uses a peptide from the scorpion chlorotoxin to target solid tumours. This peptide is engineered into extracted T-cells that are removed from patients then reintroduced as a once-off therapy. The therapy is called CLTX-CAR T.

The initial dose trialed in the first cohort was only 44 million cells. From the other approved therapies, around 200 million cells appears to be the required therapeutic dose, although that is for a systemic therapy. Chimeric Therapeutics has now started dosing the second cohort of patients who are receiving 88 million cells.

However, there is another difference between the first and second cohort. The first four patients received the injection of the re-engineered T-cells directly into the brain tumour. Cohorts two to four will receive both an injection directly into the tumour, and also into the cerebral spinal fluid (CSF) in the brain.

As can be seen from the table of approved CAR T products, the side effect profile is a major concern. It can be expected that as the therapy becomes more mainstream, the effects of the therapy will be better managed. However, CAR T products are generally prescribed as a last treatment option when all other options have been exhausted, in commercial use as a third of fifth line therapies.

In the first four patients treated with CLTX-CAR T, there were no dose-limiting toxicities, however one patient experienced a grade 3 cerebral edema that may or may not have been linked to the treatment. But as seen with the approved therapies, significant side effects should be expected. The major side effect from CAR T products is cytokine release syndrome (CRS), although management of this effect is improving. In Chimeric's study, no evidence of CRS has so far been observed. With the therapy being injected into the tumour and CSF, rather than by infusion into the bloodstream, the systemic side effect profile may be different from approved products for the treatment of blood-based cancers.

Continued over

FDA Approved CAR T Products

Therapy	Company	Indication	List Price	Efficacy	Side effects	Evaluable patients in registration study	Approved by FDA	Sales Q3 2021	Number of cells used	Target
Kymriah	Novartis (invented at Uni of Pennsylvania)	Relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)	US$474,000	83% complete remission at 3 months	9% manufacturing failure. 79% CRS (49% grade 3 or higher). 72% with neurological toxicities	63 (single arm study)	Aug-17	US$146M	$250x10^6$ (in over 50kg pts)	CD19
Yescarta	Kite Pharma (Gilead Sciences)	Large B-cell lymphoma	US$373,000	Objective response rate 72% (complete remission rate 51%)	CRS in 94% (more than grade 3 in 13% only). Neurologic toxicities in 87% (more than grade 3 in 31%)	108 (single arm study)	Oct-17	US$175M	$200x10^6$ (for 100kg pt)	CD19
Kymriah	Novartis (invented at Uni of Pennsylvania)	Large B-cell lymphoma	US$474,000	Overall response rate 50% (including 32% complete response)	74% CRS (23% grade 3 or higher). 6.9% manufacturing failure	68 (single arm study)	May-18	US$146M	$0.6\text{-}6.0 \times 10^8$	CD19
Tecartus	Kite Pharma (Gilead Sciences)	Mantle cell lymphoma	US$373,000	Objective response rate 87% (complete remission rate 62%)	91% CRS (18% with more than grade 3 CRS)	60 (single arm study)	Jul-20	US$47M	$200x10^6$ (for 100kg pt)	CD19
Breyanzi	Celgene (BMS)	B-Cell lymphoma	US$410,300	73% overall response rate with 54% complete response	46% with CRS, although only 4% with grade 3 or higher. (8% recovered with median duration of 5 days.	192 (single arm study)	Feb-21	US$30M	$50\text{-}110 \times 10^6$	CD19
Abecma	Celgene (BMS)	Multiple myeloma (following failing four lines of therapy)	US$419,000	72% Objective Response Rate (ORR), complete response in 28% of patients	9% of pp with CRS grade 3 or higher	100 (single arm study)	Mar-21	US$71M	$150\text{-}450 \times 10^6$	BCMA
Yescarta	Kite Pharma (Gilead Sciences)	Relapsing remitting follicular lymphoma (iNHL)	US$373,000	Objective response rate 91% (complete remission 60%)	88% CRS (10% with more than grade 3 CRS)	81 (single arm study)	May-21	US$175M	$200x10^6$ (for 100kg pt)	CD19
Tecartus	Kite Pharma (Gilead Sciences)	Relapsing/remitting B-cell precursor ALL	US$373,000	52% complete response rate	92% CRS (26% with more than grade 3 CRS)	54 (single arm study)	Oct-21	US$47M	$100x10^6$ (for 100kg pt)	CD19

Notes

Bristol-Myers Squibb acquired Celgene in 2019 for US$74 billion

Gilead Sciences acquired Kite Pharma in 2017 for US$11.9 billion

Conversely, the treatment effect of CAR T products is exceptionally good; complete response rates / complete remission rates for approved therapies are 28%, 32%, 51%, 52%, 54%, 60%, 62% and 83% for the eight approved indications.

The patient population that Chimeric Therapeutics is targeting has a life expectancy of around six months. So stable disease at the lowest dose in three of four patients is a good initial outcome. Biologic activity of the cells was also measured in the tumour, indicating continued therapeutic action.

Activity was also noted in one patient where the treatment was injected with no tumour recurrence two months after treatment; whilst there was tumour growth observed in sections of the brain that had not received direct injection of the therapy. As noted above, patients are now receiving a direct injection into the brain tumours as well as cells being injected into the CSF in the brain.

Chimeric Therapeutics is currently in the second cohort of patients (88 million cells) with the third cohort expected to open early next year (220 million cells). Additional sites are also expected to open in the first half of next year, with the trial currently being conducted at the City of Hope Cancer Centre.

The company intends to start a Phase I study next year with a second CAR T program, CDH17 CAR T, which was in-licensed from the University of Pennsylvania (where Kymriah was invented). This is a third generation CAR T technology that targets CDH17, which is present on neuroendocrine tumours as well as gastrointestinal tumours.

High Level Management Team and SABs

In August this year Chimeric appointed Jennifer Chow as CEO. Chow is highly experienced in CAR T products having worked on four of the five approved therapies (Yescarta, Tecartus, Breyanzi and Abecma). Chow was formerly Head of Global Marketing Analytics and Commercial Operations at Kite Pharma. And she was the Global Cell Therapy Commercial Lead at Celgene. Both companies have since been acquired. (Kite Pharma by Gilead Sciences in 2017 for US$11.9 billion, and Celgene by Bristol-Myers Squibb in 2019 for US$74 billion.)

Chow said that an incredible amount has been learnt about CAR T with thousands of patients now treated. All CAR T products have been approved on single arm, Phase II studies. With respect to animal models, Chow said that these are very good with the data translating even better into humans than expected. With respect to the chlorotoxin peptide, Chow said that this has very strong activity to glioblastoma cells.

CAR T therapies command very high pricing, being a once off therapy with stunning efficacy results. Chow believes that payors have been comfortable so far with reimbursing these products.

The company has also installed a highly experienced glioblastoma Scientific Advisory Board and a Cellular Immunotherapy Scientific Advisory Board which comprises of 10 experts in these respective fields.

Continued over

The company's team also includes a CMO, Business Development and a Technical Operations manager who were from Celgene, Kite Pharma and Celgene and from BMS/Celgene respectively.

In-Licences Allogeneic Natural Killer Cell Program

This week Chimeric announced the acquisition of a third technology, that being an allogenic, natural killer (NK) cell immunotherapy platform from Case Western University. This technology expands the existing technology to offer allogenic (off-the shelf) treatments to not just solid tumours but also blood-based cancers. The company expects to have at least eight trials underway or completed by the end of 2023 in 10 different disease areas.

Case Western Reserve University has completed dosing in a Phase I study with its NK cell technology. That trial has treated nine patients with a range of solid and blood-based cancers. Results are expected in May next year.

In 2023, Chimeric intends to start four additional studies with this technology. The first will be with a next generation NK technology. Two other studies will be conducted that will combine the NK technology with the proprietary CLTX and CDH17 targeting domains already in development, also using chimeric antigen receptors (CAR). The fourth study focus is on an undisclosed target.

This year has seen three significant NK drug development deals completed by Merck (including a CAR NK program), BeiGene and Kite Pharma (Gilead) in addition to previous deals signed by Takeda and Janssen (Johnson & Johnson) for CAR NK technology programs and an NK technology deal completed by Sanofi.

Summary

Chimeric Therapeutics is following a similar and successful portfolio strategy to Imugene, where it is in-licensing a suite of discrete immune-oncology drug development assets and is seeking to progress the assets through to rapid proof-of-concept studies.

Chimeric Therapeutics is capitalised at $90 million.

Bioshares recommendation: **Speculative Buy Class A**

(The stock has been added to the Bioshares Model Portfolio)

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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 of 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, Antisense Therapeutics, Imugene, Exopharm, Immutep, Neuroscientific Biopharmaceuticals, Invex Therapeutics, Anteris Technologies, Chimeric Therapeutics, Neuren Pharmaceuticals, Neurotech International