EDISON

Chimeric Therapeutics

Development update

Acquiring a promising first-in-class CAR T asset

Pharma & biotech

Chimeric recently announced that it will be licensing a chimeric antigen receptor t-cell (CAR T) programme targeting cadherin 17 (CDH17) from the University of Pennsylvania. Specific financial terms are undisclosed, but they include an upfront fee, annual maintenance fees, milestones and a royalty (likely single digit, in our view). A CDH17 CAR T may have broad applicability in solid tumours, particularly in neuroendocrine, colorectal, pancreatic and gastric cancers. Importantly, preclinical evidence suggests the therapy may be able to eradicate tumours with little to no toxicity to normal tissues. The CDH17 CAR T is expected to enter the clinic in 2022.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (A$)	DPS (A$)	P/E (x)	Yield (%)
06/20	0.0	(0.1)	(62.01)	0.0	N/A	N/A
06/21e	0.0	(12.0)	(0.04)	0.0	N/A	N/A
06/22e	0.0	(14.0)	(0.04)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Targeting tumours while sparing normal cells

CDH17 is a very tumour-specific antigen with limited expression in normal cells (expression is limited to the tight junction of intestine that biologics typically do not reach). However, CDH17 is highly expressed in numerous solid tumours, such as colorectal, high-grade pancreatic, gastric and certain neuroendocrine tumours (NET) and is involved with tumour cell proliferation, cell adhesion, migration, invasion and clonogenicity.

Efficacy demonstrated in preclinical testing

In preclinical testing, CDH17 CAR T cells were able to eradicate NETs in vivo with no relapse seen. Importantly, no toxicity was seen in normal cells. This has historically been a major hurdle for solid tumour targeting CAR T therapies.

A large unmet need in solid tumours

There are currently no approved CAR T therapies for solid tumours so the current leading therapies for neuroendocrine, colorectal, pancreatic and gastric cancers are somewhat more traditional. Nevertheless, the combined sales for treatment of these cancers exceeded US$10.7bn in 2020 according to Evaluate Pharma.

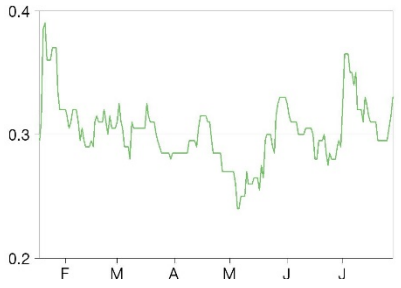
Valuation: A$327m or A$0.99 per share

We have increased our valuation to A$327m or A$0.99 per share, from A$307m or A$0.93 per basic share, mainly due to rolling forward our NPV. This was partially offset by lower net cash. Because the CDH17 programme is not yet in the clinic, we are not including it in our valuation yet, in accordance with Edison methodology. Once included, it may have a meaningful impact upon the valuation due to the size of the markets targeted by the company. Chimeric reported A$22.4m in cash as of 30 June 2021. Due to the increased R&D associated with another CAR T programme, we have increased our projected financing need through 2026 from A$52.5m to A$80m.

29 July 2021

Price	**A$0.33**
Market cap	**A$109m**
	A$1.30/US$
Net cash (A$m) at 30 June 2021	22.4
Shares in issue	330.9m
Free float	33.2%
Code	CHM
Primary exchange	ASX
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	13.8	24.5	N/A
Rel (local)	12.6	19.2	N/A
52-week high/low	A$0.39		A$0.24

Business description

Chimeric Therapeutics is an oncology-focused Australian-based company that recently went public on the ASX. The lead programme is CLTX-CAR T, currently in Phase I for the treatment of GBM. This is an innovative approach for an unmet medical need. Beyond GBM, the technology may have applicability for other tumours such as melanoma. The company recently in-licensed a CDH17 CAR T for use in solid tumours.

Next events

CLTX CAR T data update	Autumn 2021

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Edison profile page

Targeting the solid tumour holy grail

Chimeric recently announced that it will be licensing a CAR T programme targeting CDH17 from the University of Pennsylvania, a world-renowned leader in CAR T therapy research that was the source of Kymriah (tisagenlecleucel), the world's first approved CAR T therapy. As a reminder, CAR T therapies have helped revolutionise the treatment of certain cancers. CAR T therapies work by engineering the body's immune T-cells to recognise cancer cells as they would invading or diseased cells. Novartis's Kymriah, which we mention above, was the first CAR T therapy approved in the US (in 2017) and was approved for relapsing B-cell acute lymphoblastic leukemia in children and young adults. Kymriah consisted of a one-time treatment that had an 83% complete response rate in clinical trials with patients who did not respond to standard treatments. Like many revolutionary cancer therapies, Kymriah was priced at a premium of US$475,000 for the treatment. Kymriah sales in 2020 were US$474m with current consensus expectations for 2026 sales at US$1.2bn according to Evaluate Pharma. A second therapy, Yescarta, was approved later in 2017 in patients with large-B-cell lymphomas whose cancer has progressed after receiving at least two prior treatment regimens. The therapy demonstrated a 51% complete response rate and has a price of US$373,000 per treatment. Sales in 2020 for Yescarta were US$563m with consensus expectations for US$1.2bn in sales in 2025 according to Evaluate Pharma. It is important to note that Gilead acquired Yescarta through its purchase of Kite Pharmaceuticals for US$11.9bn.

CDH17 is a very tumour-specific antigen with limited expression in normal cells (its expression is limited to the tight junction of intestine that biologics typically do not reach). However, CDH17 is highly expressed in numerous solid tumours, such as colorectal, high-grade pancreatic, gastric and certain NETs among others (see Exhibit 1).

Exhibit 1: CDH17 expression in select tumours

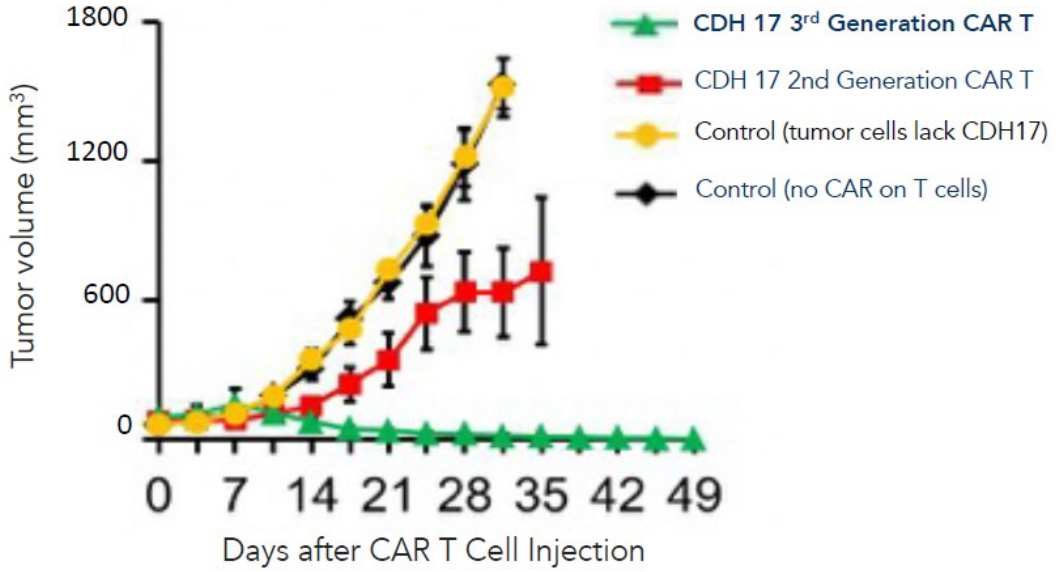
Cancer	CDH17 expression (% of samples)
Colorectal	100%
Gastric	90%
Pancreatic	50%
Oesophageal	82%
Neuroendocrine - Small intestinal	100%
Neuroendocrine - Appendiceal	100%
Neuroendocrine - Pancreatic	12%
Neuroendocrine - Bronchial	24%

Source: Panarelli et al., Tissue-specific cadherin CDH17 is a useful marker of gastrointestinal adenocarcinomas with higher sensitivity than CDX2. *American Journal of Clinical Pathology* 2012 Aug;138(2):211-22.

CDH17 has been shown to be involved with tumour cell proliferation, cell adhesion, migration, invasion and clonogenicity and has been associated with poorer prognosis.[1] Importantly, in preclinical testing, CDH17 CAR T cells were able to eradicate NETs in vivo with no relapse seen (see Exhibit 2).

1 Qiu et al., Targeting CDH17 Suppresses Tumor Progression in Gastric Cancer by Downregulating Wnt/β-Catenin Signaling. *PLoS One*. 2013; 8(3): e56959.

Exhibit 2: Efficacy of CDH17 CAR T in mouse models



Source: Chimeric Therapeutics

Importantly, no toxicity was seen in normal cells. This has historically been a major hurdle for solid tumour targeting CAR T therapies. If the target antigen is also found in normal cells, catastrophic toxicities can result. In one case involving a breast cancer patient who received an HER2 targeting CAR T, just 15 minutes after cell infusion the patient started experiencing respiratory distress and then died five days after treatment from multi-organ failure due to systematic microangiopathic injury[2]. Of course, there are other issues that have hampered solid tumour CAR T development, including suboptimal infiltration into tumour tissue and the immunosuppressive tumour microenvironment affecting efficacy.[3] It is yet to be seen if the CDH17 CAR T from Chimeric will be able to overcome these issues in humans. The in-licensed CDH17 CAR T construct does include CD28 and 4-1BB costimulatory domains, which have shown evidence of enhancing CAR T cell persistence and survival.[4,5]

While there are a number of CAR T programmes targeting solid tumours, the CDH17 CAR T that Chimeric has licensed appears to be the only one that includes CDH17 as the target. However, there are two programmes targeting CDH17 in cancer through other approaches. Boehringer Ingelheim has a bispecific antibody (BI 905711) targeting CDH17 and TRAILR2. It is currently in Phase I development for advanced gastrointestinal cancer with 140 subjects expected to be enrolled. Completion of the study is expected in 2023. Arbele Bio is a Hong Kong based start-up, that is developing ARB202, a bispecific CDH17/CD3 t-cell engager (TCE) about to enter Phase I for refractory pancreatic/bile duct cancers. The company is also working on ARB001, a CDH17-CAR NK, which is in preclinical development targeting metastases in the liver.

2 Morgan et al., Case Report of a Serious Adverse Event Following the Administration of T Cells Transduced With a Chimeric Antigen Receptor Recognizing ErbB2. *Molecular Therapy* vol. 18 no. 4, 843–851 apr. 2010

3 Marofi et al., CAR T cells in solid tumors: challenges and opportunities. *Stem Cell Research and Therapy* (2021) 12:81

4 Savoldo et al., CD28 costimulation improves expansion and persistence of chimeric antigen receptor–modified T cells in lymphoma patients. *The Journal of Clinical Investigation* 2011;121(5):1822–1826.

5 Philipson et al., 4-1BB costimulation promotes CAR T cell survival through noncanonical NF-κB signaling. *Science Signaling*. 31 Mar 2020: Vol. 13, Issue 625, eaay8248

The target markets

As mentioned, Chimeric will focus development on neuroendocrine, colorectal, pancreatic and gastric cancers. With regards to NETs, it is a very heterogeneous cancer given the multiple areas where these tumours may proliferate. About 43% develop in the gastrointestinal tract, 30% in the lung and the rest in various other areas. CDH17 seems to be particularly highly expressed in the gastrointestinal NETs and we would expect this subgroup to be the focus of development in this indication by the company. In total about 12,000 people are diagnosed in the US with a NET each year and another 175,000 are living with the diagnosis. Survival rates can vary widely based on the type of NET and the site at which it is found. The five-year survival rate at diagnosis for an advanced (distant) NET found in the colon is only 14%, while that number grows to 54% if found in the ileum (part of the small intestine).

Exhibit 3: Incidence, survival and sales in target indications

	Incidence (US)	Five-year survival at diagnosis for advanced (distant) cancer	2020 worldwide sales in the indication (US$m)	Top selling drug (and 2020 sales)
NET	12,000	14-54%	1,435	Somatuline from Ipsen (US$801m)
Colorectal	149,500	15%	7,170	Avastin from Roche (US$3.1bn)
Pancreatic	60,430	3%	790	Abraxane from Bristol Myers (US$556m)
Gastric	26,560	6%	1,333	Aitan from Jiangsu Hengrui Medicine (US$389m)

Source: National Cancer Institute, Evaluate Pharma, Canadian Cancer Society, Cancer.net

Colorectal would be the largest market of all the target indications, with 149,500 cases estimated for 2021. The five-year survival rate at diagnosis for advanced (distant) colorectal cancer is only 15%. The largest drug servicing this market is Avastin, which had sales of US$3.1bn in the indication according to Evaluate Pharma. In total colorectal cancer drugs had sales of $7.2bn per year in 2020. The National Cancer Institute forecasts 60,430 new cases of pancreatic cancer for 2021. The five-year survival for all cases was just 11%, with that of advanced (distant) pancreatic cancer at diagnosis only 3%. As mentioned before, CDH17 is only expressed in about half of pancreatic cancers, but providing help for just half is better than none and we would expect patients to be tested for CDH17 prior to enrolment. Gastric cancer has about 26,560 cases expected this year and the five-year survival at diagnosis for an advanced (distant) gastric tumour is less than 6%. So, this indication is clearly an unmet medical need, almost to the same level as pancreatic cancer.

Chimeric's lead programme CLTX CAR T continues to progress through its Phase I trial in 18–36 progressive or recurrent glioblastoma patients. The first patient in the second cohort has received treatment, which consisted of intracranial intratumoral and intracranial intraventricular dosing. The target dose is 88m CLTX CAR T cells, up from 44m in the first dosing cohort, which enrolled four patients who exhibited no dose-limiting toxicities from therapy. The company anticipates the release of a data update in the autumn of 2021 and also an expansion into other solid tumours in 2022.

Valuation

We have increased our valuation to A$327m or A$0.99 per share, from A$307m or A$0.93 per basic share, mainly due to rolling forward our NPV. This was offset in part by lower net cash. Because the CDH17 programme is not yet in the clinic, we are not including it in our valuation yet, per Edison standard methodology. Once included, it may have a meaningful impact upon our valuation due to the size of the markets targeted by the company. To provide some perspective, we attribute a A$305m value to CLTX CAR T, a Phase I programme targeting GBM which has a US incidence of around 12,000 per year. Total incidence for the cancers targeted by the CDH17 programme is estimated to be 248,490 in the US. Hence this may be a truly transformational acquisition by the company.

Exhibit 4: Chimeric valuation table

Product	Main Indication	Status	Probability of successful commercialization	Approval year	Peak sales (A$m)	Economics	rNPV (A$m)
CLTX-CAR T	GBM	Phase I	10%	2027	3,210	100% less single digit royalty to COH	305.0
Total							305.0
Net Cash (as of June 30, 2021)							22.4
Total firm value (A$m)							**327.40**
Total basic shares (m)							330.9
Value per basic share (A$)							**0.99**
Options (m)							23.0
Total number of shares (m)							353.9
Diluted value per share (A$)							0.93

Source: Edison Investment Research

Financials

In the quarterly cash flow report for the fourth quarter of FY21 (the period ending 30 June 2021), Chimeric reported A$22.4m in cash. Due to the licensure of the CDH17 CAR T programme, we have increased our projected financing need through 2026 from A$52.5m to A$80m (including A$20m in FY22) as we now forecast additional R&D spending (including A$2.7m in FY22). Specific financial terms of the CDH17 CAR T programme licensing are undisclosed, but include an upfront fee, annual maintenance fees, milestones and a royalty (likely single digit, in our view). The company has stated that the license fees will be funded entirely through existing cash reserves.

Exhibit 5: Financial summary

A$'000s	2020	2021e	2022e
Year end 30 June	AIFRS	AIFRS	AIFRS
PROFIT & LOSS			
Revenue	0	0	0
Cost of Sales	0	0	0
Gross Profit	0	0	0
Sales, General and Administrative Expenses	(64)	(7,203)	(4,007)
Research and Development Expense	0	(4,836)	(9,975)
EBITDA	(64)	(12,039)	(13,982)
Operating Profit (before amort. and except.)	(64)	(12,039)	(13,982)
Intangible Amortisation	0	0	0
Other	0	0	0
Exceptionals	0	0	0
Operating Profit	(64)	(12,039)	(13,982)
Net Interest	0	0	0
Other	0	0	0
Profit Before Tax (norm)	(64)	(12,039)	(13,982)
Profit Before Tax (FRS 3)	(64)	(12,039)	(13,982)
Tax	0	0	0
Deferred tax	(0)	(0)	(0)
Profit After Tax (norm)	(64)	(12,039)	(13,982)
Profit After Tax (FRS 3)	(64)	(12,039)	(13,982)
Average Number of Shares Outstanding (m)	0.0	335.5	338.9
EPS - normalised (c)	(6,200.80)	(3.59)	(4.13)
EPS - Reported ($)	(63.02)	(0.04)	(0.04)
Dividend per share (c)	0.0	0.0	0.0
BALANCE SHEET			
Fixed Assets	0	17,466	20,863
Intangible Assets	0	17,457	20,024
Tangible Assets	0	9	839
Other	0	0	0
Current Assets	(0)	27,211	30,278
Stocks	0	0	0
Debtors	0	0	0
Cash	(0)	22,410	25,109
Other	0	4,801	5,169
Current Liabilities	(64)	(16,219)	(16,219)
Creditors	(30)	(16,219)	(16,219)
Short term borrowings	(34)	0	0
Long Term Liabilities	0	0	(20,000)
Long term borrowings	0	0	(20,000)
Other long term liabilities	0	0	0
Net Assets	(64)	28,458	14,922
CASH FLOW			
Operating Cash Flow	(34)	(8,463)	(13,882)
Net Interest	0	0	0
Tax	0	0	0
Capex	0	(5,354)	(3,419)
Acquisitions/disposals	0	0	0
Financing	0	31,966	0
Dividends	0	0	0
Other	0	0	0
Net Cash Flow	(34)	18,149	(17,301)
Opening net debt/(cash)	0	34	(22,410)
HP finance leases initiated	0	0	0
Exchange rate movements	0	0	0
Other	0	4295	0
Closing net debt/(cash)	34	(22,410)	(5,109)

Source: Company reports, Edison Investment Research

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