Celyad

Solid tumour trial start

Colorectal patient in THINK study

Pharma & biotech

Celyad has enrolled the first patient the Phase Ib THINK study. The THINK Phase Ib trial is a major expansion of CAR therapy with five solid tumors plus AML and MM being explored. The first patient has colorectal cancer, a key move into solid tumors, and will be dosed at 3 x 108 autologous cells. In the previous Phase I study, one patient at the highest 3 x 107 dose showed unexpected signs of efficacy. The US allogenic CAR patent has been confirmed. Our interim indicative value remains at $50 per share.

Year end	Revenue ($m)	PTP* ($m)	EPADR ($)	DPADR ($)	P/E (x)	Gross yield (%)
12/14	0.2	(19.6)	(2.90)	0.0	N/A	N/A
12/15	0.0	(30.1)	(3.46)	0.0	N/A	N/A
12/16e	11.9	(26.7)	(2.87)	0.0	N/A	N/A
12/17e	0.0	(33.2)	(3.56)	0.0	N/A	N/A

Note: Converted at €0.94/US$1. *PBT and EPS are normalized, excluding amortization of acquired intangibles, exceptional items and share-based payments.

NKR-2 has a lead positon in solid tumours

Celyad has started the Belgian arm of the immuno-oncology autologous NKR-2 trials (THINK). US approval of the trial is expected soon. THINK recruits patients with two hematological and five solid tumors. Celyad has enrolled the first patient at a single dose of 3 x 10^8. Once this dose cohort completes, the dose rises to 1 x 10^9 then 3 x 10^9 cells. Celyad then aims to treat about 14 patients per tumor type at the highest dose. The expansion phase may start in H217, with six-month results possible in H218. The exploration of NKR-2 in solid tumors puts Celyad in a leading position in this area. Other CAR companies will initially have to compete for a limited number of patients in the congested CD19 area. There are a few, limited clinical trials using CAR constructs in solid tumors, but otherwise this large potential market is not being addressed by active clinical development.

Possible effect at 30m cell dose

In the completed dose-ranging and safety Phase I, Celyad noted “reports of unexpected clinical benefit”; unexpected because the single, low doses were not expected to show efficacy. A patient with acute myeloid leukemia treated with 3 x 10^7 NKR-2 CAR T-cells showed no disease progression after 12 weeks, had no further treatments and showed improved hematological parameters. Other patients with aggressive disease also showed prolonged survival (but received other therapies) and showed improvements in hematological parameters.

Valuation: Unchanged at €50 per share

Our valuation focuses on NKR-2 indications and includes five solid tumors plus the AML and multiple myeloma (MM). C-Cure is given an indicative deal value while a strategic partnering deal is negotiated. Celyad has cut its cash burn to no more than $33m per year to conserve cash to mid-2019. The interim indicative value is unchanged at $50 per share. The possible threat to value from a challenge to the US patent on allogeneic CAR therapy has been removed (see 28 November 2016 note “Unexpected CAR clinical benefit” (EU US)); the challenger cannot appeal.

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Price	**$19.7**
Market cap	**$183m**
ADR/Ord conversion ratio 1:1	
Net cash ($m) as at 30 September 2016	87m
ADRs in issue	9.31m
ADR code	CYAD
ADR exchange	NASDAQ
Underlying exchange	Euronext Brussels
Depository	CITI

ADR price performance

52-week high/low	$58.7	$16.7

Business description

Celyad is developing an innovative CAR T-cell (NKR-2) immuno-oncology technology. The THINK Phase Ib study is underway in hematological and five sold tumor types. Celyad is seeking a strategic partner for C-Cure, an autologous stem cell therapy for chronic heart disease.

Next events

Final FY16 results	Q217
US trial starts	Q117
THINK dose data	Q317
Six-month THINK efficacy	H218

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Phase Ib: Higher, multiple doses in seven tumour types

The new Phase Ib study, THINK (THerapeutic Immunotherapy with NKR-2), has been designed by Celyad as an open-label, multiple-dose US and European study. It will assess higher dose levels, safety and clinical activity of autologous NKR-2 cells in seven refractory cancers: the two haematological cancers with Phase I data (acute myeloid leukaemia [AML] and multiple myeloma [MM]) and five solid tumours (colorectal, ovarian, bladder, triple-negative breast, and pancreatic).

In the THINK Phase Ib, Celyad is starting at 3 x 10^8 cells, a dose an order of magnitude higher than the final Phase I dose. It will then rise in subsequent dose cohorts to 1 x 10^9 then 3 x 10^9. If patients have a weight of less than 60kg, these doses will be adjusted but will otherwise be standardised. At each dose, the patients will receive three successive administrations, two weeks apart, of NKR-2 T-cells. There will be 24 patients, eight per dose group. They can be from any of the above cancer types. Results from this stage of the trial are expected by Celyad in Q317.

In the expansion phase, to test efficacy Celyad intends to enrol up to 86 more patients to evaluate each tumour type independently. Combined with patients in the dose-escalation phase that have the same tumour type, this should give at least 14 patients per cancer. According to management, this stage should start in H217.

Celyad expects the six-month interim follow-up data from the cohort expansion phase in H218. The formal one-year endpoint data will therefore be available in H119 with two-year data in 2020, depending on patient survival.

Potential NKR-2 tumour markets

With the advantage of the NKG2D mechanism of cell targeting used by NKR-2, Celyad is able to run the THINK trial in multiple cancer types. NKR-2 attacks multiple targets found on severely stressed cells, a profile shown by most cancer types. A risk is that NKR-2 may attack normal but stressed cells, so some side effects are to be expected. The Phase I showed no safety issues.

A major drawback with the current CAR CD19 focus of other companies is that, while it is excellent for B-cell tumours (like leukaemias and lymphomas), CD19 will not target other cancers. Each solid tumour type has a different profile of antigens and often these are also found on normal tissues, albeit at much lower levels.

Of the leading CAR companies Novartis, Juno, Kite and Bellicum, only Bellicum has a single solid tumour trial running: a Phase I in advanced pancreatic cancer with an anti-PSCA CAR construct due to complete in 2020. A National Cancer Institute melanoma study by the Rosenberg group reported in 2016. It used CD4 CAR T-cells targeted to the MAGE antigen. There has been a clinical study using a CEA[1] targeted CAR construct in Manchester (UK) against colorectal cancer (among others) NCT01212887. This terminated due to lack of efficacy. A related trial in metastatic liver cancer in Boston was reported by Katz et al (2015) showing “encouraging signals”. There are also some CAR colorectal CAR trials running in China.

The main effort in solid tumours in immune oncology is based around checkpoint inhibitors like the marketed products Yervoy (ipilimumab), which targets cytotoxic T-lymphocyte-associated protein 4 in melanoma, and Opdivo, an anti-PD-1 monoclonal antibody used in melanoma, gastric cancer and renal cell carcinoma. It is possible that checkpoint inhibitors will be combined with CAR therapy at some point in the future, but this is currently some way off clinical development.

[1] Carcinoembryonic antigen, a marker of abdominal tumors, especially colorectal cancer.

It is too early to develop detailed predictive models for solid tumour NKR-2 sales. Exhibit 1 looks at the number of US deaths (SEER database) in each for the two haematological cancers and the five solid cancer types; the death rates are a proxy for the incidence of refractory late-stage cancers. Our value assumes $150,000 per treatment. This may be perceived as very low in the putative acute lymphoblastic leukaemia (ALL) market, where $500,000 is currently seen as affordable. ALL causes about 1,500 deaths per year in the US. All are tragic and mostly children, so this is a worthwhile indication but a small market.

Exhibit 1: NKR-2 potential indications in Phase Ib THINK study

Indication	US incidence	US deaths	Peak share	Potential US sales (US$m)	Probability	Global sales (€m)
AML	20,386	10,460	50%	127	20%	114
MM	26,850	11,240	50%	136	20%	122
Total haematological				1,324		263
Colorectal	136,830	50,310	36%	222	10%	200
Ovarian	21,290	14,180	69%	244	20%	220
Bladder	76,960	16,390	69%	141	10%	127
Breast	232,670	40,000	36%	177	10%	159
Pancreatic	46,420	39,590	69%	170	5%	153
Total solid tumors				**12,125**		**955**

Source: SEER database, Edison Investment Research

The probabilities used reflect a best estimate at this point, but have no substantive evidence base. Ovarian scores highest as there is published preclinical work. Pancreatic cancer is notoriously hard to treat, so a high market share could be expected if NKR-2 had an impact on survival, but a very low probability is assigned. The global market opportunity is based on 75% of the potential US sales as the US is the main market for high-value biological therapies. Earlier-stage cancers might be treated as well, which would magnify the market potential.

Valuation is stable, solid tumours are a big opportunity

The valuation was revised in our note Unexpected CAR clinical benefit published on 28 November 2016. It is summarized in Exhibit 2. Financial estimates are unchanged and shown in Exhibit 3.

Exhibit 2: Celyad valuation

Item	Indication	Probability	Value ($m)
CAR values	AML	20.0%	126.5
	MM	20.0%	136.0
	Solid tumours (weighted average of one success)	Variable	188.0
	Allogeneic		10.6
CAR value			461.1
C-Cure partnered value (milestones plus royalties)		35.0%	162.44
Costs	(Risk adjusted 2017-23)		(157.2)
Total indicative value			476.1
Shares			9.31
Warrants and options			0.30
Value per share ($)			**49.5**

Source: Edison Investment Research

The indicative value on the revised interim basis is $50 per share. No further dilution is expected until 2019, possibly later depending on any deals in the interim.

The solid tumour market will be further assessed as more clinical data are obtained. Although other companies are reporting successes with B-cell CAR approaches (Kite has started a rolling BLA application to the FDA and Novartis will file in early 2017), solid tumour types remain a difficult area that has not yet been explored. Celyad may have a significant lead in this much larger market.

Investors should also note that Claim 1 of US patent 9,181,527, which had been challenged (see 28 November 2016 note (EU US) has been upheld by the US Patent office. There is no appeal.

Exhibit 3: Financial summary

€000s	2014	2015	2016e	2017e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	146	3	11,250	0
Cost of Sales	(115)	(1)	0	0
Gross Profit	31	2	11,250	0
EBITDA	(18,247)	(28,639)	(25,399)	(31,254)
Operating Profit (before amort and except)	(18,440)	(28,912)	(25,672)	(31,527)
Intangible Amortisation	(677)	(760)	(760)	(760)
Other income and charges	3,778	0	0	0
Share-based payments	(1,098)	(795)	179	179
Operating Profit	(16,437)	(30,467)	(26,253)	(32,108)
Net Interest	(16)	558	500	250
Profit Before Tax (norm)	(18,456)	(28,354)	(25,172)	(31,277)
Profit Before Tax (FRS 3)	(16,453)	(29,909)	(25,753)	(31,858)
Tax	0	0	0	0
Profit After Tax (norm)	(18,456)	(28,354)	(25,172)	(31,277)
Profit After Tax (FRS 3)	(16,453)	(29,909)	(25,753)	(31,858)
Average Number of Shares Outstanding (m)	6.8	8.7	9.3	9.3
EPS - normalised (c)	(273.41)	(326.28)	(270.46)	(336.05)
EPS - (IFRS) (€)	(2.44)	(3.44)	(2.77)	(3.42)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	11,041	50,105	50,293	49,410
Intangible Assets	10,266	48,789	48,031	47,271
Tangible Assets	598	1,136	2,082	1,959
Investments	177	180	180	180
Current Assets	30,265	109,420	80,360	48,508
Stocks	0	0	0	0
Debtors	830	549	1,367	1,367
Cash	27,633	107,513	78,067	46,215
Other	1,802	1,358	926	926
Current Liabilities	(6,053)	(11,490)	(9,209)	(8,529)
Creditors	(5,276)	(10,592)	(7,906)	(7,906)
Deferred revenue	0	0	0	0
Walloon loans for cash payment	(777)	(898)	(1,303)	(623)
Long Term Liabilities	(11,239)	(36,561)	(34,014)	(34,014)
Walloon loans (non-current)	(10,778)	(10,484)	(7,519)	(7,519)
Other long term liabilities	(461)	(26,077)	(26,495)	(26,495)
Net Assets	24,014	111,474	87,430	55,375
CASH FLOW				
Operating Cash Flow	(17,398)	(27,862)	(27,144)	(30,989)
Net Interest	(16)	558	645	124
Tax	0	0	0	0
Capex	(640)	(838)	(1,500)	(150)
Acquisitions/disposals	(1,550)	(5,186)	0	0
Financing	26,417	109,155	0	0
Dividends	0	0	0	0
Other	1,638	(3,287)	(1,448)	0
Net Cash Flow	8,451	72,540	(29,446)	(31,016)
Opening net debt/(cash)	(9,557)	(16,078)	(96,131)	(69,245)
HP finance leases initiated	0	0	0	0
Walloon loan recognition (non-cash)	(1,930)	7,513	2,560	(198)
Closing net debt/(cash)	(16,078)	(96,131)	(69,245)	(38,031)

Source: Edison Investment Research estimates, Celyad reports and announcements

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