EDISON

Celyad

Clinical trial data

Revision of clinical strategy after responses seen

Pharma & biotech

Celyad has reported a complete morphological leukaemia-free status (MFLS) response in acute myeloid leukaemia (AML) in the NKR CAR T-cell THINK study. Spontaneous remission in refractory/relapsed AML is extremely rare, so this is a significant result. Importantly, the response was achieved with no toxic preconditioning. CYAD-01 has shown limited toxicities to date. The clinical strategy has been updated to focus on AML and colorectal cancer. Additionally, with the approvals of Yescarta (Gilead) at a price of $373k and Kymirah (Novartis) at $475k, we have increased our expected price for NRK CAR T-cell therapy to $200k, formerly $150k. The revised strategy and price assumption change moves the indicative value to €103 per share, formerly €51.6 per share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/15	0.00	(27.56)	(3.17)	0.0	N/A	N/A
12/16	8.52	(22.83)	(2.09)	0.0	N/A	N/A
12/17e	8.28	(27.23)	(2.86)	0.0	N/A	N/A
12/18e	9.00	(25.21)	(2.65)	0.0	N/A	N/A

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

First 'clinical validity' for NKR CAR T-cells

Celyad found one AML patient given 3x10^8 NKR CAR T-cells had a complete MLFS response. In effect, it was a near CRi; that is, a complete response with high but not normal blood cell levels. Treatment with NKR CAR T-cells has enabled him to move to stem cell transplant. Median survival of relapsed and refractory AML patients is typically less than four months (source Celyad, see AML treatment).

Revised clinical strategy

With a near complete response in AML and two stable disease cases at low dose in colorectal cancer, Celyad has decided to focus its development efforts on these two indications. The current THINK study in AML, MM and five solid cancers, including colorectal, will continue to find the optimal dose but with preferential recruitment of AML and colorectal patients. Celyad also intends to evaluate combination therapies. As the first such study, the SHRINK trial of CYAD-01 is ready to start recruitment in metastatic CRC in combination with FOLFOX chemotherapy.

Valuation: Revised to €1,047m from €524m

Our previous approach to valuing the Celyad NKR CAR T-cells portfolio was to treat AML and MM as defined indications with a probability of 20% and to take a weighted average of the five solid tumour indications. We have now focused the valuation on AML at 25% probability and colorectal at 20% (adjusted from 10% in August). The C-Cure a cardiac indication is still seeking a partner so is now given a nominal value of €10m, formerly €162m. Rebasing the valuation to January 2018 gives a new indicative value of €1,047m, formerly €524m (indicating €103 per share (formerly €51.60)). Management states that Celyad has cash to fund it through the first half of 2019. Additional cash might enable a broader and faster development of the clinical programme given its promising current outlook.

30 October 2017

Price	**€50.05**
Market cap	**€494m**
	$1.18/€
Cash (€m) at 30 June 2017	68.8
Shares in issue (at 28 August 2017)	9.86m
Free float	61%
Code	CYAD
Primary exchange	Euronext Brussels
Secondary exchange	NASDAQ

Share price performance

%	1m	3m	12m
Abs	5.8	64.9	237.4
Rel (local)	3.1	60.6	195.8
52-week high/low		€54.0	€14.8

Business description

Celyad is developing an innovative CAR T-cell (NKR-2) immuno-oncology technology. The THINK Phase Ib study is underway in haematological and five sold tumour types. SHRINK is approved to enrol patients. Celyad is seeking a strategic partner for C-Cure for chronic heart disease.

Next events

Q317 update	Q417

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Edison profile page

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THINK

Celyad is in an interesting position with very promising initial results in AML and emerging responses in solid tumours – although both are at an early stage of clinical development. It was pointed out in the recent Edison report (27 September 2017) on T-cell cancer therapies that NKR CAR T-cells therapy by targeting ubiquitous 'stress' ligands could potentially target a number of solid and haematological tumours. The first indications from the clinic that this might be a reality have now been seen. It will be important to build on the successes so far with more consistent clinical responses at higher dose levels in the THINK study. The Therapeutic Immunotherapy with NKR-2 (THINK) study (NCT03018405) is an open-label, multiple-dose US and European study currently in a dose escalation phase (Exhibit 1).

Exhibit 1: THINK trial detail

Aspect	comment
Dose level	$3x10^8$, $1x10^9$, $3x10^9$ of the natural killer receptor CAR T-cell product, CYAD-01.
Dosing	Three doses of cells are given, each 14 days apart.
Preconditioning – lymphodepletion	Preconditioning is not used with CYAD-01 although potential combinations will eventually be explored. Prior chemotherapy is essential for standard CAR-T therapies such as Kymriah (tisagenlecleucel, Novartis) and Yescarta (Axicabtagene Ciloleucel, Gilead (Kite)). Preconditioning enables rapid expansion of the transfused CAR T-cells and also reduces the tumour burden of the patient.
Dose ranging phase	This phase is at least 12 patients each in the haematological and solid cancer arms, respectively. If toxicity is seen, extra patient is recruited at that dose level. If the dose is safe, the next dose cohort is recruited. At the highest dose, an extra three patients are recruited.
Cohort expansion phase	Once a dose is established, the trial is planned to expand into separate cohorts, each with specific cancer indications. One of these cohorts will now definitely be colorectal cancer. The plan sizes 14 patients at the highest dose per cancer. However, with the revised clinical trial emphasis, it is possible that only some of these cancers will be pursued in the near term. In theory, this stage of the trial should have 98 patients in total made of 86 further patients plus the 12 at the highest dose cohort. However, under the revised strategy, not all these indications may be pursued initially.
Haematological indications	The haematological arm of the trial will recruit AML and multiple myeloma (MM) patients. Priority will now be given to AML patients.
Solid cancers	The trial is recruiting patients in the dose escalation phase with colorectal, ovarian, pancreatic, bladder and triple-negative breast cancers. So far, colorectal, pancreatic and ovarian cancer patients have been recruited. The dose escalation phase will now preferentially recruit colorectal cancer patients.
Toxicity seen to date	To date, Celyad has reported one Grade 3 toxicity in an ovarian cancer patient and one Grade 4 toxicity in a MM patient. The observed toxicities might indicate that the NKR CAR T-cells are attacking the cancer. Toxicities in approved CAR-T therapies have been linked to an immune attack on the cancer burden. However, there is no clear link between toxicities and response in CAR-T therapies like Kymriah; this might be because of preconditioning which may be a confounding factor.
Readout	As THINK is an open-label study, Celyad will report significant events as they happen. The six-month dose data are possible in H218. The two-year primary endpoint data could be due in mid-2020. However, the revised clinical strategy may mean that these dates vary for different cancer indications.

Source: Edison Investment Research based on Celyad reports and management information

THINK cohort expansion in colorectal cancer and AML will start once a clear dose has been established. Unlike the cautious safety-first approach in dose escalation, cohort expansion should be relatively rapid as there is no need for significant delays between patient dosing. AML in particular is an intractable condition. So far, T-cell therapies are early in development with no other reported therapies impact. If the pattern of complete response is maintained at higher doses, then Celyad should have no trouble in recruiting patients. Currently, Celyad has no complete responses in colorectal cancer – but then CAR T-cell therapy has no complete responses in any solid tumour type at present.

The issues around solid tumour therapy and the probable need for combination therapy are explored in detail in the report T-cell cancer therapies. Part 1 of this report provides an overview. Part 2 provides detailed investigation into multiple aspects of T-cell therapies including in solid tumours.

SHRINK

The Celyad natural killer (NKG2D) receptor CAR T-cell approach, CYAD-01, targets the ubiquitous stress ligands expressed by many cancers. These stress ligands are upregulated in response to chemotherapy. However, they are also expressed by normal cells exposed to toxic agents, if only for a short period. Chemotherapy might make the tumour more stressed and so more susceptible to CYAD-01 targeting. It might also expose some normal tissues to CYAD-01, so timing of dosing is important to allow enough normal tissue recovery post chemotherapy. In the real world, most solid cancer patients will receive chemotherapy and knowing how to combine standard chemotherapy with CAR T-cell therapy is crucial. If it proves to be synergistic, it would be a major cancer therapy breakthrough as most chemotherapy regimens show limited survival gains in a minority of patients.

The SHRINK trial is being in metastatic colorectal cancer, which is located in the liver. About 20-30% of colorectal cancer cases are found to have metastatic disease on diagnosis. SHRINK has not yet been posted on the clinical trials databases but is approved by the Belgian regulator.

Exhibit 2: SHRINK detail

Aspect	comment
Dose level	CYAD-01 doses will be adjusted to body weight and escalate from $3x10^8$ to $1x10^9$ to $3x10^9$.
Dosing	Three doses of cells are given, each 14 days apart.
Preconditioning – lymphodepletion	Preconditioning is not used to deplete the patient's immune system. However, this trial combines CYAD-01 with chemotherapy which should deplete the tumour burden.
Combination	Patients will be given prior treatment with FOLFOX chemotherapy. FOLFOX is a combination of folinic acid (leucovorin), fluorouracil (5FU) and Oxaliplatin. FOLFOX is not a regimen that targets the immune system, unlike the preconditioning regimen used in B-cell CAR T-cell therapies.
Dose ranging phase	This phase will recruit at least 18 patients, six at each dose level. If the dose is safe, the next dose cohort is recruited. Note that timing between FOLFOX and CYAD-01 will also be evaluated.
Cohort expansion phase	Once a dose is established, the trial is planned to expand to 21 patients at the highest dose.
Readout	Unknown, but this trial will be a priority. Overall survival will be crucial for widespread use, but will take some years to determine. FOLFOX alone gives median overall survival of about two years vs six months on supportive care.

Source: Edison Investment Research

Revised value

Although we have not made any substantive changes to the currently broad cancer indications forecast, we have adjusted our valuation and made some detailed adjustments to some probabilities and timings and also to price expectations. In addition, we have rebased evaluation to January 2018. These changes makes a substantial difference to the indicative value.

The changes are as follows:

- **AML** has an increase in the probability of success from 20% to 25%. The revised probability is still cautious as only one near complete response has so far been seen. A consistent pattern of complete responses at higher doses would encourage us to raise this probability further. The expected launch date remains at 2022, although noting that the FDA has rapidly reviewed the first two CAR T-cell therapies does raise the possibility that a more rapid approval could be obtained if the clinical data warrants it, particularly as refractory AML is an intractable condition.
- **Colorectal cancer** was formerly treated as one of five solid tumours, for which an average weighted value was estimated. As it has become a priority for Celyad, it is now treated separately. The probability was adjusted in August 2017 from 10% to 20% in view of two stable disease cases reported in June. As yet, no complete responses have been seen in colorectal cancer so this probability is maintained for the moment, but we would expect to increase this if complete responses are seen at higher dose levels. In this context, the AML response is very encouraging but there is no guarantee of a direct read-across. The expected colorectal launch date remains 2023. Since colorectal cancer is a major solid tumour indication, splitting it out

from the average of solid tumours has a high impact on the overall indicative value. Only refractory colorectal cancer is taken into account.

- **Multiple myeloma** remains unchanged but as it is potentially a lower priority project. We have pushed the launch date back to 2024. Probability remains at 20% given that other CAR-T therapies, notably Bluebird's bb2121, have shown good success to date in multiple myeloma. Our assessment of multiple myeloma will be adjusted as more clinical data is disclosed. There was Grade 4 toxicity seen which is an indicator that the infused CYAD-01 cells might be having some clinical effect.
- The **remaining four solid cancers** are still treated as a weighted average with unchanged probabilities. There have been some signs of efficacy with a Grade 3 toxicity in ovarian cancer. Two other cancer types, bladder and triple-negative breast cancer have not as yet been explored as no patient has yet been recruited. We have pushed all these cancer indications back to an expected launch date of 2025; this will be regularly reviewed.
- The price assumed was $150k as this approximated to immunomodulatory checkpoint inhibitor therapies. However, with Kymriah listed at $475K and Yescarta at $373k, this price is clearly too low. The eventual pricing of CAR T-cell therapies is going to be complex and will relate to efficacy, as yet unknown. We have therefore used **$200k as a current target price for CYAD-01** but this will be revised as further data emerges.
- We have taken the decision to put a **nominal value for the C-Cure cardiac therapy** into the model. The Phase III data showed a subgroup where efficacy was noted. Celyad decided to explore strategic options for the project and put development on hold although a US Phase III trial has been approved. The value was €162m but as no deal has been concluded we have reduced this to a nominal €10m. This will be revised when further information is available.
- **We have not made any adjustments to expected trial costs** as management has indicated that current financial resources are adequate to pursue the revised clinical programme. However, we note that a broader programme with faster recruitment to develop the large potential of NKR CAR T-cells therapy could perhaps be pursued if greater financial resources were available.
- The **financial model has been rebased to January 2018**. This has a significant impact by itself as the discount rate is 12.5% before probability adjustment.

Exhibit 3 shows the cancer numbers and revised NPV values. Note that the other four solid cancers are weighted as we are not at this time clear that they will all progress.

Exhibit 3: Revised CYAD-01 NPV estimates

	Indication	Deaths	Peak share	Peak US sales ($m)	Probability	NPV (US)	Global (€)
Lead indications							
	AML	10,460	39%	851	25.0%	178	201
	Colorectal	50,310	36%	3,628	20.0%	500	565
Exploratory							
	MM	11,240	39%	915	20.0%	113	128
	Solid tumours, weighted average						
	Ovarian	14,180	69%	1,951	20.0%	217	245
	Bladder	16,390	69%	2,255	10.0%	125	142
	Breast	40,000	36%	2,884	10.0%	157	178
	Pancreatic	39,590	69%	5,448	5.0%	151	171
Total other solid cancers		**110,160**		**12,539**		**651**	**736**
Weighted average						**158**	**179**

Source: Edison Investment Research

The revised valuation based on these numbers is shown in Exhibit 4.

Exhibit 4: Revised valuation

Item		Probability	Value (€m)
Lead projects	AML	25.0%	201
	Colorectal	20.0%	565
Exploratory trials	MM	20.0%	128
	Solid tumours (average of 4)	Variable	179
	Allogeneic		50.
Total CAR value			**1,123**
C-Cure Partnered value (milestones plus royalties)		Nominal	10
Net operating costs	(Risk adjusted 2018-2023)		-107
Additional royalties			21
Total indicative value			**1,047**
Shares			9.86
Warrants and options			0.30
Core value per share (€)			**103**

Source: Edison Investment Research

A faster and more comprehensive clinical development up to 2023 could be more expensive but benefit from a higher payback rate.

The value has risen significantly indicating €103 per share (formerly €51.6), but this is mostly due to the change in price assumption from $150k to $200k. If the price was left at $150k, the value would be about €77/share. If the efficacy is robust, the price could be higher than this.

Financials

Celyad has reported H117 results. Revenues were €3m in grants with R&D expenses of €11.1m. The operating loss was €13.7m and the net cash burn was €13.8m. On 30 June 2017, Celyad had €68.8m of cash. This is expected by management to be sufficient to fund the company through the first half of 2019. We have not made any changes to financial forecasts (Exhibit 5). Celyad might benefit from an enhanced cash basis to develop its cancer portfolio.

Exhibit 5: Financial summary

€000s	2015	2016	2017e	2018e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	3	8,523	8,280	9,000
Cost of Sales	(1)	(53)	0	0
Gross Profit	2	8,470	8,280	9,000
EBITDA	(27,844)	(24,065)	(26,720)	(24,700)
Operating Profit (before amort and except)	(28,117)	(24,825)	(27,480)	(25,460)
Intangible Amortisation	(760)	(756)	(756)	(756)
Other income and charges	0	(521)	0	0
Share-based payments	(795)	493	0	0
Operating Profit	(29,672)	(25,609)	(28,236)	(26,216)
Net Interest	558	1,997	250	250
Profit Before Tax (norm)	(27,559)	(22,828)	(27,230)	(25,210)
Profit Before Tax (FRS 3)	(29,114)	(23,612)	(27,986)	(25,966)
Tax	0	6	0	0
Profit After Tax (norm)	(27,559)	(19,482)	(27,230)	(25,210)
Profit After Tax (FRS 3)	(29,114)	(23,606)	(27,986)	(25,966)
Average Number of Shares Outstanding (m)	8.7	9.3	9.5	9.5
EPS – normalised (c)	(317)	(209)	(286)	(265)
EPS – (IFRS) (€)	(3.35)	(2.54)	(2.94)	(2.73)
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	50,105	53,440	73,333	71,967
Intangible Assets	48,789	49,566	70,069	69,313
Tangible Assets	1,136	3,563	2,953	2,343
Investments	180	311	311	311
Current Assets	109,420	85,366	47,007	21,293
Stocks	0	0	0	0
Debtors	549	1,359	1,359	1,359
Cash (cash plus deposits)	107,513	82,587	44,228	18,514
Other	1,358	1,420	1,420	1,420
Current Liabilities	(11,490)	(11,275)	(11,017)	(10,487)
Creditors	(10,592)	(9,960)	(9,960)	(9,960)
Deferred revenue	0	0	0	0
Walloon loans and bank loan	(898)	(1,315)	(1,057)	(527)
Long Term Liabilities	(36,561)	(36,646)	(35,796)	(35,212)
Loans (non-current) Bank and Walloon	(10,484)	(7,866)	(7,016)	(6,166)
Other long term liabilities	(26,077)	(28,780)	(28,780)	(29,046)
Net Assets	111,474	90,885	73,526	47,561
CASH FLOW				
Operating Cash Flow	(27,862)	(26,689)	(27,192)	(24,578)
Net Interest	558	1,997	861	264
Tax	0	0	0	0
Capex	(838)	(1,782)	(21,409)	(150)
Acquisitions/disposals	(5,186)	(1,561)	0	0
Financing	109,155	0	10,629	0
Dividends	0	0	0	0
Other	(3,287)	3,109	(1,249)	(1,249)
Net Cash Flow	72,540	(24,926)	(38,359)	(25,713)
Opening net debt/(cash)	(16,078)	(96,131)	(73,406)	(36,155)
HP finance leases initiated	0	0	0	0
Loan and finance movements	7,513	2,201	1,108	1,380
Closing net debt/(cash)	(96,131)	(73,406)	(36,155)	(11,822)

Source: Edison Investment Research estimates, Celyad reports and announcements. Note: the $25m 2017 payment is treated as an intangible asset expected to be amortised against sales income. The equity component is shown as an equity investment. The actual accounting treatment by Celyad may differ.

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