Celyad S.A. (CYAD)

Initiation Report

LifeSci Investment Abstract

Celyad (NasdaqGM: CYAD) is a biotherapeutics company developing cell therapies for the treatment of ischemic heart failure and cancer. The Company's Cardiopoiesis platform creates autologous cardiac progenitor cell therapies for heart failure. Celyad's lead product candidate *C-Cure* is currently in a Phase III trial in Europe, with a full data readout expected in the second half of 2016. The Company's recently in-licensed chimeric antigen receptor T cell (CAR-T) platform utilizes chimeric natural killer (NK-cell) receptors to recognize and eliminate tumor cells. CAR-NKG2D is Celyad's lead oncology product candidate that is currently in a Phase I trial for acute myeloid leukemia (AML) and multiple myeloma (MM). Data from the trial are expected in the second half of 2016.

Key Points of Discussion

- **Cardiopoiesis Platform Technology Creates Autologous Cell Therapies for Cardiac Regeneration.** Celyad is using the Cardiopoiesis platform technology to generate cardiac progenitor cells to repair tissue damage associated with ischemic heart failure. The cardiopoietic cells are engineered bone marrow derived mesenchymal stem cells (MSCs) that are injected directly into the heart, where they accumulate near the site of damage. Preclinical and clinical studies indicate that cardiopoietic cells promote tissue repair and improve heart function by integrating into the damaged area, promoting new blood vessel growth and potentially stimulating the proliferation of resident cardiac stem cells. This innovative approach aims to restore functionality to the heart, in contrast to most therapies that only slow disease progression.
- **C-Cure for Large Opportunity in Ischemic Heart Failure.** Celyad is developing its lead product candidate, *C-Cure*, for the treatment of ischemic heart failure, a condition that currently affects approximately 5 million Americans. *C-Cure* is an autologous cell therapy comprised of Celyad's proprietary cardiopoietic cells. The product is manufactured in the Company wholly owned GMP facility in Belgium. Initial signs of efficacy were shown in the *C-Cure* Phase II study, which showed significant improvement in patient cardiac function and exercise capacity following a 6 month follow up period. *C-Cure* treated patients experienced a 20% increase in left ventricular ejection fraction ($p < 0.0001$) and a 21% improvement in the 6-minute walk distance ($p < 0.01$). Celyad is currently conducting the CHART-1 Phase III study in Europe, with a full data readout expected in the second half of 2016. The Company plans to initiate the CHART-2 Phase III trial for *C-Cure* in the US and Europe in the fourth quarter of 2015.

Expected Upcoming Milestones

- Q3 2015 - Expected dosing of final patient in CHART-1 Phase III trial.
- Q4 2015 - Expected initiation of CHART-2 Phase III trial in US, pending release of FDA clinical hold.
- Q4 2015 - Interim safety data from Phase I study for CAR-NKG2D.
- H2 2016 - Expected full data readout of CHART-1 Phase III trial.
- H2 2016 - Expected readout of CAR-NKG2D data set.

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Market Data

Price	$55.62
Market Cap (M)	$514
EV (M)	$478
Shares Outstanding (M)	9.2
Avg Daily Vol	87,788
52-week Range:	$47.52 - $67.94
Cash (M)*	$36.9
Net Cash/Share	$3.94
Annualized Cash Burn (M)	$21.2
Years of Cash Left	1.7
Debt (M)	$0.5
Short Interest (M)	0.03

**pro forma*

Financials

FY Dec		2012A	2013A	2014A
EPS	H1	NA	(4.49)A	(1.26)A
	H2	NA	NA	NA
	FY	(14.30)A	(4.00)A	(3.25)A

For analyst certification and disclosures please see page 42

- **Cure Phase II Trial in Ischemic Heart Failure**. Celyad conducted an open-label, randomized Phase II trial evaluating *C-Cure* in 47 patients with NYHA Class II or III heart failure secondary to ischemic cardiomyopathy at 9 clinical sites in Europe.[1] Patients in the control arm received standard of care comprising a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker, and a diuretic. Patients in the cell therapy arm received the standard of care plus cardiopoietic cells administered via endoventricular injection. The treatment arm received an average of 700 million cells over the course of 6-26 injections. The primary endpoint for the trial was safety and feasibility. Results from the trial demonstrated that *C-Cure* is safe and well tolerated. Cardiopoietic cells were successfully generated for 21 of 28 patients, indicating that the Cardiopoiesis platform is efficient. Although 32 patients were initially randomized to the experimental arm, 2 patients did not meet the clinical inclusion criteria and 2 did not provide sufficient bone marrow material to begin the Cardiopoietic platform. All 21 patients for whom cells were derived received endoventricular injections of cardiopoietic cells. In addition, secondary endpoints measuring heart function indicated a significant improvement in left ventricular ejection fraction, left ventricular systolic volume, and 6 minute walk test.

- **Highly Differentiated CAR-NK Platform Technology Creates Targeted Immunotherapies.** On January 21, 2015, Celyad acquired Oncyte, the oncology division of Celdara Medical (private). The acquisition provided Celyad with a portfolio of immune-oncology drug product candidates including a chimeric antigen receptor T cell (CAR-T) platform. The CAR-T platform genetically modifies T cells to express chimeric natural killer (NK) cell receptors, which bind NK ligands on tumor cells and induce anti-tumor immune responses. This clever variation on CAR technology has many potential advantages including the ability to target multiple cancer types with a single cell therapy. This differentiating technology positions Celyad well within the young, competitive CAR-T space.

- **CAR-NKG2D for Acute Myeloid Leukemia and Multiple Myeloma.** Celyad is developing its lead product candidate in oncology CAR-NKG2D as a monotherapy for the treatment of acute myeloid leukemia (AML) and multiple myeloma (MM). CAR-NKG2D is a CAR therapy created by combining the NK cell receptor NKG2D with the CD3 intracellular signaling domain. This combination produces a chimeric receptor with robust antitumor activities. Preclinical studies have demonstrated that CAR-NKG2D promotes tumor free survival in both hematological and solid tumor animal models. Celyad is initially targeting AML and MM for CAR-NKG2D, with potential to broaden its development program should the therapy prove safe and effective in these initial indications. A Phase I study is ongoing in relapsed or refractory AML or MM, with full data expected in the second half of 2016.

Financial Discussion

2014 Annual Results. Celyad reported revenue of €146,000 ($160,220) from the sale of its catheter *C-Cath*$_{ez}$ for the CHART-1 trial. R&D expenses during this same period were €15.9 million ($17.4 million). The Company forecasts R&D investment of €25 million in 2015 and €30 million in 2016 as they ramp up activities associated with the CHART 1 and CHART 2 trials and advances its CAR-NK programs. Celyad's SG&A expense was €5.0 million ($5.5 million) in 2014. Other operating income was €4.4 million ($4.8 million) from government reimbursement.

Recent Financing Activity. In March, Celyad raised approximately €32 million ($35 million) through a private placement of 713,380 to investors in the United States and Europe at a price of €44.50 ($48.83) per share. The net proceeds of the private placement were approximately €29.8 million ($32.7 million).

[1] Bartunek, F. et al., 2013. Cardiopoietic Stem Cell Therapy in Heart Failure. *Journal of the American College of Cardiology*, 61(23), pp2329-2338.

On June 18th, Celyad raised $100 million by offering 1.5 million shares at $68.56. The offering consisted of 1.2 million American Depositary Shares (ADSs), which trade on the Nasdaq Global Market exchange under the symbol CYAD, and 0.3 million common shares, which trade on the Euronext Brussels and the Euronext Paris under the same symbol.

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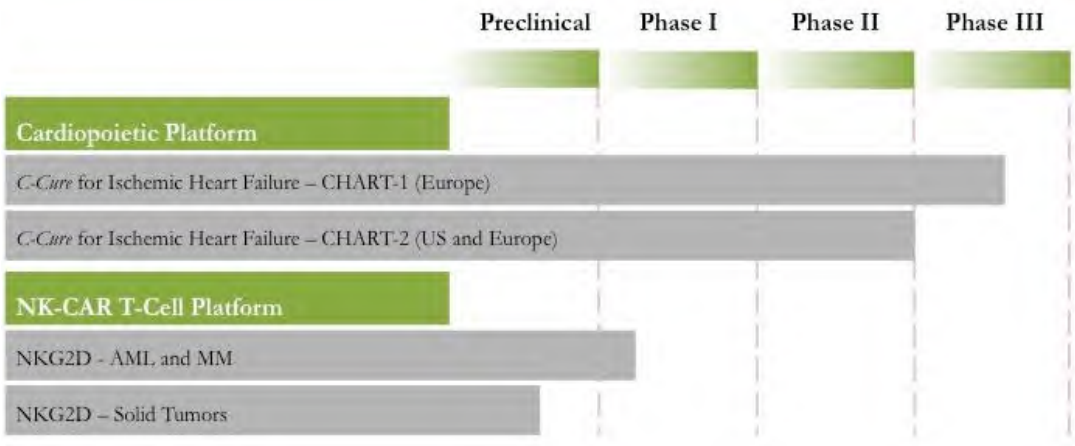
Company Description

Celyad is a clinical stage biotherapeutics company developing cell therapies for ischemic heart failure and cancer. The Company's product candidates are based on two validated and proprietary technology platforms and are manufactured in Celyad's wholly-owned GMP compliant facility. The Company's Cardiopoiesis platform produces cardiac progenitor cells for the repair of damaged cardiac tissue. Celyad's lead product candidate *C-Cure* is in a Phase III trial in Europe for ischemic heart failure, with a data readout expected in the second quarter of 2016. The Company plans to initiate a second Phase III study with *C-Cure* for the same indication in the US and Europe in the second half of 2015.

Celyad's second technology platform utilizes chimeric antigen receptor (CAR) technology to create immunotherapies for liquid and solid tumors. This differentiated CAR platform is used to genetically engineer T cells to recognize natural killer (NK) cell receptor ligands on cancer cells. Celyad's lead CAR-T cell therapy CAR-NKG2D has shown efficacy in several preclinical animal models. The Company has initiated a Phase I trial with CAR-NKG2D in refractory or relapsed acute myeloid leukemia and multiple myeloma. Data from the trial is expected in the second half of 2016. **Figure 1** shows Celyad's developmental pipeline. The indications for each platform are listed.

Figure 1. Celyad's Development Pipeline.



Source: LifeSci Capital

On January 21, 2015, Celyad acquired Oncyte LLC, the oncology division of Celdara Medical, LLC (private), a biotechnology company based in Lebanon, NH. The acquisition provided Celyad with a portfolio of drug product candidates in the immune-oncology space including three autologous CAR-T cell therapy products and an allogeneic CAR platform. Celyad purchased Oncyte with a $10.0 million upfront payment to Celdara, $6.0 million of which was paid in cash and $4.0 million of which was paid in Celyad stock.

The Cardiopoiesis Therapeutic Platform

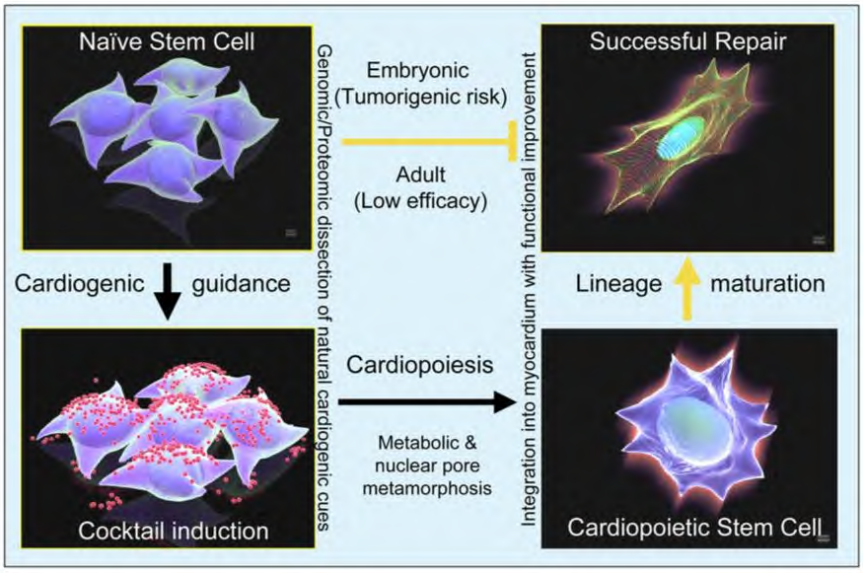
Celyad's product candidates for ischemic heart failure are based on the proprietary Cardiopoiesis platform. This technology was licensed from the Mayo Clinic and produces cardiac progenitor cells or cardiopoietic cells for the treatment of heart failure and related conditions. Unlike other organs that are capable of regenerating, the human heart has a limited capacity for repair following injury. The Cardiopoiesis platform produces cells that have the potential to repair, rejuvenate or replace damaged cardiac tissue and improve heart function. Extensive pre-clinical and clinical studies have established the therapeutic potential of cardiopoietic cells for ischemic heart failure.[2, 3] These studies provide evidence that cardiopoietic cells can form cardiomyocyte-like cells in culture, where they exhibit several hallmark features of cardiac tissue including sarcomerogenesis, mitochondrial maturation, and electromechanical coupling. These cells also incorporate into cardiac tissue when injected directly into the heart, where they simultaneously promote blood vessel formation and tissue repair.

Celyad's Cardiopoiesis platform utilizes mesenchymal stem cells (MSCs) from a patient's bone marrow to produce cardiopoietic cells. MSCs are adult stem cells that have the natural ability to differentiate into a variety of different cell types.[4] They are an attractive starting material for this platform since they are easily isolated during routine bone marrow biopsies. The use of autologous cells in the treatment of ischemic heart failure eliminates the possibility of graft versus host disease (GVHD) or the need for immunosuppressive drugs.

Cardiopoietic Cell Production and Safety. The Cardiopoiesis platform produces cardiopoietic cells by replicating the normal processes of cardiomyocyte formation during embryonic development. The heart is the first organ to form during embryogenesis. Prior to the tissue remodeling that shapes the four chambers of the heart, cardiogenic growth factors from the endoderm induce undifferentiated mesodermal cells into cardiac cell progenitors. Celyad's proprietary platform technology uses similar cardiogenic growth factors that act during embryogenesis to rapidly and efficiently differentiate a patient's bone marrow MSCs into cardiopoietic cells. As illustrated in **Figure 2**, naïve stem cells or MSCs cultured with Celyad's proprietary cardiogenic cocktail adopt metabolic and nuclear features characteristic of cardiac progenitor cells. When these cells are placed within the heart, they may mature into cardiomyocyte-like cells and help repair damaged cardiac tissue.

[2] Behfar A. et al., 2010. Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. *Journal of the American Academy of Cardiology*. 56, pp721–734.
[3] Bartunek, F. et al., 2013. Cardiopoietic Stem Cell Therapy in Heart Failure. *Journal of the American College of Cardiology*, 61(23), pp2329-2338.
[4] Caplan, A.I., et al., 2009. Why are MSCs therapeutic? New data: new insight. *Journal of Pathology,* 217(2), pp318-24.

Figure 2. MSCs Can Differentiate into Functional Cardiopoietic Cells



Source: Behfar, A. et al, 2008.

Preclinical and early clinical evidence points to a strong safety profile for cardiopoietic cells. There has been no evidence of toxicity associated with adverse immune reactions. The adverse events reported in clinical trials to date have been mild and transient. Pre-clinical animal data and *ex vivo* culturing experiments did not reveal ectopic growth, neoplasia, or tumor development.

Mechanism of Action. Cardiopoietic cells have the potential to repair damaged cardiac tissue through direct and indirect mechanisms.[5, 6] When the cells are injected into the damaged hearts of rodents, a significant portion of cells engraft into the cardiac tissue. They replace non-functioning cardiomyocytes and may improve heart function by regenerating cardiac muscle. In addition to replacing damaged tissue, cardiopoietic cells secrete factors that promote blood vessel formation, potentially facilitating rejuvenation of damaged or poorly functioning cells.

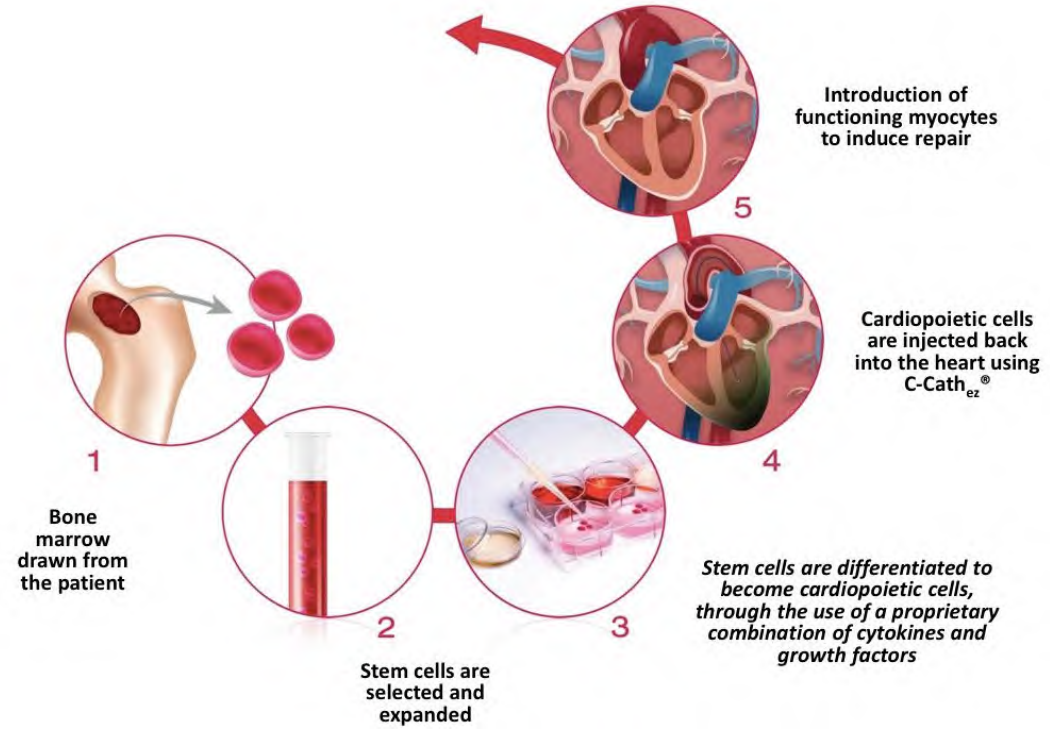
C-Cure: Cardiopoietic Stem Cell Therapy in Heart Failure

Celyad's lead product candidate *C-Cure*, is an autologous cardiopoietic cell therapy for the treatment of ischemic heart failure. It is based on proprietary technology developed by investigators at the Mayo Clinic intended to repair damaged or ischemic tissue. Phase II data for this program was published in the *Journal of the American College of Cardiology* in 2013.[7] *C-Cure* is currently being evaluated in the CHART-1 Phase III trial in Europe, with a data readout expected in the second half of 2016. A US CHART-2 trial is expected to launch in the fourth quarter of 2015.

[5] Behfar A., et al., 2007. Cardiopoietic programming of embryonic stem cells for tumor-free heart repair. *Journal of Experimental Medicine.* 204, pp405–420.
[6] Behfar A. et al., 2010. Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. *Journal of the American Academy of Cardiology*. 56, pp721–734
[7] Bartunek, F. et al., 2013. Cardiopoietic Stem Cell Therapy in Heart Failure. *Journal of the American College of Cardiology*, 61(23), pp2329-2338.

The *C-Cure* process, highlighted in **Figure 3**, begins with the isolation of a patient's bone marrow. This tissue is sent to Celyad's central GMP facility in Belgium, where MSCs are purified, re-engineered, and expanded in culture. Because MSCs in their native state exhibit a poor capacity for cardiac differentiation, they are cultured with a proprietary growth factor combination to induce the formation of cardiopoietic cells. These cells are then expanded once again before being injected into the patient's heart using Celyad's proprietary catheter *C-Cath*$_{ez}$. The use of this catheter may enhance cell viability during injection and results in a higher retention rate of the cells within the cardiac tissue. *C-Cure* carries both potential direct benefits from the grafting of healthy cardiopoietic cells into the cardiac tissue and possible indirect benefits from secreted signaling factors that stimulate the activity of resident cardiac stem cells.

Figure 3. The *C-Cure* Process



Source: Celyad Presentation

Heart Failure

Heart failure (HF) is a progressive condition where the heart cannot sufficiently generate blood flow necessary to meet the body's demands. HF is associated with symptoms including shortness of breath, leg swelling, and exercise intolerance. In the early stages, HF may primarily manifest as being often tired, feeling weak, and having shortness of breath. Myocardial infarctions, coronary artery disease, hypertension, valvular heart disease, and cardiomyopathy

are all causes of HF. Other conditions that can lead to heart failure include diabetes, disease of the pericardium, arrhythmia, long-term alcohol use, or congenital heart defects.

As part of the disease progression, the body tries to compensate for the insufficient blood flow by retaining salt and water, which increases the amount of circulating blood, heart rate, and eventually the size of the heart. These mechanisms compensate for the heart's deteriorating performance for a while, but reinforce a negative feedback loop that contributes to the disease progression. In advanced HF, inadequate blood pumping results in poorly oxygenated blood to flow to the organs in the body, eventually leading to a breakdown of vital systems.

In developed countries, HF affects approximately 2% of the adult population[8] and it's the leading cause of hospitalization in patients over the age of 65. There are more than 5 million people in the United States who have heart failure and the total cost of treating heart failure is estimated to exceed $32.4 billion each year.[9] Although survival rates have improved considerably, the 5 year survival rate for heart failure patients is approximately 50%.[10] A treatment that effectively improves the condition of HF patients would have significant direct value for patients as well as benefits to the healthcare system.

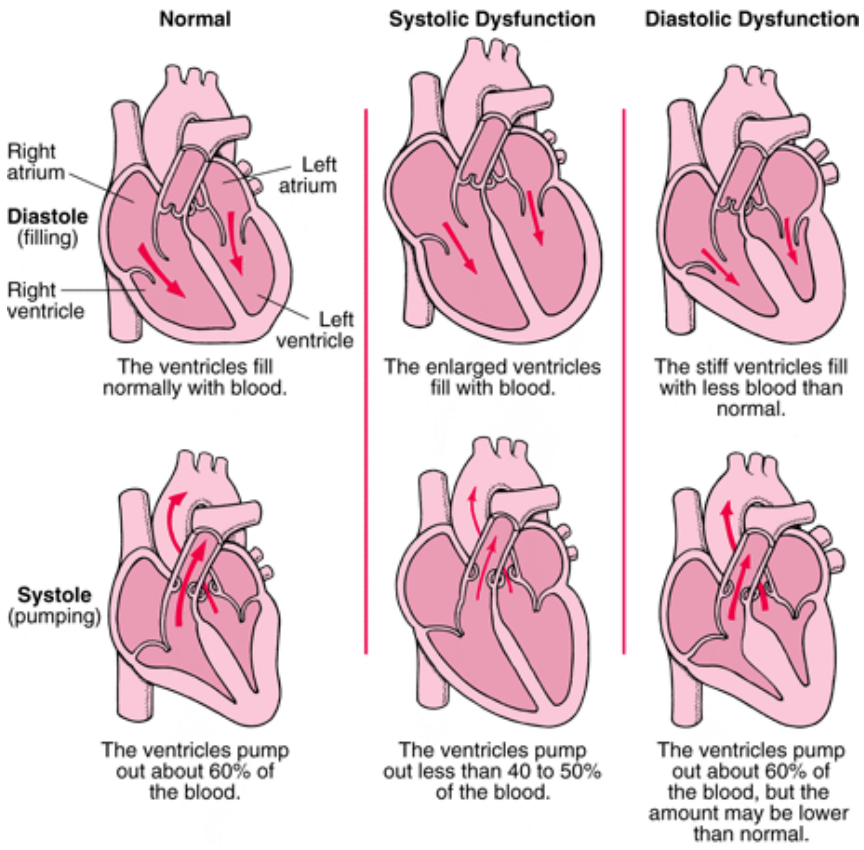
Causes & Pathogenesis of Heart Failure

There are two types of HF, systolic and diastolic, each of which affects roughly half of HF patients and has a different underlying pathology. In systolic HF, the heart muscles weaken and cannot pump sufficient amounts of blood to keep up with the body's demands. It is characterized by a reduced ejection fraction (< 40%), which is the percentage of blood that gets ejected from the left ventricle. Many congenital causes of heart failure involve alterations of the arrangement and function of myocytes and progressive damage from HF is reflected at the cellular level. Celyad is developing *C-Cure* for the treatment of systolic heart failure.

In diastolic heart failure, the heart becomes rigid and cannot properly relax, resulting in improper refilling with blood. This causes a backup of fluid entering the heart, which puts stress on the venous system and tissue surrounding the heart. The differences between normal conditions and systolic and diastolic heart failure are illustrated in **Figure 4**. In a normal heart, the blood flowing into the ventricles from the atria is efficiently pumped out of the heart into systemic circulation. However, a heart in systolic HF pumps a smaller percentage of the blood out of the ventricles, which both strains the heart further and reduces the efficacy of systemic blood circulation. In diastolic HF, the ventricles have a reduced capacity to fill with blood, and so end up pumping less blood through circulation despite normal ventricular function. Both cases put the patient at a greater risk of cardiac arrest from ventricular dysrhythmias and reduce systemic blood circulation, which can have an array of downstream consequences on other organ systems that progressively worsen as poor flow and oxygenation persist. The process accelerates as the body's attempts to compensate for low cardiac output further strain an already taxed heart.

[8] McMurray, JJV and Pfeffer, MA, 2005. Heart failure. *The Lancet*, 365, pp1877-1889.
[9] Heidenreich PA, et al., 2011. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*, 123, pp933–944.
[10] Go AS, et al., 2013. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation,* 127, pp6–245.

Figure 4. Heart Function in Normal and Dysfunctional States



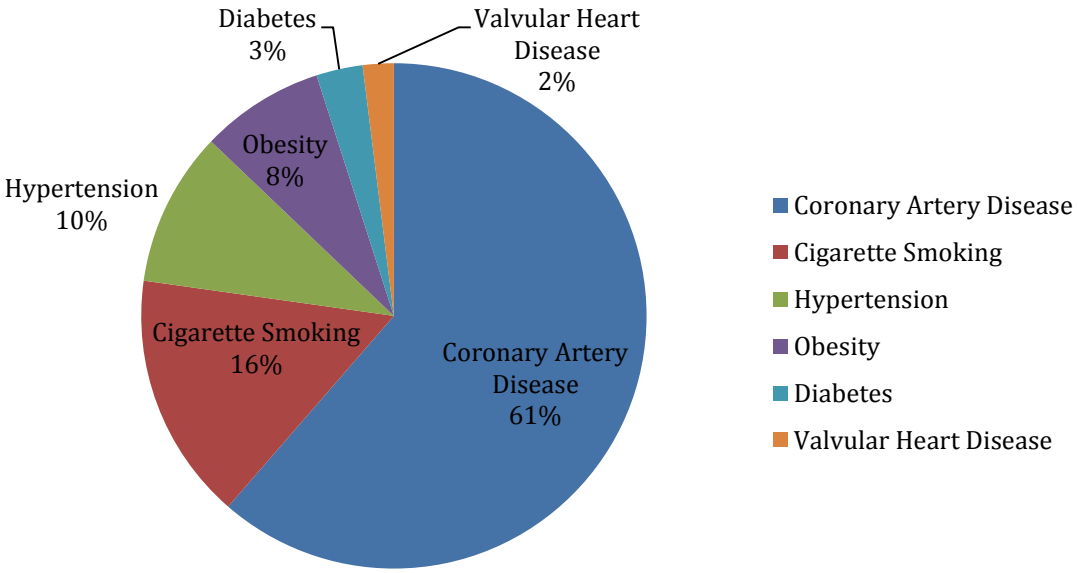
Source: Arnold, M.O. 2013 [11]

The most common cause of heart failure is coronary artery disease, where the buildup of fatty deposits in arteries that supply blood to the heart muscle itself, a process known as atherosclerosis, hampers the flow of blood to and proper oxygenation of cardiac muscles. Coronary artery disease underlies over 60% of heart failure cases in the United States.[12] The heart can also be weakened by a heart attack where a blockage in a coronary artery results in damage and death to heart muscle tissue that becomes starved for oxygen. Other contributing factors that can lead to heart failure include faulty heart valves, high blood pressure, cardiomyopathy, alcohol abuse or toxic drug effects, viral infections, congenital heart defects, and heart arrhythmias. The breakdown of causes of HF in the United States is shown in **Figure 5**.

[11] Arnold, MO, 2013. Heart Failure. In *Merck Manual Online*. Retrieved from http://www.merckmanuals.com/home/heart_and_blood_vessel_disorders/heart_failure/heart_failure.html

[12] He, J et al., 2001. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Archives of Internal Medicine*, 161, pp996-1002.

Figure 5. Causes of Heart Failure in US Adults



Source: He, J et al., 2001

Diagnosis, Classification, & Official Treatment Guidelines

HF Diagnosis and Classification. Diagnosis of heart failure is based on symptoms, a physical exam, plus blood tests, a chest x-ray, electrocardiogram (ECG), cardiac catheterization, and a stress test to look for coronary artery disease. An echocardiography is the likely first step that allows doctors to measure key benchmarks of the heart's performance, such as stroke volume and ejection fraction, with an ejection fraction less than 40% indicating impaired left ventricular systolic function. There is no single gold standard for screening heart failure; commonly used procedures include the Framingham Criteria, Boston Criteria, and Duke Criteria, which have standards for diagnosing heart failure based on the combinations of symptoms presented.

Functional classification of HF relies on designations described by the New York Heart Association, as shown in **Figure 6**. It places patients in one of four categories based on how much they are limited during physical activity. Each patient's condition is assigned a class number and letter. The class numbers describe qualitatively the physical symptoms the patient experiences and the class letters indicate the clinical stage of the disease.

Figure 6. Functional Classification of Heart Failure Stages by New York Heart Association

Class	Patient Symptoms
Class I	No limitations in activity are experienced; no symptoms in ordinary activities
Class II	Slight limitations but comfortable at rest and mild activity
Class III	Increased limitations; comfortable only at rest
Class IV	Physical activity brings discomfort; symptoms occur even at rest
Class	**Objective Assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Source: New York Heart Association

Standard Treatment for Heart Failure. Treatment for heart failure focuses on improving symptoms and preventing the progression of the condition. To prevent the condition from worsening, it is necessary to identify and treat the underlying cause. The goal of treatment is also to reduce symptoms and thus improve the patient's quality of life. Treatments include lifestyle changes, medicines, and ongoing care; in severely debilitating cases not responsive to treatment, surgical interventions, such as a pacemaker or left ventricular assist devices (LVAD), or a heart transplant, may become necessary.

Yet, while these therapies may elicit positive effects on the patient's health, they are not disease-modifying and act mainly to reduce the heart's workload. The first line of defense in heart failure is the use of angiotensin-converting enzyme (ACE) inhibitors, which dilate blood vessels, making it easier for the heart to circulate blood. ACE inhibitors have beneficial effects on mortality, morbidity, and quality of life. They may be used as early as Class I HF in order to prevent the progression of the disease. This will often be paired with a beta-adrenergic receptor

antagonist, or beta-blocker, in stable patients with systolic dysfunction, in order to decrease the workload of the heart. If symptoms persist while a patient is receiving both ACE inhibitors and beta-blockers, then an aldosterone inhibitor is usually added into the regimen. Aldosterone inhibitors block binding of aldosterone, a hormone released by the adrenal glands, which reduces the systemic buildup of fluid and strain on the heart.

Treatments for Late-stage Heart Failure. Once pharmacological interventions fail, more invasive surgical interventions often become necessary to counteract HF progression. In patients with severe cardiomyopathy, an automatic implantable cardioverter-defibrillator (ICD) is often considered to reduce the risk of life-threatening arrhythmias. Heart transplant and left ventricular assist device (LVAD) are both end-stage treatments. Only about 3,500 heart transplants are performed each year, about 2,500 of which take place in the US. The 5 and 10 year survival rates after a heart transplant are 75% and 56%, respectively.

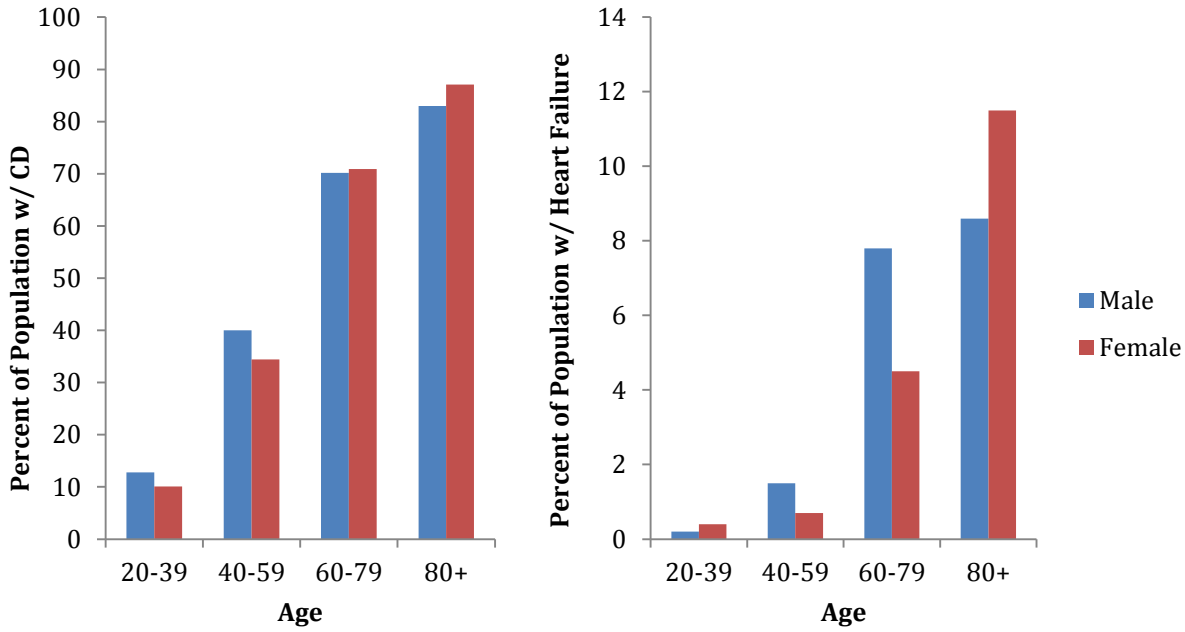
LVADs, once a temporary fix while a patient waited for a heart transplant, have become long-lasting solutions. In 2012, over 5,000 LVADs were implanted worldwide, with roughly 1,000 procedures in the United States. With an LVAD device, a tube connects the left ventricle to one end of a pump and another tube connects the other end of the pump to the aorta. It reduces strain on the heart by helping the left ventricle pump oxygenated blood into systemic circulation. The target patient population for *C-Cure* is advanced HF patients with NYHA Class III and IV symptoms of heart failure and who may become candidates for heart transplant or left ventricular assist device (LVAD). There is a large market for any heart failure therapy that can significantly delay the need for LVADs, heart transplant, and related therapies. This is particularly true for a new cell therapy that can accomplish improvements in cardiac function in a less invasive manner.

Heart Failure Market Information

There are over 5 million people in the United States afflicted by congestive heart failure, and an additional 18 million worldwide.[13] About half of HF patients die within 5 years of diagnosis,[14] indicating significant room for improvement in the management of the disease. Cardiovascular disease and the risk of HF increase substantially with age; by 80 years of age, over 80% of adults have some form of cardiovascular disease, and increasing incidence of HF. The prevalence rates of cardiovascular disease and heart failure in the US adult population can be seen in **Figure 7**.

[13] Bui, AL, et al., 2011. Epidemiology and risk profile of heart failure. *Nature Reviews Cardiology*, 8, pp30-41.
[14] Go, AS, et al., 2013. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation,* 127, pp6–245.

Figure 7. Prevalence of Cardiovascular Disease and Heart Failure by Age



Source: National Heart, Lung, and Blood Institute & LifeSci Capital

A disease-modifying therapy that can significantly slow or reverse the natural progression of heart failure may potentially affect millions of patients. Present treatments are only able to aid the failing heart and reduce strain on the muscle. Cell therapy offers enormous potential to alter the course of this progressive condition and prevent an otherwise slow deterioration of health resulting from a weakened heart. There are clear potential pharmacoeconomic benefits of a successful treatment for HF as this condition carries a heavy economic burden with annual costs now estimated to be $32.4 billion in the US.[15,16]

US Market Estimates. *C-Cure*, a cell therapy to repair and replenish damaged heart tissue, has the potential to treat a subset of the HF patient population. Estimates from the American Heart Association indicate that there are about 5 million patients affected by heart failure in the United States.[17] About half of HF cases stem from systolic heart failure, and these are the patients who are eligible for *C-Cure* treatment. *C-Cure* is currently being tested in patients with NYHA Class III and IV symptoms of HF. According to the National Heart, Lung and Blood Institute, Class III, and IV HF patients make up 30% of the HF patient population.[18] Therefore, approximately 765,000 HF patients may be eligible for treatment with *C-Cure* in the US, as outlined in **Figure 8**.

[15] Yancy, CW, et al., 2013. ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, 128, pp. 240-327.
[16] Heidenreich, PA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*, 123(8), pp933–944.
[17] Heidenreich, PA, et al., 2013. Forecasting the Impact of Heart Failure in the United States: A Policy Statement From the American Heart Association. *Circulation: Heart Failure*, 6, pp606-619.
[18] Ahmed, A, et al., 2006. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *American Heart Journal*, 151:2, pp444-450.

Figure 8. Market Estimate of Target US Patient Population

Criteria	Patients
Have Heart Failure	5,100,000
Have Systolic Heart Failure	x 50% (2,550,000)
Are NYHA Classes III and IV	x 30% (765,000)
Target Patient Population	**=** 765,000

Source: LifeSci Capital

Worldwide HF Population. In a population of roughly 900 million people in 51 countries, there are about 15 million HF patients in Europe.[19] Assuming similar distributions of systolic HF and NYHA Classes as in the US, the European target population for *C-Cure* consists of 2.3 million HF patients.

Results from the Phase II clinical trial indicate that *C-Cure* delivered by intramyocardial injection may improve patient symptoms as well as reduce clinical events and time to hospitalizations. If this effect is confirmed in the Phase III CHART-1 and CHART-2 studies, then the cost-savings for hospitals and payers would make this cell therapy an attractive treatment option. This market estimate is based solely on *C-Cure's* potential in the treatment of systolic heart failure and does not factor in other indications presently under consideration by the Company. Depending on the outcome of the Phase III trials, Celyad may develop *C-Cure* for patients with non-ischemic heart failure. This would represent a future growth area for Celyad after potential launch of *C-Cure* in the primary ischemic HF population.

C-Cure in Ischemic Heart Failure - Clinical Data Discussion

Celyad completed a Phase II trial with *C-Cure* in 2012 in which the treatment was safe and well-tolerated, and initial efficacy results suggested improvement in symptoms.[20] The Company is now conducting the CHART-1 Phase III study in Europe, with a full data readout expected in the second half of 2016.

Celyad plans to launch a second Phase III study CHART-2 in the US and Europe later this year. In September of 2014, the Company filed an amendment to the initial *C-Cure* IND for CHART-2 requesting several changes including the use of their proprietary catheter for the injection of cells into the heart. In January 2015, the FDA approached the Company seeking clarification on the design of the catheter and safety data from CHART-1, as well as requesting that the CHART-2 study include a measurement of cardiac injury 30 days post injection. The CHART-2 trial is currently on clinical hold and the Company is in active dialogue with the FDA and expects to launch the trial in the fourth quarter of 2015.

[19] Dickstein, K, et al., 2008. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *European Journal of Heart Failure*, 10(10), pp933-989.
[20] Bartunek, F, et al., 2013. Cardiopoietic Stem Cell Therapy in Heart Failure. *Journal of the American College of Cardiology*, 61(23), pp2329-2338.

***C-Cure* Phase II Trial**

Trial Design. Celyad conducted an open-label, randomized Phase II trial evaluating *C-Cure* in 47 patients with NYHA Class II or III heart failure secondary to ischemic cardiomyopathy.[21] Patients in the study were randomized 2:1 into treatment and control arms. These subjects had to have an ischemic heart failure diagnosis for at least 2 months before enrollment, and if patients were not already fitted with an implantable cardioverter-defibrillator, one was provided. Patients with moderate to severe aortic valve disease or left ventricular thrombus were excluded, as were patients who received a biventricular pacemaker within 6 months of enrollment.

Patients in the control arm received the standard of care, which included a beta-blocker, ACE inhibitor or angiotensin receptor blocker, and a diuretic. Patients in the cell therapy arm received the standard of care plus cardiopoietic cells via endoventricular injection. The treatment arm received an average of 700 million cells over the course of 6-26 injections. The primary endpoint for the trial was safety and feasibility. Safety was assessed based on occurrence of cardiovascular events and arrhythmias. Feasibility was determined by measuring the success of cell isolation, expansion, manufacturing and delivery into the patient. Secondary endpoints included the following:

- Cardiac structure/function assessed by left ventricular ejection fraction, left ventricular end systolic volume, and left ventricular end diastolic volume using an echocardiography at 6 months post therapy
- Cardiovascular performance assessed by the 6 minute walk test at 6 months post therapy

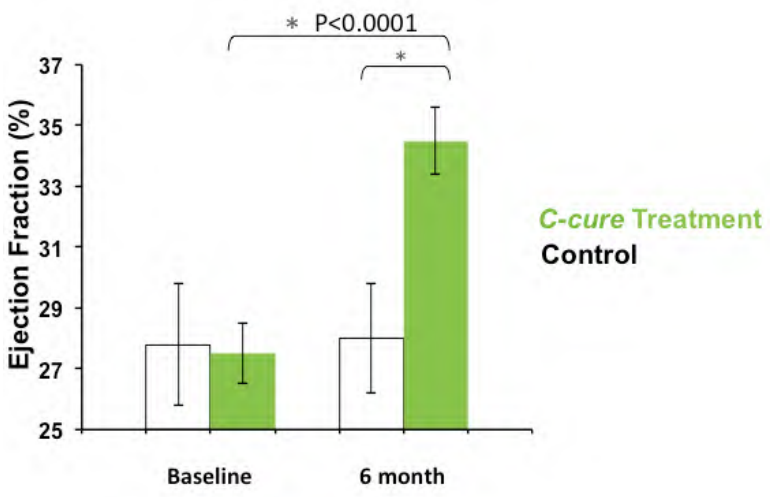
Trial Results. Regarding the primary endpoint of safety, the trial provided confirmation that *C-Cure* is safe and well tolerated. No subject was discontinued from the study due to an adverse event and there was no sign of systemic toxicity induced by the cells. One patient in the experimental arm died prior to the 24-month follow up after developing sepsis related to an elective cardiac transplantation. Throughout the 24-month follow-up period, no event was reported with a definite or probable relationship to the cell therapy.

Cardiopoietic cells were successfully generated for 21 of 28 patients. 32 patients were initially randomized to the experimental arm, however 2 patients did not meet the clinical inclusion criteria and 2 did not provide sufficient bone marrow material to begin the Cardiopoietic platform. All 21 patients for whom cells were derived received endoventricular injections of cardiopoietic cells.

Figure 9 shows that patients receiving *C-Cure* experienced a significant increase in left ventricular ejection fraction (LVEF) relative to baseline ($p < 0.0001$), as indicated by the green bars. The improvement for *C-Cure* treated patients was also significant relative to the control arm. Patients in the experimental arm experienced average increased LVEF of 7 percentage points from baseline at the 6-month follow up. In contrast, patients in the control arm did not experience a significant increase in LVEF relative to baseline.

[21] Bartunek, F, et al., 2013. Cardiopoietic Stem Cell Therapy in Heart Failure. *Journal of the American College of Cardiology*, 61(23), pp2329-2338.

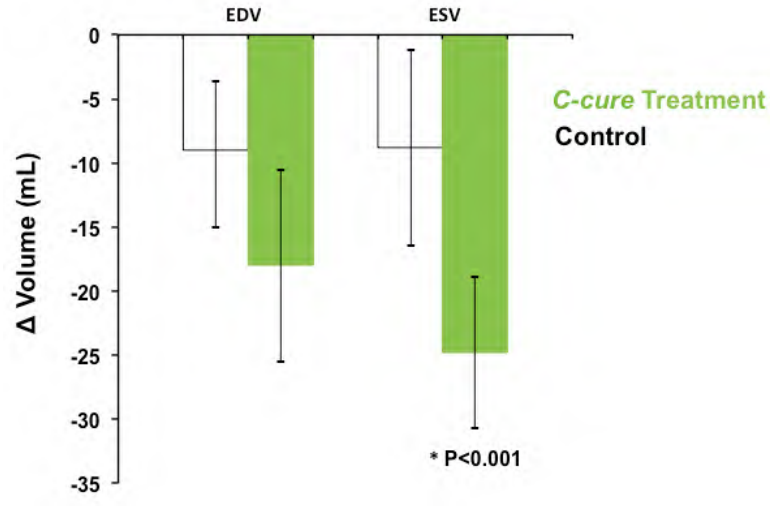
Figure 9. Patients Treated with *C-Cure* Showed Improved LVEF



Source: Company Presentations

Additional readouts for cardiac function measured in this trial were left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV), which together indicate the overall ability of the heart to pump blood back into circulation. **Figure 10** shows that *C-Cure* treatment lead to a significant decrease from baseline in ESV ($p < 0.001$) and indicates an improvement in overall cardiac function. *C-Cure* therapy significantly reduced the LVESV by -24.8 +/- 3.0 ml compared with -8.8 +/-3.9 ml in the control group ($p<0.001$). Reduction in LVEDV was -18 ml versus -9 ml in the cell therapy group and the control group, respectively, however this reduction was not statistically significant.

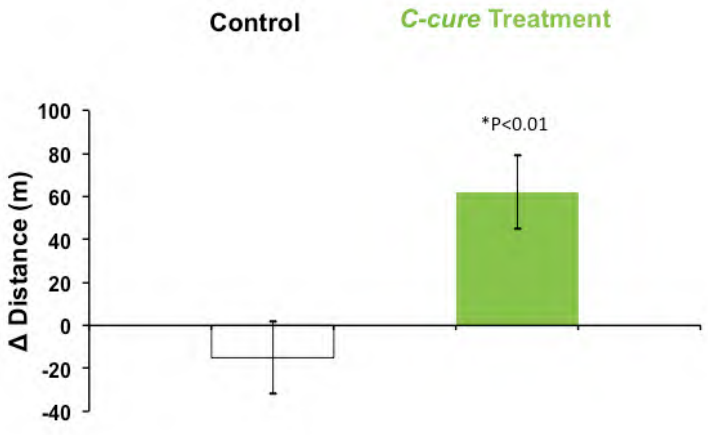
Figure 10. *C-Cure* treatment improves LVESV



Source: Company Presentations

Figure 11 shows that *C-Cure* treatment lead to a significant improvement in patient performance in the 6-minute walk test ($p < 0.01$). The test measures the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface, and is used as an index of cardiovascular performance. *C-Cure* treatment significantly improved the average patient performance from 394 meters to 456 meters in cell-treated patients, whereas average patient performance in the control group decreased from 419 meters to 404 meters ($p< 0.01$).

Figure 11. Patients Treated with *C-Cure* Demonstrated Improved 6 Minute Walk Test



Source: Company Presentations

The Minnesota Living with Heart Failure Questionnaire also improved over 6 months for *C-Cure* treated patients.[22] The questionnaire is a composite measure of health-related quality of life. Approximately 70% of *C-Cure* treated patients reported improvements in the 6-minute walk distance, LVEF and end systolic volume (ESV), indicating that the majority of patients responded to one or more metric within the questionnaire. There was no statistical improvement over the standard of care in terms of overall survival or reducing the number of hospitalizations, although two patients died from heart failure causes in the control group.

CHART-1 Phase III Trial

Trial Design. Celyad is conducting a randomized, double-blind, Phase III trial with *C-Cure* (*C3BS-CQR-1*) as a treatment for ischemic heart failure.[23, 24] 240 adults patients have been recruited across 30 clinical centers in Europe and Israel. All subjects in the trial must have been diagnosed with NYHA class IIb, III, and IVa ischemic HF. Patients were randomized 1:1 into treatment and control arms, with the groups receiving intramyocardial injections *using C-Cath*$_{ez}$ of either *C-Cure* or placebo in addition to the standard of care. The treatment protocol calls for patients to receive up to 600 million cardiopoietic cells over the course of several injections during one procedure.

[22] Rector, TS, 2005. A conceptual model of quality of life in relation to heart failure. *Journal of Cardiac Failure*. 11, pp173–6.
[23] https://clinicaltrials.gov/ct2/show/NCT01768702
[24] https://www.clinicaltrialsregister.eu/ctr-search/search?query=2011-001117-13

The main objective of the trial is to test the safety and efficacy of *C-cure* for the treatment heart failure over a 39-week period. The primary endpoint is a hierarchical composite score composed of:

- **Mortality** as measured by days to death from any cause.
- **Morbidity** in terms of number of worsening heart failure events.
- **6-minute walk test** categorization into groups of 40 meter deterioration, no change, or 40 meter improvement.
- **LVESV** measurement ranked as 15 mL deterioration, no change, or 15 mL improvement.
- **LVEF** measurement ranked as 4% absolute deterioration, no change, or 4% absolute improvement.
- **Minnesota Living with Heart Failure Questionnaire** scores categorized as a 10-point decline, no change, or 10-point increase.

Each patient in the *C-Cure* and control groups will be compared, and a comprehensive score will be derived to characterize the potential treatment benefits. Secondary endpoints for the trial include: number and cause of deaths and re-admissions, number of cardiac transplantations, number of myocardial infarctions, and number of strokes over a 104-week period. The full data readout from this trial is expected in the second half of 2016.

Preliminary Safety Results. On March 30, 2015, Celyad announced that Data and Safety Monitoring Board (DSMB) reviewed unblinded safety and efficacy data from CHART-1 and determined that the trial continue without modification to the initial protocol.

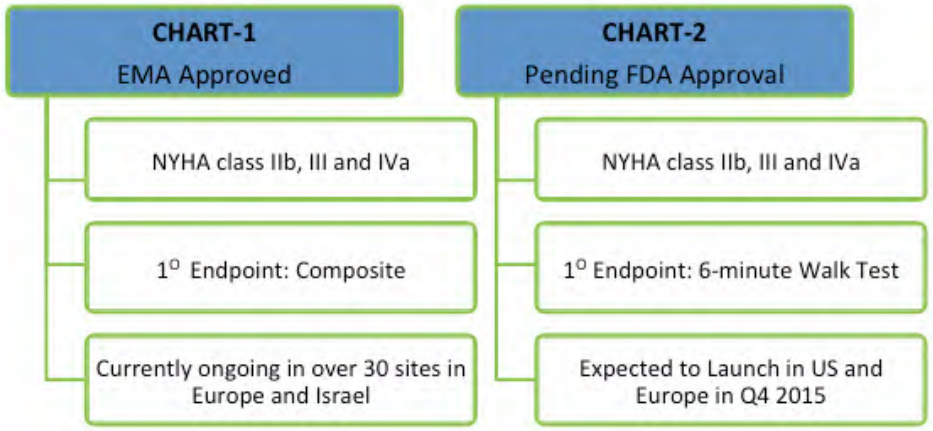
CHART-2 Phase III Trial

Trial Design. Celyad is expecting to initiate a second randomized, double-blind, Phase III trial with *C-Cure* (*C3BS-CQR-1)* in the fourth quarter of 2015.[25] 240 adult patients will be recruited in the US and Europe, and these subjects will be randomized 1:1 to receive *C-Cure* or placebo treatment on top of the standard of care. All subjects will be diagnosed with NYHA class IIb, III and IVa HF, and the treatment protocol indicates that patients will receive up to 600 million cardiopoietic cells over the course of several injections during one procedure.

The main objective of the trial is to test the safety and efficacy of bone marrow-derived cardiopoietic cells for improving exercise capacity in ischemic HF patients. The primary endpoint is the change from baseline in the 6-minute walk test over a 36-week treatment period. **Figure 12** details the designs of the CHART-1 and CHART-2 trials. Both studies target the same patient population, however efficacy will be measured differently in the trials.

[25] https://clinicaltrials.gov/ct2/show/NCT02317458

Figure 12. Summary of CHART-1 and CHART-2 Studies



Source: LifeSci Capital

Other Treatments in Development

There are many clinical trials underway testing the safety and efficacy of cell therapies for the treatment of ischemic heart failure. Recent advances in the field of cell therapy have opened up new potential avenues for HF treatment. Some of these therapies aim to repair damaged heart tissue by introducing healthy cardiomyocyte progenitors that can integrate and improve cardiac function. The main differentiating factors between trials are the type of cells used, and whether it is allogeneic or autologous therapy. Autologous cells are derived from the patient, and allogeneic cells come from a healthy donor. **Figure 13** lists selected cell therapy products in clinical development. We discuss companies with Phase III cell therapy programs for ischemic heart failure below.

Figure 13. Ongoing Cell Therapy Development Programs for HF

Company	Product Candidate	Type of Cells	Development Stage
BioCardia (private)	CardiAMP	Autologous	Phase III
Bioheart (BHRT)	MyoCell	Autologous	Phase II/III
Celyad (CYAD)	C-Cure	Autologous	Phase III
Cytori (CYTX)	OICH-D3	Autologous	Phase II
Mesoblast (MSB.AX)	MPC-150	Allogeneic	Phase III
Vericel (ATQP.F)	Ixmyelocel-T	Autologous	Phase II

Source: LifeSci Capital

CardiAMP - BioCardia

BioCardia's (private) CardiAMP is an autologous cell therapy for ischemic heart failure that can be produced and administered in a bedside procedure. The CardiAMP product is made of mononuclear cells derived from the bone marrow. Not all patients are eligible for this therapy, so the Company uses a proprietary diagnostic assay to identify individuals with optimal cell characteristics. Those patients with competent marrow undergo a 1 hour procedure in a cardiac catheterization lab that begins with a bone marrow aspirate. Cells from the biopsy are minimally processed and concentrated before being injected intramyocardially. CardiAMP has been tested in several clinical trials and has been shown to be safe and well tolerated. Initial signs of efficacy were demonstrated in a Phase II study where patients receiving CardiAMP treatment showed a significant improvement in cardiac function. The Company is currently working with the FDA to obtain approval of their Phase III program.

Phase III Trial Design. BioCardia plans to conduct a multicenter, randomized, double-blind Phase III trial for CardiAMP in patients with post-myocardial heart failure.[26] The trial will be conducted in the US and is expected to enroll approximately 250 patients. Subjects in the trial must have a diagnosis of NYHA class II or III and display a left ventricular ejection fraction (LVEF) between 20% and 40%. Patients will be divided into two study arms and will receive either injections of CardiAMP or placebo. The primary endpoint is the change from baseline in a 6-minute walk test at 12 months. Secondary endpoints include overall survival and freedom from major adverse cardiac events (MACE) as non-inferiority outcomes. Data from this trial are expected mid-2018.

MPC-150 - Mesoblast

Mesoblast's (ASX: MSB) MPC-150 is an allogeneic therapy under development for several indications including heart failure. MPC-150 is made from rare mesenchymal precursor cells (MPCs) derived from the various adult tissues. When delivered systemically, MPCs release growth factors that have been shown to induce blood vessel formation and heart muscle regeneration in preclinical studies. Initial signs of efficacy were shown in a Phase II trial in patients diagnosed with NYHA II or greater, and an ejection fraction less than 40%. Results from the study showed that of 15 heart failure patients treated with MPC-150, no hospitalization was required and no cardiac-related deaths occurred during the three-year follow up period. Pateints treated with MPC-150 experienced significant reductions in left ventricular end systolic volume ($p= 0.015$) and left ventricular end diastolic volume ($p= 0.02$), indicating an overall improvement in cardiac function. Mesoblast and partner Teva Pharmaceuticals (NYSE: TEVA) plan to launch a Phase III trial for MPC-150 in 2015. The Company is also collaborating with the NIH on a trial in 120 patients with advanced heart failure requiring an implantable left ventricular assist device (LVAD).

Phase III Trial Design. Mesoblast expects to launch a randomized, double-blind Phase III trial for MPC-150 in patients with chronic congestive heart failure. The trial aims to enroll approximately 1,700 patients and will be conducted in the US. Subjects in the trial must have a diagnosis of NYHA class II or III and an ejection fraction of less than 40%. Patients will be divided into two study arms and will receive either injections of MPC-150 or placebo, with the MPC treatment arm receiving a single injection of 150 million cells. The primary endpoint is a time-to-first event analysis of major adverse cardiac events (MACE), which is defined as a composite of cardiac related death or non-fatal heart failure events.

[26] https://clinicaltrials.gov/ct2/show/record/NCT02438306

Competitive Landscape

The current treatment landscape for HF is largely defined by therapies that aim to reduce strain on the heart and prevent the disease progression necessitating a heart transplant. Developments in cell therapy and regenerative medicine have renewed interest in less invasive means of altering and perhaps even improving the course of this disease.

There are several companies presently developing cell therapies for the treatment of HF, and Celyad's program is one of the most advanced. Unlike the late-stage products in development at BioCardia and Mesoblast, *C-Cure* is comprised of progenitor cells that exclusively make cardiac tissue. This differentiating feature may lead to higher rates of tissue engraftment and cardiac repair, which could translate into improved clinical performance and patient outcomes.

CAR-NK Platform: Cellular Immunotherapies for Oncology

Recent advances in the fields of molecular immunology and cell therapy have led to the production of a new generation of cellular immunotherapies for the treatment of cancer. To date the most clinically successful of these is chimeric antigen receptor T cell (CAR-T) therapy, which utilizes genetically modified, patient-derived T lymphocytes to recognize and eliminate tumor cells. T cells play an important role in limiting tumor growth and prolonging survival in cancer patients, however their natural anti-tumor activity is limited. CAR technology overcomes this limitation by generating large numbers of T cells *ex vivo* and engineering them with chimeric tumor associated antigen (TAA) receptors capable of inducing and sustaining robust anti-tumor activities. CARs combine a high affinity TAA receptor with an intracellular signaling domain in a single molecule. Celyad recently in-licensed a CAR platform technology from Celdera Medical (private) that does not require TAA-specific receptors. This defining and differentiating feature of the platform may position Celyad well in this young but competitive space.

Celyad's CAR-T platform engineers T lymphocytes with a natural killer (NK) cell receptor fused to the intracellular signaling domain of CD3ζ. NK cells are components of the innate immune system that recognize and kill stressed cells. Cells infected with bacteria or viruses, or those that have been transformed into tumor cells, express proteins or NK ligands on their surface that are recognized by NK cell receptors. Ligand receptor engagement activates the NK cells and initiates a series of events that ultimately eliminates the stressed cell.

Celyad's platform, illustrated in **Figure 14**, genetically modifies T cells to express chimeric NK cell receptors so they bind NK ligands on tumor cells and stimulate anti-tumor immune responses. These CAR-NK cells do not require a TAA for targeting. This means a single CAR-NK therapy can treat multiple cancer types if the tumor cells are NK ligand-positive. Preclinical studies have established the therapeutic potential of a single CAR-NK therapy for both blood, ovarian, skin, and colorectal cancers.[27, 28, 29] These pre-clinical studies provide evidence that CAR-NK T cells induce robust and long-term anti-tumor activity via direct and indirect mechanisms.

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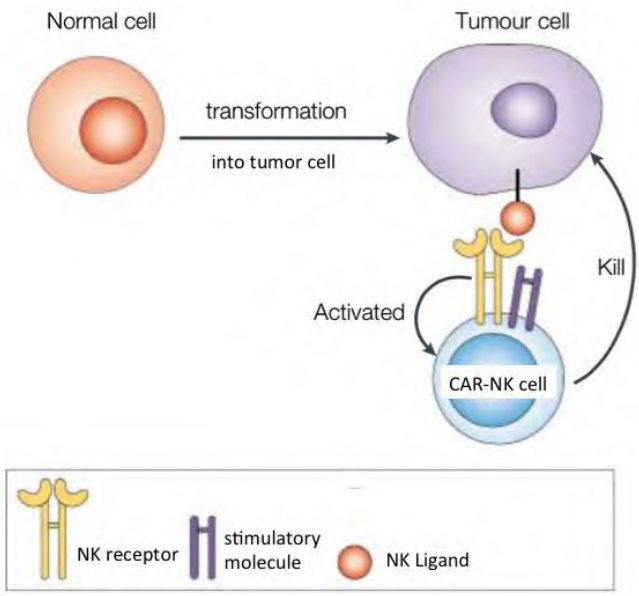
[27] Zhang, T, et al., 2005. Chimeric NKG2D-Modified T cells Inhibit Systemic T cell Lymphoma Growth in a Manner Involving Multiple Cytokine and Cytotoxic Pathways. *Cancer Research*, 67(22), pp11029-11036
[28] Barber, A, et al., 2009. Chimeric NKG2D Expressing T cells Eliminate Immunosuppression and Activate Immunity within the Ovarian Tumor Microenvironment. *Journal of Immunology*, 183, pp6939-6947
[29] Barber, A, et al., 2011. Treatment of multiple myeloma with adoptively transferred chimeric NKG2D receptor-expressing T cells. *Gene Therapy*, 18, pp509-516

Figure 14. CAR-NK T cell Technology



Source: Yokoyama et al., 2003[30] and modified by LifeSci Capital

CAR-NK T Cell Production. Celyad's CAR-NK T cell product candidates will be produced in the Company's wholly owned GMP processing facilities in Belgium and the US. The core manufacturing steps are listed below and described in more detail in this section.

- **Leukapheresis:** A patient's lymphocytes are separated from peripheral blood.
- **Activation:** T cells are activated using a variety of methods.
- **Transduction:** The CAR-NK construct is introduced into T cells using a delivery vehicle such as a virus.
- **Expansion phase:** Genetically modified CAR-NK T cells undergo a round of *ex vivo* expansion using a cell culture bioreactor to achieve the target dose.
- **Cell harvest:** CAR-NK T cells are collected, washed, and cryopreserved.
- **Cell infusion:** Patients receive IV infusion of CAR-NK T cells

Leukapheresis and T cell activation are the first manufacturing steps prior to CAR-NK viral transduction. Once T cells are collected by apheresis and separated they must be activated before transduction with the CAR-NK construct. T cell activation is achieved by exposing the cells to small beads bound by anti-CD3 and anti-CD28 monoclonal antibodies. The beads enable simultaneous positive selection and activation of T cells. Delivery of the CAR-NK construct into T cells is achieved using viral transduction. Viruses are the preferred method of transduction because they integrate into the host DNA, enabling long-term gene expression. The CAR-NK T cells are then expanded again *ex vivo* before being infused back into the patient.

[30] Yokoyma, WM, et al, 2003. Immune Functions Encoded by the Natural Killer Gene Complex. *Nature Reviews Immunology*. 3(4), pp304-316.

Mechanism of Action. CAR-NK T cells have the potential to target and eliminate a broad range of liquid and solid tumors through direct and indirect mechanisms.[31] Activated CAR-NK T cells directly lyse ligand-positive tumor cells, decreasing tumor burden and potentially activating cytotoxic T cells by exposing additional tumor antigens.[32] CAR-NK T cells also secrete the pro-inflammatory cytokines IFN-γ and GM-CSF, which promote anti-tumor activity by modifying the cell populations within the tumor microenvironment. Specifically these cytokines reduce the immunosuppressive activities of T-regulatory cells (Tregs) and stimulate cytotoxic T cell attack of tumor cells.[33] Studies have also shown that CAR-NK T cells induce a tumor-specific T cell memory response, which potentially provides long-term anti-tumor immunity. This mode of action may be unique to CAR-NK T cells and likely enhances immune cell monitoring of the tumor site and reduces the likelihood of tumor cell escape.[34]

CAR-NK Platform Versatility. The CAR-NK platform provides Celyad with versatility in developing therapies for many different types of cancers. The Company's initial focus has been on hematological malignancies, however the technology can be extended to other cancers. The main advantage of this platform is its potential to target tumors with poorly defined TAA, such as ovarian and pancreatic cancer. Should CAR-NK therapy prove safe and effective in blood cancers, Celyad will be well positioned to target a broad range of cancer types.

The Company has in-licensed 3 CAR-NKs receptors, 2 of which are still in preclinical development. These receptors could be combined into a single therapy to either enhance tumor cell targeting or induce stronger immune reactions.

Potential Allogeneic CAR-NK Platform. Patient-derived or autologous CAR-NK T cells retain their pre-existing TCR complex and would likely cause graft-versus-host disease (GVHD) if infused into a patient other than the donor. The risk of GVHD has been a considerable roadblock in generating off-the-shelf CAR products, however several recent technologies have now emerged that may permit the development of such a therapy. Celyad has a TCR Inhibitory Molecule (TIM) technology that suppresses activities associated with GVHD. This technology may allow the Company to scale-up CAR-NK T cell production and potentially treat many more patients with an off-the-shelf therapy. Celyad is therefore one of the rare companies in the field to have both an autologous and allogeneic approach.

CAR-NKG2D: A T Cell Immunotherapy for Hematological Cancers

Celyad's lead oncology product candidate CAR-NKG2D is a CAR therapy initially being developed as a monotherapy for blood cancers. It is based on proprietary technology developed by investigators at Dartmouth and has been in-licensed from Celdera Medical. CAR-NKG2D T cells express a chimeric form of the NK cell receptor NKG2D, which targets all cancer types that express NKG2D ligands. Initial signs of efficacy have been shown in several preclinical animal models. The Company has initiated a Phase I study in relapsed or refractory acute myeloid leukemia and multiple myeloma, with a full data readout expected in the second half of 2016.

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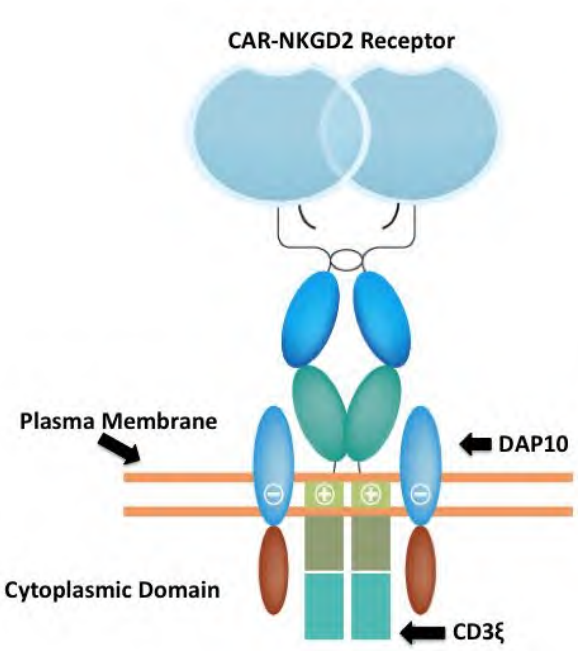
[31] Sentman, CL, et al., 2014. NKG2D CARs as Cell Therapy for Cancer. Cancer Journal, 20(2), pp156-159
[32] Zhang, T, et al., 2007. Chimeric NKG2D-Modified T cells Inhibit Systemic T cell Lymphoma Growth in a Manner Involving Multiple Cytokine and Cytotoxic Pathways. *Cancer Research*, 67(22), pp11029-11036
[33] Barber, A, et al., 2009. Chimeric NKG2D Expressing T cells Eliminate Immunosuppression and Activate Immunity within the Ovarian Tumor Microenvironment. *Journal of Immunology*, 183, pp6939-6947
[34] Barber, A, et al., 2011. Treatment of multiple myeloma with adoptively transferred chimeric NKG2D receptor-expressing T cells. *Gene Therapy*, 18, pp509-516

Chimeric NKG2D Receptor Generation. Figure 15 shows that CAR-NKG2D receptor is generated by joining the NKG2D receptor with the CD3ζ signaling fragment of the TCR complex, to encourage T cell activation and proliferation. The fusion of DNA derived from the NKG2D receptor and the CD3ζ molecule makes the receptor chimeric. The intracellular portion of the CAR-NKG2D receptor incorporates a CD3ζ signaling domain, which is expressed together with the co-stimulatory molecule DAP10 to activate the PI3-kinase/AKT pathway and promote cell activation and proliferation. Incorporation of the DAP10 co-stimulatory signaling domains allows for multiple rounds of proliferation, improved cytokine production, and improved cell survival.

Figure 15. The CAR-NKG2D Receptor



Source: Celyad Presentation and LifeSci Capital

CAR-NKG2D T cell activation is a one-step process, while T cell activation requires two signals delivered by antigen presenting cells (APCs). The first signal occurs from the binding of the TCR complex to the antigen ligand, which stimulates the activation chain of the TCR, CD3ζ. The binding of the co-stimulatory domain to the ligand on the APC is the second signal and promotes the expansion of the antigen activated T cell and differentiation into effector and memory cells. In contrast, CAR-NKG2D T cells are activated when the NKG2D receptor binds its ligands.

CAR-NKG2D Ligands. The extracellular portion of NKG2D receptor encodes specificity for multiple ligands that are expressed on different tumor types. The most commonly found NKG2D ligands include MHC class I chain–related A, MHC class I chain–related B, and UL-1 to 6–binding proteins, and they can be expressed alone or in combination on the surface of tumor cells. These features may make NKG2D ligands compelling targets for CAR based immunotherapies for two reasons. First, CARs that are able to target more than one ligand increase the likelihood of tumor recognition and decrease the possibility of tumor escape. In addition, the ability to target eight

ligands increases the absolute total number of cancer types that can be targeted. To demonstrate this point we compare cancer types targeted by known CARs and CAR-NKG2D in **Figure 16**. This shows that a single CAR-NK therapy could target more than 15 different tumor types.

Figure 16. Current Landscape of CAR and CAR-NKG2D Indications

CAR	Companies	Cancer types	CAR-NK	Companies	Cancer types
CD19	Many	ALL			Ovarian
	Many	Lymphoma			Bladder
	Novartis	MM			Breast
					Lung
L1CAM	Juno	Neuroblastoma			Hepatocellular
					Colon
MUC16	Juno	Ovarian			Renal
					Prostate
Mesothelin	Novartis	Mesothelioma	**NKG2D**	**Celyad**	AML
		Pancreatic			CML
		Ovarian			CLL
EGFRvIII	Novartis	Glioblastoma			Lymphoma
					MM
HER2	Baylor University	Glioblastoma			Melanoma
					Ewing Sarcoma
					Glioma
					Neuroblastoma

Source: LifeSci Capital

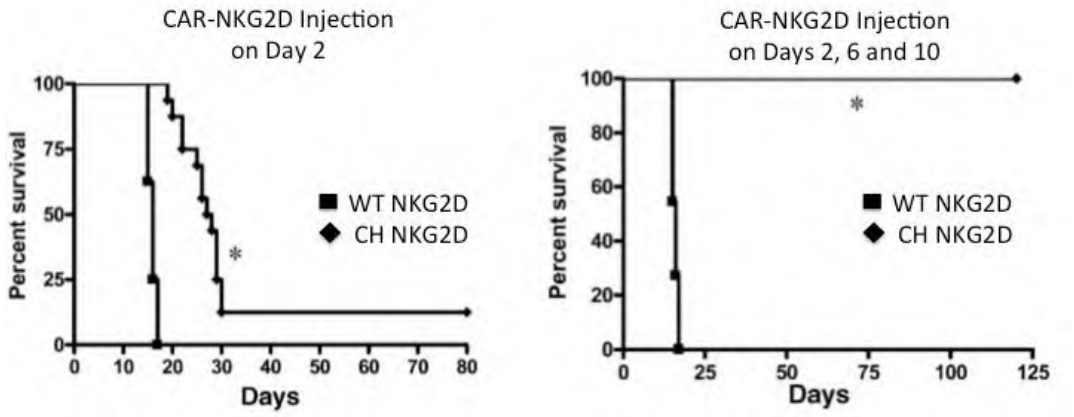
Preclinical Data

A research group at Dartmouth College has published a series of experiments demonstrating that CAR-NKG2D cells promote long-term survival in mouse models of multiple myeloma, lymphoma and ovarian cancer. The preclinical data discussed below substantiates Celyad's current clinical investigation of CAR-NKG2D in multiple myeloma and acute myeloid leukemia.

Figure 17 shows that transplantation of CAR-NKG2D T cells promotes survival in a mouse model of lymphoma. To determine the efficacy of CAR-NKG2D T cells in eliminating tumors, lymphoma cells that express an NK ligand were injected intravenously (IV) into mice. Two days after the tumor cells were injected, animals intravenously received either wild type (WT) NKG2D or chimeric (CH) NKG2D T cells. WT NKG2D T cells lack the intracellular CD3ζ signaling domain, so although they can recognize the NKG2D ligand they cannot mount an immune response. The left panel in **Figure 17** shows that treatment with a single dose of CH NKG2D T cells doubled the median survival from 15 to 30 days ($p<0.001$). 2 of 16 or 12.5% of the mice became long-term

survivors after one treatment with CH NKG2D T cells. The right panel of **Figure 17** shows that when animals were injected with WT or CH NKG2D T cells on days 2, 6 and 10, all those receiving the CH NKG2D T cells lived for more than 120 days ($p < 0.001$). In both experiments the median survival for the cohorts receiving WT NKG2D T cells was approximately 15 days.

Figure 17. Transplantation of NKG2D T Cells Promote the Survival of Lymphoma-Bearing Mice

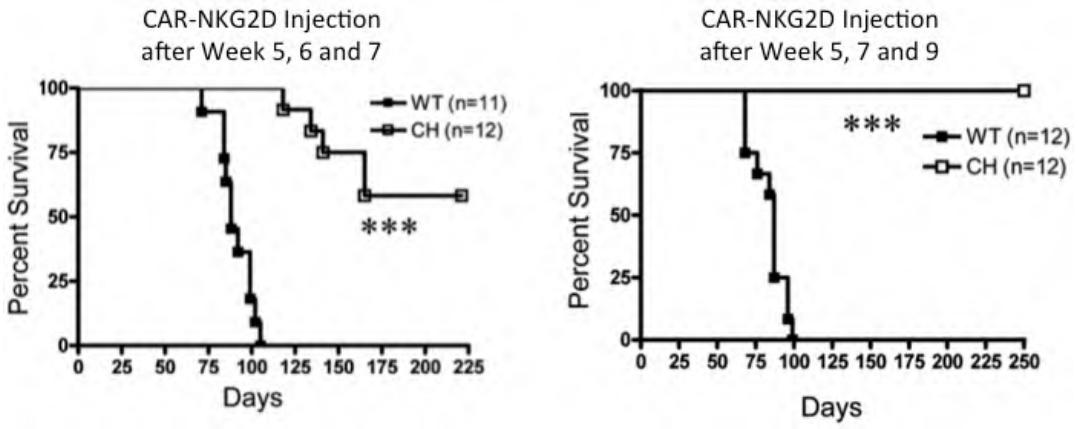


Source: Zhang, T et al., 2007[35]

Figure 18 demonstrates that CAR-NKG2D T cells promote survival in a mouse model of ovarian cancer. To determine whether treatment with CH NKG2D T cells could increase survival in mice with established ovarian tumors, WT NKG2D or CH NKG2D T cells were transferred to tumor-bearing mice 5, 6, and 7 weeks after tumor cell seeding. The left panel shows that treatment with CH NKG2D cells significantly increased the survival of tumor-bearing mice ($p < 0.001$). 7 of 12 CH NKG2D T cell-treated mice survived and were tumor-free 225 days after tumor cell injection. All animals receiving WT NKG2D T cells had large solid tumors and succumbed to their disease in this experiment, with a median survival of 88 days post tumor seeding. In the right panel in **Figure 18**, NKG2D cells were injected after weeks 5, 7 and 9. This treatment regime leads to long-term survival for 100% of the animals with CH NKG2D T cells. These experiments indicate that CH NKG2D cells can effectively eliminate solid tumors *in vivo*.

[35] Zhang, T, et al., 2007. Chimeric NKG2D-Modified T cells Inhibit Systemic T cell Lymphoma Growth in a Manner Involving Multiple Cytokine and Cytotoxic Pathways. *Cancer Research*, 67(22), pp11029-11036

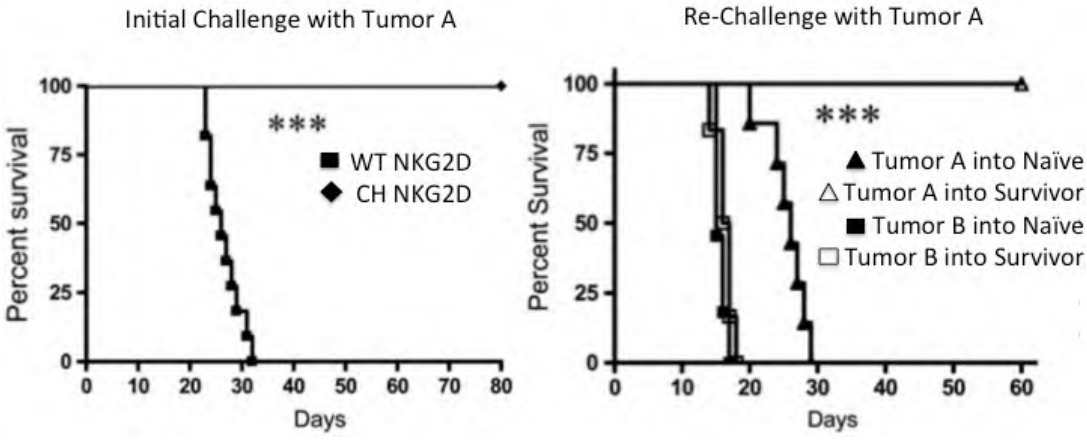
Figure 18. Chimeric NKG2D T Cells Promote Long-term Survival in an Ovarian Cancer Model



Source: Barber, A., et al., 2009[36]

Figure 19 demonstrates that CAR-NKG2D stimulates long-term anti-tumor immunity in a mouse model of multiple myeloma. To test the efficacy of CH NKG2D T cells against an established myeloma, tumor cells were injected into animals. Tumor-bearing mice were injected with two treatments of WT NKG2D or CH NKG2D T cells 5 and 12 days after tumor seeding. The left panel in **Figure 19** shows that CH NKG2D T cell-treated mice survived and were tumor-free 80 days after tumor cell injection. To determine whether the animals that had survived the myeloma challenge developed an immune cell memory response, myeloma cells were re-injected into the tumor-surviving animals 80 days after original tumor seeding. The right panel in **Figure 19** shows that all of the tumor-surviving mice survived the tumor re-challenge, while the tumor- naïve animals had a median survival of 27 days.

Figure 19. Chimeric NKG2D T Cells Provide Long-term Anti-Tumor Immunity



Source: Barber, A., et al., 2011[37]

[36] Barber, A., et al., 2009. Chimeric NKG2D Expressing T cells Eliminate Immunosuppression and Activate Immunity within the Ovarian Tumor Microenvironment. *Journal of Immunology*, 183, pp6939-6947

[37] Barber, A., et al., 2011. Treatment of multiple myeloma with adoptively transferred chimeric NKG2D receptor-expressing T cells. *Gene Therapy*, 18, pp509-516

Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is an aggressive cancer of the blood and bone marrow that is fatal if left untreated. Approximately 19,000 new cases of AML are expected to be diagnosed in the US in 2015.[38] The median age for an AML patient at diagnosis is about 67 years, and as the population ages the number of AML patients is likely to increase. AML is the most common type of adult acute leukemia, resulting in over 10,000 deaths per year. There are approximately 35,000 patients in the US who have been diagnosed with AML. Even with aggressive treatment, AML is often fatal. According to the American Cancer Society the five-year overall survival rate is 24%.

Pathogenesis and Causes of AML

AML patients have an outgrowth of cells from the myeloid lineage that accumulate in the bone marrow. The myeloid cells are predominately immature white blood cells called myeloblasts, or blasts, which are the leukemic cells. Bone marrow cell dysfunction is caused by genetic mutations that impact the normal differentiation of stem cells. Previous treatment with cytotoxic chemotherapeutic agents and radiation exposure are common factors associated with AML, since exposure to mutagenic agents may induce genetic alterations in bone marrow stem cells.

AML Classification. Two major classification systems are used to categorize patients with AML. The original classification scheme is the French, American, British (FAB) system that was originally proposed in 1976.[39] The FAB system classifies subtypes of AML from M0 to M7 and makes distinctions based upon the type of cell the cancer originated from and the maturity of the cancerous cells. An updated system was released in 2001 by the World Health Organization (WHO).[40] The WHO system groups subtypes of AML by factors which correlate with expected outcome measures. The system also differs from the FAB classification in that a blast threshold of 20% is now sufficient for an AML diagnosis instead of 30%. The WHO categories are as follows:

- Acute myeloid leukemia with recurrent genetic abnormalities.
- Acute myeloid leukemia with multi-lineage dysplasia.
- Acute myeloid leukemia and myelodysplastic syndromes, therapy-related.
- Acute myeloid leukemia, not otherwise categorized.

In addition to the historical classification systems, many cancers including AML are now also classified based on the presence or absence of particular genetic mutations. The most well-known mutations that occur in AML patients are in the genes NPM1, RUNX1, and FLT3. Inhibitors of wild type and mutated FLT3 are in clinical development for AML patients.

Symptoms and Diagnosis

According to the National Cancer Institute, the early signs of AML include fever, lethargy, easy bruising or bleeding, weakness, weight loss, and fatigue. A visual symptom is flat spots of blood under the skin called petechiae. Several

[38] American Cancer Society: Cancer Facts and Figures 2014. Atlanta, Ga: American Cancer Society, 2014. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf.
[39] Bennett, JM, et al., 1976. Proposals for the classification of the acute leukaemias French-American-British (FAB) Co-operative Group. *British Journal of Haematology*, 33(4), pp451-458.
[40] Jaffe, ES, et al., 2001. World Health Organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press.

methods with increasing complexity and invasiveness are used to diagnose AML. A complete blood count and a blood smear provide an analysis of the distribution of cells within the blood to give an initial picture of cellular imbalances. Further diagnostic tests require bone marrow aspiration and genetic analysis of the blasts. The medical diagnosis of AML requires greater than 20% leukemic blasts in the bone marrow, and features such as an abnormal hematocrit and abnormal platelet count are also typically present.

Treatment of AML

Treatment programs for AML patients depend on several variables including the patients' age, the subtype of AML, and whether the disease is newly formed, recurrent, or resistant. Another important determinant of treatment is whether the patient's disease falls into one of three risk categories: better, intermediate, or poor.

There are three major steps in the treatment of AML over the course of the disease: induction therapy, consolidation therapy, and hematopoietic stem cells transplant or HSCT. HSCT involves the intravenous infusion of autologous or allogeneic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to reestablish hematopoietic function in patients whose bone marrow or immune system is damaged or defective. Some patients undergo all 3 stages of treatment with the timing between therapies determined by the success of the previous step. However, a large proportion of patients do not follow the standard treatment course. For example, many patients are unfit to receive intensive chemotherapy regimens, including patients who are too frail for the treatment for a variety of reasons, especially advanced age. Patients over 65 are known to have a more difficult time tolerating intensive chemotherapy, but the median age for AML is about 70 years. This clearly points to the need for safer treatments.

Induction Therapy. All patients who choose to be treated receive induction chemotherapy as a first line treatment for AML. Induction therapy is intended to reduce leukemic blasts and return functionality to the bone marrow. It commonly includes a regimen of 7 days of cytarabine and followed by 3 days of an anthracycline drug such as idarubicin, daunorubicin, or mitoxantrone. Cytarabine was approved by the FDA in 1969 and is a nucleotide analog that inhibits DNA synthesis. Daunorubicin, idarubicin, and metoxantrone are intercalating agents that inhibit topoisomerase activity to block DNA synthesis. These antineoplastic chemotherapeutic drugs cause the death of all rapidly-dividing cells in the body, targeting cancerous cells but also killing many other types of cells. Therefore, induction therapy is an in-patient procedure, usually 4-6 weeks in length, which must be completed in a hospital with staff trained for the requisite side effects and high rate of infection.

Due to the damaging effects of induction therapy, mortality from high intensity chemotherapy ranges from 5-15% in younger AML patients and 20-50% in over the old of 65.[41] Because of this risk, almost 30% of patients over 65 years of age opt for palliative care only. While induction therapy often results in cancer remission, defined as a blast concentration <5% of total blood components, it is likely that some residual blasts survived the induction stage and will lead to recurrence. Therefore, post-induction treatment may be administered using a standard dose of cytarabine.

[41] Kantarjian, H.M., 2007. Therapy for elderly patients with acute myeloid leukemia. *Cancer*, 109(6), pp1007-1010.

Consolidation Therapy. Induction therapy is followed by consolidation therapy with high dose intermittent cytarabine (HiDAC) every 12 hours for 3 to 6 days. This treatment paradigm has not changed since its original description in 1994.[42]

Hematopoietic Stem Cell Transplant. The ultimate goal with the current treatment paradigm is to bridge patients to HSCT, which is usually indicated considering that 75% of AML patients relapse even after a complete remission. However, not all patients are eligible for HSCT or matching donors cannot be found. The process of identifying eligible patients and matching donors is so rigorous that the treatment is not feasible for most AML patients. Relapse is common since blasts are often not fully eradicated during treatment, making HSCT the most reliable way to extend overall survival.

Salvage Therapy. Despite treatment with aggressive chemotherapy regimens, most AML patients never achieve complete remission and many of those who do experience relapse. These patients are then treated with salvage therapy, which may take different forms. Salvage therapy often includes very toxic chemotherapy regimens, and patients are also encouraged to enter clinical trials at this stage. Identification of the proper salvage therapy is patient specific and depends on the level of remission achieved, the patient's age and comorbidities, and increasingly on any specific genetic mutations identified.

Celyad is developing CAR-NKG2D as a potential monotherapy for relapsed or refractory AML. There is a significant need for therapies that can improve outcomes for those patients who fail intensive chemotherapy. CAR-NKG2D may be an effective treatment for such populations due to its unique mechanism of action.

AML Market Information

It is estimated that there will be 19,000 new cases of AML in 2015 and approximately 10,000 deaths. While AML is the most common form of acute leukemia in adults, the standard of care has largely been unchanged for decades. Other types such as chronic myeloid leukemia (CML) have benefited from targeted therapies such as *Gleevec* (imatinib), *Sprycel* (dasatinib), *Tasigna* (nilotinib), *Iclusig* (ponatinib), and *Bosulif* (bosutinib), but most AML patients still undergo intensive chemotherapy with the goal of achieving remission. Most patients will relapse at some point, sometimes experiencing multiple relapses. As a result, only 25% of AML patients can be expected to survive for more than 3 years according to the American Cancer Society, leaving a large unmet need for this indication, especially for relapsed and refractory patients.

Market Size. The AML market is estimated at $150 million and is mostly addressed by generics, but is expected to grow contingent on potential FDA approval of targeted therapies such as Daiichi Sankyo's (DSKYF) quizartinib. As a comparison for the potential of branded drugs in the AML market, we highlight the success of Novartis's (NVS) *Gleevec* (imatinib) for the treatment of chronic myelogenous leukemia (CML). *Gleevec* brought in sales of $4.7 billion in 2013, although it is also approved in other indications. Bristol Myers-Squib is also in the CML market with 2013 sales of $1.3 billion for *Sprycel* (dasatinib), and Novartis has a second drug, *Tasigna* (nilotinib), that achieved $1.3 billion in 2013 sales. When considering these sales figures, it is worth noting that patient population for CML is half the AML patient population. The revenue potential for a targeted treatment such as CAR-NKG2D that improves

[42] Mayer, R.J., et al., 1994. Intensive post-remission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *New England Journal of Medicine*, 331(14), pp896–903.

patient outcomes is similar, especially considering the lack of existing options and the high mortality rate of the disease.

Other Treatments in Development for AML

There are many clinical trials underway testing the safety and efficacy of new treatments for AML. Recent advances in the fields of genomics and immunotherapy have opened up new potential therapeutic avenues for this indication. Some of the drugs and therapies currently in clinical development are listed in **Figure 20**. The primary differentiating factor between these development programs is the target patient population. Several of the programs listed only address patients with specific DNA mutations. This type of therapy often referred to as personalized medicine is becoming feasible due to the availability of genomic testing. Other development programs utilize either cell- or antibody-based immunotherapies. These approaches have shown promise for some cancers types, however it remains to be determined how they perform in AML.

Figure 20. Treatments in Development for AML

Company	Product Candidate	Description	Development Stage
Agios (AGIO)	AG-221	IDH2 inhibitor	Phase I
Ambit (Private)	Quizartinib	FLT3 inhibitor	Phase III
Amgen (AMGN)	AMG330	bsAb (CD33XCD3)	Phase I
Astellas (ALPMY)	ASP2215	FLT3/AXL inhibitor	Phase III
Cellectis (CLLS)	UCART123	CAR	Preclinical
Conkwest (Private)	CD33.taNK	NK cells	Phase I
Epizyme (EPZM)	EPZ-5676	DOT1L inhibitor	Phase I
Innate Pharma (IPH.PA)	Lirilumab	Anti-KIR	Phase II
Juno (JUNO)	WT-1	TCR	Phase I
Macrogenics (MGNX)	MGD006	bsAb (CD123XCD3)	Phase I
Seattle Genetics (SGEN)	SGN-33A	ADC (CD33)	Phase I

Source: LifeSci Capital

Multiple Myeloma

Multiple myeloma (MM) is a cancer of the blood and bone marrow that is fatal if left untreated. According to the American Cancer Society, approximately 26,000 new cases of MM are expected to be diagnosed in the US in 2015. The median age for an MM patient at diagnosis is about 69 years and as the population ages the number of patients is likely to increase. MM is the second most common blood cancer behind non-Hodgkin's lymphoma (NHL), resulting in more than 11,000 deaths per year. Currently there are approximately 64,000 patients in the US who have been diagnosed with MM. Even with aggressive treatment, the disease is often fatal; according to the American Cancer Society the five-year overall survival rate is estimated at 10-20%.

Pathogenesis and Causes of MM

MM patients have an outgrowth of cells from the hematopoietic lineage that accumulate in the bone marrow. These hematopoietic cells are white blood cells or plasma cells, which are important regulators of adaptive immunity. While the exact cause of MM is unknown, evidence suggests chromosomal abnormalities are linked to disease onset.

MM Classification. Two staging systems are used to classify the disease states of MM patients, but the International Staging System (ISS) is used primarily as the Durie-Salmon classifications have faded. The ISS classifications for MM rely mainly on the serum levels of albumin and beta-2-microglobulin, which were found to be strong predictors of overall patient survival in several studies. ISS, summarized below in **Figure 21**, divides MM into three stages. The main advantages of ISS over the Durie-Salmon system are its simplicity and prognostic value.

Figure 21. ISS Staging System for MM

	Albumin	beta-2 microglobulin	Median Overall Survival
Stage I	< 3.5 mg/L	= > 3 mg/dL	62 months
Stage II	Neither Stage I or III	Neither Stage I or III	44 months
Stage III	Not applicable	= > 5.5 mg/dL	29 months

Source: LifeSci Capital

In addition to the two biomarker classification systems, many cancers including MM are now also characterized based on the presence of chromosomal abnormalities. DNA deletions and translocations can be used to stratify patients into high risk, intermediate risk and standard risk disease categories,[43] which can help guide therapy. The specific genetic lesions used to stratify MM into the three risk categories are:

- **Standard risk** – trisomy, translocation (11; 14), translocation (6; 14)
- **Intermediate risk** – translocation (4; 14), deletion of Chromosome 13
- **High risk** – deletion of Chromosome 17p13, translocation (14; 16), translocation (14; 20)

Symptoms and Diagnosis of MM

According to the American Cancer Society, the early signs of MM include bone problems, low blood counts, high blood levels of calcium, kidney disease and nerve damage. Bone pain can arise in the back, hips and skull, and bone fractures often occur in the extremities. Anemia also commonly presents in patients with MM.

Several methods with increasing complexity and invasiveness are used to diagnose the disease. A complete blood count (CBC) and blood smear provide an analysis of the distribution of cells within the blood to give an initial picture of the cellular imbalances. If there are too many plasma cells in the bone marrow, the counts for other cells in the blood will be abnormally low. Another test performed to diagnose MM is the serum protein immunoelectrophoresis assay, which reports the levels of the Ig protein in the blood. In MM patients, IgA or IgG are present at much higher levels in the blood than other Ig antibodies. Further diagnostic tests for MM require bone marrow aspiration and genetic analysis of the plasma cells. The clinical diagnosis of MM requires greater than

[43] Rajkumar, SV, et al., 2012. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. American Journal of Hematology, 87, p78.

10% plasma cells in the bone marrow, and at least one of the following features:

- Low red blood cell counts
- Increase in one type of Ig protein in the blood
- Lesions in bones
- High blood calcium levels
- Poor kidney function

Once a diagnosis is confirmed, the next step includes testing for chromosomal abnormalities that help predict risk prior to treatment. Individual cases can be stratified into either high risk, intermediate risk, or standard risk MM based upon the results of fluorescence in situ hybridization (FISH) for specific DNA translocations and/or deletions.[44]

Treatment of MM

The initial goal of therapy for a patient with symptomatic MM is to induce complete remission, which is defined as less than 5% plasma cells in the bone marrow. Treatment programs depend on several variables including the patients' age, the stage of MM, and comorbidities. High dose chemotherapy followed by HSCT is considered the standard of care for eligible patients with newly diagnosed MM. Current estimates suggest that approximately 50% of newly diagnosed MM patients are candidates for bone marrow transplantation based upon age and the absence of co morbidities. However, according to the Center for International Blood and Marrow Transplant Research (CIBMTR), 5,000 patients in the US undergo transplant for myeloma, which only represents approximately 20% of newly diagnosed patients.

Treatment for transplant-eligible patients. There are two major steps in the treatment of transplant-eligible MM patients over the course of the disease: induction therapy and HSCT.

- **Induction Therapy.** All transplant-eligible patients who choose to be treated receive induction chemotherapy for two to four months as a first line treatment for MM. The therapy is intended to reduce plasma cells and return functionality to the bone marrow. Patients are typically treated with two to four cycles of one of the following four different regimens: *Thalomid* (thalidomide) plus dexamethasone, *Revlimid* (lenalidomide) plus dexamethasone (Rd), *Velcade* (bortezomid) plus dexamethasone (Vd), or *Velcade* plus *Revlimid* plus dexamethasone (VRd). There have been no Phase III trials comparing any of these regimens.

- **Bone Marrow Transplant or Hematopoietic Stem Cell Transplantation Therapy.** The ultimate goal of the current treatment paradigm for MM is to bridge patients to HSCT since it provides an overall survival benefit.[45,46] After induction therapy, transplant candidates are reevaluated for response. The most common transplant is an autologous transplant in which patients serve as their own bone marrow donors. Usually patients have their stem cells harvested in a quantity sufficient to allow for a second transplant should the disease relapse.

[44] Rajkumar, SV, et al., 2011. Treatment of multiple myeloma. *Nature Review Clinical Oncology*, 8(8), pp479
[45] Jantunen, E, et al., 2006. High-dose melphalan (200 mg/m2) supported by autologous stem cell transplantation is safe and effective in elderly (>or=65 years) myeloma patients: comparison with younger patients treated on the same protocol. *Bone Marrow Transplant*, 37(10), pp917-922.
[46] Lenhoff, S, et al., 2006. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. *British Journal of Haematology*, 133(4), pp389-396.

Since most patients who received autologous HSCT for MM eventually develop relapsed disease, trials have investigated the use of chemotherapeutic and biologic agents as maintenance therapy in an attempt to eliminate residual malignant cells after transplantation. Maintenance therapy can prolong progression-free survival, but it is unclear whether there is a survival benefit.

Treatment for relapsed or refractory MM. Treatment options for relapsed or refractory MM include hematopoietic cell transplantation, a re-challenge of previous chemotherapeutic agents, or a clinical trial. For patients who are eligible for transplant but did not undergo transplant as part of their initial treatment, high dose chemotherapy followed by HSCT is an option. For patients who have already undergone transplantation and who have experienced a durable benefit, treatment options include repeat transplantation or chemotherapy. The most common regimens recommended for the treatment of relapsed or refractory myeloma include Rd, bortezomib with cyclophosphamide and dexamethasone (VCD), bortezomib plus lenalidomide and dexamethasone (VRd), carfilzomib plus lenalidomide and dexamethasone (KRd), and pomalidomide plus dexamethasone.

Celyad is developing CAR-NKG2D as a potential monotherapy for relapsed or refractory MM. There is a significant need for therapies that can improve outcomes for patients who fail intensive chemotherapy. CAR-NKG2D may be an effective treatment for such populations due to its unique mechanism of action.

MM Market Information

About 1 in 143 people in the United States will develop multiple myeloma at some point in their life. The American Cancer Society estimates that there will be about 26,850 newly diagnosed cases in 2015 and about 11,240 deaths. Recent annual sales for biologics and targeted therapies indicated for multiple myeloma are listed in **Figure 22**. Some products are indicated for multiple diseases so sales figures do not exclusively represent revenue from MM. Several biologics and targeted therapies are indicated, some in combination with bortezomib or dexamethasone or both. Multiple myeloma represents a substantial market opportunity that is growing, with 5.6% annual growth through 2020.[47] Targeted therapies and biologics are usually reserved for refractory or second-line treatment, after initial treatment using either chemotherapy or *Velcade*.

Figure 22. Biologics and Targeted Therapies Indicated for MM (in Millions)

Drug	Area of treatment	2012 Sales	2013 Sales	2014 Sales
Bortezomib (Velcade)	1st Line	$2,400	$2,600	$3,000
Carlfilzomib (Kyprolis)	Relapsed MM	-	$71	$306
Thalidomide (Thalomid)	R/R MM	$305	$245	$220
Lenalidomide (Revlimid)	R/R MM	$3,779	$4,302	$5,004
Farydak (Panobinostat)*	R/R MM	N/A	N/A	N/A
Pomalyst (Pomalidomide)	R/R MM	$12	$305	$680

*approved March 2015 in combination with bortezomib and dexamethasone

Source: LifeSci Capital

[47] http://www.fiercebiotech.com/press-releases/multiple-myeloma-drug-market-will-experience-robust-56-percent-annual-growth

Other Treatments in Development for MM

There are many clinical trials underway testing the safety and efficacy of new treatments for MM. We highlight the development programs testing cell- or antibody-based immunotherapies in **Figure 23**. Most of these product candidates are in preclinical or early clinical development. Novartis is targeting the CD19 CAR for MM. While CD19 is normally expressed exclusively in B-cell malignancies such as ALL, NHL and CLL, an abstract presented at this year's ASCO conference[48] reported safety and efficacy results for CD19 CAR in relapsed MM patients. In this pilot study, 3 of 4 patients dosed with the CAR therapy showed evidence of clinical benefit. The researchers conducting the study hypothesize that although CD19 is not highly expressed, a subset of potentially MM stem cells may express enough of the marker to elicit a robust anti-tumor response. The Phase I trial is ongoing and is recruiting patients.

Figure 23. Treatments in Development for MM

Company	Product Candidate	Description	Development Stage
Baylor (Private)	TACTAM	T cell therapy	Phase I
Bluebird Bio (BLUE)	BB2121	CAR	Preclinical
Cellectis (CLLS)	UCART38	CAR	Preclinical
	UCARTCS1	CAR	Preclinical
Celyad (CYAD)	CAR-NKG2D	CAR-NK	Phase I
Merck (MRK)	MK-3475	Anti-PD-1	Phase I/II
Takeda (TKPYY)	MLN9708	Anti-PD-1	Phase III
NCI (Private)	Anti-BCMA	CAR	Phase I
Novartis (NVS)	CTL019	CAR	Phase I

Source: LifeSci Capital

CAR-NKGD2 in Hematological Cancers - Clinical Discussion

Phase I Trial Design. Celyad has initiated a Phase I dose escalation trial to evaluate a single intravenous dose of CAR-NKG2D in patients with AML or MM.[49] The trial is expected to enroll 12 patients and will take place at the Dana Faber Cancer Center in Boston, MA. Eligible patients are 18 years of age or older with AML that is not in remission and for which there are no reasonable standard treatment options, or for patients with relapsed/refractory MM with progressive disease. The primary endpoints of the trial are safety and feasibility at 24 months post-injection. Safety is measured by the incidence of study-related serious and non-serious adverse events. Feasibility is defined by the frequency of subjects enrolled that do not receive CAR-NKG2D T cells.

[48]Garfall, AL, et al., 2015. Safety and efficacy of anti-CD19 chimeric antigen receptor (CAR)-modified autologous T cells (CTL019) in advanced multiple myeloma. Journal of Clinical Investigation, 33 (suppl; abstr 8517), trial: NCT02135406
[49] https://clinicaltrials.gov/ct2/show/NCT02203825

This study will also aim to find the maximum tolerated dose (MTD). Doses will range from 10^6 to 3 X 10^7 cells and there will be a disease-specific expansion cohort at the MTD. Data from this trial are expected in the second half of 2016.

Competitive Landscape

CAR-T therapies have shown tremendous promise in the clinical trials that have been conducted to date. The early successes have led to a highly competitive space, especially in the hematological oncology setting. Considering the various development programs, it is important to know the differences in CAR-T technology, manufacturing, and clinical trial design to better predict future clinical success and understand company valuations. These factors are especially crucial as each company moves from small academic trials to larger multi-center trials to support approval.

The CAR-NK platform technology is a major differentiating factor that clearly separates Celyad from competitors. To our knowledge it is the only company developing a product candidate for the relapsed or refractory AML and MM based on chimeric NK receptors. The Company has licensed three CAR-NK therapies, each of which target a non-overlapping set of ligands. Should this technology prove effective, Celyad's portfolio may allow targeting of most if not all cancer types. The Company's lead product candidate has shown signs of efficacy in several animal models including MM, and is now in a Phase I clinical trial. Not only do these chimeric receptors effectively recognize and kill tumor cells, they also induce the release of cytokines that remodel the tumor microenvironment.

Modulation of the tumor microenvironment makes CAR-NK T cells especially attractive for the highly immunosuppressive solid tumor setting. Therapies that decrease immunosuppressive cell populations and induce the recruitment and activation of anti-tumor immune cells may lead to an anti-tumor immune response against solid tumors, as suggested by preclinical studies with CAR-NKG2D in an ovarian tumor model.[50]

Acquisitions and Licensing Agreements

On January 21, 2015, Celyad acquired Oncyte LLC, the oncology division of Celdara Medical, LLC (PRIVATE), a biotechnology company based in Lebanon, New Hampshire. The acquisition provided Celyad with a portfolio of drug product candidates in the immune-oncology space including three autologous CAR-T cell therapy products and an allogeneic T cell platform. Celyad purchased Oncyte for a $10.0 million upfront payment to Celdara, $6.0 million of which was paid in cash and $4.0 million of which was paid in the form of 93,087 ordinary shares of Celyad. Pursuant to the Oncyte asset purchase agreement, Celyad is obligated to make development-based milestone payments to Celdara of $40.0 million for clinical products and of $36.5 million for pre-clinical products should they progress to clinical stage, as well as sales-based milestone payments of up to $80.0 million for products based on the CAR technology, plus tiered single-digit royalty payments in connection with the sales of any product based on the CAR technology.

[50] Barber, A, et al., 2009. Chimeric NKG2D Expressing T cells Eliminate Immunosuppression and Activate Immunity within the Ovarian Tumor Microenvironment. *Journal of Immunology*, 183, pp6939-6947

On November 5, 2014, Celyad acquired CorQuest Medical, Inc. (private) for a single cash payment of €1.5 million ($1.6 million) and a potential earn-out payment to the sellers if the intellectual property acquired from CorQuest is sold, in whole or in part, to a third party before November 5, 2024. The transaction stipulates that the earn-out payment shall be 2.0% of the value of the cash and non-cash consideration from such sale or if the net revenue is €10.0 million ($10.9 million) or less. If the net revenue is greater than €10.0 million ($10.9 million), the earn-out payment shall be 4.0%.

In 2007, Celyad licensed the technology behind their *C-Cure* from the Mayo Clinic in US. Under the technology license agreement, Celyad was granted an exclusive, worldwide license to make, use, modify, enhance, promote, market and/or sell products related to the licensed technology. The exclusive license is subject to the Mayo Clinic's right to make and use products related to the licensed technology within its affiliates' own programs, and to the rights, if any, of the US government. For the licensing rights, Celyad was required to pay an upfront fee of €9,500,000 ($10.4 million), in shares, to the Mayo Clinic and agreed to provide $500,000 of directed research funding per year for the years 2012 through 2014. The Mayo License will continue until the later of ten years or as long as the Mayo Clinic has any rights to any part of the licensed inventions.

Intellectual Property

Cardiopoiesis Platform Patents

Celyad's Cardiopoiesis platform portfolio includes seven patent families, four of which were exclusively licensed from the Mayo Clinic and three of which are wholly owned by Celyad. The Mayo Cardiopoiesis Patents include three issued US patents; 16 foreign patents issued in jurisdictions including Australia, China, Europe, Hong Kong, Israel, Mexico, New Zealand, Russia, Singapore and South Africa; three pending US patent applications; and 25 foreign patent applications. These patents and patent applications relate to compositions and methods for inducing cardiogenesis in embryonic stem cells, methods of identifying cardiopoietic stem cells, and methods of using cardiopoietic stem cells to treat cardiovascular tissue. The Mayo Cardiopoiesis Patents will begin to expire in 2025, absent any adjustments or extensions. The Company expects that any patents that eventually issue from currently pending applications in the Mayo Cardiopoiesis patent portfolio will begin to expire in 2025, absent any adjustments or extensions.

Celyad's Cardiopoiesis patents include an issued patent in New Zealand; a pending US patent application; and 17 foreign patent applications, as well as an application filed under the Patent Cooperation Treaty. These patents and patent applications relate to pharmaceutical compositions containing cardiopoietic stem cells and methods of their production, as well as therapeutic targets and agents for treating ischemia reperfusion injury. The Cardiopoiesis Patents will begin to expire in 2030, absent any adjustments or extensions.

CAR-T Cell Platform Patents

Celyad's CAR-T cell portfolio includes three patent families exclusively licensed from Dartmouth, including two issued US patents; 4 pending US patent applications; and 12 pending foreign patent applications. These patents and patent applications relate to particular chimeric antigen receptors and to T cell receptor-deficient T cells. One pending US patent application relating to T cell receptor-deficient T cells has been allowed, and Celyad intends to submit additional prior art references to the US Patent and Trademark Office to assess whether they are relevant to

the claimed invention. Patents in Celyad's CAR-T cell portfolio will begin to expire in 2025. The Company expects that any patents that eventually issue from currently pending applications in the CAR-T cell platform patent portfolio will begin to expire in 2025, not accounting for possible adjustments or extensions.

Cardiac Injection Catheter Technology Patents

Celyad's cardiac injection catheter technology portfolio includes two patent families wholly owned by the Company. This portfolio includes a pending US patent application; 5 patents issued in jurisdictions including Belgium, Europe, Israel, Mexico, and New Zealand; and 13 foreign patent applications pending in jurisdictions including Australia, Brazil, Canada, China, Hong Kong, India, Japan, Russia, Singapore, South Korea, Taiwan, and the United Kingdom, as well as an application filed under the Patent Cooperation Treaty. These patents and patent applications relate to injection catheters and processes for their use. Patents in this portfolio, if issued, will begin to expire in 2025. The Company expects that any patents that eventually issue from currently pending applications in the Cardiac Injection Catheter Technology patent portfolio will begin to expire in 2029, absent any adjustments or extensions.

Heart Access Technology Patents

Celyad's heart access technology portfolio includes 5 patent families owned by CorQuest, Celyad's wholly owned subsidiary. This portfolio includes 10 pending US patent applications and 10 foreign patent applications pending in various jurisdictions. Patents in this portfolio, if issued, will begin to expire in 2032, absent any adjustments or extensions. These patents and patent applications relate to devices, assemblies and methods for treating cardiac injuries and defects.

Management Team

Christian Homsy, MD, MBA
Chief Executive Officer

Dr. Homsy has been CEO since the company's inception. Prior to Celyad, Dr. Homsy was General Manager of the biotechnology and medical device incubator Medpole. He has also held a senior R&D and business role at Guidant Corporation. Dr. Homsy received his MD from the University of Louvain and his MBA from the IMD in Lausanne. He founded the Guidant Institute for Therapy Development.

Patrick Jeanmart
Chief Financial Officer

Mr. Jeanmart joined Celyad as CFO in 2007 and brings extensive experience from his medical finance positions. These include senior management at Ion Beam Applications Group and several of its subsidiaries in the US and Europe such as IBA Molecular. He continues to act as CFO for the incubator Medpole and for Biological Manufacturing Services.

Warren Sherman, MD
Chief Medical Officer

Dr. Sherman joined Celyad in October 2014. He brings over 30 years of experience in cardiology and has devoted his career to cell-based therapies for heart attack and heart failure. Before joining Celyad, Dr. Sherman was an interventional cardiologist and assistant professor at Columbia University and served as Director of Stem Cell Research and Regenerative Medicine at the Center for Interventional Vascular Therapy. He founded the renowned Cardiovascular Research Foundation's International Conference on Cell Therapy for Cardiovascular Disease. Dr. Sherman's medical degree is from SUNY Upstate and he completed his fellowship at Oregon Health Sciences University (OHSU).

Peter de Waele, PhD
Vice President of Research and Development

Dr. De Waele joined Celyad as VP of R&D in 2010. He has experience leading international clinical trials and in pharmaceutical consulting, with an emphasis on stem cell therapies and medical devices. His current consulting engagements are for tissue banks Esperite N.V. and Stichting Cryo-Save. He is also Managing Director at Advanced Therapies Consulting. Prior to Celyad, Dr. De Waele founded and acted as COO at the stem cell focused biotech XCELLentis. He has also worked as Chief Therapeutics Officer at Innogenetics. He completed his Ph.D. in molecular biology at Ghent University where he served as an assistant professor.

Vincent Brichard, MD, PhD
Vice President of Immuno-Oncology

Dr. Vincent Brichard joined Celyad in January 2015 as VP of Immuno-Oncology. He trained as an oncologist and holds a Ph.D. in tumor immunology. Prior to Celyad, he was Senior VP of the Immunotherapeutics Business Unit at GlaxoSmithKline, in addition to serving as a member of the Vaccines Executive team. He began his career in Academia at the Ludwig Institute for Cancer Research, later moving to the Institut Curie Cancer Center in Paris and the University of Louvain

Risk to an Investment

We consider an investment in Celyad to be a high-risk investment. Celyad is currently in clinical-stage development, has generated very limited product revenue, and does not have any marketed or approved cell therapy products. Celyad is primarily focused on its *C-Cure* and CAR-NKG2D clinical program, using cell therapy to treat heart failure and target cancer, respectively. Celyad has not completed any pivotal clinical trials for either program. Failure to show convincing results in CHART Phase III clinical studies or failure to reach FDA or EMA approval could adversely affect Celyad's stock price. As a clinical-stage company, Celyad is not profitable and may need to seek additional financing from the public markets, which may result in dilution of existing shareholder value.

Celyad
7/30/2015
(All numbers in Thousands & Euros)

	FY12A	1H13A	FY13A	1H14A	FY14A
REVENUES					
Total Revenues	**€ 54**	**$ -**	**€ -**	**€ -**	**€ 146**
Expenses					
Manufacuring	2,186	993	2,415	2,641	5,136
Clinical, Quality & Regulatory	3,605	2,199	4,473	2,908	7,752
Research and Development	3,401	1,083	2,158	980	2,977
General and Administrative	1,882	890	2,988	1,539	5,016
Other Expenses (Income)	1,882	852	(64)	(2,135)	(4,413)
Total Operating Expense	**€ 12,956**	**€ 6,017**	**€ 11,969**	**€ 5,934**	**€ 16,468**
Operating Income	**€ (12,902)**	**€ (6,017)**	**€ (11,969)**	**€ (5,934)**	**€ (16,322)**
Financial Expenses	(642)	(422)	(437)	(16)	(41)
Finanical Income	19	12	60	49	277
Total Other Income (expense)	**€ (623)**	**€ (410)**	**€ (377)**	**€ 33**	**€ 236**
Net Income (Loss)	**€ (13,524)**	**€ (6,428)**	**€ (12,346)**	**€ (5,900)**	**€ (16,453)**
EPS - Basic	**€ (11.17)**	**€ (3.43)**	**€ (3.01)**	**€ (0.92)**	**€ (2.44)**
Weighted average shares outstanding	1,210,765	1,873,985	4,101,734	6,413,304	6,750,383

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