Celyad

# Letter to Shareholders 2019

**Dear Shareholder,**

As every new year brings forth the opportunity to achieve great things, the Celyad team is gearing up for an exciting 2019. We intend to continue to establish Celyad as a worldwide leader in CAR-T cell therapy, with a focus on treating cancer patients with poor prognosis.

Our positive outlook for the year ahead is only possible due to the momentum of our clinical programs established in 2018. I would like to take this opportunity to share with you some of the milestones we accomplished in the last 12 months, all of which could not have been achieved without your support.

# 1. Treating more patients and moving towards a Phase 2 clinical trial for acute myeloid leukemia

The Celyad CAR-T cell therapy programs focus on treating end-stage cancer patients. In 2018, we treated over 30 patients in various Phase 1 studies with our lead CAR-T candidates, CYAD-01 and CYAD-101. This is more than double the number of patients treated compared to the previous year. This acceleration has enabled us to gather important data from our clinical programs.

As a result of the encouraging data we have reported thus far from our Phase 1 clinical trial, we have recently made decisive moves towards initiating a Phase 2 clinical trial for the treatment of patients with relapsed/refractory acute myeloid leukemia during the second half of 2019 (see boxed text).

### Acute myeloid leukemia (AML): an aggressive blood cancer with a clear unmet need for effective treatment

AML is a cancer of myeloid cells, a type of blood cell located mostly in the bone marrow. It progresses rapidly and is typically fatal within weeks or months if left untreated[1]. AML is also associated with high rates of relapse (relapsed AML), when the disease reappears after initial treatment. In addition, some patients do not respond to treatment and are categorized as "refractory" AML patients. Salvage therapy approaches are often attempted; however, the success rates are very low.

### AML kills about 20,000 patients per year

- Approximately 40,000 patients in the United States and Europe are diagnosed each year with AML and about 20,000 deaths per year are attributed to this disease. AML patients have a median age of 68 years at initial diagnosis.
- The only recommended curative approach for the treatment of AML is a bone marrow transplant from a compatible donor. All other treatments act to delay the progression of the disease.
- Patients deemed as 'fit to transplant' are treated with an aggressive combination of chemotherapy agents to ensure that their cancer cell counts fall to below 5% of all bone marrow cells, considered a complete response. As soon as AML patients achieve this status, they are transplanted as soon as possible.

1. https://www.nhs.uk/conditions/acute-myeloid-leukaemia/

# 2. CYAD-01 demonstrating good tolerability and promising initial efficacy in absence of preconditioning

The Phase 1 THINK "standalone" trial evaluating CYAD-01 without preconditioning chemotherapy (see preconditioning boxed text) showed that five out of eight patients (62%) had relevant anti-tumor activity, including three patients who achieved various forms of complete response. The therapy continues to demonstrate good tolerability, which is also encouraging.

The observation of clinical activity of CYAD-01 in the very difficult setting of relapsed/refractory AML and in the absence of preconditioning chemotherapy is encouraging.

Dr. Marco Davila, PhD, from the Moffit Cancer Center (Florida, USA) recently noted the importance of this observation with the following statement from the 2018 Annual Meeting of the American Society of Hematology:

**"A common argument against responses seen with CAR-T cells was that they are mediated by the conditioning chemotherapy. However, the responses seen in patients treated with CYAD-01, whom had no conditioning chemotherapy, strongly argues these responses are mediated by CYAD-01 alone."**

The results observed to date in the THINK "standalone" trial are only the beginning. We are also evaluating CYAD-01 in combination with preconditioning chemotherapy in the DEPLETHINK trial. In October 2018, we enrolled the first patient in DEPLETHINK in patients with relapsed/refractory AML and we expect to release data from the trial during 2019. We anticipate that, in the presence of preconditioning, the activity of CYAD-01 should be higher than what has been observed with the "standalone" approach.

### Preconditioning, a necessary step for CAR-T Therapies

Preconditioning chemotherapy for CAR-T therapies consists of a low-intensity chemotherapy, generally cyclophosphamide and fludarabine, aimed at reducing the number of cancer cells and preparing the bone marrow to receive the CAR-T cell transplant.

To date, all CAR-T therapies, approved or in clinical development, utilize preconditioning. However, Celyad's CYAD-01 has shown activity without the need for preconditioning.

# 3. CYAD-01 falls in the promising CAR-T cell product category

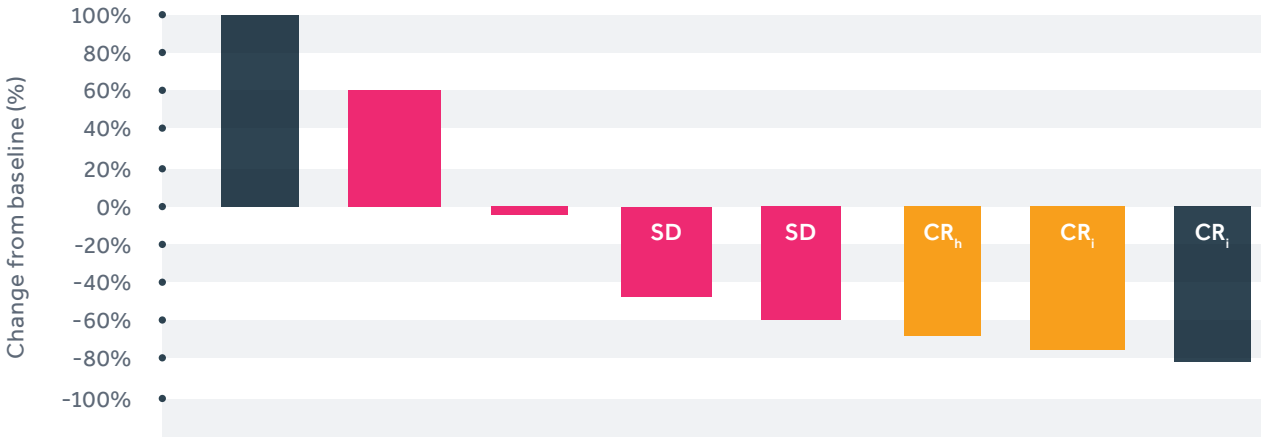
Dr. Davila presented the following data during the American Society of Hematology Annual Meeting in December 2018. During his presentation, he stated:

**" When adoptive T cell therapies work, it is not subtle. This waterfall plot is strongly suggestive of the activity of CYAD-01. Any promising CAR-T cell product had to be used in no more than ten patients before demonstrating clinical efficacy. Based on this plot, CYAD-01 squarely falls in the promising CAR-T cell product category. "**

**Late-breaking update:**

Preliminary data for the last two patients enrolled and treated at dose level 3 show one patient with relapsing MDS achieved a **complete response** while the second patient with r/r AML experienced disease stabilization.

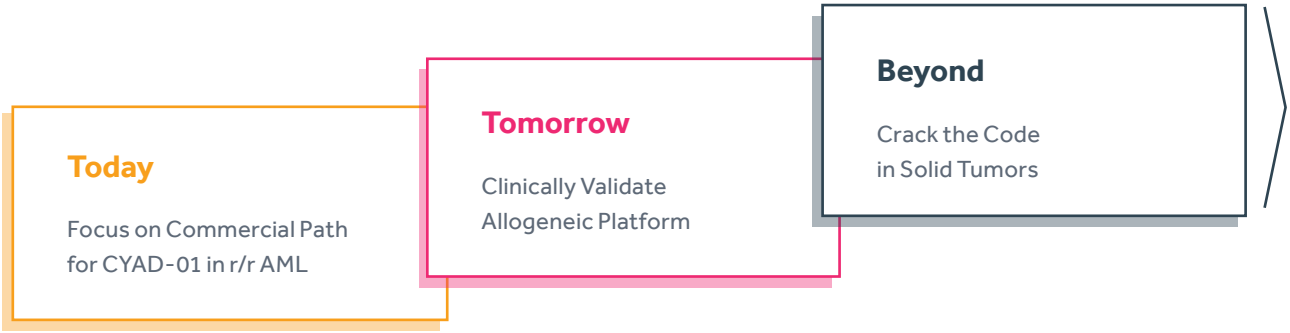
**Change in number of cancer cells in bone marrow, per patient (%)**




CYAD-01 treatment of AML patients results in a drop in the number of cancer cells, potentially catapulting CYAD-01 in the promising CAR-T cell product category.

$CR_i$ = complete remission with incomplete blood count recovery
$CR_h$ = complete remission with partial recovery of blood cells
SD = stable disease

# Our Corporate Strategy: Today, Tomorrow and Beyond




## Today

**A refocused strategy for our development pipeline now includes plans to initiate a Phase 2 trial to evaluate CYAD-01 for the treatment of relapsed/refractory AML in the second half of 2019, with a focus on driving CYAD-01 towards commercialization.**

Overall, this segment of our strategy represents where most of our resources have been and are expected to continue to be dedicated.

In 2019, we aim to:

- Confirm through a larger set of patients that the non-preconditioning approach with CYAD-01 provides a significant response rate in relapsed/refractory AML patients
- Extend the durability of response as much as possible through multiple treatment cycles and different dosing schedules
- Use the DEPLETHINK trial to explore the benefit/risk profile of treating patients with CYAD-01 with preconditioning chemotherapy—an approach used with other CAR-T therapies
- Start a Phase 2 trial in relapsed/refractory AML patients during the second half of 2019

## Tomorrow

**Looking out slightly further, our plan is to leverage our technologies and intellectual property to become a leader in the allogeneic CAR-T field.**

Over the past few years, the field of CAR-T clinical development has moved towards allogeneic technologies to help provide efficiencies in scale, cost and patient access to CAR-T therapies. Allogeneic, or off-the-shelf CAR-T cell therapies, are donor derived versus personalized or autologous therapies.

In general, when immune cells from one person are administered to another person, these cells recognize the tissues of the recipient as foreign and attack them. This is called 'Graft versus Host Disease' (GvHD) and can be fatal if not controlled.

Allogeneic CAR-T therapies utilize donor cells engineered to not recognize the recipient's tissue as foreign. These therapies lack the so-called T-Cell receptor (TCR) or have mechanisms to prevent the signal generated by the TCR.

There are three main techniques for inactivating or suppressing the TCR. They include gene editing, TCR Inhibiting Molecule (TIM®) and short hairpin RNA (shRNA):

- Gene editing approaches include CRISPR-Cas9,

MegaTAL, Talen®, Zinc Finger Nuclease (ZFN) and other techniques in development. These approaches similarly locate the TCR coding gene on a chromosome and cut it or knock it out.

- The TIM® approach interferes with the signal the TCR sends to the cell when it recognizes foreign tissue. This approach was developed primarily to work in concert with the NKG2D-based CAR-T. Celyad's CYAD-101 is currently being evaluated in metastatic colorectal patients in the Phase 1 AlloSHRINK clinical trial.

- The shRNA approach is similar to gene editing. It has the potential to work with any CAR-T therapy eliminating the TCR at the cell surface the same way as gene editing, however, only interfering with the RNA and not the DNA of a cell. It therefore acts downstream of the DNA without tampering with it. The shRNA approach is less likely to induce DNA damage, which may be very serious, as reported recently in *Nature Medicine*. It may also provide benefits such as a much simpler manufacturing process. Celyad plans to start a clinical trial to validate the shRNA platform over the next several quarters.

Celyad has exclusive licenses to two of the three approaches to inhibit the TCR including TIM® and shRNA. These technologies complement our intellectual property, especially in the United States where we have a series of granted patents that require any company wishing to market an allogeneic CAR-T, regardless of the technologies used to disrupt the TCR, to obtain a license from Celyad.

## Beyond

**Looking out even further, we believe there is an opportunity for Celyad to leverage the power of CAR-T therapies for the treatment of solid tumors.**

Solid tumors currently represent a challenge for CAR-T therapies. A CAR-T for solid tumors first requires a tumor recognition system, an antibody or receptor that will make the CAR-T recognize a tumor cell. A CAR-T targeting solid tumors also needs specific features to allow it to infiltrate the tumor. Once inside, it needs to overcome the protective barrier that the tumor has established known as the tumor micro environment or TME.

Thanks to our ongoing studies, we now understand that our NKG2D-based CAR-T targets solid tumors and is well-tolerated. We are now working to strengthen our CAR-T through various tools to better infiltrate the tumor and overcome the hostile tumor microenvironment. This approach leverages our CARGO platform and CYAD-03 program.

# 2019, an exciting year for Celyad

As you can see, we have big plans for Celyad. Our strategy remains highly focused in 2019, as we will continue to establish ourselves as a key player in the field of CAR-T therapy. We expect the next 12 months to be filled with several key catalysts that will provide opportunities to advance our CAR-T programs and drive value.

On behalf of the entire Celyad team, I wish you a happy, healthy and fulfilling New Year!

**Christian Homsy,**
CEO Celyad

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