Letter to Shareholders

Dear Shareholder,

Throughout the past year, we’ve generated a tremendous amount of positive change and focus throughout the company, which has positioned us to deliver new clinical data across our development pipeline in 2020. Each of our programs continue to build momentum as we move towards our goal of bringing cancer patients with poor prognosis innovative new CAR-T therapies. These advancements speak directly to our position as a leader in the CAR-T cell therapy industry.

This exciting time in Celyad’s history is only possible due to the hard work and dedication of each and every one of our team members, patients, physicians and collaborators. And of course, we must thank you, our shareholders, for your continued support and investment in the company as we look towards continued success and progress in 2020 and beyond.
**2019 HIGHLIGHTS**

We were delighted to introduce our new proprietary manufacturing process, OptimAb, in the first half of 2019. Our lead autologous candidate CYAD-01 produced using the OptimAb manufacturing process drives improved anti-tumor activity in an aggressive leukemia model compared to CYAD-01 produced with the previous mAb manufacturing process.

In June 2019, the U.S. Food and Drug Administration (FDA) and Belgium’s Federal Agency for Medicines and Health Products (FAMHP) accepted our proposal to use this new manufacturing process for our ongoing and planned clinical development programs. Importantly, we were able to do so under the existing Investigational New Drug (IND) application for CYAD-01, saving valuable time and resources in early-stage development.

We’ve since dosed our first patient with CYAD-01 produced by the OptimAb process in the DEPLETHINK Phase 1 trial for the treatment of relapsed/refractory acute myeloid leukemia (r/r AML).

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**Eye on Manufacturing**

We believe the OptimAb manufacturing process has the potential to become the cornerstone of our autologous CAR-T program for the treatment of r/r AML and MDS

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2019 HIGHLIGHTS

CYAD-01 Transitions to OptimAb Process in r/r AML

Encouraging clinical data from our r/r AML program continued to drive our company forward in 2019. During the year, we read out important data and achieved several strategic milestones for our NKG2D-based CYAD-01 candidate in order to broaden our clinical development plan in r/r AML. Over the past few years, we have taken a holistic approach in our development strategy and while we have different studies and various cohorts within our studies, every step forward helps us to better understand the conditions needed for successful intervention in difficult-to-treat malignancies, such as r/r AML.

Highlights for the CYAD-01 THINK and DEPLETHINK trials presented at the 2019 American Society of Hematology (ASH) 61st Annual Meeting, include:

- Eight out of 15 evaluable patients treated with CYAD-01 produced with the mAb manufacturing process (predecessor to OptimAb process) in the THINK Phase 1 trial demonstrated anti-leukemic activity, with five out of the eight patients exhibiting an objective response.
- CYAD-01 produced with the mAb manufacturing process was reported to be generally well-tolerated following preconditioning chemotherapy and without preconditioning chemotherapy.
- Preconditioning chemotherapy in the DEPLETHINK trial led to improved, dose-dependent engraftment of CYAD-01 cells as compared to cells infused with no preconditioning, as evaluated in the THINK trial.

Moving forward, both the THINK and DEPLETHINK trials will evaluate CYAD-01 produced with our OptimAb manufacturing process. The THINK trial is progressing to an expansion segment with enrollment expected to begin in first quarter 2020. In the DEPLETHINK trial, enrollment is ongoing and we plan to evaluate multiple dose levels following preconditioning chemotherapy. Preliminary data evaluating CYAD-01 produced with the OptimAb manufacturing process from the THINK and DEPLETHINK trials are expected by the end of first half of 2020.

Next Generation Candidate for r/r AML – CYAD-02

At our R&D day held in early 2019, we unveiled a novel shRNA platform to develop next-generation autologous and allogeneic CAR-T cell therapies, including CYAD-02, a candidate that incorporates short hairpin RNA (shRNA) technology to target the NKG2D ligands MICA and MICB. CYAD-02 also incorporates our proprietary OptimAb manufacturing process. In preclinical studies, we observed encouraging in vitro proliferation, in vivo engraftment and anti-tumor activity of CYAD-02.

We made great strides with CYAD-02 over the past year and in June 2019, the FDA accepted our IND application to evaluate CYAD-02, produced with the OptimAb manufacturing process, for the treatment of patients with r/r AML and MDS following preconditioning chemotherapy in the dose-escalation CYCLE-1 Phase 1 trial. Enrollment in the CYCLE-1 trial is expected to begin in early 2020 with preliminary data anticipated during second half 2020.
An exciting development in 2019 was the initial data reported from our lead allogeneic CAR-T candidate, CYAD-101, for the treatment of metastatic colorectal cancer (mCRC). We believe that CYAD-101, which combines our NKG2D receptor with our non-gene edited allogeneic TIM (T-cell receptor inhibitory molecule) technology. To our knowledge, this is the world’s first allogeneic CAR-T clinical candidate for the treatment of solid tumors.

“Based on these encouraging data for CYAD-101 we plan to expand the alloSHRINK trial to further evaluate CYAD-101 in refractory mCRC patients.”

Leveraging shRNA Platform to Drive Next-Generation Candidates

As highlighted above, our shRNA platform has already been implemented in our CYAD-02 program and we continue to focus on the potential of the technology in our next-generation allogeneic CYAD-200 series of CAR-T candidates.

The CYAD-200 series CAR-T candidates target CD3ζ to knockdown the TCR/CD3 complex to deliver novel, non-gene edited allogeneic cell therapies. Early preclinical in vivo data suggests that targeting CD3ζ leads to increased persistence of CAR-T cells and potentially reduced graft-versus-host disease. Our lead product candidate from the series, CYAD-211, targets BCMA and is expected to move towards clinical trials in 2020 for the treatment of multiple myeloma.
Over the past few years, the CAR-T landscape has rapidly experienced several evolutions. In the last decade, we have witnessed several success stories with autologous CAR-T candidates. This includes the approvals of multiple CD19-targeted products for the treatment of B-cell malignancies and generation of exciting data from BCMA-targeted clinical candidates for the treatment of multiple myeloma. Despite these triumphs, there have been three major ongoing trends:

1. A continued shift towards allogeneic or off-the-shelf approaches in developing novel CAR-T candidates;
2. A focus in CAR-T development has moved towards use of the modality for the treatment of solid tumors; and
3. The industry continues to seek additional manufacturing, storage and shipping efficiencies for product candidates as we move from early-generation products to next-generation approaches.

As we continue to advance as a CAR-T company into the next decade, our goal is to be well-positioned for success within the cell therapy landscape by being adaptive to strategic changes in the field and by embracing our leadership position in areas where Celyad’s science and technology has made significant strides.

At Celyad, we have taken crucial steps to embrace these important trends in the industry and have entered 2020 well-positioned with a balanced pipeline of CAR-T product candidates.

**Autologous**

Our future efforts in autologous will be primarily centered on our NKG2D-based CAR-T candidates for the treatment of r/r AML and underpinned by our OptimAb manufacturing process. r/r AML remains an aggressive disease with limited treatment options for patients. As such, an autologous CAR-T product candidate demonstrating clinical benefit in patients with advanced AML could play an important role in the treatment paradigm of the disease.

**Allogeneic**

We continue to strategically invest in both of our non-gene edited allogeneic platforms: TIM and shRNA. Preliminary data from our TIM technology, which is embedded in our lead allogeneic program CYAD-101, showed that a non-gene edited approach could be used to avoid GvHD in an allogeneic setting. We are excited to further investigate our TIM technology through our CYAD-100 series of NKG2D-based allogeneic programs, including our recently announced preclinical candidate CYAD-103. In addition, fully investigating the true potential of our shRNA technology to generate non-gene edited CAR-T candidates should allow us to build a diverse pipeline of off-the-shelf CAR-T assets for the treatment of both hematological malignancies and solid tumors.

**Solid tumors**

While fully understanding the significant challenges associated with the use of CAR-T cells for the treatment of solid tumor, we continue to believe that the modality will eventually be able to “crack the code” in solid tumors. One important consideration for the effective treatment of solid tumors is selection of the proper tumor targets. We believe that the NKG2D receptor holds the potential to be a key part of unlocking the success in solid tumors given its ability to target multiple ligands expressed on not only on tumors but also on cells within the tumor microenvironment and associated with tumor neovascularization.

**“All-in-One” Vector**

Finally, as we have aspired to drive efficiency into our CAR-T programs, we have designed and developed our candidates to employ a single vector approach. Relying on an ‘all-in-one’ vector approach for CAR-T generation helps streamline several processes used for all of our assets. Importantly, the ‘all-in-one’ vector approach provides tremendous flexibility but also has the potential to greatly reduce production time and costs, key factors when developing potentially life-saving therapies.
2020 Vision –
A Clear Look at the Year Ahead

Over the years, Celyad has appreciated the long-lasting support of our shareholders. We now find ourselves at a pivotal time in the company’s history with multiple clinical trials and technologies ready to deliver key milestones during 2020.

Our focus remains on helping patients who are suffering from these devastating cancers while also providing high value to our shareholders. We will continue to set ambitious goals and are excited to see the fruits of our labor this year.

On behalf of the entire Celyad team and board members, I wish you and your loved ones a happy, healthy and fulfilling 2020!

Financial calendar first half 2020

March 18th – R&D Day at Nasdaq (New York, NY)
March 24th – Year-end 2019 Results
May 5th – Annual Shareholders Meeting
May 7th – Q1 2020 Financial Results

Filippo Petti,
Celyad CEO