Pioneering innovative therapies for patients with life-threatening diseases

AML and MDS Program Update
July 2, 2019

Celyad

Forward-Looking Statements

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Strategic Update for the Autologous r/r AML and MDS Clinical Program

- Recent update from CYAD-01 program for r/r AML and MDS [1]
- Introduction of the "OptimAb" manufacturing process for CYAD-01 and CYAD-02
- Food and Drug Administration (FDA) acceptance of the Investigational New Drug (IND) for next-generation, NKG2D-based CAR-T therapy, CYAD-02
- Upcoming milestones for CYAD-01 and CYAD-02 programs

1. European Hematology Association (EHA) , June 13-16, 2019 – Abstract: PS1212.

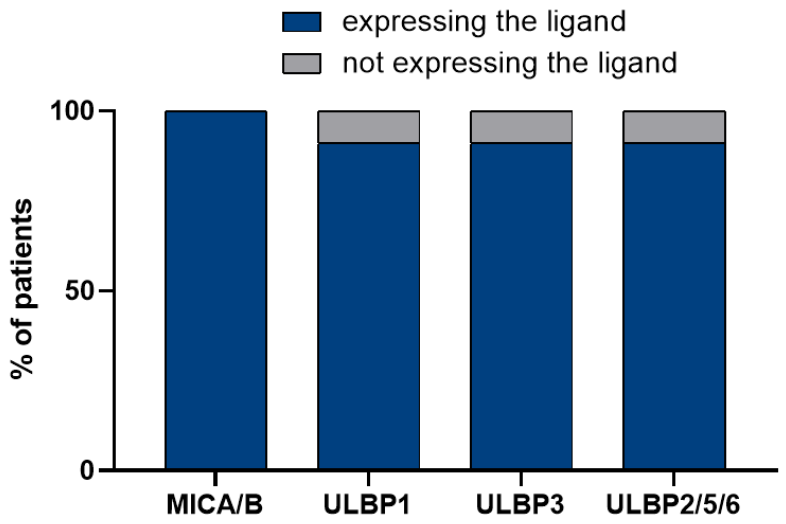
Overview of Acute Myeloid Leukemia (AML) and NKG2D Expression

Key Characteristics of AML

- AML is a heterogeneous, aggressive form of leukemia characterized by the abnormal growth of myeloid cells
- AML is the most common type of aggressive leukemia in adults, with about 40,000 new cases diagnosed each year in aggregate between the United States and Europe
- AML can develop either *de novo* in a healthy individual or in patients with a previous history of myelodysplastic syndrome (MDS)
- Limited treatment options exist, and most patients become resistant to chemotherapy and only allo-HSCT has a potential curative effect
- Lack of cell surface targets suitable for CAR-Ts / antibodies that are absent on healthy cells

NKG2D Ligand Expression in AML

- All of AML patients express at least one NKG2D ligand in the leukemic blasts [1]
- NKG2D ligand expression provides rationale for CAR-T approach targeting multi-surface tumor antigens over single target CAR-Ts



1. Based on patient data from the THINK and DEPLETHINK Phase 1 trials.

r/r AML and MDS Clinical Program for CYAD-01 [1]

Lead program CYAD-01, an autologous NKG2D-based CAR-T

- **THINK** is an open-label Phase 1 trial - two Schedule Optimization cohorts assessing a more frequent dosing schedule (six injections over two months of administration) of CYAD-01 for the treatment of r/r AML without preconditioning
  - Patients receive either Cohort 10 (1 billion cells per infusion) or Cohort 11 (3 billion cells per infusion)
    - First cycle includes three infusions of CYAD-01 separated by one-week intervals; second cycle includes three infusions of CYAD-01 separated by two-week intervals
  - The primary endpoint of the trial is safety and secondary endpoints include clinical activity and pharmacokinetics
- **DEPLETHINK** is an open-label, dose-escalation Phase 1 trial evaluating a single infusion of CYAD-01 following treatment with the standard preconditioning regimen of cyclophosphamide (300 mg/m²) and fludarabine (30 mg/m²), or CyFlu
  - Administration of CYAD-01 at three dose levels (100 million, 300 million and 1 billion cells per infusion)
  - The primary endpoint of the trial is safety and secondary endpoints include clinical activity and pharmacokinetics

1. European Hematology Association (EHA) , June 13-16, 2019 – Abstract: PS1212.

Drivers Aimed to Enhance Autologous NKG2D-based CAR-T Therapy

- The goal for the r/r AML and MDS program is to improve the initial signal from the NKG2D-based CAR-T therapy through:
    1. Optimization of treatment conditions: denser dosing schedule, standard CyFlu preconditioning chemotherapy, potential alternative preconditioning regimen and potential for bridging therapy
    2. Optimization of manufacturing process: enrich for T cells with memory-like phenotype for increased persistence and potency
    3. Improve persistence through the targeted knockdown of NKG2D ligands: incorporation of shRNA targeting NKG2D ligands MICA and MICB in to extend persistence in case of no preconditioning or post-preconditioning (i.e. CYAD-02)

CyFlu: Cyclophosphamide and fludarabine.

Initial Data for Autologous r/r AML and MDS Clinical Program [1]

- Preliminary results from the **THINK** trial for the treatment of r/r AML and myelodysplastic syndromes (MDS) demonstrated:
  - CYAD-01 was generally well tolerated at the denser dosing schedule
  - CYAD-01 has encouraging anti-leukemic activity in 46% of patients evaluable per protocol
  - CYAD-01 without preconditioning led to persistence of cells for approximately seven days
  - Preliminary data showed better cell engraftment with reduced interval dosing compared to biweekly injections of CYAD-01 without preconditioning
- Initial results from the **DEPLETHINK** trial demonstrated the regimen was well tolerated and a better time-averaged engraftment of the CAR-T cells compared to the dose-escalation segment of the THINK trial with a cycle of three injections of CYAD-01

1. European Hematology Association (EHA) , June 13-16, 2019 – Abstract: PS1212.

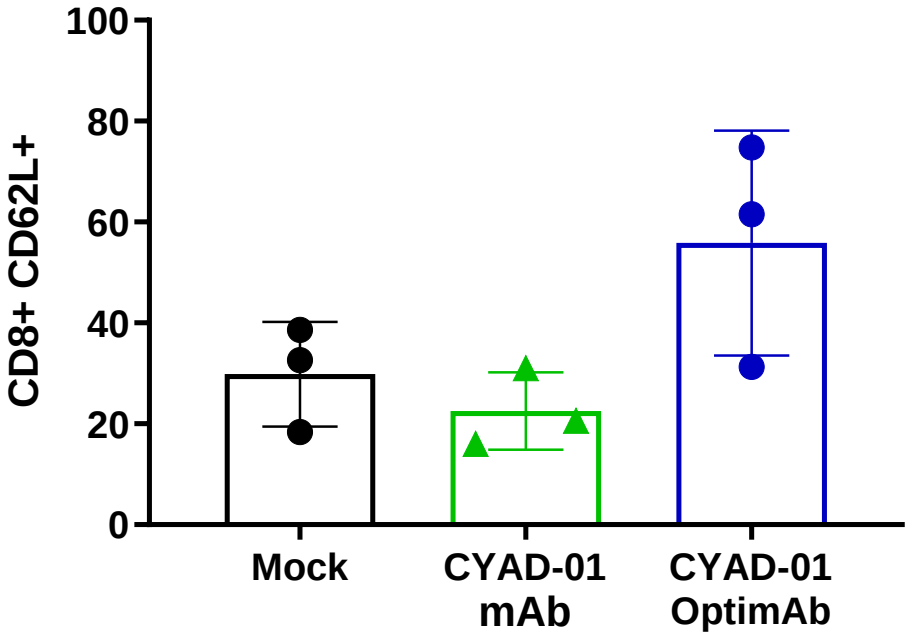
Ongoing THINK and DEPLETHINK Trials

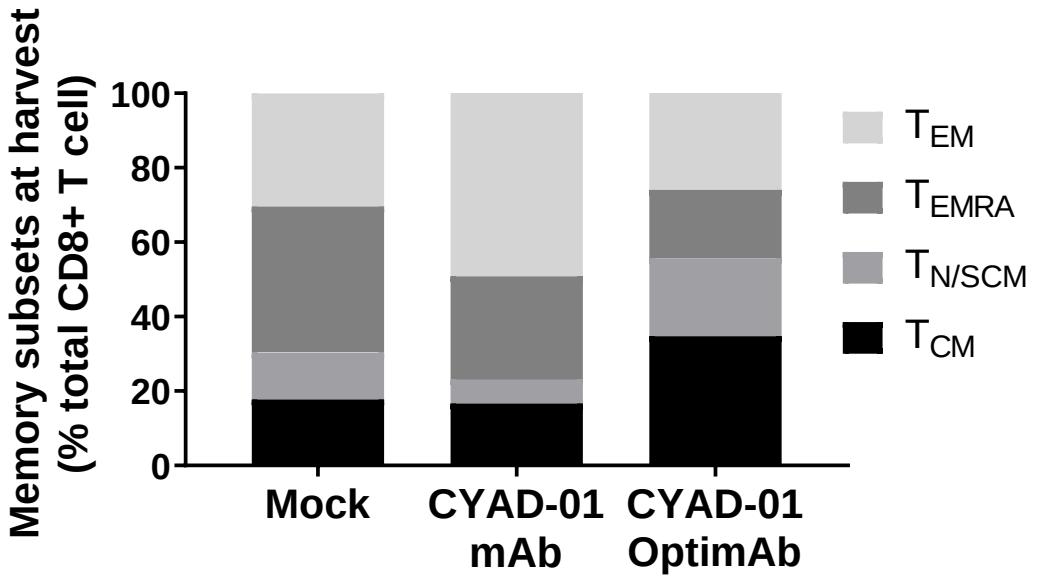
- Further investigating CYAD-01's potential through:
  - Schedule Optimization of the THINK trial
    - Patient recruitment in Cohort 11 is ongoing and preliminary results are expected in second half 2019
  - Following preconditioning chemotherapy in DEPLETHINK dose-escalation trial
    - Patient recruitment in Cohort 3 is ongoing and preliminary results are expected in second half 2019
    - Opportunity to assess updated OptimAb manufacturing process for CYAD-01 in Cohort 4 of DEPLETHINK trial

Background on "OptimAb" Manufacturing Process

- The OptimAb manufacturing process that builds upon key characteristics Celyad's first two manufacturing processes for CYAD-01, the "LY" and "mAb" processes
- Utilizes a shortened eight-day cell culture, NKG2D blocking antibody and incorporates a selective PI3K inhibitor
  - Incorporation of PI3K inhibitor helps enriches for T cells with a memory-like phenotype
  - Process maintains high level of manufacturing reliability required to support clinical development
  - Data demonstrate that OptimAb manufacturing process drives improved anti-tumor activity in aggressive *in vivo* AML model

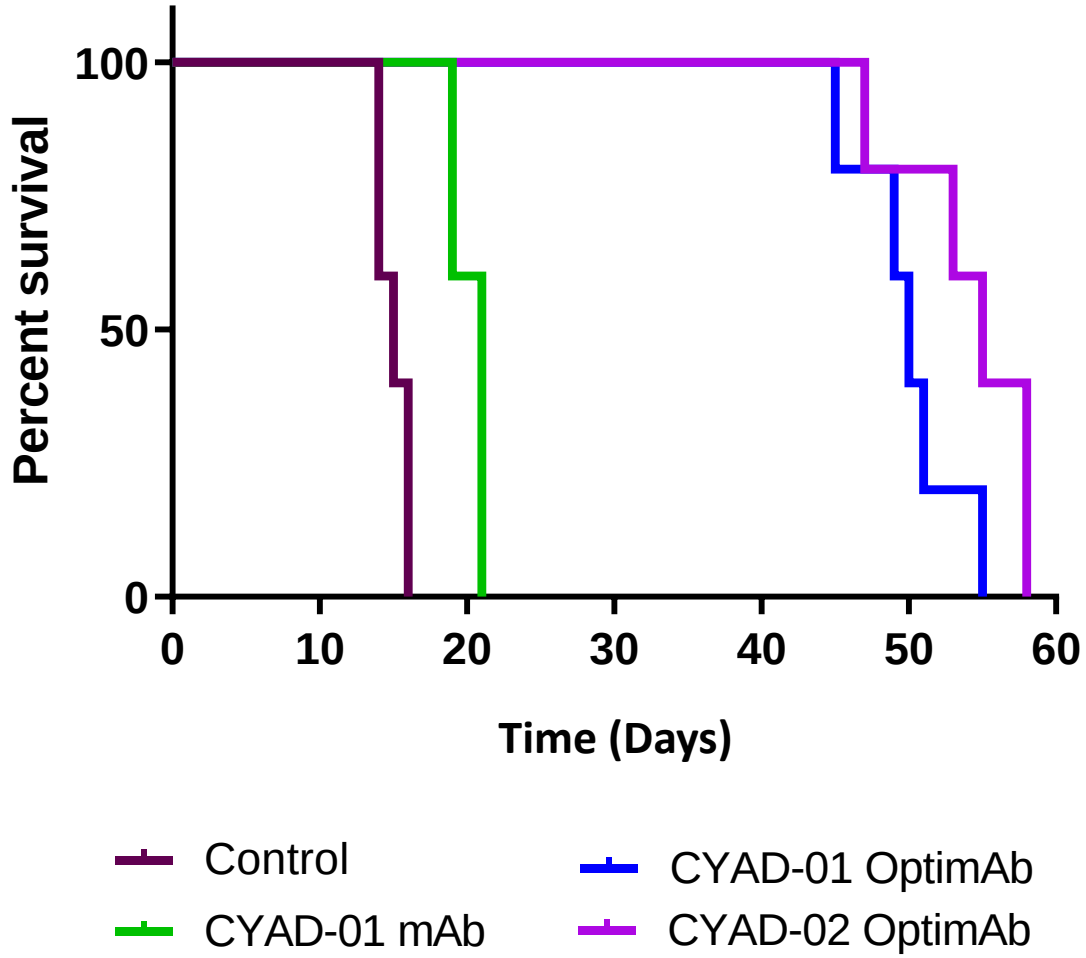
OptimAb Process Enriches for T cells with Memory-like Phenotype





OptimAb manufacturing process maintains an earlier memory phenotype, with higher percentage of central memory cells compared to mAb manufacturing process

OptimAb Process Exhibits Improved Anti-tumor Activity in AML Model



- *OptimAb process drives improved survival in an aggressive AML model, where CYAD-01 dose is titrated for minimal activity*
- *In similar conditions, CYAD-02 OptimAb has potential to further enhance anti-tumor activity beyond that seen in CYAD-01 OptimAb*

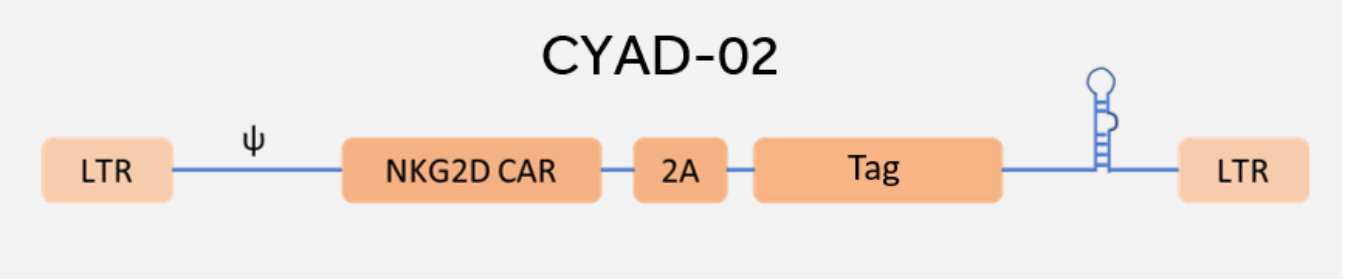
Launch of OptimAb Manufacturing Process in Clinical Trials

- Submitted Chemistry, Manufacturing, and Control (CMC) amendments related to CYAD-01's current IND to the FDA and FAMHP
  - Regulators accepted proposal to utilize with CYAD-01 program
  - Plan to treat first patient with the CYAD-01 OptimAb manufacturing process in cohort 4 of DEPLETHINK trial by August 2019
- OptimAb process will also be used with future candidates, including CYAD-02

FDA: U.S. Food and Drug Administration; FAMHP: Federal Agency for Medicines and Health Products; IND: Investigational New Drug: PI3K: Phosphoinositide 3-kinase.

Differentiation of Next-Generation NKG2D-based Candidate, CYAD-02

- Utilizes Horizon Discovery's shRNA SMARTvector technology to target the NKG2D ligands MICA and MICB
  - Single shRNA is able to modulate the expression of both ligands which translates to encouraging increase *in vitro* proliferation, *in vivo* engraftment and anti-tumor activity
  - Current data suggest potential broader applicability of targeting both ligands in all CAR-T therapies
- Offers opportunity to maintain persistence following reconstitution of patient's immune system post-preconditioning chemotherapy
- Extended IP protection



Key Attributes of NKG2D-based CAR-T Therapies for r/r AML and MDS

	CYAD-01			CYAD-02
Target	NKG2D			NKG2D
Autologous	✓	✓	✓	✓
Allogeneic				
Manufacturing Process	LY	mAb	OptimAb	OptimAb
Culture Days	8	10	8	8
NKG2D Blocking Antibody	--	✓	✓	✓
PI3K Kinase Inhibitor	✓ - pan	✓ - pan	✓ - selective	✓ - selective
shRNA Technology	--	--	--	✓
shRNA Target(s)	--	--	--	MICA / MICB
Trial(s) / Dose Level(s)	THINK / $3x10^8$	THINK † / $1x10^9$, $3x10^9$ DEPLETHINK / $1x10^8$, $3x10^8$, $1x10^9$	DEPLETHINK / $1x10^9$	CYAD-02-01 / $1x10^8$, $3x10^8$, $1x10^9$

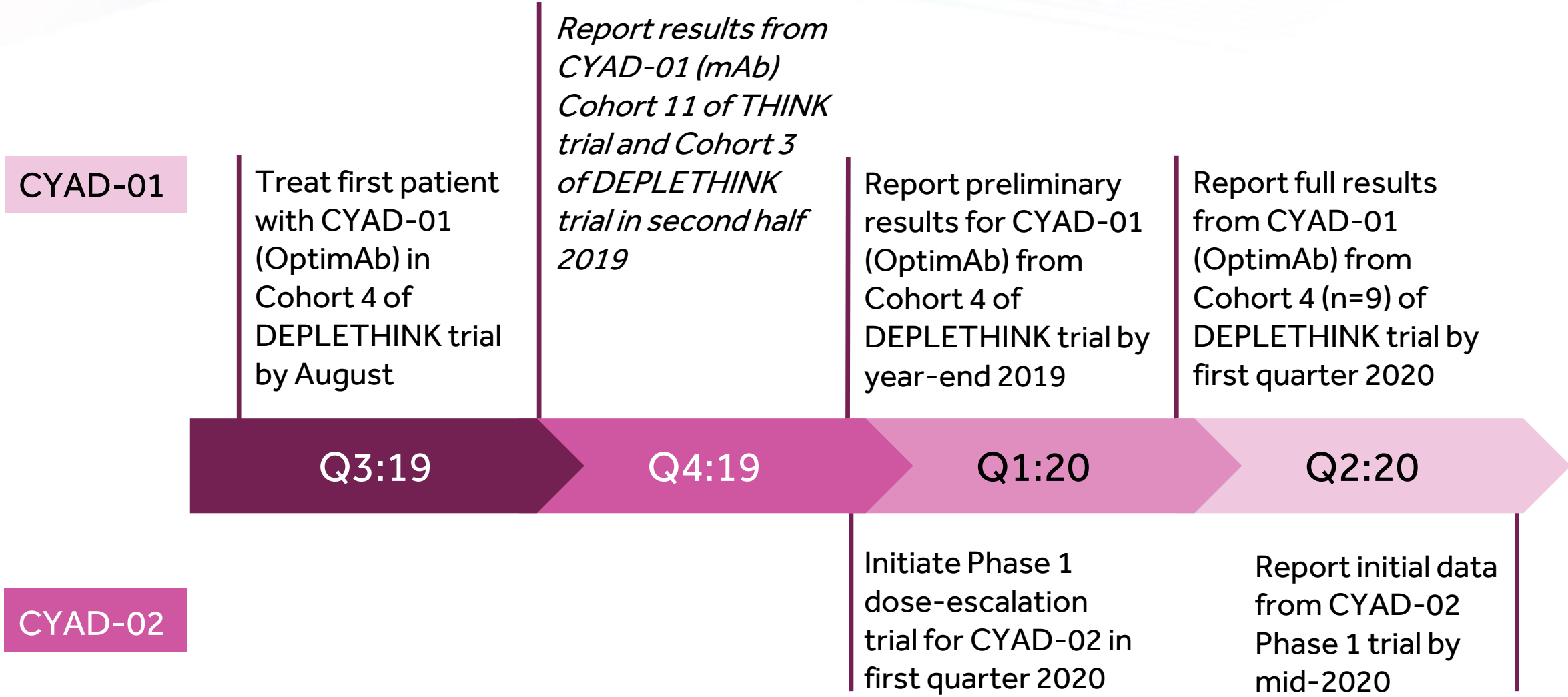
† Includes THINK Schedule Optimization, Cohorts 10 and 11.

Recent Developments for CYAD-02

- In late June, the FDA accepted the IND application for the next-generation, NKG2D-based autologous CAR-T therapy, CYAD-02, for the treatment of r/r AML and MDS
- The acceptance allows Celyad to begin a planned Phase 1 trial evaluating the safety and clinical activity of CYAD-02 with the preconditioning chemotherapy CyFlu both in the United States and Europe in early 2020

FDA: U.S. Food and Drug Administration; IND: Investigational New Drug.

Upcoming Milestones for CYAD-01 and CYAD-02 in r/r AML and MDS



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Conclusions on r/r AML and MDS Program

- To date, CYAD-01 has shown to be well-tolerated with encouraging anti-leukemic activity
- Future patients treated in the r/r AML and MDS program with either CYAD-01 and CYAD-02 will utilize the OptimAb manufacturing process
- OptimAb manufacturing process seeks to bring together the best attributes from previous processes: 1) day 8 cell culture, 2) NKG2D blocking antibody, and 3) selective PI3K inhibitor
- OptimAb manufacturing process leads to T cells with memory-like phenotype and improved anti-tumor activity in AML models
- Initial clinical data for the OptimAb manufacturing process from cohort 4 ($1x10^9$ cells) of the Phase 1 DEPLETHINK trial are expected by year-end 2019 with full results anticipated in Q1:2020
- Preliminary clinical data for the CYAD-02 Phase 1 trial are expected in mid-2020
- Future plans to assess alternative preconditioning chemotherapy in r/r AML and MDS program and potentially add bridging therapy to NKG2D-based CAR-Ts manufactured with OptimAb

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