



bluebirdbio®

Ready to RECODE

March 2019

NASDAQ: BLUE

Forward-Looking Statements

These slides and the accompanying oral presentation contain forward-looking statements and information. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward-looking statements. For example, all statements we make regarding the initiation, timing, progress and results of our preclinical and clinical studies and our research and development programs, our ability to advance product candidates into, and successfully complete, clinical studies, and the timing or likelihood of regulatory filings and approvals are forward looking. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These statements are also subject to a number of material risks and uncertainties that are described in our most recent quarterly report on Form 10-Q, as well as our subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Potential 2019 Catalysts

By Mid Year

LentiGlobin TDT

Northstar-2 (HGB-207) & Northstar-3 (HGB-212) Data Update

LentiGlobin SCD

HGB-206 Group C Data Update

bb2121 MM

KarMMa-2 & KarMMa-3 Study Start*

Pipeline

Analyst Day

By End of Year

LentiGlobin TDT

EU Approval & First Launch

Potential U.S. Filing

Northstar-2 and Northstar-3 Data Update

LentiGlobin SCD

HGB-210 Study Start

HGB-206 Group C Data Update

bb2121 MM

CRB-401 Data Update*

KarMMa-1 Data*

bb21217 MM

CRB-402 Data Update

Cash Position as of December 31, 2018: \$1.9B

CASH RUNWAY INTO 2022

WE RECODE FOR LIFE



RADICAL CARE

We care in a way that's intense
and truly sets us apart.



THIS IS PERSONAL

Gene therapy is about saving lives
one person at a time. And we are,
each of us, personally all in.



PIONEERS WITH PURPOSE

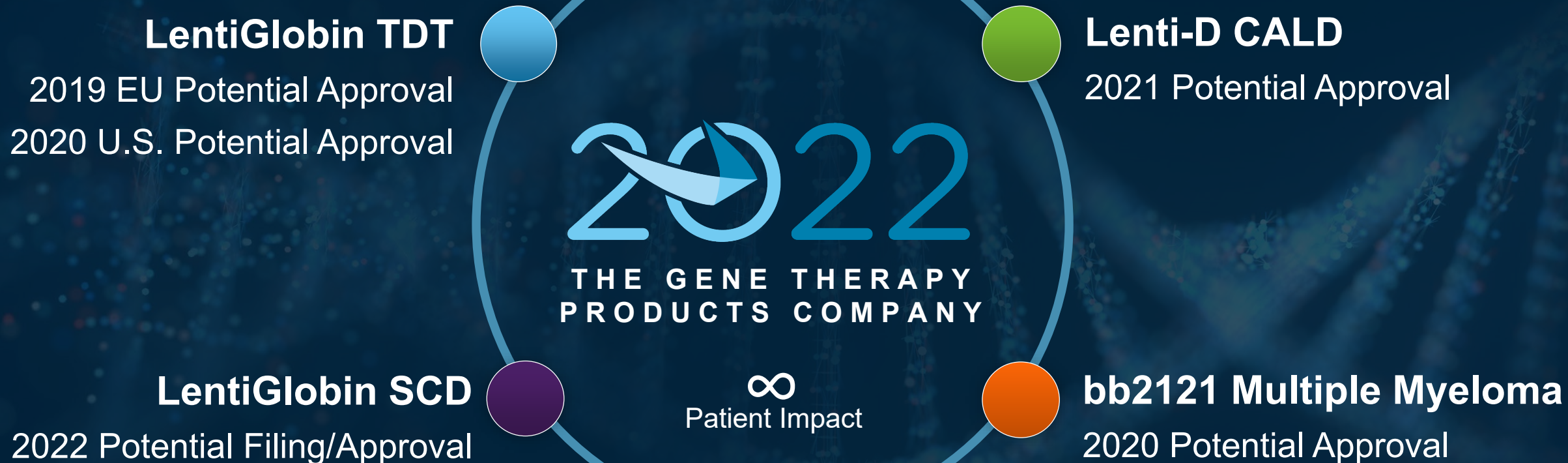
We're exploring new frontiers for
the sake of patients.

We LIVE By Our Non-negotiables

true blue | b colorful • b cooperative • b yourself



Our 2022 Vision -- Just Got BOLDER



4 Products
on the Market

5⁺ Clinical Programs

1-2 INDs Per Year Beginning 2020

UNPRECEDENTED OPPORTUNITY

Anticipated research, development, regulatory and commercial milestones



RECODE THE SCIENCE: R&D with SOUL

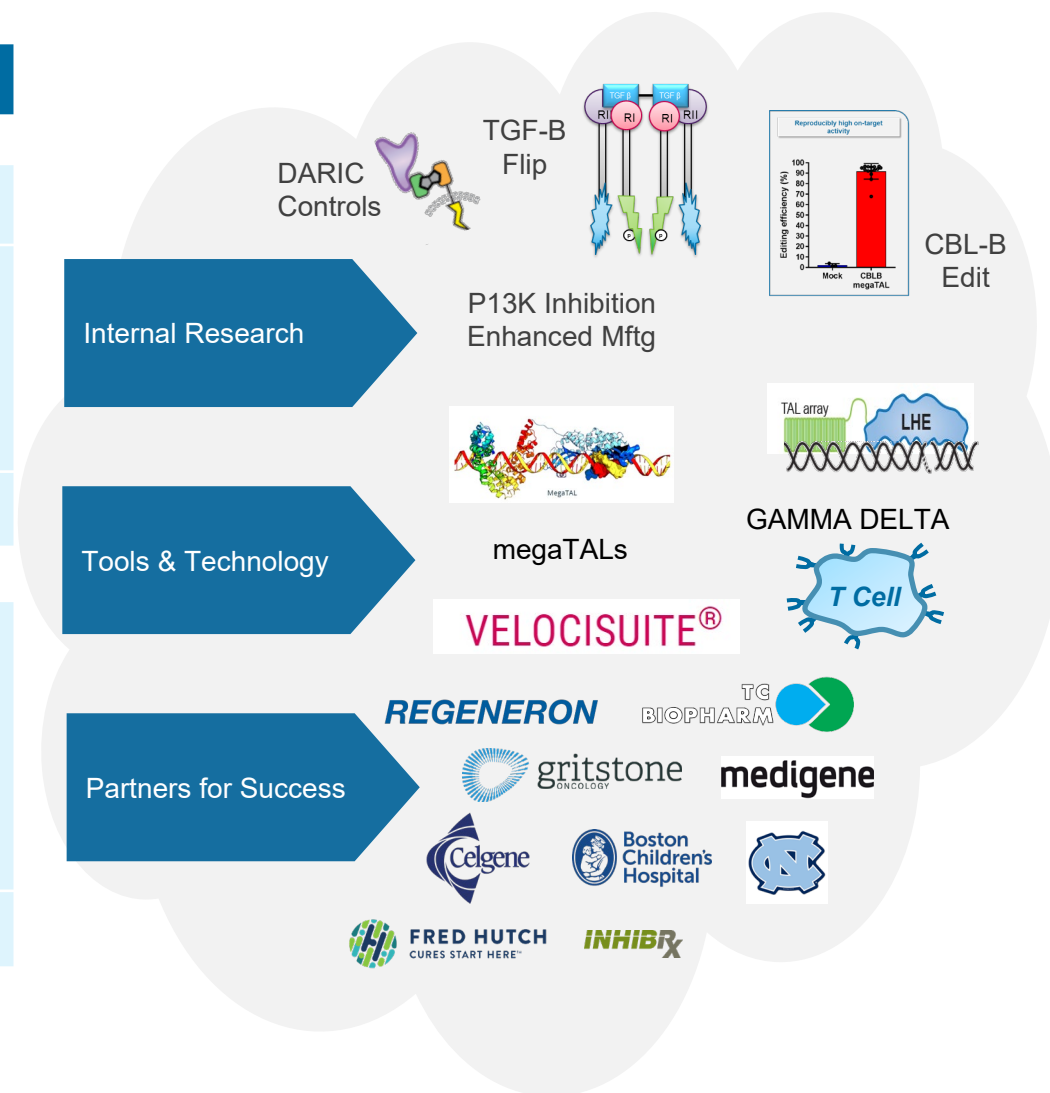
WHAT YOU SEE

PRODUCT CANDIDATES	PROGRAM AREA	PRECLINICAL	PHASE 1/2	PHASE 2/3	RIGHTS/PARTNER
Severe Genetic Diseases					
Lenti-D™ Drug Product	Cerebral Adrenoleukodystrophy				Worldwide
LentiGlobin™ Drug Product	Transfusion-Dependent β-Thalassemia Non-β ⁰ /β ⁰				Worldwide
	Transfusion-Dependent β-Thalassemia β ⁰ /β ⁰				
	Sickle Cell Disease		**		
BCL11a shRNA (miR)*	Sickle Cell Disease				Worldwide
Cancer					
bb2121	Multiple Myeloma Fourth Line				Celgene
	Multiple Myeloma Third Line**				
	Multiple Myeloma Second Line**				
	Multiple Myeloma First Line**				
bb21217	Multiple Myeloma Fourth Line				Celgene

*Development is led by Dana-Farber/Boston Children's Cancer and Blood Disorders Center

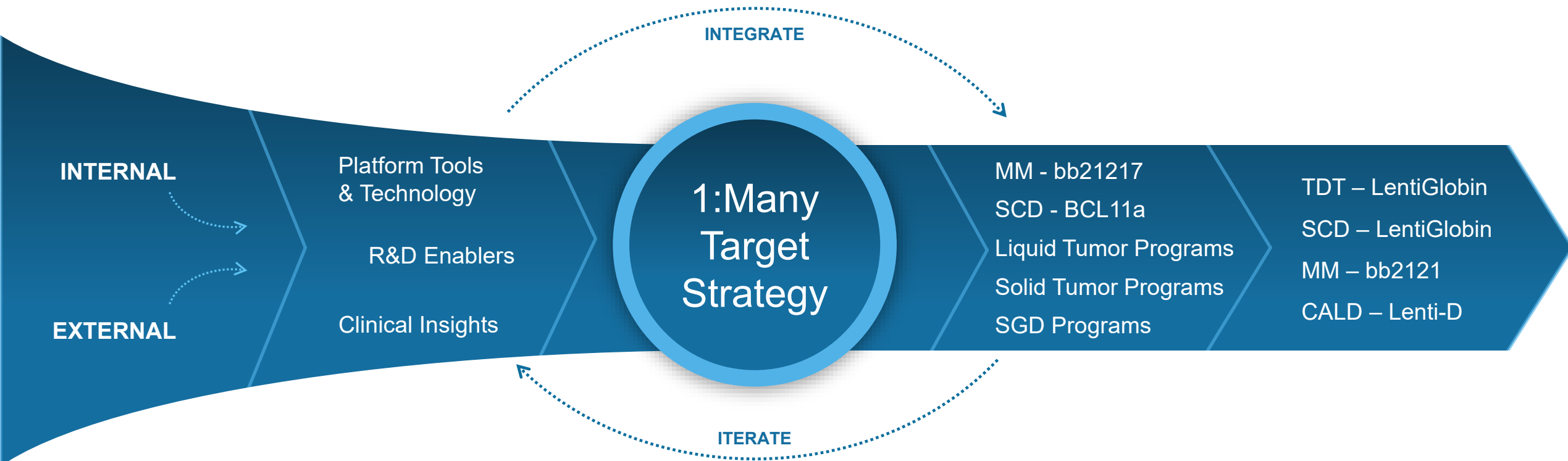
**Planned studies

WHAT YOU DON'T SEE



Anti-Pure Play Principles - What Do We Mean?

RECODING TRADITIONAL R&D



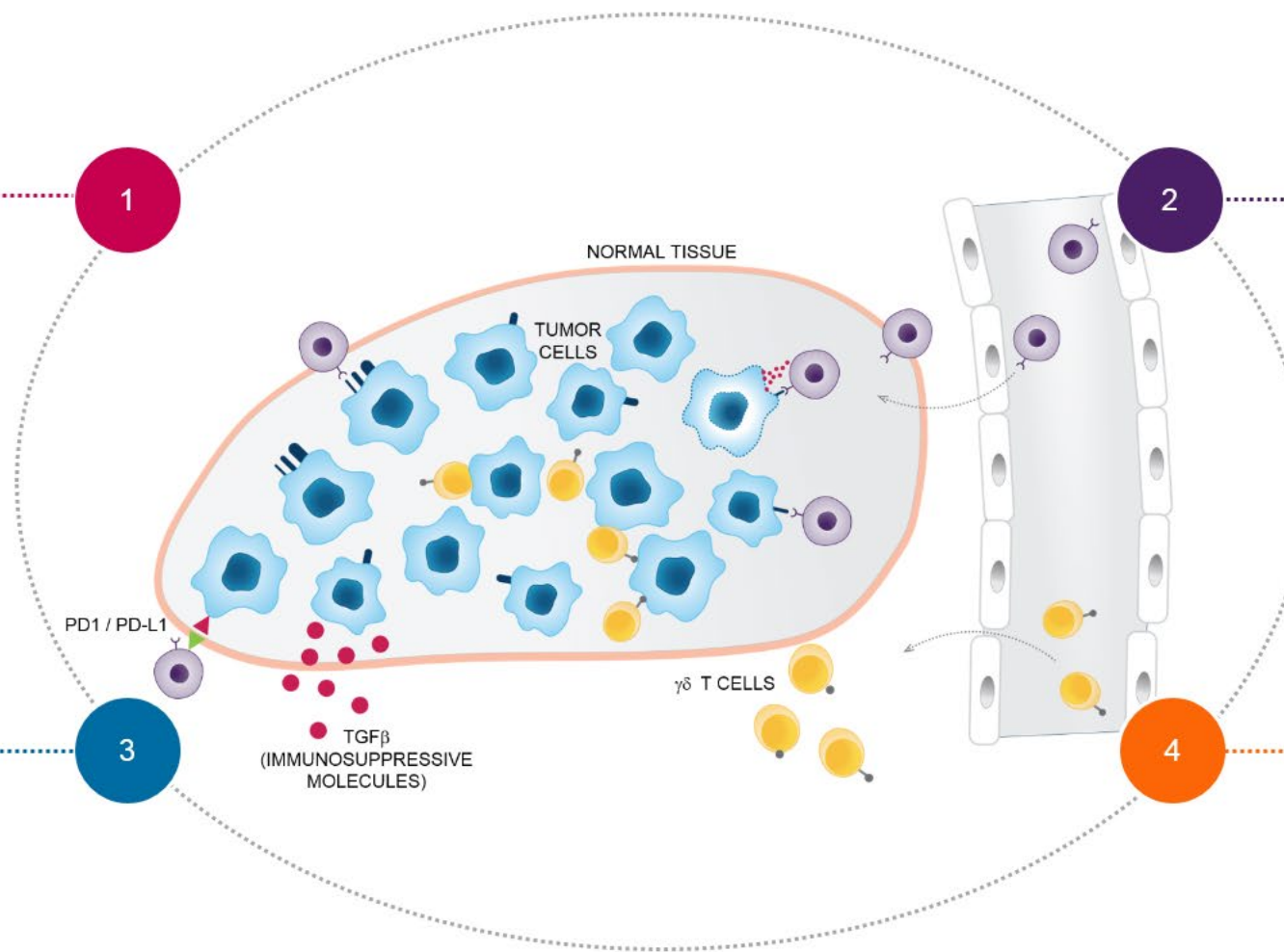
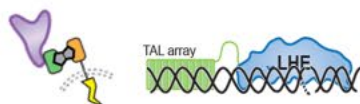
Our Philosophy Applied in a Tumor Microenvironment

TUMOR TARGET

REGENERON



POTENCY ENHANCEMENT



BINDER TECHNOLOGY

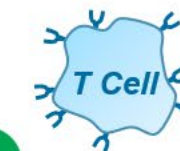
REGENERON

medigene

INHIBR_X

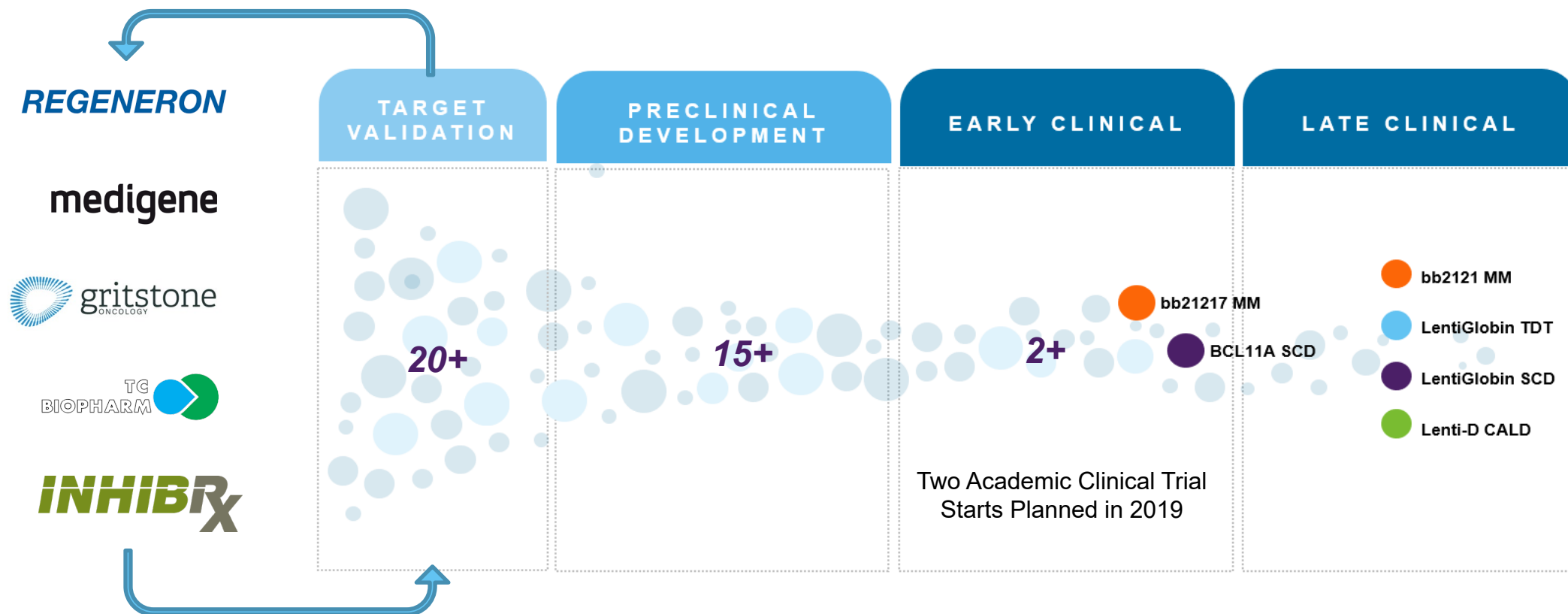


T CELL TYPES / ALLO

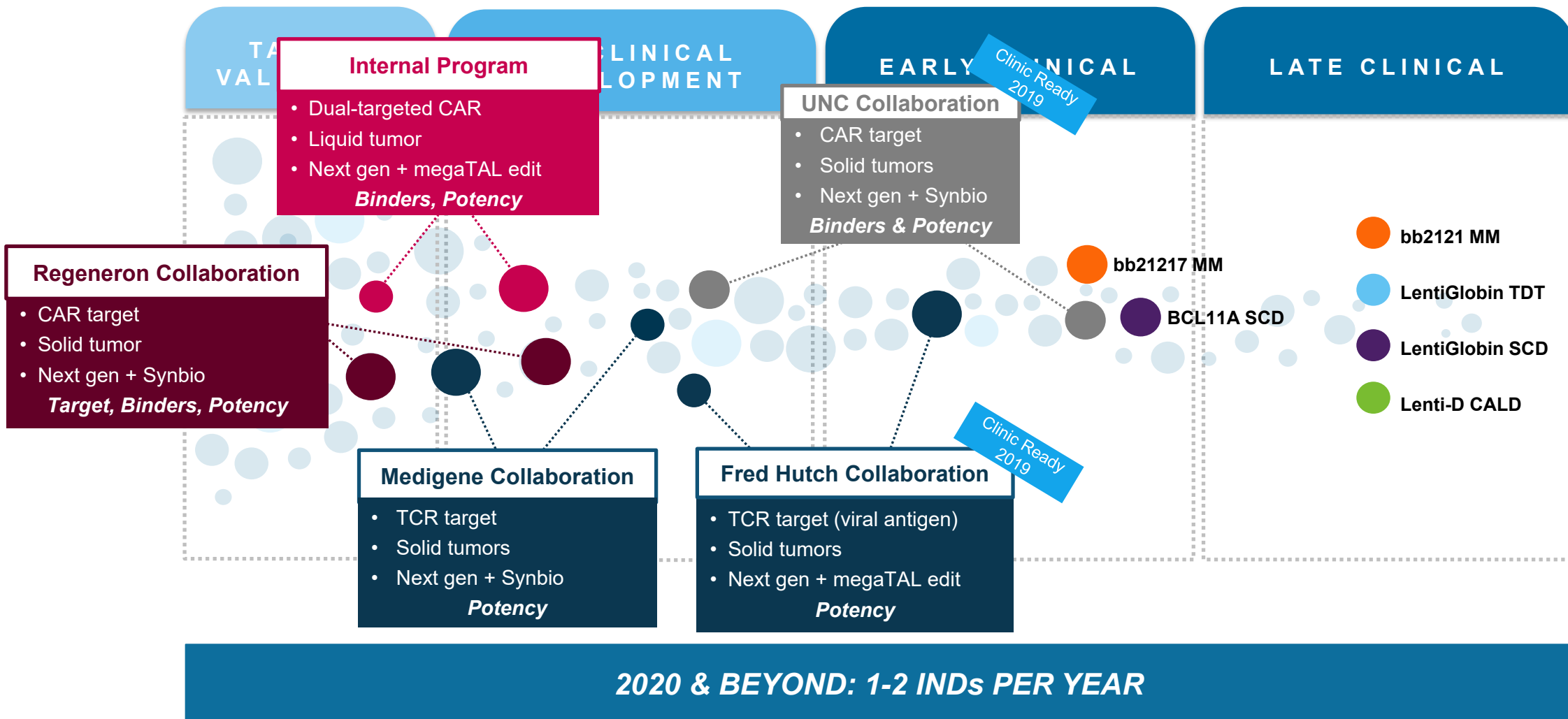


P13K Inhibition
Enhanced Mftg

Oncology Pipeline Enabled by Our Partners and Our Core Technologies



Research Strategy Yielding Emerging Oncology Pipeline



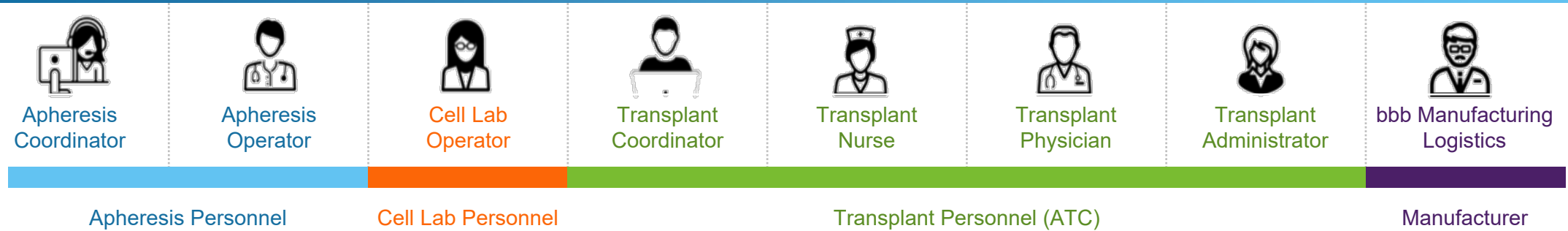
RECODE THE SYSTEMS: ANYTHING BUT TRADITIONAL



Platform Is Gearing Up for Launch

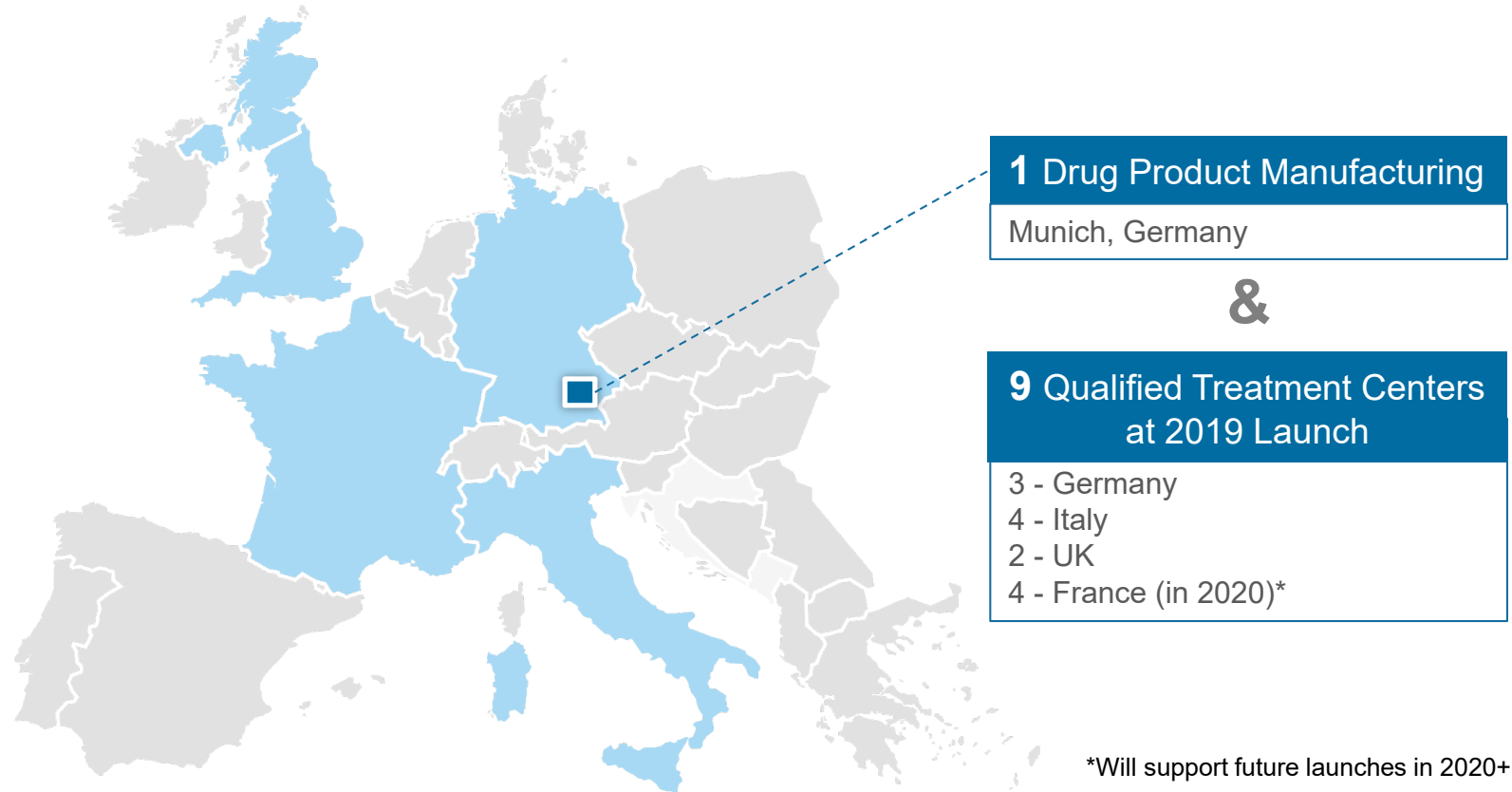


Preparing to Serve Patients in Europe in 2019



Launch Expectations:

1. Optimal patient experience through a seamless delivery network
2. Steady country by country launch with progressive build
3. Get the model right for long term success
4. Advance value-based payment over time reimbursement



*Will support future launches in 2020+

Business of Cures – Complex with Lots of Questions, Perspectives, etc.

conomy

“Can Pay-For-Results Drug Pricing Work?”

STAT

“How much would you pay for the miracle of gene therapy?”

Forbes

“Value-Based Pricing And Reimbursement: Still More Promise Than Reality”

 BioPharmaDIVE

“Gene therapy could be cost effective in SMA, but not at \$4M”

Access and Reimbursement Model – A Major Opportunity Across Stakeholders

System NOT setup for one-time potentially curative treatments

Focus is on price, NOT on value

Focus is on difficulties and barriers, NOT solutions

Growing alignment on value & outcome based payment models

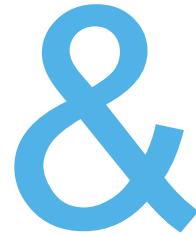
BLUEBIRD OPPORTUNITY

- **The Will To Recode**
- **One-Time Treatment**
- **Potentially Curative**
- **Product Engine**
- **Unconstrained**

Keep It Simple, Keep It Focused on the Patient & the Long Term

BLUE VALUE PRINCIPLES

- Focus on patient innovation and access
- Creative and disruptive
- Flexible and share risk
- Transparent, proud and proactive
- Don't do silly short sighted stuff



Unapologetically fund & reward innovation that matters

Focus on **real value** delivered to the patient & system

Don't truncate value because it's a one-time potentially curative treatment

Don't price at what you can get away with or what the market can bear

Our Goal Is to Simultaneously Achieve Five Key Objectives

1 **BLUE** has **CONVICTION** in the **VALUE** of the **LIFELONG** transformative benefit that our therapies may bring to patients, physicians, caregivers, healthcare systems and society at large

2 **BLUE** is willing to **SHARE** the **RISK** of uncertainty to **PROVE** the life long value of its therapies

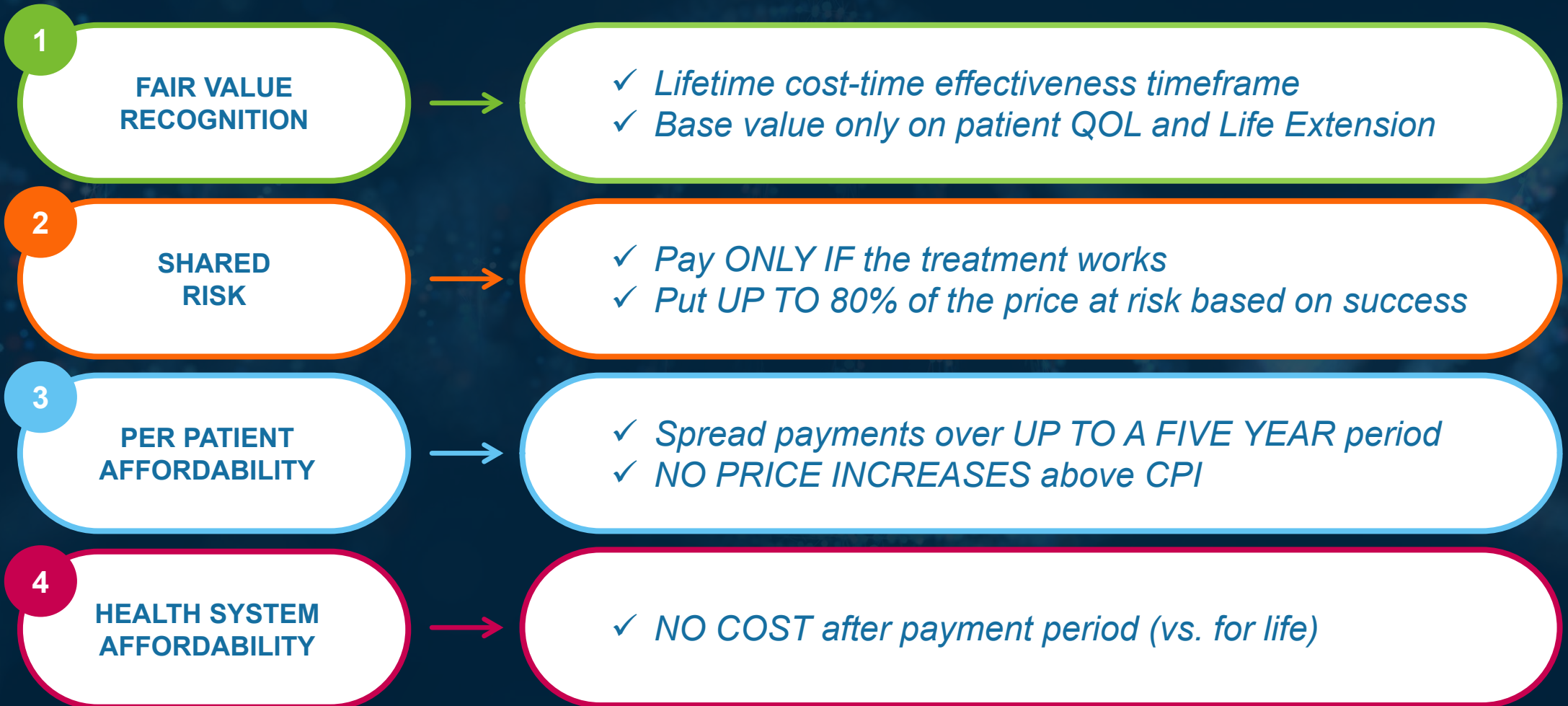
3 **BLUE** wants to make its treatments **AFFORDABLE** so **PATIENTS (and SYSTEM)** can actually
4 **REALIZE** the **VALUE** of its therapies

5 **BLUE** wants to be a **CATALYST** for **CHANGE** to establish a **SUSTAINABLE MODEL** for pricing & reimbursement of gene therapies

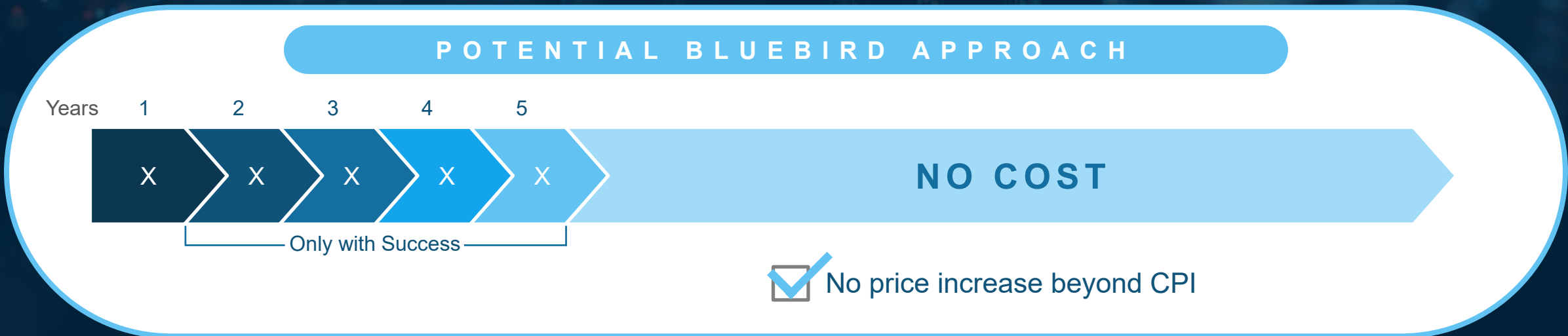
Approach – VALUE-BASED PAYMENT Over Time Based on OUTCOME

OBJECTIVE

STRATEGIC APPROACH

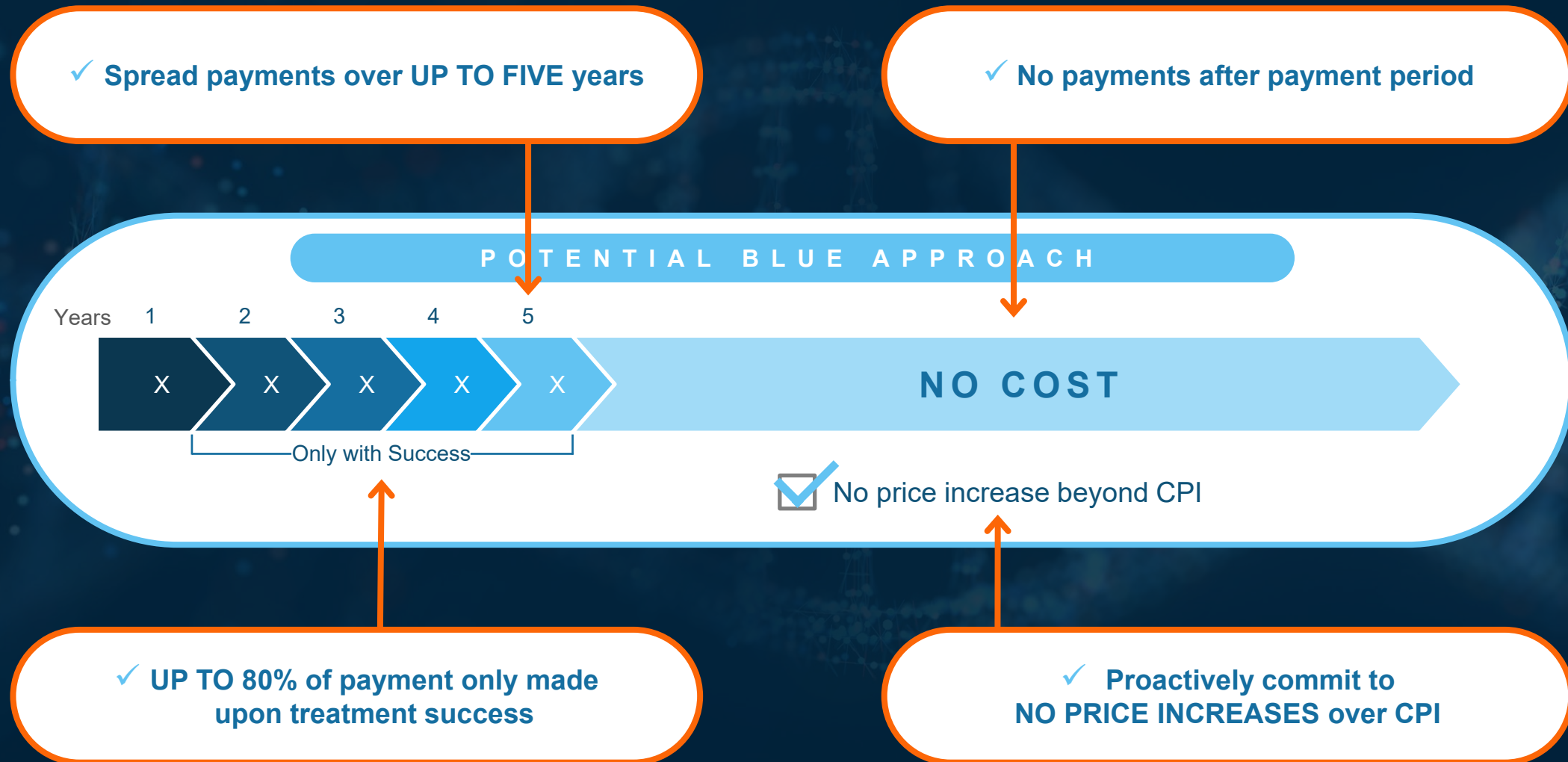


Payment Model – Patient and System Friendly

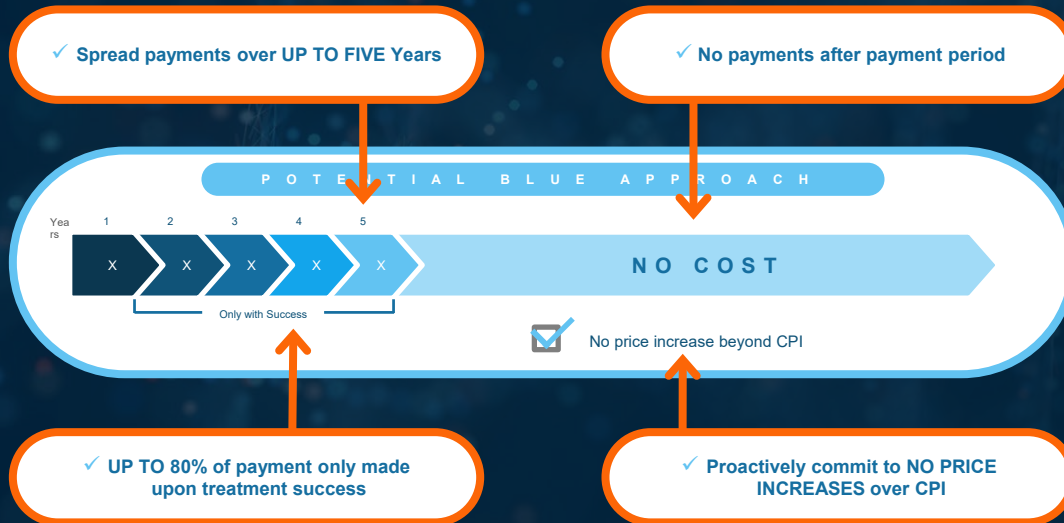


*Ranges based on 2018 U.S. list prices from a sampling of seven chronic rare disease therapies.

Payment Model – Sharing Risk & Value with the System



Not the Easy Path but the Challenges Are Solvable



TRACKABILITY?

- **Challenge:** How do you define and track outcomes?
- **Possible Solutions:** Payer to use claims and/or registry data

PORTABILITY?

- **Challenge:** What happens when patient changes payer?
- **Possible Solutions:** Address in contract negotiation, mutual recognition strategy across payers, etc.

BEST PRICE?

- **Challenge:** How do you handle Medicaid "Best Price" rules?
- **Possible Solutions:** Innovative federal or state pilot programs or waivers

VALUE-BASED PAYMENT Over Time Based on OUTCOMES

OBJECTIVE

1

FAIR VALUE
RECOGNITION



STRATEGIC APPROACH

- ✓ *Lifetime cost-time effectiveness timeframe*
- ✓ *Base value only on patient QOL and Life Extension*

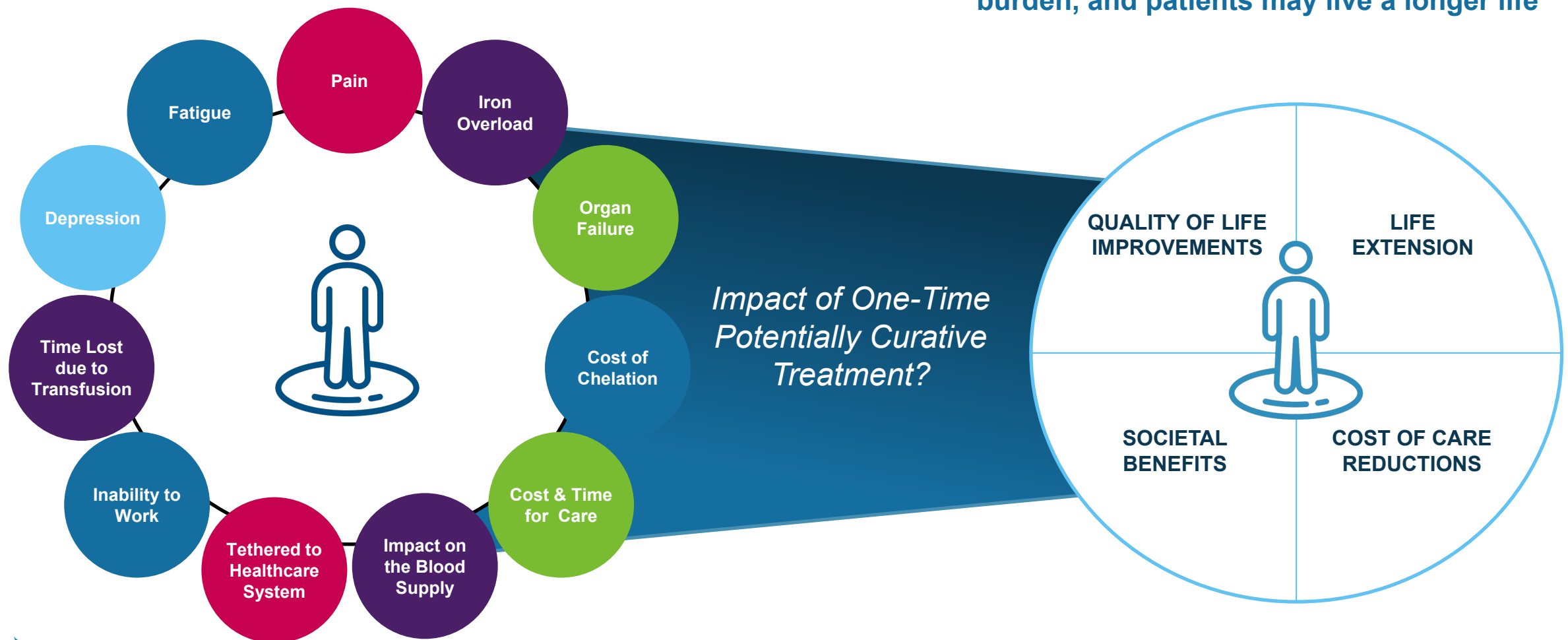
***What is the value that LentiGlobin can bring to
TDT patients, payers, system and society?***

AND how can it be fairly measured?

What Value Can LentiGlobin Bring to TDT Patients, Payers and System?

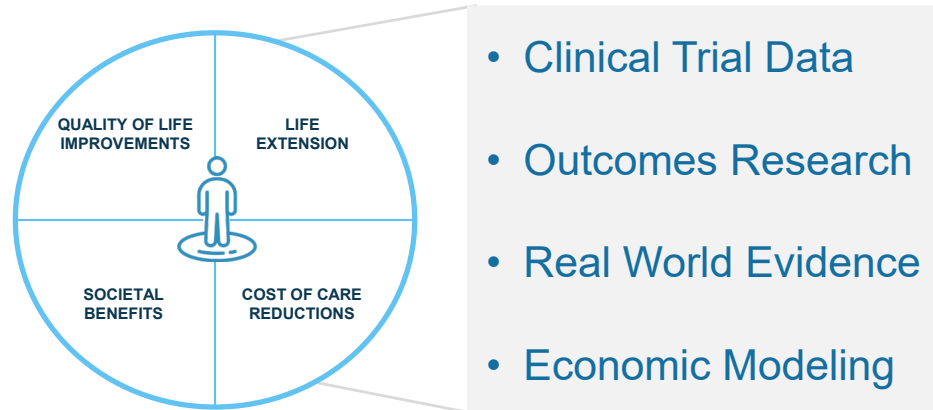
Disease and treatment-related burden builds up over time and can even lead to early death

LentiGlobin, if successful, has the potential to relieve patients of their daily disease and treatment-related burden, and patients may live a longer life

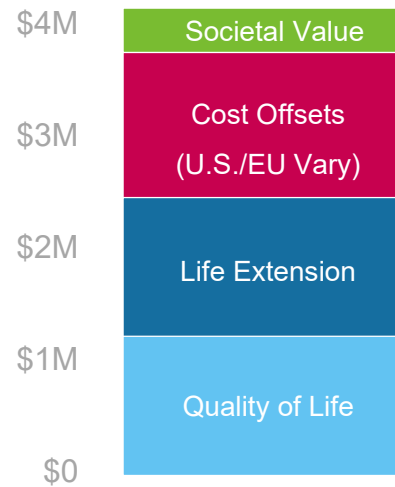


Cost Effective Analysis Focused on Actual Patient Value: QOL and Life Extension

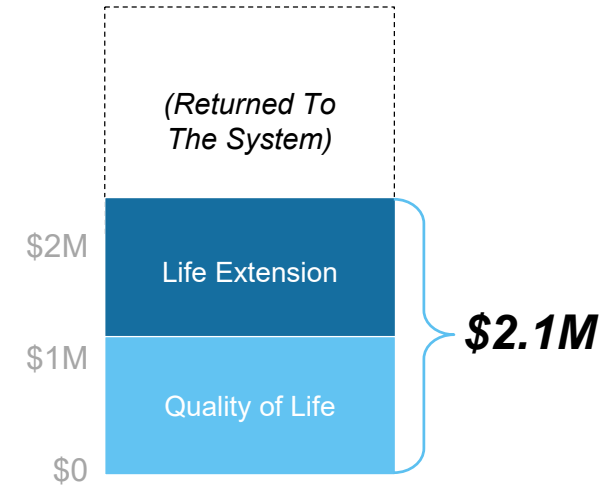
THE VALUE AT WHICH TREATMENT IS COST EFFECTIVE* (**NOT PRICE**)



Traditional
All Inclusive Calculation



LentiGlobin
Intrinsic Value



The actual LentiGlobin price is TBD, but will not exceed the intrinsic value (total value minus cost offsets).

*We have quantified the impact on patient quality of life, survival, treatment cost and society using established modeling techniques

Catalyst for Change - Recode the Status Quo for the Better



Value-based payment over time tied to outcomes



Base value only on **actual patient value** (no offsets)



Payments **over ~5 years** with **up to 80% at risk**



No price increases beyond CPI



Actual price TBD, but will **not exceed intrinsic value**

5

CATALYST FOR
CHANGE

Transfusion Dependent β -Thalassemia





Transfusion-Dependent β -Thalassemia (TDT)

- Inherited blood disease that requires lifelong, frequent blood transfusions and iron reduction therapy

PROGRAM OVERVIEW

- Filed MAA with European Medicines Agency
- General regulatory agreement with FDA for BLA filing
- Studies ongoing:
 - Northstar-2 (HGB-207)
 - Northstar-3 (HGB-212)
 - HGB-205
- Long-term follow-up: LTF-303

Transfusion-Dependent β -Thalassemia

NORTHSTAR
STUDY

HGB-204

- Basis of EU filing
- Original manufacturing process
- All genotypes

 **HGB-205**

HGB-205

- Basis of EU filing (with Northstar)
- Original manufacturing process

NORTHSTAR-2
STUDY

HGB-207

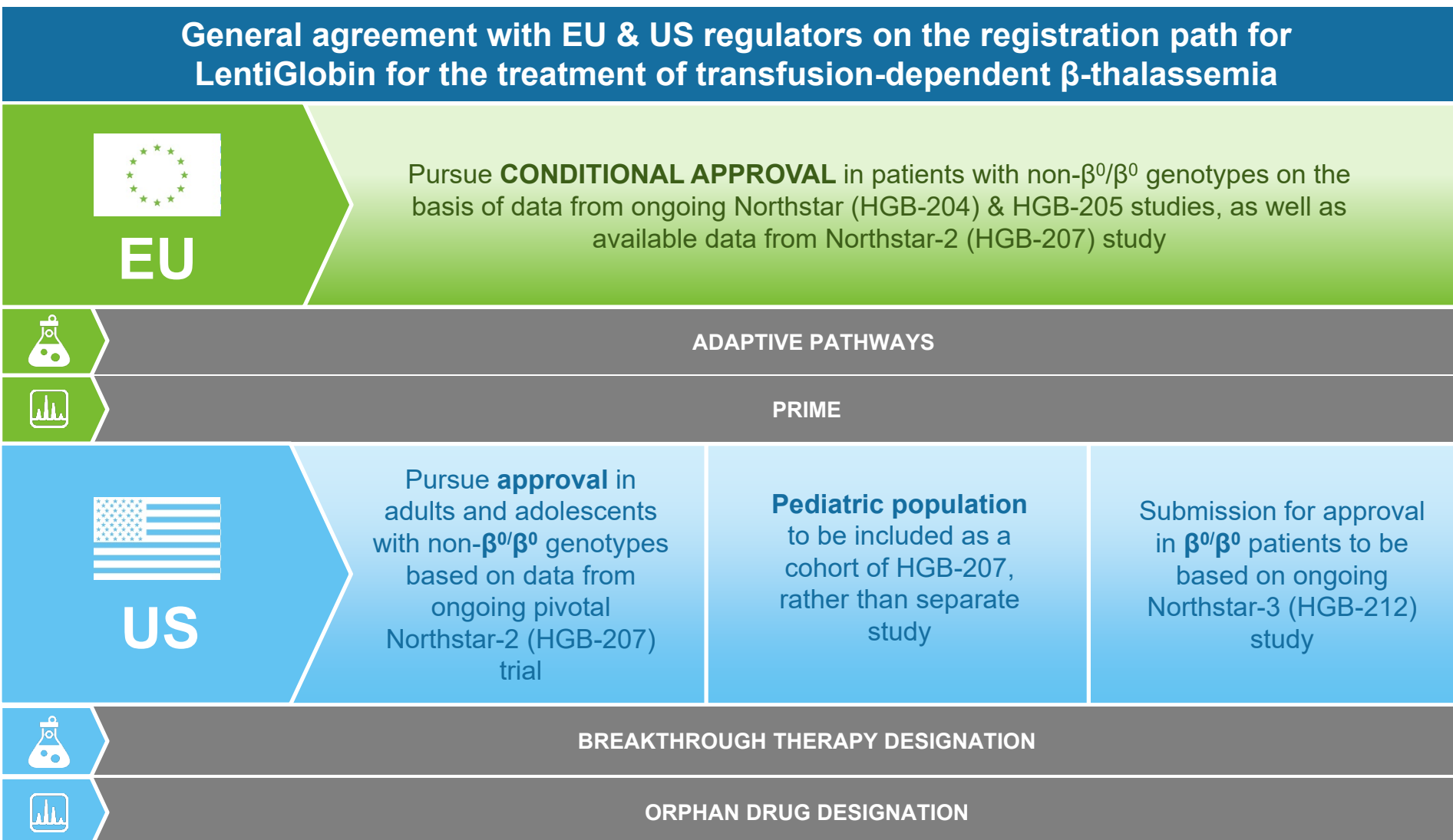
- Basis of EU and U.S. filings
- Refined manufacturing process
- Non- β^0/β^0 genotypes

NORTHSTAR-3
STUDY

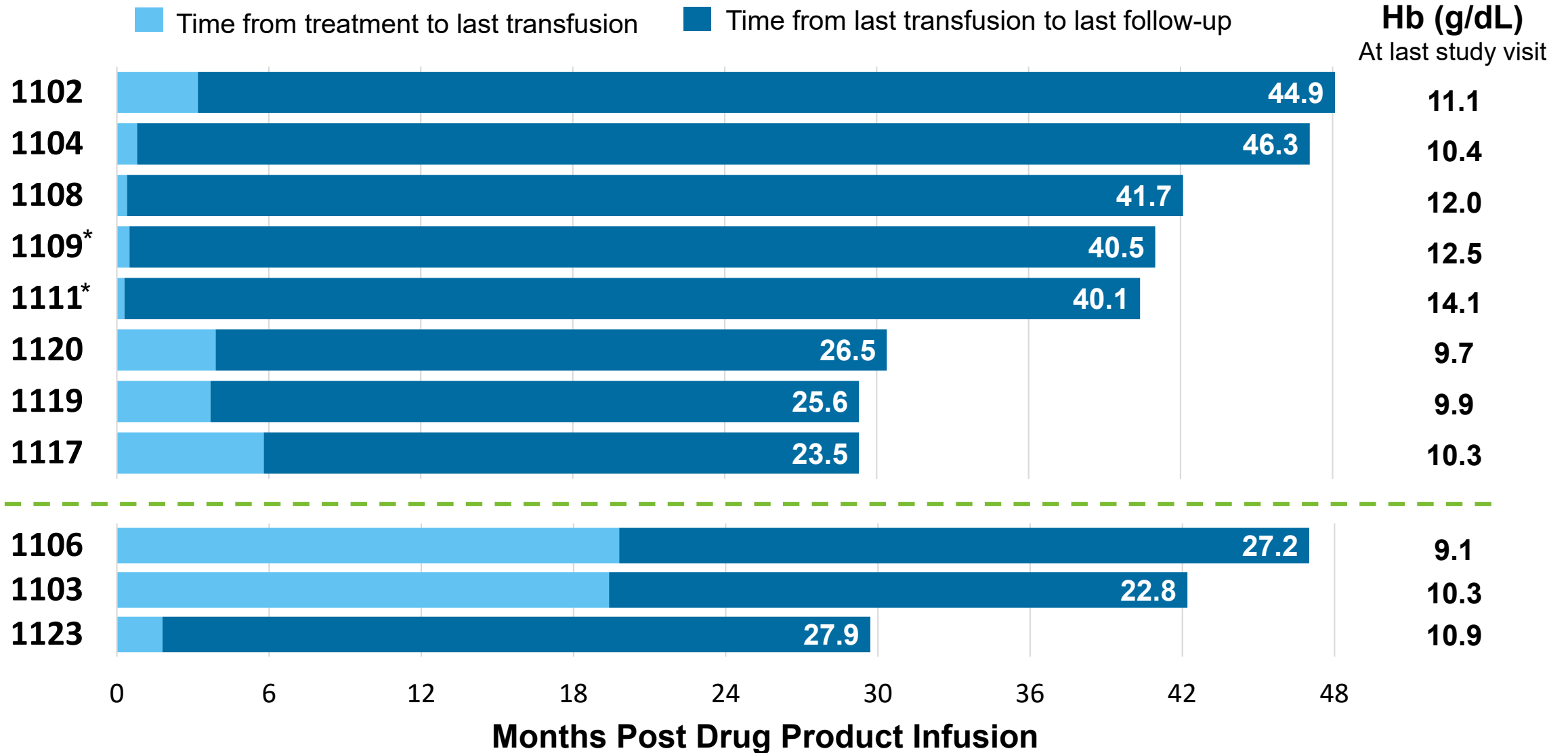
HGB-212

- β^0/β^0 genotypes
- Refined manufacturing process

TDT Registration Strategy



8/10 Patients with Non- β^0/β^0 Genotypes and 3/8 Patients with β^0/β^0 Genotypes are Free from Chronic RBC Transfusions



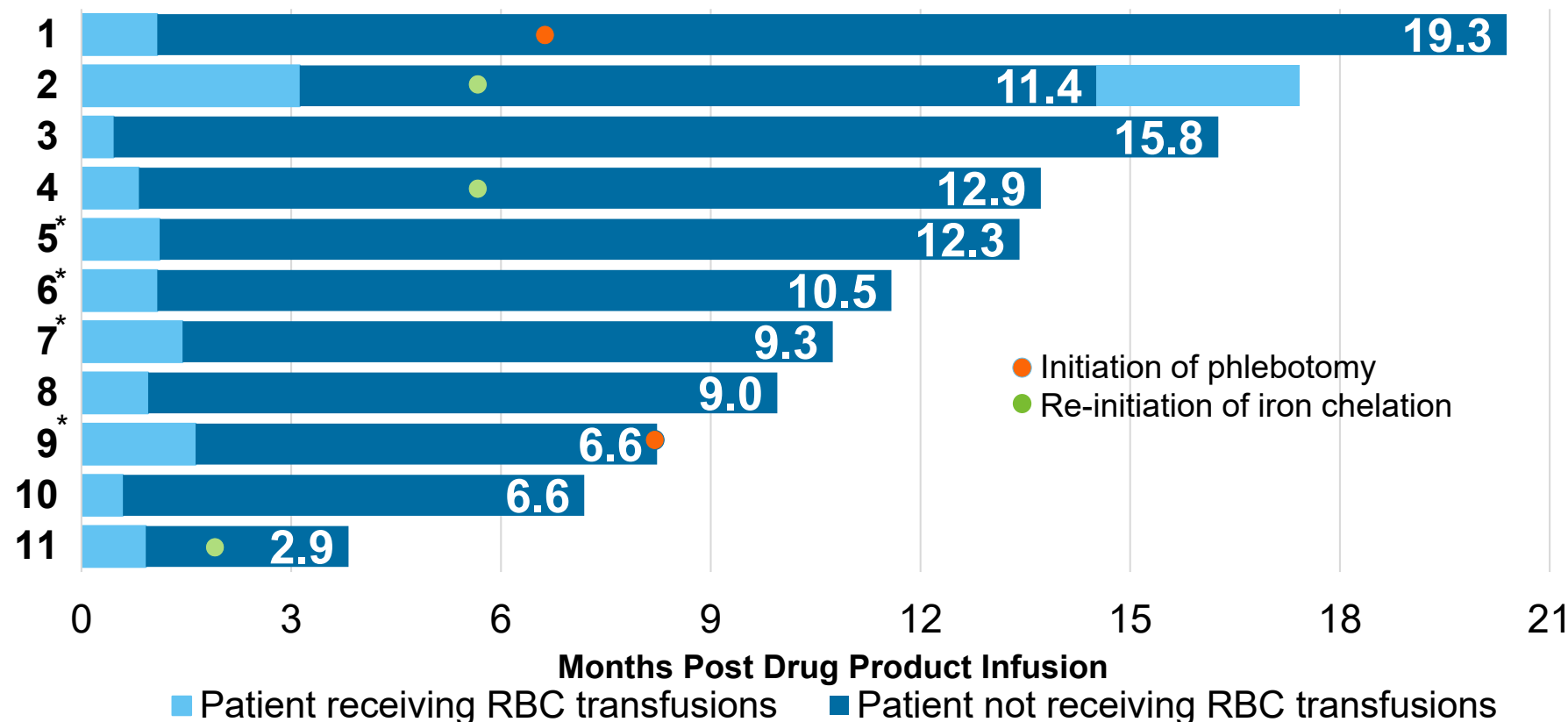
*Indicates male patients. Hb, hemoglobin; TI, transfusion independence (weighted average Hb ≥ 9 g/dL without any red blood cell transfusions for ≥ 12 months)

Data as of September 14, 2018

10/11 Patients Are Transfusion Free with Hemoglobin >11g/dL

Time free from chronic transfusions in patients with ≥3 months follow-up

Hb (g/dL) Peripheral VCN
At last study visit

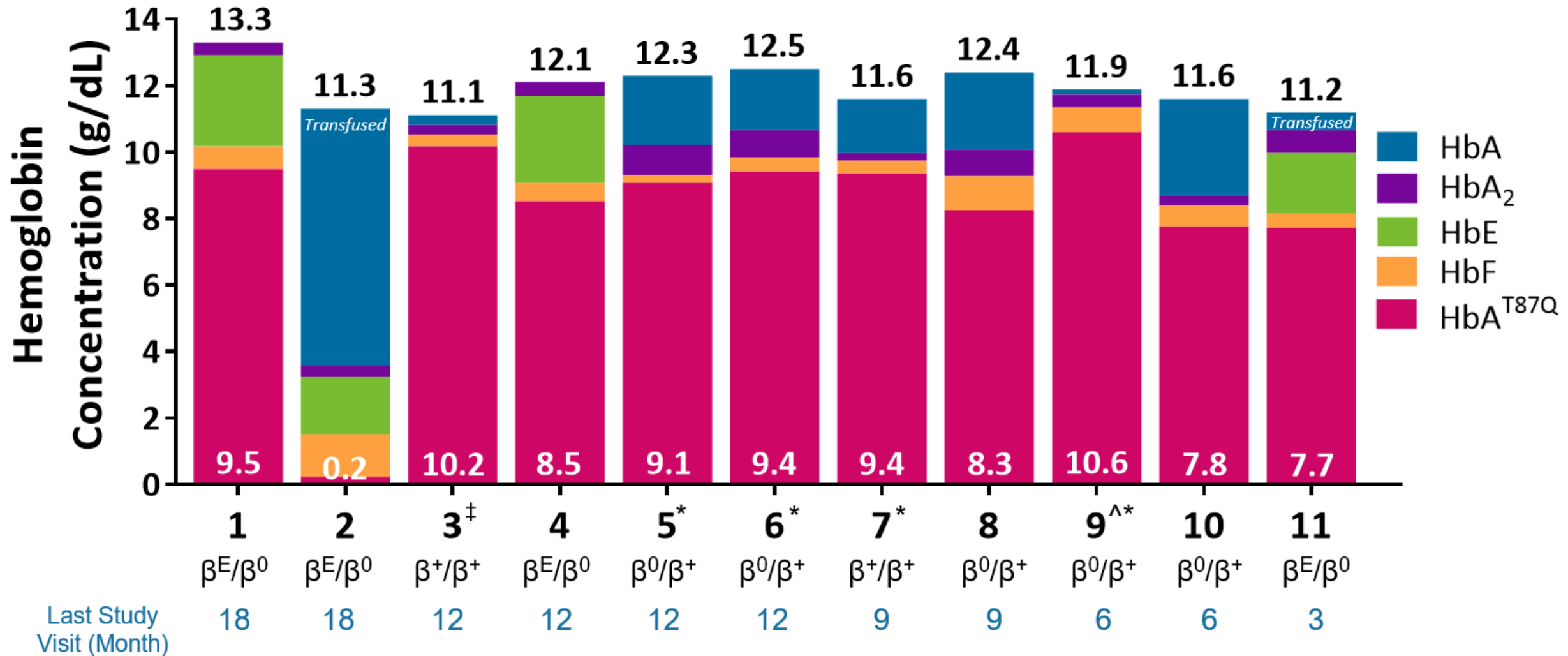


Safety profile post DP infusion remains consistent with myeloablative conditioning

Patients 1 and 3 have achieved the protocol definition of transfusion independence[†]

*Male patients; [‡]Hb supported by transfusions; [†]Weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

High Levels of Gene Therapy Derived HbA^{T87Q} in 10/11 Patients

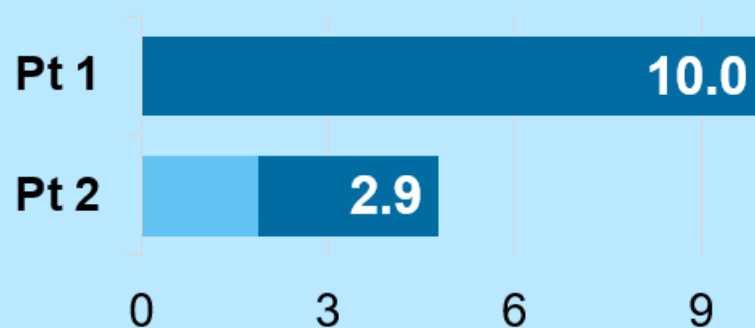


*Male patients; [‡]Patient is homozygous for IVS-I-5 β -globin mutation; [^]Patient is heterozygous for IVS-I-5 β -globin mutation. Hb, hemoglobin.

Data as of September 14, 2018

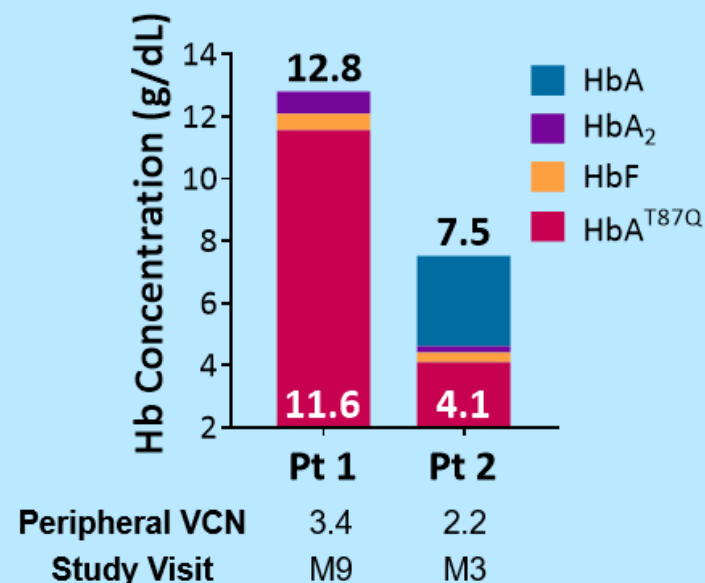
Normal Total Hemoglobin in First Northstar-3 β^0/β^0 Patient

Time free from transfusions in patients with ≥ 3 months follow-up

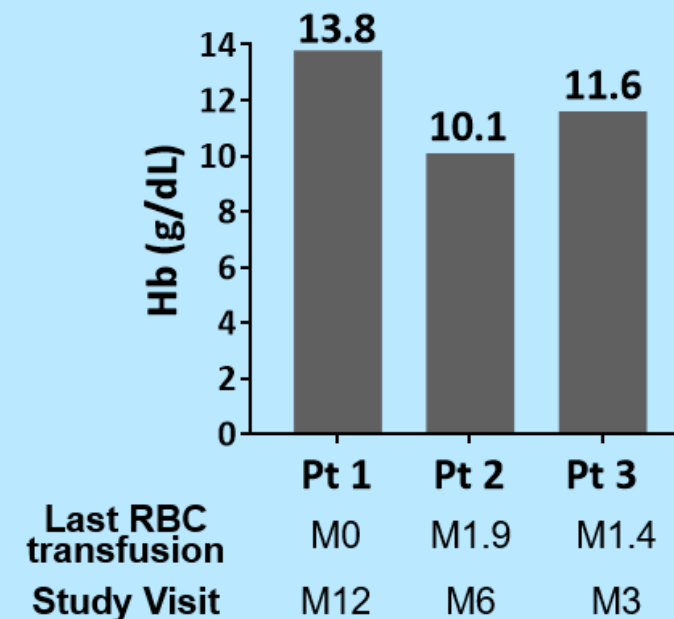


■ Time from treatment to last transfusion
■ Time from last transfusion to last follow-up

Hb fractions in patients with ≥ 3 months follow-up



Investigator reported Hb at last visit*



Safety profile post-drug product infusion remains consistent with myeloablative conditioning

*Includes investigator reported data as of November 19, 2018, not from programmed statistical outputs

AEs, adverse events; DP, drug product; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

Data as of September 14, 2018 unless otherwise noted

Sickle Cell Disease





Sickle Cell Disease (SCD)

- Severe blood disorder that causes anemia, frequent pain crises and shortened lifespan
- Global annual birth incidence ~ 300,000 – 400,000
- Mean age of death in the U.S. is 44 years¹

PROGRAM OVERVIEW

- Plan to pursue accelerated development path based on hematological primary endpoint
 - Phase 3 study to begin in 2019
- HGB-206 amended and Group C expanded

¹Paulukonis et al, California's Sickle Cell Data Collection Cohort, 2005-2015*
ASH 2017*

Increasing Momentum to #ConquerSCD

2017

- March 2017, bluebird SCD case study published in *NEJM*
- July 2017, the FDA approved Endari (L-glutamine oral powder) to address acute complications of SCD



2018

- February 2018, Admiral Brett Giroir, M.D., appointed as Assistant Secretary for Health, HHS, is shining a spotlight on the toll of SCD and the need for improved treatment options
- March 2018, NHLBI launched “Cure SCD Initiative” spearheaded by Dr. Francis Collins
- October 2018, FDA-ASH Sickle Cell Disease Clinical Endpoints Workshop

“Unfortunately, some treated [SCD] patients will have no reduction of their symptoms and the disease will continue to progress,” says Ann T. Farrell, M.D., director of the FDA’s Division of Hematology Products, CDER. “**Better therapies are desperately needed**,” Farrell explains. “We will continue to work with sponsors as much as possible to help remove roadblocks to new product development. **It’s important for the FDA to help as much as we can.**”



Accelerated Development Plan Using Novel Composite Primary Endpoint Based on Hemoglobin

EXPANDED

Updated
Primary
Endpoint

Up to add'l
21 patients

Expanded
age range

HGB-206 Group C

(Sickle Cell Disease, history of VOEs over 24 months)

Ongoing Phase 1/2, single arm, multi-center, U.S. study
N=41 (Group C)

- Primary Endpoint: HbA^{T87Q} and Total Hb
- Key Secondary Endpoint:
 - Reduction in severe VOEs
- ≥12 years of age - ≤50 years of age

HGB-210

(Sickle Cell Disease, history of VOEs over 24 months)

Phase 3, single arm, multi-center, global study

- Primary Endpoint: HbA^{T87Q} and Total Hb
- Key Secondary Endpoint:
 - Reduction in severe VOEs

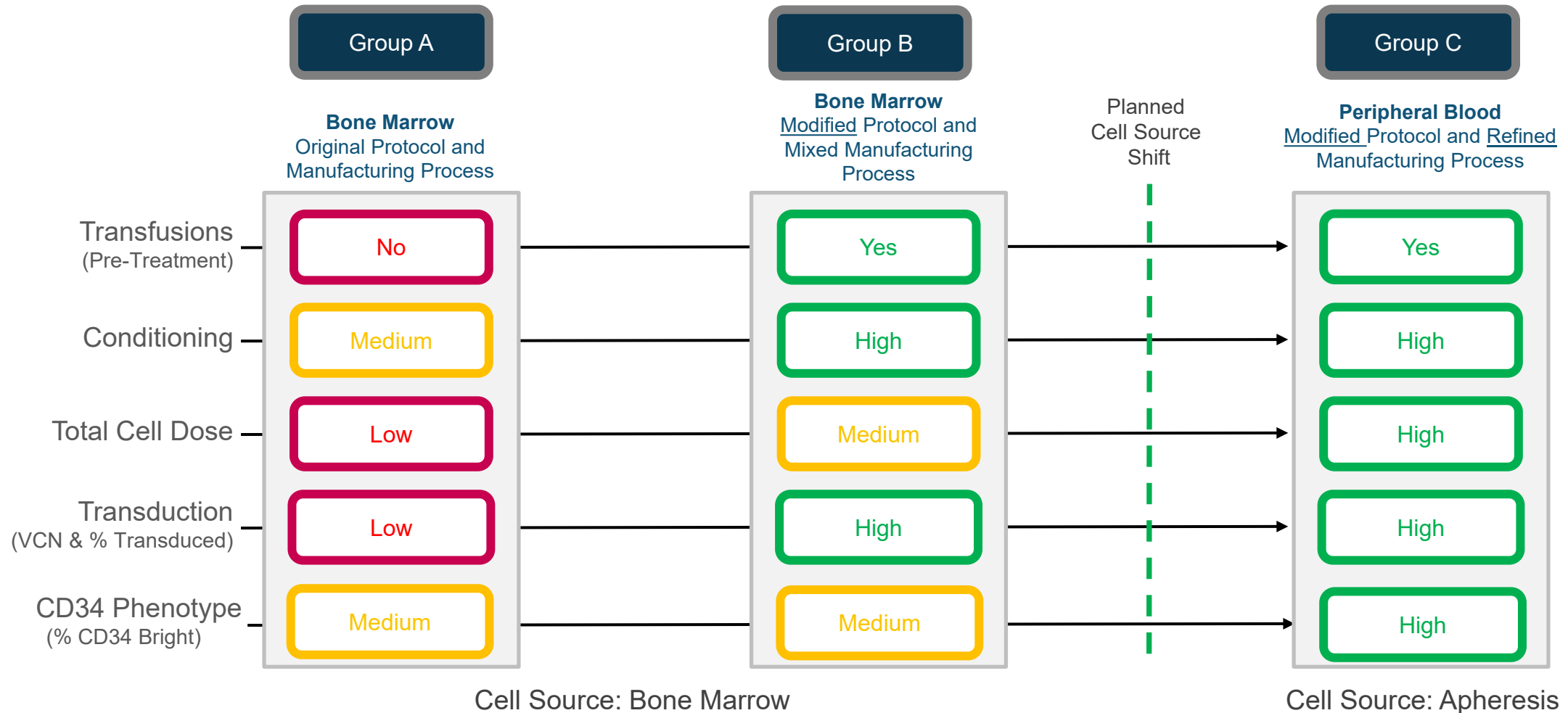
NEW

Planned
for 2019

Additional Clinical Investigation in Other Patient Types and Ages Planned

Plans Based on Ongoing Engagement with Regulators

HGB-206: Evolution of LentiGlobin in SCD



Group C: Patient Characteristics

N=14 Patients Who Started Cell Collection



Parameter	Group C N=14
Age at consent median (min – max), years	25.5 (18 – 36)
Gender	6 F 8 M
Genotype β^S/β^S	14
Prior SCD History	
Hydroxyurea use , n	8
Recurrent VOCs [*] , n Annualized no. of events, median (min – max)	9 6.5 (3.5 – 14.0)
ACS [†] , n Annualized no. of events, median (min – max)	2 1 (1 – 1)
Any history of stroke , n	3
TRJV >2.5 m/s , n	0

^{*} ≥2 events/year in preceding 2 years; [†] ≥2 episodes in preceding 2 years, with at least one episode in the past year or in the year prior to the initiation of a regular transfusion program

ACS, acute chest syndrome; F, female; M, male; VOC, vaso-occlusive crisis; pRBC, packed red blood cell; TRJV, tricuspid regurgitant jet velocity

Data as of September 14, 2018

Group C: Safety Profile Generally Consistent with Myeloablative Busulfan Conditioning



Non-hematologic* grade ≥ 3 AEs	
Post-DP infusion in ≥ 2 patient	
	n (%)
	N=9
Febrile neutropenia	6 (67)
Stomatitis	6 (67)
Serious AEs*	
Post-DP infusion in ≥ 1 patient	
	n (%)
	N=9
Abdominal pain	1 (11)
Depression	1 (11)
Drug withdrawal syndrome	1 (11)
Hallucination	1 (11)
Mucosal inflammation	1 (11)
Nausea	1 (11)
Non-cardiac chest pain	1 (11)
Splenic hematoma	1 (11)
Vomiting	1 (11)

*Hematologic AEs commonly observed post-transplant have been excluded

- **No VOEs post-DP infusion in 9 patients**
- SAEs were reported in 4 patients
 - No AE considered related to DP
 - No cases of VOD observed to date
- No vector-mediated RCL detected to date
- Integration site (IS) analysis data available for two patients at 6 month visit
 - Total IS: Showed consistent polyclonality
- One patient in Group A: MDS diagnosed 36 months post-DP infusion: no evidence of LVV integration in dysplastic cells; monosomy 7 mutation identified (associated with sporadic and chemotherapy-related MDS)

AE, adverse event; DP, drug product; RCL, replication competent lentivirus; SAE, serious adverse event; VOD, veno occlusive liver disease; VOE, vaso-occlusive event; LVV, lentiviral vector

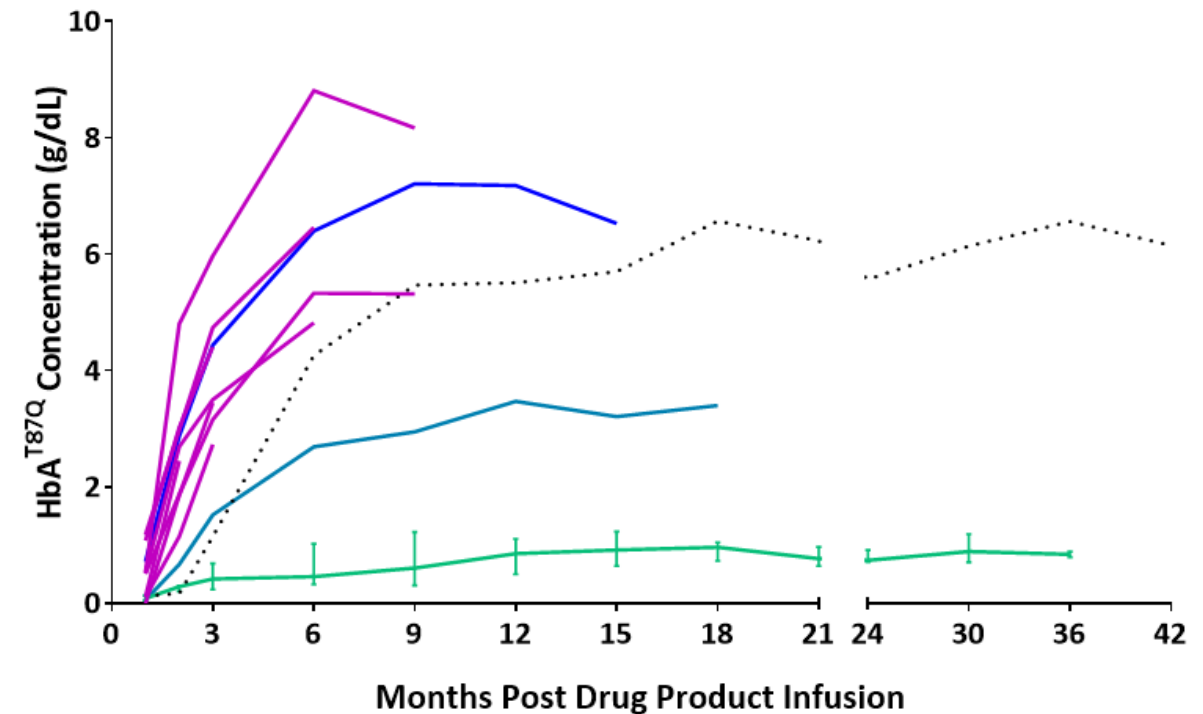
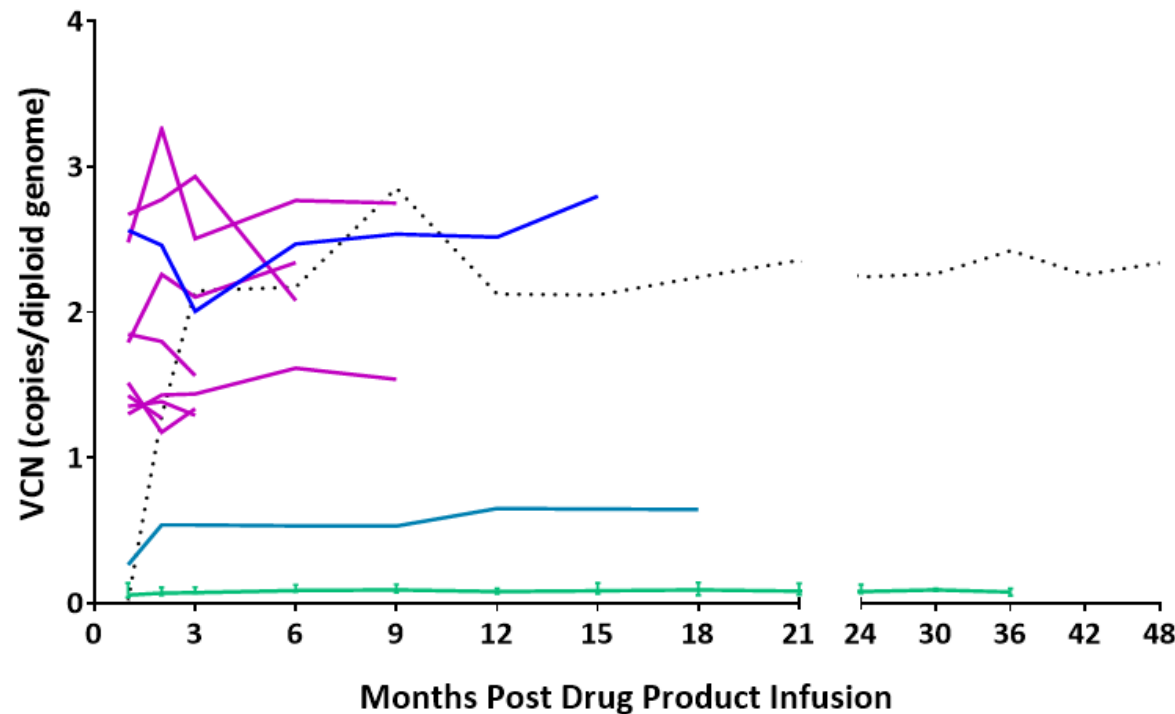
Data as of September 14, 2018

Critical Elements of LentiGlobin Success in SCD

Fundamentally Improving Red Blood Cell Physiology

GOAL	GROUP C RESULTS
High & Stable Levels of HbA ^{T87Q} Derived Hemoglobin & Total Hemoglobin	<ul style="list-style-type: none">• 4 out of 4 patients with ≥47% anti-sickling Hb (range: 47% - 62%) at 6 months• Sustained expression of HbA^{T87Q} levels through 9 months follow-up
Correction of Hemolysis	<ul style="list-style-type: none">• Normalization of reticulocyte counts, lactate dehydrogenase and bilirubin levels
Pancellular Expression of HbA ^{T87Q} Resulting in Reduction of Sickling	<ul style="list-style-type: none">• Pancellular expression shown in two independent assays of patient cells• Reduction of sickling of patient RBCs at levels consistent with sickle trait cells
Improvement of Clinical Outcomes	<ul style="list-style-type: none">• Increased total hemoglobin and robust HbA^{T87Q} production• No VOEs in early clinical follow up

Group C: Stable Peripheral Blood VCN, HbA^{T87Q} Trajectory Robust and Consistent

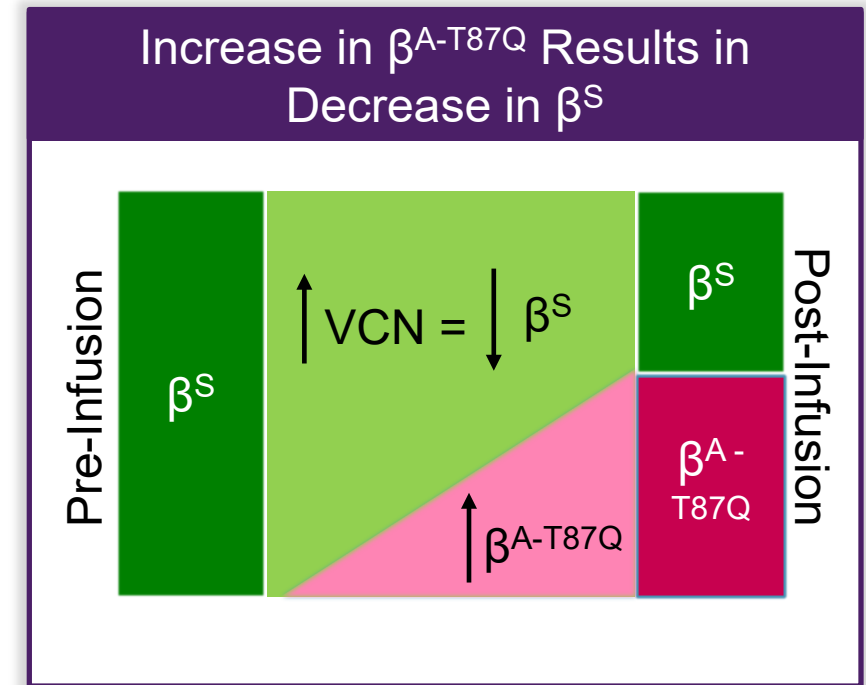
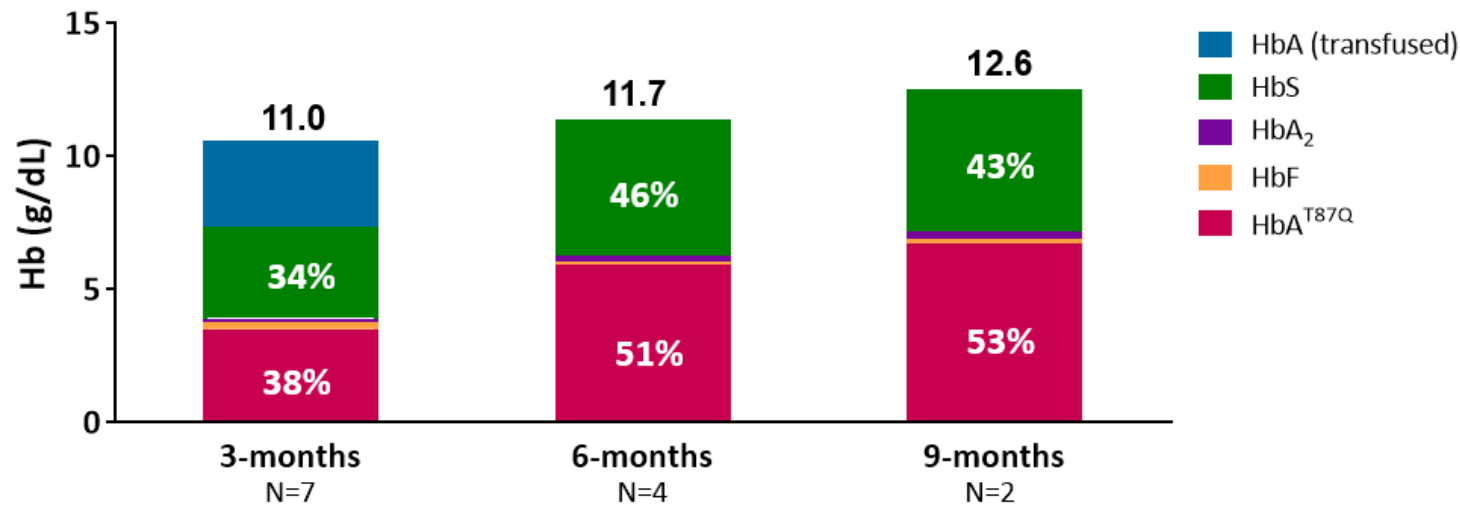


— Group A — Group B: 1312 — Group B: 1313 — Group C ... 1204

For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 36 study visit (N=2)

Data as of September 14, 2018

Group C Patients Achieving Sickle Trait-like Hemoglobin Distribution



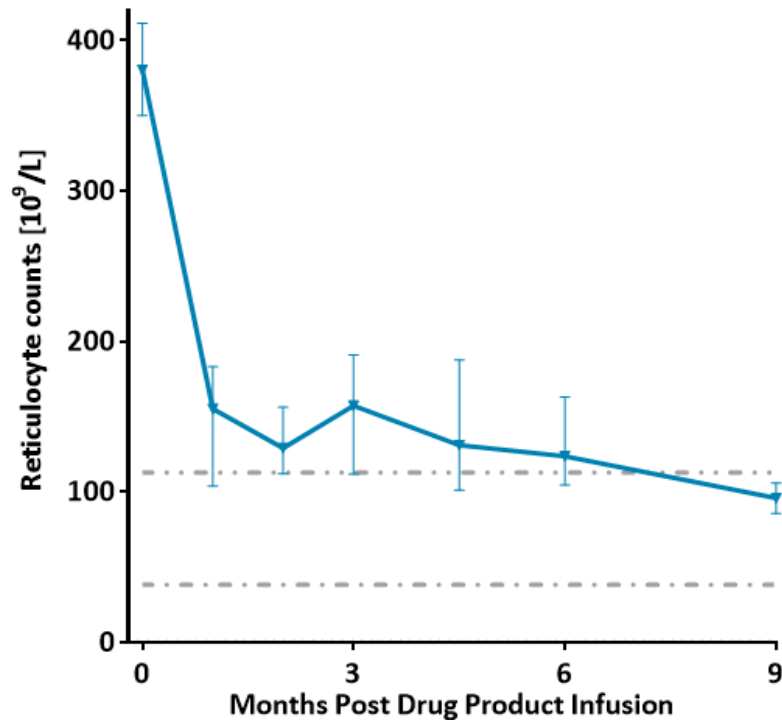
β^S -globin decreasing with increasing HbA^{T87Q}
(average concentration of hemoglobin per cell has not changed post-treatment)

Impact on Clinical Outcomes of SCD in Group C

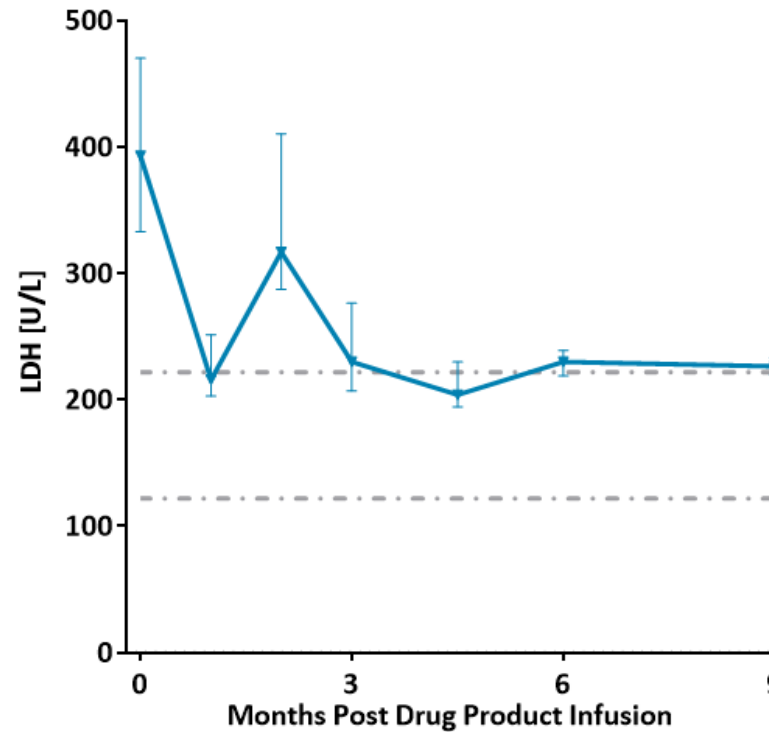
Normalization of Key Biomarkers of Hemolysis Over Time



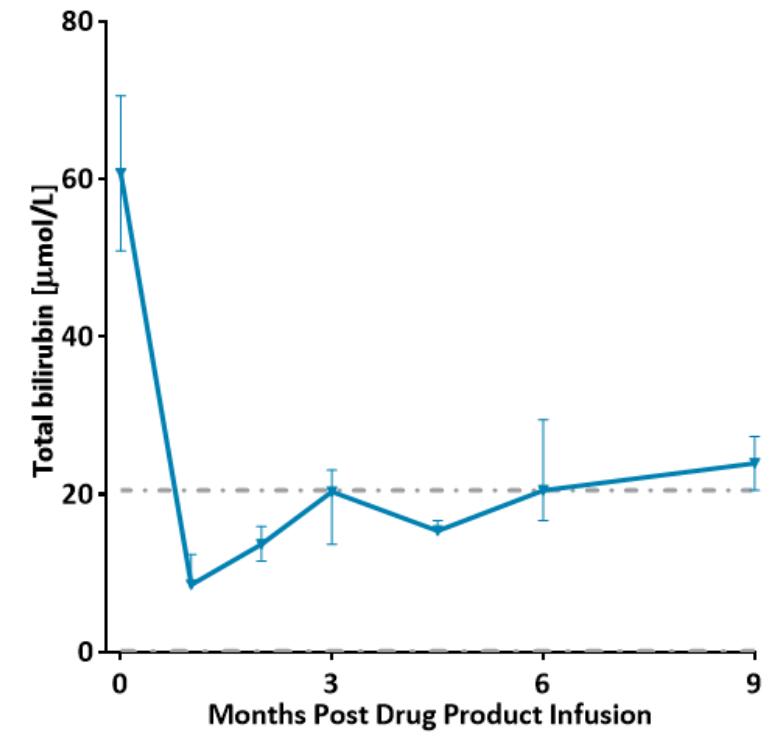
Reticulocyte Counts



Lactate Dehydrogenase



Total Bilirubin



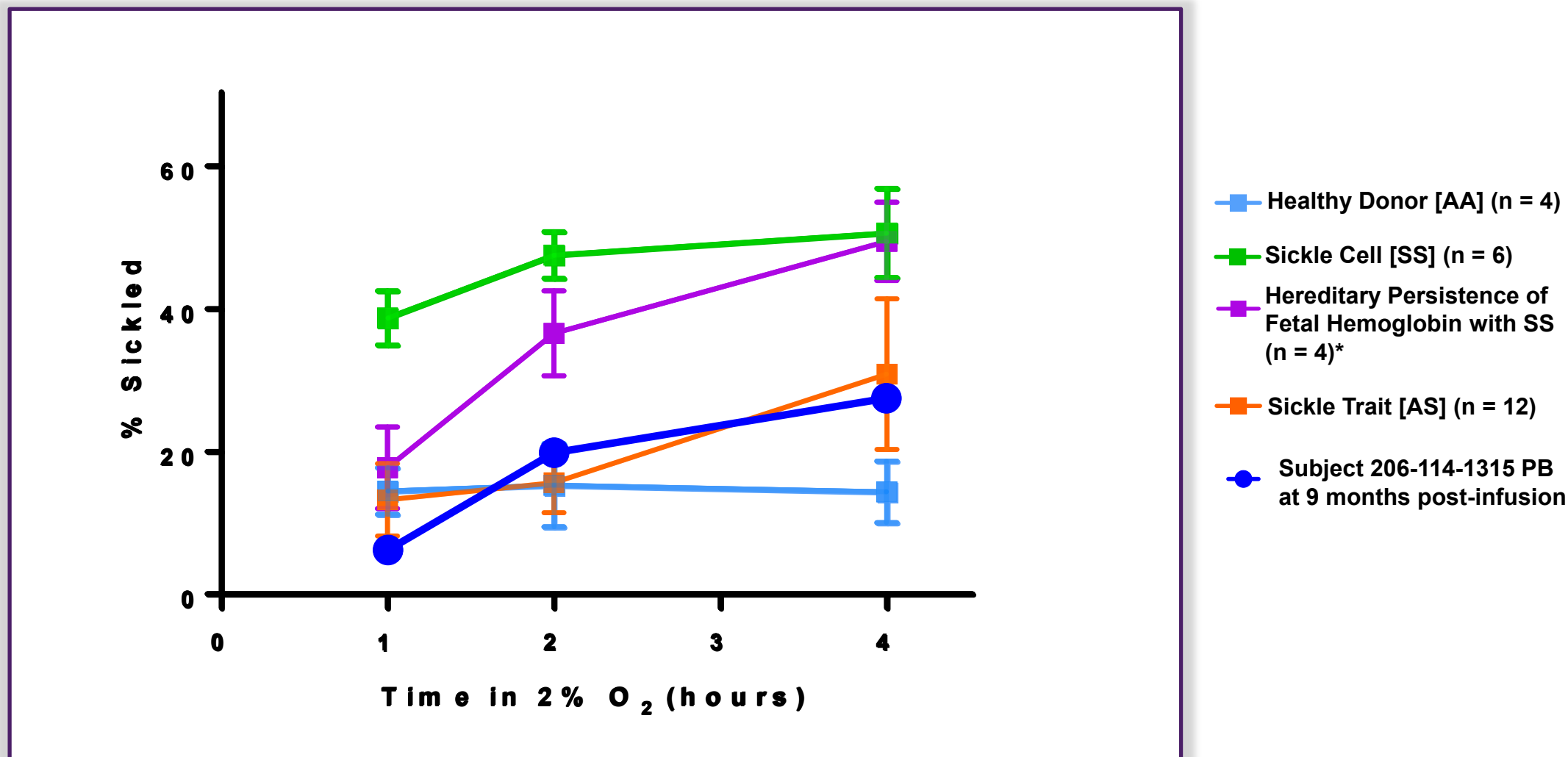
Dot-dash lines denote lower and upper limits of normal values

Median (Q1, Q3) depicted

Data as of September 14, 2018

LentiGlobin has Anti-Sickling Activity Comparable to Sickle Trait

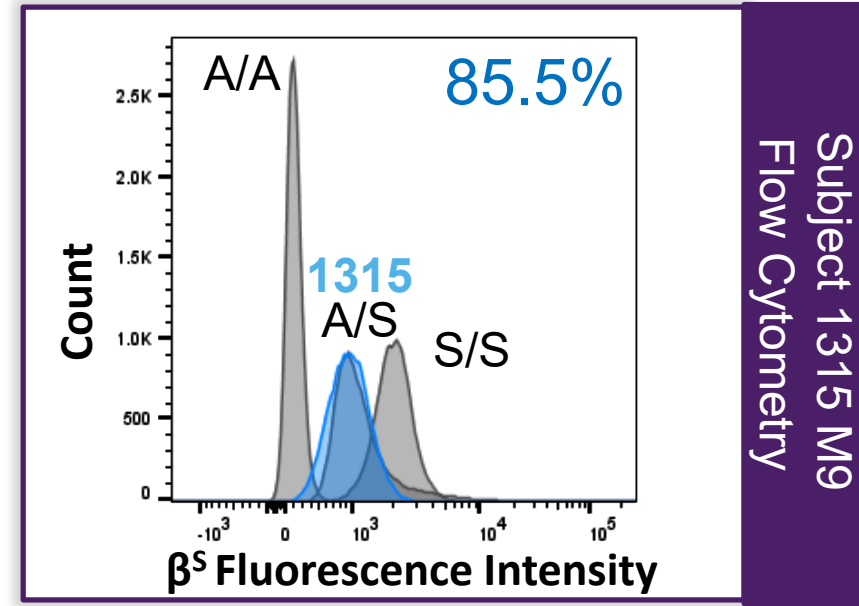
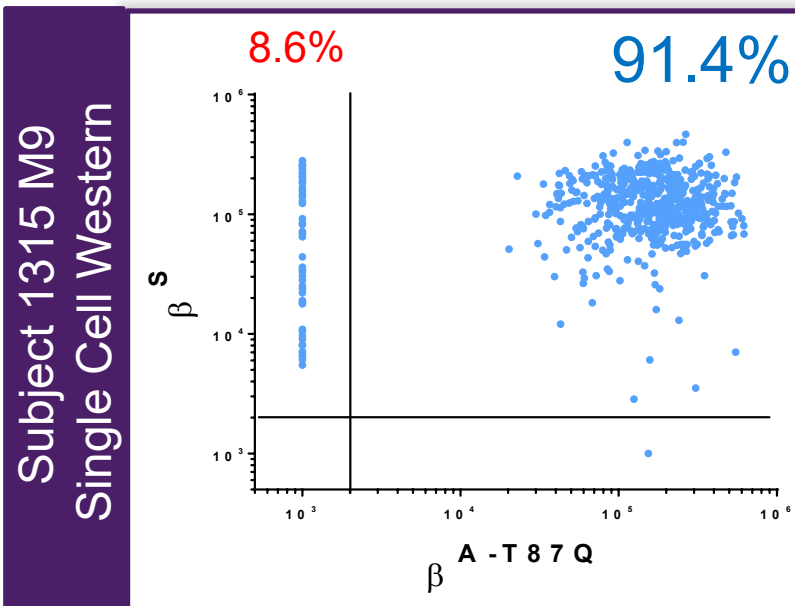
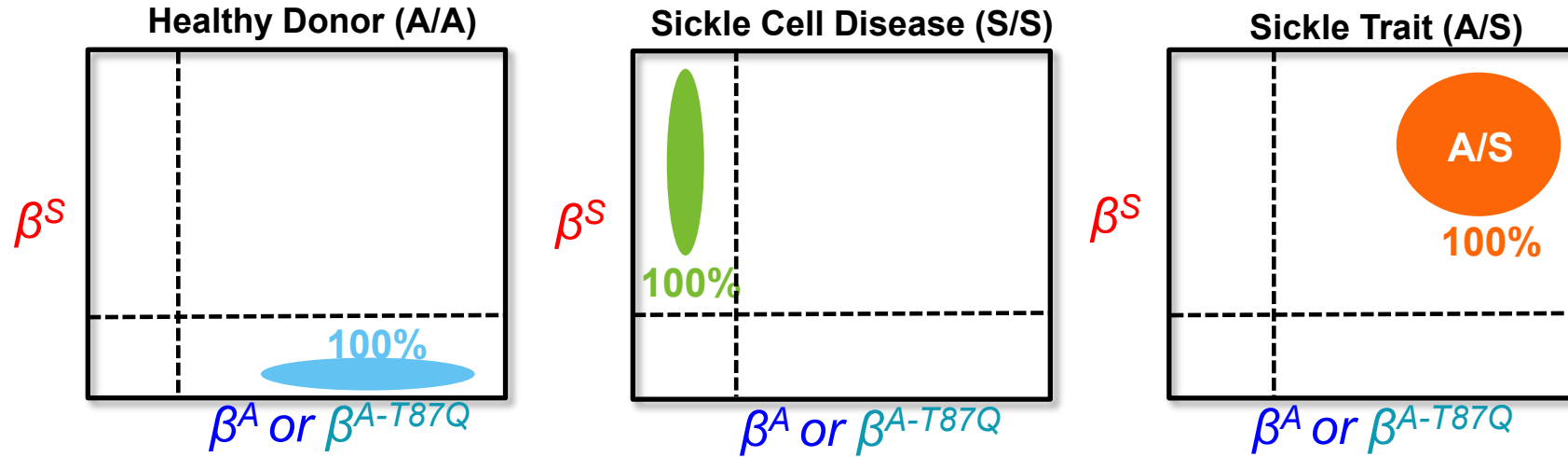
Reduction in % Sickled and Time to Sickling in Patient RBCs Post-Treatment



*HbF levels in HPFH donors ranged from 28.1 to 42.3%

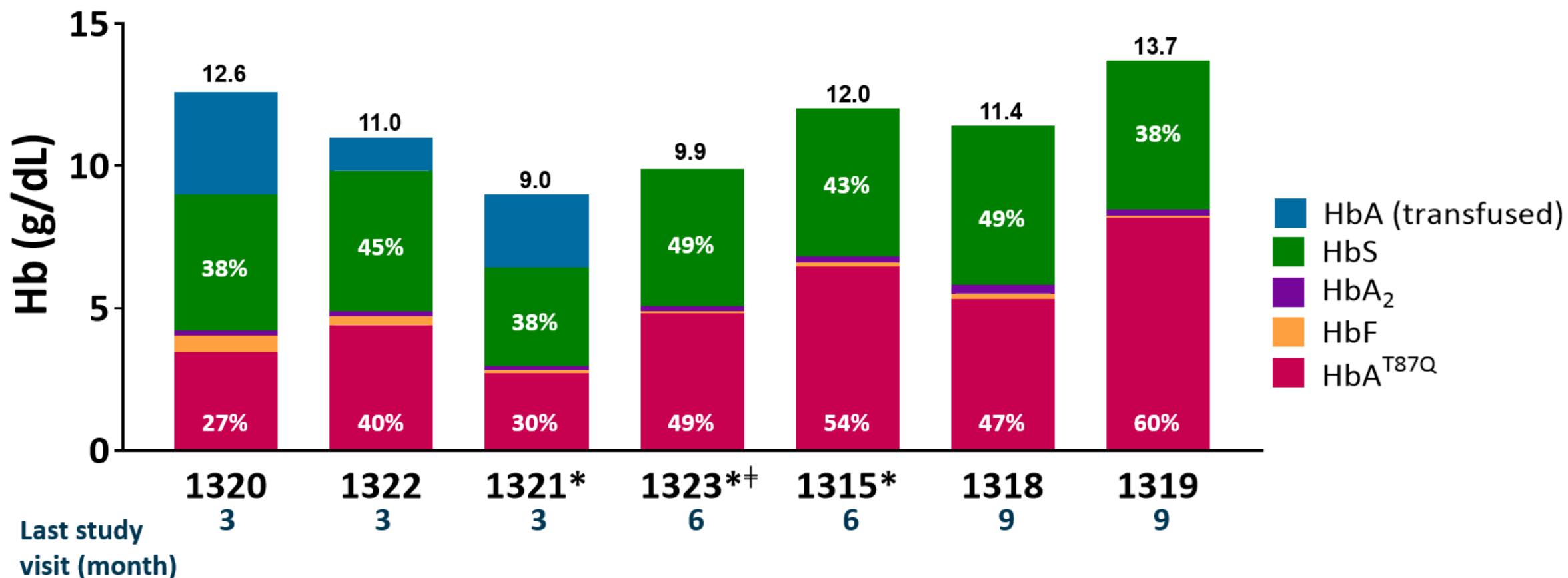
Two Independent Assays Reveal Near Pancellular β^{A-T87Q} Distribution

Majority of Patient RBCs are Positive for Anti-Sickling Globin



Impact on Clinical Outcomes of SCD

Resolution of Anemia (and Robust HbA^{T87Q} Levels) in All Patients by 6 Months; No VOEs Since DP Infusion



Group C: All patients free of VOEs as of data cut-off

* Denotes female patients; † Patient current receiving phlebotomy

Data as of September 14, 2018

A Case of Myelodysplastic Syndrome with Excess Blasts

Patient and treatment characteristics

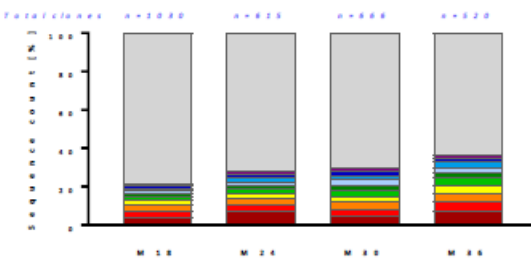
- >40 years old at LentiGlobin infusion
- Continuous hydroxyurea (HU) for 8 years before enrollment; restarted post-LentiGlobin treatment
- Received 3.3 mg/kg (200 mg) daily IV busulfan conditioning over 4 days
- LentiGlobin DP characteristics:
 - DP VCN = 1.3 copies/diploid genome
 - % LVV positive cells = 29%
 - CD34+ cell dose = 2.8×10^6 CD34+ cells/kg

A grade 4 SAE of MDS in a Group A patient ~36 months post LentiGlobin GT

- BM biopsy showed 15% myeloblasts and dysplasia
- Cytogenetics showed monosomy 7 and abnormal chromosome 19p in 8 of 20 metaphases

No evidence of clonal dominance by insertion site (IS) analysis

Frequencies of top 10 integration sites



- No single IS represents >30% of total
- Top 5 clones consistently transitory over last 18 months of follow-up

Blast cells (CD34+) had low VCN consistent with the absence of LVV integration

Cell populations from BM aspirate collected ~3 weeks post MDS diagnosis	Purity (%)	VCN (c/dg)
Unsorted	N/A	0.14
CD34-	98	0.21
CD34+, with myeloblasts as major contributors	93	0.02

Conclusions

- Given that there is no evidence of LVV-mediated oncogenesis, the MDS SAE is considered unlikely related to LentiGlobin GT*
- MDS has been reported in adults post autologous HSCT with use of alkylating agents such as busulfan (Rege KP et al., BMT 1998; Howe R et al., BMT 2003; McNerney ME et al., Nat Rev Cancer 2017)

*Per safety database

BM, bone marrow; c/dg, copies per diploid genome; DP, drug product; GT, gene therapy; HSCT, hematopoietic stem cell transplant; IV, intravenous; LVV, lentiviral vector; N/A, not applicable; VCN, vector copy number

Multiple Myeloma



Multiple Myeloma

- A lethal blood cancer that often infiltrates the bone marrow causing anemia, kidney failure, immune problems and bone fractures

BCMA PROGRAM OVERVIEW

- bb2121: Enrollment in KarMMa registration-enabling study complete (N=140)
- Additional studies advancing:
 - KarMMa-2 in 2nd line Phase 2 study enrolling soon
 - KarMMa-3 in 3rd line+ Phase 3 study enrolling soon
 - Opportunities for bb2121 in newly diagnosed MM including high risk, transplant ineligible and transplant eligible vs. transplant under evaluation



CRB-401 Data at ASCO 2018 - Baseline Demographics and Clinical Characteristics

Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) follow-up, d	345 (46, 638)	87 (29, 184)
Median (min, max) age, y	58 (37, 74)	65 (44, 75)
Male, n (%)	13 (62)	16 (73)
Median (min, max) time since diagnosis, y	4 (1, 16)	6 (1, 36)
ECOG PS, ¹ n (%)		
0	10 (48)	6 (27)
1	11 (52)	16 (72)
High-risk cytogenetics, n (%)		
del(17p), t(4;14), t(14;16)	8 (38)	9 (41)

ECOG, Eastern Cooperative Oncology Groups performance status; ISS, international staging system; NA, not available. ¹Data at screening presented.
Data cutoff: March 29, 2019

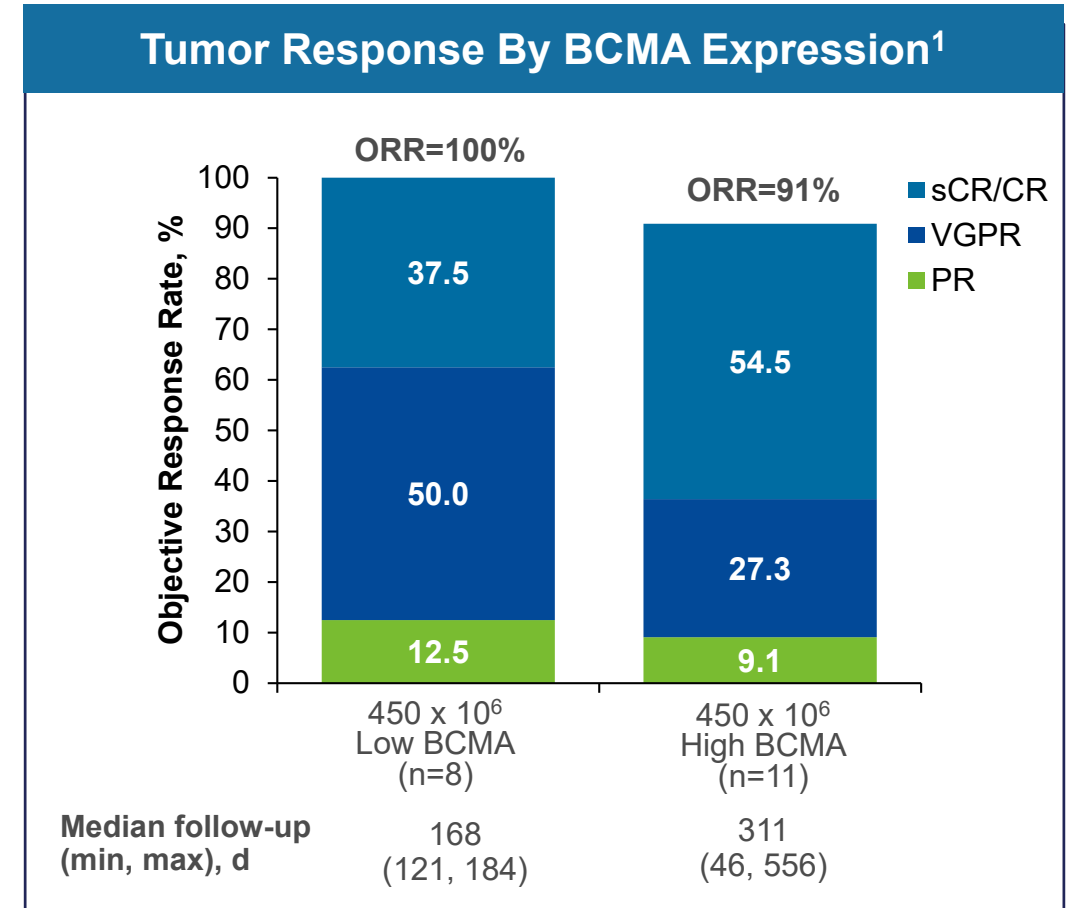
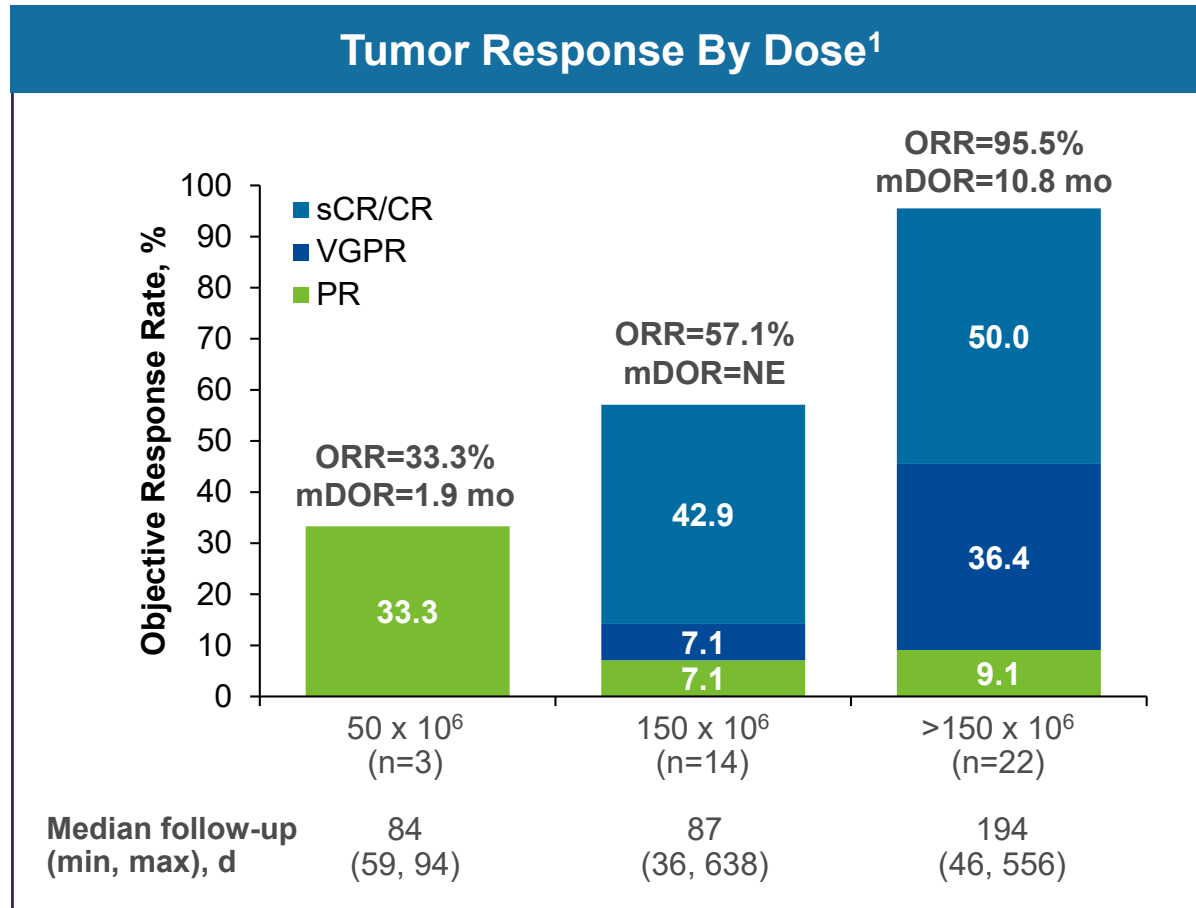
CRB-401 Data at ASCO 2018 - Heavily Pretreated Patient Population

Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

Parameter	Escalation (N=21)		Expansion (N=22)	
	Exposed	Refractory	Exposed	Refractory
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Cumulative exposure, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

SCT, stem cell transplant. Data cut-off: March 29, 2018.

CRB-401 Data at ASCO 2018 - Tumor Response: Dose-related and Independent of Myeloma BCMA Expression Levels



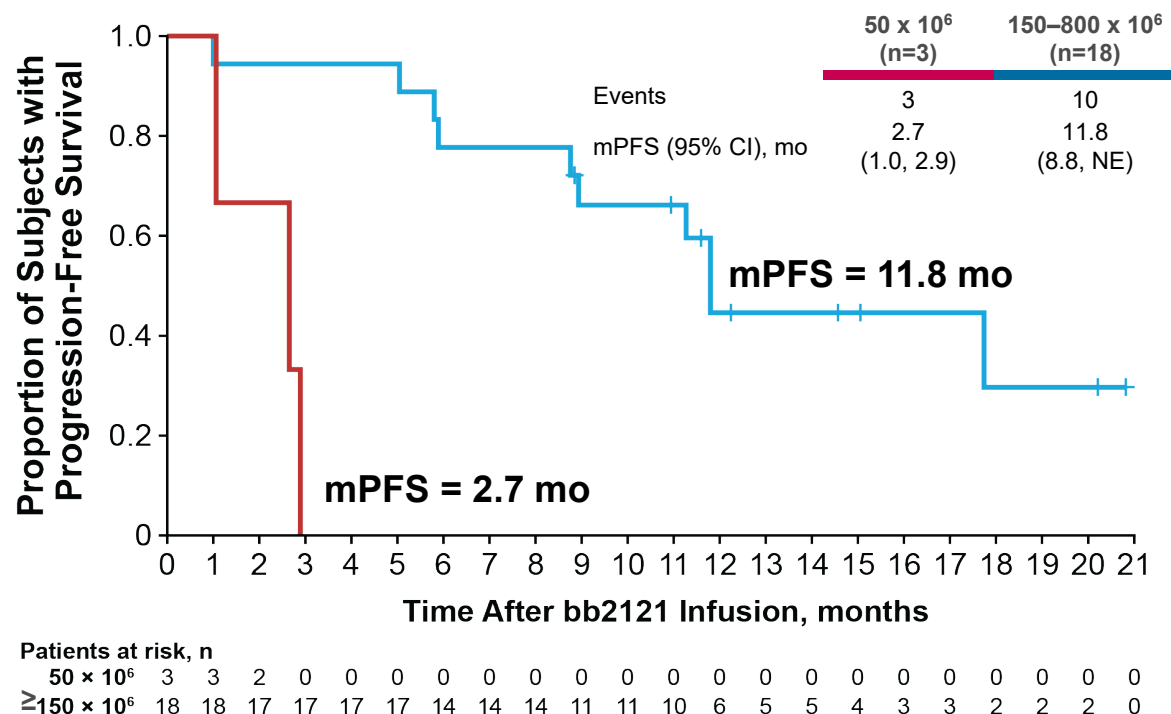
- 80.6% ORR across active dose cohorts (150-800 x 10⁶)

CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. Data cut-off: March 29, 2018. ¹Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

CRB-401 Data at ASCO 2018 - Hitting the Mark for Progression Free Survival

- mPFS of 11.8 months at active doses ($\geq 150 \times 10^6$ CAR+ T cells) in 18 subjects in dose escalation
- mPFS of 17.7 months in 16 responding subjects from all study cohorts who are MRD-negative

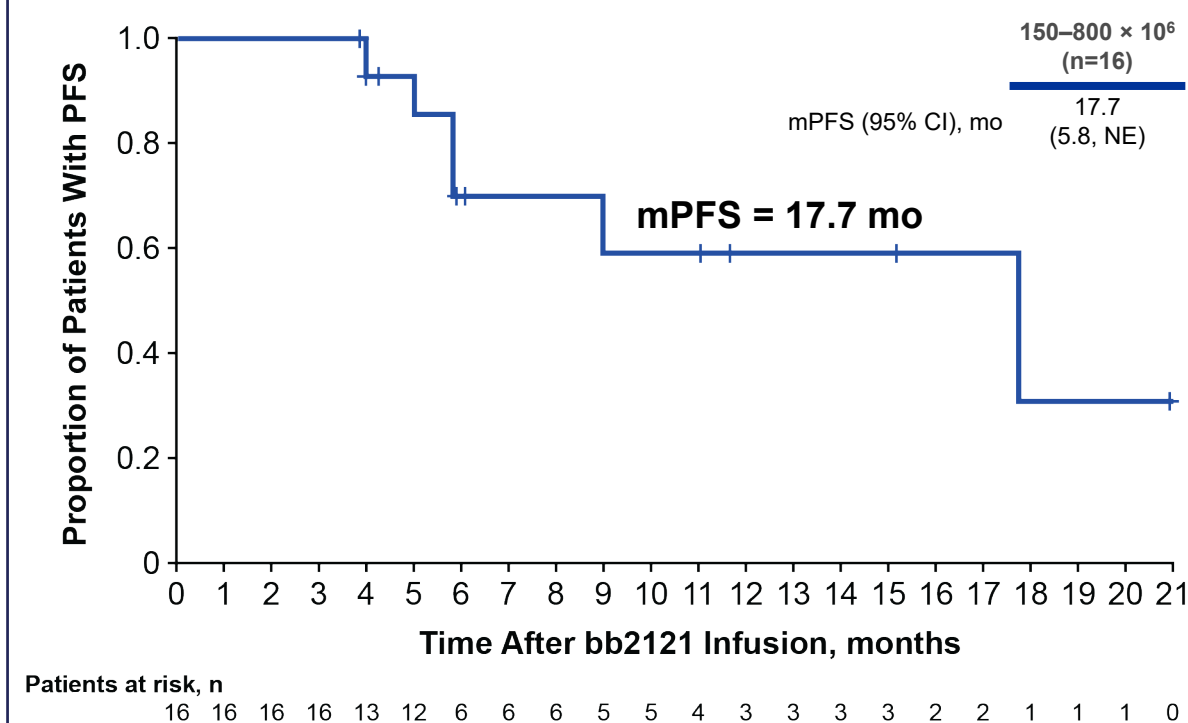
PFS at Inactive (50×10^6) and Active ($150\text{--}800 \times 10^6$) Dose Levels¹



Data cut-off: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable.

¹PFS in dose escalation cohort.

PFS in MRD-Negative Responders Escalation and Expansion Cohorts



PFS progression-free survival; MRD, minimal residual disease.

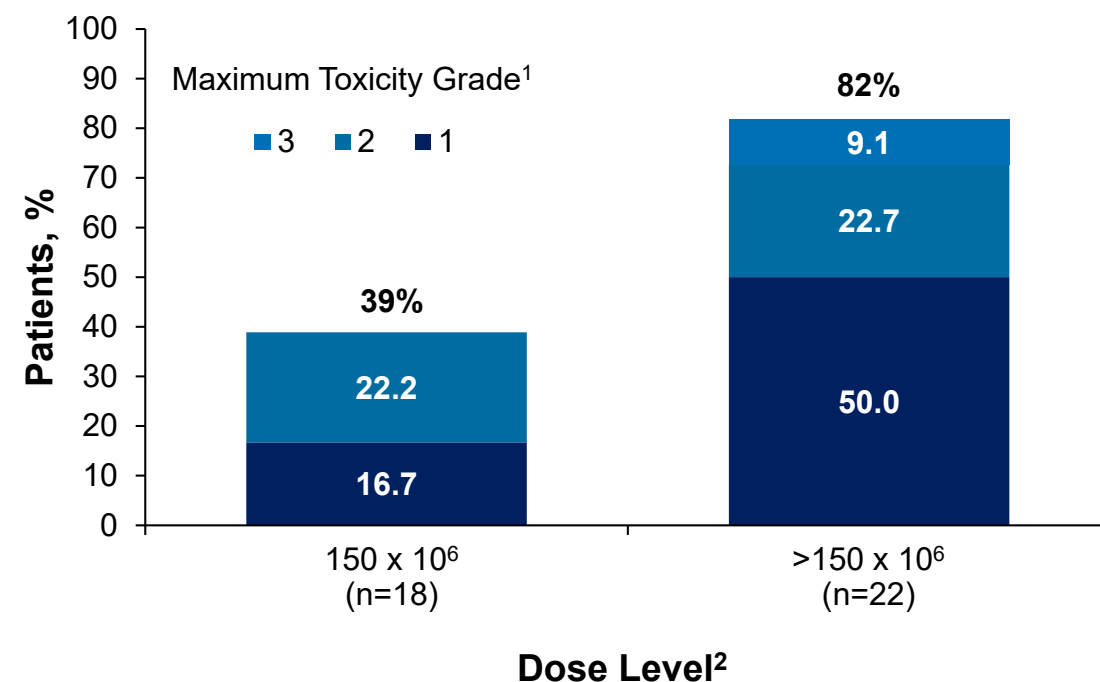
Includes patients treated with $< 50 \times 10^6$ CAR T cells who were MRD-negative at > 1 postbaseline time point

CRB-401 Data at ASCO 2018 - bb2121 Continues to be Generally Well-Tolerated; No New Safety Signals

CAR T Treatment-Emergent Adverse Events All Infused Patients (N=43)

TEAE, n (%)	Overall	Grade ≥ 3
Cytokine release syndrome ¹	27 (63)	2 (5)
Neurotoxicity ²	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anemia	24 (56)	19 (44)
Infection ³		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

Cytokine Release Syndrome By Dose Level



- No grade 4 CRS events
- No fatal CRS or neurotoxicity events

- Patients with a CRS event, 63%

Data cut-off: March 29, 2018. NE, not estimable. ¹CRS uniformly graded per Lee et al., *Blood* 2014;124:188-195. ²Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. ³Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. ⁴Includes patients treated with active doses (150–800 × 10⁶ CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. ⁵Time from first bb2121 infusion to the first grade ≤ 2 event after day 32.

Response to Current Standard of Care in Late Line RRMM

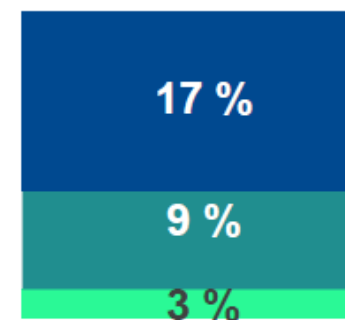
Current standard of care in RRMM after two or more lines of therapy:

	Dara	PDd	bb2121
Phase	II	I	I
N	106	103	43
Eligibility	≥ 3 prior lines Pom allowed Dara-naïve	≥ 2 prior lines Pom-naïve Dara-naïve	≥ 3 prior lines Pom allowed Dara allowed
Median prior lines	5	4	7

PDd=Pomalidomide + Daratumumab +dexamethasone.
Pom=Pomalidomide; Dara=Daratumumab

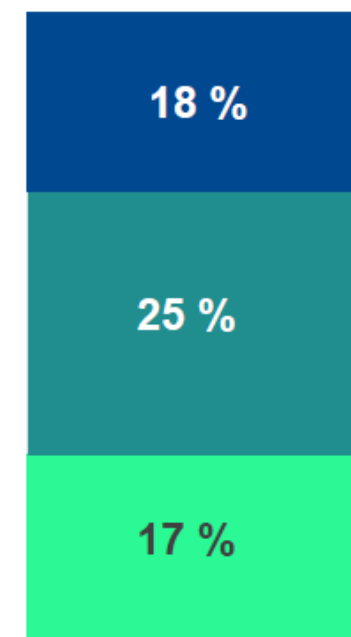
■ sCR/CR ■ VGPR ■ PR

Daratumumab monotherapy (phase II)
ORR=29%
mPFS=3.7 mo



Pomalidomide + Daratumumab + dexamethasone (phase Ib)

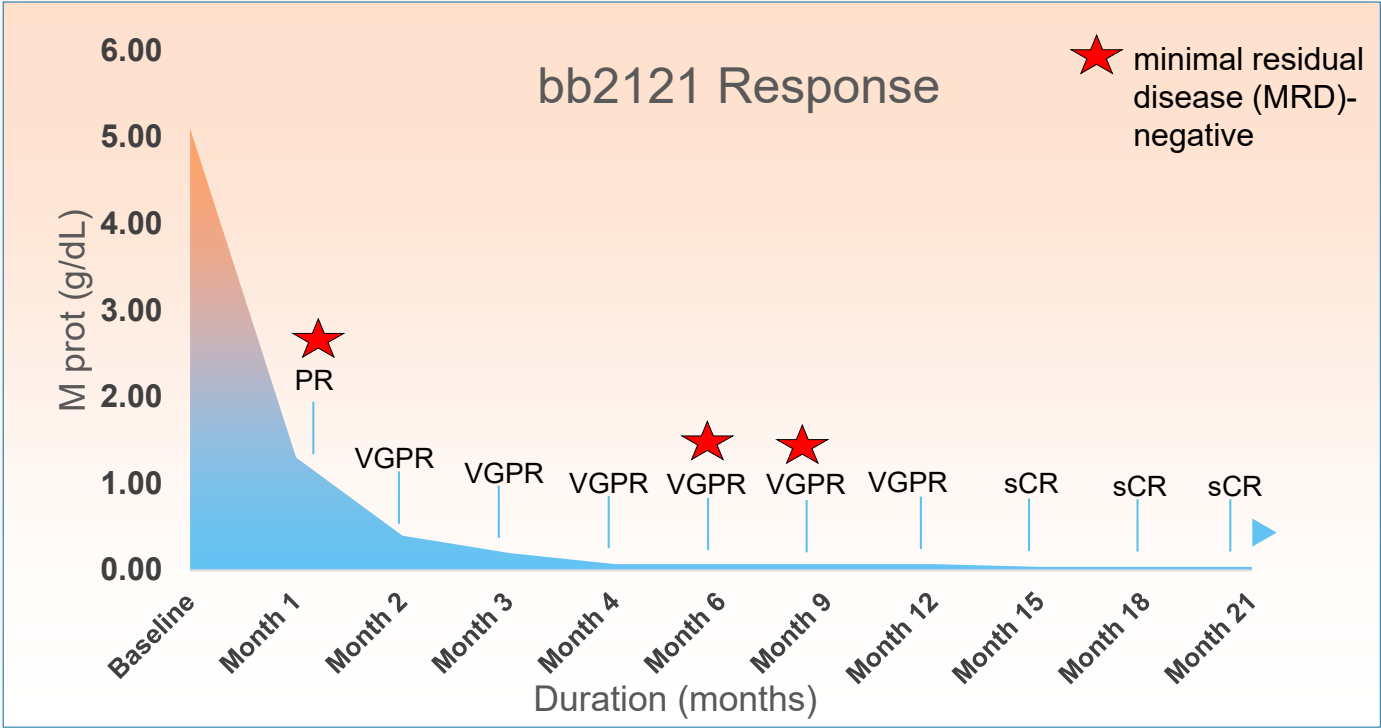
ORR=60%
mPFS=8.8 mo



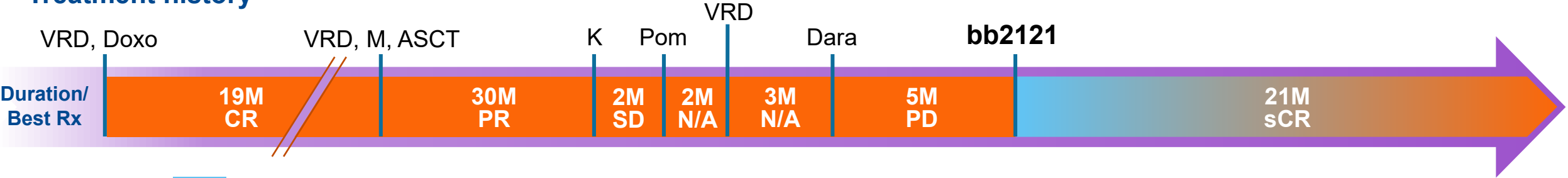
Myeloma Response

bb2121 Patient Case: 21 Months in sCR

General Information	
Age & Gender	52 year old Male
Dose group	150x10^6
Tumor Burden	High
High Risk Cytogenetics (based on FISH)	No
Number of prior regimens	6
Initial diagnosis	May, 2010
BCMA% (prescreen, baseline)	60, 75

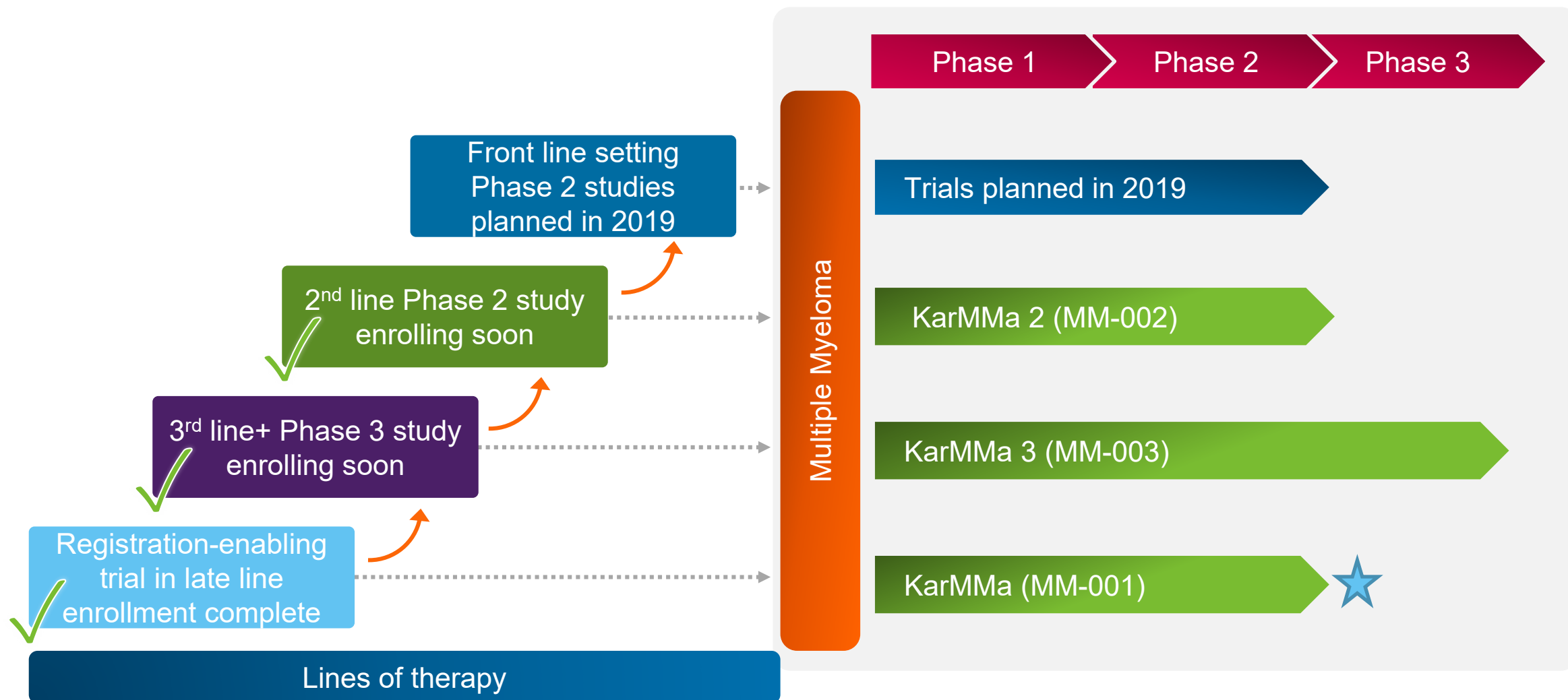


Treatment history



KEY ASCT: autologous stem cell transplant, R: Revlimid, M: melphalan, d: dexamethasone, V: Velcade, K: Kyprolis, P/Pom: Pomalyst, Vor: vorinostat, Dara: daratumumab, Doxo:Doxorubicin

Advancing bb2121 into Earlier Lines of Multiple Myeloma



Anticipated Approval in 2020

Key Takeaways from CRB-401 Presented at ASCO

Efficacy?

- 95.5% ORR in doses above 150M cells.
- 50% CR rate at doses above 150M cells.

Durability?

- 11.8 months median PFS in dose-escalation active doses.
- 17.7 months median PFS in MRD(-) patients with response (escalation and expansion).

BCMA? MRD?

- Consistent responses across BCMA expression levels.
- 16/16 responding, MRD-evaluable patients were MRD negative.

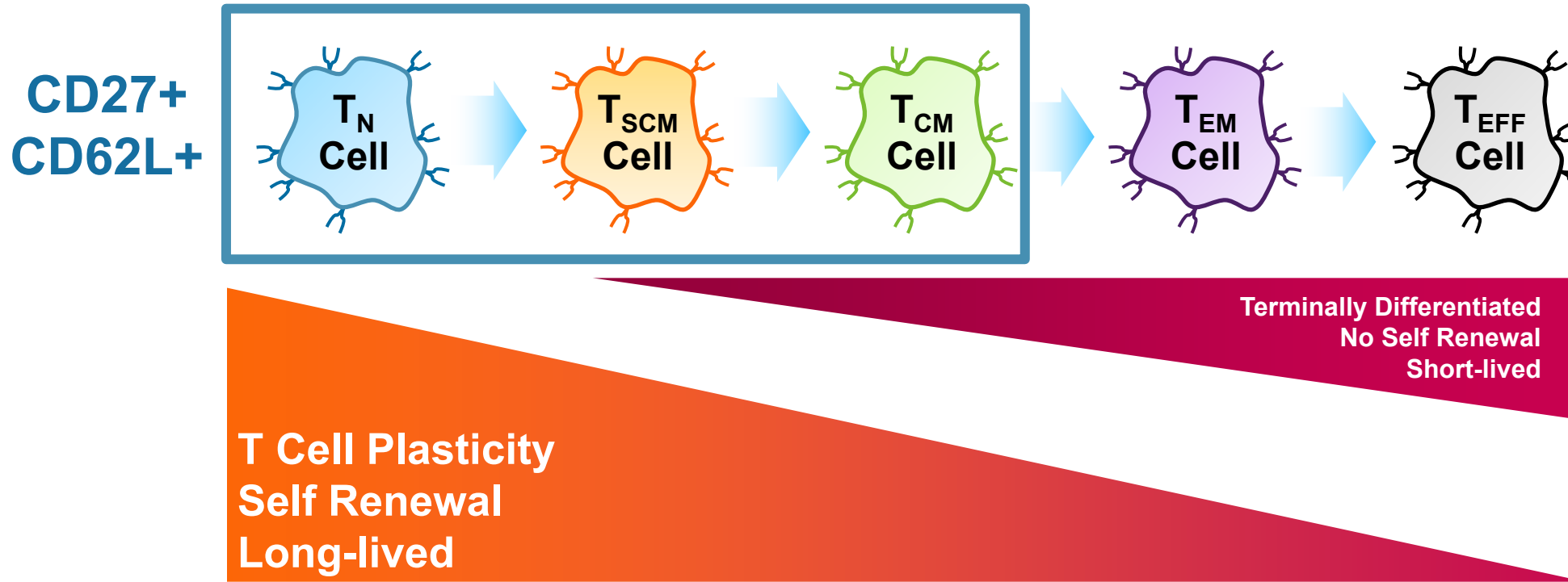
Safety?

- No new safety signals (G3/G4 CRS or Neurotox).

Path forward?

- KarMMa amendment raised high end of dose range to 450 based on observed dose-response and acceptable safety profile. Potential approval on track for 2020. Earlier line development plan advancing.

bb21217: PI3K Inhibition During Manufacturing Drives Increase in Long-lived, Memory-like T Cells

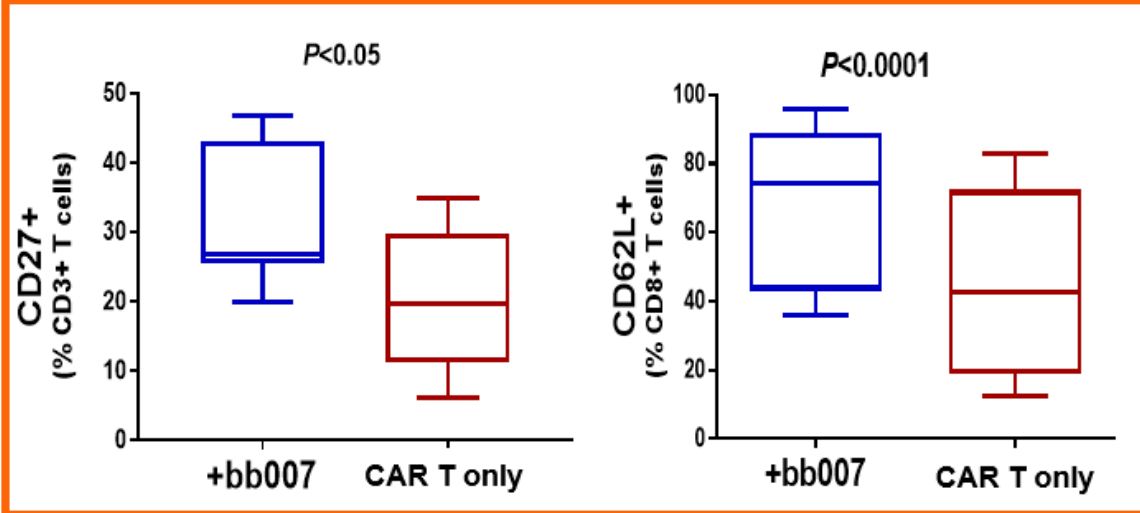


Hypothesis: Increasing long-lived, memory-like T Cell subsets in the drug product may result in enhanced persistence of functional anti-BCMA CAR T cells *in vivo*

Preclinical Models: bb21217 is Enriched for Memory-like T Cells Exhibits; Enhanced Persistence of Anti-tumor Effect

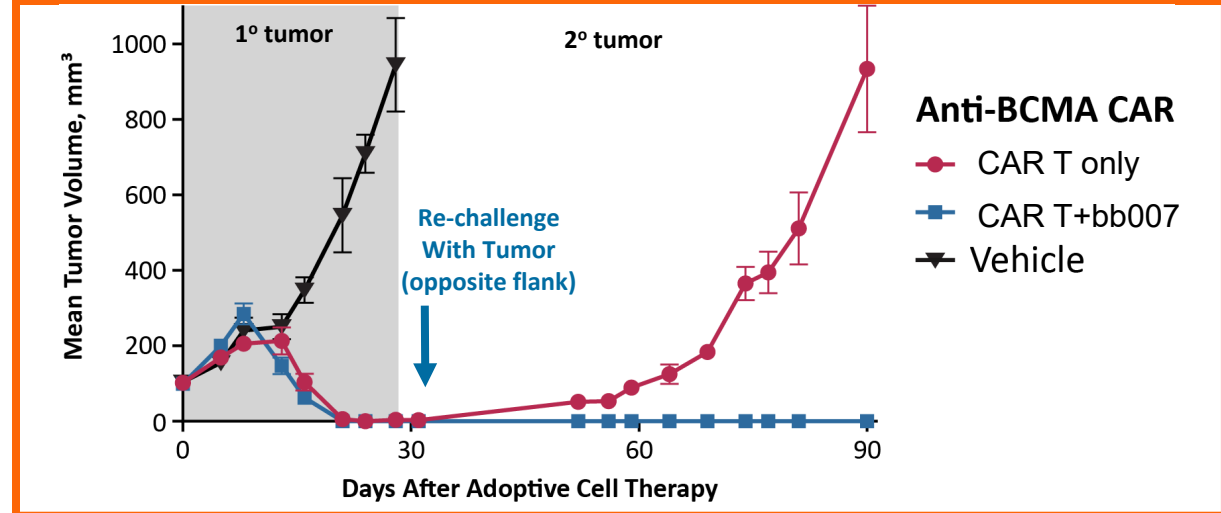


bb007 enriches for memory-like T Cell phenotype



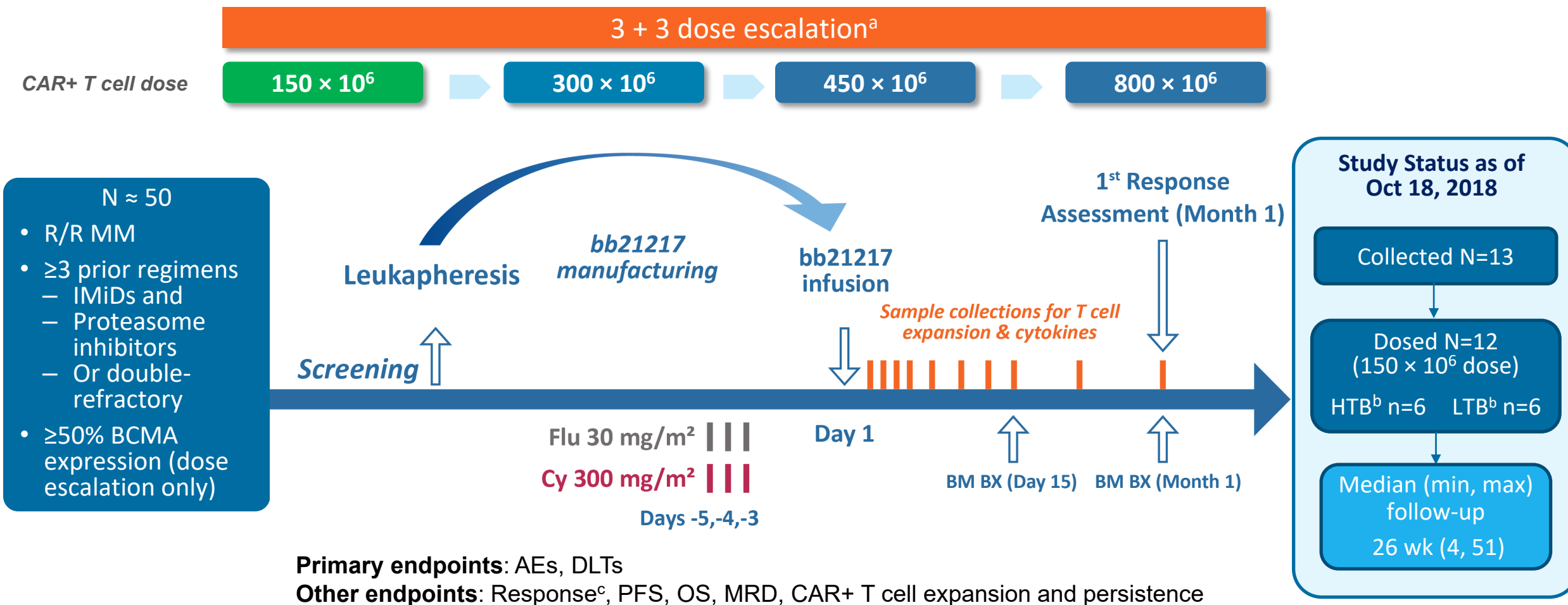
- CD62L and CD27 are markers of memory-like T cells
- bb21217 is significantly enriched for T cells with this memory-like phenotype

bb007 enhances anti-tumor effect in mouse models



- ONLY CAR T cells cultured with PI3K inhibitor bb007 (i.e. bb21217) clear a second tumor challenge
- Data are consistent with improved persistence of functional CAR T cells leading to sustained anti-tumor effect

CRB-402 Phase 1 Study Design and Status



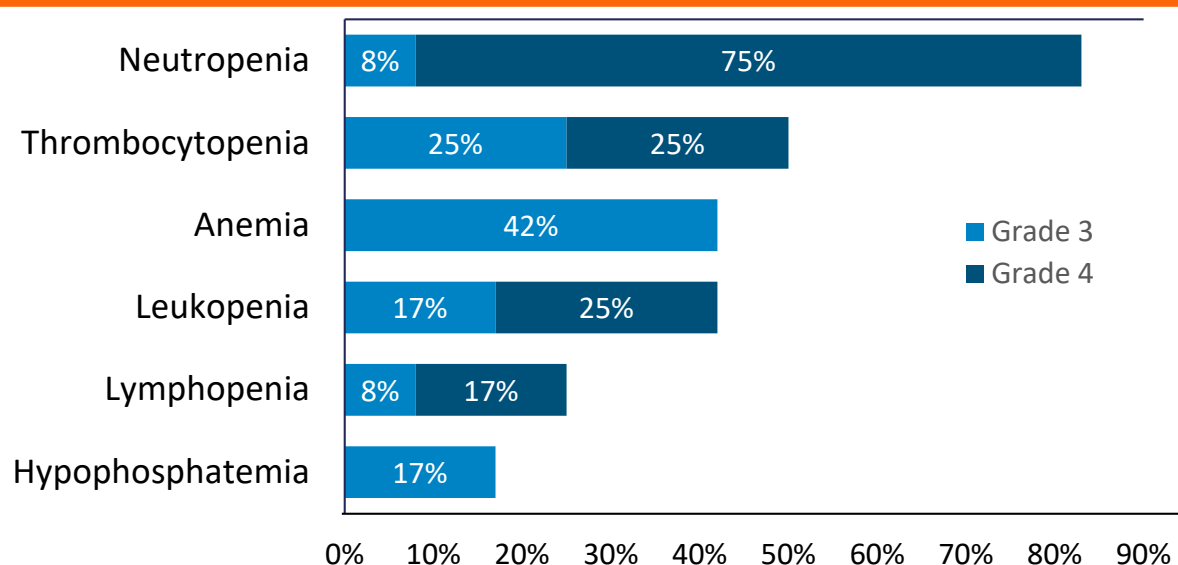
AE, adverse events; BCMA, B-cell maturation antigen; DLT, dose-limiting toxicity; HTB, high tumor burden; IMiD, immunomodulatory imide drugs; LTB, low tumor burden; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed/refractory multiple myeloma. ^aAll patients to date received 150 × 10⁶ CAR+ T cells; an intermediate dose of 300 × 10⁶ CAR+ T cells will be the next dose level. ^bHTB defined as ≥50% bone marrow plasma cells pre-infusion; LTB <50%. ^cPer International Myeloma Working Group criteria.

NCT03274219

Early Clinical Safety and Tolerability Consistent with CAR T Experience



Grade ≥3 AEs in >1 Patient^a



AEs of Special Interest^a

	Grade, n (%)			
	1	2	3	4
CRS ^b	4 (33)	3 (25)	1 (8)	–
Neurotoxicity ^c	1 (8)	1 (8)	–	1 (8)

- CRS occurred in 67% of patients
 - Mostly grade 1/2, 1 grade 3, no grade 4
 - Median time to onset of CRS 4.5 days (2,11)
 - Manageable with or without tocilizumab
- 1 patient experienced DLT (grade 4 encephalopathy and grade 3 CRS)
 - Patient had high tumor burden and rapidly accelerating disease at baseline
 - No other DLTs occurred
- 1 grade 3 catheter-related infection; no other severe infections reported to date
- 4 patients experienced 1 or more SAEs
- No deaths on study to date

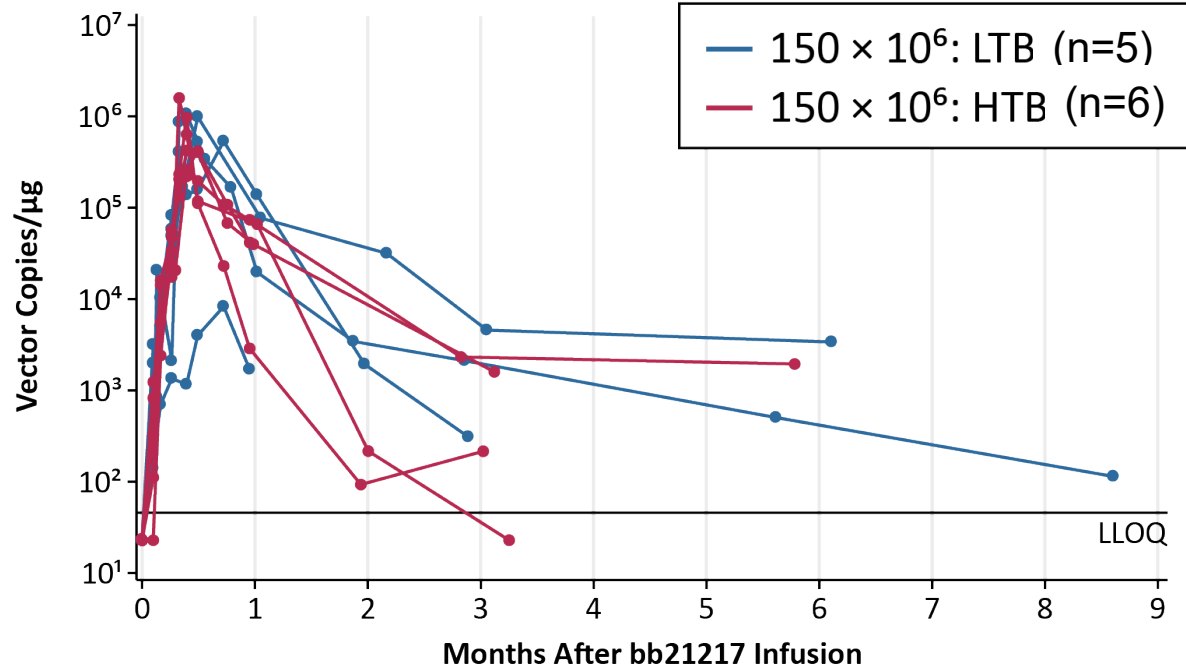
AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event. ^aAEs occurring between bb21217 infusion and disease progression. ^bCytokine release syndrome (CRS) uniformly graded according to Lee et al., *Blood* 2014;124:188-195. ^cEvents selected as CAR T neurotoxicity on the case report form occurring within 90 days after bb21217 infusion.

Data as of October 18, 2018

Clinical Data is Early But Consistent with Goal of Enhanced Persistence



Vector Copy Number Over Time by Baseline Tumor Burden



- Robust and reliable bb21217 CAR T cell expansion post-infusion observed at first dose
- Early bb21217 clinical data is consistent with robust functional CAR T cell persistence
 - Enrichment for memory-like CAR T cells observed in preclinical studies, and in patients post-infusion
- Vector detectable up to 9 months post-infusion, and in 3/3 patients at 6-month time point
- Sustained sBCMA suppression observed, reflecting ongoing plasma cell aplasia

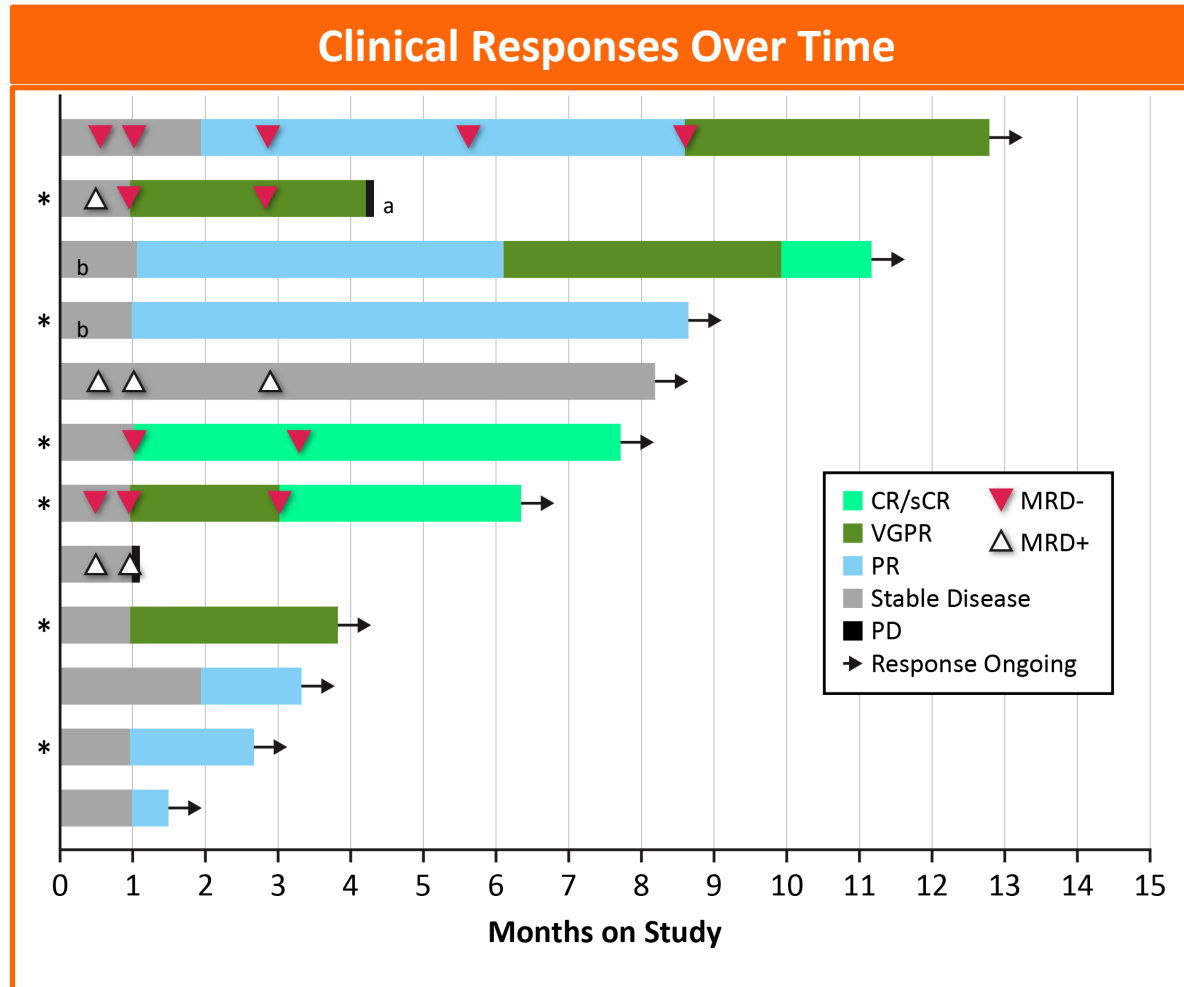
Month 1 Month 3 Month 6 Month 9

At risk, n	9	7	3	1
With detectable vector, n (%)	9 (100)	6 (86) ^a	3 (100)	1 (100)

HTB, high tumor burden; LLOQ, lower limit of quantitation; LTB, low tumor burden. ^aOne patient with undetectable vector received cyclophosphamide on day 15 for grade 4 encephalopathy.

Data as of October 18, 2018

Clinical Responses Observed in 10/12 Patients (83%) at First Dose Level Tested (150×10^6 CAR+ T cells)



- 10/12 patients (83%) achieved an objective response at the first tested dose (150×10^6 CAR+ T cells)
- Deepening responses over time; CR achieved as late as month 10
- 100% MRD negativity in 4/4 responders evaluable for MRD status
- Responses are ongoing in all but 1 responder; the first patient dosed continues response >1 year after treatment

CR, complete response; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response. *Patients with high tumor burden.
^aProgression based exclusively on appearance of new bone lesions. ^bMRD status not available.

Data as of October 18, 2018

High Clinical Response Rate Observed at First Dose Level (150×10^6 CAR+ T cells)



Clinical Response	
bb21217-Treated (N=12)	
ORR, ^a n (%) [95% CI]	10 (83.3) [51.6, 97.9]
sCR/CR	3 (25)
≥VGPR	6 (50)
MRD status in bone marrow, n	
MRD-evaluable responders ^b	4
MRD-neg	4 ^c
Median time to first response (min, max), ^{a,d} mo	1 (1, 2)
Median time to best response (min, max), ^{a,d} mo	1 (1, 10)
Median follow-up duration (min, max), mo	5.9 (1.0, 11.8)

CR, complete response; MRD, minimal residual disease; ORR, objective response rate; PR, partial response; VGPR, very good partial response.
 *Patients with high tumor burden. ^aIncludes unconfirmed responses. ^bPatients with ≥PR and valid MRD assessments. ^cTwo MRD-neg. responses at 10^{-6} and 2 at 10^{-5} sensitivity level by Adaptive next-generation sequencing. ^dAmong 10 responders with ≥PR.

Data as of October 18, 2018

Promising Early Data with Next-Generation Anti-BCMA CAR T

- bb21217 demonstrated promising early clinical activity in heavily pretreated patients with relapsed/refractory multiple myeloma at first dose level tested
 - 83% ORR with 90% of responses ongoing
 - Elimination of MRD in the bone marrow of all 4 evaluable responders
- Early indications of increased persistence using enriched CAR T cells
- Safety profile appears consistent with known toxicities of CAR T cell therapies
- Dose escalation is ongoing

CALD





Ethan's family spent nearly two years trying different medications and meeting with specialists to try and resolve his symptoms. Tragically, during this period, the ravaging effects of ALD were continuing to damage Ethan's brain and adrenal glands.

Ethan Zakes 2000 - 2011

Source: Ethan Zakes Foundation

Cerebral Adrenoleukodystrophy

- Severe, often fatal neurological disease in boys

UNMET NEED

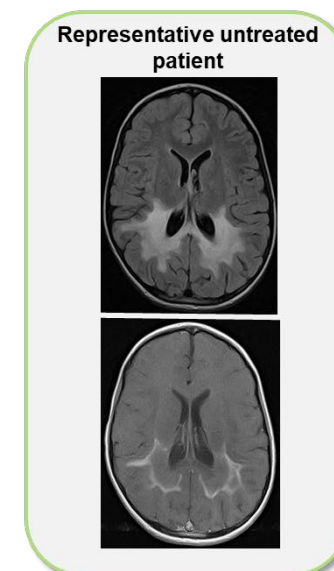
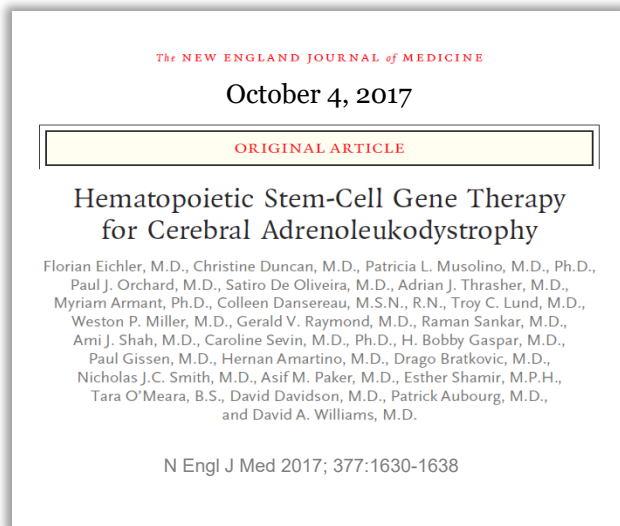
- Treatment limited to allo-HSCT
- Sometimes severe treatment-related risks and complications, especially when donor is not a matched sibling

EPIDEMIOLOGY

- Global incidence of ALD: 1 in ~21,000 newborns
- Cerebral form develops in ~40% of affected boys

¹Salzman, R., Kemp, S. (2017, December 06) Newborn Screening. Retrieved from <http://adrenoleukodystrophy.info/clinical-diagnosis/newborn-screening>

Lenti-D Treatment Halts CALD Disease Progression



Data as of March 31, 2018

4

15/17 patients (88%) alive and MFD-free at 24 months follow-up; all patients continue to be MFD-free as of April 25, 2018

- Exceeds pre-determined efficacy benchmark for the study MFD-free survival in 13/15 (76%)

12 additional patients treated in Starbeam study

- No MFDs reported as of April 25, 2018; median follow-up for this additional cohort of patients is 4.2 months (0.4 – 11.7 months)

Safety profile consistent with autologous transplantation

- No GvHD, no graft rejection

Two patients did not meet primary endpoint:

- Patient 2016: Withdrew
- Patient 2018: Rapid disease progression early in the study

Data as of April 25, 2018

Recent Collaborations



Science-Driven and Highly Complementary Partnership



Science: best-in-class technology platforms joining forces to crush cancer

Culture: science- and patient-focused companies with a willingness to push boundaries of novel technologies

Structure: Aligned and streamlined operating model to enable flexible research and decision making

Investment: All-in mindset driving shared and enhanced funding for R&D efforts

BLUE remains BLUE: Clear value proposition through product rights, shared funding and capabilities

Engaging the Right Target with the Optimal Target Binder

VELOCISUITE®

REGENERON

VELOCIGENE®

...target validation at unprecedented pace and precision

VELOCIMOUSE®

...rapid generation of genetically engineered mice

VELOCIMMUNE®

...fully human antibodies through immunization

VELOCIMAB®

...rapid identification & preclinical testing of target specific antibodies

VelociT

...fully human T cell receptors from an engineered mouse

VELOCIHUM

...immunodeficient mouse platform - study of human cells & tumors

Pick Great
Targets

Fully Human
CARs

Identify Human
TCRs

Better Models

Partnership Highlights



Research

- Five-year research collaboration
- Refreshable list of **six** targets
- Access to Regeneron *VelociSuite*® Platform technologies
- Leveraging bluebird expertise in cell biology and vector technology
- Brings together two science driven organizations with synergistic technology and expertise



Development

- bluebird leads R&D managed by a Joint Steering Committee
- bluebird retains significant product rights; Regeneron receives milestone payments and royalties
- Regeneron can opt-in to multiple products to become 50/50 partners
- Joint late-stage development and commercialization allocated between bluebird and Regeneron or future partners on a regional basis

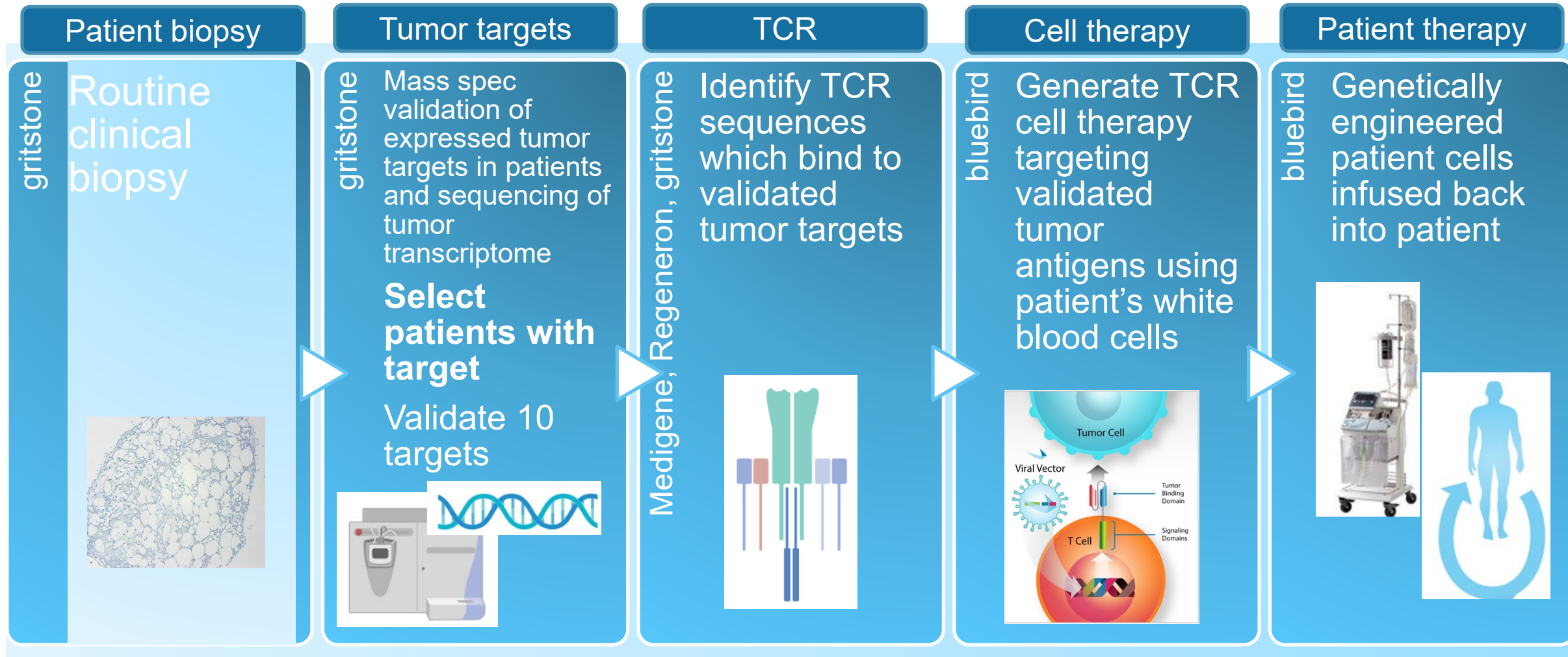


Funding

- Share costs equally through pre-IND research and into Phase 1/2 development
- For 50/50 collaboration products, development and commercialization costs (by region) are shared equally
- bluebird funds development and commercialization of its wholly-owned products
- \$100 million equity investment by Regeneron in BLUE - 420,000 shares at \$238.10 per share or a 59% premium*

**Premium of approximately \$37 million will be used to cover part of Regeneron's share of research costs; bluebird intends to use the balance of the proceeds to support its research activities in the collaboration.*

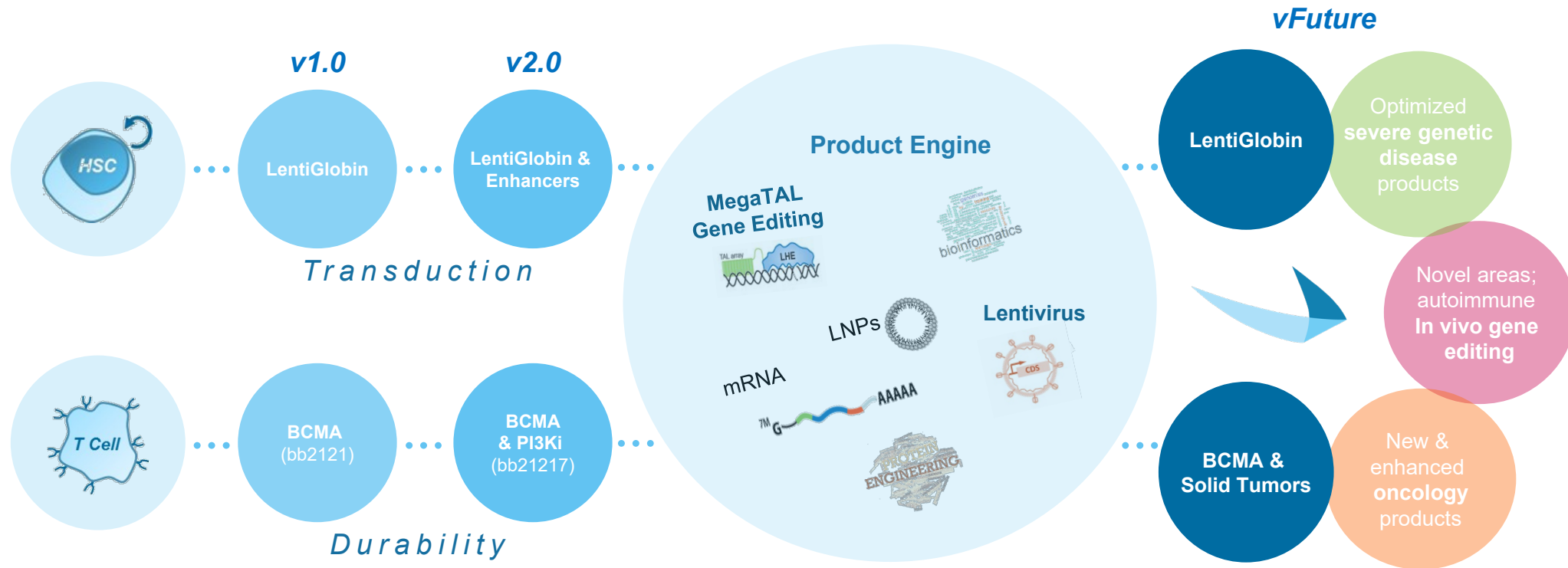
Gritstone complements bluebird's approach to generating novel therapeutics for oncology



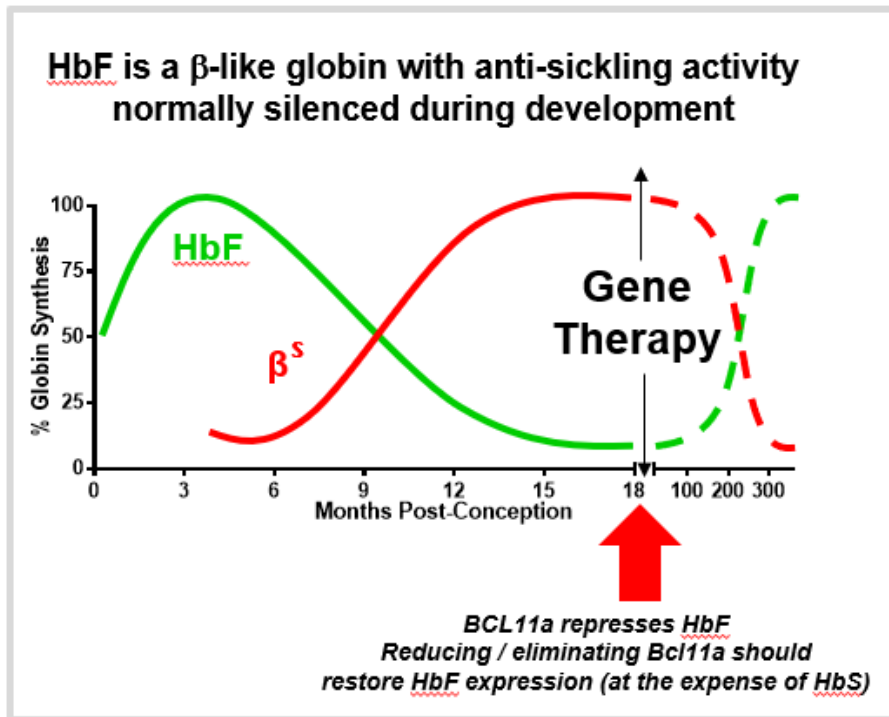
Early Pipeline



Good Is Never Good Enough For Patients: BLUE Toolbox Strategy



Initial Proof of Concept: LVV Approach to Suppression of BCL11a in SCD

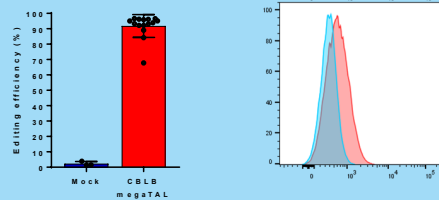


- As of July 28, 2018, one patient had received treatment with HSCs transduced with an LVV encoding the BCL11a shRNA^{miR}
- As of day 76:
 - Sustained Hb of >10 g/dL
 - 59.7% total HbF cells; 30% HbF as a fraction of all β -like globin
 - Notable absence of irreversibly sickled cells on peripheral smear
 - Low absolute reticulocyte count consistent with markedly reduced hemolysis Hb
- Safety profile consistent with myeloablative conditioning

CBLB Knock-out Enhances CAR-T Cell Anti-tumor Activity

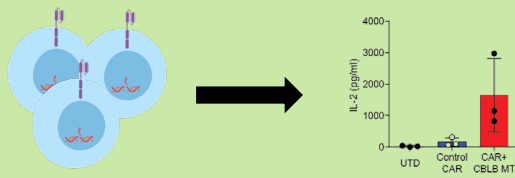
Novel Technology for Improving T Cell Function in Liquid and Solid Tumors

1



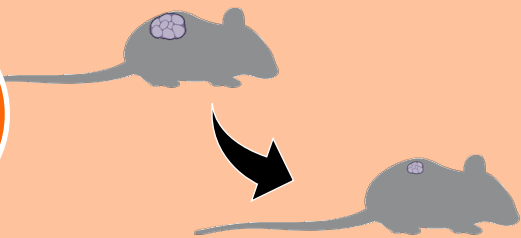
- CBLB megaTAL induces a high rate of gene editing and corresponding knockdown of CBLB protein levels

2



- CBLB megaTAL treatment enhances production of cytokines *in vitro* by CAR-T cells

3



- Genetic deletion of CBLB enhances anti-tumor activity of CAR-T cells in a mouse solid tumor xenograft model

ASH Highlights: Next Generation Programs / Platforms

First clinical demonstration of the potential to genetically manipulate HbF levels through BCL11a

- Novel LVV expressing a shRNA^{miR} to knock down BCL11a at the level *exclusively* in erythroid cells
- Robust knock down of BCL11a observed in patient cells
- At ≥4 months post-gene therapy, ~70% F cells were observed and HbF contributed ~25-30% of total Hb

Flipping the Switch: Initial Results of Genetic Targeting of the Fetal to Adult Globin Switch in Sickle Cell Patients

Esrick et al. (Abstract #801)

Example of bbb's T cell enhancement technologies aimed at delivering transformative outcomes for solid tumors

- bbb megaTAL technology used to efficiently and specifically knockout CBL-B in CAR T cells via gene editing
- Increases cytokine production in response to tumor cells *in vitro*
- Enhances anti-tumor activity of CAR T cells in a mouse xenograft model

Knockout of CBL-B Greatly Enhances Anti-Tumor Activity of CAR T Cells

Hooper et al. (Abstract #338)

Go TRUE BLUE

*We Must
Make Hope a
Reality*

