Initial Findings of the Phase 1 Trial of PBCAR0191, a CD19 Targeted Allogeneic CAR T Cell Therapy

#4107
Section 627

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INTRODUCTION

PBCAR0191 is an off-the-shelf allogeneic CD19-targeted chimeric antigen receptor (CAR) T cell product derived from qualified donor T cells that have been genetically edited to remove the expression of the endogenous T cell receptor (TCR) and insert the CAR in the same locus. The goal is to achieve anti-tumor effect and reduce the possibility of graft-versus-host disease (GvHD) when it is administered to human leukocyte antigen (HLA)-mismatched patients with CD19 expressing B-cell malignancies.

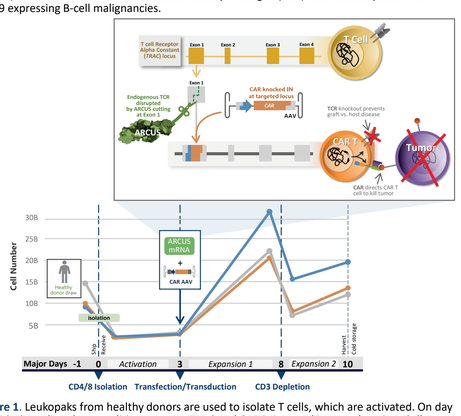


Figure 1. Leukopaks from healthy donors are used to isolate T cells, which are activated. On day 3, ARCUS-mediated gene-editing removes TRAC and CAR is inserted in same location. Cells are expanded, CD3 depleted on day 8, and re-expanded until harvest, vialing, and freezing day 10.

OBJECTIVE

Evaluate the safety and clinical activity of PBCAR0191 in adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) and adult patients with R/B B-cell non-Hodgkin lymphoma (NHL)

METHODS

Phase 1 Dose Escalation: Standard 3+3 Dose escalation

- **Dose Level 1 (DL1)** = 3.0 x 10^5/kg (~ 1.8 – 2.5 x 10^7 total cells) n=3
- **Dose Level 2 (DL2)** = 1.0 x 10^6/kg (~ 6.0 – 8.5 x 10^7 total cells) n=3
- **Dose Level 3 (DL3)** = 3.0 x 10^6/kg (~ 1.8 – 2.5 x 10^8 total cells) n=3

Maximum tolerated dose (MTD) = no more than 1 of 6 patients experience a DLT
Two cohorts evaluated independently: **Cohort A: B-ALL; Cohort N: NHL**

Primary Endpoints: The primary objective of this Phase 1 portion of the ongoing Phase 1/2a trial is to evaluate safety as measured by the occurrence of dose limiting toxicities (DLTs)

Secondary Endpoint: Secondary objectives include assessment of objective tumor responses using standard criteria, and further evaluation of AEs and adverse events of special interest, GvHD, CRS, and ICANS

Exploratory objectives/endpoints

- Cell expansion and persistence using
  - Flow cytometry
  - PCR from lysed PBMC (peripheral blood mononuclear cells)
- Peripheral cytokine analysis from serum

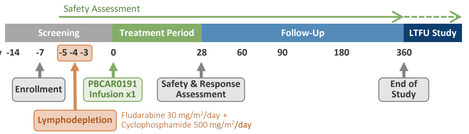
Select Inclusion Criteria

- Eastern Cooperative Oncology Group (ECOG) score (0,1)
- Adequate organ function (detailed at https://www.clinicaltrials.gov/ct2/show/NCT03666000)
- **Criteria for B-ALL**
  - R/R CD19+ B-cell ALL confirmed (≥ 5% blasts)
  - Ph-chromosome+ disease allowed if prior TKI therapy has failed
- **Criteria for NHL**
  - 2 prior chemotherapy-containing regimens or no further therapeutic options
  - Confirmed R/R CD19+ B-cell NHL confirmed by biopsy
  - Prior CAR T and/or transplant allowed, but must be >90 days prior to enrollment
  - PET-positive by Lugano Classification

Select Exclusion Criteria

- Active CNS disease
- Indwelling catheter in pleural/peritoneal/pericardial space

Figure 2. Study Design



RESULTS

Table 1. Patient Demographics

		NHL/DL1 n=3	NHL/DL2 n=3	B-ALL/DL2 n=3	Total N=9
Age (Years)	*Mean (min, max)*	54 (34,64)	73.7 (71,77)	56 (48,72)	**61.2 (34,77)**
Sex, n(%)	*Female*	1 (33%)	0	1 (33%)	**2 (22%)**
Race	*Asian*	0	1 (33%)	1 (33%)	**2 (22%)**
	White	3 (100%)	2 (67%)	2 (67%)	**7 (78%)**
Weight (kg) (at screening)	*Mean (min, max)*	88.3 (81.7, 92.0)	83.4 (62.7, 106)	88.3 (45.4, 111)	**86.7 (45.4, 111)**
Prior # of Lines of Therapy	*Median (range)*	4 (4,5)	2 (1,3)	4 (3,5)	**4 (1,5)**

Table 2. Relapsed versus Refractory to Most Recent Therapy

Response to last therapy prior to enrollment	NHL/DL1 n=3	NHL/DL2 n=3	B-ALL/DL2 n=3	Total N=9
Refractory	2/3	1/3	3/3	6/9
Relapsed	1/3	2/3	0/3	3/9

Table 3. Grade 3 or Higher Treatment Emergent Adverse Events (Cohorts N and A)

System Organ Class / Preferred Term	DL1 (n=3)	DL2 (n=3)	Overall (n=6)
NHL			
Hematologic			
Neutropenia	1 (33%)	1 (33%)	2 (33%)
Lymphocyte count decreased	1 (33%)	2 (67%)	3 (50%)
Neutrophil count decreased	1 (33%)	2 (67%)	3 (50%)
White blood cell count decreased	1 (33%)	2 (67%)	3 (50%)
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain	1 (33%)	0 (0%)	1 (17%)
Vascular disorders			
Hypertension	1 (33%)	0 (0%)	1 (17%)
Adverse Events of Special Interest (Max Grade)			
CRS – Max Grade 2	1 (33%)	0 (0%)	1 (17%)
CRS – Max Grade 1	0 (0%)	1 (33%)	1 (17%)
ICANS – Max Grade 2	0 (0%)	0 (0%)	0 (0%)
GvHD	0 (0%)	0 (0%)	0 (0%)
B-ALL	(n=3)	(n=3)	
Hematologic			
Hemoglobin decreased (anemia)	2 (67%)	2 (67%)	
Lymphocyte count decreased	3 (100%)	3 (100%)	
Neutrophil count decreased	2 (67%)	2 (67%)	
Platelet count decreased	3 (100%)	3 (100%)	
White blood cell count decreased	3 (100%)	3 (100%)	
Febrile neutropenia	1 (33%)	1 (33%)	
Gastrointestinal disorders			
Dysphagia	1 (33%)	1 (33%)	
Metabolism and nutrition disorders			
Hyperglycaemia	1 (33%)	1 (33%)	
Hypophosphataemia	1 (33%)	1 (33%)	
Nervous system disorders			
Facial nerve disorder	1 (33%)	1 (33%)	
Headache	1 (33%)	1 (33%)	
Vascular disorders			
Hypertension	1 (33%)	1 (33%)	
Adverse Events of Special Interest (Max Grade)			
CRS – Max Grade 1	1 (33%)	1 (33%)	
ICANS – Max Grade 2	1 (33%)	1 (33%)	
GvHD	0 (0%)	0 (0%)	

Table 4. Summary of Adverse Events Related to Lymphodepletion

	Maximum Grade in Distinct Patients (n=9)		
Both NHL and B-ALL Cohorts	Grade 3	Grade 4	Total
WBC decrease	-	3 (33%)	3 (33%)
Platelet decrease	-	2 (22%)	2 (22%)
Neutrophil decrease	-	2 (22%)	2 (22%)
Lymphocyte (ALC) decrease	2 (22%)	3 (33%)	5 (56%)
Hyperglycemia	1 (11%)	-	1 (11%)
Infection	0	0	0

Table 5. Summary of Objective Responses

		NHL/DL1 n=3	NHL/DL2 n=3	NHL/Total n=6	B-ALL/DL2 n=3
Best Response	*Complete*	1 (33%)	1 (33%)	2 (33%)	1 (33%)
	Partial	2 (66%)	2 (66%)	4 (66%)	0
	Progressive Disease	0	0	0	2 (66%)
Response at Day ≥28		2 (66%)	2 (66%)	4 (66%)	1 (33%)
Progressive Disease Day <28		1 (33%)	1 (33%)	2 (33%)	2 (66%)

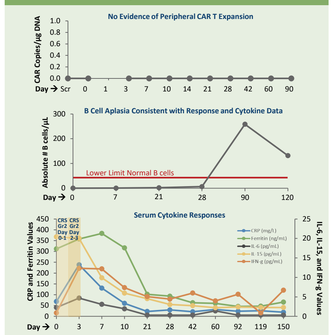
Table 6. Non-Hodgkin Lymphoma Cohort Baseline Characteristics, Prior Treatments, Prognostic Indicators, and Outcomes

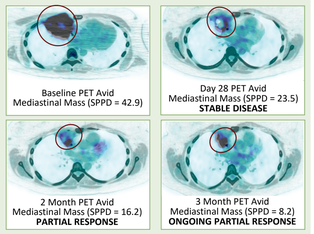
Patient ID (ID-Cohort-Dose Level)	Dx	Age (Dx/ study entry)	ECOG PS	Race/ Sex	Prior Therapy	Best Response (to regimen)	Relapsed / Refractory (Most Recent)	Prior Transplant (Y/N; Type)	Baseline SPD (pre LD)	Extranodal sites	LDH (< or > ULN)	Ki67	Best Overall Response	Best Response Day ≥28	PFS (Days)**	CRS or ICANS?	External PCR Expansion (Study Days +)#	Internal Flow Expansion (Study Days+)##
1-NHL-DL1	DLBCL	64/64	1	W/M	CVP-R	CR	Refractory	Yes (Auto)	6.82	Yes	258 (<)	65%	**Partial Response Day 28**	**Partial Response**	60	None	**Positive (Day 3)**	Negative
					Benda, R	CR												
					R-CHOP	CR												
					Auto	--												
					Obin, Rev	PD												
2-NHL-DL1	MCL	63/64	0	W/M	R-CHOP	PR	Refractory	No	2,337	Yes	241 (>)	90%	**Complete Response Day 14**	Progressive Disease	N/A	None	**Positive (Day 1)**	Negative
					R-Cyt	CR												
					Ibru	PD												
					Ibru, Vclax	PD												
3-NHL-DL1	DLBCL	32/34	0	W/F	R-CHOP	PR	Relapsed	Yes (Auto)	42.9	Yes	238 (>)	--	**Partial Response Day 60**	**Partial Response**	**180***	CRS Grade 2	Negative	Negative
					Ifos, Carbo, Etop, R	PR												
					Auto	--												
					CAR T	PR												
4-NHL-DL2	MCL	70/71	0	W/M	Len, R	--	Refractory	No	3,693	No	180 (<)	40%	**Partial Response Day 28**	**Partial Response**	60	None	**Positive (Day 1-21)**	**Positive (Days 1 – 60)**
					Benda and R	PR												
					Acala	PD												
5-NHL-DL2	MCL	64/73	0	W/M	R, Len	CR	Relapsed	No	3	Yes	159 (<)	85%	**Partial Response Day 14**	Progressive Disease	N/A	Hypotension Gr 1; No Fever; ASCTC = Not CRS*	**Positive (Day 1-10)**	**Positive (Day 1)**
					R	SD												
6-NHL-DL2	MCL	75/77	0	A/M	R	SD	Relapsed	No	10.8	Yes	416 (>)	100%	**Complete Response Day 28***	**Complete Response***	28+*	CRS Grade 1*	<LLQ; Detectable (Day 7)#*	**Positive (Days 1-3)***
					Acala, R	PR												

Table 7. Acute Lymphoblastic Leukemia Cohort Baseline Characteristics, Prior Treatments, Prognostic Indicators, and Outcomes

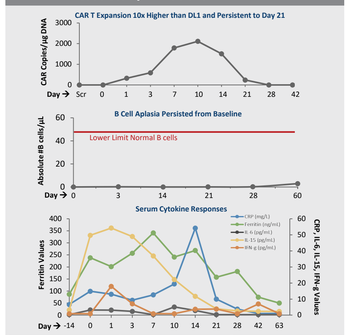
Patient ID (ID-Cohort-Dose Level)	Age (Dx/study entry)	ECOG PS	Race/ Sex	Prior Therapy	Best Response (to regimen)	Relapsed / Refractory (Most Recent)	Prior Transplant (Y/N; Type)	Blast % Bone Marrow	BCR-ABL (yes/no)	Prior Blin (Y/N)	Prior Ino (Y/N)	LDH (> or < ULN)	Prior CNS	Best Overall Response	Best Response Day ≥28	PFS (Days)**	CRS or ICANS?	External PCR Expansion (Study Days +)#	Internal Flow Expansion (Study Days+)##
7-ALL-DL2	72/72	1	W/M	Vinc, Dex, Das, IT MT/ARA-C	PD	Refractory	No	95%	Yes	No	No	674 (>)	Yes	Progressive Disease	Progressive Disease	N/A	None	Negative#	**Positive (Day 7)**
				Vinc	PD														
				Pona, Vinc, Dex	PD														
8-ALL-DL2	45/48	1	W/M	Cy, Mesna, Vinc, Dox, Dex, Cyta, MTX	CR	Refractory	No	77%	No	Yes	Yes	256 (<)	No	Progressive Disease*	Progressive Disease*	N/A*	None*	Negative#*	Negative##*
				Vinc, Pred, MTX	CR														
				Blin	PD														
				Ino	PD														
9-ALL-DL2	47/48	1	A/F	Cy, Vinc, Adria, Dex	Stable Disease	Refractory	Yes, Allo x 2	19.8%	No	Yes	Yes	719 (>)	No	**Complete Response Day 28***	**Complete Response***	28+*	CRS Grade 1; ICANS Grade 2*	**<LLQ; Detectable (Day 1, 3, 10, 14)#***	**Positive (Day 28)***
				Blin	CR														
				Allo	CR														
				Ino, IT chemo	CR														
				Allo	CR														

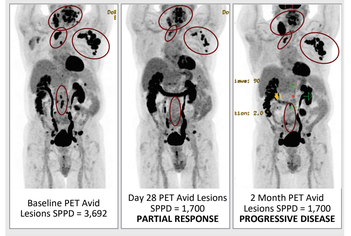
Case Study 1: Patient 3-NHL-DL1



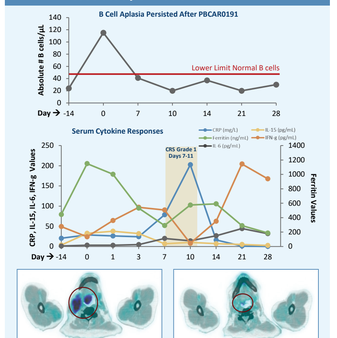


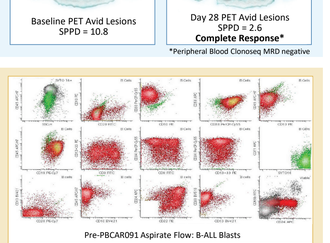
Case Study 2: Patient 4-NHL-DL2



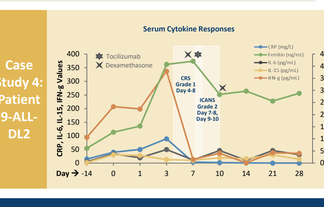


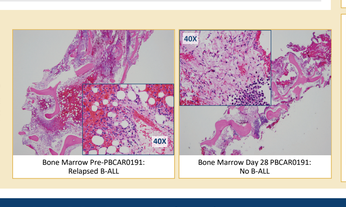
Case Study 3: Patient 6-NHL-DL2





Case Study 4: Patient 9-ALL-DL2



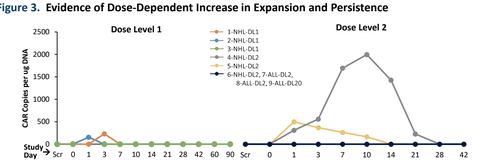


*= data after Nov 4 deadline (critical); **PFS estimated to study visit day

qPCR performed on DNA extracted from isolated PBMC. Note: extremely low PBMC isolation in 6-NHL-DL2, 7-ALL-DL2, 8-ALL-DL2, and 9-ALL-DL2 yielded low DNA quantities, making interpretation of these results difficult. They are shown for completeness

Lower limit for CAR+ cells was set as 0.03% of lymphocytes. All positive have ≥0.03%, with highest detected at 0.43%

Figure 3. Evidence of Dose-Dependent Increase in Expansion and Persistence



CONCLUSIONS

- **First-in-human study of PBCAR0191: adverse event profile is acceptable and may compare favorably with approved autologous products *(Tables 3, 6, 7)***
  - No ≥ grade 3 events of CRS or ICANS. No evidence of GvHD
  - Tocilizumab and Dexamethasone: 2 pts (22%) overall and 2/6 DL2 (33%)
- **No Maximum Tolerated Dose has yet been identified**
  - No DLTs observed in DL1 NHL cohort or in DL2 NHL or B-ALL cohorts
- **Objective evidence of cell-mediated anti-tumor effect has been observed in DL1 and DL2**
  - 7 of 9 patients have objective evidence of tumor response at any timepoint (6/6 NHL and 1/3 B-ALL) ***(Tables 5, 6, and 7)***
  - ORR in NHL cohort at Day 28 or later is 66% (4 of 6)
    - Includes 1 CR at Day 28 (still in follow-up)
    - Incudes 1 PR for 6 months
  - B-ALL cohort has 1 MRD negative CR at day 28 (33% CR/CRi rate at DL2)
    - 2 other patients had poor prognosis at study entry
- **Dose dependent demonstration of mechanism of action *(Case Studies 1-4, Figure 3, Tables 6, 7)***
  - Cell expansion observed at DL1 and increase in peak observed in DL2
  - Cell persistence through day 21 (PCR) and day 28 and 60 (Flow) in DL2
  - B cell aplasia corresponds to timing of PBCAR0191 activity
  - CRS and ICANS, clinical response, serum cytokine profiles, B cell aplasia, and cell expansion anecdotally correspond
    - Larger patient numbers required for true correlation
- **To the best of our knowledge, this is the first time, using an allogeneic CAR T product and *non-biologic* lymphodepletion, that a clinical study has shown:**
  - **Anti-tumor activity and cell expansion**
  - **No evidence of GvHD, DLTs, or > Grade 2 CRS**
  - **ORR after progression from an autologous CAR T product**

Acalabrutinib=Acal; Adriamycin=Adria; Allogeneic transplant=Allo; Autologous transplant=Auto; Bendamustine=Benda; Blinatumomab=Blin; Carboplatin=Carbo; CAR T Immunotherapy=CAR T; Complete Response=CR; Cyclophosphamide=Cy; Cytarabine=Cyta; Cytokine Release Syndrome=CRS; Dasatinib=Das; Dexamethasone=Dex; Diffuse Large B-Cell Lymphoma=DLBCL; Doxorubicin=Dox; Graft Versus Host Disease=GvHD; Hydroxyurea=Hyd; Ibrutinib=Ibru; Ifosfamide=Ifos; Immune Effector Cell Associated Neurotoxicity Syndrome=ICANS; Inotuzumab=Ino; IT MTX alternating with Ara-C=IT MTX/ARA-C; Lenalidomide=Len; Mantle Cell Lymphoma=MCL; Mesna=Mesna; Methotrexate=MTX; Obinutuzumab=Obin; Partial Response=PR; Ponatinib=Pona; Prednisone=Pred; Progression-free Survival=PFS; Progressive Disease=PD; R-Cytarabine=R-Cyt; Revlimid=Rev; Rituximab=R; Stable Disease=SD; Venetoclax=Vclax; Vincristine=Vinc.

Disclosures: Other than employees of Precision BioSciences, no author reports a financial conflict related to the conduct of this study.

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