Ex vivo Lentiviral-mediated Gene Therapy for Patients with Fanconi Anemia [Group A]: Updated Results from Global RP-L102 Clinical Trials

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Disclosures

- Consultant: Beam Therapeutics, GV, Spotlight Therapeutics, Stemodontics
- Current Equity: Beam Therapeutics, Decibel Therapeutics, Editas Medicine, Global Blood Therapeutics, GV, Magenta Therapeutics, Spotlight Therapeutics, Stemodontics, Divested Equity in last 24 months: Forty Seven, Inc.
- Intellectual property rights: Gilead Sciences, Jasper Therapeutics, Magenta Therapeutics
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Introduction

Fanconi anemia (FA) is a rare inherited disorder of defective deoxyribonucleic acid (DNA) repair characterized by:

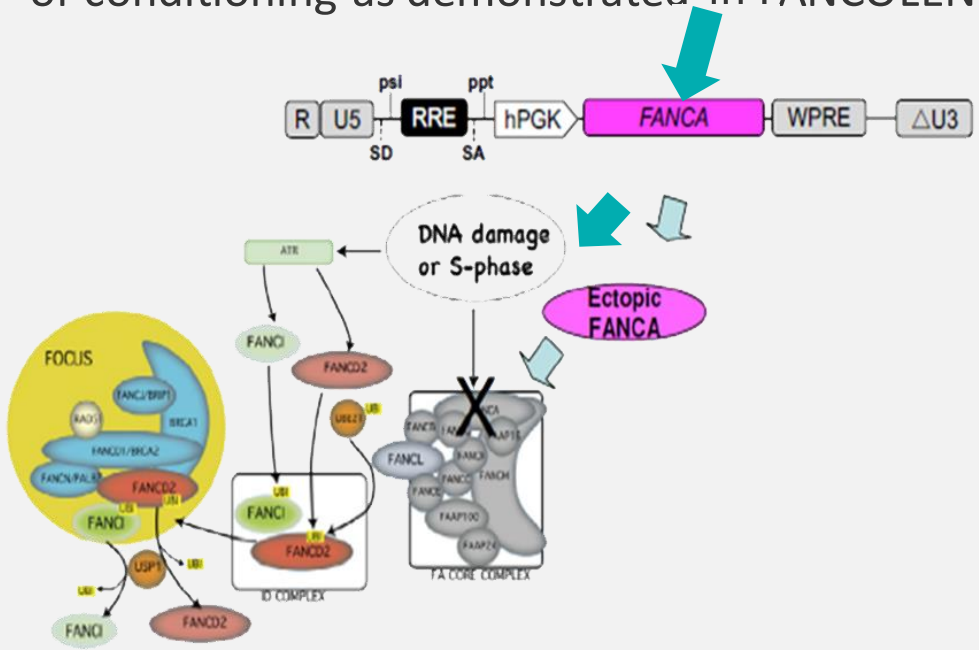
- Progressive bone marrow failure (BMF); 80% of patients experience BMF within 1st decade of life
- Predisposition to hematologic malignancies and solid tumors
- Congenital abnormalities

FA represents a significant unmet medical need

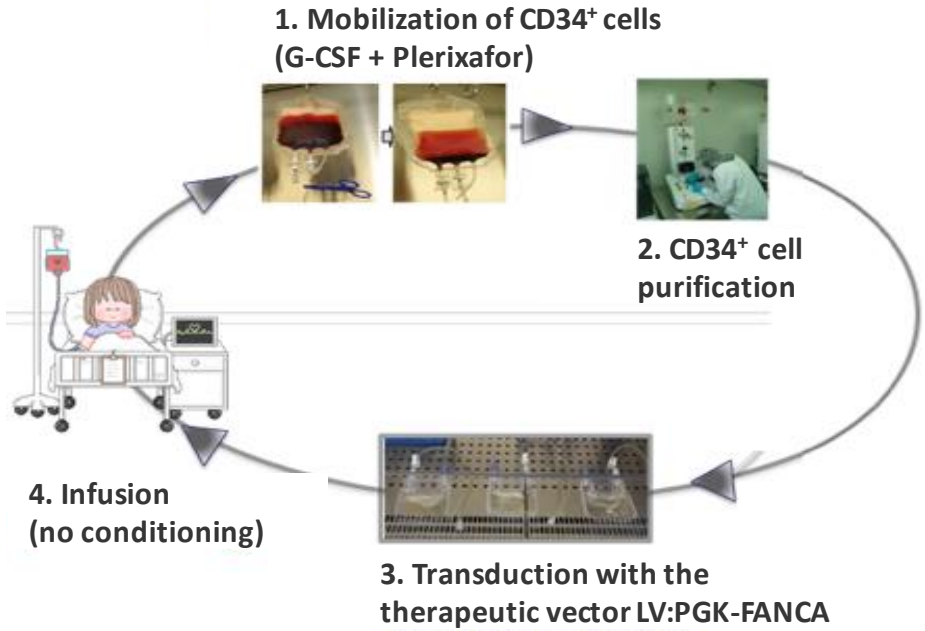
- FA complementation group A (FA-A) accounts for 60–70% of FA; prevalence of ~4,000 cases in US and Europe
- AlloHSCT is curative of BMF, but associated with significant short- and long-term toxicities, especially for ~80% pts who do not have an HLA-identical sibling donor
  - 100-day transplant-associated mortality: 10–20% in alternative donors
  - Graft-vs-host disease (GvHD)
  - 3–4x increased risk for solid organ malignancies over high FA-associated cancer risk; ↑↑ with GvHD
  - HSCT-associated coronary artery disease, musculoskeletal & neurocognitive dysfunction, endocrinopathies

RP-L102 Rationale and Study Design

- Insertion of a functional *FANCA* gene into autologous FA-A CD34+ cells confers resistance to DNA-damage & provides proliferative advantage to modified cells
- Enables engraftment in the absence of conditioning as demonstrated in FANCOLEN-I



Schematic of Product Manufacture and Treatment



Patients undergo hematopoietic stem cell (HSC) mobilization and collection, followed by CD34+ immunoselection, transduction, and subsequent infusion *without conditioning*.

Río P *et al*. Nat Med 2019; 25:1396-1401

Global RP-L102 Studies

Key Eligibility Criteria

Inclusion:

- FA complementation group A
- Minimum age: 1y
- *Maximum age: US Ph 1 (12y); US Ph 2 (none); EU Ph 2 (17y)*
- BM CD34+ cell concentration ≥30/µL (from aspirate)

Exclusion:

- Available & eligible HLA-identical sibling donor
- MDS or leukemia (including associated cytogenetic abnormalities)
- Mosaicism with stable/improved blood counts

Endpoints

Efficacy:

Engraftment: Peripheral blood (PB) and BM vector copy number (VCN)

Phenotypic correction: Increased resistance of BM cells to DNA-damaging agent mitomycin-C (MMC)

Clinical response: Prevention of BMF (stabilization or increase
in PB counts)

Safety of RP-L102

12 Patients Treated: Demographics and Investigational Product Metrics for Initial n=9

Subject #	Age at Enrollment (years)	Follow Up (months)	CD34+ Cells/kg	CFCs/kg	Mean VCN: Liquid Culture	Mean VCN: CFCs	Transduction Efficiency (%)	CFC Survival MMC 10nM (%)
1 (1001)	5	36	$2.0 \times 10^{5*}$	$5.2 \times 10^{4*}$	2.08	0.62**	67	33
2 (1002)	6	18†	$3.7 \times 10^{5*}$	$5.0 \times 10^{4*}$	2.21	0.92**	72	47
3 (2004)	3	24	4.8×10^{5}	$1.3 \times 10^{5‡}$	1.70	0.73	100	63
4 (2008)	2	21	3.2×10^{6}	$5.5 \times 10^{5‡}$	1.65	1.56	97	63
5 (2009)	3	18	1.9×10^{6}	$3.1 \times 10^{5‡}$	2.16	0.76	61	45
6 (2010)	3	21	$4.1 \times 10^{6*}$	n/a	0.62	n/a	n/a	n/a
7 (2011)	5	18	$2.8 \times 10^{6*}$	n/a	1.46	n/a	n/a	n/a
8 (2014)	6	15	$5.4 \times 10^{5*}$	$3.6 \times 10^{4*}$	3.68	pending	pending	31
9 (2016)	2	12	$3.0 \times 10^{5*}$	$2.5 \times 10^{4*}$	1.96	0.64	88	64

All patients ≤6 years at enrollment

9 patients have ≥12–36 months of follow-up

3 patients recently treated
(<1 yr follow up; CD34+ cells/kg: 2.5×10^{5} to 2.3×10^{6}/kg; other metrics pending validation)

Mean Values
VCN (liquid culture): 1.95
VCN (CFC): 0.87
Transduction eff: 81%
CFC MMC-resistance: 49%

m: months; CFCs: colony forming cells; VCN: vector copy number; n/a: not available

* Per NC200 automated count (results in ~50% lower count vs. manual count used in FANCOLEN-I)

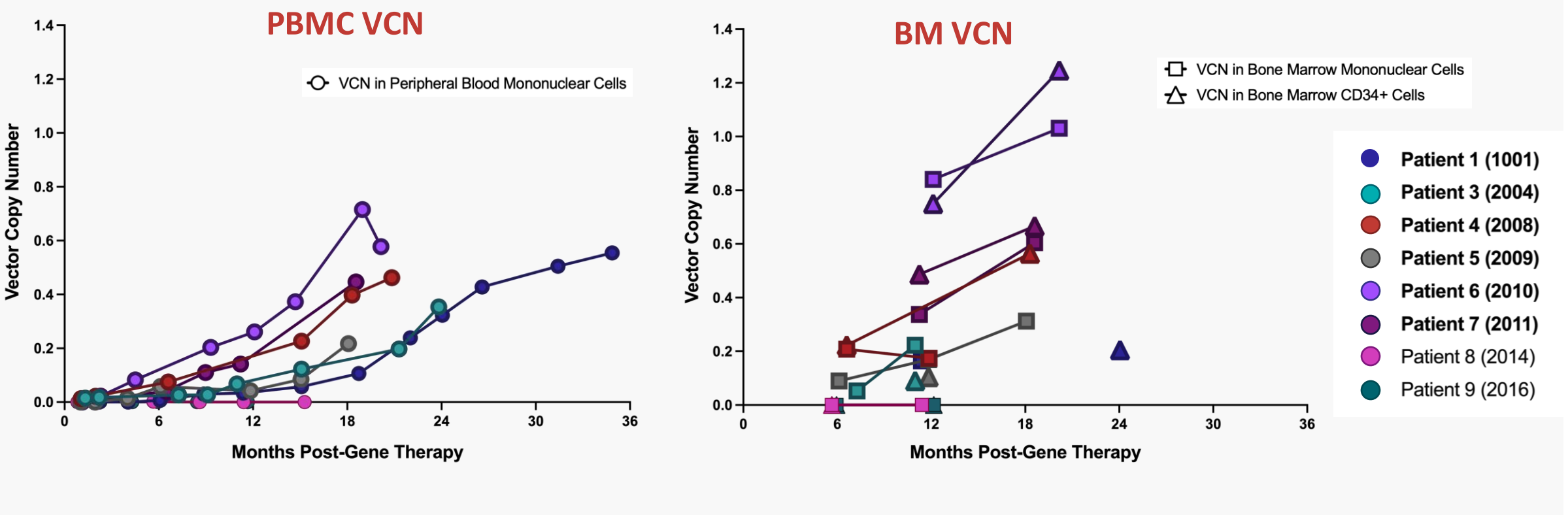
** Mean CFC VCN was assessed from a cryopreserved drug product sample

† Patient withdrawn from the study at 18 months post-RP-L102 infusion; received successful allogeneic HSCT

‡ Revised value following data validation

Data cut-off: April 4, 2022; Preliminary interim results are presented from the ongoing clinical studies.

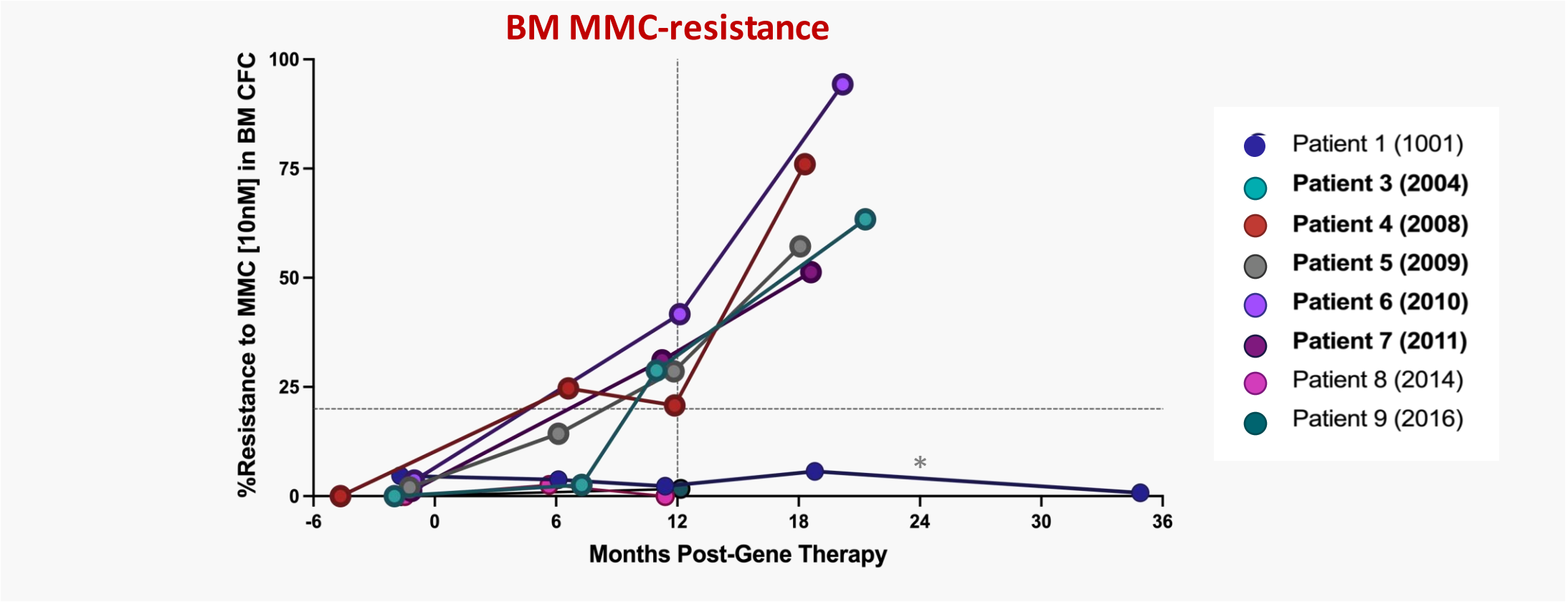
Sustained Genetic Correction in 6 of 9 Patients ≥1 year post-RP-L102



Progressive increases in gene markings in PB and BM in 6 patients

Not shown: PB and BM VCN in Patient 2 (1002), who was withdrawn from the study at 18 months post-RP-L102 infusion

Increasing Phenotypic Correction over 1-2 years post-RP-L102



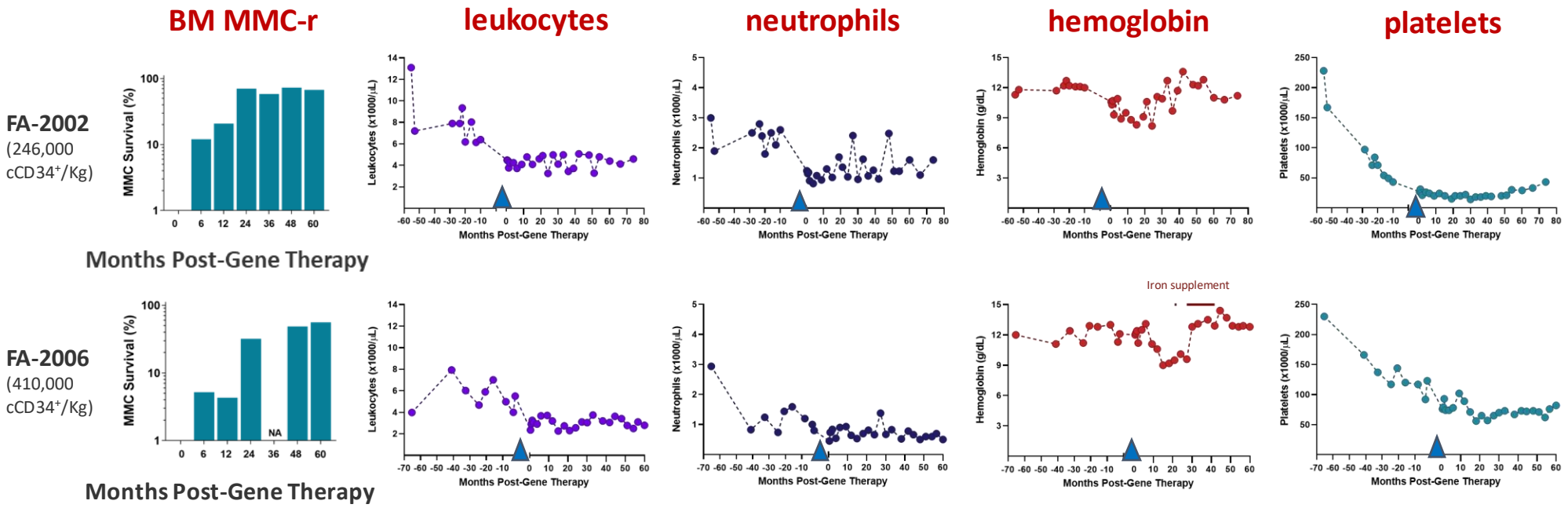
For 5 pts, increased BM CFC MMC resistance ranging from 51% to 94% observed at 18–24 months post-RP-L102 administration

MMC resistance of >20% achieved at two consecutive timepoints ≥12 months for n=5

* BM MMC-res for patient 1 (1001)'s 24 m assessment was not performed at one of the study's central laboratories and are not included.
Not shown: BM MMC-res in Patient 2 (1002), who was withdrawn from the study at 18 months post-RP-L102 infusion

BM CFC MMC Resistance is Associated with Long-term Hematologic Stability

FANCOLEN-I (investigator-initiated) long-term follow-up:



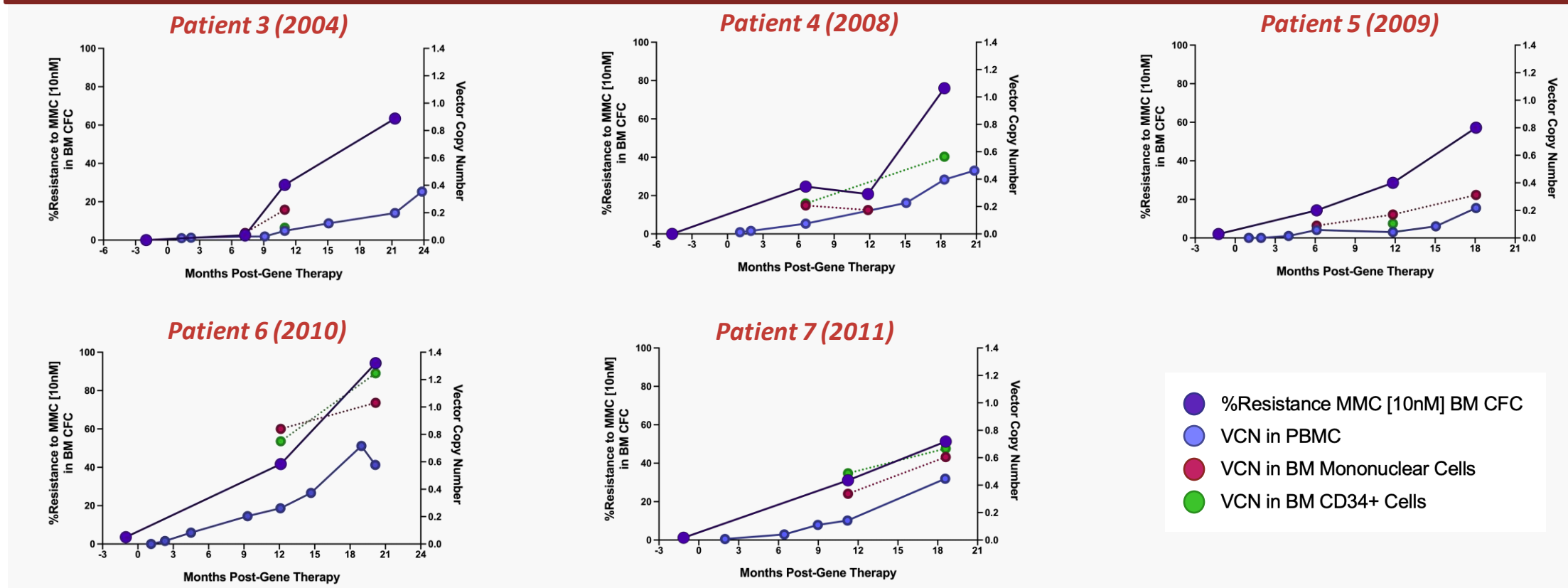
≥20% BM CFC MMC resistance is associated with long-term hematologic stability (up to 6 years post-gene therapy) as demonstrated by FANCOLEN-I patients FA-2002 and FA-2006

- FA-2002 has had concomitant sustained blood count stabilization, with trends suggesting increases in Hb and platelets after 24 and 30 m, respectively
- FA-2006 has had blood count stabilization with hemoglobin improvement

* Source data verification has not yet been performed on most recent visits. Data cut-off April 26, 2022

Genetic Correction Correlates with Phenotypic Improvement

- PB VCN strongly correlates with BM CFC MMC-Res at 12 months post-RP-L102 (r = 0.83)+*
- BM Mononuclear cell VCN strongly correlates with BM CFC MMC-Res at 12 months post-RP-L102 (r = 0.81)**

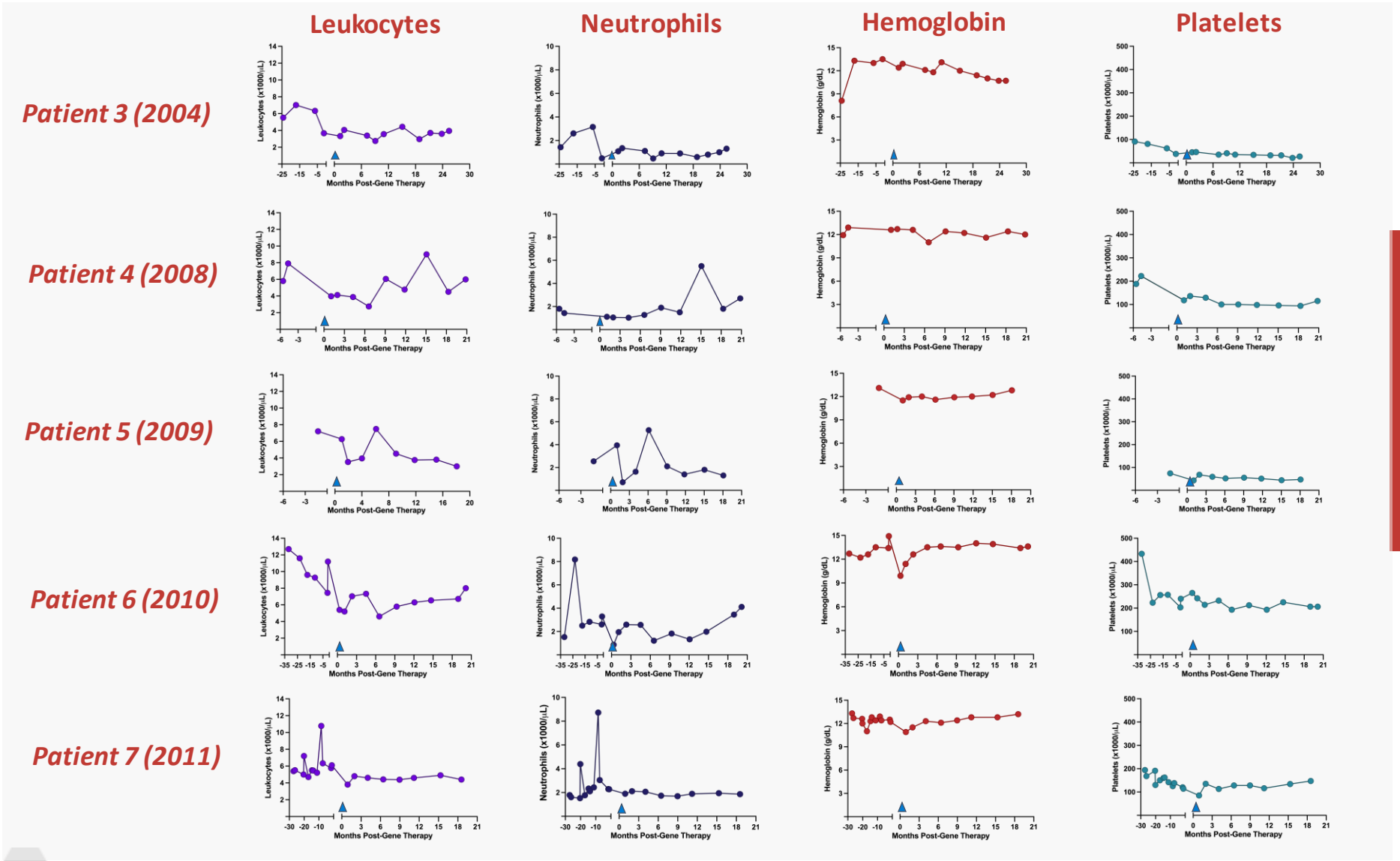


*r correlation calculated using data from n=7 patients (PB VCN data from patients 2 [1002] and 4 [2008] not available); **r correlation calculated using data from n=9 patients

+ Patient 1 (1001) has to-date demonstrated more limited correlation between VCN and MMC-Resistance

- Genetic correction has been evident via PB VCN (0.55 at 36 m study visit) and BM CD34+ VCN (0.21 at 24 m study visit).
- BM MMC-Resistance Δ was ~11% at 24 m study visit (not performed at central lab), but BM MMC-Resistance was 0.8% at 36 m study visit (central study lab).
- Patient required RBC transfusion at ~35 m post-RP-L102 in setting of potential intercurrent viral illness and recent vaccination.

Increased BM CFC MMC Resistance Associated with Hematologic Stabilization at ≥1 year post RP-L102



Concomitant blood count stabilization over 12–24 months seen in 5/5 patients with sustained and increasing BM CFC MMC resistance

RP-L102 Safety Profile Appears Highly Favorable

- Patients are treated without antecedent conditioning and attendant risks
- No signs of dysplasia, clonal dominance or oncogenic integrations
- Gene therapy does not preclude subsequent allogeneic HSCT if necessary
  - Patient 2 (1002) underwent successful allo-transplant at 18 months post-RP-L102 administration
- RP-L102 related SAE: 1 patient experienced a Grade 2 transient infusion-related reaction; resolved without any additional clinical sequelae

Data cut-off: April 4, 2022; Preliminary interim results are presented from the ongoing clinical studies.

Conclusions from Initial 9 Patients with ≥1 Year of Follow-Up

Comprehensive efficacy in multiple patients with >1 year of follow-up

- **5 patients have sustained, increasing BM CFC MMC resistance ranging from 51 to 94% at 18–24 months, and ≥20% at two consecutive timepoints**
- **Increasing BM CFC MMC resistance is accompanied by concomitant genetic markings and hematologic stabilization**
- 6 patients with sustained peripheral blood and BM genetic correction (VCN)
- 2 additional patients with 12 months follow-up, potential for engraftment 12–24m post RP-L102
- 1 patient had progressive BMF & underwent successful allogeneic transplant

Safety profile of RP-L102 is favorable

- Engraftment and phenotypic correction achieved in the ***absence of conditioning***
- No signs of dysplasia, clonal dominance or oncogenic integrations
- RP-L102 related SAEs: 1 patient experienced an infusion-related reaction (transient, Grade 2)

**** Efficacy in ≥5 patients (observed over >1 year post rx) required to reject null hypothesis***

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