

Administration of Mozafancogene Autotemcel

ICD-10 Coordination and Maintenance Committee Update
March 2025

Investigational Therapy Disclaimer

Mozafancogene autotemcel (fanca-cel) is an investigational therapy that has not been approved by any regulatory authority. The safety and effectiveness of fanca-cel has not yet been established.

Fanca-cel is a gene therapy in late-stage development for the treatment of Fanconi anemia complementation group A (FA-A)

Mozafancogene Autotemcel (Fanca-Cel) for Treatment of FA-A Fanconi Anemia Complementation Group A

| | |
|-------------------------------|---|
| Fanconi Anemia Etiology | <ul style="list-style-type: none">• Rare, inherited hematological disorder• Caused by defects in the FANCA gene• Causes a deficiency in activation of FANCD2 and FANCI proteins for DNA repair |
| Disease Characteristics | <ul style="list-style-type: none">• Severe bone marrow failure develops in 80% of patients during initial decade of life¹; 60-70% of patients have at least one major congenital malformation^{2,3,4}• Increased risk for solid and hematologic malignancies^{5,6}• Estimated incidence of 1:136,000 live births⁷ |
| Standard of Care | <ul style="list-style-type: none">• Allogeneic stem cell transplant (alloSCT) is the current standard of care for treating severe FA-A• Availability of matched donors for alloSCT is a barrier to treatment• AlloSCT associated with high rates of transplant-related mortality and morbidity |
| Fanca-Cel Product Information | One-time gene therapy consisting of autologous hematopoietic stem cells (HSCs) genetically modified with a lentivirus containing a functional copy of the FANCA gene to facilitate the expression of functional proteins and restore DNA repair function |
| Code Request | <ul style="list-style-type: none">• Currently no ICD-10-PCS code exists to specifically describe the administration of fanca-cel• Unique coding will allow for appropriate tracking, reporting, and outcomes research of fanca-cel |

1. Kutler DI, et al. *Blood*. 2003;101(4):1249-56; 2. Giampietro PF, et al. *Am J Med Genet*. 1997;68: 58-61; 3. Shimamura A and Alter BP. *Blood Rev*. 2010;24(3):101-22; 4. Wagner JE, et al. *Thomas' Hematopoietic Cell Transplantation 5th Edition*. Blackwell Publishing Ltd, Oxford, (2015); 5. Moreno OM, et al. *Biomed Rep*. 2021;15(3):74; 6. Niraj J, et al. *Annu Rev Cancer Biol*. 2019; 3:457-478; 7. Che R, et al. *Trends Genet*. 2018;34(3):171-183.

Fanca-cel is novel in that it employs genetic correction of a patient's own cells instead of relying on a suitable donor

FA is a rare inherited disorder of defective DNA repair characterized by^{1,2}

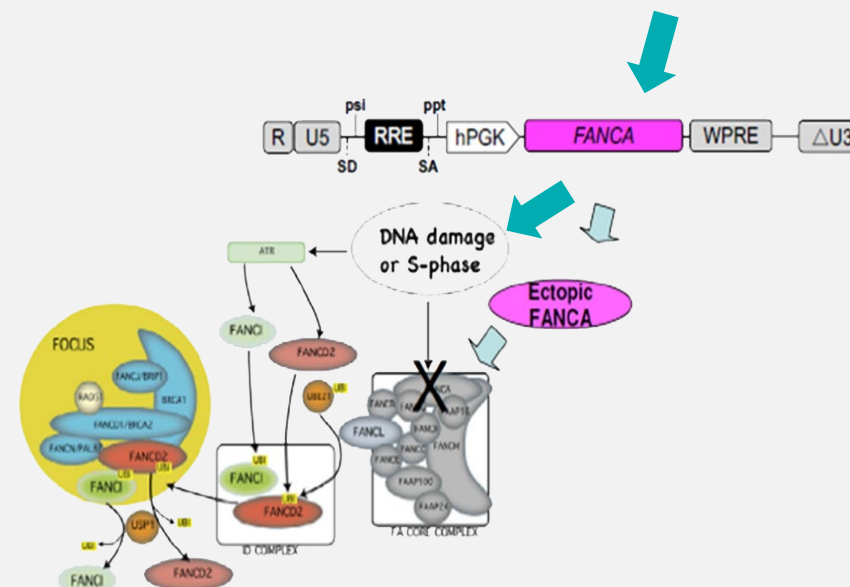
- Progressive BMF; 80% of patients experience BMF within 1st decade of life
- Predisposition to hematologic malignancies and solid tumors
- Congenital abnormalities

FA represents a significant unmet medical need^{1,2,3,4}

- FA-A accounts for 60–70% of FA; prevalence of ~5,500–7,000 cases in US and Europe
- Allogeneic HSCT is curative of BMF, but has short- and long-term toxicities, especially for patients who do not have an HLA-identical sibling donor (~80% of patients)
 - 100-day transplant-associated mortality
 - Graft-vs-host disease (GvHD)
 - 3–4x increased risk for solid organ malignancies over high FA-associated cancer risk; ↑↑ risk with GvHD
 - HSCT-associated coronary artery disease, musculoskeletal and neurocognitive dysfunction, endocrinopathies

Fanca-Cel Mechanism of Action⁵

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

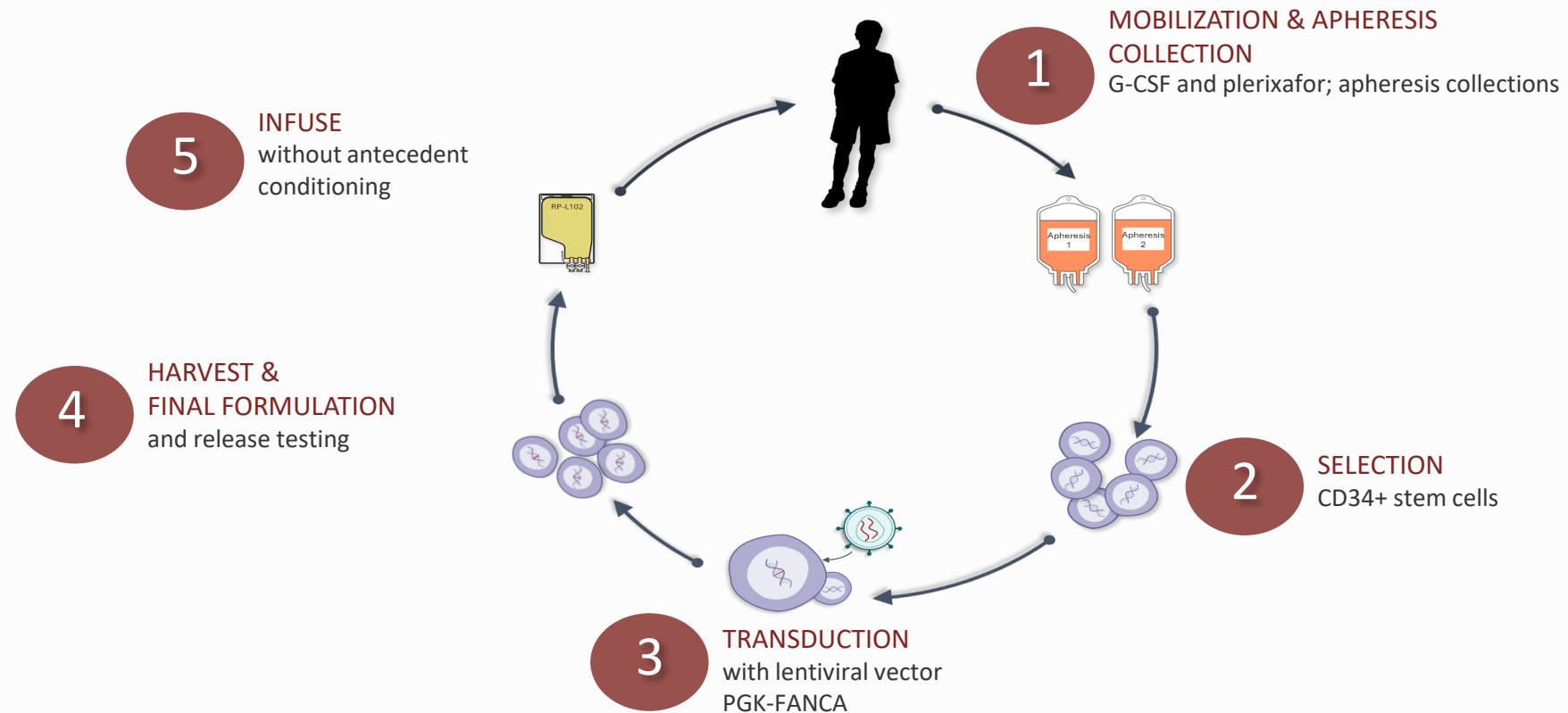


BMF, bone marrow failure; CD, cluster of differentiation; FA, Fanconi anemia; FA-A; FA complementation group A; GvHD, graft vs host disease, HLA, human leukocyte antigen.

1. Anur P et al. *Bone Marrow Transplant.* 2016; 51(7): 938-944; 2. Ebens C et al. *Biol Blood Marrow Transplant.* 2018; 24(4): 765-771; 3. Guardiola P et al. *Blood.* 2004; 103(1): 73-77; 4. Mehta P et al. *Blood.* 2017; 129(16): 2308-2315; 5. . Río P, et al. *Nat Med.* 2019;25(9):1396-1401.

Autologous cells, transduced using a lentiviral vector, are infused back into the patient to engraft into the bone marrow

Insertion of a functional *FANCA* gene into autologous FA-A CD34+ cells confers resistance to DNA damage and provides proliferative advantage to modified cells, enabling engraftment **without cytotoxic conditioning**¹



Fanca-cel was studied in a single-arm Phase I/II trial in patients diagnosed with FA-A to explore key efficacy and safety outcomes

Key Eligibility Criteria

▪ **Inclusion**

- FA complementation group A
- Minimum age of 1 year
- BM CD34+ cell concentration $\geq 30/\mu\text{L}$ (from aspirate)

▪ **Exclusion**

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

Endpoints

▪ **Efficacy**

- **Phenotypic correction:** increased resistance of BM progenitor cells (CFCs) to DNA-damaging agent mitomycin-C (MMC)
- **Engraftment:** Peripheral blood (PB) and BM vector copy number (VCN)
- **Clinical response:** hematologic stabilization

▪ **Safety**

- Evaluation of safety and tolerability

BM, bone marrow; CD, cluster of differentiation; HLA, human leukocyte antigen

1. Czechowicz A et al. Lentiviral-Mediated Gene Therapy (RP-L102) for Fanconi Anemia [Group A] is Associated With Polyclonal Integration Patterns in the Absence of Conditioning. 27th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT). Abstract #245 May 10, 2024. 2. www.clinicaltrials.gov (NCT04437771, NCT03814408, NCT04069533, NCT04248439)

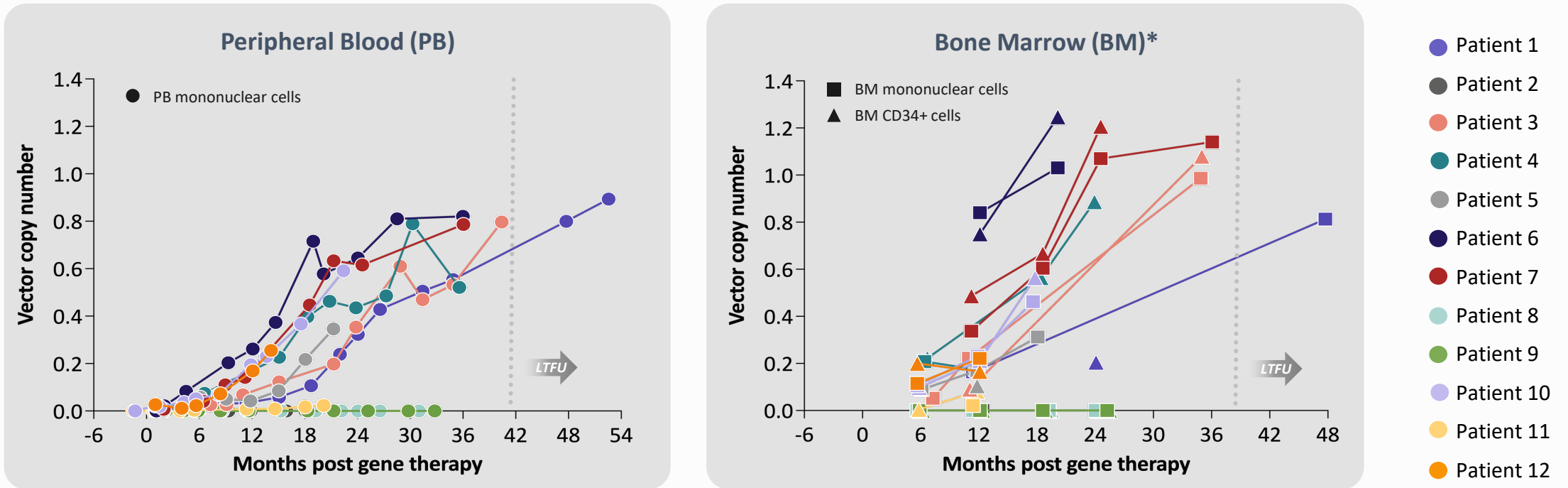
Current trial of fanca-cel includes 12 patients with at least a year of follow up and 14 patients in total

| Subject # | Age at Enrollment (years) | Follow Up (m) | CD34+ Cells/kg | CFCs/kg | Mean VCN: Liquid Culture | Mean VCN: CFCs | Transduction Efficiency (%) | CFC Survival MMC 10nM (%) | <div>All patients ≤ 6 years old at enrollment</div> <div>12 patients have ≥ 12 months of follow-up</div> <div>Trial enrollment is complete</div> <div>Median Values</div> <div>VCN (liquid culture): 1.70</div> <div>VCN (CFC): 1.75</div> <div>Transduction efficiency: 87.0%</div> <div>CFC MMC-resistance: 50.5%</div> <div>*Mean CFC VCN was assessed from a cryopreserved drug product sample.</div> <div>†Patient withdrawn from fanca-cel study at 18 months post-fanca-cel infusion; Received successful allogeneic HSCT for BMF. Safety follow up continues on LTFU study.</div> <div>‡Patient withdrawn from fanca-cel study at 28 months post-fanca-cel infusion; Received successful allogeneic HSCT for NHL. Safety follow up continues on LTFU study.</div> <div>§Not available due to assay failure.</div> |
|-----------|---------------------------|-----------------|-------------------|-------------------|--------------------------|----------------|-----------------------------|---------------------------|---|
| 1 (1001) | 5 | 54 | 2.0×10^5 | 5.2×10^4 | 2.08 | 0.62* | 67 | 33 | |
| 2 (1002) | 6 | 18 [†] | 3.7×10^5 | 5.0×10^4 | 2.21 | 0.92* | 72 | 47 | |
| 3 (2004) | 3 | 42 | 4.8×10^5 | 1.3×10^5 | 1.70 | 0.73 | 100 | 63 | |
| 4 (2008) | 2 | 36 | 3.2×10^6 | 5.5×10^5 | 1.65 | 1.56 | 97 | 63 | |
| 5 (2009) | 3 | 28 [‡] | 1.9×10^6 | 3.1×10^5 | 2.16 | 0.76 | 61 | 45 | |
| 6 (2010) | 3 | 36 | 4.1×10^6 | n/a | 0.62 | n/a | n/a | n/a | |
| 7 (2011) | 5 | 36 | 2.8×10^6 | n/a | 1.46 | n/a | n/a | n/a | |
| 8 (2014) | 6 | 32 | 5.4×10^5 | 3.6×10^4 | 3.68 | 1.93 | 87 | 31 | |
| 9 (2016) | 2 | 32 | 3.0×10^5 | 2.5×10^4 | 1.96 | 0.64 | 88 | 64 | |
| 10 (2021) | 2 | 21 | 2.3×10^6 | 4.3×10^5 | 1.55 | 1.97 | 78 | 38 | |
| 11 (2023) | 5 | 18 | 2.5×10^5 | 2.8×10^4 | 1.70 | 2.16 | 87 | 50 | |
| 12 (2024) | 1 | 15 | 1.8×10^6 | 1.7×10^5 | 1.69 | 1.91 | 88 | 93 | |
| 13 (2026) | 1 | 4 | 1.9×10^6 | 1.2×10^5 | 1.30 | 0.80 | 75 | 51 | |
| 14 (2025) | 3 | 2 | 3.5×10^5 | 5.6×10^4 | 3.45 | 2.50 | 92 | 63 | |

BMF=Bone marrow failure; CFC=colony-forming cell; HSCT=Hematopoietic stem cell transplantation; LTFU=long-term follow-up; MMC=Mitomycin-C; n/a: not available due to assay failure; NHL=Non-Hodgkin Lymphoma; VCN=vector copy number. Data cutoff: September 11, 2023

1. Czechowicz A et al. Lentiviral-Mediated Gene Therapy (RP-L102) for Fanconi Anemia [Group A] is Associated With Polyclonal Integration Patterns in the Absence of Conditioning. 27th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT). Abstract #245 May 10, 2024. 2. www.clinicaltrials.gov (NCT04437771, NCT03814408, NCT04069533, NCT04248439)

Progressively increasing and sustained genetic correction in 8 of 12 patients ≥ 1 year post fanca-cel



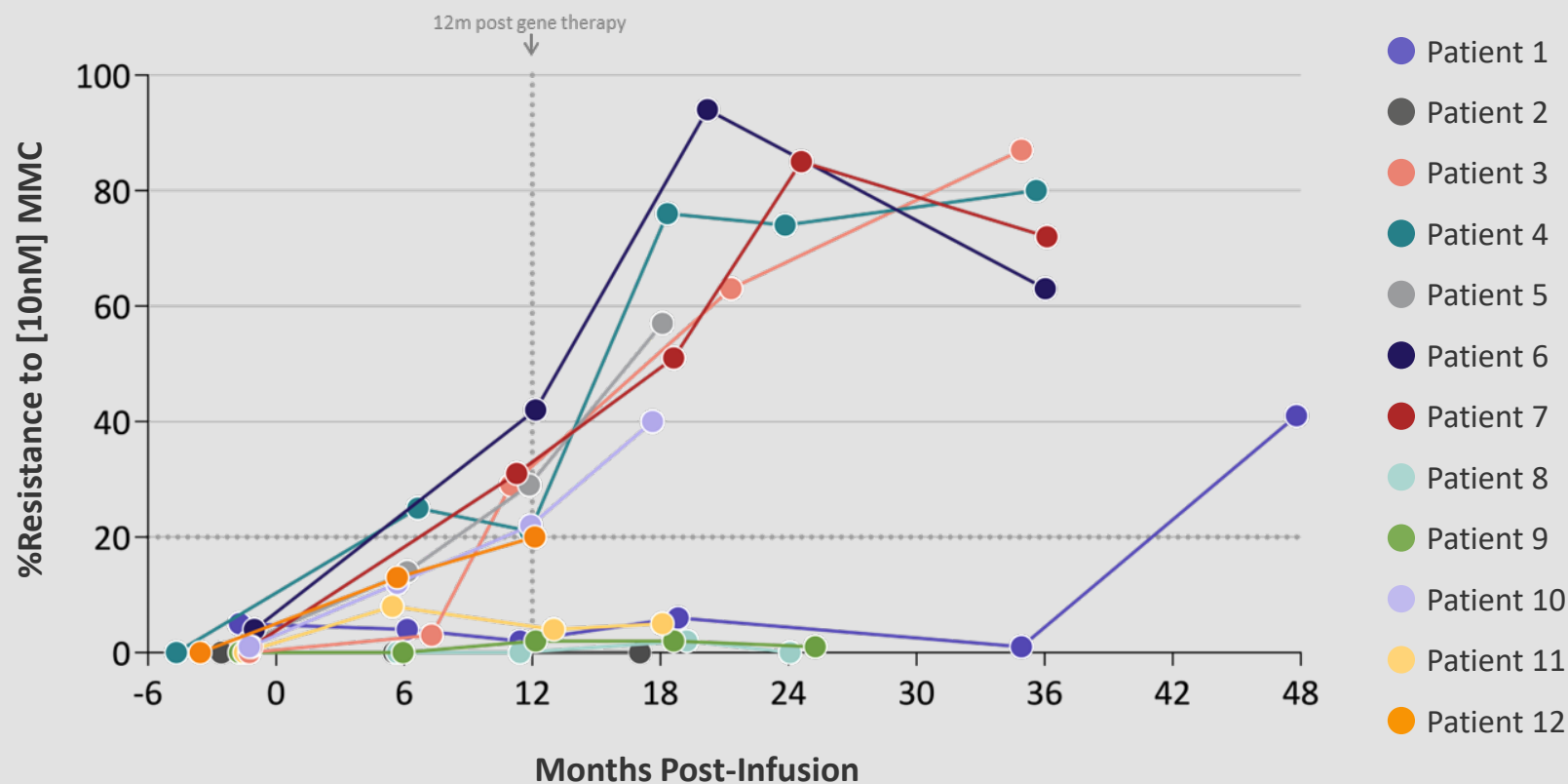
Progressive gene marking increases in BM and PB associated with MMC resistance and hematologic stability

*Vector copy number in bone marrow not available at some stipulated time points due to insufficient sample to perform assay. TFU=long-term follow-up. Data cutoff: September 11, 2023

Czechowicz A et al. Lentiviral-Mediated Gene Therapy (RP-L102) for Fanconi Anemia [Group A] is Associated With Polyclonal Integration Patterns in the Absence of Conditioning. 27th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT). Abstract #245 May 10, 2024.

Increasing phenotypic correction (MMC-resistance) over 1 to 3 years post fanca-cel in pivotal Phase II trial

BM MMC-resistance $\geq 20\%$ at 12m in 7 of 12 patients sustained BM MMC-resistance confirmed in 6 patients *



7 of 12 patients had MMC-resistance of $\geq 20\%$ at 12 months

For 6 patients, increased MMC-resistance in BM CFU (40% to 94%) was observed 18 to 24 months post fanca-cel (confirmatory assessment pending for Patient 12 (2024))



BM, bone marrow; CFU, colony-forming units; MMC, mitomycin-C.

*One additional patient (Patient 1: 1001) was noted to have BM MMC resistance of 49% at ~40 months post-fanca-cel infusion (Unscheduled visit, not shown) and ~41% at 48 months post-fanca-cel infusion.

Data cut-off: September 11, 2023; Preliminary interim results are presented from the ongoing clinical studies.

JA Bueren. Gene Therapy in Fanconi Anemia: from mouse to human. Fanconi Cancer Foundation Scientific Symposium. Sept 2024.

The safety profile for fanca-cel is well tolerated

Fanca-cel Safety Profile

- Patients are treated without antecedent conditioning and attendant risks
- Gene therapy does not preclude subsequent allogeneic HSCT if necessary
- Fanca-cel related SAE: 1 patient experienced a Grade 2 transient infusion-related reaction; resolved without any additional clinical sequelae
- Unrelated adverse event: 1 patient was diagnosed with T cell lymphoblastic lymphoma approximately 22 months post-infusion which was determined to be unrelated to fanca-cel. Lymphoma biopsy specimen demonstrated no appreciable LV integration. Tolerated chemotherapy and subsequent allo-HSCT with minimal toxicities.
- No reports of bone marrow dysplasia or insertional mutagenesis related to fanca-cel

Conclusions

- Fanca-cel is a potentially curative investigational gene therapy to prevent FA-related BMF, which can be administered without a suitable allogeneic donor or transplant related toxicities.
- **Efficacy**
 - Observed in patients with ≥ 1 year of follow-up in the absence of conditioning
 - 8 of 12 patients have demonstrated sustained and progressively increasing genetic correction
 - Phenotypic correction as demonstrated by sustained increase in BM CFC MMC resistance
 - Hematological stabilization
- **Safety**
 - Infusion was overall well tolerated
 - Polyclonal insertion patterns in Phase 2 studies demonstrated higher polyclonality and diversity of gene modified cells, relative to Fancolon-I
 - Overall, 1.3-fold higher mean VCN
 - 1.9-fold higher number of unique integrations
 - 1.4-fold lower Gini index
 - 1.5-fold higher Shannon index
 - Diverse integration patterns are indicative of long-term hematopoietic stem cell repopulation of the BM and PB and clonal diversity

BM=bone marrow; BMF=Bone marrow failure; FA=Fanconi Anemia; PB=peripheral blood; VCN=vector copy number. Data cutoff: September 11, 2023

Czechowicz A et al. Lentiviral-Mediated Gene Therapy (RP-L102) for Fanconi Anemia [Group A] is Associated With Polyclonal Integration Patterns in the Absence of Conditioning. 27th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT). Abstract #245 May 10, 2024.

Procedure description, documentation, and current coding

Procedure Description

Patients receive CD34+ hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain the CD34+ cells needed for fanca-cel manufacturing. The timing of fanca-cel infusion is coordinated so that administration begins as soon as possible after delivery to a qualified treatment center and within the expiration date and time indicated on the labels. All patients are infused with fanca-cel through the central vein in the inpatient setting after appropriate mobilization and apheresis. The minimum recommended dose of fanca-cel is 4×10^5 CD34+ cells per kilogram of body weight.

Documentation

The healthcare provider will likely document fanca-cel in the pharmacy orders and clinical notes of the patient's electronic medical record (EMR). Providers may document the drug, dosage, administration, and any relevant outcomes in the EMR. Fields in which information about fanca-cel infusion are entered may vary depending on the platform and software version utilized by the hospital/health system.

Current Coding

There is currently no ICD-10-PCS code to specifically describe the administration of fanca-cel. A unique code will allow for appropriate tracking, reporting, and outcomes research for fanca-cel.