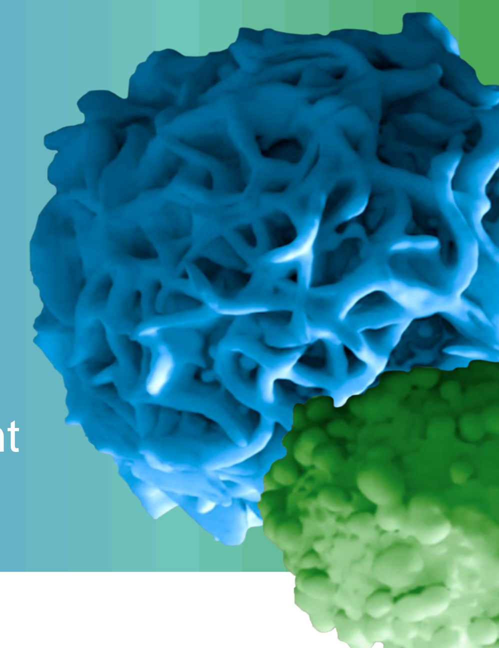
Phase 1 Study of Autologous SIRPα^{low} Macrophages (SIRPant-M™) administered by Intratumoral Injection, alone or combined with External Beam Radiotherapy in Patients with R/R Non-Hodgkin Lymphoma (NCT05967416)

SIRPant IMMUNOTHERAPEUTICS



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Introduction

While a sentinel role of macrophages in channeling immune responses has long been recognized, the opportunity to harvest, harness and deploy macrophages for therapeutic potential has been underappreciated clinically.

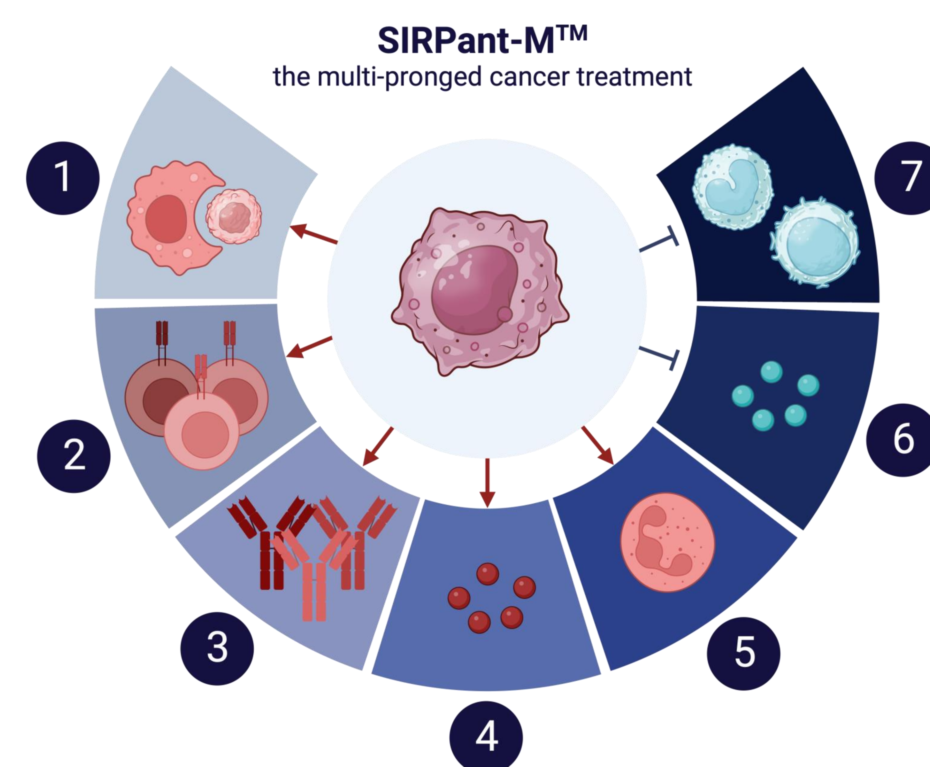
Most currently marketed and development-stage cell therapies target a single tumor-associated antigen, permitting activation of resistance and tumor escape mechanisms that frequently lead to relapse. Moreover, many T-cell lymphoma subtypes lack a readily druggable target. This first-in-human Phase 1 study advances a novel paradigm in cell-therapy, deploying autologous SIRPα-depleted activated macrophages, manufactured from a mononuclear apheresis (SIRPant-M). In the context of macrophages, SIRPα acts as a strong negative regulator of (i) phagocytosis and (ii) productive pro-inflammatory T cell stimulation; therefore abrogation of SIRPα-activity serves as a necessary precondition for robust neo-antigen-specific anti-tumor responses. Requiring no genetic modification, in pre-clinical models these SIRPα-depleted macrophages orchestrated an immune response that targets multiple individual-specific and tumor-unique neo-antigens in parallel. SIRPant-M elicits a multi-pronged polyclonal immune response that transforms the tumor microenvironment (TME) by fostering a pro-inflammatory milieu that provides for orchestrated targeting of cancer cells via both cellular and humoral effector mechanisms. Manufactured and subsequently frozen as 3 aliquots from a single apheresis, activation of the macrophages is brought about by conditioning macrophages during *ex vivo* culture with a proprietary cytokine cocktail (PhagoAct™) with the added effect of modulating activity of SIRPα.

This combination of product attributes permits the same cell product to have potential clinical applications in both solid tumors and hematologic malignancies. This Phase 1 clinical trial was designed using a standard 3+3 escalation rules to explore if autologous SIRPant-M macrophages are safe, tolerable, and effective in treating patients with relapsed/refractory non-Hodgkin's lymphoma (R/R-NHL). The trial aims to enroll ~ 15-21 DLT-evaluable subjects and further tests the secondary hypothesis that SIRPant-M treatment yields a broad and robust polyclonal adaptive immune response.

Mechanism of Action

SIRPant-M™ achieves durable elimination of treated (injected) AND non-treated tumors in a multi-pronged manner (Figure 1):

1. Phagocytosis of cancerous cells
2. Activation of polyclonal neoantigen-specific CD8 T cells
3. Elicitation of polyclonal cancer-specific antibodies
4. Secretion of pro-inflammatory molecules
5. Recruitment of pro-inflammatory neutrophil
6. Reduction in immunosuppressive molecules (e.g., TGF-B) within the TME
7. Reduction in immunosuppressive cells (e.g., Tregs, MDSC) within the TME



Why an Intratumoral Autologous Cell Therapy Approach?

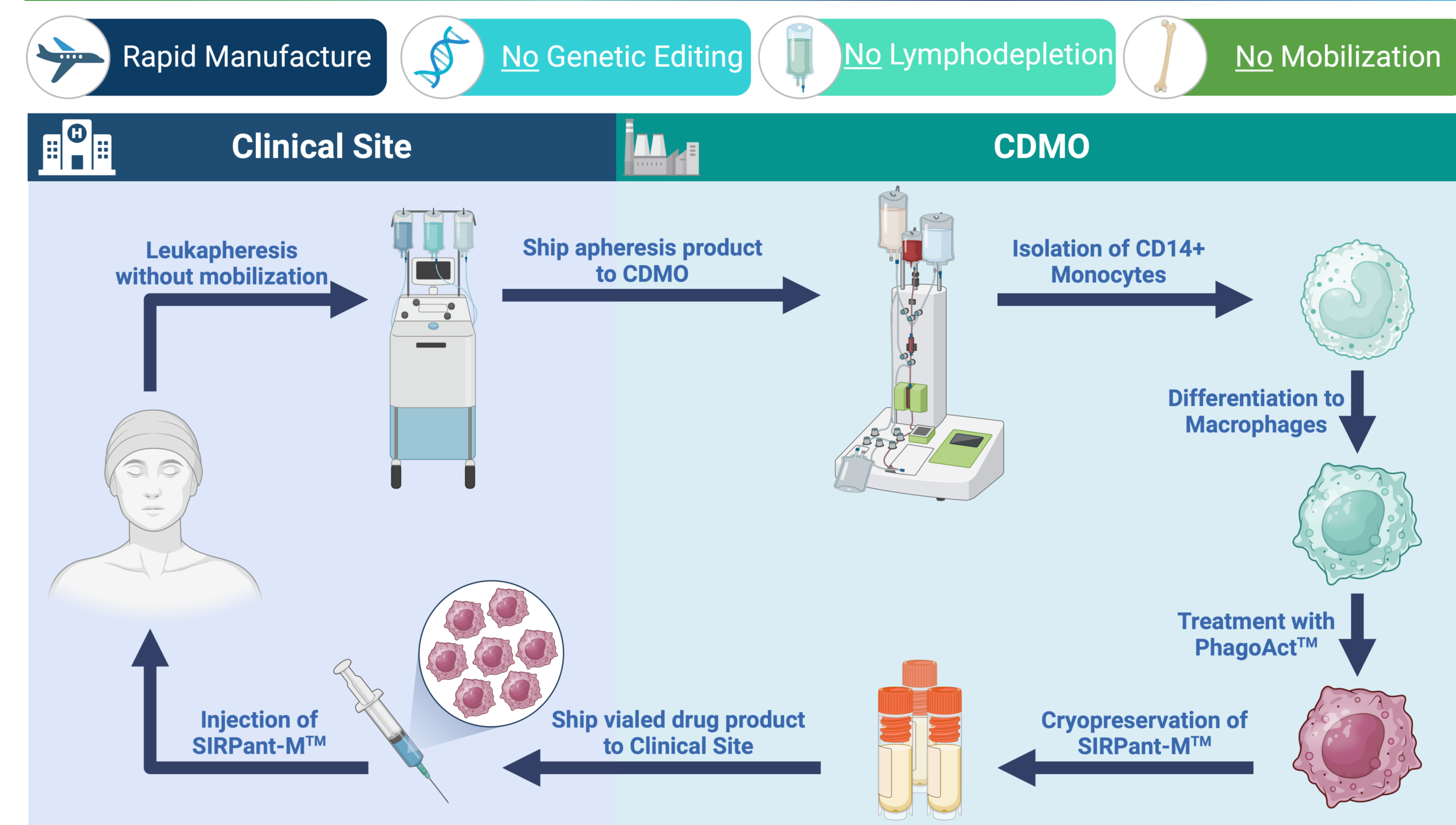
Why an intratumoral (IT) approach?

- Though macrophages may be intravenously (IV) infused, IV-administration poses several risks: **(i)** unclear efficiency of macrophage trafficking and extravasation into tumors – especially when not involving the lungs or liver, **(ii)** increased probability of incurring systemic toxicities, and **(iii)** increased manufacturing liability given that fractional macrophage penetration of tumor tissue will require more drug product to be generated and administered.
- IT injection ensures 100% of the drug product enters the tumor, which not only reduces the risk of off-tumor toxicities but also achieves higher local bioactive drug concentration in the tumor.

Why autologous cells rather than allogeneic cells?

- Allogeneic cell therapy approaches for cancer involve genetic modifications and are inherently histo-incompatible, which often incurs acute/chronic graft-versus-host disease (GVHD), worsens susceptibility to post-treatment infection, and fosters other immune-related comorbidities.
- SIRPant-M™ being an autologous cell therapy ensures histocompatibility and activation of cancer-specific adaptive immune cells, rather than non-specific activation of bystander cells that may curtail cancer-specific T cell activity (e.g., nutrient competition) or evoke autoimmunity.

7-Day Centralized Manufacture of SIRPant-M™



SIRPant-M™ Potency in Syngeneic NHL Mouse Models

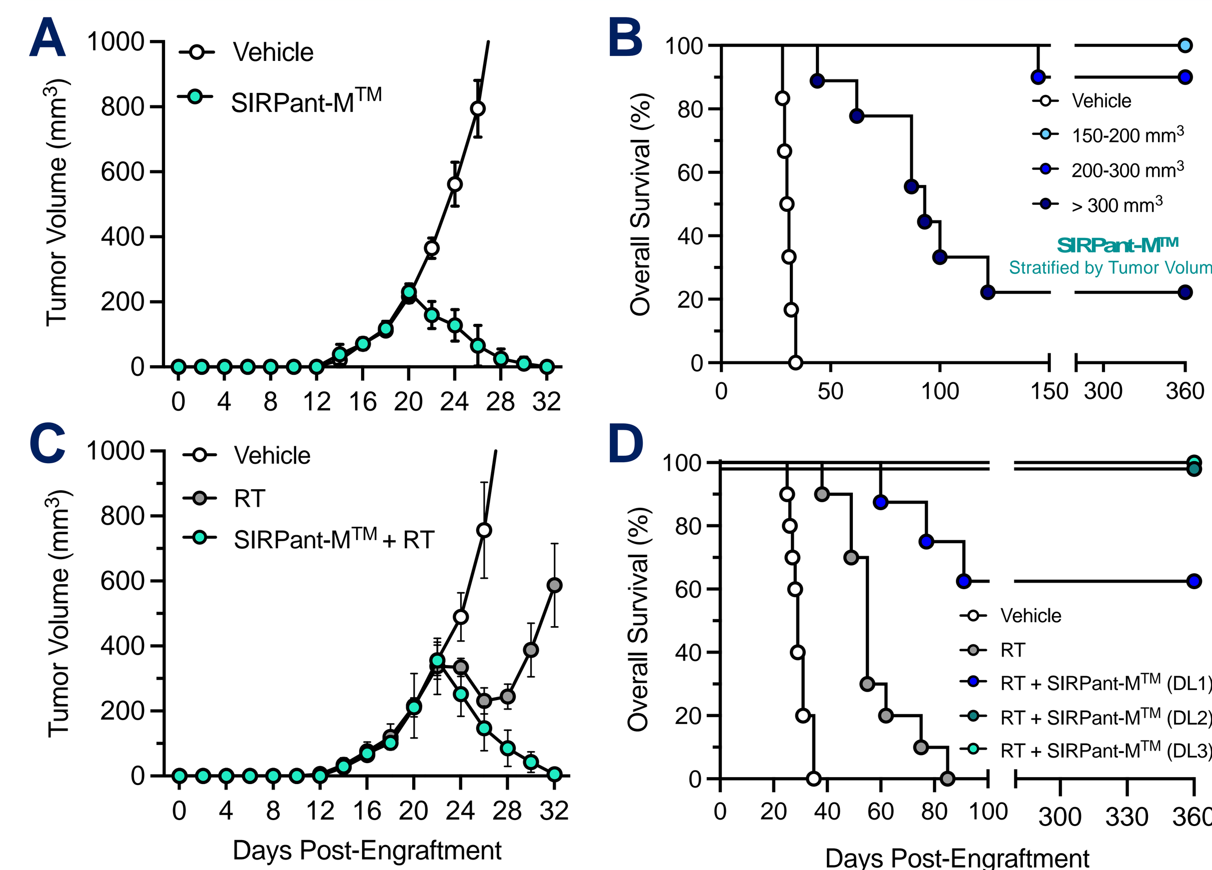


Figure 3. SIRPant-M™ alone (A, B) or in combination with tumor-directed radiotherapy (C, D) eliminates late-stage (150 – 400 mm³) syngeneic NHL tumors (EL4, subcutaneous) in mice. Though SIRPant-M™ is highly effective against less established tumors (150 – 300 mm³), it is less potent as a monotherapy against very advanced tumors (> 300 mm³) (A, B); however, the combination of SIRPant-M™ (varying dose-levels (DL) from very-low (DL1) to high dose (DL3)) and focal radiotherapy (RT) achieves durable complete remission of RT-refractory tumors (300 – 400 mm³).

SIRPant-M™ Phagocytosis of Human NHL

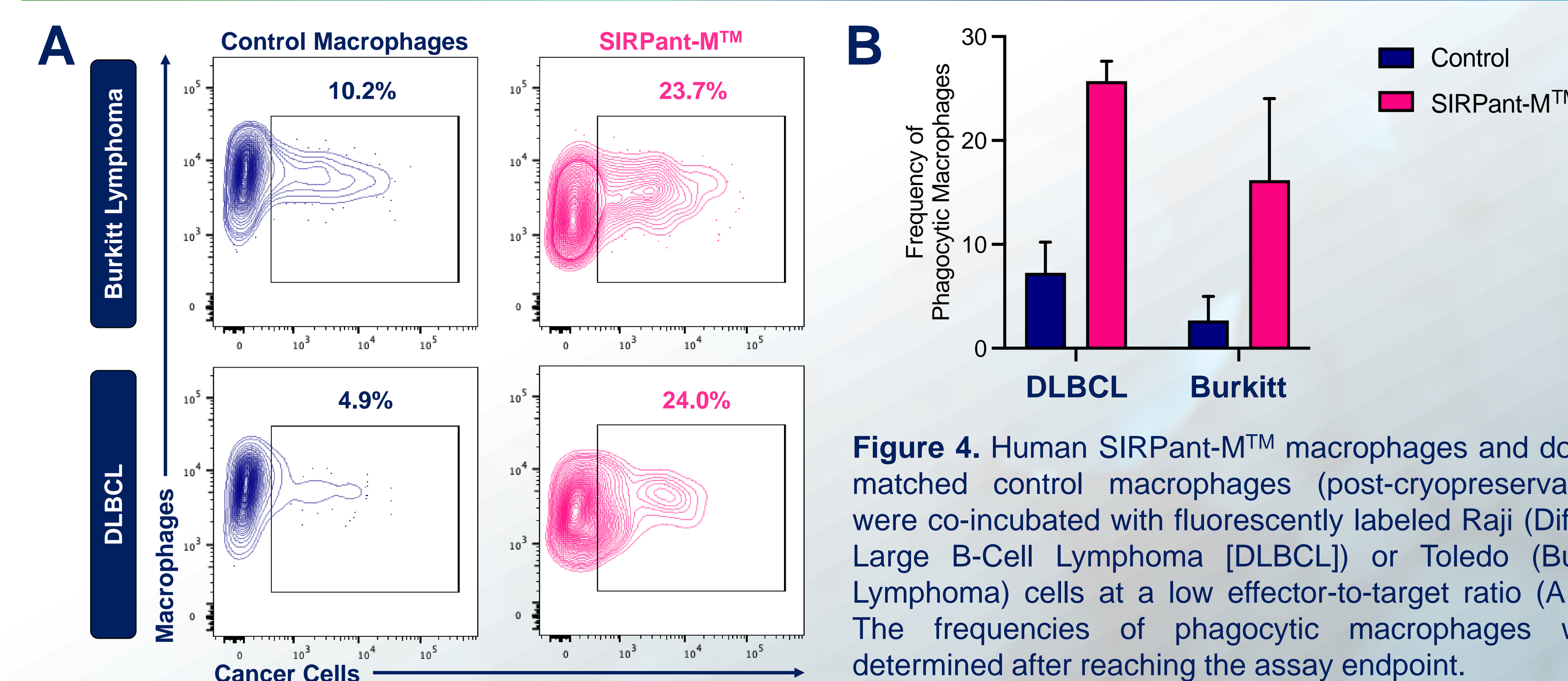


Figure 4. Human SIRPant-M™ macrophages and donor-matched control macrophages (post-cryopreservation) were co-incubated with fluorescently labeled Raji (Diffuse Large B-Cell Lymphoma [DLBCL]) or Toledo (Burkitt Lymphoma) cells at a low effector-to-target ratio (A, B). The frequencies of phagocytic macrophages were determined after reaching the assay endpoint.

Clinical Trial Design (NCT05967416)

This is a multicenter Phase 1 study (3+3) to evaluate the safety, tolerability, and preliminary efficacy of SIRPant-M alone or with XRT, targeting 15-21 R/R-NHL patients.

- Sequential cohorts will receive low (90 million macrophages) or high doses (300 million) of SIRPant-M™. Each cell dose is administered in three IT- fractions on days 1, 3, and 5.
- Upon confirmation of safety as single agent, subsequent cohorts receive cell product with XRT administered as three 2.5 Gy fractions (7.5 Gy total) to the injected tumor.

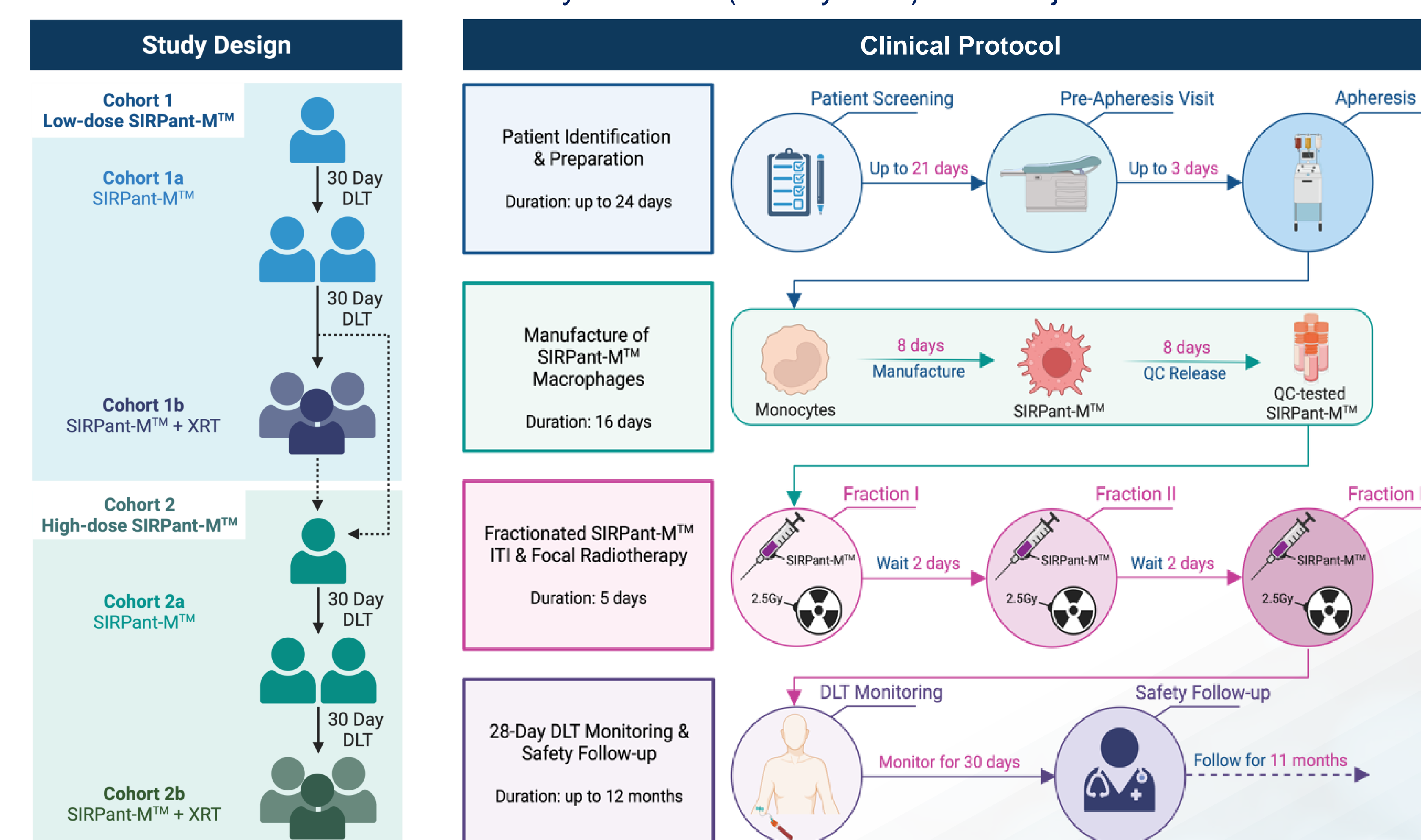


Figure 5 & Figure 6. This Phase I study is comprised of 2 cohorts – Cohort 1 is low-dose (90X10^6 cells) SIRPant-M™ and Cohort 2 is high-dose SIRPant-M (300X 10^6 cells) . Cohort 1a (low-dose monotherapy) patients are assessed for toxicity over a 30-day DLT-period, after which patients will be enrolled for Cohort 1b (low-dose XRT-combination of 3 X 2.5 Gy to the injected tumor site) or Cohort 2a (high-dose monotherapy). A schematic diagram of the clinical protocol is depicted.

Key Eligibility Criteria

- 18 years of age or older at the time of informed consent
- Received at least 2 lines of systemic therapy, be ineligible or inappropriate for other treatment regimens known to have curative potential
- Histologically or cytologically confirmed diagnosis of NHL
  - "All-comers" B- and T-cell NHL population, including systemic, peripheral and cutaneous histologies
- Must have at least one needle-accessible lymph node or cutaneous or subcutaneous lesion of 1.5 to 5 cm in one dimension as measured by CT, PET/CT or ultrasound or visual inspection for cutaneous NHL
- ECOG performance status ≤ 2

Objectives and Assessments

Primary Objectives

- Assess the safety and tolerability of 1 cycle(3 IT-injections) of SIRPant-M™ in NHL
- Assess the safety and tolerability of SIRPant-M™ in combination with low-dose focal external-beam radiotherapy
- Determine a recommended Phase 2 dose

Secondary Objectives

- Anti-Lymphoma response, including local response to the injected tumor site and systemic/abscopal response, evaluated by Lugano criteria or other Workgroup criteria as appropriate for the tumor type 2 weeks after the end of the DLT-period (Week 6), Week 12 and per SOC thereafter.

Exploratory Objectives

- Serial blood samples and a tumor biopsy before and 16 days after treatment are collected for multi-parameter analyte detection including pro-inflammatory cytokines, multiplex flow cytometry, scRNA sequencing, and ctDNA analysis to investigate pharmacodynamics and mechanism of action