723 METABOLICALLY REPROGRAMMED AUTOLOGOUS TH1/TC1 CELL THERAPY (RAPA-201) YIELDS PROMISING SAFETY AND EFFICACY IN POST-PD-(L)1 SOLID TUMOR PATIENTS WITHOUT LYMPHODEPLETING HOST CONDITIONING

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Background Polyclonal RAPA-201 is enriched for central-memory, polarized to Th1/Tc1, and rendered immune checkpoint-deficient and homeostatic cytokine-responsive.[1] RAPA-201 safely mediates disease remissions in multiple myeloma when administered after lymphodepleting conditioning.[2] RAPA-201 is also resistant to chemotherapy, including carboplatin (CBCCA), paclitaxel (PTX), and topotecan (Park JH et al, separate abstract submitted to SITC 2023). Given this background, we hypothesized that RAPA-201, when administered with immune-sparing CBCCA/PTX conditioning, would safely mediate disease regression in solid tumor patients in the post-PD-(L)1 setting.

Methods Accrual involved patients with metastatic solid tumors relapsed or refractory to standard treatments, including an anti-PD-(L)1 containing regimen just prior to study entry. Autologous RAPA-201 were manufactured using one-week culture in temsirolimus- and IFN-α-containing media (cryopreserved, 80–400 x 10^6 cells). Chemotherapy for bridging and RAPA-201 conditioning consisted of CBCCA (target AUC, 2 mg/mL/min) and PTX (80 mg/m^2) (each agent IV on days 1, 8, and 15; 28-day cycle). RAPA-201 were infused IV on cycle day 3 (up to four RAPA-201 cycles). Objectives were to confirm RAPA-201 safety and determine response rate (iRECIST Criteria) using Simon's two-stage design (≥ 2/10 responses [≥PR] required for second-stage accrual [overall goal, ≥ 6/22 responses]).

Results Ten enrolled patients are evaluable (table 1; data as of 6/24/2023). RAPA-201 was manufactured in 10/10 patients, who generally had widely metastatic and bulky disease (target lesions, SLD: median, 10 cm). RAPA-201 cycles (n=29) were administered exclusively outpatient (median RAPA-201 dose, 100 x 10^6 cells). RAPA-201 was safely administered (no CRS, ICANS, or autoimmunity); CBCCA/PTX conditioning was not significantly immune-depleting (median reduction in ALC, 12.5%). RAPA-201 yielded partial responses in 3/5 melanoma patients (PFS as long as 15.1 months) and 2/5 lung cancer patients (both small cell-type).

Conclusions A new adoptive cell therapy paradigm now emerges whereby metabolically fit T cells with a true polyclonal TCR repertoire target potential tumor antigens in vivo without lymphodepletion. The exquisite safety of the RAPA-201 platform likely reflects natural T cell signaling, lack of homeostatic cytokine spikes, and host immune cell sparing. And, the remarkable RAPA-201 response rate (overall, 50%) for end-stage malignancy likely emanates from an ability of functionally-optimized T cells to target tumors in the context of disease-specific, immune-sparing conditioning. Ongoing efforts seek to characterize RAPA-201 mechanism of action, breakout clinical trial efforts in responsive tumor types (melanoma, SCLC), and continue evaluation of RAPA-201 in potentially sensitive tumor types (NSCLC, head and neck, gastric, bladder, triple-negative breast, and renal cell).

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Trial Registration NCT05144698

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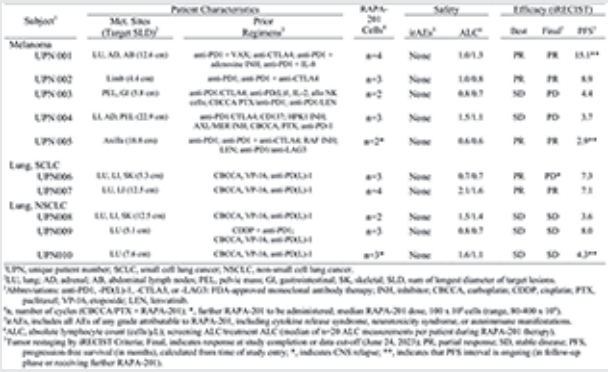
2. Dhakal B, Felizardo T, Lum LG, D'Souza A, Chhabra S, Keaton T, Mohan M, Park JH, Fowler DH, Hari P. Metabolically Reprogrammed Polyclonal Autologous Rapa-201 Cell Therapy Yields a Promising Safety and Efficacy Profile in Relapsed and Refractory Multiple Myeloma (RRMM). *Blood* 2021;**138**(Supplement 1):2838. DOI: 10.1182/blood-2021–147478.

Ethics Approval The study was approved by the WCG-IRB on 06/10/2021 (Study Number, 1310232).
Consent All participants provided written informed consent before enrollment.

Abstract 723 Table 1 RAPA-201 Therapy of Solid Tumors: Patient Characteristics, Adverse Events, Disease Response



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