

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 toptecan (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 10⁶ cells). Chemotherapy for bridging and RAPA-201 conditioning consisted of CBCCA (target AUC, 2 mg/mL/min) and PTX (80 mg/m²) (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 (\geq 2/10 responses [\geq PR] required for second-stage accrual [overall goal, \geq 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 10⁶ 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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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

Subject ¹	Met. Sites (Target SLD) ²	Patient Characteristics Prior Regimens ³	RAPA-201		Safety		Efficacy (iRECIST)		
			Cells ⁴	n/AEs ⁵	ALC ⁶	Best	Final	PFS ⁷	
Melanoma									
UPN001	EU, AD, AB (12.8 cm)	anti-PD-1 + VAX, anti-CTLA4, anti-PD-1 + atezolizumab (PD-1), anti-PD-1 + R-1	n=4	None	1.0/3.3	PR	PR	PR	15.1**
UPN002	EU, AD (1.4 cm)	anti-PD-1 + anti-CTLA4	n=3	None	1.0/8.8	PR	PR	PR	8.9
UPN003	PUL, GI (3.8 cm)	anti-PD-1 + anti-CTLA4, anti-PD-1 + R-1, anti-NK cells, CBCCA/PTX, anti-PD-1, anti-PD-1/IL2	n=2	None	8.8/7.7	SD	PD	4.4	
UPN004	EU, AD, PUL (2.8 cm)	anti-PD-1 + anti-CTLA4, CD137, MP1, DRI, AXL/MER TKI, CBCCA, PTX, anti-PD-1	n=3	None	1.5/1.1	SD	PD	3.7	
UPN005	Axilla (1.8 cm)	anti-PD-1, anti-PD-1 + anti-CTLA4, RAF DRI, LFN, anti-PD-1/anti-IL2	n=2*	None	8.8/8.6	PR	PR	2.9**	
Lung, SCLC									
UPN006	EU, LU, WJ (3 cm)	CBCCA, VP-16, anti-PD-1/1	n=3	None	8.7/6.7	PR	PD*	7.3	
UPN007	EU, LU (12.7 cm)	CBCCA, VP-16, anti-PD-1/1	n=4	None	2.1/1.6	PR	PR	7.1	
Lung, NSCLC									
UPN008	EU, LU, SK (12.7 cm)	CBCCA, VP-16, anti-PD-1/1	n=2	None	1.5/1.4	SD	SD	3.6	
UPN009	EU (1.7 cm)	CBOP + anti-PD-1, CBCCA, VP-16, anti-PD-1/1	n=3	None	8.8/7.7	SD	SD	8.8	
UPN010	EU (7.8 cm)	CBCCA, VP-16, anti-PD-1/1	n=3*	None	1.6/1.1	SD	SD	4.3**	

UPN, unique patient number; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.
¹EU, lung; AD, adrenal; AB, abdominal lymph nodes; PUL, pelvic mass; GI, gastrointestinal; SK, skeletal; SLD, size of largest diameter of target lesions.
²Abbreviations: anti-PD-1, PD-1/1, CTLA4, or 4-1BBL; FDA-approved monoclonal antibody therapy; DRI, inhibitor; CBCCA, carboplatin; CBOP, cisplatin; PTX, paclitaxel; VP-16, etoposide; LFN, lenvatinib.
³Further RAPA-201 to be administered, median RAPA-201 dose, 100 x 10⁶ cells (range, 80-400 x 10⁶).
⁴n, number of cycles (CBCCA/PTX + RAPA-201). * Further RAPA-201 to be administered, median RAPA-201 dose, 100 x 10⁶ cells (range, 80-400 x 10⁶).
⁵n/AEs, includes all AEs of any grade attributable to RAPA-201, including cytokine release syndrome, neurotoxicity syndrome, or autoimmune manifestations.
⁶ALC, absolute lymphocyte count (x10⁹/L), screening ALC treatment ALC (median of 0-29 ALC measurements per patient during RAPA-201 therapy).
⁷Tumor response by iRECIST Criteria. Final, indicates response at study completion or data cutoff (June 24, 2023); PR, partial response; SD, stable disease; PD, progressive-disease; PFS, progression-free survival (in months, calculated from time of study entry); *, indicates CNS relapse; **, indicates that PFS interval is ongoing (in follow-up phase or missing further RAPA-201).

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