CT169

A Phase Ia Study to Evaluate RO7198457, an Individualized Neoantigen-Specific Immunotherapy (iNeST), in Patients With Locally Advanced or Metastatic Solid Tumors

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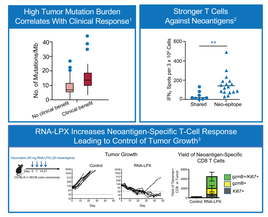
BACKGROUND

- High tumor mutation burden correlates with clinical response to immune checkpoint blockade
- Mutated neoantigens are recognized as foreign and induce stronger T-cell responses than shared antigens, likely due to the lack of central tolerance
- Most of these mutated neoantigens are not shared between patients; therefore, targeted neoantigen-specific therapy requires an individualized approach
- RO7198457 (RG6180) is a systemically administered RNA-Lipoplex Neoantigen Specific immunoTherapy (iNeST) designed to promote anti-tumor immunity by priming de novo and boosting pre-existing neoantigen-specific T-cell responses

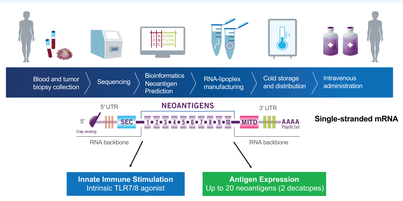
Figure 1. Individual Immune Responses to Neoantigens Necessitate the Need for Individualized Therapy



LPX, lipoplex.

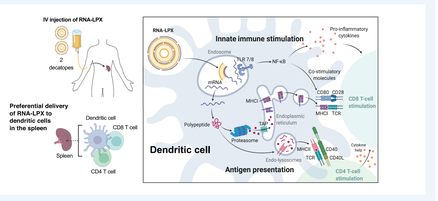
Targeting Neoantigens Requires an Individualized Approach

Figure 2. Development of Individualized RNA-LPX Technology[4-6]



Proposed Dual Mechanism of Action of RO7198457: TLR7/8 Stimulation and Neoantigen Presentation

Figure 3. Proposed Mechanism of Action[7]

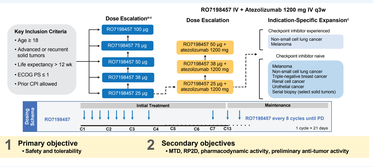


MHC, major histocompatibility complex; TCR, T-cell receptor.

METHODS

- GO39733 (NCT03289962) is a Phase Ia study of RO7198457 monotherapy in advanced solid malignancies

Figure 4. GO39733 Study Design



C, cycle; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; PD, progressive disease; q3w, every 3 weeks; RP2D, recommended Phase 2 dose.
[a] 3 + 3 dose escalation: 14-day DLT window; backfill enrollment at cleared dose levels. [c] Phase Ia patients with disease progression or loss of clinical benefit may cross over to combination therapy in Phase Ib. [d] See Lopez JS, et al. AACR II 2020. Oral CT301.

RESULTS

Patient Demographics and Disease Characteristics

Table 1. Patient Demographics and Baseline Characteristics

	Dose Escalation (N = 31)
Median (range) age, years	59 (21-77)
Female, n (%)	20 (65)
ECOG PS, n (%)	
0	14 (45)
1	17 (55)
Most common tumor types, n (%)	
Breast cancer (HER2+ or HR+)	6 (19)
Prostate cancer	5 (16)
Ovarian cancer	4 (13)
Bone sarcoma	4 (13)
Endometrial cancer	2 (7)
Gastric cancer	2 (7)
Soft tissue sarcoma	2 (7)
Median (range) number of prior systemic therapies for metastatic disease, n	5 (1-17)
Prior checkpoint inhibitors, n (%)	10 (32)
PD-L1 (Ventana SP142), n (%)	
< 5% IC and TC	28 (90)
≥ 5% IC or TC	3 (10)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER, human epidermal growth factor receptor; HR, hormone receptor; IC, tumor-infiltrating immune cell; PD-L1; programmed death-ligand 1; TC, tumor cell. Data cutoff: January 10, 2020.

Exposure and Disposition of Patients During Dose Escalation

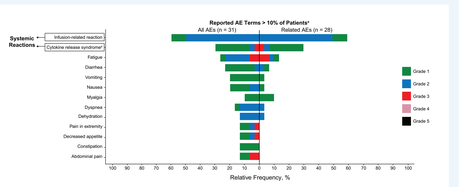
Table 2. Patient Exposure and Disposition During RO7198457 Treatment

	RO7198457 IV Dose					
	25 µg (n = 13)	38 µg (n = 5)	50 µg (n = 4)	75 µg (n = 8)	100 µg (n = 1)	Total (N = 31)
DLT, n (%)	0	0	0	0	1 (100)[a]	1 (3)
RO7198457 dose reduction, n (%)	0	1 (20)	0	0	0	1 (3)
Median (range) treatment duration, days	43 (1-123)	42 (15-128)	40 (15-254)	40 (9-69)	56 (56-56)	43 (1-254)
Continuing treatment, n (%)	0	1 (20)	1 (25)	0	0	2 (7)
Discontinued study treatment, n (%)	13 (100)	4 (80)	3 (75)	8 (100)	1 (100)	29 (94)
Reasons for treatment discontinuation, n (%)						
Crossover[b]	5 (38)	2 (40)	2 (50)	2 (25)	0	11 (35)
Disease progression	4 (31)	1 (20)	1 (25)	5 (62)	1 (100)	12 (39)
Death	0	0	0	0	0	0
AE	0	0	0	0	0	0
Withdrawal by subject	4 (31)	1 (20)	0	0	0	5 (16)
Other	0	0	0	1 (12)	0	1 (3)
Discontinued treatment due to disease progression prior to completing 6 weeks of therapy, n (%)	4 (31)	0	2 (50)	2 (25)	0	8 (26)

AE, adverse event; DLT, dose-limiting toxicity. [a] DLT event was Grade 3 cytokine release syndrome (CTCAE v5.0). [b] Phase Ia patients with disease progression or loss of clinical benefit could cross over to combination therapy in Phase Ib. Data cutoff: January 10, 2020.

Adverse Events in Patients Treated With RO7198457

Figure 5. AEs Reported in > 10% of Patients Treated With RO7198457



[a] A serious AE of malignant neoplasm progression was reported in 16% of patients (data not shown). [b] Per CTCAE v5.0.
Data cutoff: January 10, 2020.

Systemic Reactions (IRR, CRS, ILI) Were Transient and Generally Manageable in the Outpatient Setting

- Most systemic reactions occurred 2-4 hours post infusion and resolved within 1-2 hours
- Most events of hypotension and hypoxia were Grade 2

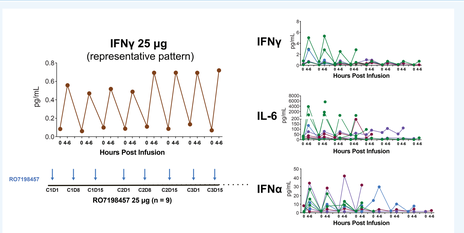
Table 3. Individual Signs and Symptoms of Systemic Reactions (CRS/IRR/ILI) in ≥ 5% of Patients

n (%)	25 µg RO7198457 (n = 13)	38 µg RO7198457 (n = 5)	50 µg RO7198457 (n = 4)	75 µg RO7198457 (n = 8)	100 µg RO7198457 (n = 1)	All Patients (N=31)
Chills	8 (62)	4 (80)	4 (100)	8 (100)	1 (100)	25 (81)
Pyrexia	6 (46)	2 (40)	3 (75)	5 (63)	1 (100)	17 (55)
Nausea	3 (23)	2 (40)	4 (100)	3 (38)	0	12 (39)
Headache	3 (23)	1 (20)	1 (25)	1 (13)	0	6 (19)
Vomiting	3 (23)	1 (20)	1 (25)	0	0	5 (16)
Hypotension	0	1 (20)	0	2 (25)	1 (100)	4 (13)
Hypoxia	0	1 (20)	0	1 (13)	1 (100)	3 (10)
Myalgia	2 (15)	0	0	1 (13)	0	3 (10)
Tachycardia	0	0	1 (25)	2 (25)	0	3 (10)
Neck pain	1 (8)	1 (20)	0	0	0	2 (7)
Sinus tachycardia	1 (8)	1 (20)	0	0	0	2 (7)
Tremor	0	1 (20)	1 (25)	0	0	2 (7)

CRS, cytokine release syndrome (CTCAE v.5.0); IRR, infusion-related reaction; ILI, influenza-like illness. Data cutoff: January 10, 2020.

RO7198457 Induced Pulsatile Release of Pro-Inflammatory Cytokines, Consistent With the Innate Immune Agonist Activity of the RNA

Figure 6. Cytokine Levels With RO7198457 Treatment



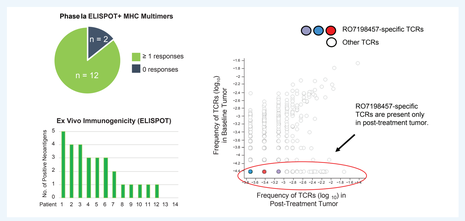
C, cycle; D, day; IFN, interferon; IL, interleukin. Data cutoff: January 10, 2020.

Immune Monitoring of T-Cell Responses Induced by RO7198457

- Ex vivo T-cell responses were detected in 86% of patients evaluated to date
  - Median number of 2 neoantigen-specific responses (range, 1-5). Ex vivo data were not available for all vaccine targets due to limited material and T-cell fitness
  - In vitro stimulation with ELISPOT as a more sensitive measure of immune response to RO7198457 is ongoing
- Preliminary evidence suggests infiltration of RO7198457-stimulated T cells in the tumor (patient with prostate cancer treated with RO7198457 75 µg)[a]

[a] In collaboration with Adaptive Biotechnologies.

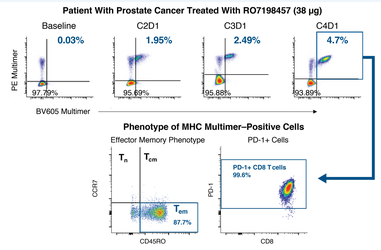
Figure 7. Neoantigen-Specific T-Cell Responses Induced by RO7198457



Data cutoff: January 10, 2020.

Immune Monitoring of Peripheral Blood–Detected T-Cell Responses Induced by RO7198457

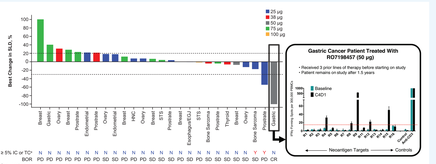
Figure 8. Kinetics and Phenotype of Neoantigen-Specific T-cell Responses



PD-1, programmed death-1.

RO7198457 Clinical Activity

Figure 9. Single-Agent Activity of RO7198457



BOR, best overall response; CPI, checkpoint inhibitor; CR, complete response; EGJ, esophagogastric junction; HNC, head and neck cancer; N, no; PBMC, peripheral blood mononuclear cell; PR, partial response; SD, stable disease; STS, soft tissue sarcoma; Y, yes.
[a] PD-L1 expression on IC/TC analyzed by SP142 Ventana assay. Data cutoff: January 10, 2020.

CONCLUSIONS

- RO7198457 was generally well tolerated
  - One DLT of Grade 3 CRS occurred in the 100-µg dose cohort; the maximum tolerated dose was not reached
  - Treatment-related AEs were primarily transient systemic reactions, manifesting as low-grade CRS, IRR or ILI symptoms. Systemic reactions were generally manageable in the outpatient setting
- Results from comprehensive immune monitoring were reflective of the dual mechanism of action of RO7198457
  - Induction of pulsatile release of pro-inflammatory cytokines was observed with each dose
  - Induction of neoantigen-specific T-cell responses was observed
  - Preliminary evidence suggests infiltration of RO7198457-stimulated T cells in the tumor; a more detailed analysis of intra-tumoral immune responses is being evaluated in a dedicated biomarker cohort
- One CR was observed in a patient with gastric cancer
- A Phase Ib study of RO7198457 in combination with atezolizumab is ongoing (see Lopez JS, et al. AACR II 2020. Abstract 9985; oral CT301)
- Two randomized Phase II studies of RO7198457 are ongoing:
  - RO7198457 + pembrolizumab for the first-line treatment of patients with melanoma (NCT03815058)
  - RO7198457 as adjuvant treatment in patients with non-small cell lung cancer (NCT04267237)

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