First report of safety/tolerability and preliminary antitumor activity of CAN-2409 in inadequate responders to immune checkpoint inhibitors for stage III/IV NSCLC

Abstract #9037

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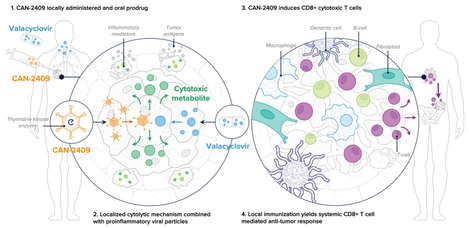
Background

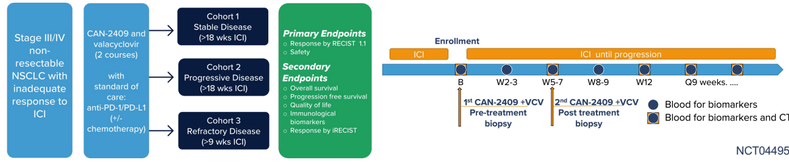
- Immune checkpoint inhibitors (ICI) are standard of care for advanced NSCLC, but a majority of patients ultimately progress
- Rational combination approaches are needed to improve outcomes
- CAN-2409 is an oncolytic viral immunotherapy capable of modulating local and systemic response to tumors
- CAN-2409 has previously demonstrated monotherapy activity in patients with NSCLC
- This Ph2 clinical trial evaluates the addition of CAN-2409 to ongoing ICI in patients with inadequate response to ICI

CAN-2409: Mechanism of action



Methods

- Open-label Ph2 clinical trial evaluating safety and clinical activity of intratumoral (IT) CAN-2409 added to ongoing first-line ICI therapy for stage III/IV NSCLC
- Three cohorts defined based on response to ICI at enrollment: stable disease (SD; Cohort 1), progressive disease (PD; Cohort 2), or ICI-refractory disease (RD; Cohort 3)
- Two doses of CAN-2409 (5x10^{11} viral particles) are given 5-7w apart via bronchoscopic or percutaneous injection into lung tumor, disease-positive lymph node, or peripheral metastatic site, followed by oral valacyclovir 2g TID for 14d
- Thirty-five patients received at least one dose of CAN-2409 and were included in the safety population
- Twenty patients received both courses of CAN-2409 followed by valacyclovir and were also evaluated for tumor response, abscopal effect, and immunologic biomarkers; radiographic response data is based on central read unless otherwise noted (data cut-off 20Apr2022)



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Clinical Results

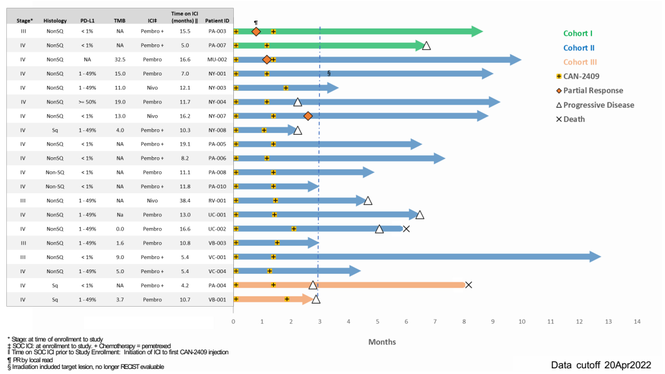
Table 1. Demographics (n=35)

Age	Years
Median (range)	69 (43-88)
Sex	**n (%)**
Male	20 (57)
Female	15 (43)
Race	**n (%)**
White/Caucasian	30 (86)
Black/African American	3 (9)
Smoking History	**n (%)**
Never	4 (11)
Former or current	28 (80); 3 (9)
ECOG Status at Enrollment	**n (%)**
0 or 1	14 (40); 21 (60)

Table 2. Most frequent treatment related AEs (n=35)

SOC/Adverse Event (>10%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total patients (n=35)
General disorders and administration site conditions				
Chills	4 (11)			4 (11)
Fatigue	8 (22)	4 (11)		12 (33)
Injection site reaction	4 (11)			4 (11)
Pyrexia	6 (17)		2 (6)	7 (20)
Investigations				
Blood creatinine increased	4 (11)	1 (3)		4 (11)

Fig 1. Swimmer plot for all evaluable patients (n=20)



* Stage at time of enrollment to study
‡ SOC ICI: at enrollment to study + Chemotherapy = pembrolizumab
# Time on SOC ICI prior to Study Enrollment: Initiation of ICI to first CAN-2409 injection
¶ PR by local read
§ Irradiation included target lesion, no longer RECIST-evaluable

Data cutoff 20Apr2022

Responses

Fig 2. Radiographic best responses for all evaluable patients

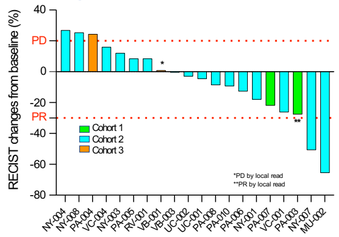


Table 3. Efficacy measures

Cohort	Completed 12-week treatment	PR	SD	PD	DCR	DoR for PR (w)	DoR for SD (w)
1	2	1**	1	0	50%	24.1+	26.9
2	16	2	12	2	87.5%	26.7-37.9+	5.4+ - 50.4+
3	2	0	0	2*	0%	n/a	n/a

PR= partial response; SD= stable disease; PD= progressive disease;
DCR = disease control rate
DoR PR= weeks from PR to progression; DoR SD=weeks from SD to progression
+ongoing response
*PD by local read; **PR by local read

Fig 3. Percent change RECIST from baseline

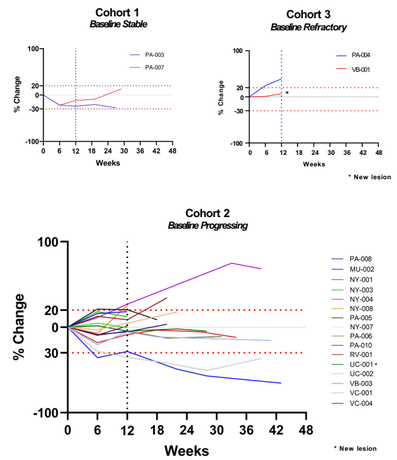
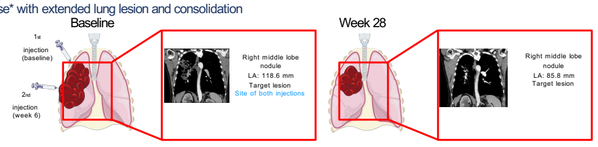


Fig 4. Patient scans representing responses in injected and uninjected lesions

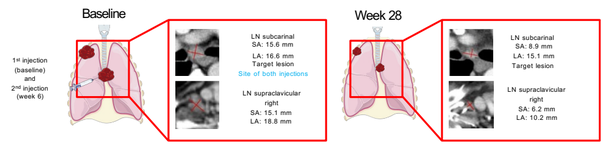
PA-003: Patient with partial response* with extended lung lesion and consolidation

PA-003 (Cohort 1)
73M, Stage III Non-SQ
PD-L1<1%
Diagnosed Jan'20
Started pembro + carbo + pemetrexed Feb'20, pembro + pemetrexed cont. from Jun'20 through trial
*PR by local read



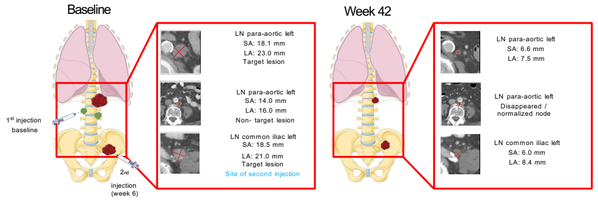
NY-007: Patient with partial response and evidence of abscopal effect

NY-007 (Cohort 2)
74M, Stage IV Non-SQ
PD-L1 <1%
Diagnosed Feb'19
cisplatin/etoposide Feb'19 to Jul'19, nivolumab monotherapy from Sep'19 thru trial
PR by local and central read



MU-002: Patient with partial response with evidence of abscopal effect

MU-002 (Cohort 2)
69F, Stage III 2013, Stage IV 2019
Non-SQ
PD-L1 unknown
Started pembro monotherapy Jan'20 thru trial
PR by local and central read



Legend
RECIST target lesions (red)
Non-target lesions (green)

Schematics to show general lesion injection orientation; not to scale
LN = lymph node; LA = long axis; SA = short axis

Biomarker analysis

Fig 5. CAN-2409 increases immune cell infiltration in post treatment biopsies

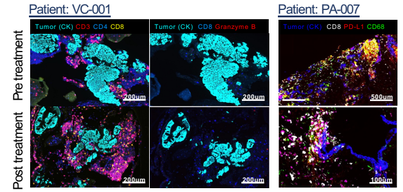
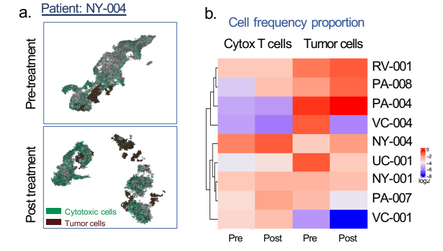


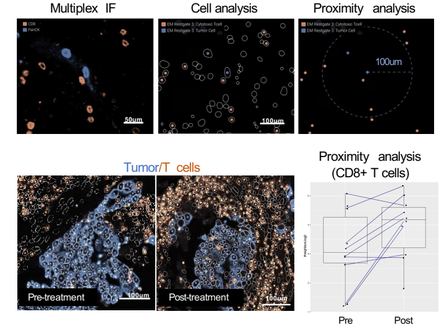
Fig 6. Frequency analysis demonstrates enrichment in cytotoxic T cells and decrease in tumor cells in post treatment biopsies



a. Vorenoi diagram illustrating frequency analysis methodology for patient NY-004 in pre and post treatment samples

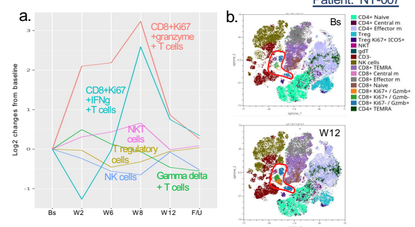
b. Heat map summarizing frequency data for paired biopsy samples for 9 eligible patients

Fig 7. Proximity analysis shows increase infiltration by cytotoxic cells in proximity of tumor cells in post treatment biopsies



Proximity analysis was applied to immunofluorescence (IF) stained samples to evaluate number of CD8+ cytotoxic cells within a distance of 100um radius from tumor cells. Significant difference was observed in post treatment samples (paired patient data represented p=0.0149 t-test).

Fig 8. CAN-2409 increases circulating cytotoxic T cells and decreases T-regulatory cells



a. Flow cytometry quantitation of cytotoxic cells and T regulatory cells; average values for subpopulations at specific time points from 14 patients' PBMCs

b. t-SNE plot representing patient MU-002 at baseline and 12 w demonstrating changes in the T cells and NK subpopulations (red outline)

Fig 9. CAN-2409 induces an increase in circulating CD8+Ki67+granzyme B+ T cells associated with elevated soluble granzymes A, B and H

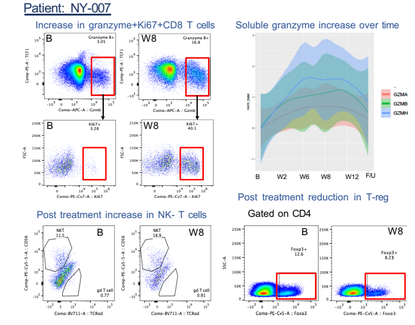
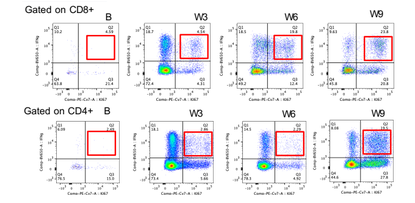


Fig 10. CAN-2409 induces systemic increase in proliferating effector CD8+ and CD4+ IFNγ producing cells



Biomarker highlights

Post treatment tumor biopsies demonstrated evidence of:
- Increased infiltration of cytotoxic T cells
- Increased T cell aggregation in proximity to tumor cells

Peripheral blood longitudinal samples demonstrate evidence of:
- Increased actively proliferating, granzyme positive T cells
- Increased actively proliferating, IFNγ+ CD4+ and CD8+T cells
- Increased soluble granzymes A, B and H

Conclusions

- Experimental treatment with CAN-2409 plus valacyclovir in patients with advanced NSCLC and inadequate response to first-line ICI (±chemo) who continued ICI treatment appears to be well tolerated
- We observed promising preliminary activity in the first 20 evaluable patients: 1) evidence for disease regression in both injected and uninjected lesions, 2) In Cohort 2 (patients who entered the study with progressive disease), a DCR of 87.5% with durable disease stabilization is ongoing in 10 out of 16 patients, 3) PR in 3 patients, and 4) increased infiltration by cytotoxic T cells in the tumor microenvironment associated with increased levels of soluble granzymes and granzyme B positive T cells in the peripheral blood
- These data are consistent with the hypothesis that CAN-2409 treatment induces immunization against tumor antigens in the injected tumor and uninjected metastases

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