Overall survival after treatment with CAN-2409 plus valacyclovir in combination with continued ICI in patients with stage III/IV NSCLC with an inadequate response to ICI

Abstract #8634

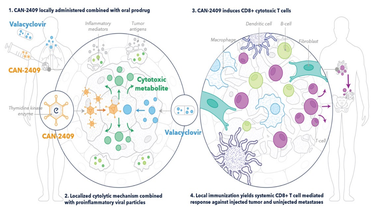
Charu Aggarwal MD, MPH[1] Daniel Sterman MD[2], Erin Alesi MD[3], Fabien Maldonado MD[4], Ranee Mehra MD[5], Christine Bestvina MD[6], Janani Reisenauer MD[7], Leigh K. Swartz MD[8], Sonam Puri MD[9], Omar Ibrahim MD[10], George Eapen MD[11], Caroline Duault PharmD PhD[12], Mina Rohani Pichavant[12], Diane M. Del Valle[13], Edgar Gonzalez-Kozlova PhD[13], Sacha Gnjatic PhD[13], Holden Maecker PhD[12], William Garrett Nichols MD[14], Francesca Barone MD, PhD[14], Paul Peter Tak MD, PhD[14]

[1]*University of Pennsylvania, Philadelphia, PA, USA;* [2]*New York University Langone Health, New York, NY, USA;* [3]*Virginia Commonwealth University, Richmond, VA, USA;* [4]*Vanderbilt University, Nashville, TN, USA;* [5]*University of Maryland-Baltimore, Baltimore, MD, USA;* [6]*University of Chicago, Chicago, IL, USA;* [7]*Mayo Clinic, Rochester, MN, USA;* [8]*Hunter Holmes McGuire VA Health, Richmond, VA, USA;* [9]*University of Utah Health, Salt Lake City, UT, USA;* [10]*University of Connecticut Health, Farmington, CT, USA;* [11]*MD Anderson Cancer Center, Houston, TX, USA;* [12]*Stanford School of Medicine, Palo Alto, CA, USA* [13]*Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [14]*Candel Therapeutics, Needham, MA, USA*

Contact: info@candeltx.com

Objective

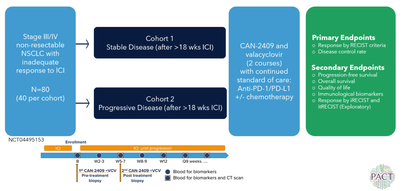
- Patients with unresectable, stage III/IV non-small cell lung cancer (NSCLC) with an inadequate response to immune checkpoint inhibitors (ICI) have very limited therapeutic options.
- Patients with progressive disease on ICI treatment have median overall survival (mOS) of < 12 months with standard of care docetaxel chemotherapy [PMID: 35658002].
- We explored whether experimental treatment with CAN-2409, a replication-defective adenovirus encoding the HSV-thymidine kinase gene, administered together with valacyclovir could improve mOS in patients treated with two injections.
- Previous work has shown that the immunological changes after the second administration of CAN-2409 ('the booster') are predictive of subsequent prolonged survival.



Methods

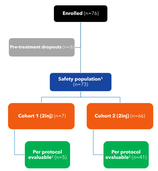
- NCT04495153 is an open-label, phase 2 clinical trial of CAN-2409 + valacyclovir in combination with continued ICI in patients with non-resectable, stage III/IV NSCLC, refractory or resistant to anti-PD-(L)1
- Patients were enrolled in 2 cohorts (C) depending on disease status at enrolment: C1, stable disease or C2, progressive disease.
- Two doses of CAN-2409 (5x10[11]vp) were given 5-7w apart via bronchoscopic or percutaneous injection into lung tumor, disease-positive lymph node, or peripheral metastasis, each followed by oral prodrug.
- Patients were assessed for safety, immunologic biomarkers, and overall survival .

Study schematic and biomarker analysis



Results

Patients enrolled



[1] Safety population: Received at least 1 injection of CAN-2409

[2] Per protocol evaluable patients are those who received 2 courses of CAN-2409 + prodrug (valacyclovir) and completed the 12-week treatment period. In addition to patients evaluable for efficacy, safety population included two cohort 1 patients who did not complete treatment due to adverse events (one pneumonitis possibly study drug related, and one pulmonary embolism unrelated to study drug). In cohort 2, four patients did not complete treatment due to AE (one possibly related empyema, one case of pneumonia, pre-syncope, and bullous dermatitis unrelated to study drug), 15 due to disease progression before they completed the treatment course, two who had incomplete treatment with prodrug, and four who withdrew for personal reasons.

Patient demographics

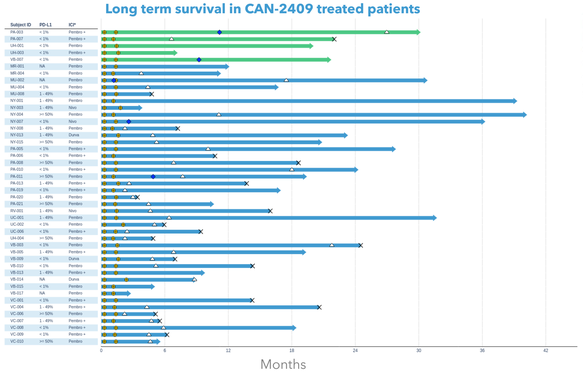
Age	Years
Median (Range)	67 (43-88)
Sex	**n (%)**
Female	32 (44)
Male	41 (56)
PD-L1 Expression	**n (%)**
<1%	35 (48)
1-49%	15 (21)
≥50%	19 (26)
Unknown	4 (5)
Histology	**n (%)**
Squamous	16 (22)
Non-Squamous	57 (78)
Treatment regimen at enrollment	**n (%)**
Single ICI	50 (68)
ICI plus pemetrexed	23 (32)

CAN-2409: favorable safety and tolerability profile

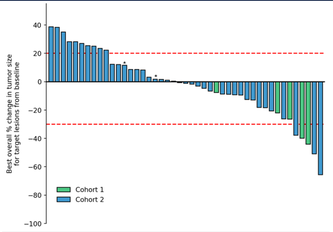
Most common TRAEs in ≥ 5% patients

SOC/Adverse Event Term (v5.0)	Grade 1	Grade 2	Grade 3	Total
Gastrointestinal disorders				
Diarrhoea	5 (7)	0 (0)	0 (0)	5 (7)
Nausea	11 (15)	4 (5)	0 (0)	15 (21)
Vomiting	4 (5)	2 (3)	0 (0)	6 (8)
General disorders and administration site conditions				
Chills	8 (11)	0 (0)	0 (0)	8 (11)
Fatigue	16 (22)	7 (10)	0 (0)	23 (32)
Influenza like illness	3 (4)	1 (1)	0 (0)	4 (5)
Pyrexia	12 (16)	1 (1)	1 (1)	14 (19)
Investigations				
Aspartate aminotransferase increased	4 (5)	0 (0)	0 (0)	4 (5)
Blood creatinine increased	4 (5)	3 (4)	0 (0)	7 (10)
Metabolism and nutrition disorders				
Decreased appetite	2 (3)	4 (5)	0 (0)	6 (8)
Nervous system disorders				
Headache	3 (4)	1 (1)	0 (0)	4 (5)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	2 (3)	4 (5)	0 (0)	6 (8)
Pneumonitis	0 (0)	2 (3)	2 (3)	4 (5)

Long term survival in CAN-2409 treated patients



Evidence that CAN-2409 can control disease



* PD due to presence of new lesion

Cohort	PR	SD	PD	N	ORR	DCR	DoR for PR[2]	DoR for SD[2]
1	2	3	0	5	40%	100%	11.6 mo (10.4+ to 12.8+)	6.2 mo (2.8+ to 16.7)
2	3	25	12	40	8%	70%	6.1 mo (2.8 to 16.3)	3.8 mo (0+ to 14.5)
Total	5	28	12	45	13%	N/A		

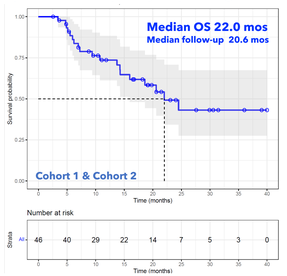
Blinded independent central review (BICR) of radiographic data per RECIST 1.1 in evaluable patients. Median (range) for DoR and SD duration.

"+" indicates response was ongoing at date of last follow up.

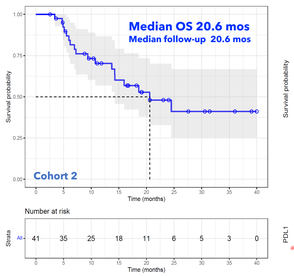
PR: partial response, SD: stable disease, PD: progressive disease, ORR: objective response rate, DCR: disease control rate, DoR: duration of response.

CAN-2409 improves overall survival in patients presenting with poor response to ICI

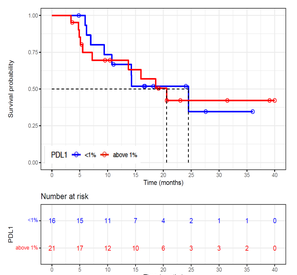
CAN-2409 improves overall survival in patients inadequately responding to ICI



CAN-2409 improves survival in patients progressing under ICI

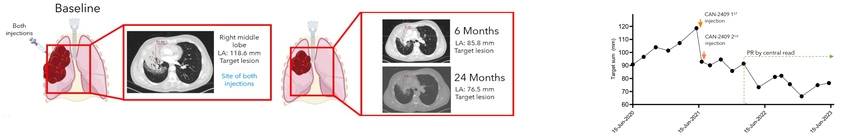


Improved survival is independent of PD-L1 status

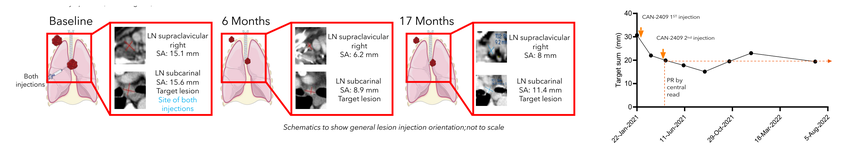


Kaplan Meier curves reporting survival in evaluable patients (2 injections and complete 12-week treatment).
Cohorts 1 & 2 safety population mOS is 14.3 mos (mFU 19.8 mos); cohort 2 safety mOS is 13.7 mos (mFU19.2 mos).

Partial response in large lung mass with durable post-treatment tumor regression after CAN-2409 treatment (>30 months, ongoing)

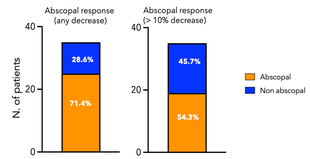


Evidence of abscopal effect with survival of more than 30 months (ongoing) after CAN-2409 treatment



Local injection of CAN-2409 induces systemic anti-tumor activity

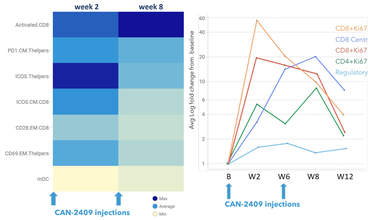
Abscopal response



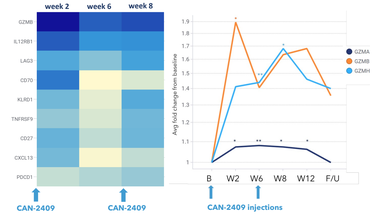
- Systemic response or abscopal response (decrease of non injected lesions) was measured on all evaluable patients with at least 1 non-injected lesion (n=35).
- Abscopal response (any decrease in non-injected lesion) was observed in two-thirds of patients.
- When using a threshold of >10% decrease still more than 50% of patients showed abscopal response.
- Abscopal response was associated with improved survival.

Systemic immune activation after CAN-2409 treatment

CAN-2409 induces significant increase in circulating T helper and cytotoxic T cells

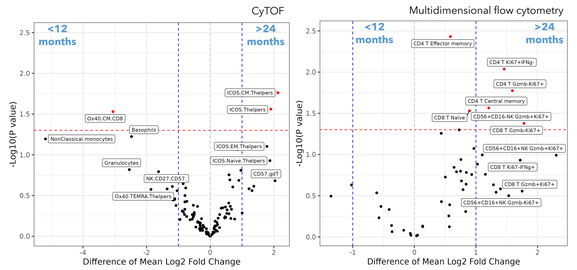


CAN-2409 induces significant increase in circulating inflammatory mediators including granzyme A, B and H



CyTOF and flow cytometry analysis (left panel, 29 evaluable patients) unveils significant changes after first and second CAN-2409 injections in both T helper and cytotoxic T cells population. Similarly, OLINK proteomic analysis revealed significant increases in proinflammatory mediators and cytotoxic enzymes (granzyme A, B and H).

Immune activation after 2nd CAN-2409 (booster) is associated with prolonged survival



Survival analysis: CyTOF analysis (left panel, above) demonstrates significant increase in ICOS+ T helper and central memory T helper cells in long survivors (OS>24 months) [increase measured between week 8 (after 2nd injection) and baseline]. Flow cytometry analysis (right panel) reveals significant increase in activated cytotoxic T cells, T helper cells, central and effector memory T cells in long survivors (OS >24 months) [increase measured between week 8 (after 2nd injection) and week 6 (before 2nd injection)]. Olink analysis reveals increase in circulating levels of granzyme H ($p<0.03$) and B (n.s.) in long survivors [increase measured between week 8 (after 2nd injection) and week 6 (pre 2nd injection)].

Conclusions

Experimental treatment of CAN-2409 + valacyclovir in NSCLC patients with an inadequate response to ICI is feasible and well tolerated, and results in median overall survival (mOS) of 22.0 months after only two administrations. We observed mOS of 20.6 months in patients with progressive disease at baseline, markedly exceeding mOS reported in this population using standard of care chemotherapy (1, 2). While 90% of the patients had stage IV disease, an abscopal effect was observed in more than 70% of the patients presenting with at least one uninjected lesion; this implies that only one or two tumors need to be injected to teach the immune cells how to recognize the patient's tumor and induce systemic and durable anti-tumor immunity.

References: 1) PMID: 24933332;2) PMID: 35658002

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