INVESTIGATIONAL PROTOCOL

CAN-2409 Plus Prodrug with Standard of Care Immune Checkpoint Inhibitor for Stage III/IV NSCLC Patients

Protocol LuTK02

Protocol Version 7

Sponsor
Candel Therapeutics
117 Kendrick St. Suite 450
Needham, MA 02494
Office: 617-916-5445
FAX: 617-916-5444

Sponsor Representative
W. Garrett Nichols, M.D.
Chief Medical Officer

Sponsor Representative Signature

DocuSigned by:
Garrett Nichols
Signer Name: Garrett Nichols
Signing Reason: I approve this document
Signing Time: 4/20/2023 | 5:02:23 PM EDT

Good Clinical Practice (GCP) Compliance Statement

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Confidentiality Statement

The information contained herein is confidential and is the property of the Sponsor. Any unauthorized use or disclosure of such information without the prior authorization of the Sponsor is expressly prohibited.

TABLE OF CONTENT

TREATMENT SCHEMAS 7
TIME AND EVENT TABLES 8
LIST OF ABBREVIATIONS 14
1. HYPOTHESIS 16
2. BACKGROUND AND RATIONALE 16
2.1. Introduction 16
2.2. NSCLC Current Standard of Care and Outcomes 17
2.3. Data Supporting the combination of CAN-2409 + prodrug and anti-pd-1 therapies 18
2.3.1. Local and Systemic Immune-Mediated Anti-Tumor Effects of CAN-2409 + Prodrug 18
2.3.2. Preclinical Studies of CAN-2409 + Prodrug and Anti-PD1 Combination 19
2.3.3. Enhancement of PD-L1 Expression by CAN-2409 + Prodrug 20
2.3.4. Clinical Data Supporting the Combination of CAN-2409 + Prodrug and Anti- PD-1 Antibodies 21
2.3.5. Clinical Experience with CAN-2409 + Prodrug Across Solid Tumors 21
2.3.6. Clinical Experience with CAN-2409 + Prodrug in NSCLC 22
2.4. CURRENT CLINICAL TRIAL 25
3. OBJECTIVES 26
3.1. Endpoints 26
3.1.1. Primary efficacy endpoint 26
3.1.2. Primary safety endpoint 26
3.1.3. Secondary endpoints 26
3.1.4. Exploratory endpoints 26
4. SUBJECT POPULATION 27
4.1. Inclusion Criteria 27
4.2. Exclusion Criteria 28
4.3. Subsets 28
5. PRETREATMENT EVALUATIONS & REGISTRATION 29
5.1. Baseline Evaluations 29

5.2. Registration Procedures 29
6. TREATMENT PLAN 29
6.1. Overview 29
6.1.1. CAN-2409 + prodrug schedule 29
6.1.2. Criteria for continuing treatment 30
6.2. Dose Limiting Toxicity and Stopping Rules 30
6.2.1. Dose limiting toxicity (DLT) is defined as any of the following study agent related* adverse events: 30
6.2.2. Stopping Rules 31
6.3. CAN-2409 ADMINISTRATION 31
6.3.1. Biopsy prior to intratumoral injection 31
6.3.2. Intratumoral injection 31
6.4. PRODRUG ADMINISTRATION 31
6.5. ADDITIONAL TREATMENT FOR NSCLC 32
7. TREATMENT EVALUATION 33
7.1. Evaluations During and After Treatment 33
7.2. Additional Research Studies 33
7.3. Post-progression Follow Up 33
7.4. Toxicity Assessment 33
7.5. CRITERIA FOR EVALUATION 33
7.6. Off Treatment Criteria 34
8. STUDY AGENTS - DESCRIPTION AND POTENTIAL RISKS 35
8.1. CAN-2409 35
8.1.1. Description 35
8.1.2. Potential Risks 35
8.1.3. Potential Biohazard Exposure to Health-Care Personnel 35
8.2. Valacyclovir 36
8.2.1. Description 36
8.2.2. Potential Risks 36
9. STATISTICAL CONSIDERATIONS 36

9.1. Sample Size 37
9.2. Evaluable Status of Patients 38
9.3. Analysis Sets 38
9.4. DLT STOPPING RULES 38
9.5. General Methods 40
9.6. Safety Analyses 41
9.7. Efficacy Analyses 41
9.7.1. Primary Endpoints 41
9.7.2. Possible Subgroup Analyses 42
9.7.3. Secondary Endpoints 42
9.7.4. Exploratory Endpoints 43
9.7.5. Viral shedding will be evaluated in collected serum and oropharyngeal samples and measured by validated identity assay by quantitative PCR. Adjustment for Multiplicity 43
10. ETHICAL AND REGULATORY CONSIDERATIONS 43
10.1. Consent Procedure 43
10.2. PATIENT REGISTRATION 43
10.3. Confidentiality 43
10.4. Risk-Benefit Ratio 43
10.5. Adverse Event Reporting 44
10.6. Data and Safety Monitoring 45
11. BIBLIOGRAPHY 47
APPENDIX 1. ..... CAN-2409 BOOSTER SUBSTUDY 51
A1-1. BACKGROUND AND RATIONALE 51
A1-2. OBJECTIVES 52
A1-2.1. Endpoints 53
A1-3. SUBJECT POPULATION 53
A1-3.1. Inclusion Criteria 53
A1-3.2. Exclusion Criteria 54
A1-4. PRETREATMENT EVALUATIONS & REGISTRATION 54

A1-4.1. Baseline Evaluations 54
A1-5. SCHEMA 54
A1-6. TREATMENT PLAN 54
A1-6.1. CAN-2409 administration 54
A1-6.2. Prodrug administration 55
A1-6.3. Additional treatment for NSCLC 55
A1-7. TREATMENT EVALUATION 55
A1-7.1. Evaluations During and After Treatment 55
A1-7.2. Additional Research Studies 55
A1-7.3. Post-progression Follow Up 55
A1-7.4. Toxicity Assessment 55
A1-7.5. Criteria for Evaluation 55
A1-7.6. Off Treatment Criteria 55
A1-8. STATISTICAL CONSIDERATIONS 56
A1-8.1. DLT Stopping Rules 56
A1-9. ETHICAL AND REGULATORY CONSIDERATIONS 56
A1-9.1. Consent Procedure 56
A1-9.2. Patient Registration 56
A1-9.3. Risk-Benefit Ratio 56
A1-9.4. Adverse Event Reporting 57
A1-9.5. Data and Safety Monitoring 57

LIST OF TABLES

Table 1 Time and Events for Patients Receiving 2 Courses of CAN-2409 Plus Prodrug (Cohorts 1A, 2A, and 3) and ICI Every 3 or Every 6 Weeks 8
Table 2 Time and Events for Patients Receiving 2 Courses of CAN-2409 Plus Prodrug (Cohorts 1A, 2A, and 3) and ICI Every 2 or 4 Weeks 9
Table 3 Time and Events for Patients Receiving 3-Courses of CAN-2409 Plus Prodrug (Cohort 1B and Cohort 2B) and ICI Every 2, 3, 4, or 6 Weeks 11
Table 4 Treatment-Related Adverse Events Reported in ≥5% of patients 22
Table 5 Valacyclovir Dosing 32
Table 6 Acyclovir Dosing 32

Table 7 Confidence Limits for a Range of ORR or DCR Outcomes Assuming a Sample Size of 40 Efficacy-Evaluable Patients....37
Table 8 Confidence Limits for a Range of ORR or DCR Outcomes Assuming a Sample Size of 20 Efficacy-Evaluable Patients....38
Table 9 Stopping Rules-Binomial Proportion 95% confidence intervals based on number of events out of total sample size (Wilson Score)....40
Table 10 Adverse Event Reporting Timing....45
Table 11 Time and Events for Booster Dose....51

LIST OF FIGURES

Figure 1 Schema for the 2-Dose Regimen In Cohorts 1A, 2A, And 3....7
Figure 2 Schema for 3-Dose Regimen in Cohorts 1B And 2B....7
Figure 3 Survival benefit from the combination of CAN-2409 + prodrug + anti-PD1 in an intracranial murine glioma model....20
Figure 4 Change in Tumor Growth Rate Pre-Study Compared to Post-CAN-2409....23

TREATMENT SCHEMAS

Figure 1 Schema for the 2-Dose Regimen In Cohorts 1A, 2A, And 3

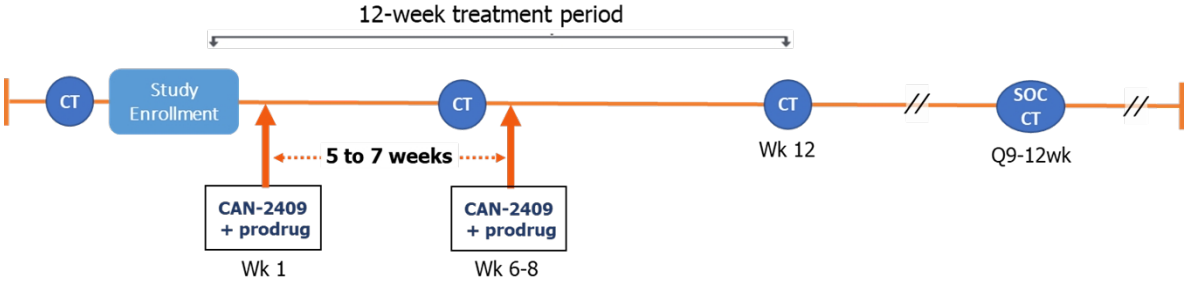
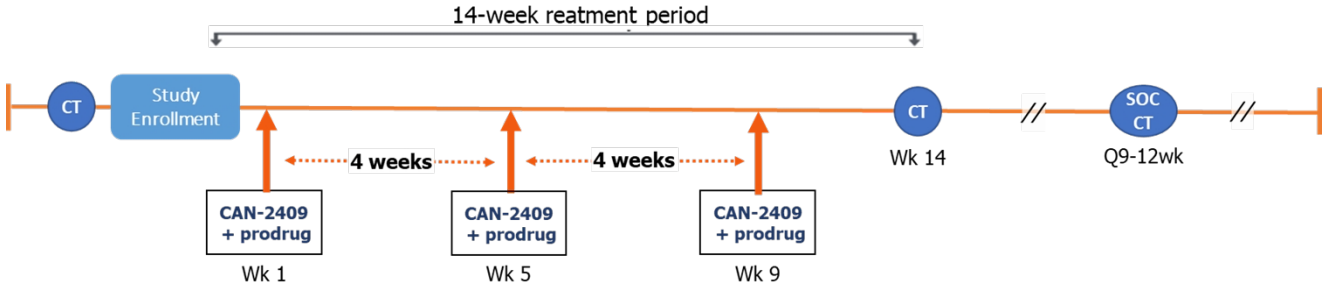


Figure 2 Schema for 3-Dose Regimen in Cohorts 1B And 2B



- All patients enter trial on standard of care immune checkpoint inhibitor which is continued as per previous schedule.
- For cohort 1B, the 3rd course of CAN-2409 + prodrug (week 9) is optional (and associated with separate consent).
- CT scans illustrated in the schematic will be used for clinical trial endpoints. For cohort 1B and 2B, after the baseline CT scan, there is not a trial-stipulated scan until week 14. If clinically warranted, CT scans may be obtained during the treatment period, but note that interpretation may be confounded due to the potential for pseudoprogression after CAN-2409 + prodrug.

TIME AND EVENT TABLES

Table 1 Time and Events for Patients Receiving 2 Courses of CAN-2409 Plus Prodrug (Cohorts 1A, 2A, and 3) and ICI Every 3 or Every 6 Weeks

***Wk** = Weeks. These times are estimates for a sample visit schedule, meant to represent how time and events are relative to each other, and may not fall cleanly into exact weeks. Assessments in a single column may occur on different days. Assessments in different columns may occur during the same week. For example, the week 6 visit may occur early in the week and week 7 may occur later in the same week. Requirements are listed below for each item. If standard of care (SOC) is delayed, evaluations for that time period and CAN-2409 + prodrug may also be delayed if appropriate. Subjects receiving ICI every 6 weeks may continue to receive ICI every 6 weeks but should follow the sample schedule below and be assessed roughly every 3 weeks during the 12-week treatment period.

^ Wk 7 Clinical Assessment, ECOG, labs and INR/aPTT should occur before the CAN-2409 injection.

ICI q3/q6 wk schedule	**Baseline [1]**	**Wk 1***	**Wk 2***	**Wk 3***	**Wk 6***	**Wk 7*^**	**Wk 8***	**Wk 9***	**Wk 12***	**Follow up until confirmed progression [9]**	**Post-confirmed progression [9]**
Informed Consent [1]	x										
Demographics	x										
CAN-2409 [2]		x				x					
Prodrug [2]		x	x			x	x				
ICI[3]	x			x	x			x	x	X [10]	
Clinical Assessment	x			x	x	x		x	x	q9-12wk [11]	
ECOG	x					x				q9-12wk	
Survival											Every 6mo
Adverse Events [4]				x	x			x	x		
New medical problems										q9-12wk	
Con Meds [5]	x			x	x			x	x		
Anti-cancer treatment										q9-12wk [5]	Every 6mo [5]
Labs [6]	x			x	x	x		x	x		
INR/aPTT [6]	x					x					
Imaging[7]	x								x	q9-12wk [11]	
Research Blood for Biomarkers [13]	x			x	x			x	x	Once [12]	
FNA/Biopsy if feasible [8]	Archive sample	x				x					
QOL	x				x				x	q9-12wk	

Table 2 Time and Events for Patients Receiving 2 Courses of CAN-2409 Plus Prodrug (Cohorts 1A, 2A, and 3) and ICI Every 2 or 4 Weeks

***Wk** = Weeks. These times are estimates for a sample visit schedule, meant to represent how time and events are relative to each other, and may not fall cleanly into exact weeks. Assessments in a single column may occur on different days. Requirements are listed below for each item. If standard of care (SOC) is delayed, evaluations for that time period and CAN-2409 + prodrug may also be delayed if appropriate. Subjects receiving ICI every 4 weeks may continue to receive ICI every 4 weeks but should follow the sample schedule below and be assessed roughly every 2-3 weeks during the 12-week treatment period.

^Wk 7 Clinical Assessment, ECOG, labs and INR/aPTT should occur before the CAN-2409 injection.

ICI q2/q4wk schedule	**Baseline [1]**	**Wk 1***	**Wk 2***	**Wk 4***	**Wk 6***	**Wk 7* ^**	**Wk 8***	**Wk 10***	**Wk 12***	**Follow up until confirmed progression [9,]**	**Post-confirmed progression [9]**
Informed Consent [1]	x										
Demographics	x										
CAN-2409 [2]		x				x					
Prodrug[2]		x	x			x	x				
ICI [3]	x		x	x	x		x	x	x	x [10]	
Clinical Assessment	x		x	x	x	x	x	x	x	q9-12wk [11]	
ECOG	x					x				q9-12wk	
Survival											Every 6mo
Adverse Events [4]			x	x	x		x	x	x		
New medical problems										q9-12wk	
Con Meds [5]	x		x	x	x		x	x	x		
Anti-cancer treatment										q9-12wk [5]	Every 6mo [5]
Labs [6]	x		x	x	x	x	x	x	x		
INR/aPTT [6]	x					x					
Imaging [7]	x								x	q9-12wk [11]	
Research Blood for Biomarkers [13]	x		x		x		x		x	Once [12]	
FNA/Biopsy if feasible [8]	Archive sample	x				x					
QOL	x				x				x	q9-12wk	

Key for above Table 1 and Table 2

1. Informed consent must be obtained prior to initiating any study procedures. Baseline evaluations within 14 days before injection except informed consent within 30 days before injection, CT with contrast within 28 days of injection. Baseline biopsy is from previous diagnostic sample when available. Labs may be repeated prior to injection if any significant changes are expected (e.g., interim illness).
2. Study treatment includes CAN-2409 injection into target lesion followed by oral valacyclovir for 14 days starting 1 day after each CAN-2409 injection (see Section 6.4 for dose adjustments or acyclovir alternative).
3. Course 1: 1st injection of CAN-2409 on day 1 of protocol and preferably at least 5-7 days prior to the next scheduled dose of ICI with or without chemotherapy to allow for assessment of adverse events between CAN-2409 and ICI.
4. Course 2: 2nd injection of CAN-2409 5-7 weeks after the first injection and preferably at least 5-7 days prior to the next scheduled dose of ICI with or without chemotherapy to allow for assessment of adverse events between CAN-2409 and ICI.
5. Immune checkpoint inhibitor (ICI) with or without chemotherapy, as per SOC. SOC treatment to continue prior to enrollment at baseline while screening is performed and following injections to stay on SOC schedule as much as possible.
6. Adverse events should be monitored continuously throughout the 12-week treatment period. After the 12-week treatment period (follow up), new medical problems should be documented at SOC visits until progression.
7. All concomitant medications should be documented during the 12-week treatment period. After the 12-week treatment period, only anti-cancer treatments need to be documented until progression. After progression during survival follow up, only general anti-cancer treatment regimens should continue to be documented.
8. CBC, platelets, differential, AST, ALT, total bilirubin, creatinine, calculated creatinine clearance, glucose and any other SOC laboratories as indicated. All labs are performed locally with assessments based on local lab ranges. Labs and aPTT/INR during an injection week are intended to be drawn before injection and checked to ensure injection criteria are met. See Section 6.1.2.1
9. SOC CT scan or other imaging as appropriate to measure/assess target and non-target lesions per RECIST criteria should be collected, preferably with the same technique, at each time point. These will be reviewed both locally and by central imaging reader(s) via Sponsor to determine RECIST response. Pre-baseline scans will be collected and reviewed by central imaging reader(s) via Sponsor.
10. Biopsy of lesion if feasible, based on safety and accessibility, prior to CAN-2409 injection plus collection of baseline sample from previous diagnostic sample when available. Samples for research to be batch shipped by clinical site to Sponsor upon request.
11. Follow up begins after 12-week treatment period, with follow up scheduled as per SOC (see #11), and continued until confirmed progression, such that SOC treatment is being changed or stopped. At confirmed progression, patients enter survival follow up, with at least biannual records review from the date of confirmed progression, +/- 1 month. Please see Section 7.3 for more detail.
12. ICI with or without chemotherapy continues as per SOC until progression.
13. Clinical assessment and CT scan as per SOC schedule, but expected to be at least every 9-12 weeks, until confirmed progression, after which patient enters post-progression follow up for survival. Radiographic progression will not be declared before 30 days from the 2nd (final) CAN-2409 injection due to the potential for pseudoprogression; under these conditions the first opportunity to assess radiographic progression will be the week 12 scan (cohort 1A, 2A, and 3). Radiographic PD should be confirmed by a scan performed at least 4 weeks after a prior scan showing progression. Additional SOC imaging performed after declaration of progression (before new treatment has been initiated) will be collected.
14. One time during follow up at the SOC visit closest to 6 months after the first CAN-2409 injection or at time of progression prior to starting new treatment, whichever time point comes first.
15. If research blood collection is done on same day as ICI treatment, research blood should be collected prior to ICI treatment

Table 3 Time and Events for Patients Receiving 3-Courses of CAN-2409 Plus Prodrug (Cohort 1B and Cohort 2B) and ICI Every 2, 3, 4, or 6 Weeks

***Wk** = Weeks. These times are estimates for a sample visit schedule, meant to represent how time and events are relative to each other, and may not fall cleanly into exact weeks. Assessments in a single column may occur on different days. Requirements are listed below for each item. If standard of care (SOC) is delayed, evaluations for that time period and CAN-2409 + prodrug may also be delayed if appropriate. Subjects may continue to receive ICI as per SOC schedule but should follow the sample schedule below and be assessed roughly every 2-3 weeks during the 14-week treatment period. ^ Clinical Assessment, ECOG, labs and INR/aPTT should occur before the CAN-2409 injection.

ICI treatment schedule as per SOC	**Baseline** [1]	**Wk 1***	**Wk 2***	**Wk 3***	**Wk 4***	**Wk 5***	**Wk 6***	**Wk 8***	**Wk 9***	**Wk 10***	**Wk 12***	**Wk 14***	**Follow-up until confirmed progression**[9]	**Post-confirmed progression**[9]
Informed Consent [1]	x													
Demographics	x													
CAN-2409 [2]		x				x			x					
Prodrug [2]		x	x			x	x		x	x				
ICI[3] (q2wk or q4wk	x		x		x		x	x		x	x	x	x[10]	
Clinical Assessment	x		x		x		x	x		x	x	x	q9-12wk [11]	
Adverse Events [4]			x		x		x	x		x	x	x		
Con Meds [5]	x		x		x		x	x		x	x	x		
Labs[6]	x		x		x		x	x		x	x	x		
INR/aPTT [6]	x				x			x						
Research blood for biomarkers [13]	x		x		x			x			x	x	Once	
Research samples for shedding- blood and oropharyngeal swab	x	x [14]	x			x [14]								
ICI [3] (q3wk or q6wk schedule)	x			x			x		x		x		x[10]	
Clinical Assessment	x			x			x		x		x	x	q9-12wk [11]	
Adverse Events [4]				x			x		x		x	x		
Con Meds [5]	x			x			x		x		x	x		
Labs [6]	x			x			x		x	x	x			

ICI treatment schedule as per SOC	**Baseline** [1]	**Wk 1***	**Wk 2***	**Wk 3***	**Wk 4***	**Wk 5***	**Wk 6***	**Wk 8***	**Wk 9***	**Wk 10***	**Wk 12***	**Wk 14***	**Follow-up until confirmed progression**[9]	**Post-confirmed progression**[9]
INR/aPTT [6]	X			X					x					
Research blood for biomarkers [13]	x			x			x		x		x	x	Once	
Research samples for shedding- blood and oropharyngeal swab	x	x[14]		x		x[14]								
ECOG	x								x				q9-12wk	
Survival													q9-12wk	Every 6mo [5]
New medical problems													q9-12 wk	
Anti-cancer treatment													q9-12wk [5]	Every 6mo [5]
Imaging [7]	x											x	q9-12wk [11]	
FNA/Biopsy if feasible (for research) [8]	Archive sample	x				x			x					
QOL	x						x					x	q9-12 wk	
Patient Experience Questionnaire												x	Once[15]	

Key for above Table 3

1. Informed consent must be obtained prior to initiating any study procedures. Perform baseline evaluations within 14 days before injection, informed consent within 30 days before injection, and CT with contrast within 28 days before injection. Baseline biopsy is from previous diagnostic sample when available. Labs may be repeated prior to injection if any significant changes are expected (e.g., interim illness).
2. Study treatment includes CAN-2409 injection into target lesion followed by oral valacyclovir for 14 days starting 1 day after each CAN-2409 injection (see Section 6.4 for dose adjustments or acyclovir alternative). Course 1: 1st injection of CAN-2409 occurs on week 1 of protocol. Course 2: 2nd injection of CAN-2409 occurs 4 weeks ± 3 days after 1st injection. Course 3: 3rd injection of CAN-2409 occurs 9 weeks ± 3 days after the first injection.
3. Immune checkpoint inhibitor (ICI) with or without chemotherapy, as per SOC. SOC treatment to continue prior to enrollment, at baseline while screening is performed, and following injections to stay on SOC schedule as much as possible.
4. Adverse events should be monitored continuously throughout the 14-week treatment period. After the 14-week treatment period (follow up), new medical problems should be documented at SOC visits until progression.
5. All concomitant medications should be documented during the 14-week treatment period. After the 14-week treatment period, only anti-cancer treatments need to be documented until progression. After progression during survival follow up, only general anti-cancer treatment regimens should continue to be documented.

6. CBC, platelets, differential, AST, ALT, total bilirubin, creatinine, calculated creatinine clearance, glucose and any other SOC laboratories as indicated. All labs are performed locally with assessments based on local lab ranges. Labs and aPTT/INR during an injection week are intended to be drawn before injection and checked to ensure injection criteria are met. See Section 6.1.2.1
7. SOC CT scan with contrast or other imaging as appropriate to measure/assess target and non-target lesions per RECIST criteria should be collected, preferably with the same technique, at each time point. These will be reviewed both locally and by central imaging reader(s) via Sponsor to determine RECIST response. Pre-baseline scans will be collected and reviewed by central imaging reader(s) via Sponsor.
8. Biopsy of lesion if feasible, based on safety and accessibility, prior to CAN-2409 injection plus collection of baseline sample from previous diagnostic sample when available. Samples for research to be batch shipped by clinical site to Sponsor upon request.
9. Follow up begins after 14-week treatment period, with follow up scheduled as per SOC (see #11), and continued until confirmed progression, such that SOC treatment is being changed or stopped. At confirmed progression, patients enter survival follow up, with at least biannual records review from the date of confirmed progression, +/- 1 month. Please see Section 7.3 for more detail.
10. ICI with or without chemotherapy continues as per SOC until progression.
11. Clinical assessment and CT scan as per SOC schedule, but expected to be at least every 9-12 weeks, until confirmed progression, after which patient enters post-progression follow up for survival. Radiographic progression will not be declared before 30 days from the 3rd (final) CAN-2409 injection due to the potential for pseudoprogression; under these conditions the first opportunity to assess radiographic progression will be the week 14 scan (cohort 1B, 2B). Radiographic PD should be confirmed by scan performed at least 4 weeks after a prior scan showing progression. Additional SOC imaging performed after declaration of progression (before new treatment has been initiated) will be collected.
12. One time during follow up at the SOC visit closest to 6 months after the first CAN-2409 injection or at time of progression prior to starting new treatment, whichever time point comes first.
13. If research blood collection is done on same day as ICI treatment, research blood should be collected prior to ICI treatment.
14. Week 1 shedding samples should be collected between 30 minutes and 4 hours post-injection of CAN-2409. Week 5 shedding samples should be collected prior to CAN-2409 injection.
15. One time during follow up at the SOC visit closest to 6 months after the first CAN-2409 injection.

LIST OF ABBREVIATIONS

CAN-2409	Aglatimagene besadenovec
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ANC	Granulocyte count
AST	Aspartate aminotransferase
BCP	Combination of bevacizumab, carboplatin, and paclitaxel
BLI	Bioluminescent imaging
Bx	Biopsy
CAN-2409	Aglatimagene besadenovec AE
CBC	Complete blood count
cc	Cubic centimeters
CD3	Cluster of differentiation 3
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
cGMP	Current Good Manufacturing Practice
CNS	Central nervous system
Cr	Creatinine
CRF	Case Report Forms
CT	Computed tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CXCL9	Chemokine ligand 9
DCR	Disease control rate
dl	Deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Eligibility Checklist
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
g	Gram
GCV	Ganciclovir
GMCI	Gene Mediated Cytotoxic Immunotherapy
HIV	Human immunodeficiency virus
hpf	High power field
HR	Hazard ratio
HSV	Herpes simplex virus
ICI	Immune checkpoint inhibitor
IFN-gamma	Interferon-gamma
IL-12	Interleukin-12
IL-2	Interleukin-2
IP	Intraperitoneal

IV	Intravenous
kg	Kilogram
LTS	Long term survivors
mcg	Microgram
MDSC	Myeloid derived suppressor cells
mg	Milligram
ml	Milliliter
mm	Millimeter
Mo	Months
mPFS	Median progression free survival
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBS	Phosphate bovine serum
PCR	Polymerase chain reaction
PD1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression free survival
PIs	Principal investigators
po	By mouth
QOL	Quality of life
RECIST	Response evaluation criteria in solid tumors
SD	Stable disease
SGOT (AST)	Serum glutamic-oxaloacetic transaminase
SOC	Standard of care
SOP	Standard operating procedure
SOP	Adverse Event
STING (pathway)	Stimulator of interferon genes
SUSAR	Serious unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
TILs	Tumor-infiltrating lymphocytes
Tk	Thymidine kinase
TPS	Tumor proportion score
T-reg	Regulatory T cells
TTP/HUS	Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
VCV	Valacyclovir
VEGF	Vascular endothelial growth factor
vp	Viral particles
wk	Week
yr	Year

1. HYPOTHESIS

The study hypothesis is that CAN-2409 plus prodrug (valacyclovir or acyclovir) added to standard of care immune checkpoint inhibitor (ICI) therapy will be safe and improve the outcome for subjects with NSCLC who have stable disease or radiographic progression after at least 18 weeks of ICI therapy.

2. BACKGROUND AND RATIONALE

2.1. Introduction

Immune checkpoint inhibitors (ICI) such as anti-PD1 and anti-PD-L1 antibodies have led to significant improvements in outcome for NSCLC patients as well as multiple other tumor types. However, only ~30-40% of patients respond. Tumors that have a low lymphocytic infiltrate and low or no PD-L1 expression ("cold tumors") are least responsive. CAN-2409 is an oncolytic viral immunotherapy that induces tumor-infiltrating T-cells and a consequent PD-L1 up- regulation. Thus, a combination of CAN-2409 added to standard of care (SOC) checkpoint inhibitors may lead to improved long-term outcomes for patients with NSCLC who have suboptimal response to ICI therapy.

This approach (formerly known as gene mediated cytotoxic immunotherapy, or GMCI) kills tumor cells and elicits a patient-specific polyvalent immune response by delivering the immune stimulating molecules to the tumor, converting 'cold' tumor microenvironments into immune-active or 'hot' microenvironments (Aguilar 2011). CAN-2409 (aglatimagene besadenovec) is a genetically modified replication-defective adenoviral vector expressing the herpes simplex virus (HSV) thymidine kinase (tk) gene. CAN-2409 is injected into the tumor site and is given in conjunction with a prodrug such as valacyclovir or acyclovir (hereafter referred to as 'CAN-2409 + prodrug'), leading to local production of nucleotide analogs that result in the death of dividing cancer cells and the consequent release of tumor neoantigens within the tumor microenvironment. The adenoviral serotype 5 capsid protein also creates the optimal conditions for vaccination against the variety of cancer neoantigens that are released in the tissue through induction of pro-inflammatory cytokines, chemokines, adhesion molecules, and other mediators of inflammation. Preclinical studies confirm that CAN-2409 + prodrug provides CD8 T cell- dependent protection against tumor re-challenge and metastases. Safety and potential efficacy have been demonstrated in multiple clinical trials in different tumor types, including NSCLC (Aggarwal 2018; Teh 2004; Wheeler 2016). A phase 3 clinical trial is ongoing in prostate cancer.

A phase 1 study in malignant pleural effusion demonstrated safety of high dose CAN-2409 delivery to the pleural space and 3 of 4 patients with stage IV NSCLC lived more than 2 years (Aggarwal 2018). A completed phase 1 dose-escalation study evaluated intratumoral delivery of CAN-2409 performed by endobronchial ultrasound (n=11) or mediastinoscopy (n=1) during the diagnostic staging procedure 3 weeks prior to surgery in resectable NSCLC. Three dose levels were evaluated: $2.5x\ 10^{11}$ (n=3), $5x10^{11}$ (n=3) and $1x10^{12}$ vector particles (n=6). There was no dose limiting toxicity or any treatment-related serious adverse events. The only treatment-related adverse events were transient and grade 1: one patient had a grade 1 fever, one had grade 1 flu-

like symptoms and a third patient had grade 1 nausea, vomiting and diarrhea. The only greater than grade 2 laboratory abnormalities after CAN-2409 + prodrug and prior to surgery were observed in 2 patients with grade 3 lymphopenia. Consistent with results in preclinical studies, CAN-2409 treatment induced an activated CD8 T cell response in the tumor at the site of the injection associated with activation of CD8 T cells in the peripheral blood. Similarly, immune stimulation after CAN-2409 + prodrug treatment has been observed in proof of mechanism clinical trials in patients with prostate cancer, high-grade glioma, and pancreatic cancer (Aguilar 2015; Chiocca 2011; Miles 2001; Rojas-Martínez 2013). In patients with pancreatic adenocarcinoma, CD8 T cell infiltration was significantly increased (on average 22-fold) in treated tumors compared to baseline (p=0.0021) with a concomitant increase in PD-L1 (Aguilar 2015). The rationale for adding CAN-2409 + prodrug to ICI treatment in patients with NSCLC who exhibit an inadequate response to ICI alone is supported by 1) data showing that clinical benefit of ICI is better in PD-L1 positive patients and 2) preclinical data showing that CAN-2409+ prodrug treatment can induce a specific CD8 T cell response against the injected tumor and uninjected metastases, while ICI treatment alone will merely lead to non-specific T cell activation (Mok 2019; Socinski 2018; Speranza 2018). Accordingly, preclinical studies in a mouse model of high-grade glioma support the potential benefit of combining CAN-2409 + prodrug with anti-PD-1 treatment (Speranza 2018). Thus, the combination of CAN-2409 + prodrug and ICI could improve the response rate and long-term benefit for NSCLC patients.

2.2. NSCLC Current Standard of Care and Outcomes

Survival outcomes for advanced NSCLC have been significantly improved with the addition of ICI treatment, and ICIs have become standard of care, either alone or in combination with chemotherapy in the first line treatment of NSCLC in patients without driver mutations of epidermal growth factor (EGFR) or anaplastic lymphoma kinase (ALK) (Reck 2022).

As a monotherapy, pembrolizumab is approved for nonsquamous or squamous NSCLC expressing PD-L1 (tumor proportion score, TPS, ≥1%) that is negative for EGFR or ALK genomic tumor aberrations and is stage III without being a candidate for surgical resection or definitive chemoradiation or is metastatic. Long-term follow up for KEYNOTE-001, a phase 1 clinical trial that included 101 treatment-naïve patients with PD-L1 TPS ≥1%, demonstrated 5- year survival of 23.2%, which is significantly better than the expected 5.5% before ICI, but it still leaves much room for improvement (Garon 2019). Increasing the response rate and duration of ICI treatment could potentially increase the number of patients that will benefit and may improve overall clinical outcomes for NSCLC patients.

For patients with lower or no PD-L1 expression or patients with faster growing disease that may require chemotherapy, ICIs are used in combination with chemotherapy as first-line treatment for metastatic NSCLC. For metastatic nonsquamous disease, pembrolizumab is approved in combination with platinum/pemetrexed chemotherapy based on a 12-month OS rate of 69.2% for the combination versus 49.4% with chemotherapy alone, and median PFS of 8.8 months versus 4.9 months (Gandhi 2018). A greater relative benefit was seen in patients with PD-L1 TPS ≥ 50%. For metastatic squamous NSCLC, pembrolizumab is approved in combination with carboplatin

and either paclitaxel or nab-paclitaxel based on a 4.6 months improvement in median OS from 11.3 months with chemotherapy alone to 15.9 months with the addition of pembrolizumab (Paz-Ares 2018). The median PFS increased from 4.8 months to 6.4 months.

Two ICIs that bind to PD-L1, atezolizumab and durvalumab, are also approved for treatment of NSCLC. Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel (BCP) demonstrated an improvement compared to BCP alone in median PFS (8.3 vs 6.8 months, HR 0.62) and OS (19.2 vs 14.7 months, HR 0.78) in metastatic nonsquamous NSCLC with a wild-type genotype, including patients with low or negative PD-L1 expression (Socinski 2018). The PFS was also improved with atezolizumab when the entire intent to treat population was evaluated, including patients with an EGFR or ALK genetic alteration. Subset analyses revealed the atezolizumab benefit in both PFS and response rate was greater in tumors with higher PD-L1 expression. In the 49% of tumors that were PD-L1 negative, PFS was only 7.1 months with atezolizumab vs 6.9 months with BCP alone (Socinski 2018). The benefit was also primarily seen in the 43% of tumors with high messenger RNA expression of an effector T-cell gene signature based on PD-L1, CXCL9 and IFN-gamma expression (Socinski 2018). Still, most patients do not benefit from the addition of atezolizumab because they have immunologically cold tumors and potentially also because the T cells have not been educated how to recognize the patient's specific cancer neoantigens. Atezolizumab has been approved by the FDA as a single agent for metastatic NSCLC with PD-L1 staining on at least 50% of tumor cells or PD-L1 staining of tumor-infiltrating immune cells covering at least 10% of the tumor area and no EGFR or ALK genomic tumor aberrations.

Durvalumab is also approved for advanced NSCLC. For stage III unresectable disease, the standard initial treatment is platinum-based doublet chemotherapy in combination with radiation therapy (concurrent chemoradiation). For patients without disease progression after chemoradiation, treatment with durvalumab significantly prolonged PFS (17.2 months versus 5.6 months) and 2-year OS was 66.3% compared to 55.6% in the placebo group (Antonia 2018; Antonia 2017). The response rate to durvalumab was 30%, compared to 17.8% in the placebo group, suggesting that responses to chemoradiation were still ongoing at the time of enrollment. In subgroup post-hoc analysis, patients with higher PD-L1 expression level at baseline before chemoradiation had a better hazard ratio for PFS and OS than subgroups with lower or no PD-L1 expression (Antonia 2018).

2.3. Data Supporting the combination of CAN-2409 + prodrug and anti-pd-1 therapies

2.3.1. Local and Systemic Immune-Mediated Anti-Tumor Effects of CAN-2409 + Prodrug

In contrast to ICIs, which induce non-specific T cell activation, CAN-2409 + prodrug leads to in situ vaccination against the patient's cancer neoantigens, resulting in infiltration, proliferation, and activation of cytotoxic CD8 T cells at the site of the tumor as well as increased levels of circulating CD8 granzyme B+ T cells and increased levels of soluble granzymes (Aggarwal 2022). Among

other immunological effects, CAN-2409 + prodrug treatment may also induce increased expression of PD-L1 in the tumor microenvironment (Aguilar 2015; Speranza 2018). ICIs have shown better responses and long-term benefit in PD-L1 positive and T cell effector gene signature high tumors. Thus, the combination of CAN-2409 + prodrug and ICI may improve the response rate and lead to improved long-term outcomes.

Local and systemic immune-mediated anti-tumor activity of CAN-2409 + prodrug, and consequent increased survival has been demonstrated consistently in subcutaneous and orthotopic tumor models for many different cancer types including lung (Eastham 1996; Hall 1997; Predina 2011). The immune-mediated activity of CAN-2409 has been demonstrated through many different types of experiments, providing evidence of systemic activity against peripheral metastasis, increased survival in treated animals and in protection against tumor re- challenge compared to controls (AdV-beta-gal vector/GCV or AdV-tk/PBS) (Hall 1997). The distant effects against metastasis were observed in immune-competent but not in immune-deficient mice. In addition, tumors from treated mice consistently showed a marked infiltration of lymphocytes not seen in control mice. Winn assays demonstrated that CD8 T cells from CAN-2409 + prodrug treated, but not control treated mice, inhibited tumor growth in tumor-naïve mice (Predina 2011; Predina 2012). Altogether, these data demonstrate that the systemic anti-tumor effect of CAN-2409 + prodrug is immune-mediated.

CAN-2409 + prodrug has shown synergy with standard cancer treatment modalities, including radiation, surgery and some chemotherapies, without overlapping toxicity (Chhikara 2001; Fridlender 2010; Predina 2011; Predina 2012; Rainov 2001; Sukin 2001; Vlachaki 2001). The synergy has also been shown to be immune-mediated, such as in a lung tumor model, where the effect was shown to be CD8 T cell dependent (Predina 2012). Debulking therapies such as surgery, radiation and chemotherapy have been shown to reduce immune inhibitory factors, such as systemic myeloid derived suppressor cells (MDSCs) and regulatory T cells (T-reg); this may be part of the mechanism behind the synergistic effects.

Initial proof of mechanism has been shown consistently in a variety of rodent models and also across multiple solid tumors in humans, including patients with NSCLC, pancreatic cancer, high-grade glioma, and prostate cancer (Aggarwal 2022; Aguilar 2015; Chiocca 2011; Teh 2004; Trask 2000; Wheeler 2016). Further details are provided in the Investigator's Brochure (IB).

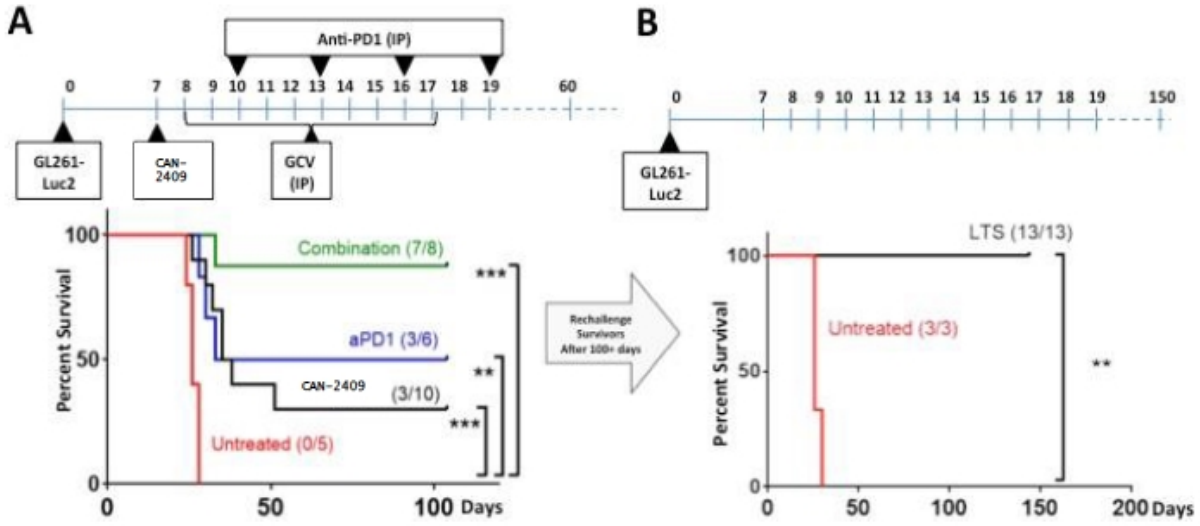
2.3.2. Preclinical Studies of CAN-2409 + Prodrug and Anti-PD1 Combination

The combination of CAN-2409 + prodrug with anti-PD1 has been evaluated in orthotopic mouse models of glioma (Speranza 2018). In the C57/BL6 GL261luc model, mice were treated with PBS control, CAN-2409 + prodrug alone, anti-mouse PD-1 alone, or the combination of CAN- 2409 + prodrug and anti-PD-1. In a representative experiment, all PBS-treated mice were dead by day 45. In the single agent treated animals, 50% (3/6) of mice treated with anti-PD-1 and 30% (3/10) treated with CAN-2409 + prodrug were alive beyond day 100. In the combination treated animals, 87% (7/8) were alive beyond day 100. Repeated studies have given similar results, with the combination consistently yielding a much higher percentage of long-term responders. These data indicate that both CAN-2409 + prodrug and anti-PD-1 treatments are effective in a subset of animals and that

the combination increased the response rate. Responses were durable with the survival curves reaching a plateau early and maintained long-term, which is qualitatively similar to clinical outcomes observed in humans with ICI.

To test whether a persistent anti-tumor immune response had been generated during the treatment phase, re-challenge experiments were performed (Speranza 2018). The mice that had long-term durable responses (alive at day >100 after tumor implantation) were re-challenged with the same tumor cells (GL261luc). Age-matched tumor naïve control mice were challenged in parallel with the same cells. Tumors were confirmed post-implantation in all mice via bioluminescent imaging (BLI). There was no treatment (anti-PD1 or CAN-2409 + prodrug) provided during this re-challenge experiment. As in the original experiment, tumor challenge in the brain of the naive control mice resulted in 100% deaths, while 100% (13/13) of the re- challenged Long Term Survivors (LTS), survived for greater than 150 days after the second tumor cell injection with no evidence of tumor growth by BLI or physical characteristics. These data indicate a persistent anti-tumor response was generated in mice responding to the initial immunotherapy.

Figure 3 Survival benefit from the combination of CAN-2409 + prodrug + anti-PD1 in an intracranial murine glioma model



(A) GL261luc cells ($1x10^4$) were implanted intra-cranially into mice at day 0. Tumor-bearing mice were randomized and received either: PBS, anti-PD1 (200µg IP each on days 10,13,16,19); CAN-2409 + prodrug ($5x10^9$ vp intra-tumoral CAN-2409 on day 7 plus GCV 20mg/kg IP b.i.d. x 10 days); or GMCI+anti-PD1. Tumors were verified by bioluminescent imaging before randomization. Survival for all control mice receiving saline injections (PBS) was less than 45 days. The group receiving CAN-2409 + prodrug+anti-PD1 had improved overall survival relative to either agent alone, with durable responses observed in all groups.
(B) The mice that survived for greater than 100 days in the initial study were subjected to re-challenge by intracranial implantation of GL-261luc cells ($1x10^4$). A control group of age matched tumor naïve C57BL6 mice received GL261luc implants in parallel. No treatment (anti-PD1 or CAN-2409 + prodrug) was provided during the re- challenge study.

2.3.3. Enhancement of PD-L1 Expression by CAN-2409 + Prodrug

Expression of PD-L1, the ligand to PD-1, is often enhanced in response to immune stimulation and inflammation. CAN-2409 + prodrug has been shown to induce immune activation with a

consequent increase in PD-L1 in both pre-clinical and clinical studies. The impact of CAN-2409+ prodrug mediated induction of tissue PD-L1 expression levels was analyzed in detail in a preclinical model of malignant glioma (Speranza 2018). Staining to detect PD-L1 on intracranial GL261luc tumors after treatment revealed an increase in PD-L1 expression on tumor cells compared to controls. Immune cell infiltrates in the brains of mice containing GL261luc tumors after treatment (CAN-2409 + prodrug, anti-PD-1, or combination) were compared to mice receiving saline (PBS). There was a marked increase in $CD3^+$ tumor-infiltrating lymphocytes (TILs) and CD8 TILs in brains from anti-PD-1, CAN-2409 + prodrug, and CAN-2409 + prodrug/anti-PD1 treated mice, respectively. A similar trend was observed with increases in the percentage of granzyme B + CD8 TILs, indicating the presence of activated cytotoxic lymphocytes. There was also a highly significant increase in the percent of TILs that were $IFN\gamma^+$ in brains of CAN-2409 + prodrug treated and combination treated mice, providing further evidence of tumor infiltration by activated cytotoxic TILs. These data provide strong justification for combining immune checkpoint inhibition with CAN-2409 + prodrug immuno-stimulation.

2.3.4. Clinical Data Supporting the Combination of CAN-2409 + Prodrug and Anti-PD-1 Antibodies

Characterization of the immune response to CAN-2409 + prodrug in multiple human tumors is ongoing and has been consistent that observed in pre-clinical models (Aguilar 2015; Chiocca 2011; Miles 2001). In a phase 1 pancreatic cancer clinical trial, where CAN-2409 + prodrug was used as an adjuvant to surgery for resectable disease, immune infiltrate and PD-L1 expression levels were analyzed in pre-treatment biopsy samples and post-resection tumor tissue (Aguilar 2015). In this study, a >21-fold average increase of CD8 TILs was observed. In addition, consistent with a pro-inflammatory response an increase in PD-L1 expression levels was also observed post- CAN-2409+ prodrug treatment in 71% (5/7) patients analyzed. In a previous proof of mechanism clinical trial in patients with resectable NSCLC, a significant increase in intratumoral activated CD8 T cells and increased PD-L1 expression was demonstrated with a concomitant increase in activated CD8 T cells in the peripheral blood (Predina 2021).

2.3.5. Clinical Experience with CAN-2409 + Prodrug Across Solid Tumors

CAN-2409 + prodrug has been extensively evaluated in clinical trials for multiple solid tumors, with over 16 clinical studies completed or ongoing, including in prostate cancer, high-grade glioma, ovarian cancer, mesothelioma, pancreatic cancer and NSCLC (Aggarwal 2018; Aguilar 2015; Ayala 2006; Chiocca 2011; Miles 2001; Rojas-Martínez 2013; Sterman 2005; Trask 2000; Van-der-Linden 2005; Wheeler 2016). Overall CAN-2409 + prodrug has been well tolerated with more than 2000 doses delivered to more than 950 patients. Consistent encouraging responses across multiple trials and a positive phase 2 clinical trial in newly diagnosed localized prostate cancer receiving RT led to the launch of a phase 3 randomized controlled clinical trial, which is currently ongoing. A phase 1 clinical trial in malignant pleural effusion demonstrated safety of high dose CAN-2409 delivery to the pleural space and 3 of 4 patients with stage IV NSCLC lived more than 2 years (Aggarwal 2018). A completed phase 1 dose-escalation clinical trial of intratumoral delivery of CAN-2409 in resectable NSCLC has demonstrated safety and immune

stimulation with up-regulation of inhibitory receptors including PD-1. Preliminary results in the first 20 evaluable patients in the current clinical trial in stage III/IV NSCLC support initial safety and show disease stabilization in most patients entering the trial with progressive disease (Aggarwal 2022).

2.3.6. Clinical Experience with CAN-2409 + Prodrug in NSCLC

An interim analysis of the current phase 2 trial was performed with data cutoff as of October 21, 2022. A total of 52 patients with NSCLC presenting with inadequate response to ICI received at least one dose of CAN-2409 were included in the safety population of the interim analysis. Overall, CAN-2409 + prodrug in combination with ICI, with or without chemotherapy, has been well tolerated (Table 4). There have been five grade 3 TRAEs occurring in four patients attributed to either CAN-2409 or prodrug, including single occurrences of pyrexia, empyema, lymphocyte count decreased, platelet count decreased and pneumonitis. No grade 4 or grade 5 TRAEs or DLTs have been reported.

Table 4 Treatment-Related Adverse Events Reported in ≥5% of patients

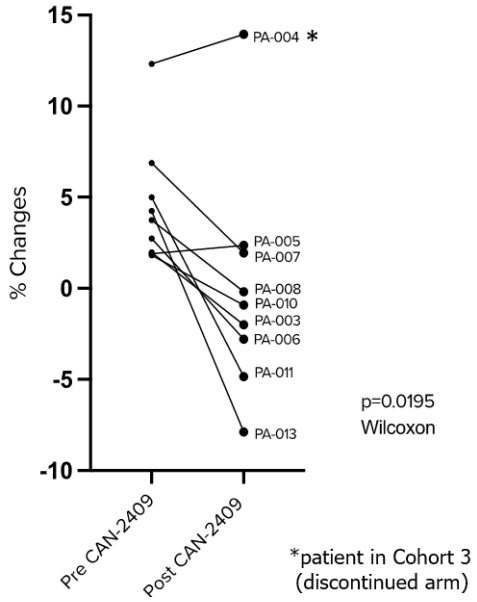
SOC/Adverse Event (≥5%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total (n=52)
Gastrointestinal disorders					
Constipation	2 (4)	1 (2)			3 (6)
Nausea	7 (13)				7 (13)
Vomiting	3 (6)				3 (6)
General disorders and administration site conditions					
Chills	3 (6)				3 (6)
Fatigue	11 (21)	3 (6)			14 (27)
Pyrexia	7 (13)		1 (2)		8 (15)
Investigations					
Alanine aminotransferase increased	3 (6)				3 (6)
Aspartate aminotransferase increased	3 (6)				3 (6)
Blood creatinine increased	5 (12)	1 (2)			6 (12)
Musculoskeletal and connective tissue disorders					
Muscular weakness	2 (4)	1 (2)			3 (6)
Respiratory, thoracic and mediastinal disorders					
Cough	2 (4)	1 (2)			3 (6)
Dyspnea	2 (4)	3 (6)			5 (10)

Patients who completed both courses of treatment and immunotherapy and had RECIST determination at week 12 were included in the efficacy evaluable population. Patients underwent CT scan and evaluation by RECIST 1.1 by a blinded independent central review at approximately week 6, week 12 and every 9 weeks thereafter.

In the efficacy evaluable population across cohorts 1 and 2 (n=30), clinical evidence of response to CAN-2409 was evident. Patients in cohort 1 (n=4 with stable disease at entry) presented an objective response rate (ORR) of 25% with a duration of response (DOR) of 4.1 months (ongoing at time of data cutoff) and a duration of stable disease (SD) of 1.4 (ongoing) to 6.2 months. Patients in cohort 2 (n=26 with progressive disease at study entry) had an ORR of 3/26 (12%) and a disease control rate (DCR) of 77%, DOR of 2.8 to 14.2+ months and SD duration of 1.4+ to 11.6 months.

In a subset of patients (n=9) for whom pre-trial CT scans were available, favorable changes in the tumor size trajectory upon study treatment were observed, with a statistically significant decrease (p=0.0195 Wilcoxon signed-rank test) in the linear tumor growth rate pre-study compared to post-treatment with CAN-2409 + prodrug (Figure 4).

Figure 4 Change in Tumor Growth Rate Pre-Study Compared to Post-CAN-2409



In the evaluable population there is also evidence of abscopal effect (decreased size of non-injected lesions, including in both RECIST target and non-target lesions). Twenty-one patients who had one or more non-injected lesion(s) thus could be evaluated for abscopal response and were included in this analysis. Of these, 17/21 patients (81%) had a decrease in the size of non-injected lesions. In 14/21 patients (66.7%) this decrease was ≥5% of the lesion size, and in 13/21 patients (61.9%) the decrease was ≥10%. These data suggest that a local intratumoral injection produces systemic anti-tumor activity demonstrated by decreased size of non-injected lesions. Abscopal response was observed in patients injected in either lymph nodes and/or lung lesions, suggesting that systemic anti-tumor activity is generated irrespective of lesion site injected.

Notably, in 5 evaluable patients there were transient increases in injected lesion size post-CAN-2409, followed by decrease in injected lesion size. This was observed in a window of time up to 4 weeks post-CAN-2409 injection, consistent with the possibility of pseudoprogression, where there is transient enlargement of lesions due to inflammation followed by demonstrable tumor shrinkage.

A preliminary estimate of median progression free survival (mPFS) in evaluable patients who received both courses of CAN-2409 + prodrug and completed the 12-week treatment window was encouraging relative to historical data. For evaluable patients in cohort 2 (n=26), mPFS was 8.1 months, and for evaluable patients in cohort 1 (n=4) the mPFS was 11.0 months. Across the two cohorts, 14/30 (47%) patients were censored (ongoing SD, PR) at time of data cutoff. Although preliminary, the durable disease stabilization observed in many patients may translate into a promising PFS.

Biomarker analysis on available samples from patients completing the 12-week treatment course show expansion of activated cytotoxic granzyme B+ CD8 T cells in the tumor microenvironment and in peripheral blood following CAN-2409 + prodrug treatment. In tissue, decreases in tumor cells and increase in immune cells in post-treatment samples were observed. Interestingly, in post-treatment samples, the CD8+ T cells were found to be in closer proximity to the cancer cells, suggesting the ability of CAN-2409 + prodrug not only to increase the number of cytotoxic cells, but also to support their antitumoral effect by enabling their migration close to the cancer cells (Aggarwal 2022).

In longitudinal peripheral blood samples, post-treatment increases in CD8+granzyme + T cells, Ki67+ (actively proliferating) CD8+ cells, CD4+ and CD8+ IFNγ producing T cells were observed. Proteomic analysis also demonstrated increases in soluble granzymes (A, B and H). The post-treatment increases in cytotoxic and effector T cells described above were transient, with peaks generally observed approximately 2 weeks post-CAN-2409 treatment, with a subsequent decrease that returned to baseline values by 4 to 6 weeks after the last CAN-2409 treatment. A similar trend was observed in soluble granzymes. Importantly, the increases observed after the second CAN-2409 injection appear to be larger than the first, suggesting an additive or synergistic effect of the repeated treatment. Collectively, these data suggest that treatment with CAN-2409 + prodrug can elicit a strong biological effect both at the site of injected tumor and in the periphery, resulting in control of tumor growth of primary and metastatic lesions that translate into meaningful progression free survival.

While these data are encouraging, we also observed a subset of seven patients in cohort 2 with rapid disease progression such that they withdrew from the study due to progressive disease prior to week 12. In six of the seven patients, early progression occurred such that they did not receive their 2nd CAN-2409 injection. Also considering the timing of post-treatment immunologic effects described previously, these observations suggest that shortening the timeframe between injections and adding a third injection to the regimen (as per the PrTK03 study of CAN-2409 plus prodrug in patients with localized prostate cancer) could improve responses further, especially for patients who, in the absence of intervention, may have rapidly progressing disease.

Based on these considerations, we propose to test the effect of three courses CAN-2409 plus prodrug in a new group of patients with progressive disease on ICIs (cohort 2B) with a shorter time between CAN-2409 injections. Specifically, the 3 injections of CAN-2409 will be administered Week 1, Week 5, and Week 9, thus reducing the time between injection to 4 weeks (the period in which we have observed the peak of the inflammatory response). Following baseline (pre-study) RECIST, the first protocol mandated RECIST evaluation will occur at week 14 to minimize the possibility to assess the patient in a phase of pseudoprogression. We believe that this new regimen will increase the proportion of patients able to receive a complete treatment regimen, ultimately improving the number of responses.

For new patients eligible for cohort 1 (i.e., stable disease on ICI at time of trial entry), the same Q4 week injection schedule will be implemented (cohort 1B) to align with the approach used in cohort 2B. Given that these patients enter the study with stable disease on ICI, administration of the third injection will be optional and associated with separate patient consent. Upon activation of Amendment 6 at each site, cohorts 1A and 2A (formerly 'cohort 1' and 'cohort 2') will be closed to new enrolment, and eligible patients will be enrolled to cohorts 1B and 2B. Patients in the 12-week treatment enrolled in cohorts 1A and 2A will be followed up as for original protocol with no changes to their treatment regimen.

2.4. CURRENT CLINICAL TRIAL

Collectively, data collected to date provide a strong rationale for the addition of the immunostimulatory CAN-2409 + prodrug to a PD-1/PD-L1 checkpoint inhibitory molecule in the treatment of NSCLC. This clinical trial evaluates the effects of adding CAN-2409 + prodrug for stage III/IV NSCLC patients who are on standard of care first line ICI treatment (for current stage of disease) with evidence that the clinical response is inadequate. The goal of this study is to evaluate the hypothesis that repeated injections of CAN- 2409 + prodrug can increase the percentage of patients that respond to continued ICI treatment.

Prior to version 6 of this protocol, we evaluated the efficacy and safety of 2 courses of CAN-2409 plus prodrug. As of version 6, we aim to explore the use of 3 courses of CAN-2409 + prodrug, separated by 4 weeks between each CAN-2409 injection.

To provide nomenclature that distinguishes the 2 and 3 course regimens, patients enrolled to a 2-course regimen in Cohorts 1 and 2 will hereafter be referred to as cohort 1A and cohort 2A, respectively, and patients enrolled into the 3-course regimen are designated cohort 1B and cohort 2B, respectively.

Patients are to continue their SOC ICI therapy, which may include ongoing maintenance chemotherapy (e.g., pemetrexed) as clinically indicated.

The entry criteria for randomization to the respective cohort and determination of inadequate ICI response are as follows:

- Cohort 1A and 1B: patients with stable disease radiographically at least 18 weeks after starting ICI treatment and who are clinically stable.

- Cohort 2A and 2B: patients with evidence of radiographic progression at least 18 weeks after starting ICI treatment but who are clinically stable.
- Cohort 3, which is now closed for recruitment, enrolled patients who had new lesions or progression of existing lesions at least 9 weeks after starting ICI but who were clinically stable.

Additionally, as of Version 7, eligible patients from the main study may be enrolled into a substudy evaluating a booster dose as described in Appendix 1.

3. OBJECTIVES

Overall, the objectives for this phase 2 clinical trial are to evaluate safety and clinical and immunological response to two courses of CAN-2409 + prodrug in combination with ICI with or without standard of care chemotherapy.

3.1. Endpoints

3.1.1. Primary efficacy endpoint

- Response by RECIST 1.1 criteria (Eisenhauer 2009) including overall response rate (ORR) and/or disease control rate (DCR)

3.1.2. Primary safety endpoint

- Safety based on standard laboratory and clinical adverse event monitoring

3.1.3. Secondary endpoints

- Duration of Response
- Overall survival
- Progression Free Survival
- Biomarker studies
- Quality of Life, measured by the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) v.1.0
- Tumor Response and Progression Free Survival by iRECIST criteria (Seymour 2017)

3.1.4. Exploratory endpoints

- Tumor Response and Progression Free Survival by itRECIST criteria (Goldmacher 2020)
- Evaluation of abscopal effect, as data allows
- Changes in non-target lesions, as data allows
- Tumor growth trajectory
- Viral shedding studies
- Quality of life specific to patient's experience of study specific procedures
- Molecular markers of tumor growth, which may include ctDNA

4. SUBJECT POPULATION

4.1. Inclusion Criteria

1. Patients with Stage III/IV* NSCLC on first line treatment with anti-PD-1/PD-L1 (ICI) +/- chemotherapy for their current stage* of disease and fits into one of the following cohorts as determined by the investigator, preferably as per RECIST 1.1:
   a. Cohort 1: must have persistent but stable disease at least 18 weeks after starting ICI treatment, or
   b. Cohort 2: must have radiographic progressive disease at least 18 weeks after starting ICI treatment

   **Patients with stage IV disease may have previously received ICI in a neoadjuvant, adjuvant, or consolidation (e.g., definitive intent) setting for a prior stage of disease provided the following conditions are met:*
   - *They must not have had disease progression during the definitive intent setting.*
   - *At least 6 months must have elapsed between completion of ICI and initiation of ICI for stage IV disease*
2. RECIST evaluable disease including a lesion that is amenable to injection
3. Able and willing to undergo a pre-treatment and on-treatment biopsies, if feasible
4. ECOG Performance status of 0 or 1
5. 18 years of age or older
6. Granulocyte count (ANC) $\geq$ 1,000/mm^3
7. Hemoglobin $\geq$ 8 g/dl (patients may be transfused to meet this criterion)
8. Platelets $\geq$ 75,000/mm^3
9. Total bilirubin $\leq$ 1.5 x upper limit of normal, except for patients with known Gilbert disease who must have total bilirubin $\leq$ 3 x upper limit of normal
10. SGOT (AST) $\leq$ 5x upper limit of normal and if elevated, not clinically significant such that ICI can continue
11. INR no more than 0.2 above upper limit of normal and aPTT not > 1.2 x upper limit of normal, and value is acceptable for patient to undergo injection procedure. If on anti-coagulation, it must be clinically acceptable to hold anti-coagulation for the injection procedures per investigator discretion
12. Serum creatinine < 2mg/dl and calculated creatinine clearance > 30ml/min

    Cr clearance formula = [(140 – age in yr) x (weight in kg)] ÷ [72 x serum Cr in mg/dL]
    multiply answer by 0.85 for women
13. Clinically stable and expected to be able to continue ICI for at least the 14-week treatment period
14. Within 6 months of enrollment, no change of ICI therapy or prior interruptions of more than 4 weeks of current ICI
15. Patients should not have received focal therapy (e.g., radiotherapy) at more than three different sites of disease within 12-months prior to enrollment
16. Patients must give study specific informed consent prior to enrollment and any study specific procedures

4.2. Exclusion Criteria

1. Patients with a history of severe immune related adverse events related to ICI
2. Patients who require ongoing therapy with disease-modifying antirheumatic drugs (DMARDs), immunomodulators, or systemic immunosuppressive drugs including systemic corticosteroids (>10 mg prednisone per day or equivalent). Premedication for ICI or chemotherapy is allowed
3. Patients with a history of active autoimmune disease requiring treatment in the past 2 years
4. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active hepatitis, or psychiatric illness/social situations that would limit compliance with study requirements
5. Women who are pregnant, lactating or intend to become pregnant during the study
6. Patients who are known to be HIV positive
7. Patients with a history of hypersensitivity or allergic reactions to valacyclovir or acyclovir
8. Patients with significant heart disease (New York Heart Association Functional Classification III or IV)
9. Patients with continuous oxygen dependence >2L/min at rest.
10. Tumor impinging on a neurovascular structure such that inflammation in the site may put patient at risk of compromise as determined by the investigator
11. Patients with uncontrolled brain metastases as per investigator
12. Patients with liver metastases involving more than half of the liver
13. Patients with known EGFR mutation, ALK fusion, or ROS1 fusion positive NSCLC, or that are receiving tyrosine kinase inhibitor (TKI) agents/ALK/ROS1 inhibitors
14. Patients with known interstitial lung diseases (ILDs) requiring active therapy (Radiographic fibrosis not requiring therapy is allowed)
15. Patients receiving vascular endothelial growth factor (VEGF) inhibitors (including bevacizumab, ramucirumab) within the past 2 months or five half-lives, whichever is longer
16. Patients must have no concurrent malignancy requiring treatment (except squamous or basal cell skin cancers)
17. Patients without contrast enhanced imaging at baseline or those with a known sensitivity or contraindication to the use of contrast.
18. Patients who are pregnant, breastfeeding, or plan to become pregnant.

4.3. Subsets

The following will be determined for each subject by the investigator and recorded on the relevant CRFs.

- Histology (e.g. nonsquamous, squamous)
- Standard of care ICI regimen (e.g., pembrolizumab, pembrolizumab plus chemotherapy, durvalumab, etc.)
- Initial responder vs never responder- only applies to patients with progressive disease at trial entry (cohort 2A and 2B)

- Site of injection for each injection: lung nodule, lymph node disease or peripheral metastasis and whether injections are into the same or different lesions
- Smoking history
- Molecular characteristics including, but not limited to: PD-L1 expression at baseline, mutation status, tumor mutational burden

5. PRETREATMENT EVALUATIONS & REGISTRATION

5.1. Baseline Evaluations

Required evaluations are listed in the time and event table at the beginning of the protocol (Table 1, Table 2, Table 3). Data for additional standard of care evaluations such as to support eligibility criteria and cohort/subset assignment will be collected. Data collected will include pre-baseline imaging (CT scans) for the 12-month period preceding the baseline visit, up to a maximum of 4 scans.

5.2. Registration Procedures

Clinical site personnel will obtain informed consent, determine eligibility of prospective subjects and complete an Eligibility Checklist (form EC). The completed form EC, copies of pre-registration evaluation reports and signed informed consent form will be submitted to the Sponsor. The Sponsor will communicate determination of eligibility to the clinical site.

6. TREATMENT PLAN

6.1. Overview

The investigational products are CAN-2409 and prodrug (valacyclovir or acyclovir). For treatment schedule, see schemas (Figure 1 and Figure 2) and time and event tables (Table 1, Table 2 and Table 3) at the beginning of the protocol.

6.1.1. CAN-2409 + prodrug schedule

Study treatment includes CAN-2409 injection into target lesion followed by prodrug (oral valacyclovir) for 14 days, starting 1 day after each CAN-2409 injection. For subjects unable to take oral medication, intravenous (IV) acyclovir may be given (Section 6.4).

Patients in cohort 1A, 2A, and 3 receive two courses of CAN-2409 + prodrug:

CAN-2409 1st injection: on day 1 of protocol (week 1)

CAN-2409 2nd injection: 5-7 weeks after the first injection (week 6-8)

Prodrug: Starts 1 day after each CAN-2409 injection and is administered for 14 days

Patients in cohort 1B* and 2B will receive 3 injections of CAN-2409 plus prodrug:

CAN-2409 1st injection: on day 1 of protocol (week 1)

CAN-2409 2nd injection: 4 weeks after the first injection (week 5)

CAN-2409 3rd injection*: 4 weeks after the 2nd injection (week 9)

Prodrug: Starts 1 day after each CAN-2409 injection and is administered for 14 days

**the 3rd injection is optional for patients in cohort 1A and associated with separate consent.*

6.1.2. Criteria for continuing treatment

6.1.2.1. Criteria for CAN-2409 injections

- ANC≥1,000/mm^3
- Platelets >50,000/mm^3
- INR/aPTT within normal limits or acceptable per investigator discretion for the injection procedure to proceed
- Calculated creatinine clearance ≥ 10 ml/min (see creatinine clearance formula in inclusion criterion #12)

6.2. Dose Limiting Toxicity and Stopping Rules

6.2.1. Dose limiting toxicity (DLT) is defined as any of the following study agent related* adverse events:

- Any grade 3 or greater allergic reaction
- Any grade 4 hematologic toxicity persisting for >7 days except lymphopenia
- Any grade 3 hypoxia lasting for 48 hours or any grade 4 hypoxia
- Any other unexpected and possibly related grade 4 non-hematologic (organ) toxicity
- Any other unexpected possibly related grade 3 non-hematologic (organ) toxicity (except fatigue, hiccups, ALT, AST, alkaline phosphatase, bilirubin or creatinine) persisting for >7 days
- Grade 3 or greater febrile neutropenia
- Grade 3 thrombocytopenia with significant bleeding

*Possibly related refers specifically to the investigational agents CAN-2409 + prodrug. Notify Sponsor immediately of any grade 3 or 4 possibly related toxicity. Assessment of toxicity relates to the relative changes from the pre-treatment status. Other anticipated toxic phenomena that are not related to vector transduction of the tumor (such as "expected" adverse events secondary to prodrug administration as described in the package insert for valacyclovir or acyclovir), or complications which can be explained by

the presence of the mass lesion and are compatible with the natural history of malignancy may require cessation of treatment (e.g. cessation of prodrug). Such occurrences would not be considered DLTs.

6.2.2. Stopping Rules

See Section 9.4.

6.3. CAN-2409 ADMINISTRATION

CAN-2409 will be injected into an accessible involved tumor site that may include a lung nodule, lymph node disease or peripheral metastasis. The second or third injection may be in the same or different lesion.

The dose of CAN-2409 is $5x10^{11}$ vector particles (vp) for each course in 1-2 ml depending on size of tumor/ node to be injected.

CAN-2409 accountability is subject to review at on-site monitoring visits or remotely, if clinical sites have electronic systems which allow (e.g. VestigoVerify).

Details for vector (CAN-2409) administration are included in the Pharmacy Manual.

Prior to each CAN-2409 injection, evaluations will be performed as described in the time and event tables (Table 1, Table 2 and Table 3) at the beginning of the protocol. See Section 6.1.2 above for criteria for CAN-2409 injections. If ICI or CAN-2409 injection is delayed due to safety concerns, please notify Candel Therapeutics as soon as possible.

6.3.1. Biopsy prior to intratumoral injection

A biopsy to confirm active tumor and to obtain tissue for immune research studies should be performed if feasible and safe, as determined by the investigator.

6.3.2. Intratumoral injection

For the injection, the needle will be inserted under imaging guidance if appropriate to ascertain that a) it is injected into the tumor, and that b) it is not injected into a blood vessel. In addition, aspiration through the syringe is routinely done to confirm absence of blood. The dose will be divided into up to 4 intratumoral quadrants in a total volume of 1-2 ml (see Pharmacy Manual).

6.4. PRODRUG ADMINISTRATION

The term ‘prodrug’ in this protocol refers to either valacyclovir or acyclovir. Valacyclovir will be used except in cases where the patient is unable to take oral medication.

The dose of valacyclovir is 2 grams by mouth (po) three times per day for 14 days starting 1 day after each CAN-2409 administration. The valacyclovir dose for each course should be adjusted if necessary, according to the calculated creatinine clearance obtained prior to each course as described in Table 5 below. The valacyclovir tablets are scored for ease of dosage adjustment. A valacyclovir administration diary will be used to monitor subject compliance to the treatment plan.

Table 5 Valacyclovir Dosing

Calculated creatinine clearance (ml/min)	Valacyclovir dosage
50 or greater	2 grams po three times a day
25 to less than 50	1.5 grams po three times a day
10 to less than 25	1.5 grams po twice a day
less than 10 or dialysis	Hold valacyclovir

For patients unable to take oral valacyclovir in tablet form, valacyclovir may be crushed and given via a feeding tube. For subjects unable to take oral medication, intravenous (IV) acyclovir at a dose of 10 mg/kg three times per day may be substituted for valacyclovir. The dose interval for acyclovir should be adjusted if the calculated creatinine clearance is less than 50 ml/min as described in Table 6.

Table 6 Acyclovir Dosing

Calculated creatinine clearance (ml/min)	Acyclovir dosage
50 or greater	10 mg/kg IV three times per day
10 to less than 50	10 mg/kg IV twice a day
less than 10 or dialysis	Hold acyclovir

6.5. ADDITIONAL TREATMENT FOR NSCLC

Immune checkpoint inhibitor is to be administered as per standard of care with or without chemotherapy if indicated. During the 12- or 14-week treatment period, subjects are required to receive ICI every 2, 3, 4, or 6 weeks depending on their ICI treatment regimen at study enrollment.

Subjects receiving ICI every 4 weeks may continue to receive ICI every 4 weeks, but should follow the ICI Q2 week sample schedule for evaluations in the time and events table. Subjects receiving ICI every 6 weeks may continue to receive ICI every 6 weeks, but should follow the ICI Q3 sample schedule for evaluations in the time and events tables (Table 1, Table 2 and Table 3).

If clinically indicated for a lesion to be irradiated, please discuss with the Sponsor for consideration of how this will impact RECIST interpretations.

Systemic corticosteroids should be avoided if possible. When clinically necessary, dose and duration should be minimized as much as clinically appropriate due to potential immunosuppressive effects that may impact the efficacy of the immunotherapy.

7. TREATMENT EVALUATION

7.1. Evaluations During and After Treatment

Patients will undergo standard of care and clinically indicated evaluations in addition to any study specific evaluations. Study specific evaluations are in time and event tables at the front of the protocol.

7.2. Additional Research Studies

- A quality of life (QOL) questionnaire (NSCLC-SAQ, v1.0), which may be supplemented by an additional questionnaire to assess the patient's experience of study specific procedures, is to be completed by patients as per time and event tables.
- Samples for shedding analysis will be collected according to the time and events table to monitor the distribution of the viral particles in plasma and oropharyngeal swabs.
- Blood for immune research studies as per time and event tables. When research blood collection falls on the same day as treatment, it should be drawn before the treatment (CAN-2409 injection, ICI treatment, chemotherapy) at each time point.
- Tumor samples from biopsies, if feasible based on safety and accessibility, for immune research studies as per time and event tables.

7.3. Post-progression Follow Up

After confirmed progression such that SOC treatment is being changed, follow up will continue every 6 months for survival, +/- 1 month. This may be done by medical record review, telephone contact or other form of communication with the patient or an outside clinician.

7.4. Toxicity Assessment

Toxicity will be assessed by the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5). Stopping rules for toxicity are described in Section 9.4 .

7.5. CRITERIA FOR EVALUATION

Images will be read both locally and confirmed by a central imaging vendor as described in the imaging charter to minimize bias in the response assessments.

- Response assessed using RECIST v1.1, iRECIST and itRECIST.
- Objective Response Rate (ORR): defined as the proportion of patients who have a partial or complete response by RECIST 1.1.
- Disease Control Rate (DCR): defined as the proportion of patients who have stable disease
- for ≥ 4 weeks, or a partial or complete response by RECIST 1.1.

- Duration of response (DoR): Time from the first CR or PR assessment to the earliest date of disease progression (per RECIST 1.1) or death for patients who achieved confirmed CR or PR after CAN-2409.
- Progression of disease (PD): evidence of radiographic progression and/or clinical deterioration that has led to changing or stopping of SOC treatment regimen. This is determined by the clinical investigator. PD should not be determined during the treatment phase and until 30 days after the last injection due to possible pseudoprogression, unless there is clinical deterioration that requires the patient to stop or change SOC therapy.
- Radiographic progression should not be declared before 30 days from the last CAN-2409 injection due to the potential for pseudoprogression; under these conditions the first opportunity to assess radiographic progression will be the week 12 scan (cohort 1A, 2A, and 3) or the 14 week scan (cohort 1B and 2B). Radiographic PD should be confirmed by scan performed at least 4 weeks later, and if confirmed the date of PD will be back dated to the prior scan showing evidence of progression.
- Overall Survival (OS): defined as time from date of first dose of CAN-2409 to death by any cause (OS-1). An additional OS will be defined as time from ICI treatment initiation to death due to any cause (OS-2).
- Progression-Free Survival (PFS): defined as time from date of first dose of CAN-2409 to post-treatment progression or death by any cause (PFS-1). An additional PFS estimate will be calculated from ICI treatment initiation (PFS-2).
- Best Response: defined as the best overall response recorded from the start of study treatment across all timepoints.

7.6. Off Treatment Criteria

Patients who need to or choose to discontinue treatment will continue follow up for toxicity and disease outcome as per the time and events tables (Table 1, Table 2 and Table 3), unless the patient withdraws consent from further follow up data collection. See Section 9.2 for evaluable status of withdrawn patients.

Reasons for discontinuing treatment include the following:

- Unacceptable toxicity as defined by DLT
- Valacyclovir intolerance
- Patients that have confirmed progression such that their SOC treatment is being changed or being stopped will move into the post-confirmed progression follow up phase of the protocol, as defined in the time and events tables (Table 1, Table 2 and Table 3)
- Investigator withdraws patient from treatment due to clinical judgment, such as due to lack of compliance or decision to change patient to a different SOC treatment
- Termination of study by Sponsor.

8. STUDY AGENTS - DESCRIPTION AND POTENTIAL RISKS

8.1. CAN-2409

8.1.1. Description

CAN-2409 is a replication defective adenoviral vector based on the dl309 serotype 5 virus. The vector has a deletion in the E1 region of the adenoviral genome substituted by a Herpes simplex virus thymidine kinase (HSV-tk) expression cassette. The dl309 backbone also has a deletion in the E3 region substituted by non-coding DNA. This vector is identical to the one used in previous clinical studies. Wild-type adenoviruses are a common human virus often associated with cold-like symptoms. Replication-defective means that the virus has been engineered, by deletion of some of its genes, so that it can replicate only in specialized laboratory cells that can complement the deleted genes. The vector is not infectious (it cannot make more viruses) in cells not engineered to be complementing, such as the target tumor cells. The HSV *tk* gene codes for the Herpes virus TK protein, which is the target of many of the FDA approved anti- herpetic drugs, such as ganciclovir, acyclovir and valacyclovir. CAN-2409 transfers this sensitivity to the target tumor cells.

The vector for this study was prepared for clinical use under current Good Manufacturing Practice (cGMP) conditions for biologics. GMP refers to the Regulations promulgated by the US Food and Drug Administration and other international regulatory bodies to ensure that products are safe, pure, and effective in what they are purported to do. The product was released with a Certificate of Analysis.

8.1.2. Potential Risks

Fever and flu-like symptoms may occur due to the local inflammatory and immune response to CAN-2409. If local inflammation is extensive or infection develops, valacyclovir may be stopped and antibiotics and/or anti-inflammatory therapy given as appropriate. Laboratory abnormalities seen most commonly after CAN-2409 injection are transient AST/ALT elevation and lymphopenia. Thrombocytopenia rarely occurs. For more information, please see the Investigator's Brochure.

8.1.3. Potential Biohazard Exposure to Health-Care Personnel

8.1.3.1. Personnel Involved in Vector Injection

There is a low potential for biohazard exposure to the personnel involved in vector injection. The viral vector is suspended in a small volume (~1-2 ml) of buffer and is contained in a glass vial with rubber stopper. The syringe is loaded from the vial with no vector loss. Intratumoral injection is made and the amount of leakage along the needle track is likely to be very minute. Procedures for handling the vector, vector disposal and accidental spills of the vector are described in the Pharmacy Manual.

8.1.3.2. Post-Procedural

There is a potential that CAN-2409 virus may escape the patient via urine, feces, saliva, mucus, tears or other secretions. Studies in non-human primates and in cotton rats indicate that the potential is low. In a phase I dose escalation study in prostate cancer, vector was detected by PCR in urine samples briefly after treatment. However, all cultures of blood and urine were negative for growth of adenovirus.

8.2. Valacyclovir

8.2.1. Description

Valacyclovir is an FDA-approved antiherpetic formulation for oral administration. Valacyclovir is a valine-ester of acyclovir, which is quickly converted to acyclovir by first pass intestinal and/or hepatic metabolism. Peak plasma valacyclovir concentrations are generally less than 0.5 mcg/ml at all doses. For additional information, please refer to the valacyclovir package insert.

8.2.2. Potential Risks

The most common reported adverse events based on the product label for valacyclovir were nausea in 6-15% of patients, headache in 14-35%, vomiting in 1-6%, dizziness or abdominal pain in 2-11%, arthralgia in 1-6% and depression in 1-7%. Laboratory abnormalities such as abnormal liver function tests were observed in 1-4% of patients while anemia, leukopenia, thrombocytopenia and elevated serum creatinine occurred in 1.8% of patients or less. In addition, the following adverse events have been identified in clinical practice: allergic reactions (anaphylaxis, angioedema, dyspnea, pruritus, rash and urticaria), CNS symptoms (confusion, hallucinations, agitation, aggressive behavior, mania), gastrointestinal (diarrhea), renal failure, erythema multiforme, facial edema, hypertension and tachycardia. A rare but serious adverse event of thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has been observed in clinical trials of high dose valacyclovir (8 grams per day) in patients with advanced HIV infection, allogeneic bone marrow transplant and renal transplant recipients.

9. STATISTICAL CONSIDERATIONS

This is a phase 2, open label, prospective study with 3 cohorts, each defined by response to ICI at time of enrollment. As of Amendment 5, the target enrollment for cohorts 1 and 2 was updated to approximately 40 evaluable patients per cohort (details below), and cohort 3 was closed due to feasibility of patients to complete 12-week treatment period. Cohort 2 is expected to reach target enrolment in 1Q2023. Cohort 1 has recruited more slowly, with 4 patients evaluable having completed the 12-week treatment window, with one additional patient in the 12-week treatment window as of last data cutoff (October 21, 2022).

In Amendment 6, cohort 1B and 2B were initiated to evaluate a 3-dose regimen of CAN-2409 + prodrug. Upon activation of Amendment 6 at each site, cohorts 1A and 2A (formerly ‘cohort 1’ and ‘cohort 2’) will be closed to new enrolment, and eligible patients will be enrolled to cohorts

1B and 2B. Patients in the 12-week treatment enrolled in cohorts 1A and 2A will be followed up as for original protocol with no changes to their treatment regimen.

All subjects enrolled, regardless of protocol version, will be included in the analysis and analyzed by cohort.

9.1. Sample Size

The study is powered to characterize the overall response rate and/or disease control rate for each cohort with an associated 90% confidence interval (CI) using an exact binomial. Confidence limits for the number of responders was updated in Amendment 5 from symmetrical to asymmetrical exact binomial confidence intervals, to better suit the analysis. With this calculation change, the target sample size was increased from approximately 32 efficacy- evaluable to 40 efficacy-evaluable patients per cohort, while maintaining the approximate width of the confidence interval.

A sample size of approximately 40 efficacy-evaluable (as defined in Section 9.3) patients per cohort has been selected to provide ORR / DCR estimates with reasonably narrow 90% CI for the point estimate (Table 7).

Patients who are discontinued before receiving two courses of CAN-2409 + prodrug, due to study-unrelated toxicity, disease progression or other non-study related issues may be replaced.

Table 7 Confidence Limits for a Range of ORR or DCR Outcomes Assuming a Sample Size of 40 Efficacy-Evaluable Patients

N	ORR or DCR	Number of Responders	Confidence Level Two sided	Lower Confidence Limit	Upper Confidence Limit
40	12.5%	5	90%	5.1%	24.5%
40	15.0%	6	90%	6.7%	27.5%
40	17.5%	7	90%	8.5%	30.4%
40	20.0%	8	90%	10.4%	33.2%
40	22.5%	9	90%	12.3%	36.0%
40	25.0%	10	90%	14.2%	38.7%
40	27.5%	11	90%	16.3%	41.4%
40	30.0%	12	90%	18.3%	44.0%

To define the target sample size to evaluate the three-dose regimen, we considered a frame of reference based on the OAK study, where treatment post-progression with atezolizumab was associated with an ORR of 7% in patients with NSCLC (Gandara 2018). We also considered the observed ORR of 12% in efficacy evaluable patients in cohort 2, as of data cutoff Oct 21 2022. An ORR of 20% with a sample size of N=20 patients (4/20 PRs) in the new cohort would have a lower confidence limit > 7%. An ORR of 30% with the same sample size of N=20 patients (6/20 PRs) in the new cohort would have a lower confidence limit > 12%. These would be sufficient to demonstrate superiority to the historical ORR rates (Table 8).

Table 8 Confidence Limits for a Range of ORR or DCR Outcomes Assuming a Sample Size of 20 Efficacy-Evaluable Patients

N	ORR or DCR	Number of Responders	Confidence Level	Lower Confidence Limit	Upper Confidence Limit
20	**5%**	**1**	**90% (2-sided)**	**0.26%**	**21.6%**
20	10%	2	90% (2-sided)	1.81%	28.3%
20	15%	3	90% (2-sided)	4.22%	34.4%
20	20%	4	90% (2-sided)	7.14%	40.1%
20	25%	5	90% (2-sided)	10.4%	45.6%
20	30%	6	90% (2-sided)	14.0%	50.8%
20	35%	7	90% (2-sided)	17.7%	55.8%
20	40%	8	90% (2-sided)	21.7%	60.6%
20	45%	9	90% (2-sided)	25.9%	65.3%
20	50%	10	90% (2-sided)	30.2%	69.8%

9.2. Evaluable Status of Patients

Evaluability of baseline and post-baseline disease assessments will be assessed.

9.3. Analysis Sets

Full Analysis Set: This analysis set consists of all patients enrolled and who received at least 1 dose of CAN-2409. This analysis set will be used as the primary analysis set in the evaluation of safety and may be used as a supplemental analysis set in the evaluation of efficacy.

Response-Evaluable Analysis Set: This analysis set consists of patients who received all intended injections* of CAN-2409 and a minimum of 7 days of prodrug for each course. Patients must also have had measurable disease at baseline and had at least one disease assessment after the treatment window (i.e., week 12 or week 14 assessment). This analysis set will be used as the primary analysis set in the evaluation of efficacy related endpoints.

*i.e., 2 courses for cohorts 1A, 2A, and 3, or 3 courses for cohorts 1B [if consented to 3rd injection] and 2B)

Additional subset analyses for safety and/or efficacy may be performed based on which cohort and on which standard of care ICI with or without chemotherapy is administered.

9.4. DLT STOPPING RULES

This study will expand the safety data obtained in previous CAN-2409 clinical trials, and DLT stopping rules are in place as described below.

The status of the trial and any DLTs, as defined in Section 6.2, will be reviewed continuously. For DLT stopping rules, the data will be analyzed after every six evaluable patients of the first 30

patients accrued to all cohorts. The proposed therapy will be considered safe in this patient population if a true DLT rate of 15% or less is observed and a failure of safety if a DLT rate of 30% or higher is observed. Accrual will be halted if the lower limit of the 95% confidence interval for DLT rate falls above 10%. Stopping rules are listed in Table 9 and are based on the overall number of patients treated and the number of DLTs observed. The first column shows the number of patients accrued to all cohorts. The second column depicts the cumulative DLTs observed within that number of patients. The third column is the actual observed toxicity rate and the 4th and 5th columns represent the 95% confidence intervals for the observed toxicity. The grayed areas depict DLT rates and study halt and evaluation. For example, accrual would be stopped due to lack of safety if 4 or more patients experience DLT during the accrual of the first 12 patients. If there are 3 or less events after twelve patients have been evaluated, the study will proceed to treat up to six more patients (for a total of 18). Of these 18 patients, if 4 or fewer experience a DLT, the study will be considered safe; if 5 or more DLTs are observed, the study will be discussed with the investigators and FDA to evaluate whether enrollment should continue at a lower dose or different schedule to increase the level of confidence or whether adjustments/termination are warranted. For patients in cohorts 1B and 2B, the same stopping rules will be applied as listed in Table 9 . Study will be stopped if in the first 6 patients 3 DLTs are observed.

Table 9 Stopping Rules-Binomial Proportion 95% confidence intervals based on number of events out of total sample size (Wilson Score)

Number of patients	Observed No. of DLTs	Observed DLT Rate	95% Confidence interval for DLT rate		Stopping point*
6 or less	0	0%	0%	39%	
	1	17%	0%	56%	
	2	33%	10%	70%	
	3	50%	19%	81%	X
12 or less	0	0%	0%	24%	
	1	8%	0%	35%	
	2	17%	4%	45%	
	3	25%	8%	53%	
	4	33%	13%	61%	X
	5	42%	19%	68%	X
18 or less	0	0%	0%	18%	
	1	6%	0%	26%	
	2	11%	3%	33%	
	3	17%	6%	39%	
	4	22%	9%	45%	
	5	28%	12%	51%	X
	6	33%	16%	56%	X
	7	39%	20%	61%	X
24 or less	5	21%	9%	40%	
	6	25%	12%	45%	X
	7	29%	15%	49%	X
	8	33%	18%	53%	X
30 or less	6	20%	10%	37%	
	7	23%	12%	41%	X
	8	27%	14%	44%	X
	9	30%	17%	48%	X

* X denotes stopping rule points where the lower limit of the 95% confidence interval is >10%.

9.5. General Methods

No statistical hypothesis testing is planned.

Descriptive analysis will be performed to evaluate the primary, secondary and exploratory endpoints. Summary tabulations will be presented by cohort. For continuous variables, the number of subjects, mean, median, standard deviation, minimum and maximum values will be presented. For categorical variables, the number of percentage of subjects within each category of the parameter will be presented. Time-to-event data will be summarized using the Kaplan- Meir methods.

9.6. Safety Analyses

Descriptive analysis will be performed to evaluate safety endpoints. Unless otherwise specified the Full Analysis Set will be used for all safety analyses.

A treatment-emergent adverse event (TEAE) is defined as an AE occurring during or after the first injection of CAN-2409 and extends to 30 days after the last dose of prodrug.

The incidence of TEAEs will be calculated overall, by System Organ Class and by preferred term. TEAEs will be further summarized by severity (grade) and relationship to treatment. Frequencies and percentages will be provided for the worst grade AE experienced by the subject by treatment arm irrespective of attribution. Those deemed possibly, probably, likely related to treatment will also be tabulated.

9.7. Efficacy Analyses

Tumor response and disease progression status will be determined per the RECIST v1.1 criteria by the Investigator. Unless otherwise specified, the Response-Evaluable Analysis Set will be used for tumor response efficacy analyses. On an exploratory basis, response and disease progression status may be determined using iRECIST and itRECIST criteria.

9.7.1. Primary Endpoints

The main goal of the phase 2 is to determine whether CAN-2409 + prodrug in combination with ICI with or without chemotherapy has sufficient clinical activity in patients with stage III/IV NSCLC to warrant more extensive clinical evaluation in these patient populations.

Current long-term outcome for the study's target population is dismal, especially for patients that do not respond to ICI therapy. Most patients that respond to ICI respond within 3 months of starting therapy (Garon 2019).

The cohorts are based on clinical experience with patients that continue with the same ICI with or without chemotherapy. Cohort 1A and B will be patients who have persistent but stable disease at least 18 weeks after starting ICI treatment. Cohort 2A and B will be patients who have radiographic progressive disease at least 18 weeks after starting ICI treatment. Cohort 3 enrolled patients with refractory disease defined as progressed by imaging at least 9 weeks after starting ICI treatment. For cohort 1A and B, the primary endpoint will be overall response rate (ORR) determined by RECIST criteria. For cohorts 2A and B and 3, both ORR and disease control rate (DCR) will be evaluated. Given that patients in cohorts 2A and B and cohort 3 have already experienced disease progression at time of entry into the trial, achieving stable disease is clinically meaningful, thus DCR will be a co-primary endpoint for these cohorts.

Overall response rate is defined as the proportion of patients who have a confirmed partial or complete response by RECIST 1.1. Disease control rate is defined as the proportion of patients who have stable disease for ≥ 4 weeks, or a confirmed partial or complete response by RECIST v1.1. For ORR and DCR, exact binomial two-sided 90% confidence intervals will be calculated.

9.7.2. Possible Subgroup Analyses

Given that there are multiple subsets in this heterogenous population with different prognostic factors, subset analyses may be performed using appropriate statistical methods. The subset analysis may include:

- Histology (e.g. non-squamous, squamous)
- Standard of care regimen (e.g. pembrolizumab alone, pembrolizumab plus chemotherapy, durvalumab)
- Initial responder vs never responder- only applies to patients with progressive disease
- Sites of injection: lung nodule, lymph node disease or peripheral metastasis and whether both injections are into the same or different lesions
- Smoking history
- Molecular subsets such as PD-L1 expression at baseline and tumor mutational burden

If a clinically significant response in a subset is observed for a given group, future enrollment or studies may be directed towards that patient population.

9.7.3. Secondary Endpoints

The cohorts will be evaluated for overall survival, progression free survival, duration of response, quality of life and late toxicity. OS and PFS will be defined from date of first dose of CAN-2409 (OS-1/PFS-1) and from date of ICI treatment initiation (OS-2/PFS-2). In addition, blood and tumor tissue will be collected from patients when feasible, to be included in immune biomarker studies.

Immunological biomarkers will be measured in blood and tissue samples collected during the study duration at specific timepoints as described above. Those will provide key information on the treatment mode of action in the tumor microenvironment and in the periphery. Where possible correlations with clinical responses will be performed. Changes from baseline immune activity in tumor and peripheral blood will be evaluated.

Evaluation of prognostic biomarker of response also will be performed. Assays will include: immunophenotyping in the blood and in the tissue, serum/plasma proteomics including measurement of cytokines and chemokines in the blood and clonal analysis of the lymphocytes in the tissue and in the blood (TCR and BCR analysis). Finally, we will measure ctDNA in the samples obtained at different time points during therapy to obtain an additional and more sensitive measure of tumor response over time.

Descriptive statistics and probability distribution of these endpoints will be estimated using appropriate methods to generate a baseline for comparison in larger definitive studies.

9.7.4. Exploratory Endpoints

Response (ORR, DCR, and/or progression-free survival) will also be evaluated by iRECIST and itRECIST criteria in addition to RECIST. As the data allows, changes in non-target lesions and tumor growth trajectory for each measurable lesion will be evaluated.

9.7.5. Viral shedding will be evaluated in collected serum and oropharyngeal samples and measured by validated identity assay by quantitative PCR. Adjustment for Multiplicity

No formal statistical testing will be performed for this study; therefore, no adjustment for multiple comparisons will be made.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. Consent Procedure

All patients must sign an approved informed consent form in order to be eligible for this study. This may be done using eConsent or other form of documenting signature prior to enrolment, if necessary, as per institutional approved procedures.

The subjects for this study will be identified by the Principal investigator or one of the Co-investigators of this study. The investigator will discuss the purpose of the research, the scientific background, the study procedures, the potential side effects, and alternative therapies with the patient. The investigator will answer questions at this time and also be available to answer further questions in the future. Patients who indicate interest in the study will be given time to review, in detail, the content of the consent form including procedures, duration of the study, potential side effects, voluntary participation, etc. Questions will be answered. When a patient decides to participate, they will need to sign and date the consent form as per institutional approved procedures and begin scheduling the procedures. All study participants will receive a copy of the signed consent form.

10.2. PATIENT REGISTRATION

Eligible patients must be registered with the Sponsor prior to treatment to verify eligibility and ensure that a waiting period is not in effect. This process utilizes a form sent from the clinical site to the Sponsor containing eligibility information about the patient. Sponsor will communicate determination of eligibility to the clinical site.

10.3. Confidentiality

Protected health information may be collected throughout the duration of this investigation and confidentiality of patients' records will be maintained within legal limits. The data from this study may be published; however, no patient will be named or identified.

10.4. Risk-Benefit Ratio

As summarized in Section 2.3.6, two courses of intratumoral CAN-2409 + prodrug can elicit a strong biological effect both at the site of injected tumor and in the periphery, resulting in control

of tumor growth of primary and metastatic lesions that may translate into meaningful progression free survival. Two CAN-2409 injections were reasonably well tolerated, with no DLTs or Grade 4-5 TRAEs reported to date; the most common treatment related AEs consistent with its mechanism of action (fever, fatigue) and Grade 1-2 in severity. While these data are encouraging, we also observed a subset of seven patients in Cohort 2 with rapid disease progression such that they withdrew from the study due to progressive disease prior to week 12. In six of the seven patients, early progression occurred such that they did not receive their 2nd CAN-2409 injection. Considering also the timing of post-treatment immunologic effects described previously, these observations suggest that shortening the timeframe between injections and adding a third injection to the regimen (as per the PrTK03 study of CAN-2409 plus prodrug in patients with localized prostate cancer) could improve responses further, especially for patients who, in the absence of intervention, may have rapidly progressing disease.

Starting with version 6 of this study, we will test the effect of additional CAN-2409 plus prodrug cycles in a new group of patients with progressive disease on ICIs (cohort 2B), with a new therapeutic regimen of 3 courses of CAN-2409 plus prodrug (given at Week 1, Week 5 and Week 9) aimed at reducing the time between injection to 4 weeks (the period in which we have observed the peak of the inflammatory response). We believe that this new regimen will increase the proportion of patients able to receive a complete treatment regimen, ultimately improving the number of responses.

The same schedule will be applied in patients with stable disease on ICI (cohort 1B), but with the third injection as optional. One of four evaluable patients from cohort 1A had an objective response; for patients who opt for the third injection, it is possible that more objective responses could be observed.

These benefits likely outweigh the risks of alternative therapies, which comprise treatment with ICIs beyond progression alone or conventional taxane-based chemotherapy, and the risks of therapy with CAN-2409 plus prodrug (primarily limited to localized inflammation). The overall risk benefit ratio appears favorable for the two and three cycle regimens of CAN-2409 plus prodrug in patients with ICI-refractory NSCLC.

10.5. Adverse Event Reporting

Adverse events should be reported to the Sponsor Adverse events will be collected from the day of the first injection of CAN-2409 and extends for approximately 12 weeks (cohort 1A, 2A, 3) or 14 weeks (cohort 1B or 2B), or 30 days after the last dose of study drug (CAN-2409 or prodrug). This is the Acute Toxicity Monitoring Period, also known as the 14-Week Treatment Period.

SAEs must be reported to the Sponsor within 24 hours of awareness. Additional information for the initial SAE must be reported as a follow-up to the original episode within 24 hours of awareness of additional information. The investigator must follow the event to resolution, or until the event is deemed and documented as irreversible, whichever is longer. Adverse events which are unexpected and associated with the use of the investigational product will be reported to the FDA according to the schedule below.

Adverse events which are unexpected and associated with the use of the investigational product will be reported to the FDA according to the schedule below (Table 10). An adverse event that is not listed in the investigator brochure or general investigative plan (e.g. protocol, informed consent form) or is not listed at the specificity or severity that has been observed will be considered unexpected. The Sponsor will notify the FDA of any unexpected, fatal or life-threatening suspected adverse reaction (expedited report) as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information.

For other serious unexpected suspected adverse reaction (i.e. SUSAR that are not fatal or life-threatening), the Sponsor will notify the FDA as soon as possible, but no later than 15 days, of the initial receipt of information. Reporting to the institutional review boards will be done according to the requirements of the institution. The principal investigator or their designee will be responsible for reporting to the institutional review boards and to the Sponsor. The Sponsor will be responsible for reporting to the FDA. The appropriate forms for adverse event reporting will be used for each agency.

Table 10 Adverse Event Reporting Timing

Type of event	**Timing of Report***
Fatal or life-threatening	As soon as possible, no later than 7 calendar days
1. Serious adverse event resulting in one of the following: 2. Inpatient hospitalization or prolongation of hospitalization 3. A persistent or significant disability or incapacity 4. A congenital anomaly or birth defect 5. Important medical event that, based on the medical judgment of the investigator, may require medical or surgical intervention to prevent one of the outcomes listed above	As soon as possible, no later than 15 calendar days
Any other unexpected adverse experiences associated with the use of the product	In the annual report

***** Timing is relative to when the person responsible for making the report becomes aware of the event and it is determined that it qualifies for reporting.

Pregnancies, if they occur, should be promptly reported according to the Safety Monitoring Plan, and will be followed to outcome.

10.6. Data and Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety.

All subject data relating to the investigation will be recorded on printed or electronic CRF. These forms will be used to transmit information collected during the study to Candel Therapeutics.

The CRF data for this study are being collected with a validated electronic data capture (EDC) system called DataTrak (product version 14.6.0 or higher). The EDC system and the eCRFs will comply with 21 CFR Part 11. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF and must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data. Source data may include but is not limited to clinical assessments, medication lists, medical history, laboratory reports, and other reports including pathology and imaging. Imaging conducted pre-trial will also be collected for purpose of documenting disease status (stable disease or progression) and to support the exploratory endpoint of tumor growth trajectory modeling.

Candel Therapeutics and/or its representatives are responsible for the data monitoring of this study, including quality checking of the data. In accordance with 21 CFR 312.53(d), Sponsor monitors will be qualified by training and experience to monitor the progress of the investigation. Sponsor monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents. Sponsor monitors will ensure that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol, any other study agreements, ICH GCP, and all appliable regulatory requirements.

The principal investigators (PIs) of the trial will review toxicities, responses of the trial where applicable and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion.

Furthermore, a Data Safety Monitoring Board (DSMB) will serve in an advisory capacity to the Overall PI(s) and Sponsor to monitor patient safety. The DSMB will operate as per the charter.

The results of this research study may be used in scientific publications or presented at medical conventions. Results will be published or presented only in a way that does not identify any individual subject.

11. BIBLIOGRAPHY

Aggarwal, C.,A. R. Haas,S. Metzger,L. K. Aguilar,E. Aguilar-Cordova,A. G. Manzanera, D. H. Sterman (2018). "Phase I Study of Intrapleural Gene-Mediated Cytotoxic Immunotherapy in Patients with Malignant Pleural Effusion." Molecular therapy : the journal of the American Society of Gene Therapy 26(5): 1198-1205.

Aggarwal, C., Haas, Andrew., Gorgon, S.W., Mehra, R., Lee, P.M., Bestvina, C.M., Maldonado, F., Velcheti, V., Herbst, R.S., Bell, S.D., Gillmor, R., Manzanera, A., Matheny, C.J., Aguilar-Cordova, E., Aguilar, L.K., Barone, F., Tak, P., Sterman, D. (2022). "First report of safety/tolerability and preliminary antitumor activity of CAN-2409 in inadequate responders to immune checkpoint inhibitors for stage III/IV NSCLC." Journal of Clinical Oncology 40(16 suppl): 9037-9037.

Aguilar, L. K.,B. W. Guzik, E. Aguilar-Cordova (2011). "Cytotoxic immunotherapy strategies for cancer: mechanisms and clinical development." Journal of cellular biochemistry 112(8): 1969-1977.

Aguilar, L. K.,L. A. Shirley,V. M. Chung,C. L. Marsh,J. Walker,W. Coyle, M. Bloomston (2015). "Gene-mediated cytotoxic immunotherapy as adjuvant to surgery or chemoradiation for pancreatic adenocarcinoma." Cancer immunology, immunotherapy : CII 64(6): 727-736.

Antonia, S. J.,A. Villegas,D. Daniel,D. Vicente,S. Murakami,R. Hui, . M. Özgüroğlu (2018). "Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC." New England Journal of Medicine 379(24): 2342-2350.

Antonia, S. J.,A. Villegas,D. Daniel,D. Vicente,S. Murakami,R. Hui, M. Özgüroğlu (2017). "Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer." New England Journal of Medicine 377(20): 1919-1929.

Ayala, G.,T. Satoh,R. Li,M. Shalev,Y. Gdor,E. Aguilar-Cordova, D. Kadmon (2006). "Biological response determinants in HSV-tk + ganciclovir gene therapy for prostate cancer." Molecular therapy : the journal of the American Society of Gene Therapy 13(4): 716-728.

Chhikara, M.,H. Huang,M. T. Vlachaki,X. Zhu,B. Teh,K. J. Chiu, . . . E. Aguilar-Cordova (2001). "Enhanced therapeutic effect of HSV-tk+GCV gene therapy and ionizing radiation for prostate cancer." Molecular therapy : the journal of the American Society of Gene Therapy 3(4): 536-542.

Chiocca, E. A.,L. K. Aguilar,S. D. Bell,B. Kaur,J. Hardcastle,R. Cavaliere, P. Z. New (2011). "Phase IB study of gene-mediated cytotoxic immunotherapy adjuvant to up-front surgery and intensive timing radiation for malignant glioma." Journal of clinical oncology 29(27): 3611-3619.

Eastham, J. a.,S. H. Chen,I. Sehgal,G. Yang,T. L. Timme,S. J. Hall, T. C. Thompson (1996). "Prostate cancer gene therapy: herpes simplex virus thymidine kinase gene transduction followed by ganciclovir in mouse and human prostate cancer models." Human gene therapy 7(4): 515-523.

Eisenhauer, E. A., Therasse, P. Bogaerts, J., Schwartz, L.H. Sargent, D. Ford, R. Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., Rubinstein, L., Shankar, L., Dodd, L. Kaplan, R., Lacombe, D., Verweij, J. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer 45(2): 228-247.

Fridlender, Z. G.,J. Sun,S. Singhal,V. Kapoor,G. Cheng,E. Suzuki, S. M. Albelda (2010). "Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via

multiple immune-mediated mechanisms." Molecular therapy : the journal of the American Society of Gene Therapy 18(11): 1947-1959.

Gandara, D. R.,J. von Pawel,J. Mazieres,R. Sullivan,A. Helland,J. Han, L. Fehrenbacher (2018). "Atezolizumab Treatment Beyond Progression in Advanced NSCLC: Results From the Randomized, Phase III OAK Study." J Thorac Oncol. 13(12): 1906-1918.

Gandhi, L.,D. Rodríguez-Abreu,S. Gadgeel,E. Esteban,E. Felip,F. De Angelis, M. C. Garassino (2018). "Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer." New England Journal of Medicine 378(22): 2078-2092.

Garon, E. B.,M. D. Hellmann,N. A. Rizvi,E. Carcereny,N. B. Leighl,M.-J. Ahn, R. Hui (2019). "Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study." Journal of Clinical Oncology: JCO.19.00934.

Goldmacher, G. V., Khilnani, A.D., Andtbacka, R.H.I., Luke, J.J., Hodi, F.S., Marabelle, A., Harrington, K., Perrone, A., Tse, A., Madoff, D.C., Schwartz, L.H. (2020). "Response Criteria for Intratumoral Immunotherapy in Solid Tumors: itRECIST." Journal of Clinical Oncology 38(23): 2668-2676.

Hall, S. J.,S. E. Mutchnik,S. H. Chen,S. L. Woo, T. C. Thompson (1997). "Adenovirus-mediated herpes simplex virus thymidine kinase gene and ganciclovir therapy leads to systemic activity against spontaneous and induced metastasis in an orthotopic mouse model of prostate cancer." International journal of cancer. Journal international du cancer 70(2): 183-187.

Miles, B. J.,M. Shalev,E. Aguilar-Cordova,T. L. Timme,H. M. Lee,G. Yang, T. C. Thompson (2001). "Prostate-specific antigen response and systemic T cell activation after in situ gene therapy in prostate cancer patients failing radiotherapy." Human gene therapy 12(16): 1955-1967.

Mok, T. S. K.,Y.-L. Wu,I. Kudaba,D. M. Kowalski,B. C. Cho,H. Z. Turna, A. Zippelius (2019). "Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial." The Lancet 393(10183): 1819-1830.

Paz-Ares, L.,A. Luft,D. Vicente,A. Tafreshi,M. Gümüş,J. Mazières, D. M. Kowalski (2018). "Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer." New England Journal of Medicine 379(21): 2040-2051.

Predina, J. D., Haas, A.R., Martinez, M., O'Brien, S., Moon, E.K., Woodruff, P., Stadanlick, J., Corbett, C., Frenzel-Sulyok, L., Bryski, M.G., Eruslanov, E., Deshpande, C., Langer, C., Aguilar, L.K., Guzik, B.W., Manzanera, A.G., Aguilar-Cordova, E, Singhal, S. & Albelda, S.M. (2021). "Neoadjuvant Gene-Mediated Cytotoxic Immunotherapy for Non-Small-Cell Lung Cancer: Safety and Immunologic Activity." Mol Ther 29(2): 658-670.

Predina, J. D.,B. Judy,L. A. Aliperti,Z. G. Fridlender,A. Blouin,V. Kapoor, S. Singhal (2011). "Neoadjuvant in situ gene-mediated cytotoxic immunotherapy improves postoperative outcomes in novel syngeneic esophageal carcinoma models." Cancer Gene Therapy 18(12): 871-883.

Predina, J. D.,V. Kapoor,B. F. Judy,G. Cheng,Z. Fridlender,S. M. Albelda, S. Singhal (2012). "Cytoreduction surgery reduces systemic myeloid suppressor cell populations and restores intratumoral immunotherapy effectiveness." Journal of Hematology & Oncology 5(1): 34-34.

Rainov, N. G.,C. Fels,J. W. Droege,C. Schäfer,C. M. Kramm, T. C. Chou (2001). "Temozolomide enhances herpes simplex virus thymidine kinase/ganciclovir therapy of malignant glioma." Cancer gene therapy 8(9): 662-668.

Reck, M.,J. Remon, M. D. Hellmann (2022). "First-Line Immunotherapy for Non-Small-Cell Lung Cancer." Journal of Clinical Oncology 40(6): 586-597.

Rojas-Martínez, A.,A. G. Manzanera,S. W. Sukin,J. Esteban-María,J. F. González-Guerrero,L. Gomez-Guerra, E. Aguilar-Cordova (2013). "Intraprostatic distribution and long-term follow-up after AdV-tk immunotherapy as neoadjuvant to surgery in patients with prostate cancer." Cancer gene therapy 20(11): 642-649.

Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L.H., Mandrekar, S., Lin, N.U., Litiere, S. Dancey, J., Chen, A., Hodi, F.S., Therasse, P., Hoekstra, O.S., Shankar, L.K., Wolchok, J.D., Ballinger, M., Caramella, C., de Vries, E.G.E. (2017). "iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics." Lancet Oncol 18: e143-152.

Socinski, M. A.,R. M. Jotte,F. Cappuzzo,F. Orlandi,D. Stroyakovskiy,N. Nogami, . . . I. M. S. Group (2018). "Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC." N Engl J Med 378(24): 2288-2301.

Speranza, M.-C.,C. Passaro,F. Ricklefs,K. Kasai,S. R. Klein,H. Nakashima, S. E. Lawler (2018). "Preclinical investigation of combined gene-mediated cytotoxic immunotherapy and immune checkpoint blockade in glioblastoma." Neuro-Oncology 20(2): 225-235.

Sterman, D. H.,A. Recio,A. Vachani,J. Sun,L. Cheung,P. DeLong, . . . S. M. Albelda (2005). "Long-term follow-up of patients with malignant pleural mesothelioma receiving high-dose adenovirus herpes simplex thymidine kinase/ganciclovir suicide gene therapy." Clinical cancer research : an official journal of the American Association for Cancer Research 11(20): 7444-7453.

Sukin, S. W.,M. Chhikara,X. Zhu,G. Ayala,L. K. Aguilar,E. O'Brian Smith, E. Aguilar-Cordova (2001). "In vivo surgical resection plus adjuvant gene therapy in the treatment of mammary and prostate cancer." Molecular therapy : the journal of the American Society of Gene Therapy 3(4): 500-506.

Teh, B. S.,G. Ayala,L. Aguilar,W.-Y. Mai,T. L. Timme,M. T. Vlachaki, . . . E. B. Butler (2004). "Phase I-II trial evaluating combined intensity-modulated radiotherapy and in situ gene therapy with or without hormonal therapy in treatment of prostate cancer-interim report on PSA response and biopsy data." International journal of radiation oncology, biology, physics 58(5): 1520-1529.

Trask, T. W.,R. P. Trask,E. Aguilar-Cordova,H. D. Shine,P. R. Wyde,J. C. Goodman, R. G. Grossman (2000). "Phase I study of adenoviral delivery of the HSV-tk gene and ganciclovir administration in patients with current malignant brain tumors." Molecular therapy : the journal of the American Society of Gene Therapy 1(2): 195-203.

Van-der-Linden, R. R. M.,B. L. Haagmans,P. Mongiat-Artus,G. J. van Doornum,R. Kraaij,D. Kadmon, . . . R. R. M. Van-der-Linden (2005). "Virus specific immune responses after human neoadjuvant adenovirus-mediated suicide gene therapy for prostate cancer." European urology 48(1): 153-161.

Vlachaki, M. T.,M. Chhikara,L. Aguilar,X. Zhu,K. J. Chiu,S. Woo, . . . E. Aguilar-Cordova (2001). "Enhanced therapeutic effect of multiple injections of HSV-TK + GCV gene therapy in combination with ionizing radiation in a mouse mammary tumor model." International journal of radiation oncology, biology, physics 51(4): 1008-1017.

Wheeler, L. A.,A. G. Manzanera,S. D. Bell,R. Cavaliere,J. M. McGregor,J. C. Grecula, E. A. Chiocca (2016). "Phase II multicenter study of gene-mediated cytotoxic immunotherapy as adjuvant to surgical resection for newly diagnosed malignant glioma." Neuro-oncology 18(8): 1137-1145.

APPENDIX 1. CAN-2409 BOOSTER SUBSTUDY

A1-1. BACKGROUND AND RATIONALE

The purpose of this substudy is to investigate the safety, immunological, and radiographic effects of a CAN-2409 booster injection, followed by 14 days of prodrug, in patients previously treated with CAN-2409 in the main study. In this substudy, a booster injection refers to an additional course of CAN-2409 + prodrug which is provided at least 12 months but not more than 18 months after the initial CAN-2409 injection in the main study. To be eligible for the booster dose, patients must have clinically stable disease and ongoing treatment with the same ICI therapy as at study enrollment (see Section A1-4 for additional eligibility criteria). Patients must sign an informed consent specific to this substudy.

The time window for the booster injection (12-18 months after previous CAN-2409 injections) was selected to 1) explore the concept of an approximately annual 'booster dose' for patients who have detectable disease and are clinically stable, while 2) minimally impacting the primary study readouts.

Table 11 Time and Events for Booster Dose

	Pre-booster baseline[1]	**Visit 1***	**Visit 2***	**Visit 3***	**Follow up until confirmed progression**	**Post-confirmed progression**
Informed consent[1]	X					
CAN-2409[2]		X				
Prodrug[2]		X				
ICI[3]	As per SOC schedule[10]					
Clinical assessment	X		X	X	q9-12wk [11]	
ECOG	X				q9-12wk	
Survival						Every 6mo
Adverse events[4]			X	X		
New medical problems					q9-12wk	
Con meds[5]	X		X	X		
Anti-cancer treatment					q9-12wk[5]	Every 6mo[5]
Labs[6]	X		X	X		
INR/aPTT[6]	X					
Imaging[7]	X	As per SOC, but not sooner than 9 weeks after pre-booster scan[7]			q9-12wk[11]	
Research blood for biomarkers[13]	X		X	X	Once[12]	

	Pre-booster baseline[1]	Visit 1*	Visit 2*	Visit 3*	Follow up until confirmed progression	Post-confirmed progression
FNA/biopsy if feasible[8]		X				

*Timing of visits: CAN-2409 injection occurs at Visit 1. Visit 2 should occur 2 weeks +/- 3 days (ICI q2w/q4w) or 3 weeks +/- 3 days (ICI q3w/q6w) after Visit 3 and may be aligned with ICI administration. Visit 3 should occur 2 weeks +/- 3 days (ICI q2w/q4w) or 3 weeks +/- 3 days (ICI q3w/q6w) after Visit 2 and may be aligned with ICI administration.

1. Informed consent must be obtained prior to initiating any booster substudy procedures. Perform booster baseline evaluations within 14 days before CAN-2409 injection, informed consent within 30 days before injection, and CT with contrast within 28 days before injection. Labs may be repeated prior to injection if any significant changes are expected (e.g., interim illness).
2. Study treatment includes CAN-2409 injection into target lesion followed by oral valacyclovir for 14 days starting 1 day after CAN-2409 injection (see main protocol, Section 6.4 for dose adjustments or acyclovir alternative).
3. Immune checkpoint inhibitor (ICI) with or without chemotherapy, as per SOC. SOC treatment to continue prior to enrollment into booster substudy and following injection, remaining on SOC schedule as much as possible.
4. Adverse events should be monitored for 30 days after the last dose of study drug (CAN-2409 or valacyclovir). In the follow-up period, new medical problems should be documented at SOC visits until progression.
5. All concomitant medications should be documented through Visit 3. During the follow-up period, only anti-cancer treatments need to be documented until progression. After progression during survival follow up, only general anti-cancer treatment regimens should continue to be documented.
6. CBC, platelets, differential, AST, ALT, total bilirubin, creatinine, calculated creatinine clearance, glucose and any other SOC laboratories as indicated. All labs are performed locally with assessments based on local lab ranges.
7. SOC CT scan with contrast or other imaging as appropriate to measure/assess target and non-target lesions per RECIST criteria should be collected, preferably with the same technique, at each time point. These will be reviewed both locally and by central imaging reader(s) via Sponsor to determine RECIST response. First scan after the CAN-2409 booster injection as per SOC but should be no sooner than 9 weeks after pre-booster scan. The baseline scan may be part of a follow-up until progression visit from the main study and does not need to be repeated if falls within the window mentioned in footnote 1.
8. Biopsy of lesion if feasible, based on safety and accessibility, prior to CAN-2409 injection. Samples for research to be batch shipped by clinical site to Sponsor upon request.
9. Follow up is scheduled as per SOC (see footnote #11), and continued until confirmed progression, such that SOC treatment is being changed or stopped. At confirmed progression, patients enter survival follow up, with at least biannual records review from the date of confirmed progression, +/- 1 month. Please see main protocol, Section 7.3 for more detail.
10. ICI with or without chemotherapy continues as per SOC until progression.
11. Clinical assessment and CT scan as per SOC schedule, but expected to be at least every 9-12 weeks, until confirmed progression, after which patient enters post-progression follow up for survival.
12. One time during follow up at the SOC visit closest to 6 months after the CAN-2409 injection or at time of progression prior to starting new treatment, whichever time point comes first.
13. If research blood collection is done on same day as ICI treatment, research blood should be collected prior to ICI treatment.

A1-2. OBJECTIVES

This substudy will generate preliminary safety, immunologic, and radiographic data for a booster dose of CAN-2409 + prodrug in patients previously treated in the main study. The hypothesis is that the booster will be safe and adequately tolerated, produce immunologic changes consistent with the mechanism of action for CAN-2409, and may produce evidence of further disease control.

The substudy objectives are to:

- Characterize safety and tolerability of a booster dose of CAN-2409 + prodrug
- Characterize immunologic changes post- vs. pre-booster
- Characterize radiographic changes post- vs. pre-booster
    - Evaluate radiographic evidence of activity based on RECIST 1.1
    - Evaluate radiographic evidence of activity in individual lesions (injected and non-injected)

A1-2.1. Endpoints

As the expected sample size will be limited (up to approximately 10 patients), all endpoints for this substudy are considered exploratory (see also A1-8 Statistical Considerations). Endpoints include:

- Safety data based on standard laboratory and clinical adverse event monitoring
- Response by RECIST 1.1 criteria using the pre-booster visit scan as the baseline scan
- Changes in size of individual lesions (injected and non-injected) pre- vs. post-booster
- Immunologic biomarkers in blood and tissue pre- and post- booster

A1-3. SUBJECT POPULATION

A1-3.1. Inclusion Criteria

1. Patients treated in the main study who received at least 2 doses of CAN-2409 with each injection followed by at least 7 days of prodrug.
2. At least 12 months, but not more than 18 months, elapsed since 1st injection of CAN-2409
3. ICI has not been changed or interrupted for more than 12 weeks
4. Clinically stable and expected to be able to continue ICI
5. Radiographic disease status may be SD or PD relative to baseline or nadir (as appropriate) from the main study. Documented progression is acceptable if patient is clinically stable and ICI has not changed since study enrollment.
6. Must have RECIST evaluable disease
7. Must have a lesion that is amenable to injection based on investigator assessment
8. Patients must meet required criteria for CAN-2409 injections as described in Section 6.2 of the main protocol.
9. Patients must consent to booster injection via separate substudy informed consent form

A1-3.2. Exclusion Criteria

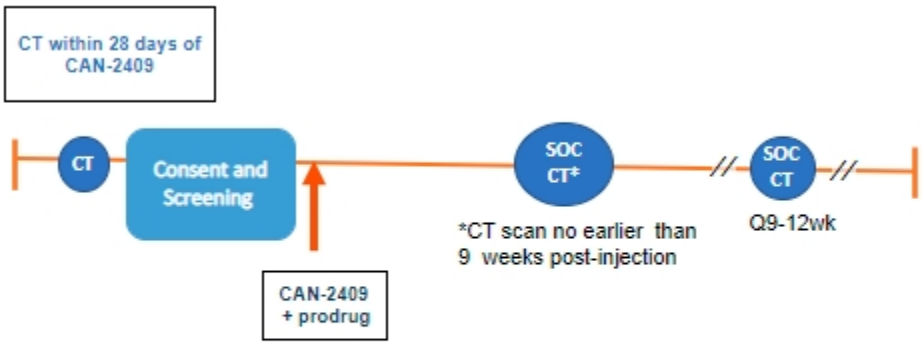
1. Patients who have changed or discontinued ICI or have received additional systemic anti-cancer therapies since enrollment on the main protocol.
2. Patients with ongoing partial response (PR) as per RECIST 1.1 criteria
3. Patient should not have any exclusion criteria following main protocol criteria

A1-4. PRETREATMENT EVALUATIONS & REGISTRATION

A1-4.1. Baseline Evaluations

Required evaluations and baseline laboratory assessments are listed in the time and events table (Table 11) and in Section 6.1.2 (Criteria for CAN-2409 injections).

A1-5. SCHEMA



Timing of SOC imaging is as per site/PI practice

A1-6. TREATMENT PLAN

The investigational products are CAN-2409 and prodrug (valacyclovir or acyclovir). For CAN-2409 + prodrug schedule, see schema and time and events table.

A1-6.1. CAN-2409 administration

Prior to CAN-2409 administration, evaluations will be performed as described in the time and events table and in Section 6.1.2 (Criteria for CAN-2409 injections). An FDG-PET is encouraged, but not required, as a SOC test and to inform site(s) of active disease amenable to injection.

A biopsy prior to CAN-2409 injection to confirm active tumor and to obtain tissue for immune research studies should be performed if feasible and safe, as determined by the investigator.

CAN-2409 will be injected into an accessible involved tumor site that may include a lung nodule, lymph node disease or peripheral metastasis. The injection may be in the same or different lesions than previous ones.

The dose of CAN-2409 will be the same as previous courses, which is $5x10^{11}$ vp in 1-2 ml depending on size of the tumor/ node to be injected. Refer to Section 6.3.2 in main protocol and pharmacy manual for details on the administration of the intratumoral injection of CAN-2409.

A1-6.2. Prodrug administration

Refer to Section 6.4 in main protocol.

A1-6.3. Additional treatment for NSCLC

Refer to Section 6.5 in main protocol.

A1-7. TREATMENT EVALUATION

A1-7.1. Evaluations During and After Treatment

Patients will undergo standard of care and clinically indicated evaluations in addition to any study specific evaluations. Refer to time and events table (Table 11) for details.

A1-7.2. Additional Research Studies

Blood for immune research studies as per time and event table (Table 11). When research blood collection falls on the same day as treatment, it should be drawn before the treatment (CAN- 2409 injection, ICI treatment, chemotherapy) at each time point.

- Tumor samples from biopsies, if feasible based on safety and accessibility, for immune research studies as per Time and Events Table (Table 11).

A1-7.3. Post-progression Follow Up

As per Time and Events Table (Table 11).

A1-7.4. Toxicity Assessment

This substudy will expand the safety data obtained in the main protocol (see Section 7.4). For Dose Limiting Toxicity criteria and definitions, refer to Section 6.2.1 in the main protocol.

A1-7.5. Criteria for Evaluation

A1-7.6. Off Treatment Criteria

Patients who need to or choose to discontinue treatment (in the booster substudy, this equates to stopping treatment with prodrug before completing at least 7 days treatment) will continue follow up for toxicity and disease outcome as per the Time and Events Table (Table 11), unless the patient withdraws consent from further follow up data collection.

See Section 9.2 for evaluable status of withdrawn patients. See Section 7.6 for summary of reasons for discontinuing treatment.

A1-8. STATISTICAL CONSIDERATIONS

A limited number of patients in the main study are expected to be eligible for and participate in this substudy (up to approximately 10 patients). No formal statistical hypothesis will be tested. Patients in this substudy will be summarized separately and may be incorporated into the analysis of patients who are not in this substudy. The details will be presented in the statistical analysis plan.

A1-8.1. DLT Stopping Rules

Refer to Section 9.4 in the main protocol.

A1-9. ETHICAL AND REGULATORY CONSIDERATIONS

A1-9.1. Consent Procedure

See Section 10.1 of the main protocol for details on the consent procedure, which apply to this substudy as well. Eligible patients must sign a separate Informed Consent Form specific to the booster injection.

A1-9.2. Patient Registration

Eligible patients must be registered with the Sponsor prior to treatment to verify eligibility and ensure that a waiting period is not in effect. This process utilizes a form sent from the clinical site to the Sponsor containing eligibility information about the patient. Sponsor will communicate determination of eligibility to the clinical site.

A1-9.3. Risk-Benefit Ratio

As summarized in Section 2.3.6 in the main protocol, two courses of intratumoral CAN-2409 + prodrug can elicit a strong biological effect both at the site of injected tumor and in the periphery, resulting in control of tumor growth of primary and metastatic lesions that may translate into meaningful progression free survival. Preliminary data from the current trial with two CAN-2409 injections has demonstrated initial safety, with no DLTs or grade 4-5 treatment related adverse events reported to date; the most common observed AEs are consistent with the mechanism of action (fever, fatigue, chills) and grade 1-2 in severity. For further details, please refer to Section 10.4 in the main protocol.

Considering the timing of post-treatment immunologic effects previously described, observations suggest that shortening the timeframe between injections, addition of a third injection in the initial treatment regimen and, in this substudy adding option of an annual booster to the regimen, could further improve responses, especially for patients who, in the absence of intervention, may have rapidly progressing disease.

The potential benefits of this booster injection likely outweigh the risks of alternative therapies (such as switch to systemic taxane-based chemotherapy), particularly given the tolerability of CAN-2409 plus prodrug and the potential to elicit RECIST responses in those who have stable disease or slowly progressive disease. The overall risk benefit ratio appears favorable for the booster regimen of CAN-2409 plus prodrug in patients who have clinically stable disease that is either radiographically stable or progressing at time of booster regimen.

A1-9.4. Adverse Event Reporting

Adverse events should be reported to the sponsor and will be collected from the day of the injection of CAN-2409 to 30 days after the last dose of study drugs (CAN-2409 or prodrug, whichever is later). Serious adverse events must be reported to the sponsor within 24 hours of awareness. For details on reporting timing and specifics please refer to Section 10.5 and Table 10 in the main protocol.

A1-9.5. Data and Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. For more details, refer to the main protocol, monitoring plan (Section 10.6) and the study procedures manual.