VANTRIX ONCOLOGY, INC. • PHASE II STUDY

A Phase II, Open-Label, Single-Arm Study of Velanixib (VNX-1803) in Combination with Pembrolizumab in Patients with Advanced Non-Small Cell Lung Cancer Harboring KRAS G12C Mutations

"KITE-II: KRAS Inhibitor Trial Evaluation — Part II"

Protocol Number	VNX-NSCLC-201
IND Number	IND 156,847 (FDA)
EudraCT Number	2025-002384-11
Phase	II
Version / Date	Version 2.1 / 10 June 2025
Sponsor	Vantrix Oncology, Inc.
Medical Monitor	Dr. Catherine R. Hollis, MD, PhD
Regulatory Contact	Mr. James T. Nguyen, RAC

Contents

1 Protocol Synopsis

Title	A Phase II, Open-Label, Single-Arm Study of Velanixib (VNX-1803) plus Pembrolizumab in Previously Treated Advanced KRAS G12C-Mutant NSCLC (KITE-II)
Protocol Number	VNX-NSCLC-201 / Version 2.1
Sponsor	Vantrix Oncology, Inc., 1200 Harbor Blvd, Suite 400, Boston, MA 02210, USA
Phase	II
Study Design	Open-label, single-arm, multi-centre, proof-of-concept
Indication	Advanced/metastatic NSCLC (non-squamous) with confirmed KRAS G12C, after $\geq$1 prior platinum-based regimen
Investigational Products	Velanixib 240 mg oral QD + Pembrolizumab 200 mg IV Q3W
Primary Endpoint	Objective Response Rate (ORR) per RECIST v1.1 by BICR
Key Secondary Endpoints	DCR, DoR, PFS, OS, Safety & tolerability, PROs
Sample Size	62 evaluable (82 enrolled; 25% screen failure assumed)
Duration	Treatment: up to 24 months; Follow-up: 12 months post-treatment
Study Sites	$\sim$18 sites across USA and EU
Regulatory Status	FDA IND 156,847 (active); EMA Scientific Advice obtained Dec 2024

2 Background and Rationale

2.1 Disease Context

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually. Despite transformative advances in immune checkpoint inhibitor (ICI) therapy and targeted agents, patients whose tumours harbour *KRAS* mutations — representing 25–30% of all lung adenocarcinomas — have historically lacked effective molecularly targeted options.

The *KRAS* G12C substitution is the most prevalent oncogenic *KRAS* allele in NSCLC ($\sim$13% of cases). The landmark approval of sotorasib in 2021 validated KRAS G12C as a druggable target; however, median PFS of 6.8 months and an ORR of 37% in the second-line setting underscore the need for more durable strategies.

2.2 Velanixib (VNX-1803)

Velanixib is a novel, potent, highly selective, orally bioavailable covalent inhibitor of KRAS G12C (IC_{50} = 0.42 nM, SOS1-displacement biochemical assay). Preclinical studies demonstrate nanomolar growth inhibition in KRAS G12C-positive cell lines (NCI-H23, MIA PaCa-2) and durable tumour regression in xenograft models. Importantly, VNX-1803 achieves brain-penetrant concentrations ($K_{\mathrm{p,uu,brain}} = 0.38$), addressing a major unmet need given the 30–50% incidence of CNS metastases in advanced NSCLC.

Phase I dose-escalation (VNX-NSCLC-101; $n = 48$) established the recommended Phase II dose (RP2D) of 240 mg QD, with a manageable safety profile (dose-limiting toxicity: Grade 3 fatigue at 360 mg in 2 patients). Preliminary efficacy data yielded an ORR of 44% and a 12-month OS rate of 68% in KRAS G12C NSCLC.

2.3 Scientific Rationale for Combination

Accumulating evidence supports synergistic interaction between KRAS inhibition and PD-1 blockade:

- KRAS G12C inhibition upregulates MHC-I surface expression and increases tumour-infiltrating lymphocyte density in preclinical models.
- Immune evasion via KRAS-driven MAPK pathway suppresses interferon-γ signalling; VNX-1803 reverses this immunosuppressive phenotype.
- Clinical data from the CodeBreaK 101 study suggest sotorasib plus pembrolizumab is feasible, though hepatotoxicity requires monitoring.
- VNX-1803 exhibits a differentiated hepatic safety profile (ALT elevation $> 3\times$ULN: 6% vs. 23% for sotorasib) and is hypothesised to enable safer combination use.

The KITE-II study tests the hypothesis that dual blockade of the KRAS G12C oncogenic driver and the PD-1/PD-L1 immune checkpoint will produce superior and more durable responses compared with either agent alone in a biomarker-selected NSCLC population.

3 Objectives and Endpoints

3.1 Primary Objective

To evaluate the antitumour activity of velanixib plus pembrolizumab, as measured by ORR per RECIST v1.1 (BICR), in patients with previously treated advanced KRAS G12C-mutant NSCLC.

3.2 Secondary and Exploratory Objectives

Objective	Endpoint	Method
Secondary 1	Disease Control Rate (CR+PR+SD $\geq$12 weeks)	BICR, RECIST v1.1
Secondary 2	Duration of Response (DoR)	BICR
Secondary 3	Progression-Free Survival (PFS)	BICR
Secondary 4	Overall Survival (OS)	Kaplan-Meier
Secondary 5	PROs: LCSS, EQ-5D-5L	ePRO
Secondary 6	PK of VNX-1803 and pembrolizumab	Sparse PK sampling
Secondary 7	Immunogenicity of pembrolizumab	ADA ELISA
Exploratory	ctDNA KRAS G12C allele frequency dynamics	Plasma NGS
Exploratory	Tumour mutational burden (TMB), PD-L1 TPS	IHC / NGS
Exploratory	Mechanisms of acquired resistance at progression	Biopsy WES

4 Study Design

4.1 Overview

KITE-II is a Phase II, open-label, single-arm, multi-centre study enrolling approximately 82 patients across $\sim$18 investigational sites. There is no randomisation or blinding of investigators; however, tumour response assessment will be performed by a blinded independent central review (BICR) committee to minimise ascertainment bias.

4.2 Treatment Regimen

Eligible patients will receive:

- **Velanixib (VNX-1803):** 240 mg orally, once daily (QD), continuously in 21-day cycles.
- **Pembrolizumab:** 200 mg IV over 30 minutes on Day 1 of each 21-day cycle.

Treatment continues until radiographic progression per RECIST v1.1 (confirmed by BICR), unacceptable toxicity, patient withdrawal, or a maximum of 24 months (pembrolizumab), whichever occurs first. Velanixib may continue beyond 24 months at investigator discretion if clinical benefit is maintained.

4.3 Study Periods

1. **Screening:** Up to 28 days prior to Cycle 1 Day 1 (C1D1).
2. **Treatment Period:** C1D1 until end of treatment (EoT).
3. **Safety Follow-Up:** 30-day safety visit after last dose.
4. **Survival Follow-Up:** Minimum 12 months post-EoT (Q12W contacts).

5 Eligibility Criteria

5.1 Inclusion Criteria

Patients must meet **all** of the following:

1. Histologically or cytologically confirmed advanced or metastatic NSCLC (Stage IIIB–IVB per AJCC 8th ed.), predominantly non-squamous histology.
2. Documented *KRAS* G12C mutation by a validated local or central NGS or PCR assay.
3. Receipt of at least one prior platinum-containing chemotherapy regimen for advanced/metastatic disease; prior immunotherapy permitted if not within 6 months.
4. Age $\geq$18 years at time of informed consent.
5. ECOG Performance Status 0 or 1.
6. Measurable disease per RECIST v1.1 (target lesion $\geq$10 mm in longest diameter, or $\geq$15 mm for lymph nodes in short axis).
7. Adequate organ function within 10 days prior to C1D1:
   - ANC $\geq 1.5 \times 10^9$/L; Haemoglobin $\geq$9 g/dL; Platelets $\geq 100 \times 10^9$/L.
   - Creatinine $\leq$1.5$\times$ULN or GFR $\geq$50 mL/min/1.73 m^2.
   - AST and ALT $\leq$2.5$\times$ULN ($\leq$5$\times$ULN if hepatic metastases).
   - Total bilirubin $\leq$1.5$\times$ULN (Gilbert syndrome: $\leq$3$\times$ULN).
8. Female patients of childbearing potential: negative serum pregnancy test within 72 hours of C1D1; agree to highly effective contraception during treatment and 6 months after last dose.
9. Ability to swallow oral medication.
10. Written informed consent prior to any study-specific procedure.

5.2 Exclusion Criteria

Patients must not meet **any** of the following:

1. Known activating *EGFR* mutation (exon 19 del or L858R) or *ALK*/*ROS1*/*RET*/*MET* exon 14 alteration qualifying for approved targeted therapy.
2. Prior treatment with any KRAS G12C inhibitor.
3. Uncontrolled or symptomatic brain metastases. (Stable, treated CNS metastases off steroids $\geq$14 days are eligible.)
4. Active autoimmune disease requiring systemic treatment within 2 years. Replacement therapies are permitted.
5. Systemic immunosuppressive agents within 14 days of C1D1.
6. History of pneumonitis requiring systemic steroids, or current non-infectious pneumonitis.
7. Active hepatitis B (HBsAg+) or hepatitis C (HCV RNA detectable).
8. Known HIV with CD4 $<$350 cells/μL or detectable viral load within 6 months.
9. Concurrent malignancy (except adequately treated basal/squamous cell skin carcinoma or cervical carcinoma in situ).
10. Significant cardiovascular disease: uncontrolled hypertension (BP $>$160/100), NYHA Class III/IV HF, MI within 6 months, QTcF $>$470 ms (female) or $>$450 ms (male).
11. Major surgery within 28 days prior to C1D1.

12. Pregnancy or breast-feeding.
13. Any condition that in the investigator's judgement would make the patient unsuitable for participation.

6 Schedule of Assessments

X = required; ○ = at investigator discretion; blank = not required.

Assessment	Scr	On-Treatment (Cycle, Day 1 unless noted)						EoT	SFU	SuFU
	−28d	C1	C2	C3	C4	C6	C9+		+30d	Q12W
Informed consent	X									
Eligibility review	X									
Medical history / demographics	X									
Physical examination	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X		
12-lead ECG	X	X		X		X		X		
Haematology (CBC/diff)	X	X	X	X	X	X	X	X	X	
Chemistry (LFTs, renal)	X	X	X	X	X	X	X	X	X	
Coagulation (PT, aPTT)	X			X		X		X		
Serum pregnancy test (FOCBP)	X	X		X		X		X		
Thyroid function (TSH, fT4)	X			X		X		X		
Urinalysis	X		X		X		X			
CT chest/abdomen/pelvis	X			X		X	X	X		○
Brain MRI	X					X		X		
KRAS G12C confirmation (local/central)	X									
PD-L1 TPS (IHC 22C3)	X									
ctDNA plasma sample	X	X		X		X		X		○
Tumour biopsy (archival or fresh)	X							○		
PK blood sampling (VNX-1803)		X		X		X				
ADA sampling (pembrolizumab)		X		X		X		X		
PRO: LCSS questionnaire	X	X	X	X	X	X	X	X		
PRO: EQ-5D-5L	X	X	X	X	X	X	X	X		
Survival status / OS										X
Adverse event review		X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	
IP dispensing		X	X	X	X	X	X			

Scr = Screening; EoT = End of Treatment; SFU = Safety Follow-Up; SuFU = Survival Follow-Up; FOCBP = Female of Childbearing Potential

7 Statistical Considerations

7.1 Sample Size and Power

The primary endpoint is ORR assessed by BICR. Based on published Phase II data for KRAS G12C-targeted agents:

- **Null hypothesis (H_0):** ORR $\leq$25% (historical second-line docetaxel).
- **Alternative hypothesis (H_1):** ORR $\geq$45% (anticipated for the combination).
- **Statistical test:** One-sample exact binomial test (one-sided $\alpha = 0.05$).
- **Power:** $\geq$85% to reject H_0 if true ORR = 45%.
- **Sample size:** 62 evaluable patients; ~82 enrolled (25% screen failure).

Calculated using the exact binomial method (nQuery Advisor v10.0; one-sided $\alpha = 0.05$, power $= 85\%$, $p_0 = 0.25$, $p_1 = 0.45$). Sensitivity analysis confirms $n = 62$ yields >90% power if true ORR $= 50\%$.

7.2 Analysis Populations

Population	Definition
Full Analysis Set (FAS)	All enrolled patients who received $\geq$1 dose of any study drug. Primary efficacy population.
Efficacy Evaluable Set (EES)	FAS patients with confirmed KRAS G12C and $\geq$1 post-baseline RECIST assessment. Sensitivity analysis.
Safety Population	All patients who received $\geq$1 dose of any study drug. Primary safety population.
PK Population	All patients with $\geq$1 evaluable PK sample.

7.3 Statistical Methods

Primary endpoint (ORR): The point estimate and exact 95% Clopper-Pearson confidence interval will be computed. A one-sided one-sample exact binomial test will be conducted at $\alpha = 0.05$. H_0 will be rejected if the lower bound of the 95% CI exceeds 25%.

Time-to-event endpoints: PFS, OS, and DoR will be estimated using the Kaplan-Meier method. Medians and 95% CIs (Brookmeyer-Crowley method) will be reported. Landmark analyses at 6, 12, and 18 months will be performed.

Subgroup analyses: Pre-specified subgroup analyses will explore ORR by PD-L1 TPS (<1%, 1–49%, $\geq$50%), prior immunotherapy history, CNS metastases, and ctDNA kinetics. These are considered exploratory.

Missing data: No imputation for the primary endpoint (non-responders classified as failures). Sensitivity analyses with per-protocol and worst-case imputation will be conducted for secondary endpoints.

8 Safety and Adverse Event Reporting

8.1 Adverse Event Definitions

All AEs will be graded per **NCI CTCAE Version 5.0**.

- **Adverse Event (AE):** Any untoward medical occurrence, not necessarily causally related to study treatment.
- **Serious Adverse Event (SAE):** Any AE resulting in: death; life-threatening condition; new/prolonged hospitalisation; persistent significant disability; congenital anomaly; or medically significant event.
- **Dose-Limiting Toxicity (DLT):** As defined in the Phase I VNX-NSCLC-101 study and the Investigator's Brochure (Section 7.3).
- **Adverse Event of Special Interest (AESI):** Immune-related AEs (irAEs), hepatotoxicity (ALT/AST $\geq 3\times$ULN), interstitial lung disease/pneumonitis, QTc prolongation $>$60 ms from baseline or absolute $>$500 ms.

8.2 SAE Reporting Timelines

- **Fatal or Life-Threatening SAEs:** Report to Sponsor Medical Monitor within **24 hours**. Initial report may be verbal; written follow-up required.
- **All other SAEs:** Report to Sponsor within **72 hours** using the study SAE form.
- **Sponsor-to-Regulatory (SUSARs):** Fatal/life-threatening: **7 calendar days**; all others: **15 calendar days** (per 21 CFR 312.32; EudraVigilance).
- **IRB/IEC:** Per local requirements, typically within 10 business days.
- **DSMB:** All Grade 4–5 AEs regardless of attribution within **14 days**.

8.3 Dose Modifications

8.3.1 Velanixib Dose Levels

Dose levels: Level 0 (starting) 240 mg QD; Level -1: 160 mg QD; Level -2: 80 mg QD. No re-escalation permitted after reduction.

- Grade 2 persisting $>$7 days: Interrupt until $\leq$ Grade 1; restart at same dose.
- Grade 3 (first): Interrupt; restart at Level -1 after recovery.
- Grade 3 (second) or Grade 4: Permanently discontinue velanixib.

8.3.2 Pembrolizumab

No dose reduction scheme; pembrolizumab is withheld or permanently discontinued per irAE grade (Keytruda® USPI and site-specific irAE management guidelines):

- Grade 2 irAE: Withhold; restart when $\leq$ Grade 1 and steroids $\leq$10 mg prednisone equivalent.
- Grade 3 irAE: Withhold + high-dose corticosteroids (1–2 mg/kg). Permanently discontinue if not improved to $\leq$ Grade 1 within 12 weeks.
- Grade 4 irAE (non-endocrinopathy): Permanently discontinue pembrolizumab.

8.4 Data Safety Monitoring Board (DSMB)

An independent DSMB (three oncologists, one biostatistician, one patient advocate) will conduct scheduled safety reviews after every 20 enrolled patients and after the first 40 patients complete

Cycle 3. Pre-specified stopping rules:

- $\geq$5 Grade 5 AEs considered at least possibly treatment-related.
- $\geq$30% incidence of Grade $\geq$3 hepatotoxicity (ALT/AST $\geq 5\times$ULN confirmed).
- $\geq$20% incidence of Grade $\geq$3 pneumonitis.

9 Ethics and Informed Consent

9.1 Ethical Principles

This study will be conducted in full compliance with:

- The Declaration of Helsinki (Fortaleza 2013 revision).
- ICH E6(R2) Good Clinical Practice guidelines.
- ICH E8(R1) General Considerations for Clinical Studies.
- 21 CFR Parts 50, 56, and 312 (USA); EU Clinical Trials Regulation No. 536/2014.

9.2 IRB/IEC Approval

The final protocol, ICF, and all patient-facing materials must receive written approval from the accredited IRB/IEC at each site prior to any study-specific procedures. Protocol amendments must be approved before implementation unless necessary to eliminate an immediate safety hazard.

9.3 Informed Consent Process

1. The investigator or delegated, trained team member will explain the study in full in a private setting, using plain-language materials appropriate to the patient's comprehension level.
2. Adequate time (minimum 24 hours) will be provided for the patient to consider participation; involvement of family or an independent advocate is encouraged.
3. Written informed consent must be obtained **before** any study-specific procedure, including eligibility blood or tissue collection.
4. For patients with diminished decision-making capacity, consent of a legally authorised representative will be sought per applicable law.
5. Patients may withdraw at any time without penalty or loss of otherwise-entitled benefit.
6. Re-consent is required for amendments affecting patient participation, risk, or data collection.

9.4 Data Protection and Confidentiality

Patient data will be coded by unique patient identification number; no identifying information will be transmitted to the Sponsor. Data will be processed in accordance with GDPR (EU 2016/679) and HIPAA (45 CFR Parts 160 and 164) as applicable, and stored in a validated, access-controlled EDC system (Medidata Rave, Version 6.x).

9.5 Publication Policy

Results will be submitted for peer-reviewed publication within 12 months of primary data lock, regardless of outcome, per ICMJE guidelines. All investigators contributing $\geq$3 enrolled patients will review manuscripts prior to submission.

10 Regulatory and Administrative Provisions

10.1 Protocol Amendments

Amendments will be formalised as numbered changes requiring Sponsor, Medical Monitor, and IRB/IEC approval (unless urgent safety measures). All amendments will be tracked in the Protocol Amendment Log (Appendix E).

10.2 Investigator Responsibilities

Each principal investigator (PI) is responsible for: conducting the study per protocol, GCP, and applicable regulations; maintaining delegation logs, training records, and site staff CVs; accurate timely EDC data entry; IP storage and dispensing per the IMP management plan; and immediate SAE and protocol deviation reporting to the Sponsor.

10.3 Record Retention

All study documents (source data, signed ICFs, IP accountability records, regulatory correspondence) must be retained for a minimum of 15 years after study completion or as required by applicable regulation.

10.4 Monitoring

Monitoring will be performed by Sponsor-appointed CRAs or a CRO. Site initiation, routine (risk-based, minimum Q3M), and close-out visits are planned. Remote monitoring may be used as appropriate.

Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
ANC	Absolute neutrophil count
AESI	Adverse event of special interest
BICR	Blinded independent central review
CBC	Complete blood count
CNS	Central nervous system
CR	Complete response
CRO	Contract research organisation
CT	Computed tomography
ctDNA	Circulating tumour DNA
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EoT	End of treatment
FOCBP	Female of childbearing potential
GCP	Good clinical practice
GDPR	General Data Protection Regulation
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IHC	Immunohistochemistry
IND	Investigational new drug
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional review board
KRAS	Kirsten rat sarcoma viral proto-oncogene
LCSS	Lung Cancer Symptom Scale
LFT	Liver function test
MRI	Magnetic resonance imaging
NCI CTCAE	NCI Common Terminology Criteria for Adverse Events
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

Signature Page

By signing below, the undersigned confirm they have read and understood Protocol VNX-NSCLC-201 (Version 2.1, 10 June 2025) and agree to conduct the study in accordance with this protocol, GCP, and all applicable regulatory requirements.

Name / Title	Signature	Date
Dr. Catherine R. Hollis, MD, PhD Chief Medical Officer & Medical Monitor Vantrix Oncology, Inc.		
Mr. James T. Nguyen, RAC Vice President, Regulatory Affairs Vantrix Oncology, Inc.		
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