A phase Ib/II open label study of CDX-3379, a human monoclonal antibody targeting ERBB3, in combination with the MEK inhibitor, trametinib, in patients with advanced stage *NRAS* mutant and *BRAF*/*NRAS* wildtype (WT) melanoma

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List of Abbreviations

ADA	Anti-drug antibodies/immunogenicity
AE	Adverse event
AKT	Protein kinase B
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BCNU	Bis-chloroethylnitrosourea
CBC	Complete blood count
CBR	Clinical benefit response
CBRD	Center for Biospecimen Research & Development
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTO	Clinical Trials Office
DLT	Dose limiting toxicty
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data Safety and Monitoring Committee
DTIC	Dacarbazine
EC	Ethics Committee
ECOG (PS)	Eastern Cooperative Oncology Group (performance status)
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EKG	Electrocardiogram
ErbB	Epidermal growth factor family of receptor tyrosine kinases
ERK	Extracellular signal-related kinase
FDA	Food and Drug Administration

FDG	Fluorodeoxyglucose
FNA	Fine needle aspiration
FOXD3	Forkhead box D3 transcription factor
g	Gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GR	Grade
HER3	Human epidermal growth factor receptor 3
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRG	Heregulin
IB	Investigator's Brochure
ICH	International conference on harmonization
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational new drug application
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IV	Intravenous
kg	Kilogram
m_2	Meter squared
mAb	Monocloncal antibody
MAP kinase	Mitogen activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated kinase/Extracellular signal-related kinas
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	NCI Common Terminology Criteria for Adverse Events
NRG	Neuregulin
NSCLC	Non Small cell lung cancer

ORR	Objective Response Rate
OS	Overall survival
pErbB3	Phosphprylated ErbB3
PO	Per os (oral administration)
PET-CT	Positron emission tomography - computed tomography
PFS	Progression free survival
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic(s)
PR	Partial response
PTEN	Phosphate and tensin homolog
Q3W	Every 3 weeks
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interface
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Stable Disease
$T_{1/2}$	Half-life
ULN	Upper limit of normal
US	United States

Study Summary

Title	A phase Ib/II open label study of CDX-3379, a human monoclonal antibody targeting ERBB3, in combination with the MEK inhibitor, trametinib in patients with advanced stage *NRAS* mutant and *BRAF*/*NRAS* wildtype (WT) melanoma
Short Title	ERBB3 and MEK Inhibition in *NRAS* Mutant and WT Advanced Melanoma
Protocol Number	S17-00363
Phase	Phase Ib/II
Methodology	Open label
Study Duration	2 years
Study Center(s)	Initially NYU, with plans to open at possibly one additional site, University of Pennsylvania (PI: Lynn Schuchter, MD)
Objectives	**Primary Objectives:** **Phase 1b:** To determine the RP2D and assess the toxicity and tolerability of the combination of CDX-3379 (ERBB3 antibody) and trametinib (MEK inhibitor) in *NRAS* and *BRAF*/*NRAS* WT melanoma patients **Phase 2:** To estimate the response rates and duration of response of the combination of CDX-3379 (ERBB3 antibody) and trametinib in *NRAS* positive and *BRAF*/*NRAS* WT melanoma patients **Secondary/Exploratory Objectives:** **Phase 1b:** To assess clinical activity and steady-state pharmacokinetics of CDX-3379 and trametinib **Phase 2:** To compare the efficacy of the combination of CDX-3379 (ERBB3 antibody) and trametinib is more effective than a MEK inhibitor alone in *NRAS* positive and *BRAF*/*NRAS* WT melanoma patients alone using locally assessed progression free survival (PFS) and overall survival (OS) **Exploratory Objectives:** To evaluate ERBB3 signaling pathway and MAPK signaling pathway components, in addition to pathway ligands (including NRG1/HRG1 (neuregulin 1/heregulin 1, ERBB3 ligand), expression and correlate this with treatment response.
Number of Subjects	6 participants in phase Ib (up to 18 if needed due to toxicity); 38 in phase II (19 on each arm)
Diagnosis and Main Inclusion Criteria	Unresectable Stage III and Stage IV melanoma who are positive for *NRAS* mutation or who are *BRAF*/*NRAS* WT and failed or are ineligible for standard treatment options
Study Product, Dose, Route, Regimen	CDX-3379 – ERBB3 human monoclonal antibody: 15mg/kg IV every three weeks Trametinib (Mekinist®) – MEK inhibitor: 2 mg PO daily

Duration of administration	CDX-3379 infusion every three weeks and trametinib orally daily until disease progression, intolerable side effects, patient choice, or study closure
Reference therapy	Phase 2 results of response rates will be compared to results from the NEMO trial for *NRAS* mutant melanoma – single agent MEK inhibitor (binimetinib) compared to DTIC – and WT melanoma to results from a phase I trial of trametinib in WT melanoma. For Phase 2 exploratory objectives, PFS can be compared where PFS was 2.8 months for trametinib compared to 1.5 months for DTIC in *NRAS* mutant melanoma and PFS was 2 months for trametinib in WT melanoma.
Statistical Methodology	**Phase 1b:** Safety run in of the combination of CDX-3379 and trametinib and monitored for DLTs. If DLT occurs in 2 or more participants, then de-escalated cohorts will be evaluated. Six to 18 evaluable participants will be treated to identify the MTD/RP2D prior to advancing to phase 2. **Phase 2:** There are two Arms of the study – Arm A: *NRAS* mutant melanoma patients, and Arm B: WT melanoma patients. This is the first part of a Simon Minimax design. Each Arm will initially enroll 19 patients. If, after the 19 patients in each cohort, there are two or fewer responses, the cohort will be stopped. Otherwise, the study will be amended to accrue a total of 36 to each arm (an additional 17 participants per arm). If a true response rate is 0.20, we will have a probability of 0.46 of stopping early and a probability of 0.90 of deciding that the treatment is useful.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Melanoma is the most aggressive form of skin cancer. Its incidence continues to increase yearly, with a prediction for approximately 87,110 new invasive melanoma cases and 9,730 deaths related to melanoma in 2017.[1] New advances in recent years in melanoma have resulted in improved treatment options for patients with advanced stage melanoma (defined as unresectable Stage III or metastatic melanoma). These treatments include ipilimumab, the CTLA-4 antagonist [2]; PD1 antagonists pembrolizumab [3] and nivolumab [4]; vemurafenib [5] and dabrafenib [6], targeted BRAF inhibitors; and trametinib and cobimetinib, targeted MEK inhibitors [7-9]. Newer drugs like MEK inhibitor, binimetinib and BRAF inhibitor encorafenib are undergoing phase III trials [10]. These treatment advances have led to an increase in overall survival benefit in patients with advanced melanoma, which had been lacking with previous melanoma therapies that included traditional chemotherapy, as well as immunotherapy approaches [2,11-13].

A number of these treatment advances are due to the identification of genetic events integral to melanoma pathogenesis and the pairing of therapies directed towards these molecular events and genetic aberrations. In addition to identification of specific somatic mutations in melanoma tumors, the techniques available to detect these mutations have also rapidly evolved. In combination, these powerful tools have advanced the field, changing the landscape and offering promising treatment options for patients.

There is a lack of targeted therapies for melanomas that are *NRAS* mutant and *BRAF* and *NRAS* wildtype (WT). Approximately 20% of melanomas have a NRAS mutation[14-16] and 30% of melanomas are WT[17-20]. Despite recent FDA approval of the CTLA-4 antagonist antibody ipilimumab, and PD-1 antagonist antibodies pembrolizumab and nivolumab, outcomes in advanced melanoma remain poor. In addition, patients can experience significant immune related adverse events that produce considerable morbidity. There is an emerging body of literature, in addition to our preliminary data, that support the involvement of ERBB3 (HER3) in melanoma cell growth and proliferation in this patient subset, and a strong dependency on the MAP kinase pathway[21] which support targeting both ERBB3 and MEK in WT melanoma.

ERBB3 functions as a critical signaling node in tumor pathogenesis and disease progression in a number of solid tumors including melanoma[22-26]. Moreover, high levels of ERBB3 have been associated with poor survival in melanoma patients [27,28], in both *BRAF* mutant and *BRAF* WT samples, as demonstrated by immunohistochemistry, and was also noted to be higher in metastatic lesions compared to paired primary melanoma samples with unknown *BRAF* status[24]. Furthermore, ERBB3 knockdown by RNA interference resulted in decreased melanoma cell proliferation, migration, and invasion *in vitro*[24]. ERBB3 inhibition in combination with RAF and/or MEK inhibition in *BRAF* V600 mutant melanoma demonstrating durable tumor responses, supporting a role for ERBB3 in BRAF resistance [29-32]. A recent study demonstrated that treatment of WT melanoma cell lines with a pan-erbB tyrosine kinase inhibitor decreased ligand-dependent erbB signaling and effective growth inhibition[31]. Targeting ERBB3 with specific neutralizing antibodies decreased cell growth and ERBB3 signaling[25], supporting its importance in *BRAF* WT melanoma.

Numerous studies have established the importance of MAP kinase (MAPK) activation and signaling in melanoma[5,15,16], even in the absence of activating somatic mutations in pathway components[24,31]. Loss of pathway negative regulators and reliance on autocrine signaling contributes to enhanced signaling through the MAPK pathway[33,34]. Treatment of WT melanomas with the RAF inhibitor, RAF265, resulted in reduction of tumor growth[35]. Patient-derived melanoma xenografts were transplanted into nude mice and evaluated for response to treatment with RAF265[35]. Of the seven tumor samples that responded, three (43%) were WT melanoma, and these samples demonstrated decreased tumor growth and activated MEK, the signaling molecule downstream of RAF in the MAPK pathway[35]. These results suggest that the MAPK pathway is a critical signaling node in WT melanoma, independent of acquired somatic mutations.

The combination of MEK inhibition with ERBB3 inhibition results in decreased cell growth and proliferation in WT melanoma cell lines[25]. ERBB3 is a member of the epidermal growth factor receptor family of receptor tyrosine kinases and regulates cell growth and proliferation by heterodimerizing with receptor family members, as well as other receptor tyrosine kinases. CDX-3379 is an ERBB3 antibody which inhibits ligand binding, receptor heterodimerization, and activation of ERBB3 signaling cascade.

MEK inhibitors have been used in the treatment of mutant *BRAF* melanoma [7,36,37]and most recently in clinical trials to target *NRAS* mutant melanoma [38,39]. However, there is promising evidence that MEK inhibition targets the MAPK pathway and decreasing cell growth in WT melanoma cell lines[25]. Indeed, early studies have observed partial response in 10% (4/39) of *BRAF* WT melanoma patients treated with the MEK inhibitor, trametinib[7]. Although there has been significant progress in molecularly targeted therapy in *BRAF*, *NRAS*, and *KIT* mutant melanomas, there remains a substantial number of patients who are not current candidates for targeted therapy. Therefore, targeting these parallel pathways represents a feasible and rational combination strategy which could result in improvement in survival in patients with WT melanomas.

There are limited treatment options beyond immunotherapy for patients with advanced stage *NRAS* mutant melanoma and WT melanoma (*BRAF*/*NRAS* wildtype). Recent studies have demonstrated the importance of the MAPK pathway in these two cohorts of melanoma patients. In addition, ERBB3 overexpression and activation have been identified as a critical signaling pathway in overcoming MAPK inhibition and integral to cell growth and survival. This proposed clinical trial fulfills an unmet need in the treatment of *NRAS* mutant and WT melanoma and provides a unique targeted therapy approach in these two melanoma patient populations.

1.1.1 CDX-3379

A brief description of CDX-3379 and summary of available data is provided below. The CDX-3379 Investigator's Brochure should be consulted for detailed technical information, a complete discussion of nonclinical evaluations and relevant information regarding the known and theoretical safety profile of CDX-3379. The Investigator's Brochure is the Single Reference Safety Document that provides complete and relevant information about the known safety profile of CDX-3379. Updates to these data will be provided as revisions to the Investigator's Brochure and through Investigational New Drug (IND) Safety Reports submitted to the investigator by Celldex, rather than by amendment to this section of the protocol.

CDX-3379 is a human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that specifically binds ErbB3 at a unique epitope and locks ErbB3 in an auto-inhibited configuration making the ErbB3 incapable of binding ligand or dimerizing with known tumor growth drivers such as HER2 and possibly EGFR. The heavy chain CH2 domain of CDX-3379 contains 3 amino acid substitutions that are referred to as YTE (M253Y/S255T/T257E; M252Y/S254T/T256E, according to the EU numbering system). The YTE mutations increase IgG affinity for human fragment crystallizable receptor – neonatal (FcRn) resulting in significantly increased half-life (T1/2) and serum exposure in cynomolgus monkeys; similar effects are predicted in humans [40].

It is hypothesized that CDX-3379 will inhibit ErbB3 via two distinct primary mechanisms of action, ligand-dependent and ligand-independent. The crystal structure of CDX-3379 binding to ErbB3 has been solved and identified a unique binding epitope that gives the structural basis for CDX-3379's potency and dual mechanism of action. CDX-3379 binds ErbB3 outside of the ligand domain and locks ErbB3 in an auto-inhibited configuration making the ErbB3 incapable of binding either ligand or dimerizing with HER2. Locking the receptor in the auto-inhibited state with potent binding affinity should result in comprehensive blockage of ErbB3 signaling that is either neuregulin-driven or directly by interaction with other ErbB receptors (ligand-independent). The antitumor activity of CDX-3379 utilizing both ligand-dependent and ligand-independent inhibition of ErbB3 has been demonstrated nonclinically in multiple xenograft tumor mouse models. An attractive feature of CDX-3379 based on the nonclinical pharmacodynamics studies is the capacity for CDX-3379 to add to the antitumor activity of currently approved therapeutic agents targeting other ErbB family members (dual ErbB blockage), for example, cetuximab targeting EGFR in ligand-dependent models, and trastuzumab targeting HER2 in ligand-independent models.

1.1.2 Trametinib (Mekinist®)

MAPK pathways are evolutionarily conserved kinase modules that link extracellular signals to the machinery that controls fundamental cellular processes such as growth, proliferation, differentiation, migration and apoptosis[41]. This signaling pathway is an attractive therapeutic target because it is aberrantly activated in many human cancers.

Trametinib (Mekinist®) is a reversible and highly selective allosteric inhibitor of MEK1 and MEK2. MEK proteins are critical components of the MAPK pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both BRAF and RAS signal through MEK1 or MEK2. Trametinib was first approved by the FDA in 2013 as a single -agent oral treatment for unresectable or metastatic melanoma in adult patients with *BRAF* V600 mutations. Trametinib is currently also approved in the EU, Canada, and

Australia and multiple other countries for the treatment of adult patients with unresectable or metastatic melanoma. The recommended dose of trametinib is 2 mg once daily (QD).

Trametinib in combination with dabrafenib was first approved by the FDA in 2014 to treat unresectable or metastatic melanoma in adult patients with *BRAF* V600 mutations. The combination therapy is currently also approved in the EU, Australia, Chile, Canada, and multiple other countries.

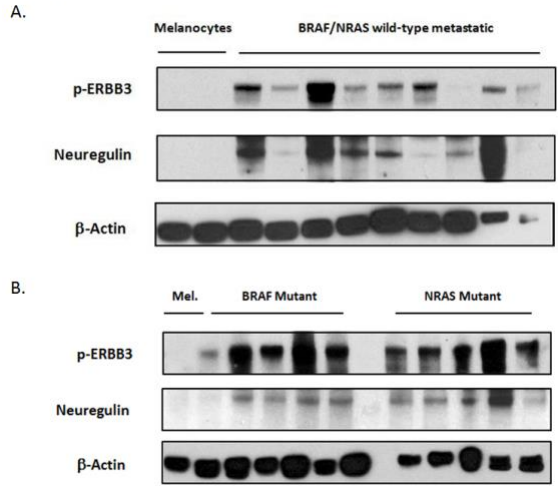
NRAS mutations signal through multiple intracellular signaling pathways of which MAPK pathway is one. MEK inhibitors have been used most recently in clinical trials to target *NRAS* mutant melanoma[15,38,39]. In a recent study, indirect inhibition of NRAS signaling using a MEK inhibitor was evaluated. Advanced stage melanoma patients with a *NRAS* mutation were randomized to treatment with single agent MEK inhibitor, binimetinib, versus DTIC[15]. Results demonstrated that median PFS for patients treated with binimetinib was 2.8 months compared to 1.5 months in patients treated with DTIC, with an objective response rate of 15% compared to 7%, respectively[15]. These results suggest the possibility for future use of targeted therapy in *NRAS* mutant melanoma treatment.

1.1.3 Combination of CDX-3379 and Trametinib

Together, the observations of enhanced ERBB3 and MAPK signaling in advanced melanoma suggest that these signaling pathways may serve as integral mechanisms of tumor growth in a subset of NRAS mutant and WT melanomas and the combination of ERBB3 and MEK inhibition would be synergistic in inhibiting tumor growth, as both MAPK and PI3K signaling pathways would be inhibited.

MEK inhibitors have been used in the treatment of mutant *BRAF* melanoma[7,36,37] and most recently in clinical trials to target *NRAS* mutant melanoma[15,38,39]. However, there is promising evidence that MEK inhibition targets the MAPK pathway and decreasing cell growth in WT melanoma cell lines. Indeed, early studies have observed partial response in 10% (4/39) of *BRAF* WT melanoma patients treated with the MEK inhibitor, trametinib[7]. Although there has been significant progress in molecularly targeted therapy in *BRAF*, *NRAS*, and *KIT* mutant melanomas, there remains a substantial number of patients who are not current candidates for targeted therapy. Therefore, targeting these parallel pathways – ERBB3 and MAPK pathways - represents a feasible and rational combination strategy which could result in improvement in survival in patients with WT melanomas.

Figure 1



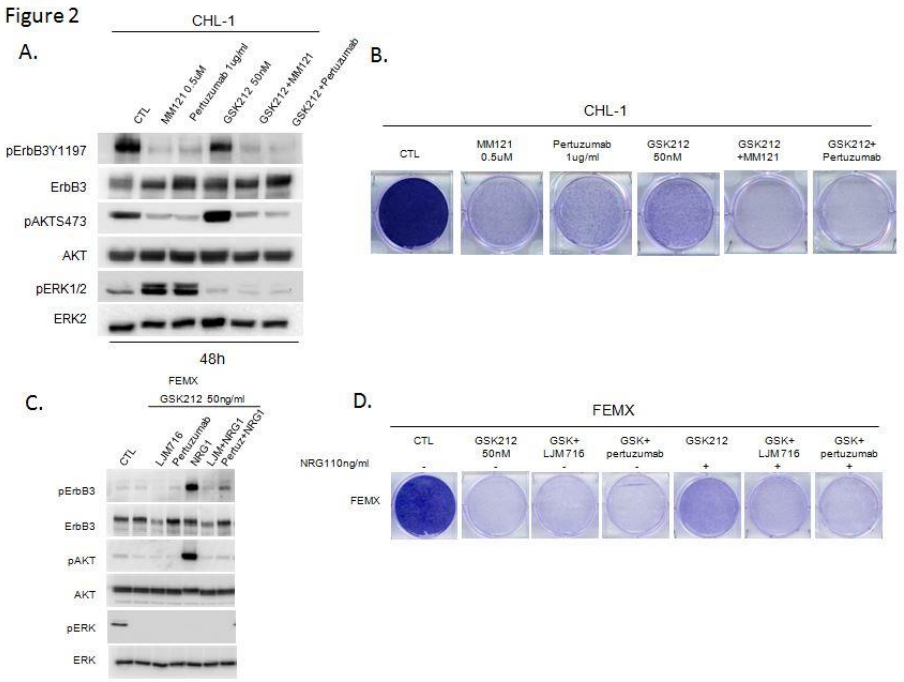
We have preliminary data which support the combination of ERBB3 and MEK inhibition *in vitro* from experiments performed with my collaborators, as well as studies performed here at NYU.

ERBB3 and its ligand, neuregulin, are upregulated in WT melanoma tumor samples

Since enhanced ERRB3 signaling may be integral to WT melanomas, we next analyzed the nine WT melanoma tumor samples by Western blot analysis for activation of ERBB3. In the nine WT melanoma tumor samples, we detected increased phospho-ERBB3 (pERBB3) in eight out of nine samples as compared to control melanocytes, normalized to β-actin (Figure 1A). We also observed expression of activated pERBB3 in *BRAF* mutant and *NRAS* mutant melanoma tumor samples (Figure 1B). Recent data from early phase clinical trials, as well as a recent study with another ERBB3 antibody[42], demonstrated that expression of ERBB3 ligand, neuregulin (NRG1), is a crucial determinant for response to ERBB3 inhibition. We evaluated this relationship in our WT tumor samples. Western blot analysis demonstrated variable levels of neuregulin in the WT samples, levels which were higher than in control melanocytes (Figure 1A), consistent with NRG1 mediated signaling.

Combination ERBB3 and MEK inhibition results in decreased cell growth in WT melanoma cell lines

Capparelli et al.[25] demonstrated decreased cell growth and proliferation in WT melanoma cell lines when treated with the combination of ERBB3 antibody and MEK inhibitor (Figure 2), similar to their recently published data[25]. CHL-1 is a WT melanoma cell line that depends upon the NRG1 autocrine pathway. A Western blot demonstrates that treatment with ERBB3 antibody (MM-121) decreases signaling through ERBB3 and the PI3K



pathway, confirmed by decreased phospho-AKT (pAKTS473) and pERBB3 (pErbB3Y1197) (Figure 2A). The MAPK pathway molecule, ERK, is phosphorylated after 48 hr of treatment (pERK1/2). Using an inhibitor of the MAPK pathway, the MEK inhibitor GSK212, EKR phosphorylation is inhibited, but after 48hr of treatment, AKT phosphorylation is increased. However, combination of both the ERBB3 antibody and MEK inhibitor results in decreased phosphorylation of AKT and ERK, indicative of pathway inhibition. Pertuzumab, a HER2(ERBB2) inhibiting antibody confirms that ERBB2 is the signaling partner for ERBB3, as previously demonstrated[25,43], as ERBB3 has no intracellular signaling moiety and signals through heterodimerization with a receptor in the EGFR family. These data are supported by growth assays with CHL-1 cells and crystal violet staining (Figure 2B) where the combination of ERBB3 and MEK inhibitors produced more growth inhibition than either treatment alone. FEMX is a WT melanoma cell line that expresses ERBB3, but does not express NRG1. In these cells, treatment with the MEK inhibitor, GSK212, inhibits ERK phosphorylation (pERK), but does not affect pERBB3 levels (Figure 2C). Treatment with exogenous NRG1 results in activation of ERBB3 signaling with increased pERBB3 and pAKT, but pERK remains decreased. In the presence of exogenous NRG1, treatment with the combination of an ERBB3 antibody (LJM716) and GSK212 results in inhibition of ERBB3 and MAPK pathway activation, again with decreased pAKT and pERK. Results are recapitulated with pertuzumab, confirming that the ERBB3 signaling partner is ERBB2. Again, these data are supported by *in vitro* growth assays, demonstrating decreased cell growth in the setting of pathway inhibition with the combination of compounds, especially in the presence of NRG1 (Figure 2D). In sum, these *in vitro* data strongly support a role for ERBB3 inhibition, either alone or in combination with MEK inhibition, in WT melanoma.

1.2 Investigational Agent

This clinical trial uses the investigational agent CDX-3379, an ERBB3 monoclonal antibody which inhibits ligand binding, receptor heterodimerization, and activation of ERBB3 signaling cascade. This clinical trial will also use the MEK inhibitor, trametinib, in melanoma populations for which it is not currently approved, *NRAS* mutant and *BRAF*/*NRAS* wildtype (WT) melanomas.

1.2.1 CDX-3379

Detailed technical information regarding CDX-3379 is provided in the Investigator's Brochure.

CDX-3379 isa human IgG1λ mAb that specifically binds ErbB3 at a unique epitope and locks ErbB3 in an auto-inhibited configuration making the ErbB3 incapable of binding ligand or dimerizing with known tumor growth drivers such as HER2 and possibly EGFR.

1.2.2 Trametinib (Mekinist®)

Trametinib is absorbed orally with median time to achieve peak concentrations (tmax) of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72%. The increase in exposure (Cmax and AUC) was dose proportional following repeat dosing. Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 127 hours (5.3 days) after single oral dose administration. Steady-state was achieved by Day 15. *In vitro* and *in vivo* studies demonstrated that trametinib is metabolized predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolized by glucuronidation. The deacetylation is mediated by the carboxyl -esterases 1b, 1c and 2, with possible contributions by other hydrolytic enzymes. Drug-related material was excreted predominantly in the feces (≥ 81% of recovered radioactivity) and to a small extent in urine (≤19%). Less than 0.1% of the excreted dose was recovered in urine.

1.3 Preclinical Data

1.3.1 CDX-3379 - Summary of Nonclinical Experience

CDX-3379 has shown the following activity in nonclinical studies as summarized in greater detail in the CDX-3379 investigator brochure:

- In vivo antitumor activity in ligand-independent xenograft models in which the tumor is driven by HER2. High levels of heterodimerization partners of ErbB3 through amplification or mutation (such as EGFR or HER2) may drive tumor growth without involvement of NRG
- Significant in vivo antitumor activity in ligand-dependent xenograft models in which an autocrine loop drives growth (tumor provides NRG and ErbB3) including models of HNSCC, squamous NSCLC and BRAF mutated tumors. Evaluation of human tumors indicates that the highest prevalence of NRG is observed in squamous tumors such as HNSCC, NSCLC and esophageal as well as BRAF mutated thyroid samples. Analysis of human HNSCC tumors indicates NRG is expressed broadly and independent of anatomical site and expressed in both HPV positive and negative tumors, although NRG levels are higher in HPV negative tumors.
- Significant in vivo antitumor activity including tumor regression when given in combination with agents that target other ErbB family members (in combination with cetuximab, which inhibits EGFR, in combination with afatinib, which inhibits EGFR, and in combination with trastuzumab, which inhibits HER2).

- Increased expression of ErbB3 and sensitivity to NRG stimulation in response to BRAF mutated cells after treatment with BRAF inhibitors or MEK inhibitors. Combination treatment of tumor bearing mice with CDX-3379 with either a MEK inhibitor, a BRAF inhibitor, or their combination did not enhance antitumor activity in BRAF mutated tumor models that lack NRG expression, but resulted in enhanced antitumor activity in tumor models which express NRG.

To obtain sufficient nonclinical data on the safety and efficacy of CDX-3379 to support use in clinical trials and approval to market, the nonclinical testing program was designed to address efficacy and safety. The mouse and cynomolgus monkey were selected as pharmacologically relevant species for evaluation of safety of CDX-3379 based on sequence homology of ErbB3, affinity for binding of CDX-3379 to ErbB3, and comparable in vitro functional activity (ability to block NRG-induced ErbB3 phosphorylation).

CDX-3379 overall exhibited non-linear PK. Following the intravenous (IV) bolus administration of CDX-3379, exposure (area under the concentration time curve; AUC) increased in a greater than dose-proportional manner and clearance of CDX-3379 decreased from 96.0 to 49.9 milliliters (mL)/day/kilogram (kg) as the dose increased from 10 to 150 mg/kg twice weekly in mice, 41.0 to 5.74 mL/day/kg as the dose increased from 0.3 (single dose) to 150 mg/kg (weekly dose) in cynomolgus monkeys. There was moderate accumulation of CDX-3379 in mice and cynomolgus monkeys after repeat IV administrations. The accumulation ratio (AR) ranged from 1.2 to 2.3 for mice (twice weekly dosing), and 1.1 to 3.5 for cynomolgus monkeys (weekly dosing). No differences in the pharmacokinetics (PK) were observed between male and female animals. The presence of antibodies against CDX-3379 (anti-drug antibodies, ADA) within the dosing phase appeared to reduce CDX-3379 exposure in some animals.

There were no observed adverse effects in cluster of differentiation 1 (CD-1) mice or cynomolgus monkeys that were attributed to repeated IV administration of up to 150 mg/kg/dose of CDX-3379, the highest dose tested. In the Good Laboratory Practice (GLP) CD-1 mouse study, 8 toxicity animals and 14 toxicokinetic (TK) animals administered CDX-3379 died or were euthanized in moribund condition; however, the effects were not considered directly related to CDX-3379, but were attributed to anaphylactoid reactions from repeated exposure to a foreign antigen (because CDX-3379 is a human IgG1). In cynomolgus monkeys, there were also no CDX-3379-related effects on safety pharmacology parameters including behavior (as assessed by standard clinical observations), heart rate, body temperature, blood pressure, or electrocardiogram (ECG) measurements in cynomolgus monkeys. There were no adverse effects on local tolerance following IV bolus or infusion administration of CDX-3379 to CD-1 mice or cynomolgus monkeys.

1.3.2 Trametinib (Mekinist®) – Summary of Nonclinical Experience

See IB for detailed information

1.4 Clinical Data to Date

1.4.1 CDX-3379 - Summary of Clinical Experience

The clinical experience with CDX-3379 has included three clinical studies.

Study KTN3379-CL-001 was a first-in-human Phase 1/1b study of adult patients with advanced solid tumors refractory to standard therapy (or for which no standard therapy existed). Patients received a 60-minute IV infusion of CDX-3379 once every three weeks as monotherapy (Phase 1) or in combination with other targeted anticancer agents (Phase 1b). In the Phase 1 study portion, a total of 21 patients were treated across three dose-escalation cohorts (5, 10, and 20 mg/kg), an intermediate-dose level cohort (15 mg/kg), and a flat-dose cohort (1200 mg). As no dose limiting toxicities were reported, a maximum tolerated dose for CDX-3379 monotherapy was not determined. Pharmacokinetic (PK) analysis showed trough CDX-3379 plasma levels exceeding target concentrations at doses ≥10 mg/kg. During this portion of the study, plasma ErbB3 levels increased in all patients at all doses consistent with target engagement; however, no objective tumor responses were reported.

In the Phase 1b study portion, a total of 43 patients were treated with CDX-3379 in combination with cetuximab (head and neck cancer or K Ras wild type colon cancer), erlotinib (non-small cell lung cancer), vemurafenib (BRAF mutated melanoma), or trastuzumab (HER2 positive breast or gastric cancer). Patients with other cancer types and no other standard therapeutic options were also treated in Part II if thought to have the potential to benefit from therapy. The starting dose of CDX-3379 in all cohorts was 20 mg/kg. However, due to the occurrence of two dose-limiting toxicities in the cetuximab combination cohort (Grade 3 diarrhea and Grade 3 mucositis), the starting dose of CDX-3379 was reduced to 15 mg/kg for new patients receiving treatment of cetuximab and CDX-3379. The starting dose of CDX-3379 was also reduced to 15 mg/kg in the trastuzumab combination cohort after a patient with gastroesophageal cancer experienced grade 4 pulmonary hypertension and pulseless electrical activity arrest resulting in death. However, this event was ultimately assessed as associated with progression of disease and right-sided cardiomyopathy and unrelated to study therapy. Additional dose-limiting toxicity (DLT) were a second case of Grade 3 diarrhea in the cetuximab cohort (after reduction of the CDX-3379 dose to 15 mg/kg); Grade 3 diarrhea in the erlotinib combination cohort (per final data as per communication with Celldex 12 Oct 2017). Per a preliminary PK analysis conducted in May 2016, half-life of CDX-3379 was 17 days and the clearance for CDX-3379 was 2.6 mL/kg/day. All patients achieved serum concentrations required for maximal antitumor activity in animal tumor models. RECIST tumor responses were observed in this portion of the study. One patient with advanced HNSCC who had previously progressed on single-agent cetuximab experienced a complete response with CDX-3379 20 mg/kg and cetuximab. The patient remained on study therapy without progression for over 10 months compared with a 5 month progression free interval during his prior therapy with single agent cetuximab. The patient's cancer history was notable for having undergone multiple surgeries and prior treatment with chemoradiation (cisplatin), cisplatin/5-fluorouracil in addition to single agent cetuximab. The patient's cancer tissue tested positive for NRG mRNA. Two patients with BRAF-mutated non-small cell lung cancer achieved partial responses with CDX-3379 and vemurafenib. One of these patients had progressive disease as best response after 2 months of an alternative BRAF inhibitor (dabrafenib), but received CDX-3379 and vemurafenib for 13 months before experiencing disease progression. Finally, one patient with multifocal papillary thyroid cancer experienced a partial response at a single timepoint before discontinuing study due to adverse events of diarrhea, hypokalemia and hypophosphatemia.

Study KTN3379-CL-002 was conducted to evaluate ErbB3 phosphorylation (pErbB3) and other molecular endpoints in tumor tissue before and after treatment with CDX-3379. In this study, twelve patients with surgically resectable, untreated HNSCC were treated with CDX-3379 every 14 days at a dose of 1000 mg IV over 60 minutes, for a maximum of 3 doses prior to surgical resection. Interim data analysis from the first five patients showed that CDX-3379 treatment resulted in a decrease in pErbB3 in post-treatment tumor tissue in 3 of 5 patients. One marked clinical response was noted. A patient with recently diagnosed HPV-negative squamous cell carcinoma of the floor of the mouth experienced a 26% decrease in target lesions radiographically, reported to represent 92% reduction in tumor volume by physical exam. The patient also experienced marked improvement in pain and ability to eat.

Study KTN3379-CL-003 was a pilot study to determine whether the combination of vemurafenib and CDX-3379 can increase tumoral iodine incorporation sufficient to warrant ^{131}I treatment as determined by PET/CT lesional dosimetry, for patients with BRAF mutant, radioiodine-refractory (RAIR) thyroid cancer. This study was closed to accrual after enrollment of 7 patients due to slow enrollment and project prioritization.

1.4.2 Trametinib (Mekinist) - Summary of Clinical Experience

Phase II dosing of trametinib was determined to be 2 mg once a day based on the phase I dose-escalation trial [7,44] of 206 advanced solid tumor patients which included 97 patients with both *BRAF* mutant and wild type melanoma. The loading dose of trameitnib at 10mg daily for two days followed by 3 mg daily thereafter exceeded the maximum tolerated dose, with dose-limiting toxicities including rash, diarrhea, and retinopathy. Trametinib 3 mg daily was deemed to be the maximum tolerated dose and after the first cycle, 1 patient discontinued therapy due to fatigue, 5 patients required dose interruptions, and 2 patients required dose-reduction. Pharmacodynamic testing of trametinib 2 mg once daily in *BRAF* mutant patients showed a 62% inhibition of pERK, 83% inhibition of Ki67, and 171% increase of p27, which were improved from the pre-clinical target threshholds [44]. Trametinib produced a response rate of 33% in the 30 *BRAF* mutant patients including 2 complete responses and 5 partial responses among the 16 patients on a dose of 2 mg once daily. Treatment-related adverse events included acneiform dermatitis or rash, (82%), diarrhea (45%), peripheral edema (35%),

fatigue (35%), nausea (12%), ocular events (10%) (which occurred mostly at doses greater than 2 mg daily), and a decrease in ejection fraction (7%) [7].

See IB for further detailed information

1.5 Dose Rationale

Participants on this clinical trial will receive CDX-3379 at 15mg/kg IV every three weeks and trametinib 2mg PO daily.

A single agent study evaluated CDX-3379 at a range of concentrations, with upper limit of 20mg/kg without observed dose limiting toxicity. Pharmacokinetic (PK) analysis showed trough CDX-3379 plasma levels exceeding target concentrations at doses ≥10 mg/kg. In combination studies of CDX-3379 with other monoclonal antibodies, a few patients experienced side effects at the 20mg/kg dosing, requiring decrease to 15mg/kg. CDX-3379 in combination with another oral TKI that disrupts the BRAF/MEK/ERK pathway (vemurafinib) was well tolerated with no reported DLTs with doses up to 20mg/kg. At 15mg/kg, objective tumor responses were observed.

The recommended dose of trametinib is 2mg daily. This dose was chosen based on a number of clinical trials as the recommended dosing, even though the maximum tolerated dose being 3 mg daily.

Given the cumulative information regarding dosing and observed response, the recommended starting doses for the combination of ERBB3 and trametinib were chosen to be CDX-3379 at 15mg/kg IV every three weeks and trametinib 2mg PO daily.

1.6 Research Risks & Benefits

1.6.1 Risk of Study Drug

1.6.1.1 CDX-3379

CDX-3379 has been given to approximately 80 patients with different types of advanced cancers in three clinical studies. More than half of these patients have received CDX-3379 in combination with another anticancer treatment. The patients who received CDX-3379 in combination with other anticancer medications, including cetuximab, tended to experience more frequent and more severe side effects.

Overall, side effects thought to be related to study treatment have included the following:

- Frequent side effects (occurring in >20% of the patients):
  - Diarrhea *(54%; diarrhea)*
  - Nausea *(27%; nausea)*
  - Fatigue *(28%; fatigue)*
  - Rash *(21%; Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic)*
- Somewhat frequent side effects (occurring in 11-20% of the patients):
  - Mucositis/Stomatitis (painful inflammation and ulceration of the mucous membranes lining the mouth or digestive tract) *(16%; Mucosal inflammation, Stomatitis)*
  - Vomiting *(15%; vomiting)*
  - Low blood potassium *(15%, Hypokalaemia, Blood potassium decreased)*

  - Decreased appetite *(12%; Decreased appetite)*
- Less frequent side effects (occurring in 6-10% of the patients):
  - Bad taste in the mouth *(10%; Dysgeusia)*
  - "Pimply" (or acne-like) rash *(10%; Dermititis acneiform)*
  - Weight loss *(9%; Weight decreased)*
  - Low blood magnesium *(9%; Hypomagnesaemia, Blood magnesium decreased)*
  - Dehydration *(7%; Dehydration)*
  - Itching *(7%; Pruritus)*
  - Weakness *(6%; Asthenia)*
  - Dizziness *(6%; Dizziness)*
  - Dry skin *(6%; Dry skin)*

Some of the above events required hospitalization or were otherwise considered serious.

The adverse drug reactions (ADRs; expected adverse events) listed were identified by the Sponsor based on reasonable evidence of casual association with CDX- 3379, based on clinical experience as of May 24, 2017. The Sponsor consults this section as reference for expectedness of SAEs with regard to expedited reporting requirements for regulatory purposes. A SAE will be considered "unexpected" if not consistent in nature or severity with the listed ADRs, with consideration to the noted serious adverse drug reactions (SARs; treatment related SAEs recorded per CTCAE v4.03 criteria). The table of ADRs is not a complete list of adverse events reported in clinical trials. A cumulative tabulation of all adverse events assessed as treatment-related by the investigators across all Celldex-sponsored studies of CDX-3379 are provided in the IB.

1.6.1.1.1 Management of Toxicity Related to CDX-3379

Potential toxicity and guidance for the management of toxicity is summarized below. However, the CDX-3379 Investigator's Brochure is the Single Reference Safety Document that provides complete and relevant information about the known safety profile of CDX-3379. Updates to these data will be provided as revisions to the Investigator's Brochures and through Investigational New Drug (IND) Safety Reports submitted to the investigator by Celldex, rather than by amendment to this section of the protocol.

CDX-3379 alone has been well tolerated with mild to moderate adverse events including diarrhea, rash, mucositis, fatigue and dry mouth and severe toxicity (diarrhea, hypokalemia) reported in only two of 21 patients. Most common adverse events reported in the Phase 1b study for the combination of CDX-3379 and targeted agents (including other EGFR or BRAF inhibitors) have included diarrhea, mucositis and rash with diarrhea and mucositis meeting criteria for DLTs.

As a routine precaution, the investigative site's medical staff is to closely observe patients for the duration of the CDX-3379 infusion and for at least 1 hour after the end of the infusion, in an area with resuscitation equipment and agents used for management of infusion related reactions (e.g., antihistamines, epinephrine, corticosteroids). A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area.

In order to mitigate the risk and severity of adverse events resulting from study therapy, patients will undergo extensive monitoring throughout the study and guidelines will be implemented per this protocol to ensure that study therapy is discontinued and/or modified as necessary and medical therapy is instituted when appropriate to manage adverse events.

Dermatologic Toxicity
Dermatologic toxicities have been reported with CDX-3379 as single agent in the Phase 1 trial in advanced cancer patients, and have also been reported in study KTN3379-CL-001 amongst patients treated with the

combinations containing CDX-3379. Supportive management with topical, oral antibiotic therapy or other measures should be taken according to institutional standards.
Recommended dose modification for grade 3 or 4 acneiform rash is provided in Table 5.

Table 5. Dose Modification Guidance for Rash

	CDX-3379
1st Occurrence	Delay infusion by 1-2 weeks · Improvement: Resume at same dose · No Improvement: Discontinue
2nd Occurrence	Delay infusion by 1-2 weeks · Improvement: Resume at same dose · No Improvement: Discontinue
3rd Occurrence	Delay infusion by 1-2 weeks · Improvement: Reduce dose by one level · No Improvement: Discontinue
4th Occurrence	Delay infusion by 1-2 weeks · Improvement: Reduce dose by one level · No Improvement: Discontinue

Diarrhea

Diarrhea is a common toxicity associated with cancer treatments in general and occurs frequently with mAb and tyrosine kinase inhibitors that target the ErbB family of receptors (Stein et al, 2010). Specifically, diarrhea was reported in the Phase 1 study of CDX-3379 conducted in patients with advanced solid tumors and was also a frequent adverse event among patients treated with the combination of CDX-3379 and targeted agents.

Treatment guidelines exist for the management of cancer treatment-induced diarrhea that include, but are not limited to, the following key elements independent of dose modifications:

- Patient education
- Maintaining oral hydration
- Early intervention with and frequent use of anti-diarrheals until sustained resolution (eg., loperamide initial dose of 4 mg followed by 2 mg every 2 hours)
- Frequent monitoring and replacement of electrolyes (eg., potassium, magnesium)

Patients should be managed according to institutional standards and patients should be carefully instructed to monitor for diarrhea as well as be instructed on proper management of these symptoms as they occur or change during the course of study therapy.

Patients with grade 4 diarrhea should discontinue study therapies unless the toxicity resolves quickly and the patient is benefitting from therapy, in which case the therapy may be continued at a reduced dose after discussion with the Medical Monitor.

Recommended dose modification grade 2 or 3 diarrhea is provided in Table 6.

Table 6. Dose Modification Guidance for Diarrhea

Grade 3 or Persistent Grade 2 Diarrhea*	**CDX-3379**

1st Occurrence	· Delay infusion by 1-2 weeks till diarrhea ≤ Grade 1 · Resume at same dose
2nd Occurrence	· Delay infusion by 1-2 weeks till diarrhea ≤ Grade 1 · Reduce dose by one level
3rd Occurrence	· Delay infusion by 1-2 weeks till diarrhea ≤ Grade 1 · Reduce dose by one level
Additional occurance(s)	· Delay infusion by 1-2 weeks till diarrhea ≤ Grade 1 · Reduce dose by one level or discontinue

* Despite maximum medical therapy with anti-diarrheals. Persistent is defined as diarrhea that lasts ≥ 3 days.

Infusion Reactions
Infusion reactions, including those that are severe, are possible with CDX-3379. Infusion reactions may occur during the infusion of CDX-3379 or may be delayed until any time after the infusion.

For infusion-related reactions that occur during the administration of CDX-3379 consider temporarily or permanently discontinuing CDX-3379depending on the severity of the infusion reaction and the required interventions. For NCI CTC Grade 1 or Grade 2 infusion reactions, the infusion may be resumed at a 50% reduction in rate after symptoms have resolved and may be considered for subsequent cycles. For Grade 1 or Grade 2 infusion reactions, patients will be treated with Benadryl and/or Solucortef for their first infusion related reaction. If patients experience an infusion related reaction, patients will be pre-medicated with Benadryl and/or Solucortef prior to their next infusion. The following infusion will resume at the full dose. If a second infusion related reaction occurs, subsequent infusions will be given at a 50% reduction. Immediately and permanently discontinue CDX-3370 for serious infusion reactions, requiring medical intervention and / or hospitalization.

Patients who develop a grade 3 or 4 infusion reaction during CDX-3379 should not receive further treatment with CDX-3379. Grade 3 or Grade 4 reactions will be treated with Benadryl, Solucortef and/or an H2 blocker.

1.6.1.2 Trametinib (Mekinist®)

The safety profile of trametinib has been well established and detailed in the product's package insert and IB. The most common adverse reactions (occurring in greater than 20% of patients) include rash, diarrhea, and lymphedema (package insert). Additional common side effects (occurring in greater than 10% of patients) dermatitis acneiform, dry skin, pruritis, paronychia, stomatitis, abdominal pain, hypertension, and hemorrhage (package insert). Additional side effects (occurring in less than 10% of patients) include blurred vision, dry eye, dizziness, dysgeusia, folliculitis, pustular rash, cellulits, bradycardia, cardiomyopathy, xerostomia, and rhabdomyolysis (package insert). Rare adverse events (occurring in less than 5% of patients) include retinal pigment epithelial detachment (RPED), retinal vein occlusion (EVO), and interstitial lung disease (package insert). Laboratory abnormalities (occurring in greater than 5% of patients) include increased AST, increased ALT, hypoalbuminemia, anemia, and increased alkaline phosphatase (package insert).

Trametinib is an inducer of CYP3A4 *in vitro*. However, trametinib's efficacious dose of 2 mg once daily results in a low systemic maximal concentration (22.2 ng/mL or 0.036 μM), relative to its *in vitro* inhibition potency of CYP enzymes and transporters, rendering the risk of an inhibitory effect of trametinib on the PK of co-administered CYP or transporter substrates low. Trametinib is eliminated primarily via deacetylation and possibly other hydrolases. There is little evidence from clinical studies for drug interactions mediated by carbox ylesterases. Trametinib is also a substrate of P-gp and BSEP. However, due to its high passive permeability, these active transport processes are likely of limited relevance. Therefore, a clinically relevant effect of a co-administered P-gp or BSEP inhibitor on the PK of trametinib is unlikely.

1.6.1.2.1 Management of Toxicity Related to Trametinib

Table 1. Recommended Dose Modifications for Trametinib

Target Organ	Adverse Reaction[a]	Dose Modification
Cutaneous	Grade 2 rash (tolerable)	Continue treatment and monitor
	Intolerable Grade 2 rash or Grade 3 or 4 rash	Withhold Trametinib for up to 3 weeks If improved within 3 weeks, resume Trametinib at a lower dose (reduced by 0.5 mg) or discontinue Trametinib in patients taking Trametinib 1 mg daily
	Intolerable Grade 2 or Grade 3 or 4 rash that does not improve within 3 weeks despite interruption of Trametinib dosing	Permanently discontinue Trametinib
Cardiac	Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value	Withhold Trametinib for up to 4 weeks. If improved within 4 weeks, resume Trametinib at a lower dose (reduced by 0.5 mg) or discontinue Trametinib in patients taking Trametinib 1 mg daily
	- Symptomatic congestive heart failure - Absolute decrease in LVEF of greater than 20% from baseline that is below LLN - Absolute decrease in LVEF of 10% or greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption of Trametinib	Permanently discontinue Trametinib
Ocular	Grade 2-3 retinal pigment epithelial detachments (RPED)	Withhold Trametinib for up to 3 weeks. If improved to ≤ Grade 1 within 3 weeks, resume Trametinib at a lower dose (reduced by 0.5 mg) or discontinue Trametinib in patients taking Trametinib 1 mg daily. If it does not improve to ≤ Grade 1 within 3 weeks, discontinue Trametinib.

Ocular	Retinal Vein Occlusion	Permanently discontinue Trametinib
Pulmonary	Interstitial lung disease/pneumonitis	Permanently discontinue Trametinib
Other	Intolerable Grade 2 adverse reaction Grade 3 adverse reaction	Withhold Trametinib for up to 3 weeks. If Grade 3 adverse reaction improves to ≤ Grade 1 following interruption of Trametinib within 3 weeks then reduce dose of Trametinib by 0.5mg or discontinue Trametinib in patients taking Trametinib 1 mg daily.
	Grade 4 adverse reaction or Grade 3 adverse reaction that does not improve to Grade 0-1 within 3 weeks	Permanently discontinue Trametinib

1.6.2 Overlapping Toxicities

Unless a side effect is specific to only trametinib (cardiac (red LVEF), ocular (RPED, RVO), and/or pneumonitis), both drugs should be held together. With the exception of the trametinib specific side effects, all other side effects can be considered from either medication.

1.6.3 Dose-Limiting Toxicities

For this study, DLT is defined as all toxicities regardless of attribution to study drug, with the exception of toxicities clearly due to disease progression or identified extraneous cause.

The following AEs will be considered to be DLTs:

- Any toxicity that requires permanent discontinuation of either drug. Note: this would include retinal vein occlusion, interstitial lung disease, and any toxicity identified in the dose modification guidelines for CDX-3379.
- Any toxicity regardless of grade that requires an interruption of more than 4 weeks.
- Any fatal adverse event.

Hematologic Toxicity:

-Grade 4 neutropenia (absolute neutrophil count (ANC) < 500/ul) lasting > 7 days.

-Febrile neutropenia (ANC<1,000/ul).

-Grade 4 thrombocytopenia (platelet count < 25,000/ul).

-Grade 3 thrombocytopenia (platelet count 25,000/ul to 50,000/ul) with clinically important bleeding.

Nonhematologic Toxicity:

All other Grade 3 or higher nonhematologic toxicities with the following exceptions:

-Alopecia

-Grade 3 nausea, vomiting, and/or diarrhea that lasts <72 hours with adequate antiemetic and supportive care.

- Grade 3 electrolyte abnormalities that are asymptomatic and last ≤ 24 hours with medical intervention.

1.6.4 Other Risks of Study Participation

Risks of study participation may be that the drugs under study will not be effective for some participants. In this case, the study drugs will be discontinued and participants will continue regular care by their provider to determine the next appropriate step in therapy. The study may also require additional outpatient visits, blood tests, and tissue biopsies that may otherwise not be required off study. The risks associated with blood draw include weakness, redness, pain, bruising, bleeding, or infection at the needle site. The effects of FNA and core biopsies are generally mild; slight discomfort and light bleeding are to be expected. Participants have the option of discontinuing study treatment at any time. Trial investigators will determine the appropriate drug dose and will administer this in the phase 2 portion of the trial. There has been clinical experience previously with all of the study drugs and investigators will continually monitor for adverse events.

1.6.5 Potential Benefit

Participants participating in the research study will have access to combination therapy with trametinib and CDX-3379, an ERBB3 inhibitor. The information obtained from this research may help others with this disease in the future. Subjects' health may improve while on the trial, but it may not. It is hoped that results from this trial may help others with this disease**.**

2 Study Objectives

Primary Objectives:

Phase 1b: To determine the MTD/RP2D and asses the toxicity and tolerability of the combination of CDX-3379 (ERBB3 antibody) and trametinib (MEK inhibitor) in *NRAS* and *BRAF*/*NRAS* WT melanoma patients

Phase 2: To estimate the response rate and duration of response of the combination CDX-3379 and trametinib in *NRAS* mutant and *BRAF*/*NRAS* WT melanoma patients

Secondary/Exploratory Objectives:

Phase 2: To compare the efficacy of the combination of CDX-3379 (ERBB3 antibody) and trametinib is more effective than a MEK inhibitor alone in *NRAS* positive and *BRAF*/*NRAS* WT melanoma patients alone using locally assessed progression free survival (PFS) and overall survival (OS)

Exploratory Objectives:

To evaluate ERBB3 signaling pathway and MAPK signaling pathway components, in addition to pathway ligands, including NRG1/HRG1 (neuregulin 1/heregulin 1, ERBB3 ligand) expression and correlate this with treatment response.

- archival tissue and pre-treatment, on treatment, and progression tumor samples will also be obtained for all patients in Phase Ib and the first 5 patients with *NRAS* mutant melanoma and the first 5 patients with WT melanoma in Phase II.

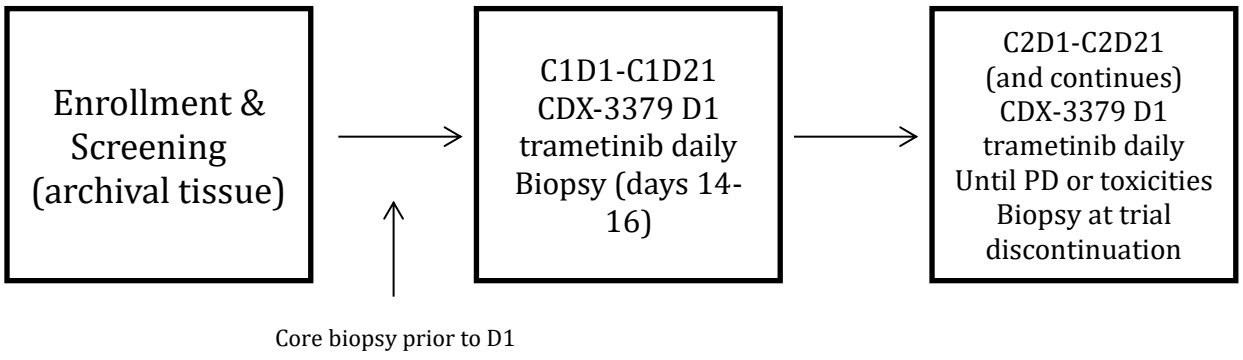
3 Study Design

3.1 General Design

This study is an open-label, non-randomized phase Ib/II study in patients with unresectable stage III or stage IV *NRAS* mutant or *BRAF*/*NRAS* WT melanoma.

Following signing informed consent and evaluation of initial eligibility criteria, all participants will provide an archived tissue sample (which meets the requirements for collection and processing as outlined in the study lab manual). In addition, all patients enrolled on Phase Ib and the first five NRAS mutant melanoma participants and first five WT melanoma participants on Phase II will undergo a mandatory core biopsy for pretreatment tumor tissue. For these procedures, investigators are asked to choose an easily accessible tumor lesion to minimize any possible risk associated with the collection of the tissue. As a general guideline, if the selected procedural location of the core needle biopsy or FNA has an established serious complication rate of >2% at the institution completing the procedure, this is considered a high risk procedure and should be avoided.

The purpose of this phase Ib study is to determine the MTD/RP2D and assess the toxicity and tolerability of combination of CDX-3379 (ERBB3 inhibitor) and trametinib (MEK inhibitor) in *NRAS* mutant and WT advanced stage melanoma. The purpose of phase II study is to estimate the response rate and duration of response of the combination in each cohort of participants that are *NRAS* mutant and WT advanced stage melanoma



Abbreviations: C = cycle; D = day; PD = progressive disease.
Figure 1: Phase Ib study design

Phase 1b: 6-18 evaluable subjects will be treated to identify the MTD/RP2D prior to advancing to phase II.

Definition of MTD/RP2D -

Once the subject has completed the screening procedures and is deemed eligible for the study, the subjects will be assigned to the following therapy:

Trametinib: 2 mg PO daily
ERBB3 antibody (CDX-3379) 15mg/kg IV on day 1 of each 21-day cycle

MTD/RPRD will be determined by combining ERBB3 antibody (CDX-3379) 15mg/kg IV Q3W with 2mg trametinib. Dose de-escalation of ERBB3 antibody (CDX-3379) and/or trametinib, if needed, will be allowed if significant toxicity is experienced with the two drugs at their recommended doses (which were previously determined).

Cohort levels for MTD/RP2D:

No of pts	***Cohort Level***	***CDX-3379***	***Trametinib***
6	1	15mg/kg IV Q 3wks	2mg daily
6	-1A	15mg/kg IV Q 3wks	1.5mg daily
6	-1B	10 mg/kg IV Q 3wks	1.5mg daily
6	-2A	10mg/kg IV Q 3wks	1.0 mg daily
6	-2B	5 mg/kg IV Q 3wks	1.0mg daily

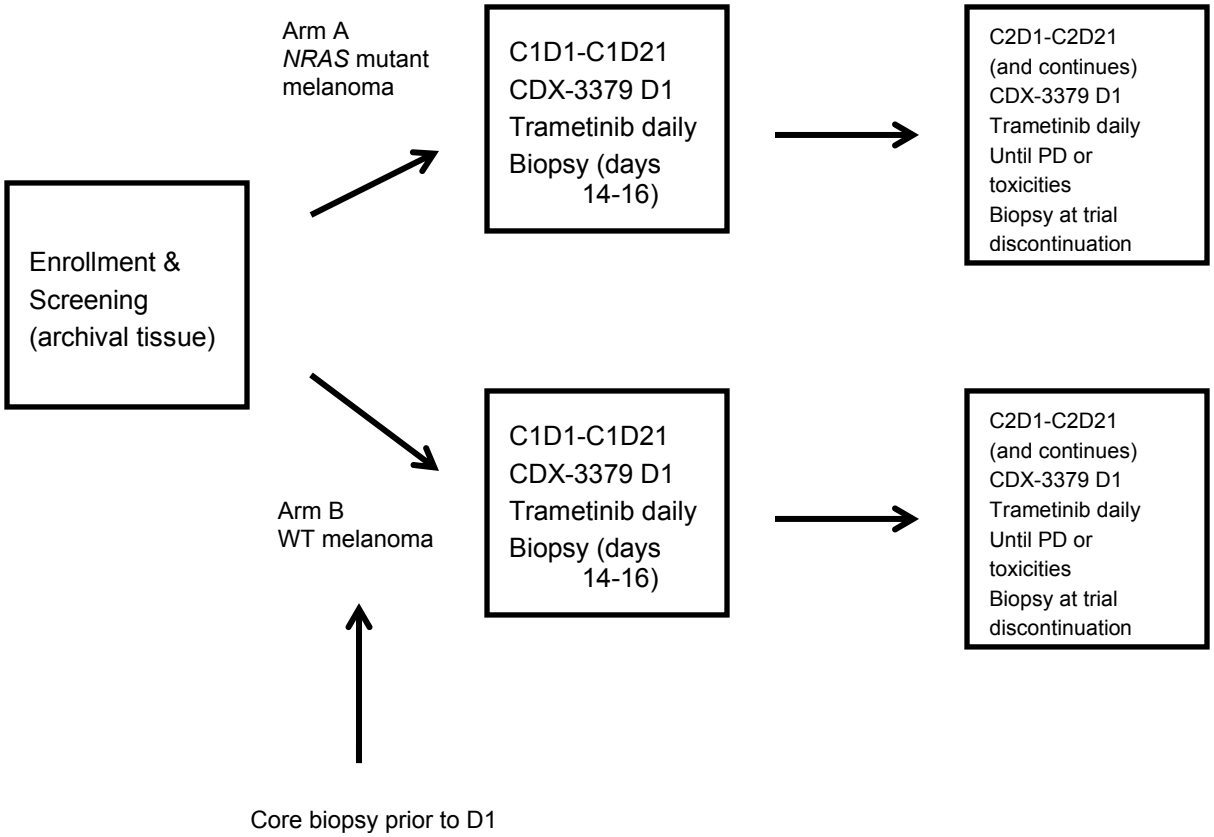
Safety has been established for the combination of CDX-3379 (ERBB3 antibody) and chemotherapeutic agents and targeted therapy at the standard doses with maximum dose of 20mg/kg. In addition, the recommended treatment dose of trametinib is 2mg. However, no data is available for the combination of CDX-3379 (ERBB3 antibody) and trametinib. In Phase Ib, all patients will start treatment at the cohort 1 doses. Six patients will be enrolled at this dose level and monitored for DLTs for 6 weeks (which is two treatment cycles (42 days)).

In these six participants, if none or one subject experiences a DLT, then dose cohort 1 will be considered the RP2D, and phase II of the clinical trial will proceed. After the first 20 patients are enrolled in the initial cohort, enrollment will be placed on hold to monitor for toxicity. At this point, a stopping rule for the cohort expansion portion of the trial for excessive toxicity such that if ≥ 30% of patients enrolled across groups discontinue treatment due to toxicity, enrollment will pause and an assessment of the toxicity of the treatment regimen(s) will be performed. This assessment, along with justification for resumption of enrollment, should be submitted to FDA. This stopping rule for the cohort expansion portion of the trial for excessive toxicity applies regardless of which dose is selected as the RP2D. Toxicities will be reviewed by study sponsor (NYU Langone Health) and DSMC. If ≤33 % of patients experience DLT based on review, then the study will continue enrollment. If > 33% of patients experience a DLT, then the study sponsor (NYU Langone Health), DSMC will convene to determine the best course of action (i.e. enrollment at decreased dosing cohort, etc).

If two or more of the six subjects experience DLT, we will consider the initial dose cohort beyond the MTD and we will enroll six more patients in cohort 1A or 1B, based on the toxicity pattern observed that is felt to be attributed to a particular drug. Dose reduction to -1A or -2A is specifically for toxicity related to trametinib, LVEF reduction, RPED, pneumonitis and LFT abnormalities. -1A is the first reduction, followed by –2A as the second reduction. For all other observed toxicities the default dose-reduced cohort is -1B followed by -2B. In the new dose cohort, if none or one patient experiences a DLT, then the study will open to full enrollment on the Phase II portion of the trial. If two or more of these additional six patients experience DLT, we will then enroll six

additional patients at additional dose de-escalation cohorts, to be determined by sponsor (NYULMC) and NYU DSMC), again based on toxicity pattern observed and drug attribution. If two or more patients experience DLT at this new dose cohort, then the trial will be terminated.

Phase 2: There are two Arms - Arm A (*NRAS* mutant melanoma patients) and Arm B (WT melanoma patients). This is the first part of a Simon Minimax design. Each arm will initially enroll 19 subjects. If there are three or fewer responses, then accrual to that cohort will be stopped. Otherwise, the study will be amended to enroll a total of 36 subjects to each approved arm/cohort.



Abbreviations: C = cycle; D = day; PD = progressive disease.
Figure 2: Phase II study design

Translational Research -

We will perform biopsies on all phase Ib patients (expected 6 patients, but could be up to 18) and five patients on each Arm of the study for Phase II. Biopsies will be obtained pre-treatment, on-treatment between day 14-16, and at the time of disease progression. Archival tissue will also be collected. We will investigate pathway inhibition of ERBB3 signaling and MAPK signaling pathways by analyzing components of the signaling pathways in addition to key components integral in these signaling pathways. We will also evaluate NRG1/HRG1 (neuregulin 1/heregulin 1, ERBB3 ligand) expression and correlate this with treatment response.

Analysis will be performed using immunohistochemistry, Western Blot analysis (if there is enough tissue), and in situ hybridization.

3.2 Primary Study Endpoints

For Phase Ib, the primary endpoint is identification of toxicities, tolerability and definition of a recommended phase II dose (RP2D) of Q3WK infusions of CDX-3379 in combination with once daily oral administration of trametinib.

For Phase II, the primary endpoint is an estimation of the overall response rate and duration of response in patients treated with CDX-3379 in combination with trametinib in *NRAS* mutant and WT melanoma.

3.3 Secondary Study Endpoints

For Phase 1b, the secondary endpoints are to assess clinical activity and steady-state pharmacokinetics of CDX-3379 and trametinib

For Phase II, the secondary endpoints are description of antitumor activity of the combination CDX-3379 and trametinib and include progression free survival (PFS) and overall survival (OS).

3.4 Exploratory Endpoints

Exploratory endpoints for both phase Ib and II include evaluation of pharmacodynamic markers of CDX-3379 and trametinib activity in serial tumor biopsies and potential predictive biomarkers of response and resistance to CDX-3379 and trametinib. Evaluations may include, but are not limited to, ERBB3, pERBB3, FOXD3, ERBB2, pERBB2, EGFR, pAKT, PTEN, ERK1/1, pERK1/2, DUSP4, NRG1 (neuregulin), NRG2, transforming growth factor alpha (TGFα) and amphiregulin (AREG), as well as other markers identified to be integral to ERBB3 and MEK inhibition.

3.5 Primary Safety Endpoints

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events as well as blood monitoring of hematologic and chemistry values with each cycle of therapy.
Patients will also be clinically assessed with regular monitoring of vital signs and physical exam. The secondary endpoints of the phase Ib portion of the study includes adverse event rates. Refer to Section 8 for further information on safety monitoring.

Determination of final MTD/RP2D will be guided by the incidence of drug-related side effects and dose de-escalations occurring within 6 weeks (two cycles) which allows for substantial amount of time for unexpected toxicities with combination of CDX-3379 with trametinib. This is detailed in section 3.1.

4 Subject Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Read, understood, and provided written informed consent and, if applicable, Health Insurance Portability and Accountability Act (HIPAA) authorization after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.
2. Male or female patients who are 18 years of age or older.
3. Patients with a diagnosis of histologically confirmed advanced (defined as unresectable stage III or IV) melanoma with the *NRAS* Q61 mutation or *BRAF*/*NRAS* WT who are refractory to or intolerant of existing therap(ies) known to provide clinical benefit for their condition, including anti PD-1 and/or CTLA-4 agent.
    - Any CLIA certified mutation testing is acceptable to document mutation status.
4. Patients must have adequate cardiac function as demonstrated by a left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram.
5. Patients must have archival tissue and at least one disease site amenable to biopsy:
    - For phase Ib, all patients will undergo fresh tumor biopsy
    - For phase II, five patients with NRAS mutation and five patients with BRAF/NRAS WT melanoma will undergo fresh tumor biopsy
6. Measurable (target) disease by Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria. Target lesions selected for tumor measurements should be those where additional (eg palliative) treatments are not indicated or anticipated.
    - Measurable disease per RECIST 1.1 requirements: defined as longest diameter to be recorded for non-nodal lesions > 10mm and short axis for nodal lesions >15 mm using conventional techniques
7. All residual toxicity related to prior radiotherapy or anticancer therapies (excluding alopecia, grade 2 fatigue, vitiligo or endocrinopathies on stable replacement therapy) must resolve to grade 1 severity or less (or returned to baseline) prior to receipt of study treatment.
8. Adequate electrolytes, liver, renal, and hematology function as defined below:
    a. Hemoglobin ≥ 9 g/dL
    b. Absolute neutrophil count ≥ 1500/mm^3
    c. Platelet count ≥ 100,000/mm^3
    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) (≤ 5 × ULN for cases involving liver metastasis)
    e. Bilirubin ≤ 1.5 × ULN (≤ 5 × ULN for cases of documented or suspected Gilbert's disease)
    f. Serum creatinine ≤ 1.5 g/dL or calculated creatinine clearance (CrCl) ≥60 mL/min for patients with serum creatinine > 1.5 x ULN
    g. Serum magnesium, calcium and potassium within normal limits
9. Life expectancy ≥ 12 weeks
10. ECOG performance status (PS) $\leq$ 1
11. Willing and able to comply with scheduled visits, treatment plan, and laboratory tests.
12. Screening EKG without clinically significant abnormalities.
13. Corrected (Fridericia's) QTcF must be < 480 milliseconds.

14. Allowance of prior therapy regimens:
    - No limit on prior number of regimens
    - Must have completed prior cytotoxic chemotherapy a minimum of 4 weeks prior to starting study treatment (except for bis-chlorethynitrosurea (BCNU)), which must have been completed a minimum of 6 weeks prior to starting therapy.
    - Prior localized radiation therapy must have been completed a minimum of 2 weeks prior to starting therapy and the patient must have baseline imaging with a full body PET-CT or CT scans of the chest, abdomen, and pelvis and within 4 weeks prior to study enrollment.
    - For CNS metastases, disease must be treated and demonstrate stability with Brain MRI a minimum of 4 weeks prior to starting therapy.
15. Both male and female patients enrolled in this trial must agree to use highly effective contraception during the course of the trial and for at least for 6 months after the final dose of CDX-3379 (an effective form of contraception is an oral contraceptive or a double barrier method), or greater, as in accordance with the label requirements for trametinib. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.
    - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months after stopping study drug. Highly effective contraception methods include:
        - Total abstinence or
        - Male or female sterilization or
        - Combination of any two of the following (a+b or a+c or b+c):
    - (a) Use of oral, injected or implanted hormonal methods of contraception; hormonal contraceptives are not acceptable as a sole method of contraception.
    - (b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - (c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

16. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

4.2 Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

1. Received CDX-3379 or other anti-ErbB3 targeted agents previously.

2. Received trametinib or other MEK inhibitor agents previously.

3. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

4. Other prior malignancy active within 2 years, except for localized prostate cancer, cervical carcinoma in situ, non-melanomatous carcinoma of the skin, stage 1 differentiated thyroid cancer or ductal carcinoma in situ of the breast that has/have undergone curative surgery or radiation.

5. Active central nervous system (CNS) metastases are excluded. Known brain metastases must have been previously treated and asymptomatic for 2 weeks and not progressive in size or number for 4 weeks prior to enrollment, documented via scans. Continued use of anticonvulsants (in the absence of any suspicion of progressive brain metastases) is acceptable. Patients must currently be on a stable, lowest possible dose of steroids.
6. Radiation therapy within 14 days prior to the first scheduled dose in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation.
7. Known HIV, hepatitis B or hepatitis C infection, or active infection requiring systemic intravenous therapy.
8. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyper viscosity or hypercoagulability syndromes).
9. Use of any monoclonal based therapies within 4 weeks (excluding cetuximab which does not require a wash-out), and all other immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) within 2 weeks, prior to the first dose of study treatment.
10. Chemotherapy within 4 weeks (except for bis-chlorethynitrosurea (BCNU), which must have been completed a minimum of 6 weeks) prior to starting therapy.
11. Major surgery within 4 weeks prior to the first dose of study treatment. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and patients should be recovered.
12. Use of other investigational drugs within 2 weeks or 5 half-lives (whichever is longer) prior to study treatment administration.
13. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 ms); additional risk factors for torsades de pointes (TdP) (e.g., a history of heart failure, family history of Long QT Syndrome, or active hypokalemia or uncorrectable electrolyte abnormality); significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension or arrhythmia, congestive heart failure (New York Heart Association Class III or IV) related to primary cardiac disease, uncontrolled ischemic or severe valvular heart disease; or any of the following within 6 months prior to the first dose of study treatment: myocardial infarction, severe/unstable angina, coronary artery bypass graft, congestive heart failure, cerebrovascular accident, transient ischemic attack.
14. Requirement for chronic immunosuppressive medication including systemic corticosteroids above the physiologic dose (defined as 20 mg/day prednisone or the equivalent).
15. Any other acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or trial drug administration or could interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for entry into the trial.
16. Known alcohol or drug abuse.
17. Sexually active males must use a condom during intercourse while taking the drug and for 3 months after stopping study drug and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
18. Inability to swallow pills
19. Patients unwilling or unable to comply with the protocol.

4.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4.4 Subject Recruitment and Screening

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations.

Eligible patients with advanced stage *NRAS* mutant and WT melanoma age 18 years and older who agree to participate in the study will be identified from the Laura and Isaac Perlmutter Cancer Center outpatient melanoma practice of the clinical investigators during a routine office visit or consult. Patients will also be recruited through NYU Langone Health and an additional site, the University of Pennsylvania, which will be added. All participants will be required to sign informed consent prior to trial enrollment. After signing informed consent, subjects will provide an archived tissue sample.

4.4.1 Method of Subject Identification and Recruitment

Target enrollment for this study is 44 patients. The target accrual goal at NYU is 10 patients per year.

The patients who are eligible for this research study come directly from the study investigators' clinical patient population. Thus, the investigators are very familiar with their patients' disease status and potential eligibility given the protocol's inclusion and exclusion criteria. The investigator will approach eligible potential subjects and explain the study in a private room, including the reasons why subjects will be eligible, risks, benefits, and the regimes to be evaluated. They will also receive the informed consent document to read. Consent will be obtained in a private room by the PI, Co-Investigator, or research coordinator/research nurse at the time of the subject's visit prior to any study assessments/procedures. The subjects will be given a chance to ask questions to the person consenting him/her and will be able to take the consent home to discuss it with family/friends prior to signing. If the subject agrees s/he will sign the consent form either at the first contact (if the investigator/delegate is convinced that the subject understands) or at the time of a return visit after having had time to study the consent in more depth. Study procedures will not begin until after the consent form has been properly obtained. The subject is entitled to decide not to participate in the trial, without affecting their right to other medical care, and may discontinue participation in the trial at any time without penalty or loss of benefits to which they are entitled.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.

2. Determine patient eligibility; see Section 4.1 and 4.2

3. Submit registration to NYU Langone Health Perlmutter Cancer Center CTO

4. Receive registration confirmation from the NYU Langone Health Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

The informed consent process and documentation follows that established procedures of the NYU Langone Health Perlmutter Cancer Center Clinical Trials Office.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

A subject may withdraw from the study at any time and for any reason. Discontinuation of therapy will not affect the subject's relationship with the treating physician. It is intended that subjects will be treated until investigator-determined progressive disease (radiologic or clinical deterioration) or unacceptable toxicity. Reasons for withdrawal from treatment include, but are not limited to: progressive disease as determined by RECIST v1.1, clinical deterioration, adverse events, protocol violation, non-compliance, withdrawal of consent, investigator or sponsor decision, or if the subject is lost to follow-up. Withdrawal from the study can be made in writing to the Principal Investigator, Dr. Weber. Any samples/specimens remaining after formal withdrawal, will be destroyed/discarded per Institutional guidelines.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

When a subject is discontinued from treatment for any reason, they are to undergo the assessments in the end of treatment visit within 4 weeks of the last dose. All subjects who discontinue treatment as a result of an adverse event must be followed until resolution or stabilization of the adverse event. If a subject withdraws from study treatment, attempts should be made to contact the subject to determine the reason(s) for discontinuation. The subject will continue to be followed for survival information every 3 months after completion of the End of Treatment visit. All subjects, including subjects who discontinue treatment for other reasons than progressive disease per RECIST 1.1, should undergo a scan to assess disease status prior to termination from the study.

If a subject does not return to the clinic for the end of treatment visit or is not reached for overall survival follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject. If the subject does not respond to these requests, the date of death should be captured from public records.

4.5.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

5 Study Drug

5.1 Description

5.1.1 CDX-3379 -Description, Packaging, and Labeling

Detailed technical information regarding CDX-3379 is provided in the Investigator's Brochure.

CDX-3379 is a human IgG1λ mAb that specifically binds ErbB3 at a unique epitope and locks ErbB3 in an auto-inhibited configuration making the ErbB3 incapable of binding ligand or dimerizing with known tumor growth drivers such as HER2 and possibly EGFR.

CDX-3379, manufactured by MedImmune for Celldex, is supplied as a clear to opalescent, colorless to brown-yellow liquid, free from or practically free from visible particulates. CDX-3379 will be provided at a 1.0 mL or 2.0 mL fill volume in a 3 cc glass vial, as a 50 mg/mL solution containing 25 millimolar (mM) histidine/histidine-hydrochloride, 205 mM sucrose and 0.02% (weight/volume) polysorbate 80, at a pH of 6.0. CDX-3379 is manufactured in accordance with Good Manufacturing Practices (GMP) and labeled according.

5.1.2 Trametinib (Mekinist®)

Trametinib tablets (also referred to as GSK1120212B Tablets, TMT212-NXA Tablets) are immediate release tablets for oral administration containing trametinib dimethyl sulfoxide (GSK1120212B/TMT212-NXA) equivalent to 0.125 mg, 0.5 mg or 2 mg of trametinib (GSK1120212/TMT212, non-solvated parent). Trametinib Tablets, 0.125 mg are dark pink, round, biconvex, film-coated tablets. Trametinib Tablets, 0.5 mg are yellow, modified oval, biconvex, film-coated tablets. Trametinib Tablets, 2 mg are pink, round, biconvex, filmcoated tablets. Trametinib Tablets are packaged into a high density polyethylene (HDPE) bottle that contains desiccant with a child-resistant closure that includes an induction seal liner.

List of Excipients
Tablet Core
- Mannitol
- Microcrystalline cellulose
- Hypromellose
- Croscarmellose sodium
- Magnesium stearate (non-animal)
- Colloidal silicon dioxide
- Sodium lauryl sulfate

Film-coat (aqueous film-coating; water is removed during processing)
- Opadry Red 03B25344 (0.125 mg) containing hypromellose, titanium dioxide, polyethylene glycol, and iron oxide red
- Opadry Yellow 03B120006 (0.5 mg) containing hypromellose, titanium dioxide, polyethylene glycol, and iron oxide yellow
- Opadry Pink YS-1-14762-A (2 mg) containing hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, and iron oxide red.

All excipients used in the tablet core are standard and of pharmacopoeial quality. The coating pre-mixes (Opadry) are a combination of standard ingredients, which are of pharmacopoeial or international standards' quality.

5.2 Treatment Regimen

CDX-3379 will be given IV at 15mg/kg every three weeks of a 21-day cycle. Trametinib will be given at a dose of 2 mg PO daily. Treatment will continue until disease progression, intolerable side effects, subject choice, or study closure.

5.3 *Method for Assigning Subjects to Treatment Gro*ups

This is an open label, non-randomized study. All subjects with *NRAS* mutant or WT melanoma will be enrolled on the Phase 1B portion of the study. During Phase 2, subjects with *NRAS* mutant or WT melanoma will be enrolled and assigned to their respective study arm – based on mutation status – for the purpose of analysis.

5.4 Preparation and Administration of Study Drug

5.4.1 CDX-3379 Storage and Handling

CDX-3379 is shipped in insulated shippers and must be stored at 2 - 8°C (36 - 46°F) until use. Do not freeze CDX-3379 solutions. A temperature log must be kept to document the refrigerator temperature. If the temperature is not maintained, Celldex should be contacted.

CDX-3379 is not formulated with a preservative. Therefore, once the sterile vials are entered (i.e., needle puncture of the vial), the drug should be used as soon as possible (typically within 3 hours if kept at room temperature or within 6 hours if refrigerated; or in accordance with any applicable institutional guidance). Additional guidance regarding storage and handling of CDX-3379 will be provided on the pharmacy sheet provided by Celldex.

5.4.2 CDX-3379 Administration

The dose of CDX-3379 is 15 mg/kg, administered intravenously every 3 weeks (on day 1 of each 21-day cycle). Subjects will be treated with CDX-3379 until progressive disease, unacceptable toxicity, or other criteria for discontinuation of study treatment.

Subjects will receive CDX-3379 as an IV infusion over 60 ± 5 minutes. As a routine precaution, the investigative site's medical staff is to closely observe patients for the duration of CDX-3379 infusion and for at least 1 hour after the end of the infusion.

The entire contents of the IV bag should be administered through an IV administration set with a low protein binding 0.2-µm in-line filter. Since the compatibility of CDX-3379 with other IV medications and solutions other than normal saline (0.9% [w/v] Sodium Chloride for Injection) is not known, the CDX-3379 solution shall not be infused through an IV line in which other solutions or medications are being co-administered. The date, start time, interruption, and completion time of CDX-3379 administration must be recorded in the source documents.

5.4.3 Trametinib Storage and Handling

The recommended storage conditions, shelf-life and expiry date, where required, are stated on the product label. Trametinib will be provided as 0.5 mg and 2 mg tablets. Trametinib tablets must be kept refrigerated.

5.4.4 Trametinib Administration

Trametinib will be administered orally daily at 2 mg (on an empty stomach either one hour prior to or two hours after eating). On days where the subject receives both CDX-7739 and trametinib, the subject will take trametinib immediately following infusion of CDX-3379 (on an empty stomach either one hour prior to or two hours after eating). Do not take a missed dose within 12 hours of the next dose. Subjects are expected to be treated until investigator assessed progressive disease is noted, in the event of unacceptable toxicity, subject choice, or study closure.

5.5 Subject Compliance Monitoring

CDX-3379 will be administered by study staff, and details regarding each administration will be recorded in the subject's medical record and the CRFs. Trametinib will be self-administered, and a medication diary will be provided to subjects.

5.6 Prior and Concomitant Therapy

No other investigational agents or concurrent therapy for melanoma will be allowed during treatment on this clinical trial.

There are no restrictions on the number of prior therapies, however, subjects may not have been treated previously with an ERBB3 or MEK inhibitor.

Drug Interactions: No formal drug interaction studies have been conducted with trametinib. Trametinib is not a substrate of CYP enzymes or efflux transporters P-gp or BCRP *in vitro*. Based on *in vitro* studies, trametinib is not an inhibitor of CYP450 including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 or of transporters including OATP1B1, OATP1B3, P-gp, and BCRP at a clinically relevant systemic concentration of 0.04 μM. Trametinib is an inhibitor of CYP2C8 *in vitro* (trametinib package insert).

Trametinib is an inducer of CYP3A4 in vitro. Based on cross-study comparisons, oral administration of trametinib 2mg once daily with everolimus (sensitive CYP3A4 substrate) 5 mg once daily, had no clinically important effect on the AUC and C_{max} of everolimus (trametinib package insert).

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g., such as anti-emetics, anti-diarrhea) and safety of the subject are allowed.

Subjects are permitted to use the following medications during study treatment:
- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for subjects who develop diarrhea.
- Pain medication to allow the subject to be as comfortable as possible.
- Bone targeted therapies (e.g., bisphosphonates, denosumab) to treat bone metastases or to prevent skeletal related events.
- Palliative radiotherapy: any radiotherapy must be listed on the 'Surgical and Medical Procedures' eCRF.
- Immunosuppressive agents to treat suspected AEs.
- Nutritional support or appetite stimulants (e.g., megestrol).
- Oxygen therapy and blood products or transfusions.
- Limited-field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy. Such local therapies administered during the study treatment
- Inactivated vaccines.
- The subject must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Surgical and Medical Procedures eCRF.

5.7 Blinding of Study Drug

This is an open label, non-randomized study. There is no blinding of treatments.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.8.2 Storage and Handling

5.9.2.1 CDX-3379

CDX-3379 is shipped in insulated shippers and must be stored at 2 - 8°C (36 - 46°F) until use. Do not freeze CDX-3379 solutions. A temperature log must be kept to document the refrigerator temperature. If the temperature is not maintained, Celldex should be contacted.

CDX-3379 is not formulated with a preservative. Therefore, once the sterile vials are entered (i.e., needle puncture of the vial), the drug should be used as soon as possible (typically within 3 hours if kept at room temperature or within 6 hours if refrigerated; or in accordance with any applicable institutional guidance). Additional guidance regarding storage and handling of CDX-3379 will be provided on the pharmacy sheet provided by Celldex.

5.9.2.2 Trametinib

Store refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

5.8.3 Dispensing of Study Drug

5.9.3.1 CDX-3379 Preparation

General notes regarding the preparation of CDX-3379:

- Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biotherapeutic agents.
- Aseptic technique should be employed in the preparation of all study drugs.
- CDX-3379 is expected to be free from, or essentially free from, visible particulates. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If significant particulate matter is present or the solution is discolored, the vial should not be used.
- Refrigerated solutions should be equilibrated to room temperature prior to administration.
- Before use, the vial should be gently swirled to ensure uniform mixing of the contents. Solution should be gently withdrawn (avoiding foaming and excess shearing).

A designated member(s) of the investigational site's pharmacy staff with appropriate training and experience (i.e., the pharmacist) will prepare CDX-3379. The pharmacist(s) will be required to complete a Dosage Preparation Record to document the preparation process for each dose of CDX-3379. Additional guidance will be provided within a pharmacy sheet provided by Celldex.

Dose Calculation

Doses of CDX-3379 will be based on body weight in kilograms. Patients are to be weighed at the start of each cycle and the dose adjusted based on current body weight and rounded to the nearest mg of CDX-3379. Half milligrams (mgs) should be rounded up to the next mg of dose. If body weight is within ±10% of the baseline measurement, the baseline weight may be used for dose calculation and preparation.

Dose Preparation Steps

CDX-3379 is diluted with 0.9% (w/v) saline to a minimum final volume of 100 mL, in an appropriately sized polyolefin, IV infusion bag. The final CDX-3379 concentration in the admixture shall be maintained in the qualified range of 1.8 to 13.8 mg/mL. Diluted CDX-3379 is administered to the patient via IV infusion, through an IV administration set with a low protein binding, 0.2-µm in-line filter.

5.9.3.2 Trametinib

The investigator or responsible site personnel must instruct the subject or caregiver to take trametinib as per protocol. This study drug will be dispensed to the subject by authorized site personnel only. All dosages prescribed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. Trametinib with instructions for administration will be provided to subjects for self-administration at home, until their next scheduled study visit.

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secure location. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored and appropriate temperature logs maintained as source data. Appropriate documentation of the subject specific dispensing process must be maintained. Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the subject.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply. Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction.

Trametinib will be either sourced as local commercial supply or provided as global clinical open label supply. Global clinical open label supply will be provided in bottles. Study treatment labels will comply with the legal requirements of each country and will include storage conditions.

Novartis Drug Supply Management supplied treatments will also contain a unique medication number (corresponding to study treatment and strength).

Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the subject. If the label has 2 parts (base plus tear-off label), immediately before dispensing the package to the subject, site personnel will detach the tear-off part of the label from the package and affix it to the subject's source document.

5.8.4 Return or Destruction of Study Drug

5.9.4.1 – CDX-3379

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

CDX-3379 will be supplied by Celldex as open-label stock. The investigational product is to be used only for this protocol and not for any other purpose, and must be kept in an appropriate, secure area (e.g., locked refrigerator/cabinet) and stored in accordance with the conditions specified in this protocol/on the labels.

The investigator will assume responsibility for administration and dispensation of study medication. An accurate record of all study drugs received, dispensed, returned, and destroyed must be maintained. Drug supplies will be inventoried and accounted for throughout the study, and accountability records must be available for inspection at any time and provided to Celldex upon the completion of the study.

Upon receipt of any investigational product, an inventory must be conducted to confirm the quantity and condition of material received, and verification of receipt must be completed and returned in accordance with instructions provided by Celldex.

Resupply of study medication may be requested in accordance with instructions provided by Celldex.

Used, partly used, and/or remaining unused investigational product will be either returned to Celldex or destroyed according to the site's Standard Operating Procedures (SOPs), as directed by Celldex, and a record of this disposition will be maintained.

5.9.4.2 -Trametinib

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the CRA during site visits and at

the completion of the study. Subjects will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

Any waste material should be disposed of in accordance with local regulations and according to institutional guidelines. If local regulations disallow storage of empty or pierced vials at the site, the site is able to destroy the vials as per local requirements and procedures. Documentation regarding the local regulations and the destruction of the empty vials will be provided to the Sponsor to ensure full drug accountability.

5.9 Pharmacokinetic Variables and Assessments

Blood samples will be collected to determine the levels of CDX-3379 and Trametinib. Approximately 5 ml of blood will be collected. The time of blood collection must be documented. A laboratory manual will be provided with instructions for collecting, processing, and shipping the samples.

Pharmacokinetic blood samples will be drawn from study patients at the time points indicated in Section 6.6 during the Phase Ib portion of the study. For cycles 1 and 2, blood will be drawn prior to treatment with CDX-3379, following CDX-3379 adminstration, and one hour after trametinib. On days where both CDX-3379 and trametinib are administered, trametinib will be taken immediately following CDX-3379 infusion. On cycle 3 day 1, blood will be drawn prior to treatment with CDX-3379 for minimum concentration (Cmin) determination. Serum concentrations will be determined for CDX-3379 and trametinib. All samples will be stored at the CBRD, until future use, which is detailed in the lab manual. Trametinib PK samples will be analyzed by Covance. This study provides the opportunity to assess PK of CDX-3379 in combination with trametinib. We believe that CDX-3379 and trametinib will be well tolerated and safe.

5.10 Biomarker Samples

Biomarker data will be explored from archived tissue and pre-treatment, on-treatment, and disease progression tumor biopsy samples during Phase Ib and from ten subjects during the Phase II portion of the study (five subjects with *NRAS* mutation and five subjects with BRAF/NRAS WT melanoma), to assess potential associations with tumor response. These samples will be collected prior to treatment on cycle 1 day 1, on day 14-16 after initial treatment, and at the time of disease progression. These samples will be used to assess additional clinically relevant biomarkers, including but not limited to expression levels of ERBB3, cMET, ERBB2, and EGFR and will include assessment of respective receptor ligands. Efficacy outcomes considered for pre-specified mechanistic biomarker analysis will include PFS, objective response rate, and OS based on investigator assessments.

5.10.1 Archived Tumor Samples

If available, formalin-fixed paraffin embedded tumor samples (either a tumor block or freshly cut slides) from the patient's most recent tumor sampling will be collected for biomarker analysis. Tumor samples obtained at the time of metastasis are preferred over tumor samples obtained at the time of primary diagnosis; however, in the event that both are available for analysis, we ask that samples from both time points should be submitted. Directions and requirements for processing and shipping the archived tumor samples can be found in the laboratory manual.

5.10.2 Tumor Biopsy

Core biopsies are required for the Phase Ib and Phase II portion of the study, in order to perform correlative studies. Core biopsies will be collected pre-treatment, on-treatment (day 14-16), and at the time

of progression during Phase Ib and from ten patients during the Phase II portion of the study (five NRAS mutant melanoma and five WT melanoma), to assess potential associations with tumor response.

6 Study Procedures

Screening

The screening phase begins once written informed consent is provided and ends after 28 days or when subject receives the first treatment dose.

Subjects must sign an informed consent form (ICF) prior to any study specific screening evaluations, within 28 days prior to the first dose of study treatment. Following completion of screening procedures and verifying subject eligibility based on assessments, the subject will be enrolled via the Interactive Response Technology (IRT) system.

6.1 Visit 1 – Screening

An initial screening visit will occur to ensure subjects meet the inclusion criteria. This visit will include a physical exam and medical history, baseline EKG, ophthalmologic exam, baseline laboratory tests including a comprehensive metabolic panel and a complete blood count, and a clinical evaluation to ensure the patient has no factors that would render them ineligible for the study. Subjects will be required to give information regarding their medical history and melanoma treatment course.

Subjects will undergo screening procedures, including documentation of a medical history, patient demographics, vital signs, and ECOG performance status. Labs drawn will include CBC, chemistry, and coagulation profile. Archival tumor biopsy samples should be obtained from tissue available from any time prior to signing consent for this trial, focusing on samples since last treatment regimen until signing consent for this trial. Pre-treatment tumor biopsy will be performed prior to treatment administration during the screening period. A Pregnancy test will be performed on all women of childbearing potential. Baseline EKG and ECHO screening will be performed. Subjects will be asked to identify all concomitant medications they are or will be taking during the time of the study. Baseline imaging with a full body PET-CT or CT scans of the chest, abdomen, pelvis and areas of disease, along with brain MRI must be completed within 4 weeks prior to study enrollment.

6.2 Visit 2, 4

Visit 2 will consist of the start date of the study treatment, representing day 1 of week 1 of cycle 1. Visit 4 will represent day 1 of week 1 of cycle 2. As with all clinical visits, vital signs and ECOG performance status will be recorded, an ophthalmologic exam will be performed and CBC and chemistry will be drawn from the subject as well as serum samples for PK during the first two cycles of treatment in the Phase 1b group. All assessments must be resulted prior to administration of CDX-3379. Medication review will be performed as will AE assessment and reporting. CDX-3379 will be administered at visit 2 and will continue once every three weeks thereafter until disease progression, unacceptable toxicity, subject decision to withdrawal, study closure, or another reason as determined by the study investigators. Dosing is 15mg/kg IV. Blood will be drawn prior to CDX-3379 infusion, immediately following CDX-3379 infusion. Following infusion and blood draw, trametinib will be started at 2mg and should be taken on a continuous basis as prescribed unless otherwise instructed by study investigators. Blood will be drawn one hour after trametinib administration.

6.3 Visit 3, 5

Visit 3 and 5 will represent day 1 of week 2 of cycles 1 and 2, respectively. This visit will include documentation of vital signs, ECOG performance status, current medications, and AE assessment and reporting. Blood will be drawn for CBC, chemistry, and PK.

6.4 Visit 6

Visit 6 will represent day 1 of week 1 of cycle 3. Blood will be drawn for CBC and chemistry, and an ophthalmologic exam will be performed. Serum samples for PK will be obtained before treatment administration. All assessments must be resulted prior to administration of CDX-3379. For each visit thereafter, subjects will be seen and evaluated on the first day of each cycle when they receive CDX-3379. Disease evaluation should be reported every 12 weeks after the first dose of CDX-3379.

6.5 End of Treatment Visit

The end of treatment visit should be completed within 4 weeks of the last dose of the study drug. Vital signs, ECOG performance status, AE assessment and reporting, and disease evaluation should be performed. Blood will be drawn for CBC, chemistry, and PK. Progression tumor biopsy should be obtained within 4 weeks of last dose of study drug (last dose of study drug is calculated from the last dose of trametinib).

6.6 Survival Follow-up

Survival data will be collected via telephone or clinic visits every 3 months (±10 days) from the date of last treatment (date of last treatment is calculated from the last dose of trametinib) until death, loss to follow-up, withdrawal of consent, study termination by the Sponsor, or up to 5 years. In addition, any new anti-cancer therapies and procedures should be collected and documented. Should subjects refuse or drop out of survival follow-up, attempts should be made to obtain any death information via public records whenever possible.

6.7 Schedule of Assessments Summary

		Cycle 1[4]			**Cycle 2[4]**			**Additional cycle[4]**			**Every 12 weeks or sooner, at the discretion of the physician**	**End of Treatment (EoT)[8]**	**Survival Follow-up[12]**
Procedure	**Screening**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 1**	**Wk 2**	**Wk 3**			
Informed Consent	X												
Medical History	X												
Demographics	X												
Physical Exam	X	X	X		X	X		X				X	
Vital Signs	X	X			X			X				X	
ECOG PS	X	X			X			X				X	
CBC	X	X			X			X				X	
Serum Chemistry[13]	X	X			X			X				X	
Tumor Biopsy	X												
	X												

Baseline imaging within 4 weeks prior to enrollment (CT/PET-CT/MRI)													
Pregnancy Test (Urine)	X	X			X			X					
EKG	X	X[11]			X[11]			X[11]					
Archived tumor	X												
Fresh Core Biopsy	X[2]		X[3]	X[3]								X	
Pharmacokinetic blood samples		X[10]	X		X[10]	X		X				X	
Immunogenicity sample		X			X							X	
Concomitant meds	X	X	X		X			X				X	
CDX-3379 dosing[16]		X			X			X					
Trametinib dosing		X	X	X	X	X	X	X	X	X			
AE assessment and reporting		X	X		X			X				X	
Disease evaluation[5,7]	X										X[9]	X[1]	
Overall Survival Reporting[6]													X
Echocardiogram/MUGA[15]	X										X		
Ophthalmologic Exam[14]	X	X			X			X					

Footnotes:

1 = Unless performed in the prior 6 weeks as part of a previous visit

2= prior to first treatment with CDX-3379 and trametinib

3= performed between days 14-16

4= All procedures should occur ±2 calendar days from scheduled date of visit

5 = Disease evaluation per RECIST version 1.1.

6 = Should patients refuse or drop out of survival follow-up, attempts should be made to obtain any death information available via public records.

7 = Upon disease progression determination

8 = End of treatment visit should be completed within 4 weeks of the last dose of study drug

9 = end of treatment biopsy/disease progression. Should occur within 4 weeks of last treatment.

10 = PK blood samples are collected predose before CDX-3379, immediately following CDX-3379 infusion, and 1 hour post dose following trametinib

11= one reading prior to the start of CDX_3379 infusion

12= Survival data will be collected via telephone or clinic visits every 3 months (±10 days) from the date of last treatment until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor

13= Comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, calcium, protein total, albumin, AST, ATL, alkaline phosphatase and total bilirubin), LDH, magnesium, and phosphorus.

14 = With hand held Ophthalmoscope. Patients will also be asked about eye symptoms at each visit. A formal ophthalmologic examination will be performed as per standard of care if patients develop signs or symptoms of ocular toxicity.
15= ECHO/MUGA should be performed every 12 weeks, or at the discretion of the physician.
16= Pre and post infusion vitals (HR, Blood pressure, O2 sat, temperature) will be taken prior to infusion +/-15 minutes, 30 minutes into the infusion +/- 5 mins, at the end of the infusion (which is 60 minutes) +/- 15 minutes, and 60 minutes after the infusion has finished +/- 15 minutes

7 Statistical Plan

7.1 Sample Size Determination

For Phase Ib:
No data are available for the combination of CDX-3379 (ERBB3 antibody) and trametinib. Six subjects will be enrolled at an initial dose level – a safety run-in - and monitored for DLTs. In these six subjects, if none or one subject experiences a DLT, then dose cohort 1 will be considered the RP2D, and phase II of the clinical trial will proceed. If two or more of the six subjects experience DLT, we will consider the initial dose cohort beyond the MTD and we will enroll six more subjects on a de-escalated cohort, based on toxicity pattern observed attributed to a particular drug (Cohort -1A or -1B). In this new dose cohort, if none or one subject experiences a DLT, then the study will open to full enrollment on the Phase II portion of the trial. If two or more of these additional six subjects experience DLT, we will then enroll six additional subjects at an additional dose de-escalation cohort -2, to be determined by sponsor (NYUL Health) and DSMC), again based on toxicity pattern observed and drug attribution. If two or more subjects experience DLT at this new dose cohort, then the trial will be terminated.

For Phase 2: There are two Arms - Arm A (*NRAS* mutant melanoma participants) and Arm B (WT melanoma participants). This is the first part of a Simon Minimax design. Each Arm will initially enroll 19 patients. If there are two or fewer responses, the specific cohort will be stopped. Otherwise, the study will be amended to enroll a total of 36 patients to each approved Arm/cohort (an additional 17 patients per arm). If a true response rate is 0.20, we will have a probability of 0.46 of stopping early and a probability of 0.90 of deciding that the treatment is useful.

7.2 Statistical Methods

Data collection will begin from time of enrollment and subjects will be followed until death (PFS and OS endpoints). If subjects are still alive, they will be censored at the time of evaluation. We will first investigate the association between biomarker expression and disease characteristics using t-test, ANOVA, or Chi-squared tests. We will then investigate the association between biomarker expression and PFS and OS using Kaplan-Meier approach and log rank test where biomarker expression is dichotomized. We may also use Cox proportional models to assess the association between biomarkers and outcome with adjustment for potential confounders such as disease characteristics. Biomarkers measured pre-, on-and post-treatment will be examined and are mainly exploratory at this time. Future tests will be derived from these results. For phase 2, the primary efficacy endpoint, response rate, will be compared with the historically reported response rate for the single agent trametinib in *NRAS* mutant and *BRAF*/*NRAS* WT melanoma.For secondary endpoints, we will estimate median PFS, OS and 95% CI using the Kaplan-Meier approach. In NRAS mutant melanoma patients treated with single agent MEK inhibitor, response rate was 15% and median PFS was 2.8 months[15], and in BRAF/NRAS WT melanoma

patients treated with single agent MEK inhibitor, response rate was 10% and median PFS was 2 months[7]

Assuming a true response rate of 0.20, Simon's two-stage Minimax design will test the null hypothesis that RR ≤0.20; the sample size of 36 patients provides an alpha level of 0.10 and power of 0.80. Nineteen patients will be enrolled to the NRAS mutant arm of the study and 19 patients will be enrolled to the BRAF/NRAS WT arm of the study in the phase 2. If at least 3 patients respond (PR or better) out of 19 evaluable patients, then the study will be amended to enroll an additional 17 patients (for a total of 36 evaluable patients). If the Simon two-stage Minimax design is fully completed, a minimum of 10 patients must demonstrate a response (PR or better) to reject the null hypothesis.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and completed prior to database lock. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

7.3 Subject Population(s) for Analysis

All subjects enrolled on the study who are treated will have data collected at the pre-specified time points and this data will be subjected to the study analysis. Data analysis will be intention to treat, based on all subjects enrolled onto the study protocol.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening

- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Abnormal lab values that are not clinically significant are not considered adverse events.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 days of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm (see definitions, section 8.1)

Events should be reported using the NYU CTO Medical Events Form (see section 8.3.1 below).

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DSMC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMC/study sponsor within 24 hours of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 days of the IR's receipt of the report of the problem from the investigator.

Serious adverse event reporting will begin in conjunction with the date of informed consent. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the Sponsor or its designee and recorded on the case report form.

All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism and the NYU Langone Health IRB by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyumc.org whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of study drug (CDX-3379 or trametinib), even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor immediately (within 1 working day) using the AE and SAE forms supplied by NYU Langone Health PCC. Overdose of study drug will be defined as ≥16.5mg/kg of CDX-3379 and 2 mg of trametinib.

All other serious adverse events must be reported to the sponsor and DSMC within 24 hours by phone (212) 273-2748 or e-mail (NYUPCCsafetyreports@nyumc.org) . Details are outlined in the study procedure manuals. The Serious Adverse Event Form must also be faxed to the sponsor and DSMC within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the DSMC if meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB, DSMC, and FDA.

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the study sponsor

Since multiple sites may be participating, the following describes events that must be reported to the study sponsor (NYU Langone Health PCC), Celldex Therapeutics and Novartis in an expedited fashion.

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:

The following events must be reported to the study sponsor (NYULMC PCC) by email within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to:

NYUPCCsafetyreports@nyumc.org
(212) 273-2748

AND

Jeffrey Weber, MD, PhD
160 E. 34th Street, 13th Floor
New York, NY 10016
Phone: 212-263-9333
Fax: 212-731-6017
Jeffrey.weber@nyulangone.org

Events of Clinical Interest (any medical event that is deemed significant via Principal Investigator's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Sponsor specifications.

Follow-up report: within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

Reporting to Celldex

Expedited reporting by investigator to Celldex. *Note that reporting to Celldex is required in addition to reporting to the FDA, as necessary, and does not replace the requirement to notify the FDA, if required.*

- NYU will inform Celldex in writing using an SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event (see Section 8.1X for the definition of SAE). The written report must be completed and supplied to Celldex by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report.

- Completed SAE reports are to be submitted to:

  Celldex Therapeutics, Inc.
  Pharmacovigilance
  Facsimile : 781-644-6434
  Email: SAE@celldex.com (note-check for removal of HIPAA identifiers prior to sending information)

Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3.3 Sponsor reporting: *Notifying the FDA*

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  – associated with the use of the study drug
  – unexpected,
  – fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  – associated with the use of the study drug,
  – unexpected, and
  – serious, but not fatal or life-threatening
  -or-
  – a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  – suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Celldex Reporting guidelines:

Additional Reporting Requirements for the Sponsor

Reporting to the FDA

- Serious and unexpected suspected adverse reactions will be reported to the FDA no later than 15 calendar days after the sponsor determines that the requirements for an IND safety report have been met. The FDA will be notified using an FDA Form 3500a.
- Unexpected fatal or life-threatening suspected adverse reactions will be reported to the FDA no later than 7 calendar days after the Sponsor receives the initial information of the event. The FDA will be notified using an FDA Form 3500a.
- Other adverse event information will be sent to the FDA in the IND annual report.

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form; see Attachment 1), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

NYU Langone Health Contacts:

NYUPCCsafetyreports@nyulangone.org

AND

Jeffrey Weber, MD, PhD
160 E. 34th Street, 13th Floor
New York, NY 10016
Phone: 212-263-9333
Fax: 212-731-6017
Jeffrey.Weber@nyulangone.org

8.3.4 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above in section 8.3.3. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

We will put a Safety Management Plan in place in order to report any adverse events to Celldex Therapeutics and Novartis, also allowing the study sponsor to receive any cross-reports from Celldex Therapeutics and Novartis studies as well.

8.4 Reporting of Pregnancy

Should a pregnancy occur, it must be reported immediately to the principal investigator, and NYUPCCsafetyreports@nyumc.org in accordance with the procedures described below. Celldex and Novartis will be notified in accordance with procedures detailed below. Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication. This will be reported to the IRB if necessary.

Pregnancy reporting to Novartis
To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.
Warnings and precautions

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below.
Adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of adverse events via email initially, and then reviewed at the next DSMC monthly meeting.
The Data Safety and Monitoring Committee (DSMC) will review the study at least quarterly, with outcome data presented upon completion of each cohort. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Data and Safety Monitoring Committee

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University Langone Medical Center Perlmutter Cancer Center (NYULMC PCC). The DSMC operates based on the National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the New York University Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the New York University Langone Medical Center Perlmutter Cancer Center.

Per the NYULMC PCC Data Safety and Monitoring Plan, this phase (Ib/II) trial will be monitored by DSMC at least quarterly(from the date the first patient is enrolled), subsequent cohort activation, and at the completion

of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Accrual to the next dose within a cohort will be held until real-time review of the toxicity from the prior cohort has occurred to assure no defined DLTs have occurred prior to proceeding to the next level or expanding the current cohort. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, and external information. The DSMC will review safety data every 3 months.

Other external sites will be monitored and informed of other adverse events by the DSMC within 7 days of toxicities and within 3 business days of SAE. Scheduled conference calls will be conducted after 3 patients are enrolled. Additional conference calls will be scheduled as indicated based on the recommendations from the DSMC and the PI of the study.

9 Data Handling and Record Keeping

9.1 Confidentiality

The study team will maintain clinical and laboratory data in a designed manner to ensure patient confidentiality. All study personnel have passed human subject protection courses. If applicable, tissue samples sent to collaborators outside of NYULMC will only be labeled with an assigned protocol-patient identification number without subject identifiers. Systems used for electronic data capture are compliant with HIPAA and applicable local regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for specific study personnel, CTO quality assurance specialists, and authorized representatives of regulatory agencies as described in the informed consent document. Samples sent to commercial labs or collaborating labs as per study protocol will be coded. Samples remaining after completion of the study will be destroyed once this study is completed. None of the samples collected in this study will be used to create a repository for future research studies.

9.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to to evaluate ERBB3 signaling pathway and MAPK signaling pathway components in subjects with advanced *NRAS* mutant melanoma. No genetic testing will be performed.
- Storage: Access to stored samples will be limited to the study team. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using Trialmaster.
    - Disposition at the completion of the study: All stored samples will be sent to CBRD. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

9.3 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at NYU Langone Health. After the study is completed, the de-identified, archived data will be transmitted to and stored via an electronic database system, under the supervision of Dr. Jeffrey Weber, with the potential for use by other researchers including those outside of the study. Storage of samples, specimens, and data are required to participate in this study and will be included in the informed consent.

With the participant's approval and as approved by local IRs, de-identified biological samples will be stored at the NYU Center for Biospecimen Research & Development., These samples could be used for research into identifying mechanisms for pathway activation at the cellular level of advanced melanomas, its complications and other conditions for which individuals with advanced melanomas are at increased risk, and to improve treatment. The purpose of future research is unknown at this time. The stored specimen and data will be coded, and de-identified; the linking key will be maintained by the Principal Investigator. The CBRD will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the supervision of the principal Investigator, Dr. Jeffrey Weber.

9.4 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.5 Data and Source Documentation

TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the

system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into any electronic medical record or Trial master. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

9.6 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Quality Assurance and Quality Control Study Monitoring Plan

Overall study monitoring will be conducted through a combination of on-site visit and centralized monitoring. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist, will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct , which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies

may review the conduct or results of the study at the investigational site. The investigator must promptly inform Celldex Therapeutics and Novartis of any audit requests by health authorities, and will provide Celldex Therapeutics and Novartis with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

At the NYULMC Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will monitor this trial every 4-6 weeks, this includes real-time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB/EC members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11.1 Informed Consent

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients who are evaluated and/or treated by physicians in the oncology program will be given a consent form describing participation in the study. Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, nurse practitioner, or research nurse all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read; a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

The informed consent will be signed and personally date by the subject and by the individual who conducted the informed consent discussion.

11.1.1 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

11.2 Registration Procedures

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

11.3 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's quarterly Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PPC Clinical Trial Office, Quality Assurance Unit will provide a remote interim monitoring visit, beginning within the first 6-8 weeks of the first subject enrollment and every 6-8 weeks thereafter to ensure completeness, accuracy and consistency of the data.

11.4 Patient Registrations at Additional Sites

Enrollment at addition sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyumc.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyumc.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all

data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Weber. All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Subjects must not start any protocol procedures prior to registration; each participating institution will order the study agent directly from the suppliers, Celldex (CDX-3379) and Novartis (trametinib).

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy.

Please email all SAEs to NYUPCCsafetyreports@nyulangone.org, Dr. Weber, and the NYU Langone Health CTO regulatory specialist.

12 Study Finances

12.1 Funding Source

The study will be financed with support from Celldex Therapeutics and Novartis. In addition, application for foundation grants will be submitted to in order to fund correlative studies, in addition to philanthropy.

Conflict of Interest
Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

12.2 Subject Stipends or Payments

No subjects will receive payments or stipends for participation in this research study. Celldex Therapeutics and Novartis may provide coverage for tests and/or procedures that are part of the research study if they are not covered by a subject's insurance company.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. Any formal presentation or publication of data from this trial may be published after review and comment by Celldex Therapeutics and Novartis and prior to any outside submission. Celldex Therapeutics and Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Celldex Therapeutics' and Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Celldex Therapeutics and Novartis and, in accord with the trial contract and shall not permit disclosure of Celldex Therapeutics and Novartis confidential or proprietary information.

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15 Attachments

1. FDA Form 3500A (MEDWATCH Form)
2. Informed Consent
3. CDX-3379 IB
4. Trametinib IB
5. Trametinib package insert