PROTOCOL CDX3379-04

A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of CDX-3379 in Combination with Cetuximab in Patients with Advanced Head and Neck Squamous Cell Carcinoma

Sponsor: Celldex Therapeutics, Inc.
[redacted]

IND Number: 116023

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Original Protocol: 19 May 2017

This study is to be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with ICH guidelines on Good Clinical Practice and regulatory requirements as applicable.

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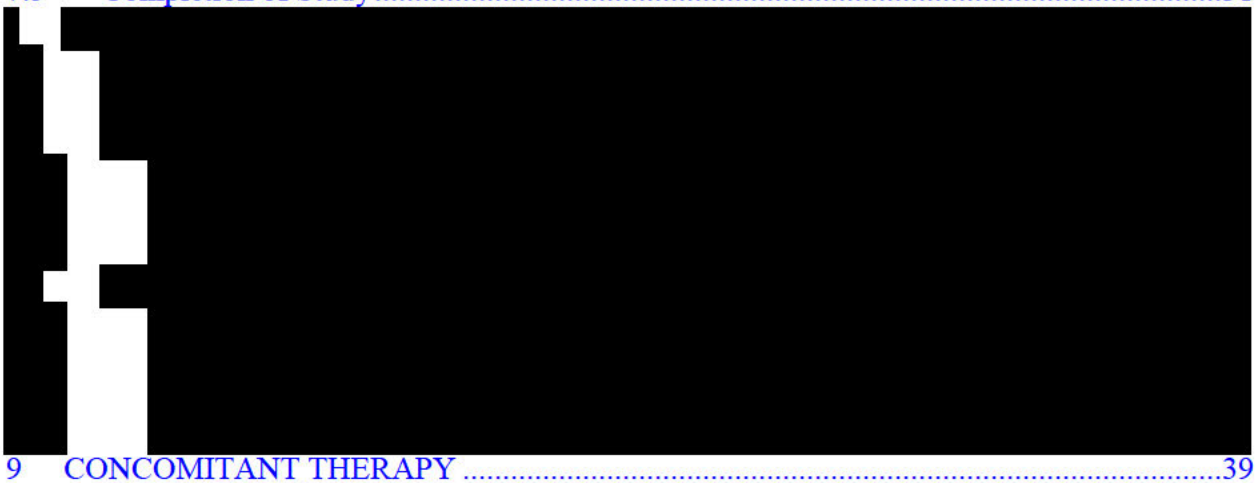

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1 STUDY PERSONNEL AND STUDY ADMINISTRATION

Information regarding key personnel involved in the conduct of the study, including names and contact details for the Celldex Medical Monitor, protocol signatory, monitors, and other staff, participating investigators, clinical laboratories and other medical and/or technical departments and/or institutions, and members of additional study committees, will be found in the study files of Celldex. Names and contact details of relevant study staff (including the responsible Medical Monitor) will be provided to all participating investigators.

For multinational studies, Celldex will assign the coordinating investigator responsible for signing the Clinical Study Report.

Note: As used throughout this document, "Celldex" refers to Celldex Therapeutics, Inc. or any designee to whom study-related responsibilities have been appropriately delegated.

2 GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies/immunogenicity
AE	Adverse event
ALT	Alanine aminotransferase
AKT	Protein kinase B
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
CBR	Clinical benefit response
CI	Confidence interval
C_{max}	Maximum concentration
CPS	Combined Positive Score
CRF	Case report form
CR	Complete response
CT	Computed tomography
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ErbB /EGFR	Epidermal growth factor receptor
ErbB1	Human epidermal growth factor receptor 1; HER1
ErbB2	Human epidermal growth factor receptor 2; HER2
ErbB3	Human epidermal growth factor receptor 3; HER3
ErbB4	Human epidermal growth factor receptor 4; HER4
EU	European Union
FAT1	FAT Atypical Cadherin 1
FcRn	Fragment crystallizable receptor – neonatal
FDA	Food and Drug Administration
FNA	Fine needle aspirate
5-FU	5-Fluorouracil
GCP	Good Clinical Practice

Abbreviation	Definition
GMP	Good Manufacturing Practice
HER	Human epidermal growth factor
HIPAA	Health Insurance Portability and Accountability Act
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
ICF	Informed consent form
IgG1λ	Immunoglobulin G1 lambda
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational new drug application
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
kg	Kilogram
m^2	Meter squared
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliters
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOTCH	NOTCH family of cell-signaling receptors
NRG	Neuregulin/heregulin
OS	Overall survival
PCR	Polymerase chain reaction
PD-1	Programmed death receptor-1
PD-L1	Programmed death-ligand 1
pErbB3	Phosphorylated ErbB3
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics

Abbreviation	Definition
PR	Partial response
PTEN	Phosphatase and tensin homolog
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RTK	Receptor tyrosine kinases
SAE	Serious adverse event
SD	Stable disease
$T_{1/2}$	Half-life
ULN	Upper limit of normal
YAP1	Yes-associated protein 1
YTE	M253Y/S255T/T257E; M252Y/S254T/T256E, according to the EU numbering system

3 PROTOCOL SYNOPSIS

Protocol Number:	CDX3379-04
Protocol Title:	A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of CDX-3379 in Combination with Cetuximab in Patients with Advanced Head and Neck Squamous Cell Carcinoma
Phase of Development:	Phase 2
Investigational Treatment:	CDX-3379; a human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that selectively binds and inhibits ErbB3 activity
Additional Therapy:	Cetuximab; a recombinant, human/mouse chimeric monoclonal antibody that specifically binds epidermal growth factor receptor (EGFR) and competitively inhibits ligand binding.
Indication:	Advanced head and neck squamous cell carcinoma (HNSCC)
Number of Patients:	Approximately 45
Number of Study Centers:	Approximately 10-15
Objectives:	Primary Objective: • To estimate the objective response rate (ORR) for CDX-3379 in combination with cetuximab in patients with cetuximab-resistant advanced HNSCC Secondary Objective(s): • To estimate the clinical benefit response (CBR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) for patients with cetuximab-resistant advanced HNSCC treated with CDX-3379 in combination with cetuximab • To evaluate the safety of CDX-3379 in combination with cetuximab • To evaluate the pharmacokinetics (PK) of CDX-3379 in combination with cetuximab • To evaluate the anti-drug antibodies (ADA)/immunogenicity of CDX-3379 in combination with cetuximab To evaluate tumor DNA biomarkers for CDX-3379 in combination with cetuximab and assess correlation with efficacy. [redacted]
Overview of Study Design:	This is an open-label, multicenter Phase 2 study of CDX-3379 in combination with cetuximab in patients with cetuximab-resistant HNSCC. The study was initially designed according to a Simon's 2-stage design in which one tumor response (complete response [CR] or partial response [PR]) would need to be observed in the first 13 evaluable patients before completion of accrual to a total of 27 evaluable patients. Patients who discontinue treatment in the absence of progression/symptomatic deterioration/death before the first tumor assessment will be considered unevaluable for primary analysis and will be replaced. Following completion of stage 1 of the study, where 1 complete response was observed, emerging biomarker data were reviewed to assess correlation with efficacy in the overall CDX-3379 development program. In a small patient dataset, FAT1 and NOTCH1, NOTCH2 and NOTCH3 mutations appeared to be associated with clinical activity, including objective response and durable stable disease. Given these findings, the study design has been amended to enroll up to approximately 45 total patients, including at least 15 patients whose tumor harbor a FAT1 mutation based on retrospective

	gene sequencing. Screening tissue samples will be required to be submitted as directed by the Sponsor at the time of enrollment to allow for gene sequencing and tracking the number of patients whose tumor harbor a FAT1 mutation. Tumor assessments will be performed approximately every 6 weeks during treatment. Patients who discontinue treatment in the absence of progression will continue to have assessments approximately every 12 weeks until documented progression or initiation of alternate anticancer therapies. Tumor response will be assessed by the investigator in accordance with RECIST 1.1 guidelines (Eisenhauer, et al. 2009) (Section 10.2.1 and Appendix 2). Continuous evaluation of toxicity will be performed by the investigators and Celldex throughout the entire course of patient treatment and through 30 days following the last dose of CDX-3379. Subsequently, patients will be followed for survival, with contact every 12 weeks until study closure.
[redacted]	[redacted]
Eligibility Criteria:	Key inclusion/exclusion criteria include: • Male or female patients who are 18 years of age or older who have provided written informed consent • Histologically or cytologically confirmed HNSCC that is recurrent or metastatic, not curable with local treatment modalities (e.g., surgery, radiation), and progressive (based on radiographic, clinical or pathologic assessment) during or subsequent to last therapy. • Human papilloma virus (HPV) negative tumor, as established by the local site. Acceptable standards include p16 immunohistochemistry (where a tumor is classified as p16-positive when showing diffuse nuclear and cytoplasmic staining in at least 70% of tumor cells) and/or assessment of HPV deoxyribonucleic acid (DNA). • Prior treatment must include (in any combination or sequence): o check-point inhibitor targeting programmed death receptor-1 axis (PD-1/PDL-1), unless not a candidate

	○ cetuximab, with tumor progression during or within 6 months after completing treatment (regardless of any intervening therapies) • Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, et al. 2009) (Appendix 2) • Willingness to consent for tumor biopsy from an accessible site (primary or metastatic) prior to initiating study therapy. In cases where a fresh biopsy is not feasible (i.e., if an accessible site cannot be biopsied with acceptable clinical risk or upon patient refusal), archival tissue may be submitted instead, after discussion with and approval by the medical monitor. See Section 7.2.2 for complete inclusion/exclusion criteria.
Endpoints:	Primary Endpoint: • ORR: The percentage of patients who achieve a CR or PR, confirmed according to RECIST 1.1. Best response is recorded between the date of first dose and the date of documented progression per RECIST 1.1 or the date of subsequent anti-cancer treatment, whichever occurs first. For patients without documented progression or subsequent anti-cancer treatment, all available tumor assessments will contribute to the best response assessment. Secondary Endpoints: • CBR: The percentage of patients who achieve best response of confirmed CR or PR, or stable disease (SD) for at least 12 weeks. Best response is assessed as described for ORR. • DOR: The interval from which measurement criteria are first met for CR or PR until the first date that progressive disease is objectively documented or death, whichever occurs first. Patients who have not progressed or died will be censored on the date of last evaluable tumor assessment; patients who did not have any on-study assessments and have not died will be censored on the date of first dose. If a patient receives subsequent anti-cancer treatment before documented progression, then DOR will be censored on the last evaluable tumor assessment on or before the start date of subsequent anti-cancer treatment. • PFS: The time from start of CDX-3379 to time of progression or death, whichever occurs first. Patients who have not progressed or died will be censored on the date of last evaluable tumor assessment; patients who did not have any on-study assessments and have not died will be censored on the date of first dose. If a patient receives subsequent anti-cancer treatment before documented progression, then PFS will be censored on the last evaluable tumor assessment on or before the start date of subsequent anti-cancer treatment. • OS: The time from start of CDX-3379 to death. Patients who have not died will be censored on the date of last contact. • Safety: Safety will be assessed by vital sign measurements, clinical laboratory tests, physical exams, ECGs, and the incidence and severity of adverse events (graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE v 5.0.)). • Pharmacokinetics: Noncompartmental PK parameters will be determined using CDX-3379 serum concentration data obtained prior to, at completion of, and one hour after each CDX-3379 administration, as well as on days 8 and 15 of the first cycle, and 30 days post-treatment. • Immunogenicity: Patients will be monitored for the development of anti-drug antibodies (ADA) to CDX-3379. Samples will be collected for future evaluation of the neutralizing capacity of ADA.

	• Biomarkers: DNA sequencing will be conducted on tumor samples to assess for mutations in cancer-related genes such as FAT1, NOTCH1, NOTCH2, NOTCH3, AKT/PI3K, phosphatase and tensin homolog (PTEN) and/or ErbB family members.
	[redacted]
Statistical Methods:	Sample Size The original sample size for the study was based on Simon's 2-stage MinMax design. The first stage was completed, and the futility stopping rule was not met. The current amendment will increase the total sample size from 30 to approximately 45 treated patients, including at least 15 patients whose tumors harbor a FAT1 mutation based on retrospective gene sequencing. Shown below are the confidence intervals associated with a range of observed ORRs in all treated patients (n=45) and in those who are FAT1 mutation-positive (n=15) that would provide sufficient precision to rule out < 10%, < 15%, and < 20% ORR based on the lower 95% confidence bound for different underlying true response rates (true p). The table also shows the likelihood of observing at least the number of responses associated with each of these thresholds (power). If the true response rate is ≥ 30%, a sample size of 45 treated patients provides sufficient power to rule out < 10% ORR; if the true response rate is ≥ 40%, then the study is adequately powered to rule out < 20% ORR. A cohort size of 15 treated patients in the FAT1 mutation-positive cohort provides ≥70% power to rule out <10% ORR if the true response is ≥ 30%; ≥ 78% power to rule out < 15% ORR if the true ORR is ≥ 40%; and ≥ 70% power to rule out < 20% ORR if the true ORR is ≥ 50%.

Observed ORR and Associated Precision and Power Calculations Under Varying Cohort Sample Sizes and Underlying Response Rates

Cohort	Observed No. Responses r (ORR)	95% CI [a] of ORR (%)	Power: P (No. observed responses ≥ r | true p)*100 true p = 50%	true p = 40%	true p = 30%	true p = 20%
All Treated Patients n=45	9/45 (20.0%)	(9.6, 34.6)	> 99%	> 99%	95%	56%
	12/45 (26.7%)	(14.6, 41.9)	> 99%	98%	74%	17%
	15/45 (33.3%)	(20.0, 49.0)	> 99%	86%	37%	2%
FAT1 mutation positive n=15	4/15 (26.7%)	(7.8, 55.1)	98%	91%	70%	35%
	5/15 (33.3%)	(11.8, 61.6)	94%	78%	48%	16%
	7/15 (46.7%)	(21.3, 73.4)	70%	39%	13%	2%

[a] Clopper-Pearson

Analysis Population(s)

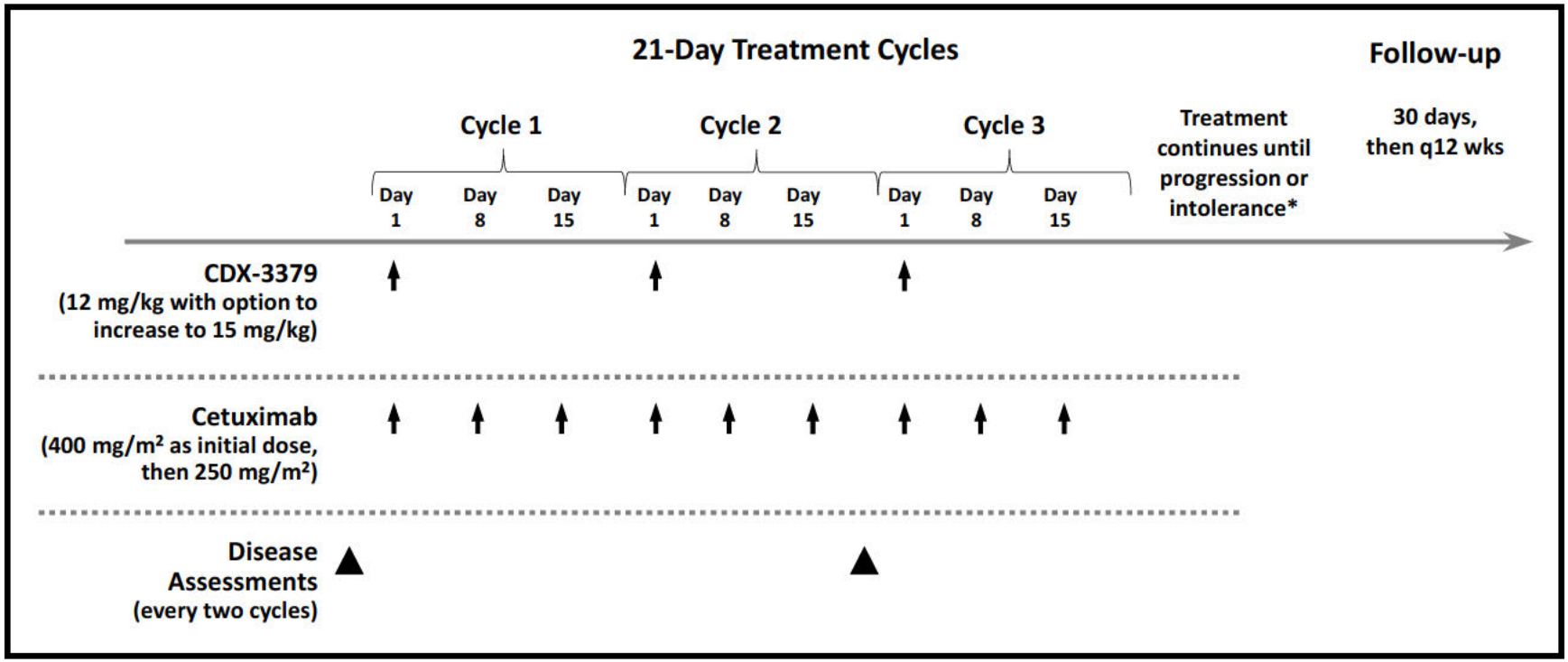
All treated population: All patients treated with CDX-3379. The primary efficacy analysis as well as all safety, PK, and biomarker analyses will be performed in this population. Efficacy analyses will also be conducted in the following subgroups: FAT1 mutation-positive treated patients, FAT1 or NOTCH mutation-positive treated patients, and all treated patients with a primary tumor site of oral cavity.

	Response-evaluable population: All patients who have measurable disease at baseline and receive one full dose of both CDX-3379 and cetuximab and have post baseline tumor response assessment or discontinue study prematurely for disease progression, symptomatic deterioration, or death. Patients who discontinue treatment prior to the first tumor assessment for other reasons will be excluded from this population. Sensitivity analyses for efficacy endpoints will be performed in this population. Analysis Methods Best overall response (as defined by RECIST 1.1) will be summarized for the all treated population. The ORR calculated as defined above, and the corresponding 95% exact CI will be calculated using the Clopper-Pearson method. CBR will be analyzed using the same approach as ORR. DOR will be estimated using the Kaplan-Meier (KM) product limit method. The KM estimate of the median DOR will be reported along with the two-sided 95% CI using Brookmeyer and Crowley's method (log-log transformation). Progression-Free Survival and Overall Survival will be analyzed using the same approach as DOR. Additional analyses may be conducted including estimating objective response rate and other efficacy parameters for the response-evaluable population and within biomarker defined subgroups. Safety analyses will consist of data summaries for clinical and laboratory parameters, and for adverse events (AEs). The number and percentage of patients experiencing one or more AEs will be summarized by the relationship to study drug and severity based on NCI CTCAE v 5.0. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory parameters will be summarized using descriptive statistics, by post-treatment shifts relative to baseline, and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized using descriptive statistics. Serum CDX-3379 concentration data will be tabulated by overall study population together with descriptive statistics. Individual and mean serum concentration-time profiles of CDX-3379 will be generated. Noncompartmental PK data analysis will be performed and descriptive statistics provided. If data allows, descriptive statistics of noncompartmental PK parameters (AUC, C_{max}, CL, t½) will be provided. A population PK analysis may also be performed and various PK compartmental models may be explored to characterize the PK of CDX-3379 in patients with HNSCC. Exposure response modeling will be performed to examine the relationship between CDX-3379 serum exposure and clinical endpoints. The impact of physiologically relevant patient characteristics (covariates) and disease on PK/pharmacodynamic parameters (and possibly clinical endpoints) may be tested. The number and percentage of patients who develop detectable CDX-3379 ADA will be summarized. ADA titers will be reported for confirmed ADA-positive patients, and the impact of ADA on PK will be assessed if data allow. Biomarker data will be summarized descriptively and any correlation with outcome (efficacy) will be investigated. Analyses may include estimating objective response rate and other efficacy parameters within biomarker defined subgroups (i.e., defined by degree of expression or presence of genetic variation).

4 STUDY SCHEMA AND SCHEDULE OF ASSESSMENTS

The study schema is shown in Figure 1 and the schedule of assessments is provided in Table 1.

Figure 1: Study Schema



* If CDX-3379 is discontinued, the patient is considered to be discontinued from the study treatment.

Table 1: Schedule of Assessments

	Screening	Treatment Period				End of Treatment[3]	Follow-up Period[4]	
		Cycle 1			Cycle 2 and subsequent cycles			
		Day 1	Day 8	Day 15	Day 1		30-day	Survival follow-up
Visit Window[1]	*Day –28 to –1*		*(+/- 1 day)*	*(+/- 1 day)*			*(+/- 3 days)*	*Every 12 (±2) weeks until study closure*
Informed consent[2]	X							
Demographics and Medical history[5]	X	X						
Tumor tissue	X[6]							
Pregnancy test[7]	X	X						
Vital signs[8]	X	X	X	X	X	X	X	
Physical examination[9]	X	X	X	X	X	X	X	
ECOG Performance Status (Appendix 3)	X	X			X	X		
12-Lead Electrocardiogram[10]		X	X			X		
Serum chemistry[11]	X	X[12]	X	X	X	X	X	
Hematology[11]	X	X[12]	X	X	X	X	X	
Urinalysis[11]	X	X[12]			X	X		
CDX-3379 PK sample[13]		X[14,15]	X[14]	X[14]	X[14,15]		X[16]	
Biomarker blood sample[13]	X	X[15]	X	X	X[15,17]		X[16]	
Immunogenicity blood sample[13]		X[15]			X[15]		X	
Diagnostic Imaging / Response Assessment[18]	X				X[18]	X[18]		X[18]
Administer CDX-3379[19]		X			X			
Administer Cetuximab[20]		→						
Concomitant medication review[21]	X	X	X	X	X	X	X	X
Adverse event monitoring[22]		X	X	X	X	X	X	X
Survival follow-up								X

Footnotes on next page

Footnotes for Table 1:

1. A delay in study treatment or performance of study visits due to holidays, weekends, inclement weather, or other unforeseen circumstances will be permitted and not considered a protocol deviation. However, significant delays (i.e., greater than one week) due to these reasons should be discussed with the Celldex Medical Monitor to reach consensus on subsequent scheduling. See Section 8.2 and Section 8.3 for management of dosing delays due to toxicity.
2. No study-specific procedures will be performed prior to receipt of signed Informed Consent (and, if applicable, Health Insurance Portability and Accountability Act [HIPAA] authorization). However, assessments performed according to standard of care prior to receipt of Informed Consent may be utilized to fulfill the screening requirement, if completed within the required window for screening.
3. The End-of-Treatment (EOT) visit should be performed as soon as feasible following the decision to discontinue study drug dosing and prior to initiation of alternate therapies. This visit may be combined with the 30-day post-treatment follow-up visit, if the windows overlap, with required assessments completed once for the combined visit.
4. Follow-up visit should occur 30 (±3) days after the last dose of CDX-3379. Thereafter, patients should be contacted (may be via telephone) every 12 (±2) weeks until study closure for survival status and subsequent therapies. For patients who have discontinued study therapy for reasons other than progression, imaging studies to assess response should be obtained every 12 (±2) weeks (relative to last disease assessment) until disease progression or until patients are started on subsequent therapy, whichever occurs sooner. For these patients, the first survival status may be scheduled to coincide with the first post-treatment disease assessment, rather than relative to the 30-day follow-up.
5. Medical history includes prior/concurrent conditions and cancer history including cancer mutation status and HPV status, prior treatments and surgical history. At Day 1, medical history is updated prior to administration of study drug.
6. Unless prior agreement is reached with the Medical Monitor for submission of archival tumor, biopsy is to be performed of an accessible site (primary or metastatic) that can be biopsied with acceptable clinical risk (as judged by the investigator), obtaining a minimum of 3-5 core biopsies for biomarker analysis. FNAs are not acceptable. The biopsy site chosen should not have been previously irradiated and must be distinct from RECIST 1.1 target lesions, unless the biopsy is obtained prior to the screening disease assessment.
7. Pregnancy tests are required only for women of childbearing potential (excluding patients who are post-menopausal with absence of menses for at least 1 year and/or surgically sterilized). A serum pregnancy test must be performed during Screening. If the serum pregnancy test is performed more than 7 days prior to Day 1, then a urine or serum pregnancy test must also be performed on Day 1 with results reviewed prior to dosing.
8. Vital signs should include heart rate, respiratory rate, blood pressure, temperature, and weight. Height should be recorded at Screen only, while weight is recorded only once per visit. Patients will be monitored during and after infusion of CDX-3379 and cetuximab with assessment of vital signs pre-infusion (within 30 minutes of the start of infusion), at 30 (± 5) minutes during the infusion, at the end of the infusion (within 5 minutes), and as clinically indicated during the 1-hour post-treatment observation period. When cetuximab is administered over two hours, vital signs should additionally be assessed at 60 (± 5) minutes and 90 (± 5) minutes.
9. Complete physical examination should be performed at screening; thereafter, symptom-directed physical examinations are acceptable.
10. Twelve-lead ECGs will be obtained prior to dosing and at 30-60 minutes following the CDX-3379 infusion on day 1 and 8 of cycle 1. A second original copy of the ECG tracing should be retained for possible submission to Celldex.
11. Laboratory assessments to be performed locally, as well as requirements for review prior to CDX-3379 and cetuximab dosing, are specified in Section 10.2.5.5. See Section 8 for guidance regarding dosing modifications/delays due to laboratory toxicity.
12. Assessments do not need to be repeated if performed within 24 hours of Cycle 1 dosing as part of the screening assessment.

13. Analyses will be performed centrally. Sample collection, processing and shipping instructions will be provided separately.
14. Blood samples for CDX-3379 PK analysis will be drawn predose, immediately after the end of infusion (within 5 minutes), and 60 minutes (± 5 minutes) post-infusion on Day 1 of each cycle prior to cetuximab administration. PK samples will also be collected prior to cetuximab dosing on Day 8 and 15 of Cycle 1.
15. Predose blood sample may be collected within 24 hours prior to CDX-3379 administration.
16. To be collected at 30-day follow-up visit, only if additional anticancer therapy has not been started.
17. Biomarker blood samples to be collected predose at cycle 2, 3, 5, 7, and 9.
18. See Section 10.2.1 and Appendix 2. Disease evaluation done at screening, near the end of every 2nd cycle (i.e., after day 15 of cycles 2, 4, 6, 8, etc. and prior to dosing for the next cycle), and, for patients who have not experienced progression at end of treatment, every 12 (±2) weeks until progression or initiation of alternate cancer therapies. Disease evaluation is required at end of treatment only if disease progression is not previously document. If a partial or complete response is noted, a follow-up radiographic assessment must be done no sooner than 28 days later to confirm response. Prior to any intervention (such as surgical resection, palliative radiation or alternate anticancer therapy), every effort should be made to perform a tumor response assessment in order to document progression and/or confirm an objective response.
19. Unless otherwise specified, all study assessments should be performed prior to administration of study treatment and may be performed up to 24 hours prior to treatment administration if assessments remain within the specified visit window. CDX-3379 should be administered first, with a 1-hour observation period before administration of cetuximab. Diarrhea prophylaxis is required in accordance with Section 8.4.1.4
20. Cetuximab will be administered weekly on Days 1, 8, and 15 of each cycle. On Day 1 of each Cycle, cetuximab should be administered approximately 1 hour after the completion of CDX-3379 administration and after collection of the 60 minute post-infusion PK blood sample. As a routine precaution, patients should be observed for at least 1 hour after the end of the cetuximab infusion. See Section 8.4.2 for guidance on cetuximab premedication and diarrhea prophylaxis. See Section 8 for additional details regarding study treatment dosing, precautions, monitoring, and management of toxicity.
21. All concomitant medications will be documented if taken within 28 days prior to Day 1, and either (whichever occurs sooner): a) through the 30-day post-treatment follow-up, or b) initiation of alternate anticancer therapy. In addition, all anticancer surgeries or medications and response to those medications, as well as any concomitant medications required to treat study drug-related serious adverse events (SAEs), should also be recorded throughout the duration of study follow-up. See Section 9 for further guidance.
22. Documentation of AEs will continue until the 30-day post-treatment follow-up, or until the initiation of subsequent anticancer treatment, whichever occurs first. For AEs or SAEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve to ≤ grade 1, or stabilize for at least three months after the last administration of study treatment (whichever is sooner). In addition, any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study treatment is suspected. See Section 10.2.5.1, Section 10.2.5.2, Section 10.2.5.3 and Section 10.2.5.4 for further guidance.

[redacted]

6 STUDY OBJECTIVES

The primary objective of this study is to estimate the ORR for the combination of CDX-3379 in combination with cetuximab in patients with cetuximab-resistant advanced HNSCC

The secondary objectives of this study are to:

- Estimate the clinical benefit response (CBR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) for patients with cetuximab-resistant advanced HNSCC treated with CDX-3379 in combination with cetuximab
- Evaluate the safety of CDX-3379 in combination with cetuximab
- Evaluate the PK of CDX-3379 in combination with cetuximab
- Evaluate the anti-drug antibodies (ADA)/immunogenicity of CDX-3379 in combination with cetuximab
- Evaluate tumor DNA biomarkers for CDX-3379 in combination with cetuximab and assess correlation with efficacy.

[redacted]

7 INVESTIGATIONAL PLAN

7.1 Overall Design and Plan of the Study

This is an open-label, multicenter Phase 2 study of CDX-3379 in combination with cetuximab in patients with cetuximab-resistant HNSCC. Patients will be treated with CDX-3379 plus cetuximab until progressive disease, unacceptable toxicity, or other criteria for discontinuation of study treatment (Section 7.4.1) are met.

The study was initially designed according to a Simon's 2-stage design in which one tumor response (CR or PR) would need to be observed in the first 13 evaluable patients before completion of accrual to a total of 27 evaluable patients. Patients who discontinue treatment in the absence of progression/symptomatic deterioration/death before the first tumor assessment will be considered unevaluable for primary analysis and will be replaced. Following completion of stage 1 of the study, where 1 complete response was observed, emerging biomarker data were reviewed to assess correlation with efficacy. In the overall CDX-3379 development program, in a small patient dataset, FAT1 and NOTCH1, NOTCH2 and NOTCH3 mutations appeared to be associated with clinical activity including objective response and durable stable disease. Given these findings, the study design has been amended to enroll up to approximately 45 total patients, including at least 15 patients whose tumor harbor a FAT1 mutation based on retrospective gene sequencing. Screening tissue samples will be required to be submitted as directed by the Sponsor at the time of enrollment to allow for gene sequencing and tracking the number of patients whose tumor harbor a FAT1 mutation.

Tumor assessments will be performed approximately every 6 weeks during treatment. Patients who discontinue treatment in the absence of progression will continue to have assessments approximately every 12 weeks until documented progression or initiation of alternate anticancer therapies. Tumor response will be assessed by the investigator in accordance with RECIST 1.1 guidelines (Eisenhauer, et al. 2009) (Section 10.2.1 and Appendix 2).

Continuous evaluation of toxicity will be performed by the investigators and Celldex throughout the entire course of patient treatment and through 30 days following the last dose of CDX-3379. Subsequently, patients will be followed for survival, with contact every 12 weeks until study closure.

7.2 Selection of Study Population

7.2.1 Number of Patients

It is anticipated that approximately 45 patients will be accrued. Enrollment will be competitive with no maximum per site.

7.2.2 Patient Eligibility

7.2.2.1 Inclusion Criteria

Patients may be included in the study only if they meet all of the following inclusion criteria prior to receiving study treatment:

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. Histologically or cytologically confirmed HNSCC that is recurrent or metastatic, not curable with local treatment modalities (e.g., surgery, radiation), and progressive (based on radiographic, clinical or pathologic assessment) during or subsequent to last therapy.
4. Human papilloma virus (HPV) negative tumor, as established by the local site. Acceptable standards include p16 immunohistochemistry (where a tumor is classified as p16-positive when showing diffuse nuclear and cytoplasmic staining in at least 70% of tumor cells) and/or assessment of HPV deoxyribonucleic acid (DNA).
5. Prior treatment must include (in any combination or sequence):
    a. check-point inhibitor targeting programmed death receptor-1 axis (PD-1/PDL-1), unless not a candidate
    b. cetuximab, with tumor progression during or within 6 months after completing treatment (regardless of any intervening therapies)
6. Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, et al. 2009) (Appendix 2). Target lesions selected for tumor measurements should be those where additional (e.g., palliative) treatments are not indicated or anticipated.
7. Willingness to consent for tumor biopsy from an accessible site (primary or metastatic) prior to initiating study therapy. In cases where a fresh biopsy is not feasible (i.e., if an accessible site cannot be biopsied with acceptable clinical risk or upon patient refusal), archival tissue may be submitted instead, after discussion with and approval by the medical monitor.
8. 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.
9. Adequate electrolytes, liver, renal, and hematology function as defined below:
    a. Hemoglobin $\geq$ 9 g/dL
    b. Absolute neutrophil count $\geq$ 1500/mm^3
    c. Platelet count $\geq$ 100,000/mm^3
    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ upper limit of normal (ULN) ($\leq$ 5 $\times$ ULN for cases involving liver metastasis)
    e. Bilirubin $\leq$ 1.5 $\times$ ULN ($\leq$ 5 $\times$ 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 ≤ 1.5 × ULN

h. Serum calcium and potassium within normal limits

10. Life expectancy ≥ 12 weeks

11. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 3)

12. 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 or cetuximab, whichever is later. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.

7.2.2.2 Exclusion Criteria

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

1. Nasal, paranasal sinus, or nasopharyngeal carcinoma, aside from WHO Type I and II (keratinizing, non-EBV positive) nasopharyngeal carcinoma which will be allowed.

2. Received CDX-3379 or other anti-ErbB3 targeted 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 3 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. Known brain metastases, unless previously treated and asymptomatic for 2 months and not progressive in size or number for 2 months prior to enrollment. Continued use of anticonvulsants (in the absence of any suspicion of progressive brain metastases) is acceptable.

6. Known HIV, hepatitis B or hepatitis C infection, or active infection requiring systemic intravenous therapy

7. 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.

8. Chemotherapy within 21 days or at least 5 half-lives (whichever is shorter) prior to the planned start of study treatment

9. 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.

10. Use of other investigational drugs within 2 weeks or 5 half-lives (whichever is longer) prior to study treatment administration

11. 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,); the use of concomitant medications that prolong the QT/QTc interval; 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.

12. Requirement for chronic immunosuppressive medication including systemic corticosteroids above the physiologic dose (defined as 30 mg/day hydrocortisone or the equivalent).

13. 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.

14. Known alcohol or drug abuse.

15. Women who are pregnant or nursing. All female patients with reproductive potential must have a negative pregnancy test prior to starting treatment

16. Known allergy or past administration reaction including infusion reactions, anaphylactic, or anaphylactoid reactions to any component of the CDX-3379 formulation.

17. Prior history of clinically significant hypersensitivity reaction or significant intolerance to cetuximab; history of allergic reactions attributed to compounds of chemical or biologic composition similar to those of cetuximab.

7.3 Measures to Minimize Bias

This is non-randomized open-label study. The analysis of tumor response and progression-free survival will be based on tumor response assessments performed by the investigator according to standardized, objective response criteria (RECIST 1.1). In addition, in the event of a positive study outcome, an additional assessment of tumor response and progression may be performed by an independent review committee blinded to investigator assessments.

7.4 Withdrawal and Replacement of Patients

Every effort should be made within the bounds of safety and patient choice to have each patient complete the study.

Patients who discontinue the study for reasons other than disease progression, symptomatic deterioration or death prior to the first radiographic assessment will be considered unevaluable for primary analysis and will be replaced.

An explanation will be recorded for each patient taken off study treatment or discontinuing the study.

7.4.1 Discontinuation of Study Treatment

Reasons for permanent discontinuation of study treatment may include:

- Progressive disease, as assessed by the treating investigator in accordance with RECIST 1.1 criteria (Appendix 2);
- Symptomatic deterioration (clinical deterioration suggesting that no further benefit from treatment is likely);

  Note: This category is applicable to patients with a global deterioration of health status requiring discontinuation of treatment. However, per RECIST 1.1, symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. Thus, every effort should be made to continue disease assessments per protocol until documented objective progression or initiation of alternate therapy.
- Request of the patient or the patient's legal representative;

  Note: Withdrawal of consent for continued study treatment should be differentiated from withdrawal of consent for study follow-up, and every effort should be made within the bounds of safety and patient choice to have each patient complete the study follow-up.
- Adverse event;
- Non-compliance of the patient;
- Physician decision (for reasons other than the above);
- Pregnancy;
- Death, otherwise not explainable by the above options; and
- Patient lost to follow-up. A patient should be considered lost to follow-up only after multiple efforts have been made to contact the patient to assess his/her health status after failure of the patient to attend scheduled visits. If after two documented phone calls the investigative site is still unable to contact the patient, a certified letter should be sent to his/her home for immediate response. If there is still no response, the patient is to be considered lost to follow-up. A record of the patient being lost to follow-up should be noted in the source documents along with the phone contacts and the returned certified mail (if sent back).

Patients who discontinue CDX-3379 should be seen for an End-of-Treatment (EOT) Visit, and should undergo additional post-treatment follow-up for safety, disease progression, and survival, as described in Section 10.1.3, when feasible.

7.4.2 Discontinuation from Study

Reasons for patient removal from the study follow-up include:

- Request of the patient or the patient's legal representative (withdrawal of consent for the study follow-up);
- Patient lost to follow-up (as noted above).

7.5 Completion of Study

It is anticipated that the enrollment period will be approximately 2 years. All patients will be followed with regard to survival until death, discontinuation from study follow-up, or termination/completion of study. Patients who die or complete the study follow up through study closure will be considered to have "completed" the study.

The study will be declared complete when sufficient data is obtained to complete study analyses and conclude the study. This is estimated at approximately 1 year from the date of end of patient recruitment. The "end of the clinical trial" will be defined as the date of the last visit of the last subject.

Subject to establishment of the appropriate mechanisms for continued provision of CDX-3379, patients may be allowed to continue receiving treatment after study closure until disease progression or commercial availability of CDX-3379, provided that there is clinical rationale and drug is available.

Premature termination of this study may occur because of a regulatory authority decision, drug safety issues, or at the discretion of Celldex. In addition, Celldex retains the right to discontinue development of CDX-3379 at any time. In the event of an early trial termination, efforts will be made to minimize inconvenience or harm to study subjects.

[redacted]

9 CONCOMITANT THERAPY

Please refer to the study entry criteria for the required "wash-out" period for specific therapies, relative to start of study treatment.

Required prophylactic medications are described in Section 8.4.

Patients may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. However, efforts should be made to maintain stable doses of concomitant medications during the course of study treatment. Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care, such as those outlined in Section 8.3.1, Section 8.4.1.4. and 8.4.2.

However, while on study, when clinically appropriate, patients should strictly follow the study-prescribed treatment regimen. The following are prohibited throughout the treatment period:

- Concurrent administration of any anticancer therapies (including chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy) and/or other investigational agents (Note: concurrent use of hormones for conditions unrelated to cancer [e.g., insulin for diabetes and hormone replacement therapy] is acceptable.)
    - Following treatment, patients may receive any appropriate alternate therapies.

The Medical Monitor must be notified if a patient receives any prohibited medication during the treatment period.

All concomitant medication will be documented in the patient's medical record and CRF if taken within 28 days prior to randomization/enrollment, and either (whichever occurs sooner): a) 28 days after last dose of study treatment (either CDX-3379 or cetuximab), or b) initiation of alternate anticancer therapy. All anticancer medications taken throughout the study (including follow-up) should also be recorded, as should concomitant medications required to treat study drug-related serious adverse events (SAEs).

10 STUDY PROCEDURES

10.1 Schedule of Investigations and Data Collection

The study is divided into three phases: Screening, Treatment, and Post-Treatment Follow-up. Each phase has associated evaluations and procedures that must be performed at specific time points, as described in the following sections. Table 1 summarizes the frequency and timing of various activities, safety, and other measurements.

10.1.1 Screening Phase

Prior to the performance of any study-specific procedures, the patient will have the nature of the study explained to him/her, and will be asked to give written informed consent and if applicable, HIPAA authorization. Informed consent/HIPAA authorization must be obtained prior to any study-specific procedures that do not form a part of the patient's normal care. However, assessments performed according to standard of care prior to receipt of informed consent may be utilized to fulfill the screening requirement, if completed within the required window for screening.

The assessments outlined in for the Screening Visit in the Schedule of Assessments (Table 1) will be completed for each patient prior to inclusion in the study. The screening evaluations may be carried out over more than one visit.

Patients who are screened but do not meet all entry criteria (i.e., screen failures) will not be entered in the clinical database. Instead, a log of patients screened for the study, including the reason for study ineligibility, will be maintained at the study center. Once assigned, patient numbers for any screening failures, non-treated, unevaluable, or discontinued patients will not be re-used.

Study enrollment will occur only after confirming all inclusion criteria and none of the exclusion criteria have been met, and in accordance with instructions provided by Celldex.

10.1.2 Treatment Phase

Study treatment administration is discussed in Section 8. Specific procedures to be performed at each visit during the treatment phase are listed in Table 1.

The EOT Visit should be performed as soon as feasible following the decision to discontinue study drug dosing and prior to initiation of alternate therapies. This visit may be combined with the 30-day post-treatment follow-up visit, if the windows overlap, with required assessments completed once for the combined visit. Specific procedures to be performed at this visit are illustrated in Table 1.

10.1.3 Post-Treatment Follow-up Phase

A follow-up visit is to be completed on Day 30 (± 3 days) following the last dose of CDX-3379. Subsequently, patients should be followed on study for survival, with visits or telephone contact every 12 (± 2) weeks until the study is closed.

Additionally, during the post-treatment follow-up:

- Patients who have discontinued study therapy for reasons other than progression should undergo imaging studies to assess response approximately every 12 (± 2) weeks until disease progression or until initiation of subsequent anticancer therapy, whichever occurs sooner.
- Throughout the follow-up phase, documentation and follow-up of AEs and concomitant medications should continue in accordance with Section 9 and Section 10.1.3.

Specific procedures to be performed throughout the follow-up phase are illustrated in Table 1.

10.2 Methods of Assessment

10.2.1 Activity

Tumor response and progression-free survival will be assessed via imaging-based evaluation per RECIST 1.1 (Appendix 2).

Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, as well as all other suspected disease sites is required. Magnetic resonance imaging (MRI) exams of the brain, abdomen, and pelvis can be performed in lieu of a CT; however, MRI exams of the chest are not recommended. In the event that a chest MRI is performed, a non-contrast chest CT is strongly recommended to evaluate the lung parenchyma. Brain and/or bone scans are required for any patients with a history of metastases to bone and/or brain or where symptomatology raises the suspicion for bone and/or brain metastases. Lesions identified on bone scans should be confirmed by a CT or MRI at baseline, and, if identified as target lesions due to soft tissue component, they should continue to be followed by the same methodology (i.e., CT or MRI scan). However, bone lesions followed as non-target disease may be subsequently followed by bone scans only. Lesions that cannot be imaged but are assessable by clinical exam may be assessed by color photography including a ruler (preferred method) or measured with calipers.

Normally, all target and non-target disease sites should be evaluated at each assessment. However, for patients with non-target bone disease, bone scans need only be repeated every twelve to

eighteen weeks, or more frequently if clinically indicated. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.

10.2.2 Pharmacokinetic Evaluation

Table 7 details the PK sample collection schedule. Details will be provided separately in a laboratory manual to include procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information.

Table 7: Schedule of CDX-3379 PK Sampling Times

Day	Time
Day 1 for all Cycles	Predose (within 24 hours of CDX-3379 infusion) Immediately after the end of CDX-3379 infusion (within 5 minutes) Post CDX-3379 dose at 60 minutes after end of CDX-3379 infusion (± 5 minutes) and prior to cetuximab administration
Cycle 1, Day 8	During visit prior to cetuximab administration
Cycle 1, Day 15	During visit prior to cetuximab administration
30-Day Follow-up	During visit, in cases where new anticancer therapy hasn't yet been started

10.2.3 Immunogenicity of CDX-3379

Table 8 details the immunogenicity sample collection schedule. Details will be provided separately in a laboratory manual to include procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information.

The ADA titer will be reported for samples confirmed positive for the presence of anti-CDX-3379 antibodies. Tiered analysis will be performed to include screening, confirmatory and titer assay components and Positive-Negative cut points will be employed that were statistically determined from CDX-3379-naïve validation samples.

Samples will be collected for assessing the neutralization capacity in the future.

Table 8: Schedule of CDX-3379 ADA Sampling Times

Cycle and Day	Time
Day 1 of each Cycle	Predose (within 24 hours prior to CDX-3379 infusion)
30-Day Follow-up	During visit

10.2.4 Biomarker Evaluation and Methods

Pre-treatment biopsy tumor samples (fresh preferred, archival upon approval by the Medical Monitor) are planned to be evaluated for biomarkers that may enrich for patient benefit to CDX-3379. Details on performing the core or excisional biopsies (a minimum 3-5 core or excisional biopsies preferred, FNAs are not acceptable), preparing the samples and shipping instructions can be found in the laboratory manual.

Briefly, DNA sequencing will be conducted on tumor samples to assess for mutations in cancer-related genes such as FAT1, NOTCH1, NOTCH2, NOTCH3, AKT/PI3K, phosphatase and tensin homolog (PTEN) and/or ErbB family members.

Tumor samples may also be utilized for RNA expression analysis or protein analysis of proteins and/or genes related to cancer and/or ErbB3 and EGFR signaling.

[redacted]

No test above will lead to disclosure of individual genetic information including sequences or genotypes.

Table 9 details the blood biomarker sample collection schedule. Details will be provided separately in a laboratory manual to include procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information.

Table 9: Schedule of CDX-3379 Blood Biomarker Sampling Times

Day	Time
Screening	
Day 1 of Cycles 1, 2, 3, 5, 7, 9	Predose (within 24 hours prior to CDX-3379 infusion)
Cycle 1, Day 8	During visit prior to cetuximab administration
Cycle 1, Day 15	During visit prior to cetuximab administration
30-Day Follow-up	During visit, in cases where new anti-cancer therapy hasn't yet been started

Other biomarkers may be evaluated as determined by additional data.

10.2.5 Safety Variables

10.2.5.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. All observed or volunteered AEs regardless of suspected causal relationship to the study treatment will be reported as described in the following sections. For the purposes of this current study, CDX-3379 and cetuximab are considered "study treatment".

For all AEs, the investigator is responsible for obtaining information adequate to determine the:

- Appropriate descriptive term: Adverse events should be reported using concise medical terminology, preferably referring to the syndrome/diagnosis rather than symptoms, when possible.
- Severity of the event: adverse event severity will be primarily assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, division of Cancer Treatment and Diagnosis (DCTD), NCI, National Institute of Health (NIH), Department of Health and Human Services (DHHS) published November 17, 2017 at

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

- Onset/resolution dates and outcome
- Causality: the relationship of each AE to study drug will be defined as "unrelated" or "related" to study treatment:
    - Unrelated: There is little or no possibility that the study drug caused the reported AE; and other factor(s) including concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications appear to explain the AE.
    - Related: there exists at least a reasonable possibility that the study treatments caused or contributed to the AE; an inability to identify an alternate etiology for an AE should not, by itself, justify a "related" attribution.
- Whether it meets the criteria for classification as an SAE (see Section 10.2.5.2)

The following study-specific points of clarification should be noted when considering AE reporting and recording:

- Progression of neoplasia should not be reported as an AE or SAE. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an AE, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. If there is any uncertainty about a finding or event being due solely to progression of neoplasia, the finding or event should be reported as an AE or SAE as appropriate.
- Death due to disease progression occurring within 28 days of study treatment should be reported to Celldex within 24 hours of the site's awareness of the event; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as an SAE.
- Withdrawal due to an AE should be distinguished from withdrawal due to insufficient response, and recorded on the appropriate AE CRF page. For example, if an AE due to recurrence/progression of disease necessitates discontinuation from the study, the primary reason for study discontinuation should be recorded as "Progression of Disease" (not AE).

[redacted]

- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

- Any AEs/SAEs resulting in death should be recorded with an end date equal to the death date, while other events ongoing at the time of death should be recorded with an outcome of "ongoing". If requested, a summary of available autopsy findings should be submitted as soon as possible to Celldex.

10.2.5.2 Serious Adverse Events: Definition

A SAE is any AE from this study that results in one of the following outcomes:

- Death (any AE that has a fatal outcome must be assigned NCI CTCAE grade 5.)
- Requires initial or prolonged inpatient hospitalization exceeding 24 hours. As well, any event occurring while the patient is hospitalized which would otherwise require hospitalization or requires transfer within the hospital to an acute/intensive care unit should also be reported under this criterion. This criterion would exclude hospitalization in the absence of a precipitating AE, such as admission for treatment of a preexisting condition not associated with a new/worsening AE, or admission for elective surgery. As well, admission to rehabilitation/hospice/nursing facilities and outpatient admission for same-day surgeries are not considered "hospitalizations" for the purpose of this criterion.)
- Is life-threatening (An AE is considered "life-threatening" if, in the view of either the investigator or Celldex, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)
- Is a persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions,
- Congenital anomaly/birth defect
- Other significant medical hazard (Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other SAE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.)

10.2.5.3 Adverse Event/Serious Adverse Event Reporting

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

Adverse events and SAEs should be recorded on the CRF from the time the patient has received at least one dose of study treatment through (whichever occurs first) either a) the 30-day post-treatment follow-up visit, or b) initiation of alternate anticancer therapy.

However;

- Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study treatment is suspected.
- For AEs or SAEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve to ≤ grade 1, or stabilize for at least three months after the last administration of study treatment (whichever is sooner).

All AEs will be reported on the AE page(s) of the CRF, while SAEs will also be reported in an expedited fashion using the SAE report. The AE CRFs and SAE reports must be completed in a consistent manner; for example, the same AE term, causality, severity, and onset/resolution dates should be used on both forms.

In case of an SAE (regardless of causality), an SAE report must be completed and submitted to Celldex within 24 hours of the site's notification of the event, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. The investigator is obligated to pursue additional information required for thorough evaluation of each SAE as may be requested by Celldex.

Serious adverse event reporting to regulatory authorities and all participating investigators will be conducted by Celldex in accordance with 21 Code of Federal Regulations (CFR) 312.32 and international regulations, as appropriate.

10.2.5.4 Rapid Notification of Adverse Events of Interest

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events, even if the nature of the adverse event is not deemed serious:

- Any overdose (defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important).
- Any suspected transmission of an infectious agent via study treatment. An infectious agent is defined as any organism, virus, or infectious particle, pathogenic or nonpathogenic.
- Potential Drug-induced liver injury (DILI), defined as:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation > 3 times upper limit of normal (ULN)

      AND

    - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

      AND

    - No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

- Death due to disease progression occurring within 28 days of study treatment; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as a serious adverse event.
- If a female becomes, or is found to be, pregnant within 6 months of exposure to the study treatments (maternal exposure) or if a male has been exposed to the study treatments within 6 months prior to contraception (paternal exposure).
- Any follow-up to the above-referenced events, including outcome of pregnancy. Further follow-up of birth outcomes will be handled on a case-by-case basis. In the case of paternal exposure, the investigator must obtain permission from the patient's partner in order to conduct any follow-up or collect any information.

10.2.5.5 Laboratory Safety Data

The following clinical laboratory tests will be performed at the study visits outlined in Table 1.

Table 10: Clinical Laboratory Tests to be Performed During Study

Hematology:	**Clinical Chemistry:**	**Urinalysis**
Hemoglobin*	Sodium*	Protein
Hematocrit*	Potassium*	Glucose
Mean corpuscular volume (MCV)	Chloride*	Specific gravity
Erythrocyte count (RBC)	Bicarbonate*	Blood
Leukocytes (WBC)*	Glucose (nonfasting)	
Platelets*	Blood urea nitrogen (BUN)*	*Microscopic examination will be performed if indicated*
Differential:*	Creatinine*	
Neutrophils	Calcium*	
Lymphocytes	Magnesium*	**Thyroid Function**
Monocytes	Phosphate	Thyroid stimulating hormone (TSH)
Eosinophils	Alkaline phosphatase*	Free T4§
Basophils	Alanine transaminase (ALT/SGPT)*	Free T3§
	Aspartate transaminase (AST/SGOT)*	
Differential should be reported consistently throughout the study as either an absolute count (preferred) or as a percentage.	Total protein	*§ Free T4 and free T3 performed at screening, and then only if TSH is abnormal at subsequent visits.*
	Albumin	
	Lactate Dehydrogenase (LDH)	
	Total Bilirubin*	
	Uric acid	
	Amylase*	*If thyroid function tests are abnormal at end of treatment, continue monitoring to resolution or clinical stabilization.*
	Lipase*	
Coagulation Panel		
Prothrombin time (PT)/ Partial thromboplastin time (PTT) International normalized ratio (INR)		
The coagulation panel should be done at screening		

* On study treatment days, tests must be performed within 24 hours prior to dosing, and results must be reviewed prior to study treatment administration. For all other laboratory tests, results from the prior visit must be reviewed before the administration of study treatment. See Section 8.2 for guidance regarding dosing modifications/delays due to toxicity, including laboratory abnormalities.

Investigators must document their review of each laboratory report by signing or initialing and dating each report, as well as addressing the clinical significance and causality (for significant abnormalities). Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours). Section 10.2.5.1 provides further guidance as to when abnormal laboratory results are to be reported as adverse events.

10.2.5.6 Other Safety Data

The following evaluations will also be performed during the study to measure the safety and tolerability of study treatment:

- ECGs
- Vital sign measurements
- Physical examinations

11 SAFETY MONITORING

As this study is a single-arm, Phase 2 design, an IDMC will not be utilized. To ensure both study integrity and patient safety, processes are in place within Celldex for regular review and monitoring of emerging safety data. Celldex will regularly communicate study conduct and safety information to participating investigators.

12 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be developed and maintained by Celldex.

The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

12.1 Sample Size and Power Calculation

The original sample size for the study was based on Simon's 2-stage MinMax design. The first stage was completed, and the futility stopping rule was not met. The current amendment will increase the total sample size from 30 to approximately 45 treated patients, including at least 15 patients whose tumors harbor a FAT1 mutation based on retrospective gene sequencing.

Table 11 shows confidence intervals associated with a range of observed ORRs in all treated patients (n=45) and in those who are FAT1 mutation-positive (n=15) that would provide sufficient precision to rule out < 10%, < 15%, and< 20% ORR based on the lower 95% confidence bound for different underlying true response rates (true p). The table also shows the likelihood of observing at least the number of responses associated with each of these thresholds (power).

If the true response rate is ≥ 30%, a sample size of 45 treated patients provides sufficient power to rule out < 10% ORR; if the true response rate is ≥ 40%, then the study is adequately powered to rule out < 20% ORR.

A cohort size of 15 treated patients in the FAT1 mutation-positive cohort provides ≥ 70% power to rule out < 10% ORR if the true response is ≥ 30%; ≥ 78% power to rule out < 15% ORR if the true ORR is ≥ 40%; and ≥ 70% power to rule out < 20% ORR if the true ORR is ≥ 50%.

Table 11: Observed ORR and Associated Precision and Power Calculations under Varying Cohort Sample Sizes and Underlying Response Rates

Cohort	Observed No. Responses r (ORR)	95% CI [a] of ORR (%)	Power: P (No. observed responses ≥ r | true p)*100			
			true p = 50%	true p = 40%	true p = 30%	true p = 20%
All Treated Patients n=45	9/45 (20.0%)	(9.6, 34.6)	> 99%	> 99%	95%	56%
	12/45 (26.7%)	(14.6, 41.9)	> 99%	98%	74%	17%
	15/45 (33.3%)	(20.0, 49.0)	> 99%	86%	37%	2%
FAT1 mutation positive n=15	4/15 (26.7%)	(7.8, 55.1)	98%	91%	70%	35%
	5/15 (33.3%)	(11.8, 61.6)	94%	78%	48%	16%
	7/15 (46.7%)	(21.3, 73.4)	70%	39%	13%	2%

[a] Clopper-Pearson

12.2 Analysis Endpoints

Primary Endpoint:

- ORR: The percentage of patients who achieve a best response of CR or PR, confirmed according to RECIST 1.1. Best response is recorded between the date of first dose and the date of documented progression per RECIST 1.1 or the date of subsequent anti-cancer treatment, whichever occurs first. For patients without documented progression or subsequent anti-cancer treatment, all available tumor assessments will contribute to the best response assessment.

Secondary Endpoints:

- CBR: The percentage of patients who achieve best response of confirmed CR or PR, or stable disease (SD) for at least 12 weeks. Best response is assessed as described for ORR.
- DOR: The interval from which measurement criteria are first met for CR or PR until the first date that progressive disease is objectively documented or death, whichever occurs first. Patients who have not progressed or died will be censored on the date of last evaluable tumor assessment; patients who did not have any on-study assessments and have not died will be censored on the date of first dose. If a patient receives subsequent anti-cancer treatment before documented progression, then DOR will be censored on the last evaluable tumor assessment on or before the start date of subsequent anti-cancer treatment.
- PFS: The time from start of CDX-3379 to time of progression or death, whichever occurs first. Patients who have not progressed or died will be censored on the date of last evaluable tumor assessment; patients who did not have any on-study assessments and did not die will be censored on the date of first dose. If a patient receives subsequent anti-cancer treatment before documented progression, then PFS will be censored on the last evaluable tumor assessment on or before the start date of subsequent anti-cancer treatment.
- OS: The time from start of CDX-3379 to death. Patients who have not died will be censored on the date of last contact.
- Safety: Safety will be assessed by vital sign measurements, clinical laboratory tests, physical exams, ECGs, and the incidence and severity of adverse events (graded according to NCI CTCAE v 5.0).
- Pharmacokinetics: Noncompartmental PK parameters will be determined using CDX-3379 serum concentration data obtained prior to, at completion of, and one hour after each CDX-3379 administration as well as on days 8 and 15 of the first cycle; and 30 days post-treatment.
- Immunogenicity: Patients will be monitored for the development of ADA to CDX-3379. Samples will be collected for future evaluation of the neutralizing capacity of ADA.
- Biomarkers: DNA sequencing will be conducted on tumor samples to assess for mutations in cancer-related genes such as FAT1, NOTCH1, NOTCH2, NOTCH3, AKT/PI3K, phosphatase and tensin homolog (PTEN) or ErbB family members.

[redacted]

12.3 Interim Analysis

No formal interim analysis is planned for this study. The sponsor may periodically conduct descriptive analyses while the study is ongoing. Because no formal hypothesis testing is planned, these periodic reviews will not require the overall type 1 error to be adjusted.

12.4 Analysis Populations

All treated population: All patients treated with CDX-3379. The primary efficacy analysis as well as all safety, PK, and biomarker analyses will be performed in this population. Efficacy analyses will also be conducted in the following subgroups: FAT1 mutation-positive treated patients, FAT1 or NOTCH mutation-positive treated patients, and all treated patients with a primary tumor site of oral cavity.

Response-evaluable population: All patients who have measurable disease at baseline and receive one full dose of both CDX-3379 and cetuximab and have post baseline tumor response assessment or discontinue study prematurely for disease progression, symptomatic deterioration, or death. Patients who discontinue treatment prior to the first tumor assessment for other reasons will be excluded from this population. Sensitivity analyses for efficacy endpoints will be performed in this population.

12.5 Statistical Methods

The primary study analysis is planned upon achievement of complete data for ORR assessment (i.e., after all treated patients have either experienced a tumor response or discontinued study treatment, or 6 months after the last patient has received their first dose, whichever occurs sooner).

Following primary analysis, study follow-up will continue until adequate data are available to support secondary analyses (see Section 7.5). Final analysis will be performed upon completion of the study, after the resulting clinical database has been cleaned, quality checked, and frozen.

12.5.1 Efficacy Analyses

Best overall response (as defined by RECIST 1.1) will be summarized for the all treated population. ORR will be calculated as defined above, and the corresponding 95% exact CI will be calculated using the Clopper-Pearson method.

CBR will be analyzed using the same approach as ORR.

DOR will be estimated using the Kaplan-Meier (KM) product limit method. The KM estimate of the median DOR will be reported along with the two-sided 95% CI using Brookmeyer and Crowley's method (log-log transformation).

Progression-Free Survival and Overall Survival will be analyzed using the same approach as DOR.

Additional analyses may be conducted including estimating objective response rate and other efficacy parameters for the response-evaluable population and within biomarker defined subgroups.

12.5.2 Safety Analyses

Safety analyses will consist of data summaries for clinical and laboratory parameters, and for AEs. The number and percentage of patients experiencing one or more AEs will be summarized by the relationship to study drug and severity based on NCI CTCAE v 5.0. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory parameters will be summarized using descriptive statistics, by post-treatment shifts relative to baseline, and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized using descriptive statistics.

12.5.3 Pharmacokinetic Analyses

Serum CDX-3379 concentration data will be tabulated by overall study population together with descriptive statistics. Individual and mean serum concentration-time profiles of CDX-3379 will be generated. Noncompartmental PK data analysis will be performed and descriptive statistics provided. If data allows, descriptive statistics of noncompartmental PK parameters (AUC, C_{max}, CL, t½) will be provided. A population PK analysis may also be performed and various PK compartmental models may be explored to characterize the PK of CDX-3379 in patients with HNSCC. Exposure-response modeling will be performed to examine the relationship between CDX-3379 serum exposure and clinical endpoints. The impact of physiologically relevant patient characteristics (covariates) and disease on PK/pharmacodynamic parameters (and possibly clinical endpoints) may be tested.

12.5.4 Immunogenicity Analyses

The number and percentage of patients who develop detectable CDX-3379 ADA will be summarized. ADA will be reported for confirmed ADA-positive patients, and the impact of ADA on PK will be assessed if data allow.

12.5.5 Biomarker Analyses

Biomarker data will be summarized descriptively and any correlation with outcome (efficacy) will be investigated. Analyses may include estimating objective response rate and other efficacy parameters within biomarker defined subgroups (i.e., defined by degree of expression or presence of genetic variation).

12.5.6 Study Treatment and Medications

The duration of treatment, total number of doses and total dose administered will be tabulated for study treatments. The primary reason for treatment modifications will be tabulated.

All medications will be coded using WHO Drug Dictionary, and they will be listed and summarized by anatomical therapeutic class and preferred name.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Quality Assurance

Monitoring and auditing procedures defined by Celldex will be followed in order to comply with Good Clinical Practice (GCP) guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. All the information required by the protocol should be provided; any omissions require explanation.

Celldex will provide CRFs for the recording and collection of data. The CRF will either be in paper or via an electronic data capture (EDC) system. Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. Corrections to CRFs and source data will be made only by authorized members of the study staff, clearly entered, initialed and dated. The investigator will sign the CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the investigator will be made aware of the corrections and his/her approval will be documented by re-signing. In cases where an EDC system is utilized, an electronic audit trail is maintained.

The investigator will permit Celldex direct access to source data/documents for trial-related monitoring, audits, review, and inspection(s). Through ongoing monitoring visits at the investigational sites, Celldex will periodically check the patient data recorded in the CRF's against source documents, to ensure accuracy, completeness, and adherence to the protocol, regulatory compliance, and the maintenance of comprehensive clinical records.

The study may be audited by Celldex and/or regulatory agencies at any time. If requested, the investigator will provide Celldex, applicable regulatory agencies, and/or applicable ethical review boards with direct access to original source documents, which may include applicable electronic medical record system(s).

13.2 Archiving of Study Documentation

To enable evaluations and/or audits by regulatory authorities or Celldex, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms (ICFs), copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The duration of record retention by the investigator should be according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Celldex should be prospectively notified. The study records must be transferred to a designee acceptable to Celldex, such as another investigator,

another institution, or to an independent third party arranged by Celldex. The investigator must obtain written permission from Celldex before disposing of any records, even if retention requirements have been met.

14 ETHICAL CONSIDERATIONS

14.1 Institutional Review Board or Ethics Committee

International Conference on Harmonisation GCP guidelines require that all investigational drug studies be conducted under the auspices of an Institutional Review Board/Ethics Committee (IRB/EC). This committee, the makeup of which must conform to national, state, and local guidelines regarding such, will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent. The investigator will provide Celldex with a copy of the communication from the IRB/EC to the investigator indicating approval/favorable opinion of the protocol and consent form. All changes to the protocol or consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human patients.

The investigator will provide Celldex with documentation of ethical review board approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The investigator will also be responsible for obtaining periodic IRB/EC re-approval throughout the duration of the study. Copies of the investigator's periodic report to the IRB/EC and copies of the IRB/EC's continuance of approval must be retained in the site study files and furnished to Celldex.

The IRB/ECs must supply to Celldex, upon request, a list of the IRB/EC members involved in the vote and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

14.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that Celldex and investigator abide by GCP Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). The investigator is responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

14.3 Patients Information and Informed Consent

Sample ICFs will be provided. Prior to the beginning of the study, the investigator must have the IRB/EC's written approval/favorable opinion of the written ICF and any other written information to be provided to patients. The written approval of the IRB/EC together with the approved patient information/ICFs must be filed in the study files. The ICF must contain all elements required ICH GCP Guidelines (E6) in addition to any other elements required by national, state, local or institutional policy.

The investigator will be responsible for obtaining an ICF signed by each patient or his/her legally authorized representative, prior to his/her participation in the study, in accordance with ICH GCP guidelines. Informed Consent will be obtained from a patient or his/her legally authorized representative after a full explanation of the purpose of the study, the risks and discomforts involved, potential benefits, etc., have been provided by the investigator or designee, both verbally and in writing. The investigator is responsible to see that informed consent is obtained from each patient or legal representative and to obtain the appropriate signatures and dates on the ICF document prior to the performance of any protocol-specific procedures and prior to the administration of study drug. Participation in the study and date of informed consent given by the patient should be documented appropriately in the patient's files. The investigator will be responsible for communicating in a timely fashion any new findings, including amendments to the protocol, that could affect a patient's willingness to continue in the study.

The original or copy of the signed copy of the ICF must be maintained in the institution's records and is subject to inspection by Celldex or regulatory agencies. The patient or his/her legally authorized representative will also be given a copy of the signed consent form.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by patients or their legal representatives.

14.4 Protocol Amendments

Modifications to the study protocol will not be implemented by either Celldex or the investigator without agreement by each party and IRB/EC approval/favorable opinion. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IRB/EC/Celldex approval/favorable opinion. In these cases, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment, should be submitted to the IRB/EC and Celldex as soon as practical. Any deviations from the protocol must be fully explained and documented by the investigator with notification to the Sponsor and IRB/EC as appropriate.

14.5 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to Celldex. Only the patient number and patient initials (as permissible) will be recorded in the CRF, and if the patient name appears on any other document (e.g., pathologist's report), it must be obliterated before a copy of the document is supplied to Celldex. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of Celldex, IRB/EC, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients' records to be identified.

15 PUBLICATION POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of Celldex, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Celldex supports publication of the results of this trial in appropriate scientific journals and meetings. In accord with standard editorial and ethical practice, Celldex encourages publication of multicenter trials only in their entirety and not as individual center data. Any presentation or publication of data collected from this study will be generated in accordance with the following principles:

- Authorship (including identification of a lead author and corresponding author) will be determined by mutual agreement in accordance with the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, according to overall contribution to study conduct, chiefly by leadership in study design and decision making, and then by contribution. All meaningful contributions will be acknowledged.

- Authors will follow Good Publication Practice (GPP) and other recognized standards and will work together to: discuss practical considerations (e.g., choice of potential journals or congresses); avoid duplicate publication; ensure that publications are accurate, balanced, transparent and produced in a timely manner; assume responsibility for the content, accuracy and completeness of the publication; establish a process based on honest scientific debate to resolve differences in interpretation of data; disclose all potential conflicts of interest; disclose funding sources including Celldex support for the study (funding and in-kind support such as medical writing); and assume responsibility for all final decisions on publication content and for final approval of the version for submission or presentation.

- Celldex will provide authors with access to all relevant study documents needed to support the publication, including protocols, statistical analysis plans, clinical study reports (when available), and data tables; describe editorial and other support that may be available to the authors for the development of a publication and ensure that all authors agree to any support to be provided; and provide a timely review of the publication or presentation.

- Additionally, authors and Celldex will avoid premature release of study information that could jeopardize publication and respect embargoes set by journals and congresses.

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Appendix 1. Investigator Signature

Investigator Signature
Protocol CDX3379-04

I confirm that I have read this protocol; I understand it; and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable laws and regulations of the country of the study site for which I am responsible. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in the protocol and my agreement with Celldex Therapeutics, Inc. I will promptly submit the protocol to applicable ethical review board(s) and will not begin the study until regulatory approval has been obtained and all required essential documents have been completed.

Instructions to the investigator: Please SIGN and DATE this signature page and PRINT your name. Return a completed and signed version to Celldex Therapeutics, Inc., and retain a copy with this protocol.

Signature of Investigator	Date
Investigator Name (Please Print)	Investigator Title
Name of Facility	Location of Facility (City, State (if applicable), Country)

Appendix 2. RECIST 1.1 Criteria

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination, unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. (See "Methods of Lesion Measurement" for further guidance.)

At baseline, lesions should be identified as either "Target" or "Non-Target" as follows:

Target Lesions:

- Up to a maximum of five measurable target lesions total (with a maximum of two target lesions per organ) should be identified as target lesions and will be recorded and measured at baseline. (This means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded.)
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- All target lesion measurements should be recorded in metric notation, using calipers if clinically assessed.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. (See "Tumor response evaluation".)

Non-Target Lesions:

- All other measurable/non-measurable lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. It is acceptable to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').
- Non-target lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. (See "Tumor response evaluation".) While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively.

MEASURABILITY OF TUMOR AT BASELINE

- Measurable: Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
    - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
    - 20mm by chest X-ray.

  Note: To be considered pathologically enlarged and measurable, a lymph node must be • 15mm in short axis when assessed by CT scan (for lymph nodes, only the short axis is measured and followed).
- Non-measurable: All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with • 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

- Malignant lymph nodes: Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. At baseline and in follow-up, only the short axis will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be • 15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). All other pathological nodes (those with short axis • 10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.
- Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS OF LESION MEASUREMENT

- Clinical exam: Clinical lesions will only be considered measurable when they are superficial and • 10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression. (See “Tumor Response Evaluation”.)
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

TUMOR RESPONSE EVALUATION

Evaluation of target lesions:

Target lesions will be assigned an overall response assessment at each evaluation time point according to the following definitions:

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

- Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions:

Non-target lesions will be assigned an overall response assessment at each evaluation time point according to the following definitions:

- *Complete Response (CR):* Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *Progressive Disease (PD):* Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease:

- When the patient also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New lesions:

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important.

- There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. (A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.)
    - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of overall response:

It is assumed that at each protocol specified time point, an overall response assessment occurs. The patient's overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Table 12 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 13 is to be used.

Special notes on evaluation of overall response:

- Missing assessments and inevaluable designation:
  - When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.
  - If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.
- 'Symptomatic deterioration': Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 12 and Table 13.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.
- Confirmation of response: In the event of complete or partial responses, efforts should be made to obtain a confirmatory scan (no sooner than 28 days later).

Table 12: Overall response: patients with target +/–non-target disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 13. Overall response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

FREQUENTLY ASKED QUESTIONS

What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?

Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters.

How large does a new lesion have to be to count as progression? Does any small sub-centimeter lesion qualify, or should the lesion be at least measurable?

New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists.

How should one lesion be measured if on subsequent exams it is split into two?

Measure the longest diameter of each lesion and add this into the sum.

Does the definition of progression depend on the status of all target lesions or only one?

As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum.

What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?

RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness.

What should we record when target lesions become so small they are below the 10 mm 'measurable' size?

Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded

If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?

Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD.

When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?

The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up). The

only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up.

Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used). What is the effect this has on the other target lesions and the overall response?

What may be done in such cases is one of the following:

(a) If the patient is still being treated, call the center to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable

(b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability

(c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel.

It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favor of a response.

What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?

Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding.

A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?

It is not infrequent that tumor shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD.

A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?

CT scan. Always follow by imaging if that option exists since it can be reviewed and verified.

A lesion which was solid at baseline has become necrotic in the center. How should this be measured?

The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect.

If I am going to use MRI to follow disease, what is minimum size for measurability?

MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Can PET–CT be used with RECIST?

At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Adapted from Eisenhower 2009 (Eisenhauer, et al. 2009)

Appendix 3. ECOG Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

* As published in Am. J. Clin. Oncol (Oken, et al. 1982)

Appendix 4. Summary of Changes

The following changes have been made to protocol CDX3379-04 as of Amendment 1.

Section(s)	Change/Rationale
2 Glossary of Abbreviations	New terms were added to the glossary
3 Protocol Synopsis **4 Study Schema and Schedule of Assessments** **7.2.2.1 Inclusion Criteria**	Now requires patients to be HPV negative and no longer requires on treatment tissue biopsies
5.1 Disease Background	Updated PD-1 status and regulatory approvals
5.3 CDX-3379	Crossed out "utilizing both ligand dependent and ligand independent inhibition of ErbB3" and well as "and trastuzumab targeting HER2 in ligand independent models"
5.3.1 Summary of Clinical Experience	Addition of "Tumor DNA sequencing identified a FAT1 mutation" twice, as well as adding 3 parenthetical references to CDX-3379
5.3.2 Summary of CDX-3379/ Cetuximab Combination Experience	Addition of testing guidelines to identify FAT1 and NOTCH2 mutations, addition of Stage 1 data, crossed out data for "next generation sequencing"
5.4 Rationale for Study	Change from 13 of 15 patients to 10 of 12 patients in evidence of target engagement, addition of Stage 1 data, rewording of section outlining original exclusion of HPV positive patients
3 Protocol Synopsis **6 Study Objectives**	Moved the DNA biomarker analysis to a secondary objective
7.1 Overall Design and Plan of the Study	Rewording of the introduction, addition of Stage 1 data and findings
3 Protocol Synopsis **7.2.1 Number of Patients** **12.1 Sample Size**	Changed number of patients to be enrolled from 30 to 45
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
9 Concomitant Therapy	Addition of required prophylactic medications
[redacted]	[redacted]
10.2.5.1 Adverse Events	Up versioned from CTCAE v. 4 to CTCAE v.5
[redacted]	[redacted]
12.3 Interim Analysis	Addition of periodical analysis from the sponsor, crossed out assessment of Stage 1
12.4 Analysis Population	Addition of Stage 1 findings for "all treated population" and rewording "response-evaluable population"
12.5 Statistical Methods	Rewording about the 6 month follow up
12.5.1 Efficacy Analyses	Changed to the all treated population, change in calculations using different methods (Koyama and Chen method to Clopper-Pearson method), removed explanation of Kaplan-Meier method and Overall Survival summary