Celldex Therapeutics, Inc.

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

Version 1
Statistical Analysis Plan

June 24, 2020

Prepared by:

Statistics Collaborative, Inc.

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Celldex Therapeutics, Inc.

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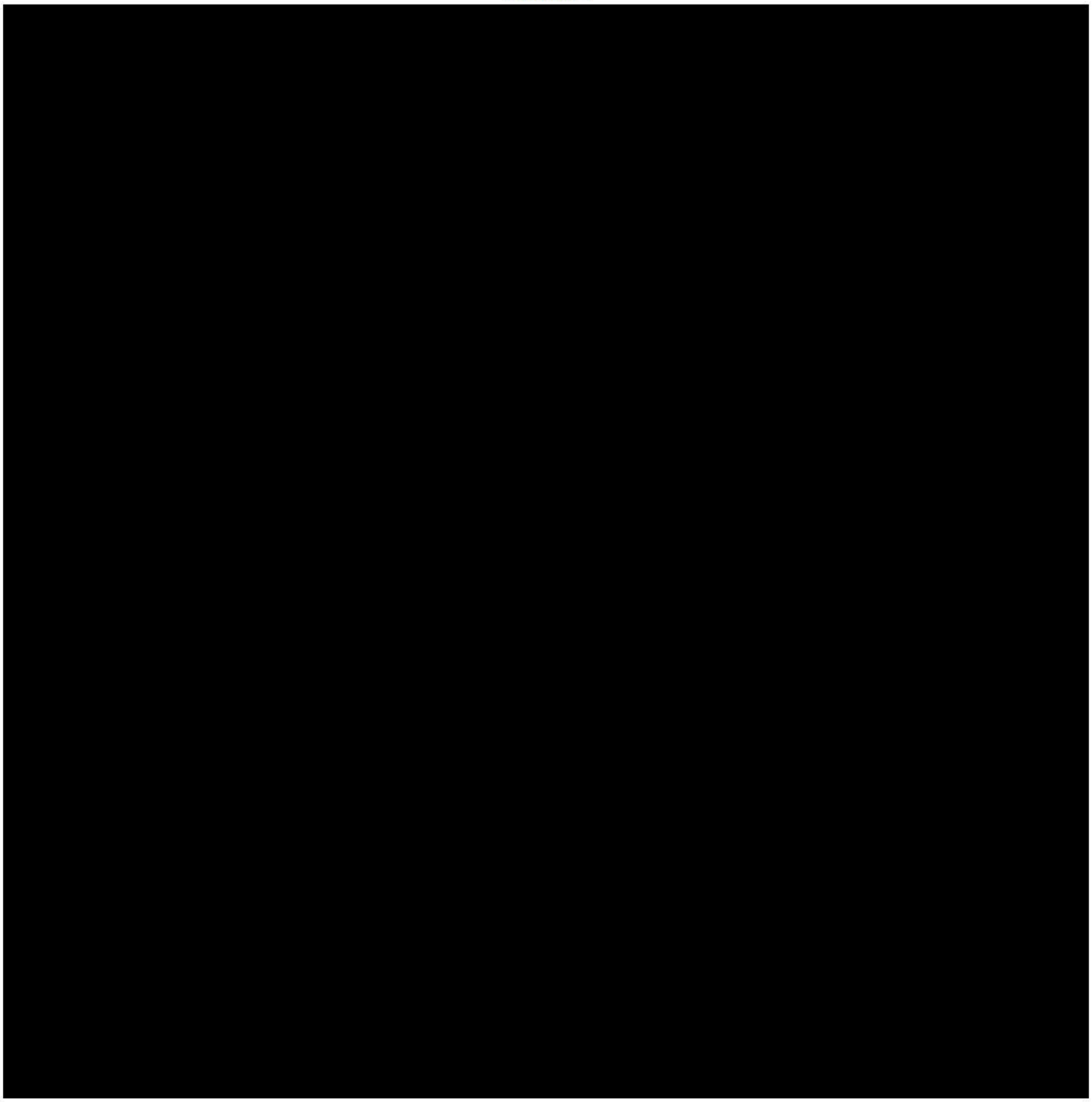

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Abbreviations

ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
BMI	body mass index
BOR	best overall response
BSA	body surface area
CBR	clinical benefit response
CI	confidence interval
Cmax	maximum plasma concentration
CR	complete response
CT	computed tomography
DCR	disease control rate
DNA	deoxyribose nucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EOT	End of Treatment
ErbB3	human epidermal growth factor receptor 3
FAT1	FAT Atypical Cadherin 1
FNA	fine needle aspirate
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLT	high level term
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
ICH	International Conference on Harmonization
INR	international normalized ratio
IV	intravenous

Abbreviations, continued

kg	kilogram(s)
KM	Kaplan-Meier
m^2	meter squared
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NOTCH	NOTCH family of cell-signaling receptors
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetic(s)
PR	partial response
PR interval	period from the beginning of the P wave until the beginning of the QRS complex
PT	preferred term
PTEN	phosphatase and tensin homolog
QRS interval	combination of the Q wave, R wave, and S wave
QT interval	period from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RR interval	time elapsed between two successive R waves
SAE	serious adverse event
SAP	statistical analysis plan
SCI	Statistics Collaborative, Inc.
SD	stable disease
SOC	system organ class
t½	apparent elimination half-life
TEAE	treatment emergent adverse event
TdP	torsades de pointes
WHO	World Health Organization

Definitions

Adverse event	An adverse event (AE) is any reaction, side effect, or other untoward event, regardless of relationship to study drug, which occurs anytime during the study in a patient administered study treatment.
All treated population	All patients treated with CDX-3379
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.
Serious AE	An AE occurring at any dose that: results in death; is a life-threatening experience; requires inpatient hospitalization or prolongation of an existing hospitalization; results in a persistent or significant disability/incapacity; or is a congenital anomaly/birth defect in the offspring of a patient who received study drug.
Treatment-emergent AE	AEs with an onset time after the initial dose of study drug.

1. Introduction

This statistical analysis plan (SAP) is based on Celldex's Protocol CDX3379-04 Amendment 1 [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], dated June 28, 2019. The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the planned statistical methods addressing the study aims. To the extent that analyses described in this SAP differ from those described in the protocol, the methods of the SAP prevail. Any deviations to the SAP will be documented in the final clinical study report. Pharmacokinetic (PK) data analyses will be addressed in a separate analysis plan.

The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) guidelines E9 (Statistical Principles for Clinical Trials) [1].

2. Study description

2.1. Study design

This is an open-label, multicenter Phase 2 study of CDX-3379 in combination with cetuximab in patients with cetuximab-resistant head and neck squamous cell carcinoma (HNSCC). In this single-arm study, patients will be treated with CDX-3379 plus cetuximab until progressive disease, unacceptable toxicity, or other criteria for discontinuation of study treatment are met.

Prior to Amendment 1 of the protocol, 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 one CR was observed, emerging biomarker data were reviewed to

assess correlation with efficacy. In the overall CDX-3379 development program, in a small patient dataset, FAT Atypical Cadherin 1 (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 was amended to enroll up to approximately 45 total patients, including at least 15 patients whose tumors harbor a FAT1 mutation based on retrospective gene sequencing. Screening tissue samples will be required to be submitted as directed by Celldex at the time of enrollment to allow for gene sequencing and tracking the number of patients whose tumors harbor a FAT1 mutation.

Tumor assessments will be performed approximately every six 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. The investigator will assess tumor response in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines [2] (see Section 10.3).

Study investigators and Celldex will continuously evaluate adverse events (AEs) throughout the entire course of patient treatment and through 30 days following the last dose of CDX-3379. For AEs or serious adverse events (SAEs) with a causal relationship to the investigational product, follow-up 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). Subsequently, patients will be followed for survival, with contact every 12 weeks until study closure.

2.2. Study objectives

The primary objective of this study is to estimate the objective response rate (ORR) for the combination of CDX-3379 and cetuximab in patients with cetuximab-resistant advanced HNSCC.

The secondary objectives of this study are as follows:

- 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 deoxyribose nucleic acid (DNA) biomarkers for CDX-3379 in combination with cetuximab and assess correlation with efficacy.

[redacted]

- [redacted]

2.3. Study treatments

Patients will be treated with CDX-3379 plus cetuximab until progressive disease, unacceptable toxicity, or other criteria for discontinuation of study treatment.

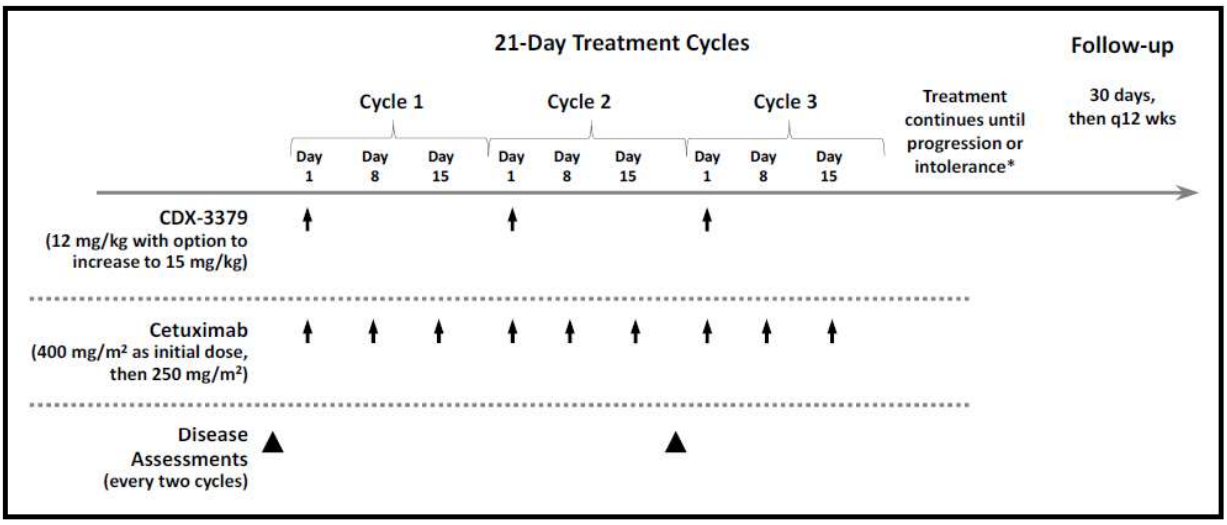
A cycle is defined as 21 days. The dose of CDX-3379 is 12 mg/kg, with the option to increase the dose to 15 mg/kg if tolerated, delivered via intravenous (IV) infusion over 60 minutes. CDX-3379 will be administered every 3 weeks (on Day 1 of each 21-day cycle).

Cetuximab will be dosed with an initial loading dose of 400 mg/m^2 on Day 1 over 2 hours, followed by weekly doses of 250 mg/m^2 over 60 minutes. Patients who were previously treated with cetuximab within three months of study enrollment and required dose reduction due to adverse events attributed solely to cetuximab (e.g., rash) may initiate cetuximab at the same dose as was last received in the prior regimen, with or without an initial loading dose, as clinically appropriate. Cetuximab will be administered on Days 1, 8, and 15 of each 21-day

cycle. On Day 1 of each cycle, cetuximab should be administered approximately one hour after the completion of CDX-3379 infusions (and after completion of PK sampling).

As a routine precaution, the investigative site's medical staff is to closely observe patients for the duration of the cetuximab and CDX-3379 infusions and for at least one hour after the end of the infusions.

Exhibit 1. Study schema



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

[redacted]

2.4. Study visits and assessments

The study is divided into three periods: Screening, Treatment, and Post-Treatment Follow-up. Exhibit 4 summarizes the specific procedures that must be performed at specific time points during each period.

The three periods are defined as follows:

- Screening: Day -28 to Day -1. Patients who are screened but do not meet all entry criteria (i.e., screen failures) will not be entered in the clinical database.
- Treatment: Cycle 1 Day 1 to End of Treatment (EOT). 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.
- Post-Treatment Follow-up: 30 days post-EOT to study closure.

Exhibit 4. Schedule of assessments

	Screening	Treatment Period				End of Treatment (EOT)[2]	Follow-up Period[3]	
		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 weeks ± 2 weeks until study closure
Informed consent[4]	×							
Demographics and medical history[5]	×	×						
Tumor tissue	×[6]							
Pregnancy test[7]	×	×						

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.
2. 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.
3. 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.
4. 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.
5. Medical history includes prior/concurrent conditions and cancer history including cancer mutation status and human papilloma virus (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 three to five core biopsies for biomarker analysis. Fine needle aspirates (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 one 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.

Continued (page 1 of 3)

Exhibit 4. Schedule of assessments, continued

	Screening	Treatment Period				End of Treatment (EOT)[2]	Follow-up Period[3]	
		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 weeks ± 2 weeks until study closure
Vital signs[8] and physical exam[9]	×	×	×	×	×	×	×	
ECOG performance status	×	×			×	×		
12-lead electrocardiogram (ECG)[10]		×	×			×		
Serum chemistry[11] and hematology[11]	×	×[12]	×	×	×	×	×	
Urinalysis[11]	×	×[12]			×	×		
CDX-3379 PK sample[13]		×[14, 15]	×[14]	×[14]	×[14, 15]		×[16]	
Biomarker blood sample[13]	×	×[15]	×	×	×[15, 17]		×[16]	
Immunogenicity blood sample[13]		×[15]			×[15]		×	

8. Vital signs should include heart rate, respiratory rate, blood pressure, temperature, and weight. Height should be recorded at Screening 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 2 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.
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.

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Exhibit 4. Schedule of assessments, continued

	Screening	Treatment Period				End of Treatment (EOT)[2]	Follow-up Period[3]	
		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 weeks ± 2 weeks until study closure
Diagnostic imaging/ response assessment[18]	×				×[18]	×[18]		×[18]
Administer CDX-3379[19]		×			×			
Administer cetuximab[20]		×	×	×	×			
Concomitant medication review[21]	×	×	×	×	×	×	×	×
Adverse event monitoring[22]		×	×	×	×	×	×	×
Survival follow-up								×

18. 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.
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.
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.
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.

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2.5. Eligibility

Patients must meet all of the inclusion criteria in Exhibit 5 prior to receiving study treatment to be included in the study.

Exhibit 5. Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
• Read, understood, and provided informed consent • Eighteen years of age or older • Histologically or cytologically confirmed HNSCC that is recurrent or metastatic, not curable with local treatment modalities, and progressive during or subsequent to last therapy • Human papilloma virus (HPV) negative tumor • Prior treatment must include: a check-point inhibitor targeting programmed death receptor-1 axis, unless not a candidate, and cetuximab with tumor progression during or within six months after completing treatment • Measurable disease by RECIST 1.1 criteria • Willingness to consent for tumor biopsy from an accessible site prior to initiating study therapy • All residual toxicity related to prior radiotherapy or anticancer therapies must resolve to Grade 1 severity or less prior to receipt of study treatment • Adequate electrolytes, liver, renal, and hematology function (see protocol for precise definition) • Life expectancy ≥ 12 weeks • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 • 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	• Nasal, paranasal sinus, or nasopharyngeal carcinoma, aside from World Health Organization (WHO) Type I and II nasopharyngeal carcinoma • Received CDX-3379 or other anti-human epidermal growth factor receptor 3 (ErbB3) targeted agents previously • Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment • Other prior malignancy active within three years (see protocol for exceptions) • Known brain metastases, unless previously treated and asymptomatic for two months and not progressive in size or number for two months prior to enrollment • Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection, or active infection requiring systemic IV therapy • Use of any monoclonal based therapies within four weeks, excluding cetuximab, and all other immunotherapy within two weeks, prior to the first dose of study treatment • Chemotherapy within 21 days or at least 5 half-lives prior to the planned start of study treatment • Major surgery within four weeks prior to the first dose of study treatment • Use of other investigational drugs within two weeks or five half-lives prior to study treatment administration • A marked baseline prolongation of QT/corrected QT (QTc) interval; additional risk factors for torsades de pointes (TdP); the use of concomitant medications that prolong the QT/QTc interval; significant cardiovascular disease; or any of the following within six 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 • Requirement for chronic immunosuppressive medication • Any other acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation • Known alcohol or drug abuse • Women who are pregnant or nursing • Known allergy or past administration reaction including infusion reactions, anaphylactic, or anaphylactoid reactions to any component of the CDX-3379 formulation • 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

2.6. Blinding and measures to minimize bias

This is non-randomized open-label study. The analysis of tumor response and progression-free survival (PFS) 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.

3. Analysis populations

3.1.1. All treated population

All patients treated with CDX-3379. The primary and secondary efficacy analyses as well as all safety and biomarker analyses will be performed in this population.

3.1.2. Response-evaluable population

All patients who have (a) measurable disease at baseline, (b) receive one full dose of both CDX-3379 and cetuximab, and (c) 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.

3.1.3. Biomarker-evaluable population

All patients who have a biomarker result for the biomarker analysis of interest, e.g., FAT1 or NOTCH or both.

4. General conventions and statistical considerations

4.1. Study centers

A study center is defined as a treatment administration site or group of such sites under the control and supervision of the same Principal Investigator (PI). This study is being conducted at approximately 10-15 study centers. Given that the study has many investigative sites relative to the number of randomized patients, analyses will not be stratified by site. All sites use the same protocol, entry criteria, data collection methods, and endpoints; sites are monitored to verify compliance with the protocol. According to Meinert [3] these criteria justify pooling results across centers.

4.2. Presentation of results

Descriptive statistics will summarize results. Unless otherwise stated, confidence intervals (CIs) will be computed using a two-sided α=0.05 level of significance.

Standard descriptive statistics, such as mean, standard deviation, median, quartiles, minimum, and maximum, will be calculated for continuous variables. For discrete variables, descriptive analyses will be based on numbers of patients and related percentages of patients with non-missing data. Unless otherwise specified, tables and figures will present such descriptive statistics for both the observed values and change at each scheduled visit.

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). Prior and concomitant medications will be coded using World Health Organization Drug (WHO) Global dictionary.

In addition to tabular summaries, by-patient listings will present all relevant electronic case report form (eCRF) data.

4.3. Software

All data listings, summaries, figures, and statistical analyses will be generated using SAS Version 9.4 or higher [4] or other validated software.

4.4. Units of time

The following conversion factors will be used to convert days to months or years:
1 month = 30.4375 days and 1 year = 365.25 days.

4.5. Study days and duration

For the purpose of the analysis, study day will be calculated relative to Cycle 1 Day 1. Cycle 1 Day 1 is the planned time point for the first dose administration.

For assessments on or after the start of study treatment, Study Day = Assessment Date – First Dose Date + 1. For dates prior to the start of study treatment, Study Day = Date – First Dose Date. By this convention, there is no Study Day of zero.

For duration calculations requiring two dates, Duration (days) = End Date – Start Date + 1. DOR, PFS, and OS will be presented in months.

4.6. Visit windows

The planned analyses do not require visit window calculations.

4.7. Baseline

Unless otherwise noted, baseline is defined as the last non-missing measurement recorded prior to the date and time of the first dose of study treatment. Measurements taken once per visit will be assumed to occur prior to dosing unless otherwise specified. Unscheduled visits will be used in the determination of baseline values, when applicable.

4.8. Missing data

4.8.1. Partial or missing dates

Missing and partial date or time data will be handled using endpoint-specific procedures detailed as follows. The imputed dates must be logical, e.g., ensuring that no end date is after database lock, after death, or before the start date.

If date of response is completely missing or the day and month are missing, date of response will not be imputed. If response year and month are present and day is missing, the response day is the first day of the month.

If date of progression is completely missing or the day and month are missing, date of progression will not be imputed. If progression year and month are present and day is missing, the progression day is the first day of the month. If death date is present, the minimum of the imputed progression date and date of death will be considered as the date of progression.

Timing of observations relative to dosing will rely on time point labels in the case of vital signs, electrocardiograms (ECGs), and PK/biomarker blood samples, and will otherwise be assumed to be prior to infusion of study drug. Hence, missing first dose times will not be imputed.

If date of prior diagnosis or prior treatment start is complete missing, the date will not be imputed. If year is present and month and day are missing, the month and day are July 1. If month and year are present and day is missing, the day is the 15th of the month. If imputed date is on or after the first dose date, the date will be set to the day before the date of first dose.

If AE onset date is completely missing, the date is set to the date of first dose. If year is present and month and day are missing:

- If year = year of first dose, the month and day are the month and day of first dose.
- If year > year of first dose, then month and day is January 1.

If month and year of AE onset date are present and day is missing:

- If year = year of first dose and
  - month = month of first dose, then day is the day of first dose date.
  - month > month of first dose, then day is the first day of month.
- If year > year of first dose, then day is the first day of month.

For all other cases, the date is the date of first dose.

If year of AE end date is present and month and day are missing, the month and day is December 31. If month and year of AE end date are present and day is missing, the day is the last day of the month. If the event is fatal, the date is the minimum of the imputed end date and the death date. For all other cases, the date is missing and the event is considered ongoing.

If concomitant medication start date is completely missing, the start date will not be imputed. If start year is present and month and day are missing, the start month and day is January 1. If start year and month are present and day is missing, the start day is the first day of the month. If end date is completely missing, the end date will not be imputed. If end year is present and month and day are missing, the end month and day is December 31. If end year and month are present and day is missing, the end day is the last day of the month.

4.9. Sample size determination 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. Protocol Amendment 1 increased 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.

According to the protocol, the planned sample size of 45 treated patients provides >80% power to rule out <20% ORR based on the lower 95% confidence bound for the for different underlying true response rates if the true response rate is ≥40%.

The cohort size of 15 treated patients in the FAT1 mutation-positive cohort provides nearly 80% power to rule out <15% ORR if the true response rate is ≥40%.

4.10. Censoring

Censoring methods for the primary and secondary efficacy endpoints are outlined in Section 6.

4.11. Changes to planned analyses

Changes to the analyses described in this plan will be fully documented in a revised version of the plan prior to locking the study database and conducting the primary efficacy analysis.

[redacted]

5. Study population characteristics

5.1. Patient accrual

Patient accrual will be presented as the number and percentage of patients enrolled at each study center.

5.2. Patient disposition

The number and percentage of patients will be presented for each of the following:

- Treated
- Response-evaluable
- Reason for not being response-evaluable
- Biomarker evaluable
- Discontinued study treatment
- Reason for treatment discontinuation
- Discontinued the study
- Reason for study discontinuation (including study completion)
- Survival status
- Cause of death

5.3. Protocol violations

Deviations from the eligibility criteria and on-study requirements that affect the interpretation of primary and secondary efficacy and safety outcomes will be considered important protocol deviations. (Note: ICH E3 defines "important protocol deviations" as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being). These protocol deviations will be identified through manual clinical reviews and recorded separately for inclusion in the clinical study report.

Important protocol deviations will be determined by medical review prior to database lock.

5.4. Demographics and baseline characteristics

Patient demographics and baseline characteristics will be summarized for the all treated population. Information to be summarized includes age in years, categorical age (<65, ≥65 -<75, ≥75 years), gender, race, ethnicity, height (in meters), and weight (in kilograms). Age will be calculated in years relative to the informed consent date.

Other baseline characteristics include medical and surgical history, cancer history, and disease characteristics. Descriptive statistics will be presented for age, height, weight, body mass index (BMI; in kg/m^2), categorical BMI (<25, 25 -<30, ≥30 kg/m^2) and the following intervals relative to first dose date:

- Time since initial diagnosis
- Time since initial advanced disease
- Time since initial metastatic disease
- Time since last progression

Frequency counts and percentages will be presented for sex, ethnicity, race, and other baseline characteristics to include:

- Stage at initial diagnosis
- Number of prior relapses
- Stage at study entry
- Prior treatment with PD-1
- Prior treatment with cetuximab
- Metastasis staging at study entry
- Mutations or other relevant tumor aberrations
- Baseline human papillomavirus (HPV) status

The number and percentage of patients in each of the following subgroups will be presented: FAT1 mutation-positive treated patients, FAT1 or NOTCH mutation-positive treated patients, and all treated patients with a primary tumor site of oral cavity.

5.5. Prior and concomitant medications

Prior and concomitant medication verbatim terms on eCRFs will be coded to Anatomical Therapeutic Chemical (ATC) class and Preferred Names using the WHODrug Global dictionary. The dictionary will be up-versioned to the most current version available, as feasible, prior to database lock.

Prior medications are those medications taken within 28 days prior to the initial dose of study drug, with the exception of prior anti-cancer therapies. Prior anti-cancer therapies will be included regardless of their timing relative to first dose. Concomitant medications are those medications taken after the initial dose of study drug. A medication can be classified as both prior and concomitant. If it cannot be determined whether the medication was a prior (or concomitant) medication due to a partial start or stop date then it will be counted as both.

Prior and concomitant medications will be summarized by WHO ATC class and Preferred Name. These summaries will present the number and percentage of patients using each medication. Patients may have more than one medication per ATC class and Preferred Name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and Preferred Name within each ATC class.

5.6. Prior anti-cancer therapies

The number and percentage of patients who underwent prior cancer-related surgery, radiation, and systemic therapies will be summarized. Prior systemic therapy regimens will be categorized and presented by WHODrug Preferred Name and summarized as:

- The number and percentage of prior systemic cancer therapy regimens (1, 2, 3, 4, 5 or more),
- The number and percentage of prior systemic cancer therapy regimens in the advanced/metastatic setting, and
- Types of prior systemic cancer therapies of interest, as categorized by medical review.

The best response (CR, PR, stable disease [SD], progressive disease [PD], or unknown) to the most recent prior regimen will be presented in addition to the reason for discontinuing.

6. Efficacy analyses

To support calculation of ORR, CBR, DOR, and PFS, tumor assessments will be performed approximately every six 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 anti-cancer therapies. The investigator will assess tumor response in accordance with RECIST 1.1 guidelines [2] (see Section 10.3). The investigator will record the overall response at each timepoint (CR, PR, SD, PD, or NE) as well as the date of first response (CR or PR) and date of PD. Best overall response (BOR) will be derived from timepoint responses per RECIST 1.1 guidelines.

The efficacy analyses will be conducted within the estimand framework. The details are provided in Appendix 10.1.

The primary analysis is planned upon achievement of complete data for ORR, i.e., after all treated patients have been followed for at least six months after receiving their first dose of study treatment or after all patients have discontinued study treatment, whichever occurs sooner.

Following the primary analysis, study follow-up will continue until adequate data are available to support secondary analyses.

The primary efficacy analysis will be based on the all treated population. Additional supportive efficacy analyses will be performed using the FAT1 mutation-positive treated patients, FAT1 or NOTCH mutation-positive treated patients, and all treated patients with a primary tumor site of oral cavity. A patient is considered NOTCH mutation-positive if they express a mutation in any one of the NOTCH family genes (NOTCH1, NOTCH2, or NOTCH3).

If more than five patients have a dose delay that impacts the timing of tumor assessments, additional analyses may be performed to assess the impact of delayed treatment and tumor assessment schedule on duration of response and PFS.

6.1. Primary efficacy endpoint

The primary efficacy endpoint of this study is ORR, defined as the percentage of patients who achieve a best response of CR or PR, confirmed according to RECIST 1.1. That is, the criteria for response (CR or PR) must be met again at the next scheduled tumor assessment no sooner than 28 days after the initial documentation. 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. Anti-cancer treatment includes (a) systemic anti-cancer therapy or (b) radiation or surgical resection of a target or non-target lesion. All anti-cancer treatments will be reviewed and confirmed by the Celldex medical team. For patients without documented progression or subsequent anti-cancer treatment, all available tumor assessments will contribute to the best response assessment.

The number and percentage of patients in each category of BOR (CR, PR, SD, PD, or not evaluable [NE]) will be summarized for the all treated population. ORR will be calculated as defined above, and the corresponding two-sided 95% exact CI will be calculated using the Clopper-Pearson method.

A waterfall plot showing the maximum change from the baseline sum of the diameters of target lesions will be produced for the response-evaluable population. Subgroup waterfall plots may be produced.

A swimmer plot will be produced to present individual patient's tumor response and duration of response over time.

A spider plot will be produced to present change in an individual patient's tumor size with tumor size relative to baseline plotted against month from baseline scan; new lesion and end of treatment dates will be annotated in the plot. Subgroup spider plots may be produced.

Change from baseline in tumor size will be calculated as: Sum of diameters at Week X (mm) – Sum of diameters at Baseline (mm). Percent change from baseline in tumor size will be calculated as: (Sum of diameters at Week X (mm) – Sum of diameters at Baseline (mm)) / Sum of diameters at Baseline (mm) * 100%.

All primary and secondary efficacy outcomes (BOR, DOR if applicable, date of PD if applicable, PFS status, and OS status) will be presented in a single by-patient listing. Individual timepoint assessment data for each lesion will be presented in a separate listing.

6.2. Secondary efficacy endpoints

6.2.1. Duration of response

DOR is defined as 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 initiation of subsequent anti-cancer treatment. The censoring rules are outlined in Exhibit 6.

DOR will be estimated in the all treated population using the Kaplan-Meier (KM) product limit method and displayed graphically. The KM estimate of the median DOR and the corresponding two-sided 95% CI, calculated using the Brookmeyer and Crowley's method (log-log transformation), will be presented.

Time to response, defined as the time from first dose date to the date of first confirmed response (CR or PR), will also be estimated in the all treated population using the Kaplan-Meier (KM) product limit method. The KM estimate of the median time to response and the corresponding two-sided 95% CI, calculated using the Brookmeyer and Crowley's method (log-log transformation), will be presented alongside DOR.

6.2.2. Clinical benefit response

CBR, defined as the percentage of patients who achieve a best response of confirmed CR or PR, or SD for at least 12 weeks. Best response is assessed as described for ORR.

CBR will be calculated in the all treated population as defined above, and the corresponding two-sided 95% exact CI will be calculated using the Clopper-Pearson method.

6.2.3. Disease control rate

Disease control rate (DCR), defined as the percentage of patients who achieve a best response of confirmed CR or PR, or SD. Best response is assessed as described for ORR.

DCR will be calculated in the all treated population as defined above, and the corresponding two-sided 95% exact CI will be calculated using the Clopper-Pearson method.

6.2.4. Progression-free survival

PFS is defined as the time from the start of study treatment to the 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 initiation of subsequent anti-cancer treatment. The censoring rules are outlined in Exhibit 6.

Exhibit 6. Censoring rules

Situation	Date of Event or Censoring	Outcome
Progression	Date of progression	Event
Death without progression	Date of death	Event
No baseline disease assessment	Date of first dose	Censored
No on-study disease assessments and no death	Date of first dose	Censored
No progression and no death	Date of last evaluable tumor assessment	Censored
Subsequent anti-cancer therapy before documented progression	Date of last evaluable tumor assessment on or before initiation of subsequent anti-cancer therapy	Censored

PFS will be estimated in the all treated population using the KM product limit method and displayed graphically. The KM estimate of the median PFS and the corresponding two-sided 95% CI, calculated using the Brookmeyer and Crowley's method (log-log transformation), will be presented.

The number and percentage of patients with an event and the type of event (progression or death) will be summarized. The status of patients who are censored in the PFS KM analysis will be presented using the following categories:

- No baseline or inadequate baseline assessment
- No post-baseline or death before first scheduled assessment
- Received additional anti-cancer therapy
- Death or progression after ≥2 missed assessments
- Alive and without disease progression

The KM estimates of the median PFS rate at 3 months and 6 months will be presented with the corresponding 95% CIs.

6.2.4.1. Subsequent therapy

The number and percentage of patients receiving subsequent cancer therapies will be summarized by the type of therapy as reported on the eCRF (radiotherapy, cancer medication, other anti-cancer treatment, biopsy, resection, or other surgery). Biopsies will not be considered for censoring purposes.

A by-patient listing of subsequent therapy will be produced for patients who had any subsequent therapy.

6.2.5. Overall survival

OS is defined as the time from the start of study treatment to the time of death. Patients who have not died will be censored on the last known alive date.

OS will be estimated in the all treated population using the KM product limit method and displayed graphically. The KM estimate of the median OS and the corresponding two-sided 95% CI, calculated using the Brookmeyer and Crowley's method (log-log transformation), will be presented.

The number and percentage of patients with an event will be summarized. The status of patients who are censored in the OS KM analysis will be presented using the following categories:

- Alive
- Lost to follow-up
- Withdrawal of consent
- Study closure

The KM estimates of the median OS rate 6 months, 9 months, 12 months, and 18 months will be presented with the corresponding 95% CIs.

6.3. Subgroup analyses

The primary and secondary efficacy analyses will be repeated for each of the following subgroups using the methods described in Sections 6.1 and 6.2:

- FAT1 mutation status (positive vs. negative) among treated subjects who have evaluable FAT1 results
- FAT1/NOTCH mutation status (positive for either FAT1 or NOTCH vs. negative for both) among treated subjects who have evaluable FAT1 and NOTCH results
- Primary tumor site (oral cavity vs. other) in all treated subjects

Specifically, the number and percentage of patients in each category of BOR will be summarized for each subgroup. The estimates of ORR, CBR, and DCR and the corresponding two-sided 95% exact CIs for each subgroup will be presented in forest plots for each endpoint.

DOR, PFS, and OS will be estimated in each subgroup using the KM product limit method and displayed graphically with the estimated median and two-sided 95% CI. The median estimates for each subgroup will also be presented in forest plots.

6.4. Handling of dropouts or missing data for the primary and secondary analyses

No imputations will be made for missing values. Summaries will be based on observed data only.

6.5. Interim analyses and data monitoring

There are no planned interim analyses for this study.

6.6. Multiplicity

No adjustments for multiplicity will be made in this study.

7. Safety summaries

All safety analyses will be based on the all treated population.

7.1. Extent of exposure

Study drug exposure will be summarized for the all treated population. Summaries will be separated for CDX-3379 and cetuximab. Summaries will include the number of infusions per patient as well as cumulative dose received, relative dose intensity, and duration of treatment. These parameters are defined in Exhibit 7.

Exhibit 7. Study drug parameter definitions

	CDX-3379	Cetuximab
Dosing schedule per protocol	12 mg/kg every 3 weeks, with option to increase to 15 mg/kg	400 mg/m^2 IV (loading dose) once, then 250 mg/m^2 weekly
Dose	Dose (mg/kg) is defined as total dose administered (mg)/most recent weight (kg).	Dose (mg/m^2) is defined as total dose administered (mg)/most recent body surface area (BSA) (m^2).
Cumulative dose	Cumulative dose (mg/kg) is the sum of the doses administered to a patient.	Cumulative dose (mg/m^2) is the sum of the doses administered to a patient.
Dose intensity[a]	Cumulative dose / [(Last dose date - first dose date + 21)/7]	Cumulative dose - first dose / [(Last dose date - second dose date + 7)/7]
Relative dose intensity (%)[b]	(Dose intensity/4 mg/kg/wk)*100	(Dose intensity/250 mg/m^2/wk)*100
Duration of treatment (weeks)	(Last dose date - First dose date)/7	(Last dose date - First dose date)/7

a. Dose intensity reported in mg/kg/wk for CDX-3379 and mg/m^2/week for cetuximab. Dose intensity for cetuximab starts at the second dose.
b. Relative dose intensity for cetuximab starts at the second dose.

Dose delays will be summarized as the number of patients with at least one delay, the number of doses delayed per patient, and the reason for the delay. [redacted]

7.2. Adverse events

Adverse events will be coded by MedDRA and summarized by system organ class (SOC), high level term (HLT), and preferred term (PT), and worst National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0) grade per patient. If a

patient reports more than one AE that was coded to the same SOC, HLT, or PT, the patient will be counted only once for that specific SOC, HLT, or PT.

Investigators will assess the relationship of each adverse event to each study drug. The relationship of each adverse event to study drug will be categorized as unrelated or related. If attribution is missing, the event will be assumed to be related to study drug.

All AE tables and listings will summarize treatment-emergent adverse events (TEAEs) defined as adverse events with onset on or after the date or the first dose of study drug or onset prior to the first dose of study drug but with worsened severity post-treatment. AEs without a severity rating that are reported post-treatment will be considered treatment-emergent. Presentations will include all adverse events through the 30 days following the last dose date.

The following TEAEs will be presented by severity:

- Serious adverse events
- All adverse events
- Adverse events related to CDX-3379
- Adverse events related to cetuximab, and
- Adverse events leading to study discontinuation.

All adverse events will be listed with MedDRA coding, onset and resolution dates, duration, seriousness, severity, relationship, actions, and outcome.

7.3. Deaths

The number of patients who died will be summarized in a by-patient listing of deaths including death date, cause of death, and relationship to study treatment.

7.4. Vital signs

Vital signs (weight, blood pressure, pulse rate, temperature, and respiratory rate) are collected according to the schedule in Exhibit 4 and categorized according to time point label. Patients will be monitored during and after infusion of CDX-3379 and cetuximab with assessment of

vital signs within 30 minutes pre-infusion, at 30 minutes during the infusion, within 5 minutes post-infusion, 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 minutes and 90 minutes during the infusion.

For each vital sign parameter, summary statistics on the analysis value and change from baseline will be calculated by time point within each scheduled assessment. Pre-infusion values will be presented for by-visit reporting in tables and figures.

7.5. Electrocardiogram

Electrocardiogram (ECG) is administered according to the schedule in Exhibit 4 to collect heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF both pre- and post-infusion.

For each ECG parameter, summary statistics on the analysis value and change from baseline will be calculated by time point within each scheduled assessment. Pre-infusion values will be presented for by-visit reporting in tables and figures. In addition, a by-visit shift table of pre- vs. post-infusion values will be presented.

7.6. Eastern Cooperative Oncology Group (ECOG) performance status

ECOG performance status will be assessed at Screening, on Day 1 of each cycle, and at EOT. Shift from baseline to worst post-baseline value will be presented. Further details on the ECOG assessment can be found in Appendix 10.2.

7.7. Clinical laboratory parameters

Laboratory tests are conducted according to the schedule in Exhibit 4. For each quantitative, laboratory parameter (Exhibit 8) and scheduled visit, summary statistics on the analysis value and the change from baseline will be calculated and presented in SI units. If multiple records are available for a parameter on the same date, the results will be averaged to calculate the analysis value for reporting. Select laboratory parameters will be graded based on NCI CTCAE v5.0, and the shift from baseline to worst post-baseline grade will be presented.

Liver function test (ALT, AST, total bilirubin, and alkaline phosphatase [ALP]) elevations will be presented in categories relative to the upper limit of normal to identify potential cases of drug-induced liver injury. An evaluation of drug-induced serious hepatotoxicity (eDISH) plot that includes all pairs of ALT and total bilirubin values at scheduled and unscheduled assessments will also be presented.

All clinically significant abnormalities in laboratory values will be presented in a data listing. Urinalysis results will not be summarized but will be provided in a data listing.

Exhibit 8. Clinical laboratory parameters

Clinical chemistry	Hematology & differential panel	Coagulation panel	Urinalysis	Thyroid function
Sodium	Hemoglobin	Prothrombin time (PT)	Protein	Thyroid stimulating hormone (TSH)
Potassium	Hematocrit	Activated partial thromboplastin time (aPTT)	Glucose	Free T4
Chloride	Mean corpuscular volume (MCV)	International normalized ratio (INR)	Specific gravity	Free T3
Bicarbonate	Erythrocyte count (RBC)		Blood	
Glucose	Platelets			
Blood urea nitrogen	Leukocytes (WBC)			
Creatinine	Neutrophil bands			
Calcium	Absolute neutrophils			
Magnesium	Absolute lymphocytes			
Phosphate	Absolute monocytes			
Alkaline phosphatase (ALP)	Absolute eosinophils			
Alanine transaminase (ALT)				
Aspartate transaminase (AST)				
Total protein				
Albumin				
Lactate dehydrogenase				
Total bilirubin				
Uric acid				
Amylase				
Lipase				

Table created manually.

8. Biomarker analyses

DNA sequencing will be conducted on pre-treatment 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.

Blood samples for biomarker analyses will be collected pre-infusion of CDX-3379, immediately after infusion, 60 minutes post-infusion on Day 1 of each cycle, and prior to cetuximab dosing on Days 8 and 15 of Cycle 1.

Baseline biomarker data for the subgroups of interest (FAT1 or NOTCH or both) will be summarized descriptively and any correlation with efficacy endpoints will be investigated as described in Section 6.3. [redacted]

9. References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). International Conference on Harmonization; 1998.

2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.

3. Meinert, C. Clinical Trials: Design, Conduct, and Analysis. New York: Oxford University Press, 1986.

4. *SAS*, Version 9.4, Cary NC: SAS Institute; 2013.

5. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

10. Appendices

10.1. Estimand framework

A summary of the attributes of the primary estimand is provided in Table 1.

Table 1. Estimand attributes for the primary efficacy analysis

Estimand attribute	Description of attribute
Target population	All treated population: All patients treated with CDX-3379.
Primary patient-level variable	Best overall response (BOR) according to RECIST 1.1. Patients can have a BOR of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or unknown.
Handling of intercurrent events	Alternative anti-cancer therapies will be intercurrent events in the determination of BOR. Assessments that occur after the date of documented progression per RECIST 1.1. or the date of anti-cancer treatment, whichever occurs first, will not contribute to the determination of BOR.
Population-level summary	ORR, defined as the percentage of patients who achieve a best response of CR or PR, confirmed according to RECIST 1.1., for all patients treated with CDX-3379 in combination with cetuximab.

The trial product estimand is defined as ORR based on assessments on or prior to the date of PD or data of anti-cancer therapy, whichever occurs first. Patients who discontinue study therapy for reasons other than progression will continue to have tumor assessments until disease progression or initiation of subsequent anti-cancer therapy, whichever occurs first. Therefore, treatment discontinuation is not considered an intercurrent event. The primary efficacy analysis will be an estimation analysis for this estimand (point estimate of ORR and associated 95% confidence interval).

Duration of response is an important secondary analysis because it characterizes ORR. A summary of the attributes of the estimand associated with this important secondary endpoint is provided in Table 2.

Table 2. Estimand attributes for the important secondary efficacy analysis

Estimand attribute	Description of attribute
Target population	All patients treated with CDX-3379 who have a BOR of confirmed CR or PR (objective response).
Primary patient-level variable	Duration of response is calculated as the date of first CR or PR that is subsequently confirmed to date of documented disease progression or death due to any cause, whichever occurs first. In patients who have objective response and are progression-free and alive at the time of the analysis, duration of response is calculated as the date of first CR or PR that is subsequently confirmed to the date of last evaluable tumor assessment.
Handling of intercurrent events	Alternative anti-cancer therapies may be intercurrent events in the calculation of duration of response. In patients with objective response who receive an anti-cancer therapy prior to documented disease progression, duration of response will be censored on the start date of the anti-cancer therapy.
Population-level summary	A Kaplan-Meier plot will show duration of response in patients who have objective response. The median duration of response will be shown as a population-level summary statistic.

10.2. ECOG Performance Status

Exhibit 9. 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 [5]

10.3. 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 four 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.

10.3.1. 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:

o 10mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm).

o 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

o 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 tumor. 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 magnetic resonance imaging (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.

10.3.2. 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 (e.g., 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.

10.3.3. 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.

<u>Evaluation of overall response:</u>

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.

Exhibit 10 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, Exhibit 11 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 Exhibit 10 and Exhibit 11.
- 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).

Exhibit 10. 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.

Exhibit 11. 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
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.

Exhibit 12. Best overall response when confirmation of CR and PR is required

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria[b] for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

a. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

b. Minimum criteria for SD duration is 12 weeks for this study.

Adapted from Eisenhower 2009 [2]

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