Official Title: An Open-Label, Phase IIIb, Single-Arm, Multicenter Study of Atezolizumab Plus Nab-Paclitaxel in the Treatment of Unresectable Locally Advanced or Metastatic PD-L1 Positive Triple-Negative Breast Cancer

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**AN OPEN-LABEL, PHASE IIIB, SINGLE-ARM, MULTICENTER STUDY OF ATEZOLIZUMAB PLUS NAB-PACLITAXEL IN THE TREATMENT OF UNRESECTABLE LOCALLY ADVANCED OR METASTATIC PD-L1 POSITIVE TRIPLE-NEGATIVE BREAST CANCER**
STUDY NUMBER:	MO39874
STUDY NAME:	EL1SSAR
VERSION NUMBER:	1.0
ROCHE COMPOUND(S):	Atezolizumab (RO5541267)
EUDRACT NUMBER:	2019-002488-91
IND NUMBER:	Not applicable
NCT NUMBER:	NCT04148911
PLAN PREPARED BY:	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

See electronic signature on the final page of this document.

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document.

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v5.0 (22 February 2023).

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic date stamp on the last page of this document.	Version 5, 22 February 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
AESI	adverse event of special interest
ASCO	American Society of Clinical Oncology
BMI	body mass index
BOR	best overall response
CAP	College of American Pathologists
[redacted]	
CI	confidence interval
CNS	central nervous system
[redacted]	
COVID-19	coronavirus disease 2019
CR	complete response
CSR	Clinical Study Report
DCR	disease control rate
DMC	Data Monitoring Committee
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
IA	interim analysis
IC	tumor-infiltrating immune cell
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
imAE	immune-mediated adverse event
IMC	Internal Monitoring Committee
IRF	Independent Review Facility
ITT	intent to treat
IxRx	interactive voice/web-based response system
IV	intravenous
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
ORR	objective response rate

Abbreviation or Term	Description
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PgR	progesterone receptor
PR	partial response
PS	performance status
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse events
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TNBC	triple-negative breast cancer
ULN	upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses that are planned to be performed for the Clinical Study Report (CSR) of Study MO39874 (EL1SSAR). The analyses described in this SAP will supersede those specified in Protocol MO39874. Any deviations from protocol are described in Section 4.8.

1.1 OBJECTIVES AND ENDPOINTS

The primary aim of this study is to evaluate the safety of atezolizumab plus nab-paclitaxel in patients with programmed death-ligand 1(PD-L1)-positive unresectable locally advanced or metastatic triple-negative adenocarcinoma of the breast (TNBC) who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC. The study will also evaluate treatment efficacy. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Primary Objectives and Corresponding Endpoints

Primary Safety Objective	Primary Safety Endpoints
• To evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with unresectable locally advanced or metastatic PD-L1 positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• Incidence of treatment-emergent Grade ≥ 3 AEs • Incidence of treatment-emergent Grade ≥ 2 imAEs [a]

AE = adverse event; imAE = immune-mediated adverse event; PD-L1 = programmed death-ligand 1; TNBC = triple-negative breast cancer.

[a] Immune-mediated adverse events (imAEs) are events that resemble autoimmune diseases and are known side effects of immune checkpoint inhibitors, including atezolizumab; refer to Protocol Section 1.2.3.4 for details.

Table 2 Secondary/Exploratory Objectives and Endpoints

Secondary Safety Objective	Secondary Safety Endpoints
• To further evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• Incidence of all treatment-emergent AEs • Incidence of treatment-emergent SAEs
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints**
• To evaluate the effect of atezolizumab plus nab-paclitaxel on key survival outcomes in patients with unresectable locally advanced or metastatic PD-L1 positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• OS, defined as the time from initiation of study treatment to death from any cause (analyzed in the safety-evaluable population, and in the subset of patients with centrally confirmed PD-L1 positive tumor status) • PFS, defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first (analyzed in the safety-evaluable population, and in the subset of patients with centrally confirmed PD-L1 positive tumor status). PFS will be assessed by the investigator according to RECIST v1.1
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the anti-tumor effects of atezolizumab plus nab-paclitaxel, as measured by investigator-determined ORR, DCR, and DoR according to RECIST v1.1 in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• Unconfirmed ORR, defined as the percentage of patients with measurable disease at baseline, who have achieved unconfirmed CR or PR as determined by the investigator using RECIST v1.1. • DCR, defined as the sum of the unconfirmed CR, PR and SD rates. • DoR, defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first In addition, [redacted]

• To further describe the safety and efficacy of atezolizumab plus nab-paclitaxel in subgroups of patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	Selected safety and efficacy endpoints will be described by subgroups determined at baseline according to the following parameters: • Presence of CNS metastases (yes vs. no) • ECOG performance status (0 or 1 vs. 2) • Prior anticancer treatment (yes vs. no) • Prior anticancer treatment with PD-1/PD-L1 (yes vs. no) • Prior use of taxane vs. non-taxane therapy in (neo)adjuvant settings
Exploratory Biomarker Objectives	**Exploratory Endpoints**
• To evaluate the inter-observer concordance in PD-L1 status determined by local vs central laboratory testing, using the VENTANA PD-L1 SP142 Assay	• PD-L1 status determined by local vs central laboratory testing, using the VENTANA PD-L1 SP142 Assay

AE = adverse event; CNS = central nervous system; CR = complete response; DCR = disease control rate; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; ER/PgR = estrogen receptor/progesterone receptor; imAE = immune-mediated adverse event; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TNBC = triple-negative breast cancer; v = version.

1.2 STUDY DESIGN

Study MO39874 is an open-label, Phase IIIb, single arm, global study conducted in patients with unresectable locally advanced or metastatic PD-L1 positive TNBC who have not received chemotherapy for their unresectable locally advanced or metastatic disease. TNBC is defined as human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER) and progesterone receptor (PgR)-negative disease, determined in accordance with the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Hammond et al. 2010; Wolff et al. 2018; Allison et al. 2020). Confirmation of TNBC status will be completed locally and PD-L1 testing (using the VENTANA® PD-L1 SP142 assay) will be completed locally and centrally.

PD-L1-positive status (PD-L1 expression ≥ 1% on tumor-infiltrating ICs as percentage per tumor area, assessed by immunohistochemistry [IHC]) will be determined as follows:

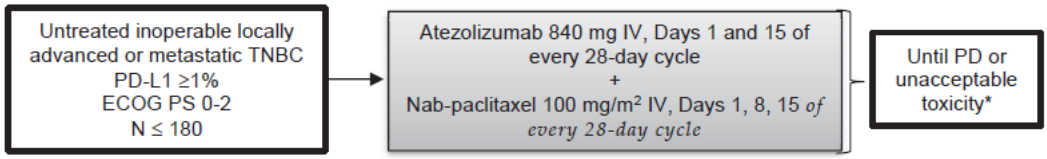
- Locally using the VENTANA PD-L1 SP142 IHC assay, to determine eligibility. If multiple tumor specimens are available, patients may be eligible if at least one specimen is evaluable for PD-L1 testing and shows PD-L1 expression on ≥ 1% ICs; the highest score measured will be used as the PD-L1 score for patient selection;
- Centrally, using the VENTANA PD-L1 SP142 IHC assay, to confirm PD-L1-positive tumor status.

In the absence of disease progression (PD) or unacceptable toxicity, study treatment will continue until the end of the study (EOS). Atezolizumab or nab-paclitaxel may be discontinued for toxicity and re-started independently of one another in the absence of disease progression.

Follow-up for new anti-cancer therapy and survival will continue for up to [redacted] after the last patient is enrolled in the study.

The EOS is defined as the last patient last visit (LPLV), and will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for [redacted] since the last study patient was enrolled, whichever occurs first. The Sponsor may terminate the trial at any time.

Figure 1 Study Schema



Abbreviations: ECOG = Eastern Cooperative Oncology Group; IV = intravenous(ly); N = number of patients; PD = disease progression; PD-L1 = programmed death-ligand 1; PS = Performance Status; TNBC = triple-negative breast cancer

* Additional reasons for study treatment discontinuation may include loss of clinical benefit as determined by the investigator, or patient decision.

1.2.1 Treatment Assignment

This is an open-label, single-arm safety study in which all patients will receive atezolizumab in combination with nab-paclitaxel.

Enrolled patients will begin treatment with:

- Atezolizumab 840 mg administered via intravenous (IV) infusion on Days 1 and 15 of every 28-day cycle in combination with
- Nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle.

1.2.2 Independent Review Facility

No Independent Review Facility (IRF) is planned for this study.

1.2.3 Data Monitoring

An Internal Monitoring Committee (IMC) will be established for the study to review all AEs, SAEs and AESI and cumulative safety data. Details of the composition of the IMC, the safety review plan and procedures for data review will be provided in the IMC Charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

This is a single-arm safety study. There are no formal statistical hypotheses, and all analyses will be descriptive.

2.2 SAMPLE SIZE DETERMINATION

A sample size of approximately 180 PD-L1-positive TNBC patients is planned for the study. For the purpose of the estimation of sample size, the incidence of treatment-emergent Grade≥3 AEs, and the incidence of treatment-emergent Grade≥2 immune-mediated AEs (imAEs) were chosen as the endpoint of primary interest.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 3.

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
ITT	All enrolled participants.
SE	All enrolled participants who have received at least one dose of any study treatment (either atezolizumab or nab-paclitaxel).
Responder-evaluable population	All patients in the safety-evaluable population with a RECIST-like objective response.

ITT = intent to treat; SE = safety-evaluable population.

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

All efficacy and safety analyses will be performed on the safety-evaluable population, unless otherwise specified.

The baseline value will be defined as the last available value recorded on or prior to the first administration of any study treatment.

Continuous variables will be summarized by the mean, standard deviation, median and range (minimum and maximum). Categorical variables will be summarized by number/percentage of participants.

The final study analysis that includes all endpoints will be conducted after the end of the study (i.e., when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for [redacted] since the last study patient was enrolled, whichever occurs first).

4.2 PRIMARY ENDPOINTS ANALYSIS

The primary safety analysis will be performed on the safety-evaluable population.

4.2.1 Definition of Primary Endpoints

The primary endpoint of the study is the incidence of treatment-emergent Grade $\geq$ 3 AEs, and the incidence of treatment-emergent Grade $\geq$ 2 imAEs. Immune-mediated adverse events (imAEs) are events that resemble autoimmune diseases, and are known side effects of immune checkpoint inhibitors, including atezolizumab. Qualifying events are those AEs of special interest that were ongoing upon the initiation of systemic corticosteroid therapy and where the systemic corticosteroid therapy was administered no later than 30 days from the start of the AE. Verbatim descriptions of AEs will be mapped to MedDRA terms and graded according to the NCI CTCAE v5.0. For each patient, multiple occurrences of the same event will be counted once at the maximum severity.

4.2.2 Main Analytical Approach for Primary Endpoints

The results for the primary safety variables will be presented by descriptive statistics in frequency tables and the corresponding 95% Clopper-Pearson CIs will be provided, as applicable.

4.2.2.1 Subgroup Analyses for Primary Endpoints

As a part of exploratory analysis, primary safety endpoints will also be described by subgroups determined at baseline according to the following parameters:

- Presence of CNS metastases (yes vs. no)
- ECOG performance status (0 or 1 vs. 2)
- Prior anticancer treatment (yes vs. no)
- Prior anticancer treatment with PD-1/PD-L1 (yes vs. no)
- Prior use of taxane vs. non-taxane therapy in (neo)adjuvant settings

4.3 SECONDARY ENDPOINTS ANALYSES

4.3.1 Secondary Safety Endpoints

Secondary safety endpoints include the incidence of all treatment-emergent AEs and SAEs. The incidence of AEs will be summarized by frequency tables, with the corresponding 95% Clopper-Pearson CIs, as applicable on the safety-evaluable population.

4.3.2 Secondary Efficacy Endpoints

The secondary efficacy analyses will be performed for the safety-evaluable population and in the subset of patients with centrally confirmed PD-L1 (SP142) positive tumor status.

4.3.2.1 Overall Survival

OS is defined as the time from initiation of study treatment to death from any cause. Patients who are not reported as having died at the time of analysis (clinical cutoff) will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of first study treatment intake.

Kaplan-Meier methodology will be used to estimate median OS and to construct survival curves. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS (Brookmeyer et al. 1982). OS rate at 12-, 24-, and [redacted] will be estimated using Kaplan-Meier methodology, along with 95% CI calculated with the standard error (SE) derived from the Greenwood formula.

4.3.2.2 Progression-Free Survival

PFS is defined as the time from initiation of study treatment to the first occurrence of disease progression as determined by the investigator from tumor assessments using RECIST v1.1 or death from any cause, whichever occurs first. Patients without a PFS event will be censored at the date of their last evaluable tumor assessment or, if this is not available, at the date of first study treatment intake.

The methodology (as described in Section 4.3.2.1) used for OS will be applied for PFS. PFS rate at 6-, 9-, and 12-months will be estimated using Kaplan-Meier methodology, along with 95% CI.

4.3.3 Subgroup Analyses for Secondary Endpoints

As a part of exploratory analysis, secondary endpoints may also be described by subgroups determined at baseline according to the following parameters:

- Presence of CNS metastases (yes vs. no)
- ECOG performance status (0 or 1 vs. 2)
- Prior anticancer treatment (yes vs. no)

- Prior anticancer treatment with PD-1/PD-L1 (yes vs. no)
- Prior use of taxane vs. non-taxane therapy in (neo)adjuvant settings

4.4 EXPLORATORY ENDPOINTS ANALYSIS

The exploratory analyses will be performed on the safety-evaluable population.

4.4.1 Exploratory Efficacy Endpoints

4.4.1.1 Objective Response Rate

Best overall response (BOR) for each patient is defined as the most favorable outcome, on the basis of investigator assessment using RECIST v1.1 criteria, at any visit after first study treatment and up to the first documented disease progression. Confirmation of response is not required.

Patients will be classified as "stable disease" if assessment is at least 7 weeks from baseline. Patients will be classified as “missing or unevaluable” if no post-baseline response assessment is available or if all post-baseline response baseline assessments are unevaluable.

Objective response rate (ORR) is defined as the proportion of patients with measurable disease at baseline who achieved a documented unconfirmed response (i.e., either a partial response [PR] or a complete response [CR]) on the basis of investigator assessment using RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumor assessment, will be considered as non-responders.

An estimate of ORR and non-responders will be provided and its 95% CI will be calculated using the Clopper-Pearson method.

4.4.1.2 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with measurable disease at baseline who achieved a documented unconfirmed partial response (PR) or a complete response (CR) or a stable disease (SD).

An estimate of DCR will be provided and its 95% CI will be calculated using the Clopper-Pearson method.

4.4.1.3 Duration of Response

Duration of response (DoR) is defined as the time from the first occurrence of a documented unconfirmed response (CR or PR) until the date of disease progression as determined by the investigator from tumor assessments using RECIST v1.1 or death from any cause, whichever occurs first. DoR will be assessed in patients who achieved an unconfirmed objective response, as determined by the investigator according to RECIST v1.1.

Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of CR or PR, data for DoR will be censored at the date of the first occurrence of CR or PR+1 day.

DoR will be analyzed on the responder-evaluable population. The methodologies described for the analysis of OS will be used for the analysis of DoR.

[redacted]

C-DoR is defined as the time from the first occurrence of a documented confirmed response (CR or PR) until the date of disease progression per RECIST v1.1 or death from any cause, whichever occurs first.

Similar analyses as for ORR and DoR will be performed.

4.4.2 Exploratory Biomarker Endpoints

Exploratory biomarker analyses on tumor tissue will be performed to evaluate the inter-observer concordance between PD-L1 status determined by local vs. central laboratory testing, using the VENTANA PD-L1 SP142 Assay. Other exploratory biomarkers analysis will be analyzed and reported separately.

The concordance will be summarized for the safety-evaluable population.

4.5 OTHER SAFETY ANALYSES

Analyses will be performed on the safety-evaluable population.

4.5.1 Extent of Exposure

Exposure, including treatment duration, number of doses, dose intensity and dose modifications/discontinuation will be summarized with descriptive statistics for each drug separately (atezolizumab and nab-paclitaxel).

4.5.2 Adverse Events

Verbatim description of AEs will be mapped to MedDRA thesaurus terms and graded according to the NCI CTCAE v5.0. Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and preferred term [PT]), and when specified by NCI CTCAE grade. For each patient, if multiple incidences of the same AEs occur, the maximum severity reported will be used in the summaries.

Other safety variables studied will be summarized for the following:

- AESI
- AEs leading to study drug discontinuation or interruption.

AEs associated with COVID-19 will be listed. Confirmed or suspected COVID-19 AEs, as well as AEs associated with COVID-19 will be summarized. Further analyses might be added, if deemed relevant.

4.5.3 Additional Safety Assessments

4.5.3.1 Deaths

All deaths and causes of deaths will be summarized.

4.5.3.2 Laboratory Data

Laboratory data will be classified according to NCI CTCAE v5.0.

Summary tables of shifts in NCI CTCAE v5.0 grades from baseline to the worst post baseline value will be presented for relevant laboratory data.

Potential Hy's law patients will be listed. Potential Hy's law cases are defined as elevated ALT or AST ($>3\times$ upper limit of normal [ULN]), with concomitant elevated total bilirubin ($>2\times$ ULN) within 7 days after latest ALT or AST $>3\times$ ULN.

4.5.3.3 Vital Signs

Vital signs data will be summarized descriptively over time, including change from baseline.

4.6 OTHER ANALYSES

The following analyses will be performed on the ITT population.

4.6.1 Summaries of Conduct of Study

Study enrolment, reasons for study drug discontinuation and discontinuation from the study, concomitant medications will be summarized. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria and deviations during the study conduct, as well as major protocol deviations related to COVID-19 will be summarized.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic variables such as age, sex, race/ethnicity and other relevant baseline characteristics will be summarized.

Previous and concurrent medical history, as well as prior therapies, follow-up therapies will also be summarized.

[redacted]

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

The population used for efficacy analysis in SAP has been modified from the one in protocol from the ITT to the safety-evaluable population.

Definition of overall survival has been updated to be aligned with the Roche standard definition.

5. SUPPORTING DOCUMENTATION

Protocol Appendix 2
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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 as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) 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, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring 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 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 malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic 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 FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. 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 the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in 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.

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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-

target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

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.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring 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 node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (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 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. 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 maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.

Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of nontarget lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of nontarget lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

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, that is, 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 preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. 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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all 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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study 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.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in 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 lesions as shown in Table 1.

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.

6. REFERENCES

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