Protocol Addendum I6F-JE-JJCC (3)

A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors

NCT02836600

Approval Date: 02-April-2019

1. Statistical Analysis Plan: I6F-JE-JJCC: A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors

Generic Name (LY3039478) Indication studied

This Phase 1 study is a single center, nonrandomized, open-label, dose-escalation study of oral LY3039478 in Japanese patients with advanced and/or metastatic solid tumors.

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Protocol I6F-JE-JJCC
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 22 July 2016.
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 26 April 2017.
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 02-Apr-2019 GMT

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3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

SAP Version 2 was approved prior to the data base lock. The main objective of this revision was to removed PET metabolic response analysis since the desired results cannot be obtained through programing. It was also updated to remove the summary table for tumor markers, the napoleon plot for the treatment duration, and the plot for the vital signs because it was determined that the listings are sufficient. The summary of laboratory parameters was also clarified, and the category for toxicity grade for overall adverse event summary table was modified from "grade 3 or 4" to "grade >= 3".

SAP Version 3 was approved prior to the data base lock. It was updated to correct the categories of absolute QTcF value. Several other changes were made to clarify the definition.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the tolerability of LY3039478 up to the global recommended dose in Japanese patients with advanced solid tumors.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3039478,
- to evaluate the pharmacokinetic (PK) parameters of LY3039478
- to document any antitumor activity observed with LY3039478.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity.
- to evaluate tumor tissue and blood for biomarkers related to solid tumors, the Notch signaling pathway and drug target pathways, immune functioning, and mechanism of action of study drug, and their potential association with the study objectives.
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478.

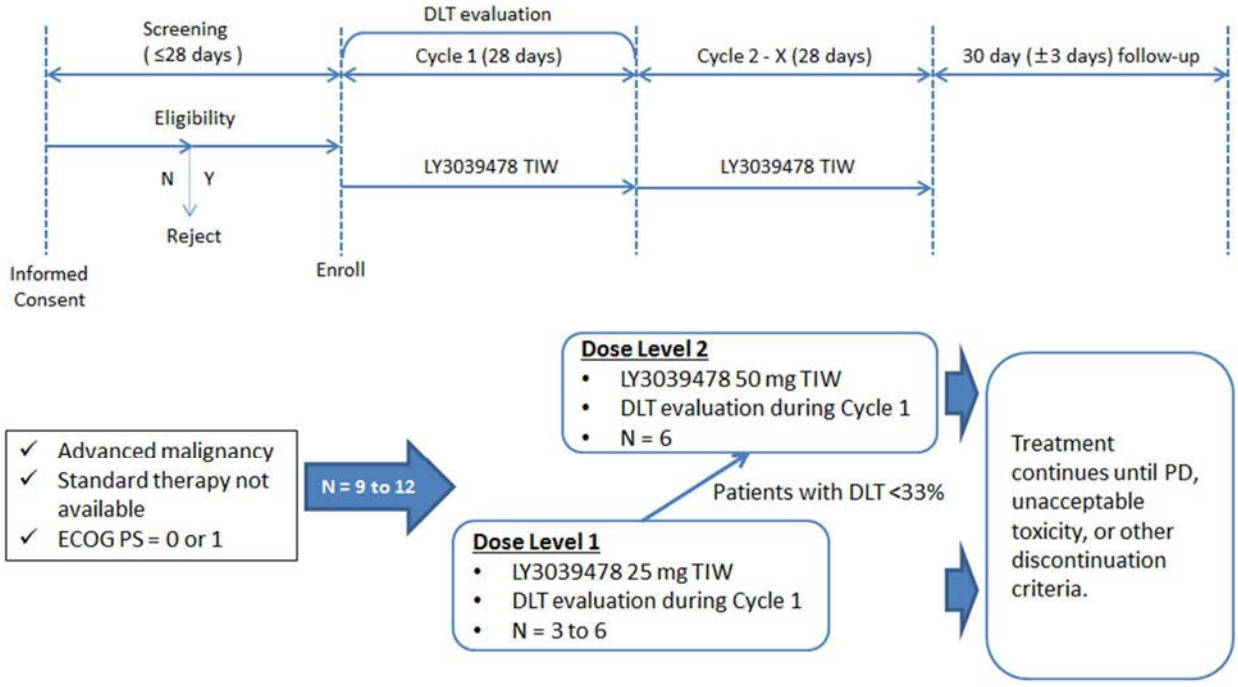
5. Study Design

5.1. Summary of Study Design

Study JJCC is a Phase 1, single center, nonrandomized, single-arm, open-label, dose-escalation study of LY3039478 in Japanese patients with advanced solid tumors.

Study JJCC will consist of 2 dose levels, 25 and 50 mg LY3039478 TIW (3 or 6 patients per dose level). Transition of dose level (from 25 to 50 mg) will proceed if the frequency of dose-limiting toxicity (DLT) observed in Cycle 1 (28 days) is <33% of patients in the first dose level (25 mg). Figure JJCC.1 illustrates the study design.

Eligible patients will be treated with LY3039478 at the assigned dose. The planned duration of treatment is not fixed. Treatment will continue until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met (Figure JJCC.1).



Abbreviations: DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; N = number of patients or no; PD = progressive disease; PS = performance status; TIW = 3 times per week; Y = yes.

Figure JJCC.1. Illustration of study design.

5.2. Determination of Sample Size

The sample size will primarily be determined by the incidence of DLTs in patients in each dose level. Following a 3+3 dose escalation scheme, the sample size calculation assumes that dose level 1 will include 3 to 6 patients and dose level 2 will have 6 patients as shown in the Figure JJCC.1. This sample size was not based on a statistical power calculation.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3039478 in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose, identification number assignment, and cohort for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly clinical research physician (CRP)/clinical research scientist (CRS).

If investigators have eligible patients who have consented concurrently, >3 patients may be entered at a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate. Data analyses will be provided by assigned dose level.

In general, continuous variables will be presented using the mean, standard deviation (SD), median, minimum, maximum and number of patients with an observation (n). For categorical variables, the population size (N), the number of events (n), the number of subjects with events (n) and the percentage of subjects with events are usually reported.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate and they will be planned in this SAP in advance.

The following data handling conventions will be used in the analysis.

Term	Definition or Rule
Relative Study Day	If assessment is on or after date of first dose then (date of assessment) – (date of first study drug dose) +1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose.
Cycle Day	If assessment is on or after date of first dose in cycle then (date of assessment) – (date of first study drug dose in cycle) +1
	There is no cycle day 0. Cycle day 1 is the date of first dose in that cycle.
Duration of treatment	(Date of Day 1 of last cycle + 28 – Date of Day 1 of Cycle 1) / 7
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration), unless otherwise specified.
Entered	Patients who have signed the informed consent document directly or through their legally acceptable representatives.
Enrolled	Patients who have been assigned to study treatment and have received at least 1 dose of study treatment.
Efficacy Analyses Set	In principle, all patients who are enrolled in this study. A patient who are considered nonevaluable for the assessment of a dose level might be excluded from the efficacy analysis set. In this case, the nonevaluable condition will be specified before the data base lock.
Safety Analyses Set	All patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

DLT Analyses Set	All patients who are deemed evaluable for DLT assessment. The evaluable patients must taken ≥75% of the assigned dose in Cycle 1 (first 28 days) or experienced a DLT in Cycle 1 (first 28 days).
PK/PD Analyses Set	All patients who have received at least 1 dose of the study drug and have had sufficient postdose samples collected to allow estimation of PK parameters will form the PK/PD analyses set.
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.

6.2. Adjustments for Covariates

Given the small sample size, no formal analysis investigating the impact of covariates is planned.

6.3. Handling of Dropouts or Missing Data

Missing data, except for dates, will not be imputed. They will be kept as missing in the data analyses, except for dates when used in calculations of relative study day, for which sponsor reporting standards will be utilized for imputation rules, defined as:

- The birth date will be imputed by assigning month and day with July 1st to calculate age.
- For the missing date of relative study day, the following imputation methods will be used:
  - If only the day of the month is unknown, the 15th of the month will be used.
  - If both the day and the month are unknown, July 1st will be used.
- When expanding the concomitant therapy, and previous therapy records across visits, the following imputation methods will be used:
  - For start date,
    - If the day component is unknown, then the 1st of the month will be used.
    - If the month are unknown, then January will be used.
    - If both the day and the month are unknown, January 1st will be used.
    - If the day, the month and the year are unknown, the date will be missing.
  - For end date,
    - If the day component is unknown, then the 30th of the month will be used.
    - If the month are unknown, then December will be used.
    - If both the day and the month are unknown, December 30th will be used.
    - If the day, the month and the year are unknown, the date will be missing.

Partial dates should be reported in all listings and not the imputed date.

Analyses of response will include all patients with measureable disease. Analyses of change in tumor size will include only patients with measureable disease and evaluable target lesion measures at baseline and at least one post-treatment visit.

6.4. Multiple Comparisons/Multiplicity

No formal hypothesis testing is planned for this study; thus, there will be no adjustments for multiplicity.

6.5. Use of an "Efficacy Subset" of Patients

Analyses of disposition will use all patients entered in to the study. Analyses of efficacy and safety analyses will utilize the efficacy analyses set and safety analysis set, respectively. Analyses will be reported according to patients assigned dose level.

6.6. Patient Disposition

Frequency distributions of the enrolled patients and patients in the efficacy analyses set, the safety analyses set, the DLT analyses set, and PK/PD analyses set will be summarized.

Summary of the screen failure and reason will be provided.

A detailed description of patient disposition will be provided for all patients entered into the study. It will include a summary of the number and percentage of patients treated and completing the study, or discontinuing (overall and by reason for discontinuation, if known). Reason for discontinuation from both study treatment and study will be listed by the pre-determined categories.

A list of deaths and reasons for death will be provided. Reasons for death will also be summarized, including the specific adverse event (AE) preferred term if reason for death is AE.

6.7. Patient Characteristics

Patient demographic and baseline disease characteristics will be summarized. Patient demographics will include age, sex, race, height, country, and screening weight and body mass index. Baseline disease characteristics will include Alcohol use, Tobacco use, ECOG performance status, disease stage period, initial pathological diagnosis, histopathological diagnosis grade and TNM at diagnosis.

6.8. Treatment Compliance

Treatment compliance will be summarized for safety analysis set. Treatment compliance information will be collected through pill counts at each visit, and the number of tablets taken relative to the number expected to be taken will be listed.

Percent compliance is calculated from dispensed and returned capsules as:

(actual drug taken (mg)) / (total drug (mg) prescribed)*100

where total drug prescribed is the drug assigned excluding dose omissions and accounting for dose adjustments.

6.9. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized. If concomitant medication use is due to an AE, the associated AE will also be listed.

A separate listing of transfusions will be listed.

Prior therapies, including systemic therapy, radiotherapy and surgeries will be summarized.

Any post-treatment therapies following discontinuation will also be listed.

6.10. Efficacy Analyses

The study was not designed to make a formal efficacy assessment. However, any tumor response data will be summarized and listed for efficacy analyses set.

6.10.1. Efficacy Definitions

The following definitions for efficacy endpoints will be used:

Overall response rate (ORR) is the proportion of efficacy patients who achieved a complete response (CR) or partial response (PR) out of all efficacy patients. Depending on the histology, tumor responses will be measured and recorded using the appropriate guidelines [RECIST 1.1 (Eisenhauer et al. 2009), the Response Assessment in Neuro-Oncology criteria for glioblastoma (Wen et al. 2010)]. To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. For patients who discontinue study treatment without objectively measured progressive disease, the radiological tumor assessment is not required.

Best response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR.

Change in tumor size will be assessed in each patient with measurable disease using radiographic imaging. Tumor size is the sum of the tumor measurements for target lesions at each tumor evaluation. Change in tumor size is defined as the percent change in tumor size from the baseline evaluation to the minimum post-dose evaluation. Other definitions of change in tumor size may be explored (including specific time points, and AUC formulations).

Duration of Response will be calculated for ORR and is defined only for responders. It is measured from the date of first evidence of a confirmed response to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of response will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Duration of Stable Disease will be calculated only for patients with best response of stable disease. It is measured from the date of start of treatment to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of stable disease will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

6.10.2. Efficacy Analyses

Tumor markers and disease progression data will be listed.

Reported lesion data (target/ non-target or measurable/ nonmeasurable) and investigator assessment of response will be listed.

The following efficacy endpoints, detailed in Section 6.10.1 will be summarized as appropriate:

- Overall response rate
- Best overall response
- Change in tumor size. A waterfall plot of change in tumor size will be produced. All patients with at least one target lesion measurement will be represented in the plot.
- PET parameters will be listed. Change in SUVmax will be presented using a waterfall plot for patients with evaluable baseline and post-treatment PET imaging data, if data warrant.
- Duration of response
- Duration of stable disease

6.11. Safety Analyses

All safety summaries and analyses will be based upon the safety analysis set. Safety data will be summarized with patient counts and percentages in each dose level.

Details of the analyses are described in the following sections.

6.11.1. Extent of Exposure

A summary of exposure will be provided, including cycle received, cumulative dose and duration on therapy.

A summary of dose intensity will also be provided. Dose intensity is calculated as:
(actual cumulative dose taken (mg)) / (duration of treatment (week))

A summary of relative dose intensity will also be provided. Percent relative dose intensity is calculated as:
(actual amount of drug taken(mg)) / (amount of drug prescribed (mg))*100

A summary of dose adjustments will be provided, including dose omissions and dose reductions, and the corresponding reasons for dose adjustment. If the reason for dose adjustment is due to an AE, the associated AE will be provided.

6.11.2. Dose-Limiting Toxicity

Dose-limiting toxicities will be summarized for DLT analysis set. Dose escalation will be driven for each treatment combination using the 3+3 method. Dose-limiting equivalent toxicity (DLET) will also be summarized for safety analysis set.

6.11.3. Adverse Events

A listing of all AEs by patient will be presented. This listing will include patient number, AE (reported term and preferred term [PT]), event start and end dates, Common Terminology Criteria for Adverse Events (CTCAE) grade, relationship to study treatment/procedure, seriousness, and outcome. A listing of serious AEs (SAEs) will be produced using the similar format.

An overall summary will be provided for AEs. The number and percent of evaluable patients will be summarized for each category below. The summary will provide counts for all AEs, and AEs related to study treatment.

- Patients with at least one treatment-emergent AE (TEAE)
- Patients with at least one grade >= 3 TEAE
- Patients with at least one SAE
- Patients who discontinued due to AE
- Patients who discontinued due to SAE
- Patients who died due to AE on study treatment
- Patients who died due to AE within 30 days of discontinuation from study treatment

Treatment-emergent adverse events (TEAE) are defined as follows:

- Any event that first occurred or worsened in severity after baseline, based on the MedDRA LLT term and CTCAE severity grade. This means that any episode of the same AE with the same grade as at baseline that starts after the first dose of study treatment will not be defined as treatment-emergent, even if now considered drug related.
- Or any pre-existing condition [PEC] (emerged prior to signing the informed consent) or any AE (emerged after signing the informed consent) that was still present prior to the first dose but has increased in severity (CTCAE grade) following the start of study treatment, regardless of causality.

As per Lilly's standard operating procedures, all "related", "probably related," "possibly related," or "does not know" AEs and SAEs will be defined as related to study treatment.

MedDRA v19.0 (or higher) will be used when reporting AEs by MedDRA terms. TEAEs and TEAEs related to study treatment will be summarized by System Organ Class [SOC] and by decreasing frequency of PT within SOC.

TEAEs will be summarized by CTCAE grade, including the total for maximum Grade 3 and 4, and Grade 3, 4 and 5. These summaries will be provided for events regardless of study treatment causality, and repeated for events deemed by the investigator to be related to study treatment.

Medical history and PECs will be summarized.

6.11.4. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

All deaths recorded in this study will be included as part of the complete AE listing, where appropriate, and listed separately. A summary of deaths may be presented for all patients on therapy if there are a sufficient number of events for this to be deemed useful.

Serious AEs will be summarized by decreasing frequency of PT within SOC. The summary will be provided for events regardless of study treatment causality, and repeated for events deemed by the investigator to be related to study treatment.

6.11.5. Clinical Laboratory Evaluation

Listings of all laboratory results will be provided (using SI units [International System of Units], when available), for hematology, coagulation, urinalysis, ECG chemistry, clinical chemistry and hepatic monitoring.

Laboratory analytes below/above quantifiable levels (data in the database recorded as "<x" and ">x) will be reported as such in listings, and imputed to the lower or upper limit of quantification in any summaries or analyses.

A calculated CTCAE grade using CTCAE v4.0 (or higher) will be provided for all laboratory results, which can be used independently of clinical judgment to determine a CTCAE severity grade. Shift tables of graded laboratory parameters from baseline to the worst value on the study will be generated.

All laboratory parameters may be plotted by time.

6.11.6. Vital Signs and Other Physical Findings

All vital sign data will be listed and will include height, weight, respiratory rate, temperature, blood pressure, pulse rate and ECOG performance status.

6.11.7. Electrocardiograms

Electrocardiogram (ECG) assessment of normality and clinical significance will be listed. Three replicate ECGs will be obtained at each time point. The average of them will be used for analysis, if applicable. If missing values exist, the average will be derived without the missing values.

QT analyses will be performed with Fridericia correction (QTcF). QTcF based on each read is calculated as follows:

- $QTcF = QT / RR^{1/3}$

ECG parameters including QTcF and time-matched plasma concentration of LY3039478 will be listed. In the listing, QTcF values which meet following criteria will be indicated,

- Absolute QTcF value: >450 msec, >480 msec, >500 msec
- Change from baseline in QTcF value: >30 msec, >60 msec

Change from baseline in QTcF will be plotted against the time-matched plasma concentration of LY3039478, if appropriate. A linear regression model will be used to investigate the relationship between the QTcF changes and the concentration of LY3039478 and the fitted model and the 90% confidential/prediction band will also be shown in this plot if warranted by the data.

6.11.8. Subgroup Analyses

Subgroup analyses are not preplanned, but some subgroup analyses may be conducted, if needed.

6.12. Protocol Violations

Important protocol deviations will be listed by pre-determined categories (e.g., inclusion/exclusion criteria, non-compliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

6.13. Interim Analyses and Data Monitoring

Interim access to safety data, including DLTs, will be performed during the study. In order to assess DLTs, which is key to proceed with dose escalation or to determine a tolerable dose, a DLT evaluation form at Dose Level 1 and Dose Level 2 will be prepared. Therefore, no database lock activities on safety CRF pages are mandatory.

Interim analyses for safety and PK may be conducted after all patients receiving Dose Level 2 complete Cycle 1 (DLT evaluation period).

Additional interim analyses may be conducted when deemed necessary (for example, in case of a safety concern).

If it is deemed that enough data is obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data cutoff date will be used for the analysis of safety, efficacy, PK, and PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data cutoff date. These data may be reported separately and the analyses on all patients, including these data, may not be performed.

6.14. Annual Report Analyses

The datasets including the following tables and listings will be generated for the Development Safety Update Report (DSUR) reports based on the resource document 'Statistical Guidance and Mock Tables for the Development Safety Update Report (DSUR) and Periodic Safety Update Report (PSUR) / Periodic Benefit Risk Evaluation Report (PBRER)':

- Summary of patients demographics by age and gender
- Summary of patients demographics by racial groups
- Summary of cumulative patient exposure information
- Listing of patients who died

- Listing of patients who discontinued study drugs or study due to AEs

Investigator's Brochure (IB) related analyses may be conducted at the same time as the DSUR analyses if applicable.

6.15. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by dose level, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a TEAE.
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. References

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010; 28(11):1963-1972.

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