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How to better understand iRECIST – a new wave in immunotherapeutic

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ABSTRACT

Compared with previous standards of care (including chemotherapy, radiotherapy etc.) for cancer patients, immunotherapy has now firmly established itself as the most important therapy advancements which brought significant improvements for patients in terms of survival and quality of life.

Using the RECIST criteria to evaluate response in patients on immunotherapy has proven difficult, as some patients have initial growth of disease or develop new small metastatic lesions followed by latent or delayed response called “pseudoprogression”. And a consensus guideline—iRECIST—was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) in cancer immunotherapy trials, to ensure standard evaluation approach in immunotherapy.

Moreover, it turns out 451 clinical trials using iRECIST criteria according to clinicaltrials.gov by 12, May 2022. The new trends are demonstrated by the continued increased clinical trials with iRECIST.

This document focuses on how to better understand iRECIST criteria especially the key points of efficacy analysis implementation to derive the most common efficacy endpoints based on exploration of the key difference between iRECIST and RECIST 1.1 from the perspective of statistical analysis.

INTRODUCTION

Immune modulators are one of the most important classes of new anticancer therapeutics [1]. RECIST 1.1 (an increase in the sum of measures of target lesions, unequivocal increase in non-target disease, or the appearance of new lesions) might not always adequately capture the unique patterns of response “pseudoprogression” that have been well described in clinical trials of these drugs in a low proportion of patients, typically reported as 10% or less, mainly in melanoma studies and unclear the true frequency in trials of other malignancies is because most trials have reported RECIST 1.1-based response rates [2]. And a higher risk of continuing ineffective therapy or increasing exposure to radiotherapy and cost for the potentially ineffective therapy or the costs of imaging might expose to patients if pseudoprogression is common. Those data are crucial to understand the dynamics of tumour response to immunotherapeutics, including whether immunotherapeutics with different mechanisms of action have varying effects.

Moreover, in 2009, modified response criteria based on WHO criteria (which include the collection of bidimensional measurements of target lesions) were proposed—the immune-related response criteria (irRC) [3]. And irRECIST 2013 which is published by researchers revised irRC using unidimensional measurements based on the original RECIST. These recommendations are often referred to as irRECIST [4], but have not always been consistently applied, leading to concerns about the comparability of data and results across trials, difficulty with pooling databases, and poor clarity regarding whether new lesions were measured, and if so, how many were captured, and whether measures were incorporated into tumour burden [5].

The RECIST working group decided to develop a guideline for the use of a modified RECIST to ensure consistent design and data collection that would facilitate the clinical trial data to be collected, submitted, analyzed, and validated in clinical trials of immune based therapies, if indicated, of a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST). iRECIST requires the confirmation of progression to rule out or confirm pseudoprogression. And working group recommends continuing to use RECIST 1.1 as the primary criteria for response-based endpoints for the design of randomized studies planned for licensing applications and iRECIST exploratory in such trials, might consider using primarily iRECIST in earlier phase trials.

COMPARISON OF RECIST 1.1 AND IRECIST

From the category of overall time-point responses, the principles used to establish objective tumor response are largely unchanged from RECIST 1.1. There are five response categories in RECIST 1.1 including Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) [6]. Response nomenclature in iRECIST is similar which is based on RECIST 1.1. iRECIST have a prefix of "i" (ie, immune) in responses—eg, "immune" complete response (iCR) or partial response (iPR), stable disease (iSD), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Consistently, PD will be confirmed in later confirmatory tumor scan as the critical difference between iRECIST and RECIST 1.1. Another category non-CR/non-PD is in use as a sort of substitute for Stable Disease if patient has no evaluable target lesions, but same way as Stable Disease (SD) is usually handled in derivation of efficacy endpoints.
Table 1 shows all differences between iRECIST and RECIS 1.1. Let's explore the details of the major difference from perspective of statistical analysis to better understand iRECIST criteria.

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1. Comparison of RECIST 1.1 and iRECIST [5]

1. **Difference of overall time-point responses:** iRECIST can have had iUPD (one or more instances) but not iCPD, before iCR, iPR, or iSD as row 2 in table 1.
    - Firstly, iRECIST defines iUPD on the basis of RECIST 1.1 principles. And according to the figure 1 [1], the assessment example clearly shows the iRECIST would continue to collect tumor assessment data after iUPD at TP1 (timepoint 1) tumor assessment. However, due to the tumor shrinkage (iSD, iPR, compared with baseline) at TP2, TP3, so the TP4 tumor assessment result is still iUPD and not be confirmed. In other words, if iSD, iPR or iCR intervenes then bar is reset and iUPD must occur again (compared with nadir values) and be confirmed (by further growth) in next assessment for iCPD to be assigned. Atypical responses of delayed responses that occur after pseudoprogression is identified and better characterized by this iRECIST approach.

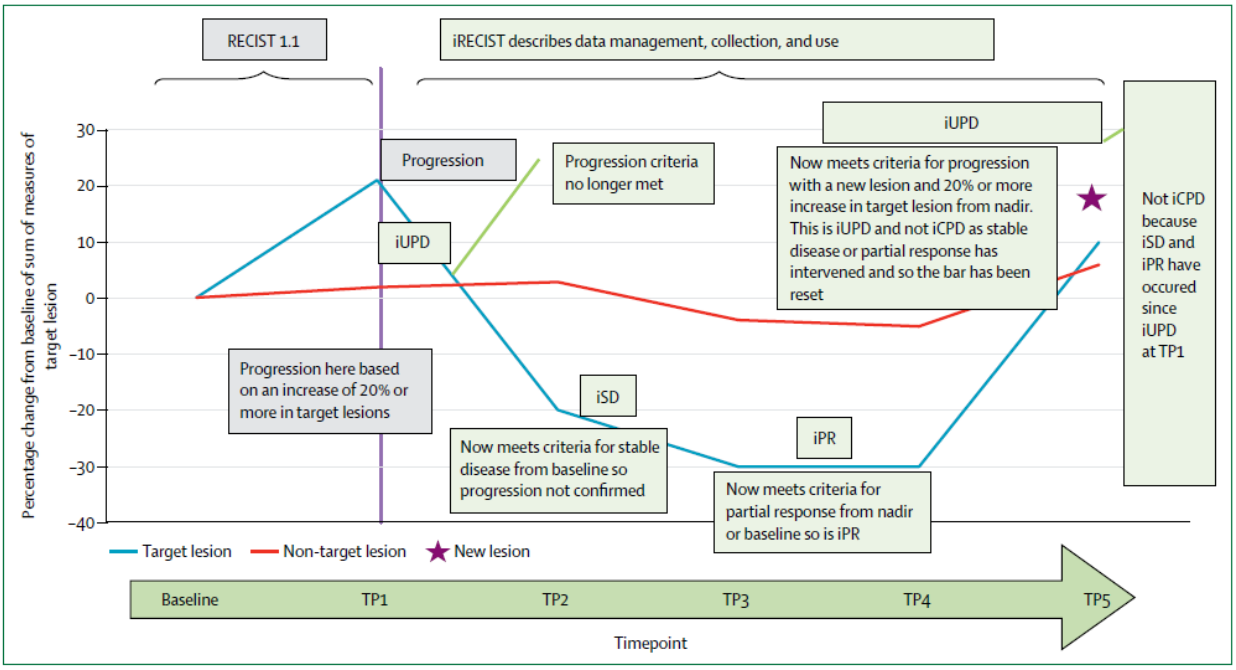


Figure 1. RECIST 1.1 and iRECIST: an example of assessment [5]

- Secondly, furthermore, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria (e.g. patient 001 at timepoint 3 in table 2). If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD which is the reason for one or more instances iUPD (e.g. patient 002 at timepoint 2, 3 in table 2).

Patient ID	Category	Baseline	TP1	TP2	TP3	TP4
001	Target Lesions (sum)	100	125	125	125	-
001	Non-target Lesions	Present	Unchanged	Unchanged	Unequivocal Increase	-
001	New Lesions		Absent	Absent	Absent	-
001	TP Response (RECIST)		PD	PD	PD	-
001	TP Response (iRECIST)		iUPD	iUPD	iCPD	-
002	Target Lesions	100	50	50	50	Not Evaluated
002	Non-target Lesions	Present	Unchanged	Unchanged	Unchanged	Not Evaluated
002	New Lesions		Absent	1 Lesion	Unchanged	Not Evaluated
002	TP Response (RECIST)		PD	PD	PD	Not Evaluated
002	TP Response (iRECIST)		iUPD	iUPD	iUPD	Not Evaluated
003	Target Lesions	100	125	50	50	120
003	Non-target Lesions	Present	Unchanged	Unchanged	Unchanged	Unchanged
003	New Lesions		1 Lesion	Unchanged	Extra New Lesion	Unchanged
003	TP Response (RECIST)		PD	PD	PD	PD
003	TP Response (iRECIST)		iUPD	iPR	iUPD	iCPD

Table 2. Example of Response Scenarios

2. **Difference in new lesions assessment and collection:** new lesions are assessed as per RECIST 1.1 but are recorded and measured separately on the case report form in target, non-target, and new lesion categories but not included in the sum of diameters for target lesions identified at baseline as row 1 and 4 in table 1.
    - We could further understand the reason from question “How to define iCPD?”. And confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD (one or more instances). As figure 2 mentioned, generally there are two ways to confirm progression including existing iUPD “get worse” and lesion category without iUPD now meets the (RECIST 1.1) criteria for PD. Therefore, it's necessary to record either if any new lesions existed or the new lesion diameter if it could be measured in target, non-target, and new lesion categories.

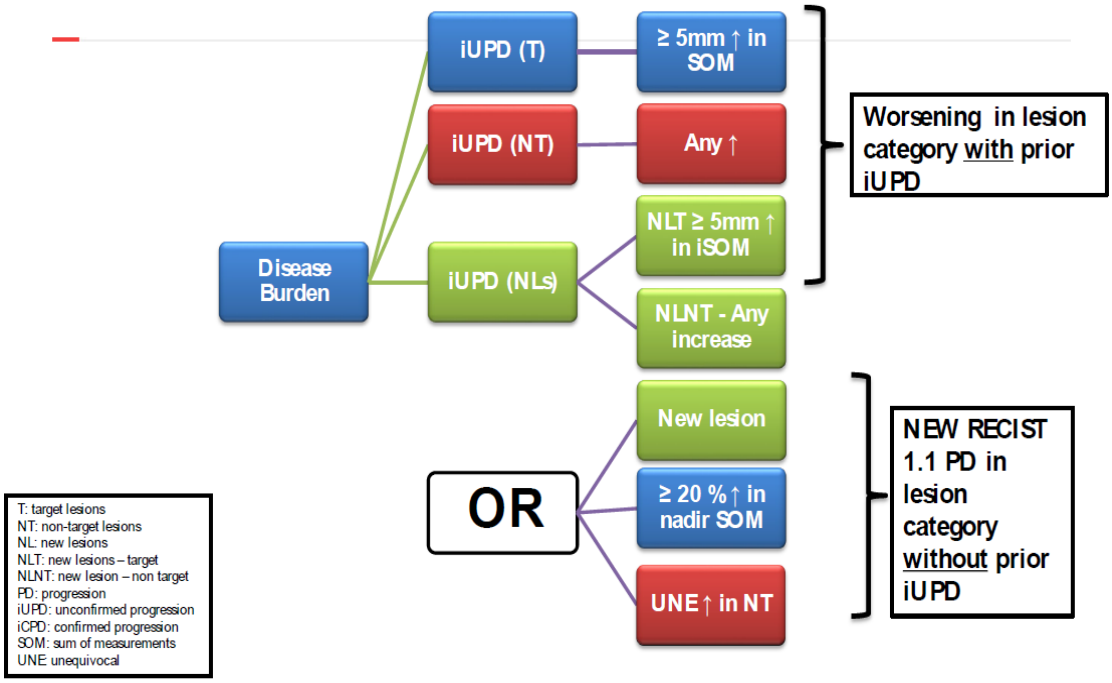


Figure 2. iRECIST: Confirming Progression [7]

3. **Difference in clinical stability consideration:** clinical stability is considered in iRECIST when deciding whether treatment is continued after iUPD as row 8 in table 1.
    - It’s possible that multiple iUPD can be assigned as long as iCPD is not confirmed at the next assessment as the reason also mentioned for difference in row 2, which has no change in tumour size or extent from iUPD occurs in target, non-target and new lesion categories. However, iRECIST are not treatment decision guideline. All decisions regarding continuation or discontinuation of therapy after iUPD should be made by the patient and their health-care provider. Moreover, iUPD could never be confirmed if patients weren’t considered to be clinically stable.

BEST OVERALL RESPONSE in iRECIST

The principles of best overall response closely follow RECIST 1.1. Assessments that are not done or not evaluable should be disregarded as RECIST 1.1. And the algorithm for patients with no previous iUPD is

identical to RECIST 1.1. However, the possibility of pseudoprogression and iUPD adds complexity of the assessment. Below is the statistical logic of iRECIST based on existing RECIST 1.1 in practice.

For unconfirmed BOR in RECIST 1.1, first select all the overall responses up to first PD date or New Anti-Cancer Treatment Start Date (pre-specified in protocol or SAP), whichever earlier, or select all tumor assessments if both dates are missing; Then pick the best of CR-PR-SD (or NON-CR/NON-PD)-PD-NE in this order with CR the best, and NE the worst; In case SD (or NON-CR/NON-PD) is the best response found: keep as SD (or NON-CR/NON-PD) only if at least one objective status of stable or better documented (i.e. CR/PR/SD (or NON-CR/NON-PD) at least lasted for more than X days. X is often 6 weeks but should reflect a duration of clinical relevance for the disease under study and should be pre-specified in the protocol and SAP), else set to "PD" if timepoint overall response PD exists, else set to "NE".

For unconfirmed BOR in iRECIST, generally first select all the overall responses up to **iCPD** or New Anti-Cancer Treatment Start Date (pre-specified in protocol or SAP), whichever earlier, or select all tumor assessments if both dates are missing; Then pick the best of iCR-iPR-iSD (or NON-iCR/NON-iUPD)-iCPD-iUPD-iNE in this order with iCR the best, and iNE the worst; In case iSD (or NON-iCR/NON-iUPD) is the best response found: keep as iSD (or NON-iCR/NON-iUPD) only if at least one objective status of stable or better documented (i.e. iCR/iPR/iSD (or NON-iCR/NON-iUPD) at least lasted for more than X days. X is often 6 weeks but should reflect a duration of clinical relevance for the disease under study and should be pre-specified in the protocol and SAP), **else set to "iCPD" if timepoint overall response iCPD exists, else set to "iUPD" if only timepoint overall response iUPD exists**, else set to "NE".

Confirmation of response is not required when using RECIST 1.1, except in non-randomised trials, and this approach is also recommended for iRECIST. For BOR based on confirmed response, the CR and PR should be confirmed. The confirmed CR, PR logics are same for both RECIST 1.1 and iRECIST including two objective statuses of CR a minimum of four weeks apart documented to be derived as confirmed CR and two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented to be derived as confirmed PR. However, some special circumstances could happen while using iRECIST criteria due to the possible pseudoprogression. iUPD between two iCRs or two iPRs is acceptable for determination of BOR as confirmed iCR and confirmed iPR separately. And the tumor assessment data in these two cases should be queried from perspective of RECIST 1.1 criteria which cannot have met criteria for progression before complete response, partial response, or stable disease.

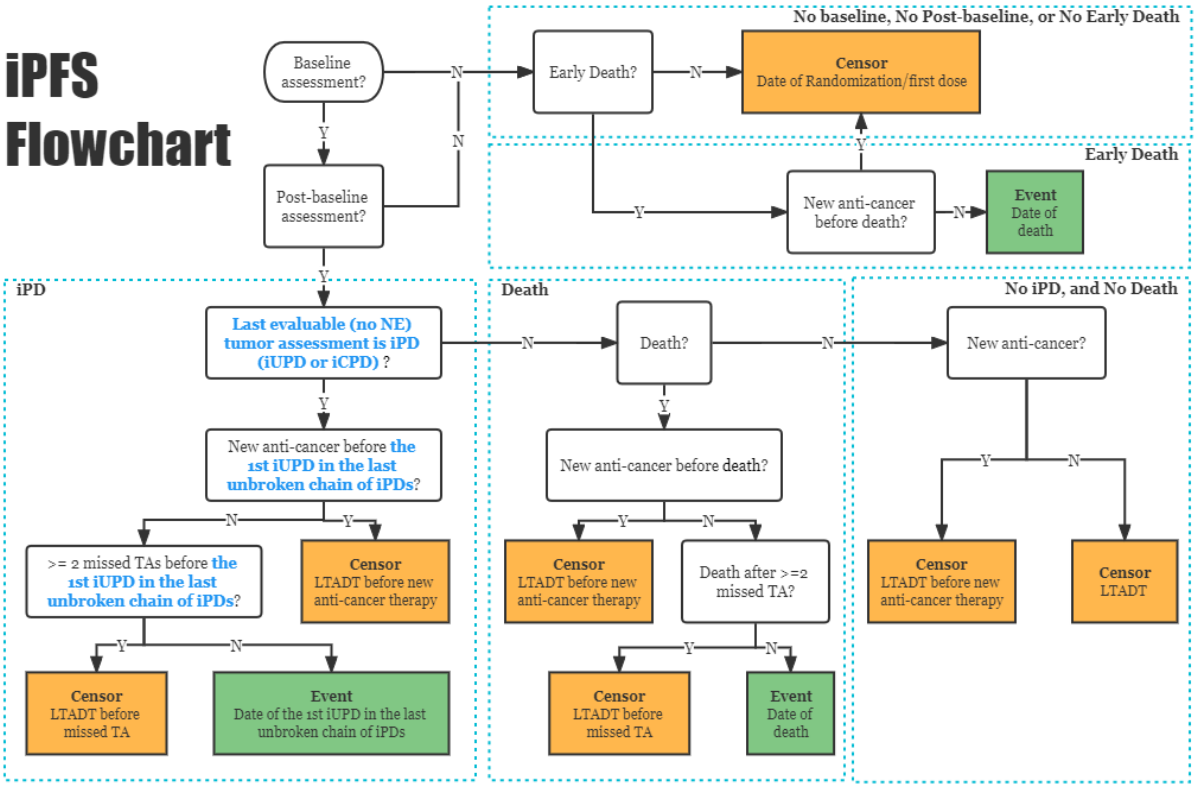
PROGRESSION-FREE SURVIAL in iRECIST

Generally, progression-free survival is the time from start date to date of event which includes first documentation of PD or death due to any cause. And the difficult and core points of event date would be how to define immune PD date in iRECIST. Per the iRECIST guideline [5], the event date for PD to be used for calculation of immune progression-free survival (iPFS) should be the 1st iUPD in the last unbroken chain of iPDs (earliest among the latest group of iUPDs with the last evaluable TA is iPD including iCPD or iUPD) based on below consideration.

1. Progression event date would be the same as RECIST 1.1 date (i.e. first iUPD date) unless iSD, iPR or iCR intervenes which is ultimately date at which progression criteria are met provided that iCPD is confirmed at the next assessment (e.g. patient 001 iRECIST PD date is TP1 in table 2). However, iUPD would be disregarded if iUPD only occurs before later iSD, iPR, or iCR, that iUPD date should not be used as the event date (e.g. patient 003 TP1 iUPD date in table 2).
2. For iUPD never confirmed, event date would be only ignored if a subsequent iSD, iPR or iCR occurs with no later iUPD or iCPD. And iUPD date would be used considering circumstances below:
    - Patient not considered to be clinically stable, stops protocol treatment and no further response assessments are done.
    - The next TPRs are all iUPD, and iCPD never occurs (e.g. patient 002 iRECIST PD date is TP1 in table 2)
    - The patient dies of cancer.

And it would be easier to use RECIST 1.1 framework to implement iRECIST logic. Moreover, iRECIST rules mentioned above especially the iUPD never confirmed are largely based on the conservative principle of protecting patients from drugs that may not work, and iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression) compared with RECIST 1.1. Therefore, We could replace the condition of "if PD happens" in RECIST 1.1 with "if last evaluable (no NE) tumor assessment is iPD (iUPD or iCPD)" in iRECIST, which event date is the 1st iUPD in the last unbroken chain of iPDs if last TA is iPD without considering two TA missing or new anti-cancer therapy happens. And the logic of new anti-cancer therapy types and two TA missing should be pre-specified in protocol or SAP. Please refer below iPFS flow chart in figure 3 based on RECIST 1.1 flow chart.

Due to the universal use of RECIST 1.1, almost every company has efficacy analysis process and efficacy ADaM specs for RECIST 1.1. Therefore, creating a set ADaM spec with iRECIST criteria based on RECIST 1.1 efficacy ADaM specs could quickly and effectively analyze the efficacy results with iRECIST.



NOTE:
LTADT: Last Adequate Tumor Assessment Date. TA: Tumor Assessment. iPD: Progressive Disease. iPFS: immune Progression-free Survival.
For censored cases, if the LTADT is baseline TA (i.e., no adequate post-baseline tumor assessment), then censor at randomization.
For non-randomized study, use the first dose date to replace randomization date.

Figure 3. iRECIST: Immune Progression Free Survival (iPFS) Flow Chart

CONCLUSION

In this article, exploring of the key difference between RECIST 1.1 and iRECIST from perspective of statistical analysis will be also presented to benefit the readers to better understand iRECIST and how to derive efficacy endpoints such as BOR, PFS or DOR (duration of response) based on existing mature RECIST 1.1 analysis process. Examples presented in this paper are hypothetical and for illustrative purpose only, and this paper puts forward a special view of iBOR and iPFS derivation logic with iRECSIT criteria based on universally accepted derivation rule for RECIST 1.1. Further detailed analysis process could depend on study protocol and statistical analysis plan (SAP), CDISC ADaM Guidance, as well as these two guidelines. Fully understand the differences between these two guidelines can lead to the standardization

of the process of derivation of efficacy endpoints with iRECIST criteria, and thus saving time and resources based on exiting RECIST 1.1 analysis frame.

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