Paper PP10

But wait, there's more: When RECIST 1.1 is not enough

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ABSTRACT

The standard framework for assessing tumor response and progression in oncology trials is the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). However, evolving clinical landscapes, including immune-oncology therapies, atypical progression patterns, and real-world evidence studies, increasingly demand non-standard efficacy endpoints such as iRECIST, mRECIST, and biomarker-integrated response definitions. This presentation explores advanced SAS® -based programming strategies to derive complex endpoints within the ADaM Response Dataset (ADRS), leveraging integration with ADSL and ADLB. We address common challenges such as immune-related response tracking, handling non-target lesions, incorporating biomarker thresholds. Real-world examples and code snippets will be used to illustrate solutions to programming challenges, with an emphasis on scalable, auditable, and CDISC-aligned approaches.

INTRODUCTION

Accurate and reproducible assessment of tumor burden is central to some oncology clinical trials and regulatory evaluation. The international standard for determining objective response and progression based on variations in the sum of longest diameters (SLD) of quantifiable lesions is still the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al., 2009). In the age of immunotherapies and molecularly targeted medicines, RECIST 1.1 may overlook significant biological dynamics because it predominantly reflects anatomic change, despite its uniformity and operational simplicity.

The initial consolidated standard, RECIST (2000), formulated a practical assumption that anatomical alterations in a restricted number of "target lesions" could act as an indicator for overall tumor response: select up to 10 lesions (no more than 5 per organ), measure the longest diameter, sum, and track change over time. In 2009, significant revisions were implemented with the introduction of RECIST V 1.1 (Eisenhauer et al., 2009), which reduced the target-lesion burden (to 5 total, 2 per organ), clarified lymph-node assessment, and reaffirmed the four response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). These categories are primarily determined by anatomic shrinkage or unequivocal progression.

Clinical practice, especially the use of immune-checkpoint inhibitors, revealed the limitations of "single-scan PD." Transient increases in size due to immune-related inflammation, mixed responses, or the emergence of small new lesions that subsequently regress were prematurely classified as progressive disease. In response to this issue, iRECIST was introduced in 2017 as a conservative modification of RECIST. The initial indication of progression, defined as either the emergence of a new lesion or a ≥20% increase from nadir, is categorized as immune unconfirmed progressive disease (iUPD). Immune confirmed progressive disease (iCPD) is designated only if a follow-up scan conducted 4–8 weeks later reveals persistent or worsening disease (Lee et al., 2021). In summary, iRECIST did not supplant RECIST 1.1; rather, it introduced a confirmation gate within the same anatomical framework.

Parallel to this, hepatocellular carcinoma (HCC) and other hypervascular tumors demonstrated that treatment benefits can be underestimated by their anatomical dimensions. mRECIST, introduced by Lencioni and Llovet in 2010 and adopted later 2019, transitioned the focus of evaluation from total lesion size to viable tumor, defined as the arterial phase enhancing segment of the lesion. This modification results in increased observed response rates and improved correlation with outcomes in hepatocellular carcinoma treated with locoregional or anti-angiogenic/immuno-oncology regimens (Yu et al., 2022; Chen et al., 2023).

The current landscape has three layers: the 2000/2009 anatomic core defined by RECIST and RECIST 1.1, the 2017 immune-specific confirmation pathway immune RECIST (iRECIST), and the 2010 viable-tumor variant for hepatocellular carcinoma modified RECIST (mRECIST). Each layer has its own rules for how to work: target, non-target lesions, clear handling of new lesions, confirmation windows for provisional progression, and evaluation of enhancing/viable tumor in hepatocellular carcinoma (HCC). At the same time, sponsors still need to make sure that the outputs are in CDISC-compatible analysis datasets. The primary opportunity is methodological: The RECIST SLD is typically stored in the tumor-response analysis dataset ADTR. New or non-target information may be found in the tumor inventory dataset ADTU and/or a progression dataset ADPROG. Biomarkers like lactate dehydrogenase (LDH), which are kept because they are thought to be useful for predicting outcomes in HCC and IO/targeted

settings, are available in ADLB for response stratification. iRECIST logic must also keep immune unconfirmed progressive disease (iUPD) status until confirmation. Integrating RECIST 1.1, iRECIST, and mRECIST into a single visit-level view with categorical calls that match the continuous percent-change profiles is a cross-domain Analysis Data Model (ADaM) task that benefits from clear programming patterns.

This work intends to show, on synthetic ADaM-like data, how to program the three main response frameworks RECIST/RECIST 1.1, iRECIST, and mRECIST in SAS from a single integrated visit-level dataset using sequential, retained-variable logic. The goal is not to redefine the clinical criteria, but to show how to implement them in an auditable, CDISC-aligned, and biomarker-extensible way.

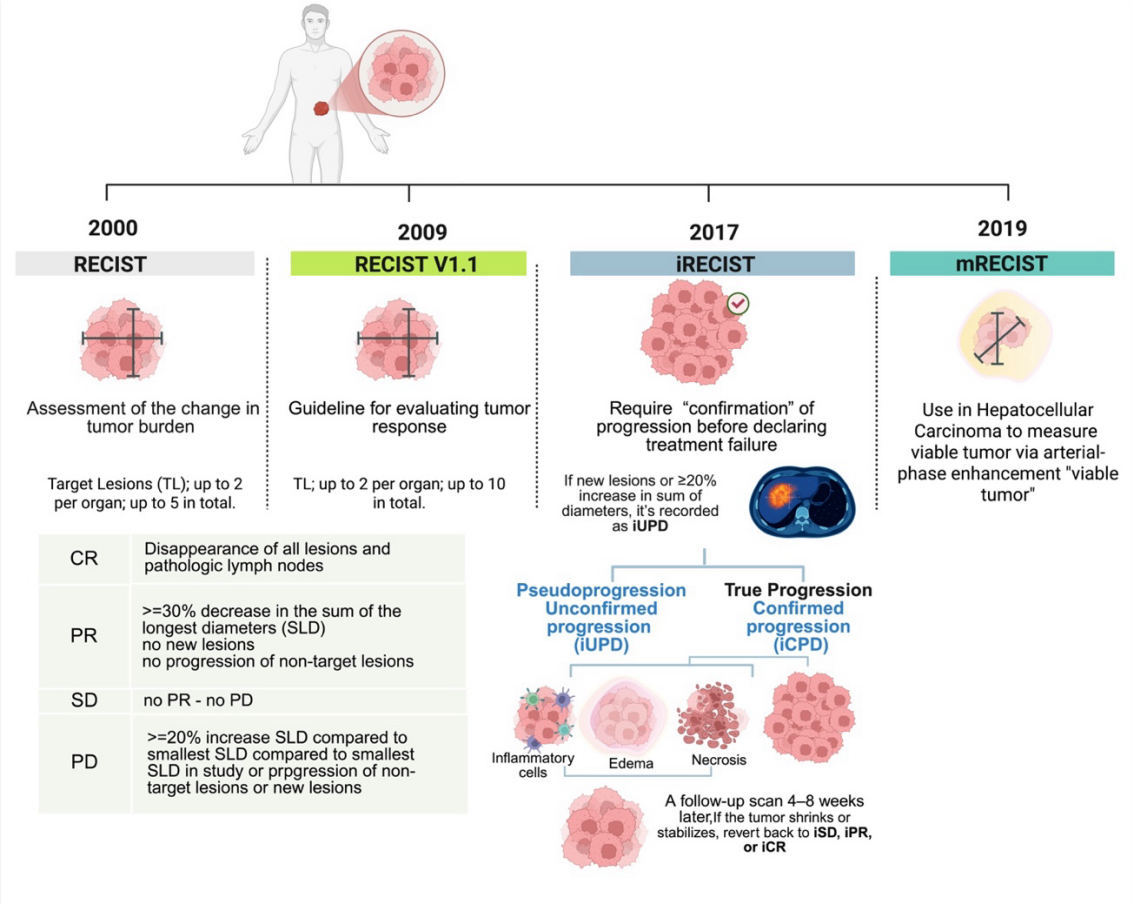

Figure 1. Timeline of solid-tumor response criteria relevant to this work. RECIST (2000) and RECIST 1.1 (2009) define the anatomic, SLD-based standard. iRECIST (2017) adds an immune-specific confirmation pathway (iUPD and iCPD) to prevent premature treatment failure calls. mRECIST (2010; widely adopted in HCC studies after 2019) focuses on viable tumor measured on arterial-phase imaging. The programming described in this paper implements these three streams on a common, CDISC-like input structure.

METHODS

DATA SIMULATION AND SOURCE DOMAINS

To demonstrate the derivations without exposing study data, we generated synthetic, CDISC-like analysis datasets for a single subject (USUBJID = SUBJ001):

ADSL (Subject-Level Analysis Dataset): demographics and treatment dates (TRTSDT) to anchor assessment timing.

ADTR (Tumor-Response Analysis Dataset): anatomic, RECIST-style target-lesion measurements expressed as the sum of longest diameters (SLD), including a baseline record (BASELINE, AVISITN=0) and four post-baseline visits at fixed dates in 2025. Variables included USUBJID, AVISIT/AVISITN, ADT (assessment date), AVAL (SLD), and BASE (baseline SLD).

ADTR_VIABLE: parallel visit-level measurements representing arterial-phase enhancing/viable tumor, used for mRECIST logic (EAVAL, EBASE).

ADPROG: non-target progression indicators and new-lesion flags at the same assessment dates.

ADTU (Tumor Inventory): per-visit lesion inventory with TUSCAT = “TARGET”, “NONTARGET”, or “NEW” so that visit-level counts of target, non-target, and new lesions could be derived.

ADLB (Laboratory): baseline lactate dehydrogenase (LDH) to enable a simple high/normal stratification (>250 U/L = High) consistent with reports of LDH as a negative prognostic marker in HCC; LDH is not part of mRECIST but is useful for biomarker-integrated summaries.

ADSL (subject-level)

Unique Subject ID	Sex	Planned Treatment Arm	Treatment Start	Age
SUBJ001	M	Drug A	05JAN2025	62

ADLB (LDH at Baseline)

Unique Subject ID	Parameter Code	Baseline Flag	Lab Value
SUBJ001	LDH	Y	280

ADTR (Target Lesions / SLD)

Visit	Date	SLD (mm)	Baseline SLD
Baseline	01JAN2025	50	50
Visit 1	05FEB2025	34	50
Visit 2	20MAR2025	43	50
Visit 3	17APR2025	35	50
Visit 4	15MAY2025	46	50

ADTR_VIABLE (eSLD for mRECIST)

Visit	Date	Viable (eSLD, mm)	Baseline Viable
Baseline	01JAN2025	40	40
Visit 1	05FEB2025	20	40
Visit 2	20MAR2025	24	40
Visit 3	17APR2025	0	40
Visit 4	15MAY2025	0	40

ADTU (Tumor Identification)

Visit	Lesion ID	Location	TUSCAT
Baseline	TL01	Liver S5	TARGET
Baseline	TL02	Lung RLL	TARGET
Baseline	NT01	LN Para	NONTARGET
Visit 4	NEW01	Liver S8	NEW

Counts per visit: #Target=2, #Non-target=1; **new lesion only at Visit 4**.

Column Lineage (ADRS_ALL)

Variable	Source
usubjid, avisit, adt, aval, base	ADTR
pchg_bl	Derived from ADTR (aval, base)
ldh_cat	Derived from ADLB (aval)
eaval, ebase	ADTR_VIABLE
nt_prog, new_lesion	ADPROG
n_tl, n_ntl, has_new	ADTU aggregated per visit
ovr, iovr, movr + nadir metrics	Derived rules

Figure 2. Cross-Domain Linkage and Input Domains. The diagram displays the keys USUBJID, AVISIT, and ADT that feed ADSL, ADLB, ADTR (SLD and viable-tumor extensions), ADPROG, and ADTU into a single integrated analytic dataset (ADTR_ALL).

INTEGRATION LAYER

All domains were merged to a single visit-level analysis table (ADTR_ALL) keyed by USUBJID, AVISIT, and ADT. This gives one row per assessment with anatomic SLD, viable-tumor measurements, progression flags, lesion-inventory signals, and LDH category.

```
proc sql;
    create table adtr_all as
    select  t.usubjid,
            t.avisit, t.avisitn, t.adt,
            t.aval, t.base,
            100*(t.aval - t.base)/t.base as pchg_bl,
            v.eaval, v.ebase,
            p.nt_prog, p.new_lesion,
            coalesce(u.has_new,0) as has_new,
            case when lb.aval>250 then 'High'
                 else 'Normal' end as ldh_cat
    from   adtr as t
    left join adtr_viable as v
           on t.usubjid=v.usubjid and t.adt=v.adt
    left join adprog as p
           on t.usubjid=p.usubjid and t.adt=p.adt
    left join adtu_visit as u
           on t.usubjid=u.usubjid and t.adt=u.adt
    left join adlb as lb
           on t.usubjid=lb.usubjid;
quit;
```

Two practical points happen here: (1) new-lesion presence is unified from ADPROG and ADTU, and (2) % change vs baseline (PCHG_BL) is computed once and reused by all frameworks.

RECIST 1.1 DERIVATION

RECIST 1.1 was implemented as a single, time-ordered SAS DATA step per subject. A retained nadir was used to support the "≥20% from nadir and ≥5 mm" PD rule. The precedence was: baseline → new/non-target progression → PD from nadir → CR → PR → SD.

```
proc sort data=adtr_all; by usubjid adt; run;

data recist_r11;
    set adtr_all;
    by usubjid adt;
    length ovr $8;
    retain nadir;
    if first.usubjid then nadir = base;
    nadir   = min(nadir, aval);
    pchg_nd = ifn(nadir>0, 100*(aval-nadir)/nadir, .);
    abschg  = aval - nadir;

    if upcase(avisit)='BASELINE' then ovr='';
    else if has_new=1 or nt_prog=1 then ovr='PD';
    else if pchg_nd>=20 and abschg>=5 then ovr='PD';
    else if aval=0 then ovr='CR';
    else if pchg_bl<=-30 then ovr='PR';
    else ovr='SD';
run;
```

IRECIST DERIVATION

iRECIST was layered on top of the RECIST result. Because iRECIST requires a confirmation window, the program retained the immune state, the date of the first immune unconfirmed PD (iUPD), and the SLD at that visit. If a scan 28–56 days later still showed progression, the call was upgraded to iCPD; if disease improved, the state was cleared.

```
data recist_irecist;
    set recist_r11;
    by usubjid adt;
    length iovr i_state $8;
    retain i_state iupd_date iupd_sld;
    format iupd_date date9.;
    recist_pd = (ovr='PD');

    if first.usubjid then do;
        i_state='NONE';
        call missing(iupd_date, iupd_sld);
    end;

    select (i_state);
        when ('NONE') do;
            if recist_pd then do;
                iovr='iUPD'; i_state='IUPD';
                iupd_date=adt; iupd_sld=aval;
            end;
            else iovr='i'||ovr;
        end;
        when ('IUPD') do;
            days_since = adt - iupd_date;
            if 28<=days_since<=56 and recist_pd then do;
                iovr='iCPD'; i_state='ICPD';
            end;
            else if not recist_pd then do;
                iovr='i'||ovr;
                i_state='NONE';
                call missing(iupd_date, iupd_sld);
            end;
            else iovr='iUPD';
        end;
        otherwise iovr='iCPD';
    end;
run;
```

mRECIST DERIVATION

For mRECIST, the same visit order was used, but rules were applied to the enhancement-based variables (EAVAL, EBASE), with a separate retained viable-tumor nadir. New lesions and non-target progression immediately defined PD; disappearance of enhancement defined CR; ≥30% decrease vs baseline viable tumor defined PR; ≥20% increase from viable-tumor nadir plus ≥5 mm defined PD; otherwise SD. (Code omitted here for brevity; it follows the same pattern as RECIST 1.1, using EAVAL/EBASE/E_NADIR instead of AVAL/BASE/NADIR.)

ADRS

To present all three frameworks in parallel, the visit-level dataset was normalized to an ADRS-like structure: one record per subject, visit, and response parameter.

```
data adrs;
    set recist_irecist; /* after mRECIST is merged in */
    length paramcd $8 avalc $12;
    /* RECIST 1.1 */
    paramcd='OVR';  avalc=ovr;  output;
    /* iRECIST */
    paramcd='IOVR'; avalc=iovr; output;
    /* mRECIST would be: paramcd='MOVR'; avalc=movr; output; */
    keep usubjid avisit adt paramcd avalc ldh_cat has_new;
run;
```

BEST OVERALL RESPONSE (BOR)
BOR, iBOR, and mBOR were derived separately by ranking visit-level responses within each framework (CR>PR>SD>PD/iUPD/iCPD) and retaining the best post-baseline category per subject. A BOR row was appended to facilitate tabular displays like the one shown in results section.

Criterion	RECIST 1.1	iRECIST	mRECIST
Measurement Basis	Anatomical SLD	Same as RECIST 1.1 with iUPD state	Viable tumor (enhancement)
Progression Logic	≥20% increase from nadir or new lesion	iUPD requires confirmation (28–56 days)	≥20% increase in viable tumor or new lesion
Response Definition	CR, PR, SD, PD	iCR, iPR, iSD, iUPD, iCPD	CR, PR, SD, PD
Key Variable	PCHG_BL	IOVR/I_STATE	E_PCHG_BL

Table 1. Overview of derivation logic across response frameworks.

RESULTS

For the simulated subject SUBJ001, the integrated SAS® framework was able to successfully extract and depict the tumor response across RECIST 1.1, iRECIST, and mRECIST criteria. With response classifications combined, Figure 3 shows the longitudinal percentage change from baseline in both SLD and viable tumor measures. Following the emergence of a new lesion, RECIST 1.1 detected Progressive Disease (PD) at Visit 4 and Partial Response (PR) at Visits 1 and 3. The iRECIST state-machine logic prevented an early designation of treatment failure by detecting brief iUPD events at Visits 2 and 4 and maintaining iPR through Visit 3. With a ≥30% decrease in viable enhancement at Visit 1, a Complete Response (CR) by Visit 3, and advancement upon the emergence of a new lesion at Visit 4, the mRECIST trajectory demonstrated a deeper biological response.

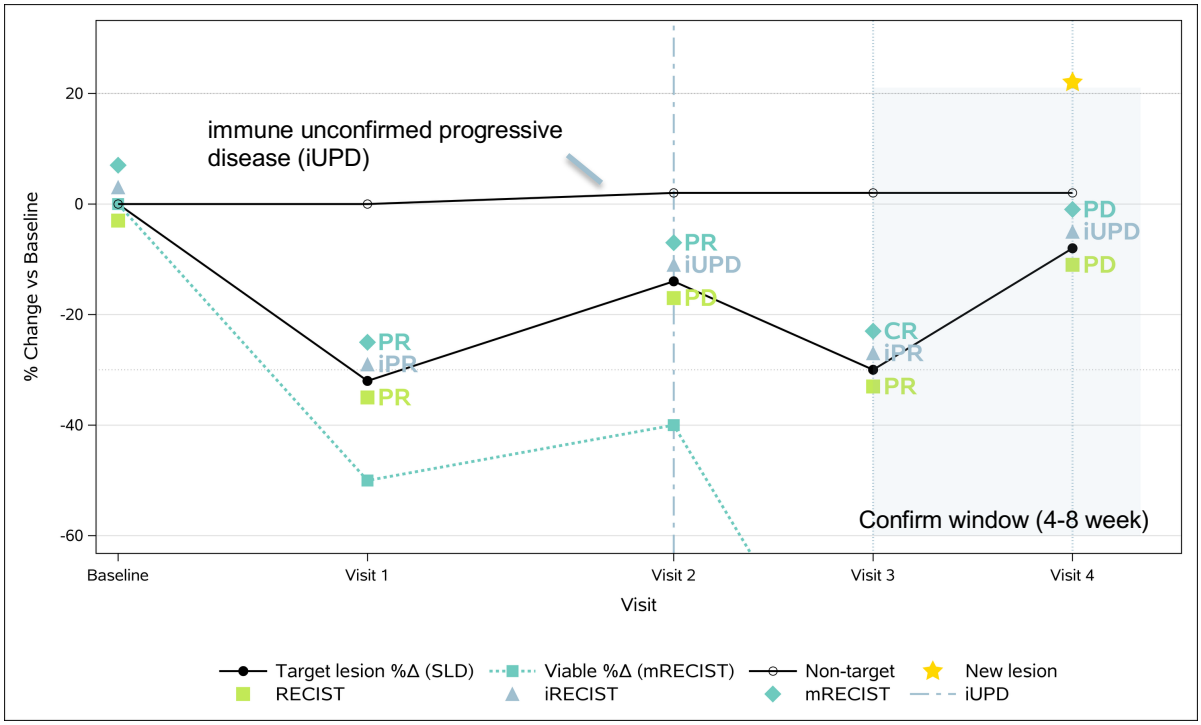

Figure 3. Shows the longitudinal percentage change for the RECIST 1.1, iRECIST, and mRECIST frameworks compared to the baseline. (Symbols = Framework response states; Cyan dotted line = Viable tumor %Δ; Black line = SLD). %Δ: percent change in viable (enhancing) tumor.

DATASET GENERATION AND INTEGRATION

The synthetic setup produced one complete subject record (SUBJ001) with five assessment timepoints: Baseline (01 Jan 2025), Visit 1 (05 Feb 2025), Visit 2 (20 Mar 2025), Visit 3 (17 Apr 2025), and Visit 4 (15 May 2025). All required inputs; anatomic SLD (ADTR), viable/enhancing tumor (ADTR_VIABLE), non-target progression and new-lesion indicators (ADPROG), lesion inventory (ADTU), and baseline LDH (ADLB), were successfully merged into a single visit-level analysis table (ADTR_ALL). The merge confirmed what **Table 2** intends to show: at each visit we could see, in one row, SLD, viable tumor, progression flags, new-lesion presence, and LDH category.

Visit	Date	SLD (mm)	%Δ vs BL	New lesion	RECIST v1.1	iRECIST	mRECIST
Baseline	2025-01-01	50	0%	No	NA	NA	NE
Visit 1	2025-02-05	34	-32%	No	PR	iPR	PR
Visit 2	2025-03-20	43	-14%	No	PD	iUPD	PR
Visit 3	2025-04-17	35	-30%	No	PR	iPR	CR
Visit 4	2025-05-15	46	-8%	Yes	PD	iUPD	PD
BOR	**NA**	**NA**	**NA**	**NA**	**PR**	**iPR**	**CR**

Table 2. Best Overall Response (BOR) and tumor response summary at the visit level for RECIST 1.1, iRECIST, and mRECIST.

Visit-level evaluations for Subject SUBJ001 are compiled in **Table 2** and interpreted in **Table 3** to demonstrate how each framework is used in practice. Although the same longitudinal measurements serve as the basis for all criteria, iRECIST and mRECIST handle progression and viability differently.

Visit (Date)	RECIST v1.1 Assessment	iRECIST Assessment	mRECIST Assessment
Baseline	Target-lesion sum: **50 mm** (baseline)	–	Viable tumor sum: **50 mm**
Visit 1(05 Feb 2025)	Target-lesion sum decreased to **34 mm**(−32% from baseline), meeting **PR**.	Mirrors RECIST: **iPR**.	Viable tumor sum decreased to **20 mm**, meeting **PR**.
Visit 2(20 Mar 2025)	Target-lesion sum increased to **43 mm**, representing a ≥20% increase from nadir (34 mm) and ≥5 mm absolute growth, fulfilling **PD**.	Classified as **iUPD** because progression requires confirmation on a subsequent scan.	Viable tumor sum remained at **24 mm** (−40% from baseline), maintaining a **PR**.
Visit 3(17 Apr 2025)	Target-lesion sum improved to **35 mm** (−30% from baseline), sustaining a **PR**.	Due to renewed tumor shrinkage, immune assessment resets to **iPR**.	Viable tumor sum reached **0 mm**, indicating **CR**.
Visit 4(15 May 2025)	A new lesion was detected and target-lesion sum increased to **46 mm**. The appearance of a new lesion defines **PD.**	Presence of a new lesion is recorded as **iUPD**, pending confirmation 4–8 weeks later.	The new lesion also defines **PD**.

Table 3 Interpretation.

DISCUSION

This work shows that RECIST 1.1, iRECIST, and mRECIST can be derived coherently from a single, integrated visit-level structure when all relevant signals: SLD, viable/enhancing tumor, non-target progression, new lesions, and a biomarker covariate, are present on the same record. In that setting, a time-ordered SAS DATA step with retained variables is sufficient to implement the key features of each framework: the "≥20% and ≥5 mm" rule and new-lesion override for RECIST 1.1, the iUPD→iCPD confirmation pathway for iRECIST, and the separate viable-tumor nadir required for mRECIST.

Two practical points emerge. First, progression information must be unified across domains (ADTU and/or ADPROG) before applying the rules; otherwise, discrepant visit-level calls are likely. Second, mRECIST must be treated as a parallel derivation, not as a small modification of RECIST 1.1, because it is based on enhancement rather than pure anatomic size.

Carrying lactate dehydrogenase (LDH) from ADLB illustrates how biomarker context can be added without altering the imaging criteria, enabling response summaries by LDH subgroup. The main limitation is that the example used an idealized, single-subject dataset; real studies will require visit-windowing, handling of missing assessments, and potentially multiple immune confirmation windows. Even so, the pattern integrates once, derive sequentially, and normalize to an ADRS-like structure provides a clear and CDISC-compatible way to present all three response frameworks side by side.

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