RECIST

iRECIST

A guideline for data management and data collection for trials testing immunotherapeutics

USING THIS SLIDE SET

- This slide contain more than 60 slides explaining the rationale, development and use of iRECIST
- You may use any or all of the slides for training purposes, depending on your audience
- Some concepts are presented more than one way so that you can choose the most appropriate for your presentation
  - Simple cartoons or diagrams
  - Detailed cartoons or diagrams
  - Radiology images with annotations
  - Scenarios with details of tumour measurements

RECIST

Overview

- Background
- Key Points
- Examples and Scenarios
- Statistical and Data Considerations
- Summary and Conclusions
- Resources
- Acknowledgements

BACKGROUND

RECIST

Immunotherapy

- Immune based therapies are a major advancement in patient care
- **BUT** unusual response patterns well described especially in melanoma

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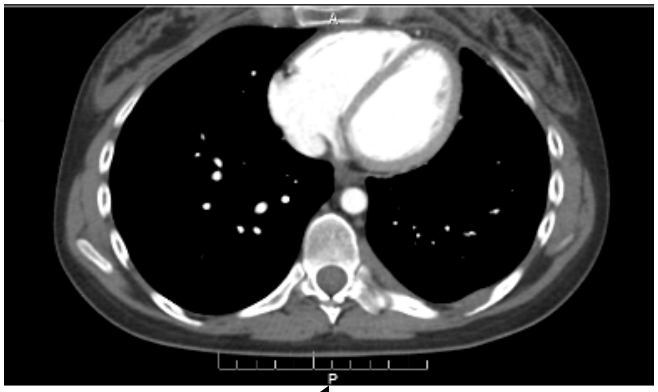
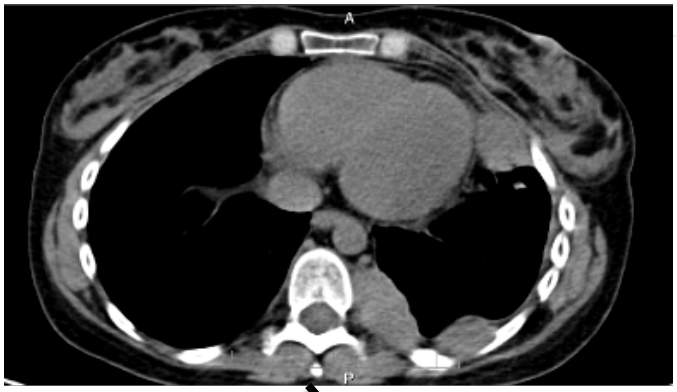
Unusual Response Patterns

TIMEPOINT 3

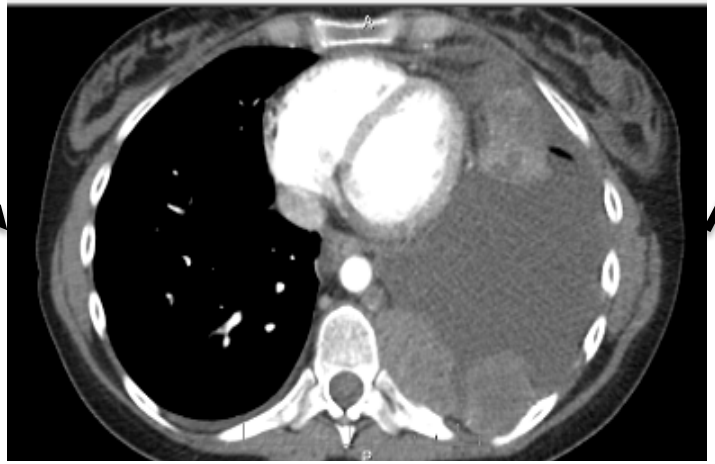
CLEAR RESPONSE





BASELINE

TIMEPOINT 2



PROGRESSION PER RECIST 1.1

"Immune Response Criteria" Developed

- irRC - consensus based recommendations (2009)
  - Based on WHO, bi-dimensional measures
  - New lesion measures included in sum of measures of target lesions
- Subsequent modifications proposed
  - Based on RECIST/RECIST 1.1

Wolchok JD, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res.* 2009;15:7412–20.

Nishino M et al. Developing a common language for tumor response to immunotherapy: Immune-Related Response Criteria using unidimensional measurements. *Clin Cancer Res.* 2013;19:3936–43.

Bohnsack O et al. Adaptation of the immune-related response criteria: irRECIST. *Ann Oncol* 2014;25 (suppl 4):iv361–iv372.

Hodi FS et al. Evaluation of Immune-Related Response Criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *JClin Oncol* **2016;34:1510–7.**

Chiou VL et al. Pseudoprogression and Immune-Related Response in Solid Tumors. *JClin Oncol* 2015;33:3541–3543.

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Versions of "Immune Response Criteria"

	RECIST 1.1	irRC (+ unidimensional variant)	"irRECIST / irRECIST1.1" variants
Bi/unidimen.?	Unidimensional	**Bidimensional**	Unidimensional
N Target	5	**15; (≥5 × 5mm)**	10 / 5 (≥10mm/ ≥10mm (15 for nodes))
New target lesions added to sum or measures (SOM)?	No	(≥5 × 5mm); **Yes** - does not automatically define PD	(RECIST or RECIST 1.1 rules) **Yes**
How many ?	NA	10 visceral, 5 cutaneous	10 / 5 (RECIST 1.1 rules)
Definition of progression (PD)	≥ 20% ↑ compared to nadir (≥ 5mm ↑)	≥ 25% ↑ compared to baseline (BL), nadir/**reset BL**	≥ 20% ↑ compared to nadir (≥ 5mm ↑)
Confirmation ?	No	Yes, required	Yes, recommended
How confirmed?	NA	**Not defined**	**Not defined;** not improved? Imager feels is worse?

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Concerns

- Multiple variations of “immune criteria’ used across trials
- Comparability across trials
- Response data /measures not always collected after RECIST defined progression
- May not be applicable to all tumour types – developed primarily in melanoma
- Patients being treated past true progression may be denied access to effective salvage therapies

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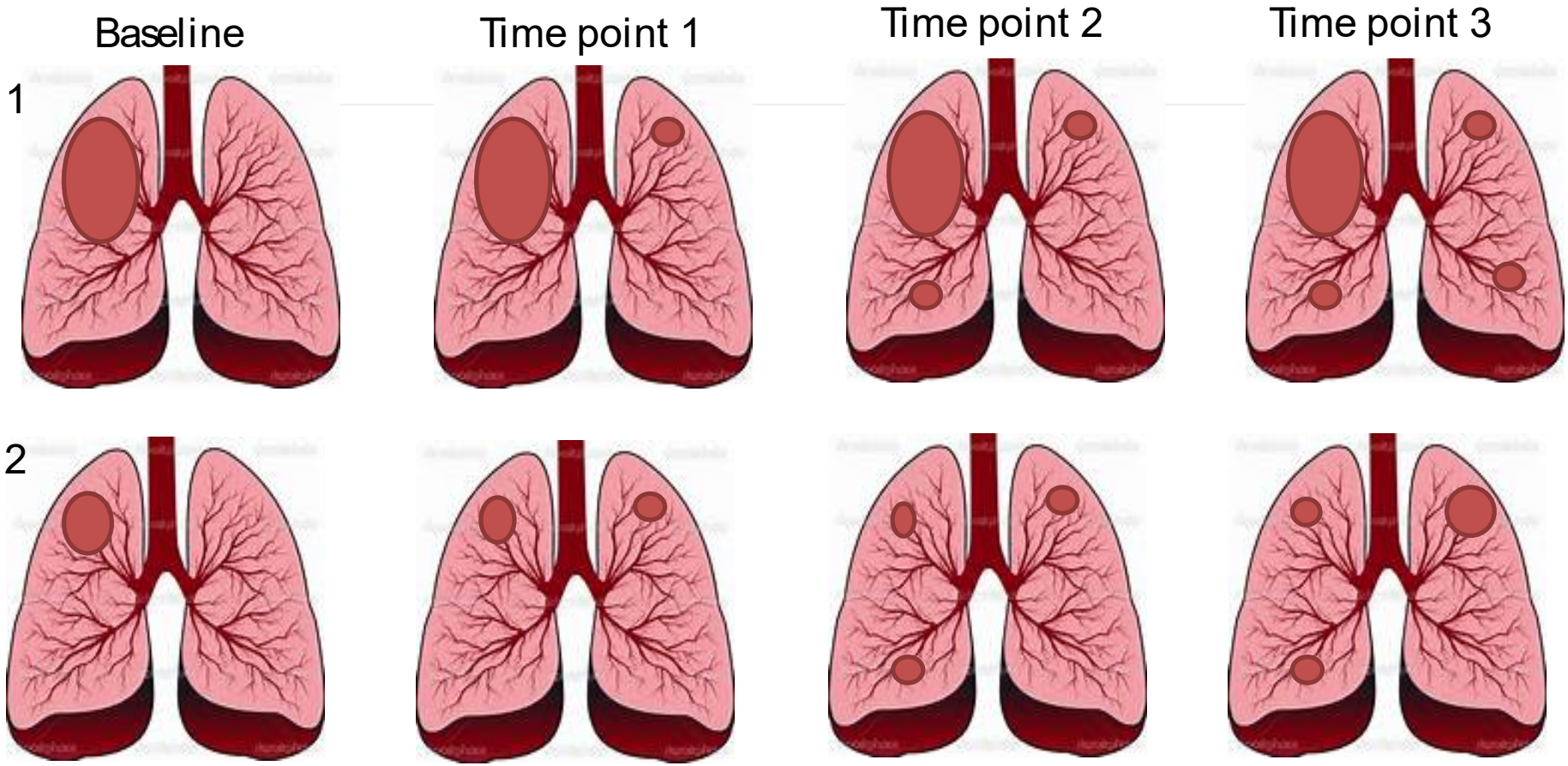

Is either scenario ‘pseudoprogression’ ?

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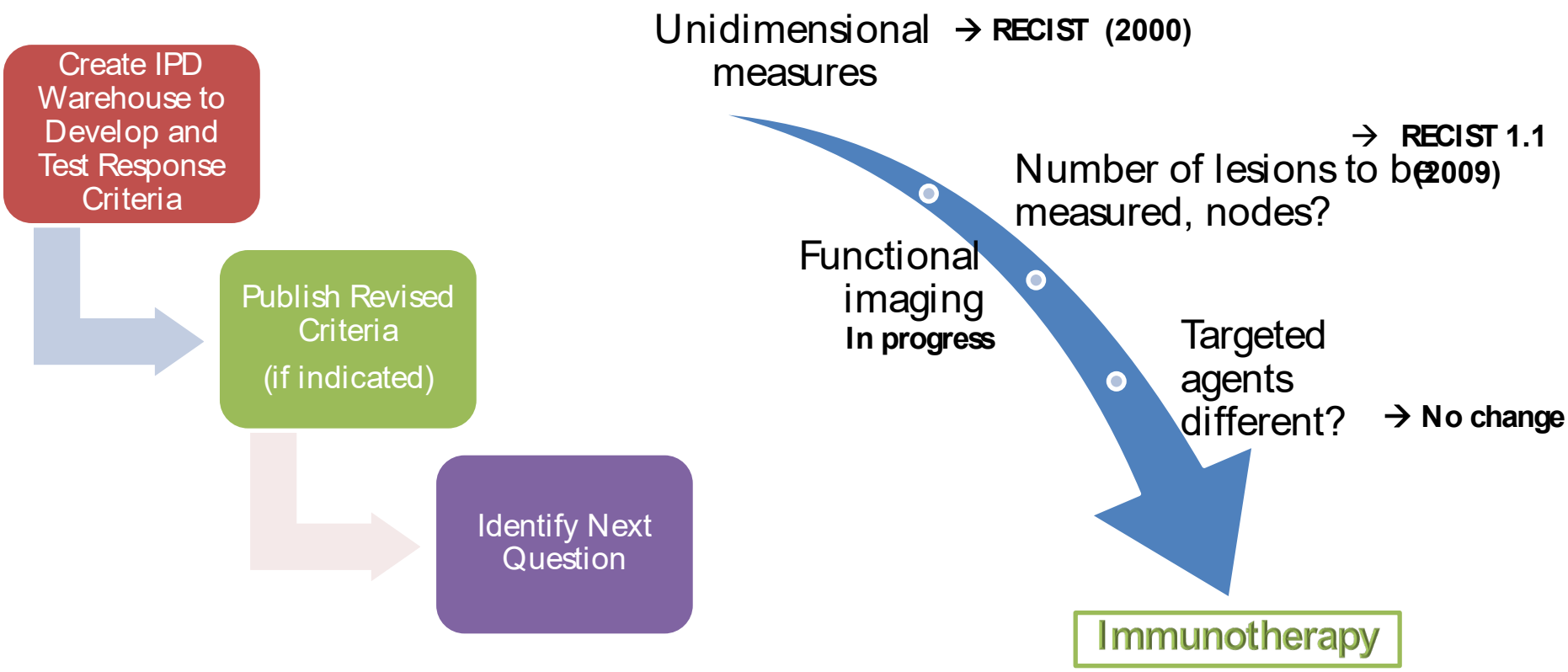
Need for Standardization and validation of Response Criteria

iRECIST

RECIST Working Group Strategy and Activity



Testing and Validating RECIST for Immunotherapy Trials

Initial plan (2012) :

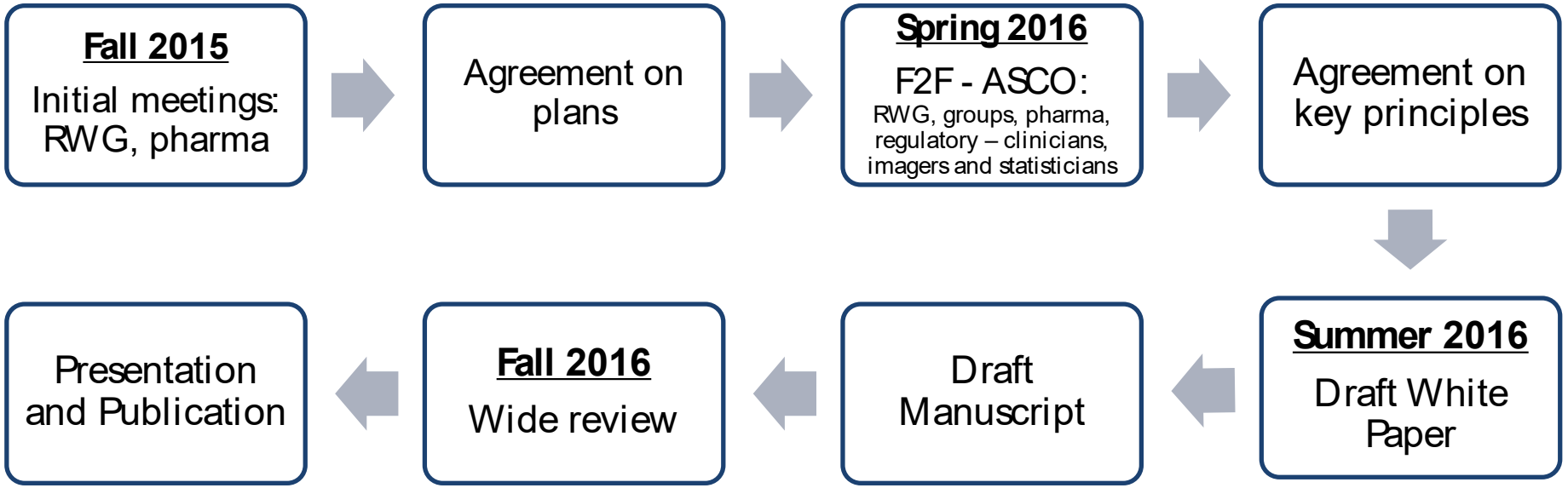
- Create a warehouse
- Validate RECIST 1.1 and / or publish new criteria

- Became apparent there were multiple similar, but distinct, interpretations of immune response criteria

Testing and Validating RECIST for Trials of Immunotherapy

- Revised plan
  - Standardise data management and collection - develop consensus guidelines (termed iRECIST)
  - Create IPD warehouse and validate criteria
    - If necessary publish updated RECIST (2?)

Development of iRECIST Guideline



Data collection ongoing and validation planned in the coming 1-2 years

iRECIST

KEY POINTS

What is iRECIST?

- Consensus guidelines developed by the RECIST Working Group, pharma, regulatory authorities and academia to ensure consistent design and data collection in order to prospectively create a data warehouse to be used to validate iRECIST or update RECIST
- iRECIST is a data management approach, not (yet) validated response criteria - will be used as exploratory endpoints usually
- iRECIST are not treatment decision guidelines
- iRECIST is based on RECIST 1.1
- Nomenclature: responses assigned using iRECIST have “i” prefix

iRECIST vs RECIST 1.1: **Unchanged**

RECIST 1.1	iRECIST
Definitions of measurable, non-measurable disease	√
Definitions of target (T) and non target (NT) lesions	√
Measurement and management of nodal disease	√
Calculation of the sum of measurement (SOM)	√
Definitions of complete (CR) and partial response (PR), stable disease (SD) and their duration	√
Confirmation of CR and PR and when applicable	√
Definition of progression in T and NT (iRECIST terms i-unconfirmed progression (iUPD))	√

iRECIST vs RECIST 1.1: **Changed**

RECIST 1.1	iRECIST
Management of new lesions	NEW
Time point response after RECIST 1.1 progression	NEW
Confirmation of progression required	NEW
Collection of reason why progression cannot be confirmed	NEW
Inclusion and recording of clinical status	NEW

iRECIST vs RECIST 1.1: **New Lesions**

New lesions (NL) are assessed using RECIST 1.1 principles:

- Classified as measurable or non-measurable
- Up to 5 (2 per site) measured (but not included in the sum of measurements of target lesions identified at baseline) and recorded as new lesions target (NL-T) with an i-sum of measurements (iSOM)
- Other new lesions (measurable/non-measurable) are recorded as new lesions non-target (NL-NT)
- New lesions do not have to resolve for subsequent iSD or iPR providing that the next assessment did not confirm progression

iRECIST vs RECIST 1.1: **Time Point Response**

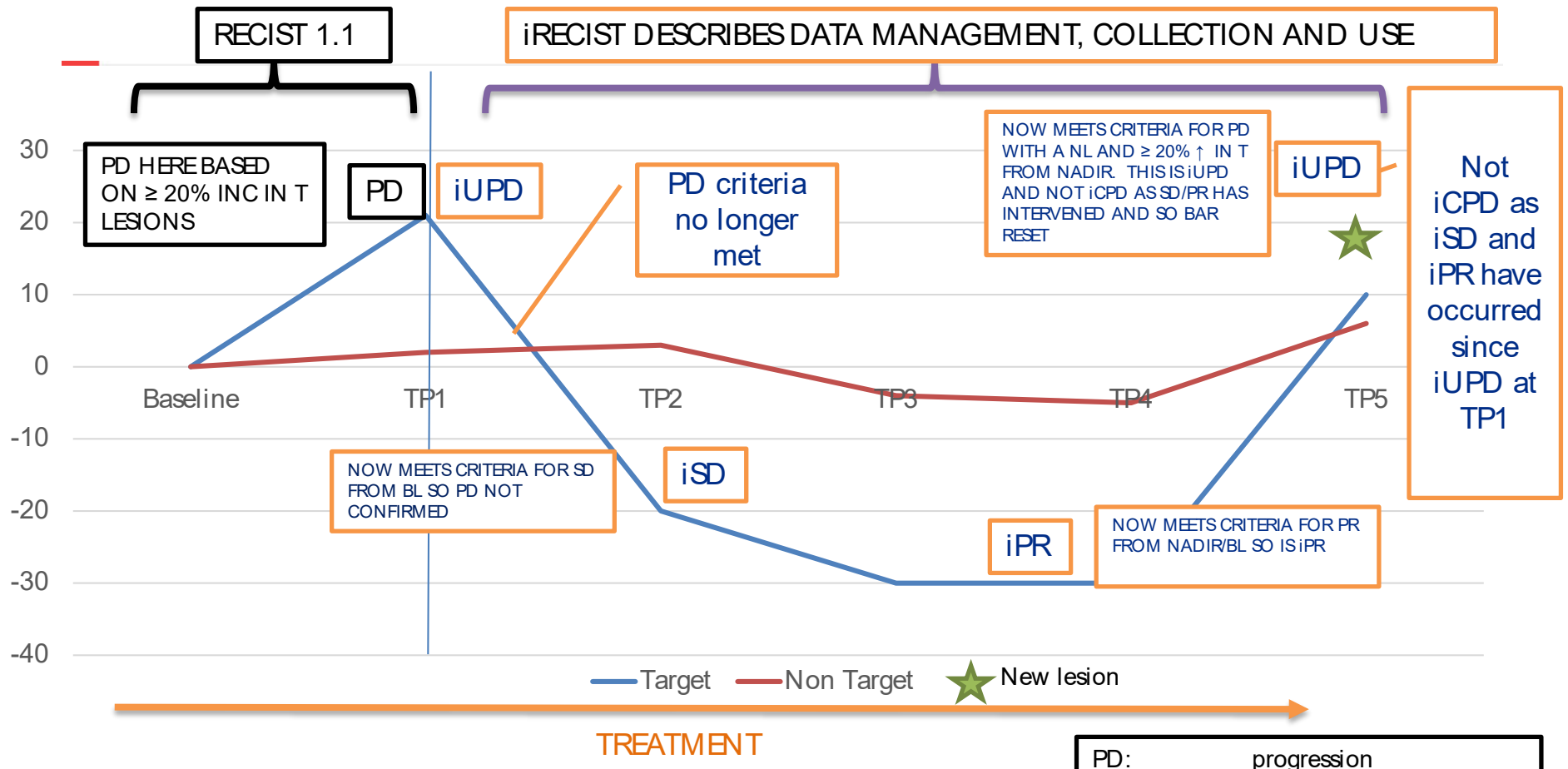
- In iRECIST there can be iSD, iPR or iCR after RECIST 1.1 PD
  - 'once a PD always a PD' is no longer the case
  - First RECIST 1.1 PD is "unconfirmed" for iRECIST – termed iUPD
  - iUPD must be confirmed at the next assessment (4-8 weeks)
  - If confirmed, termed iCPD
- Time point response is dynamic and based on:
  - Change from baseline (for iCR, iPR, iSD) or change from nadir (for PD)
  - The last i-response

iRECIST vs RECIST 1.1: **Progression**

- Treatment past RECIST 1.1 PD should only be considered if patient clinically stable*
  - No worsening of performance status.
  - No clinically relevant ↑in disease related symptoms
  - No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)
- Record the reason iUPD not confirmed
  - Not stable
  - Treatment stopped but patient not reassessed/imaging not performed
  - iCPD never occurs
  - Patient has died

* recommendation – may be protocol specific

Example of iUPD



* iSD and iPR occur AFTER iUPD
* iUPD occurs again and must be confirmed

PD:	progression
iSD:	stable disease
iPR:	partial disease
iUPD:	unconfirmed progression
TP:	time point

iRECIST: **Confirming Progression (iCPD) #1**

- There are two ways:
  - Existing iUPD "gets worse"
  - Lesion category without iUPD now meets the (RECIST 1.1) criteria for PD

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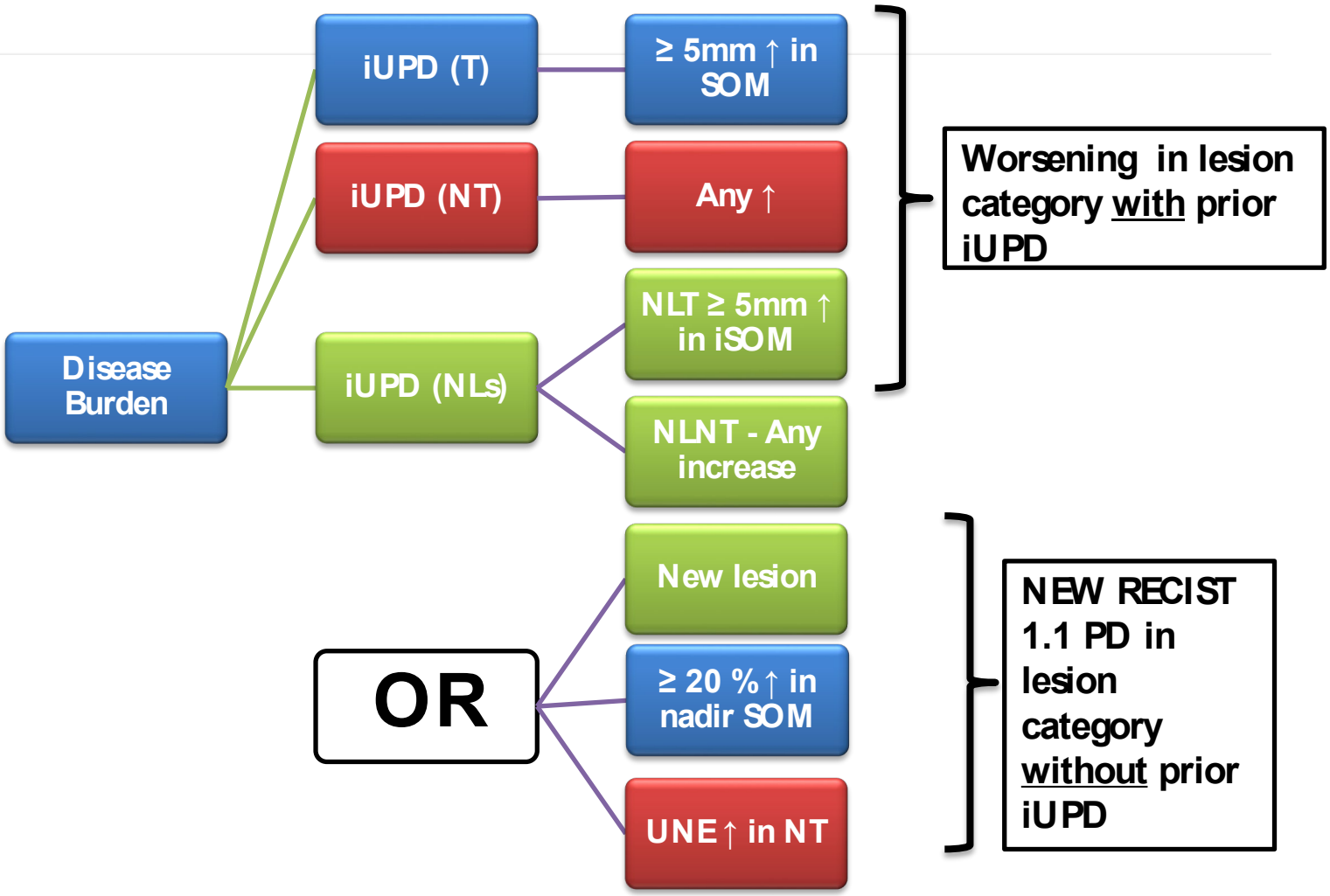
Confirming Progression (iCPD) # 2



T: target lesions
NT: non-target lesions
NL: new lesions
NLT: new lesions – target
NLNT: new lesion – non target
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
SOM: sum of measurements
UNE: unequivocal

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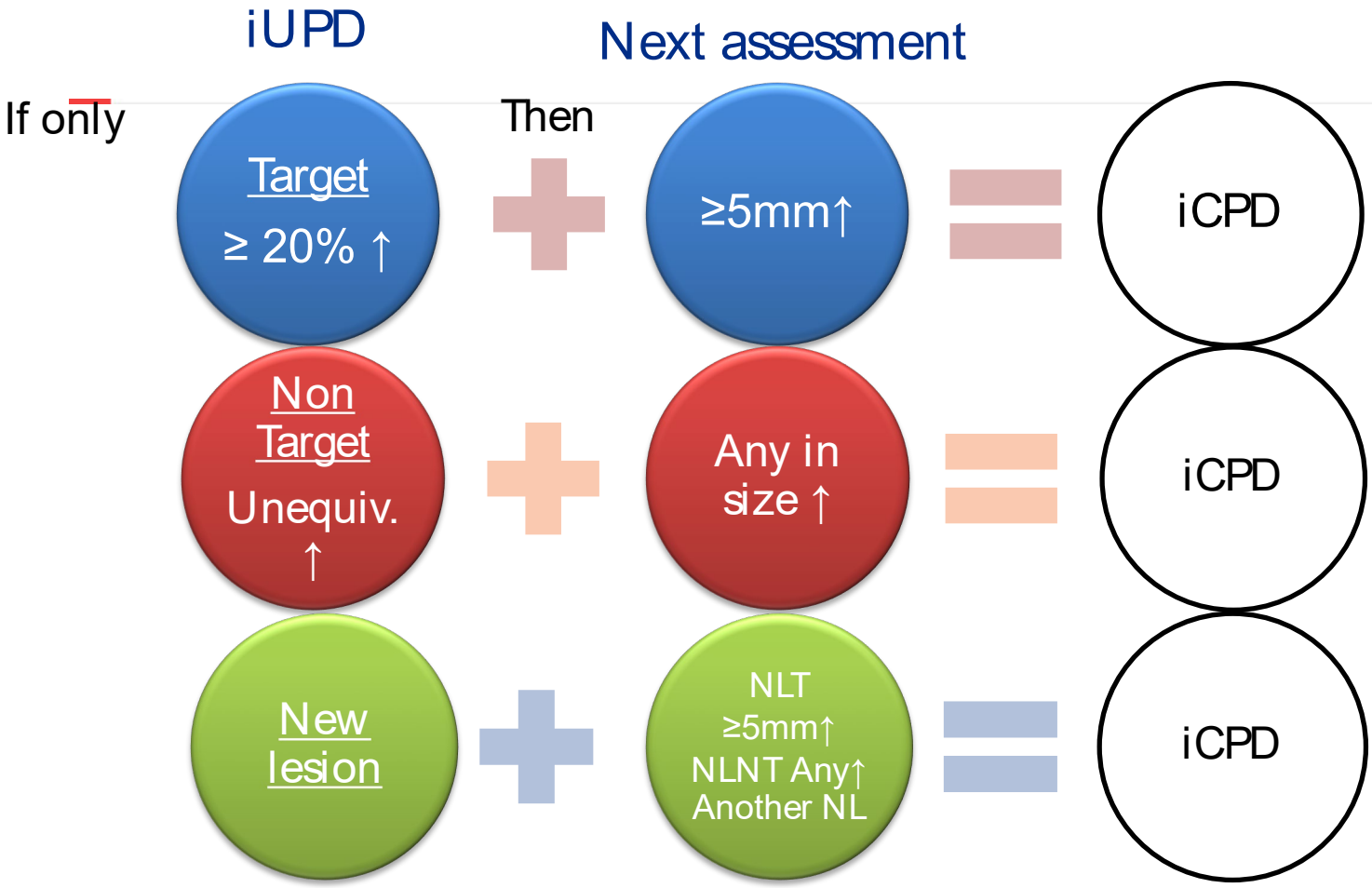
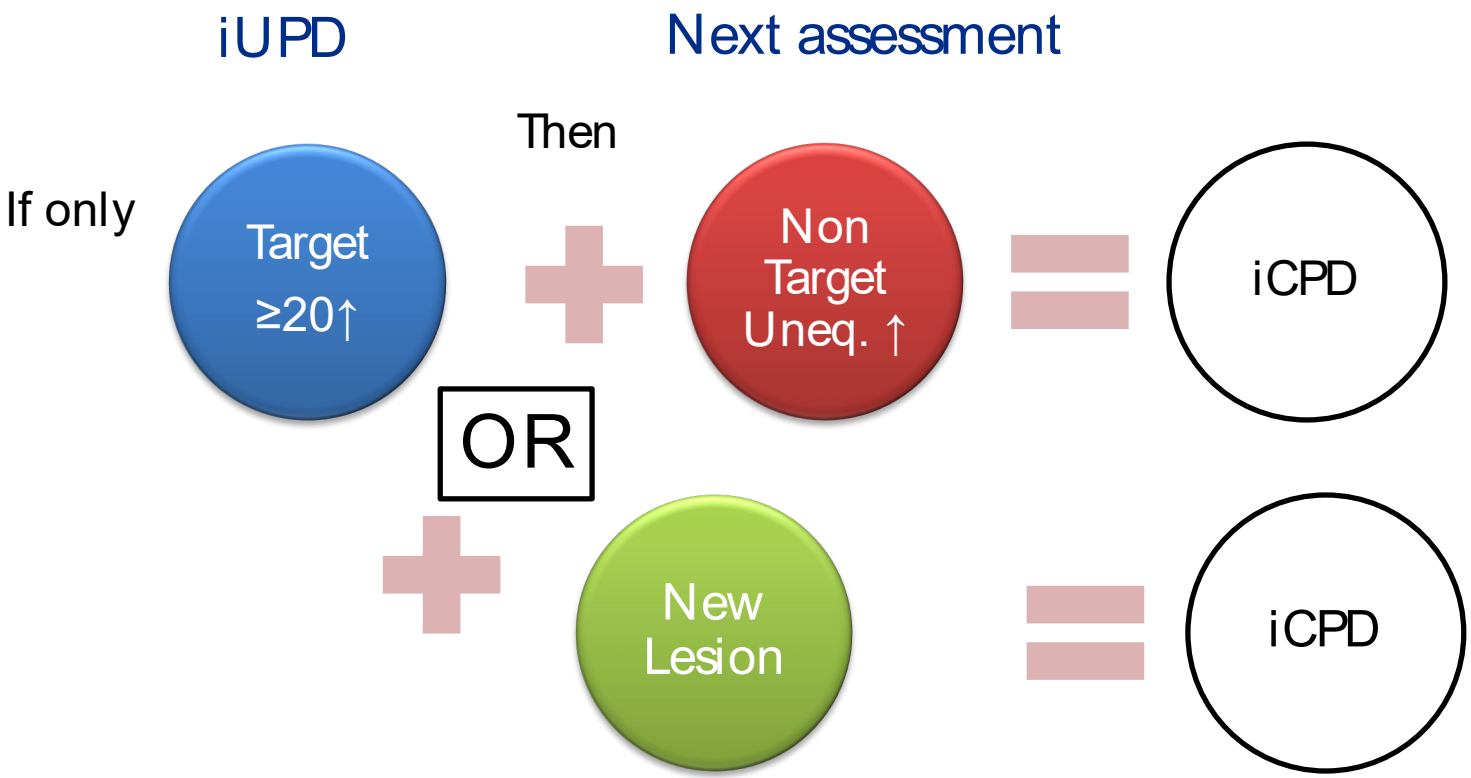
Confirming Progression (iCPD) # 3



iCPD in Lesion Category with iUPD

T: target lesions
NT: non-target lesions
NL: new lesions
NLT: new lesions – target
NLNT: new lesion – non target
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
SOM: sum of measurements
UNE: unequivocal

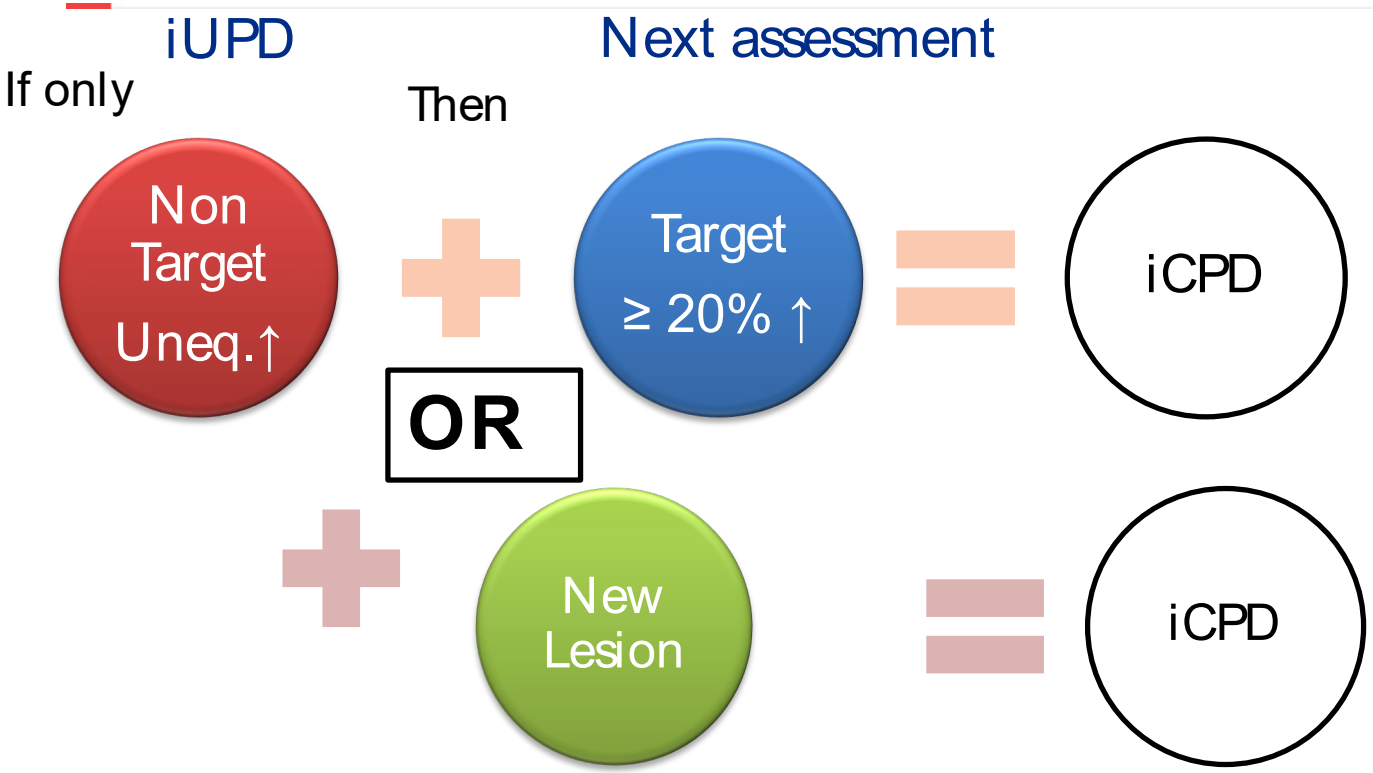
Confirming Progression (iCPD) # 4



New RECIST PD in <u>another</u> Lesion Category (previously stable or better)

T: target lesions
NT: non-target lesions
NL: new lesions
NLT: new lesions – target
NLNT: new lesion – non target
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
SOM: sum of measurements
UNE: unequivocal

Confirming Progression (iCPD) # 5



New RECIST PD in another Lesion Category (previously stable or better)

T: target lesions
NT: non-target lesions
NL: new lesions
NLT: new lesions – target
NLNT: new lesion – non target
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
SOM: sum of measurements
UNE: unequivocal

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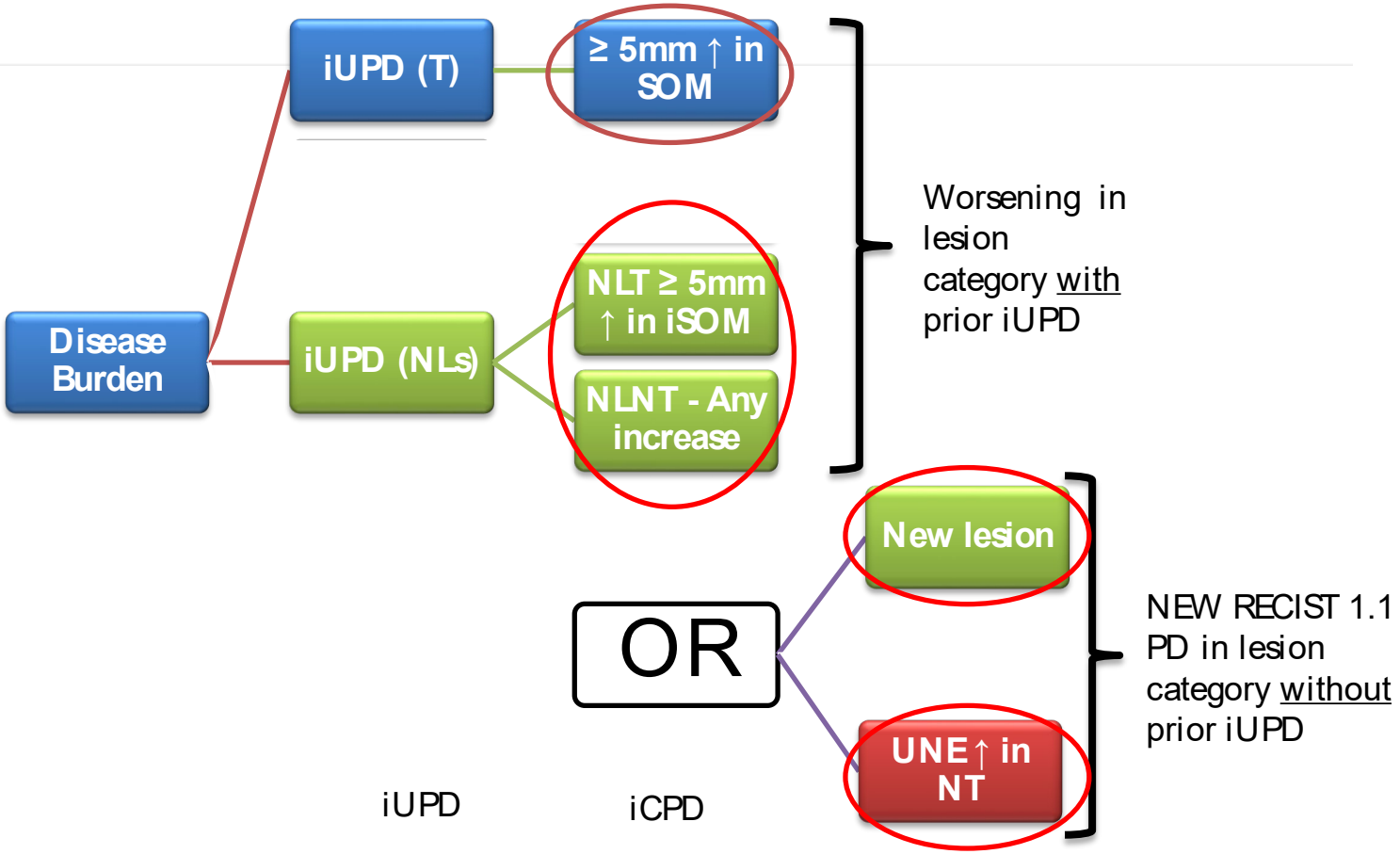
Confirming Progression (iCPD) # 6



T: target lesions
NT: non-target lesions
NL: new lesions
NLT: new lesions – target
NLNT: new lesion – non target
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
SOM: sum of measurements
UNE: unequivocal

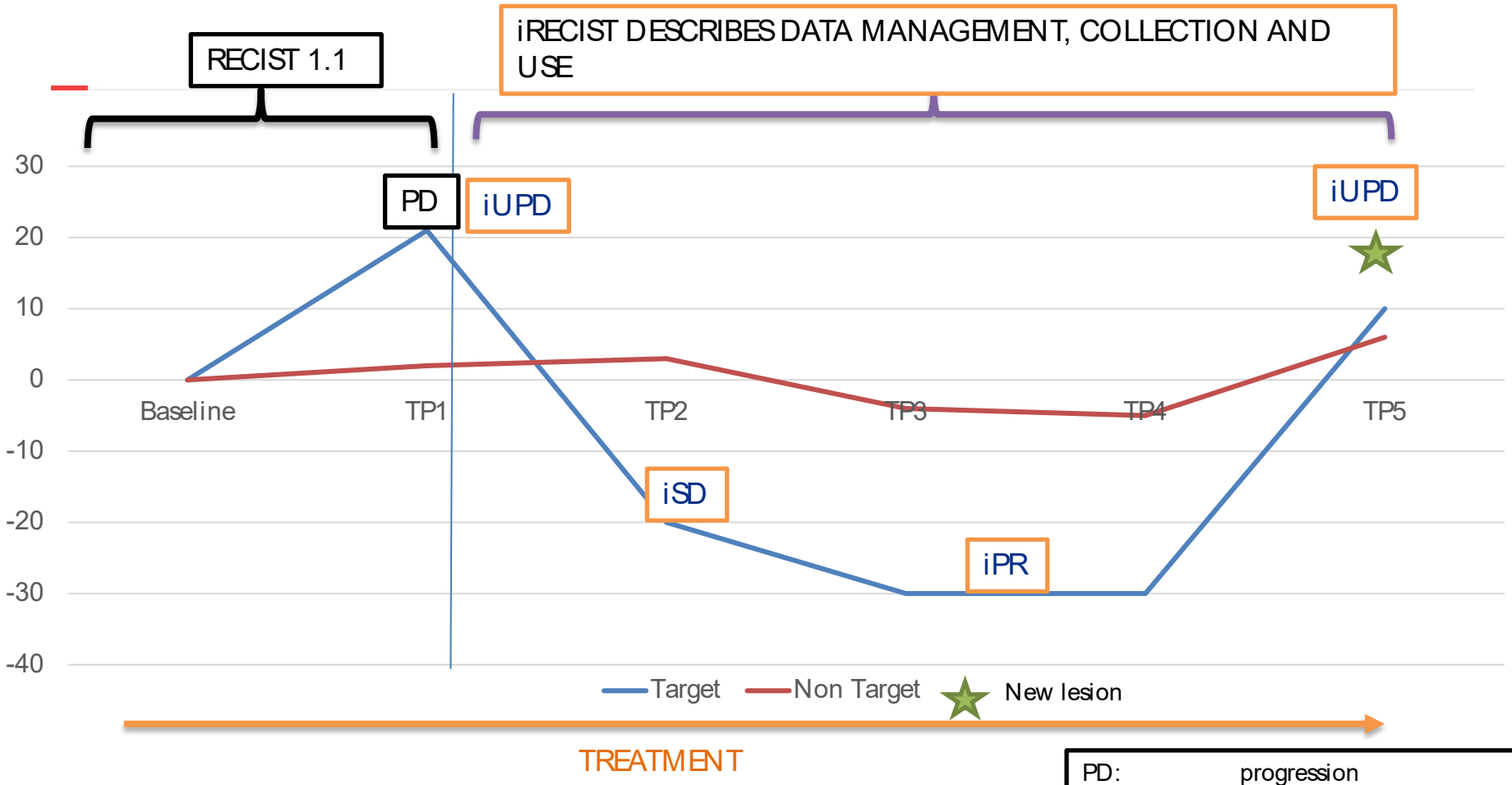
Four ways to confirm progression (iCPD)

Confirming Progression (iCPD) # 7

Notes: assigning PD in iRECIST:

- Must be the NEXT assessment – if iSD, iPR or iCR intervenes then bar is reset and iUPD must occur again and be confirmed.
- Two ways to confirm
  - Existing iUPD gets worse – "low bar"
  - Lesion category without prior iUPD now meet RECIST 1.1 criteria for PD – "RECIST PD"
- If confirmatory scans not done must document reason why

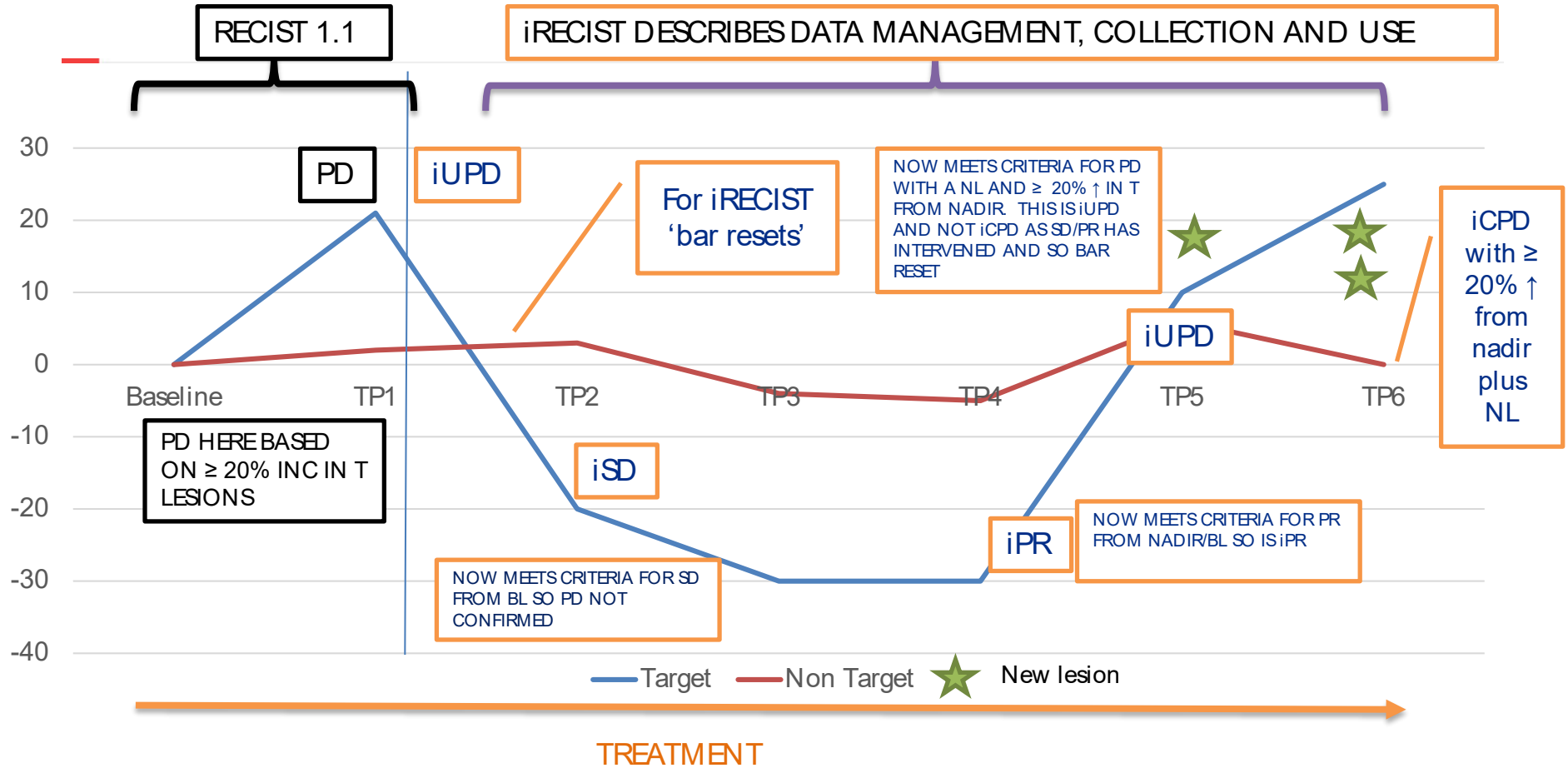
Confirming Progression (iCPD) # 8a



iUPD in T lesion plus a new lesion

PD:	progression
iSD:	stable disease
iPR:	partial disease
iUPD:	unconfirmed progression
TP:	time point

Confirming Progression (iCPD) # 8b



Progression confirmed at time point 6

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EXAMPLES AND SCENARIOS

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

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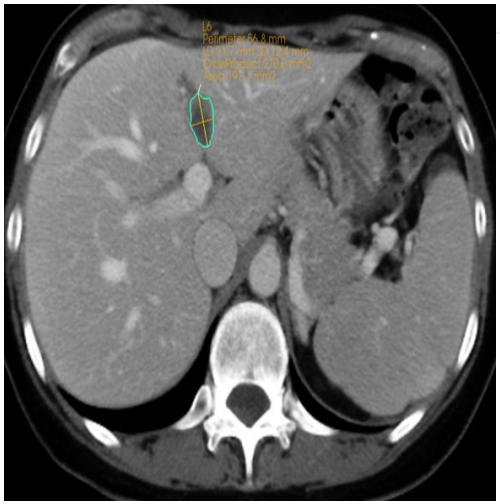
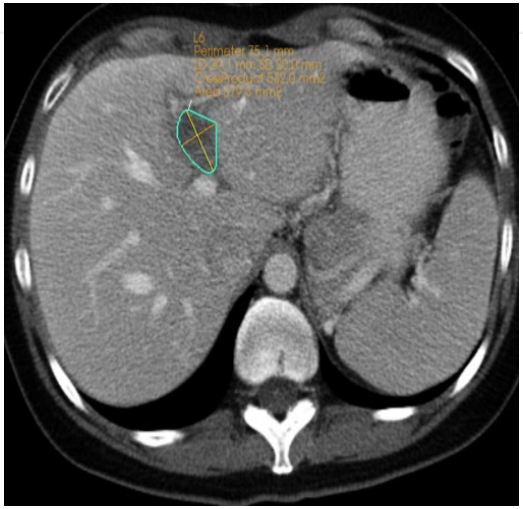
Scenarios: Imaging Examples # 1

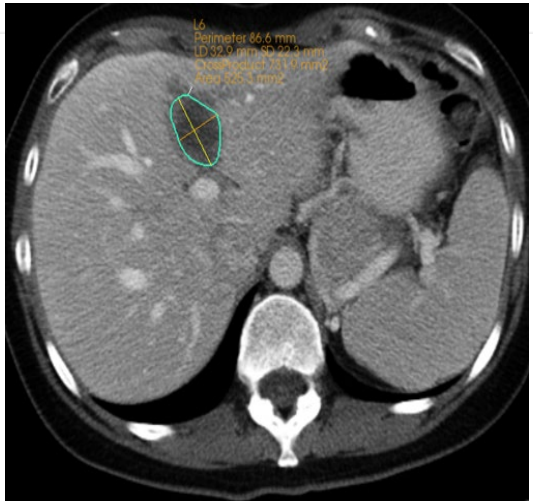


Baseline



TP 1:

- ≥20% ↑ in SOM = **PD by RECIST 1.1**
- **iUPD by iRECIST**
- Clinically stable



TP 2 (4 wks later):

- SOM ↑ ≥ 5mm above iUPD
- **iCPD**

iCPD: Target PD followed by ≥ 5mm↑

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

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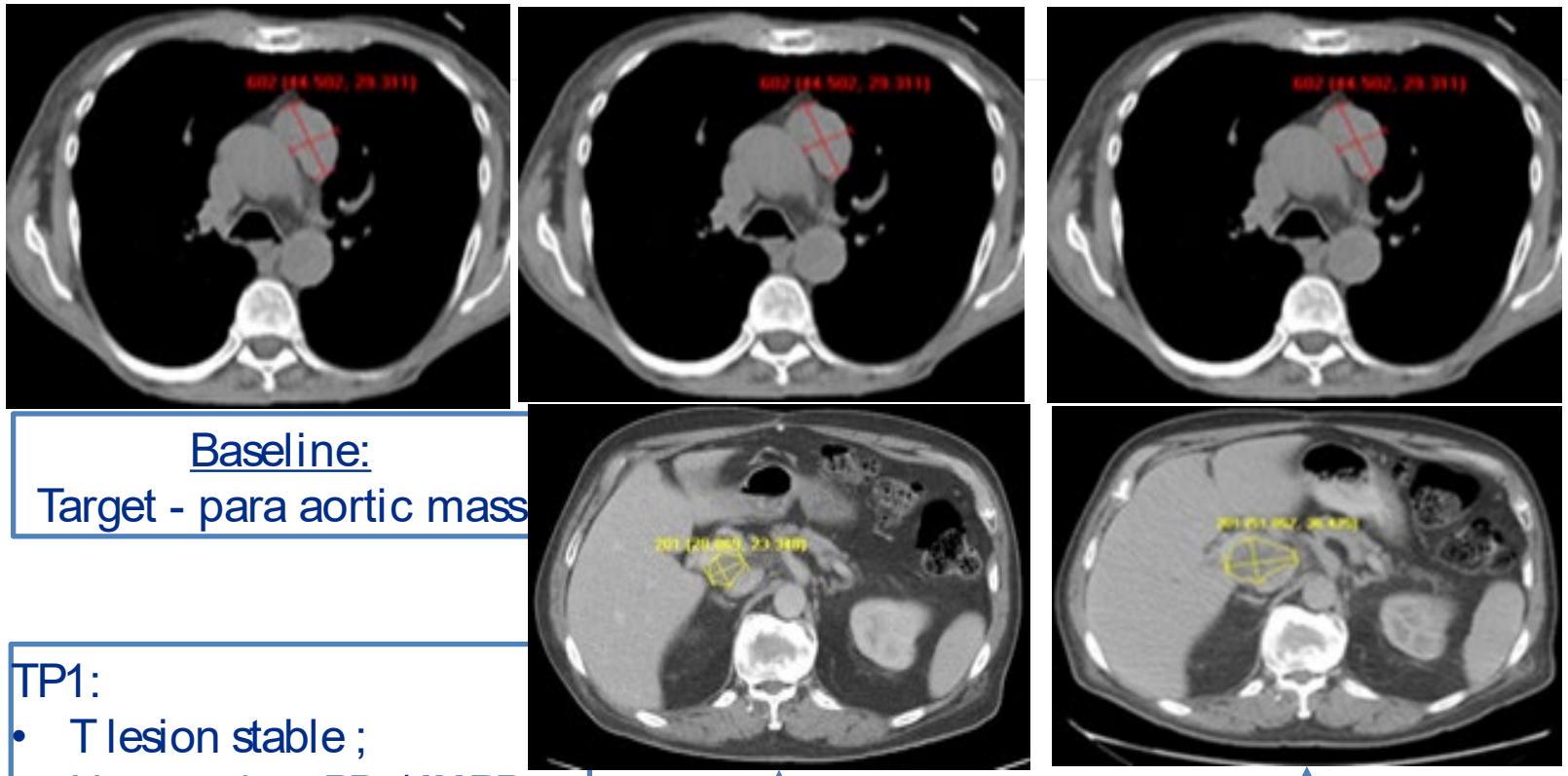
Scenarios: Imaging Examples # 2



Baseline:
Target - para aortic mass

TP1:
- T lesion stable ;
- New node = PD / **iUPD**
- Clinically stable.

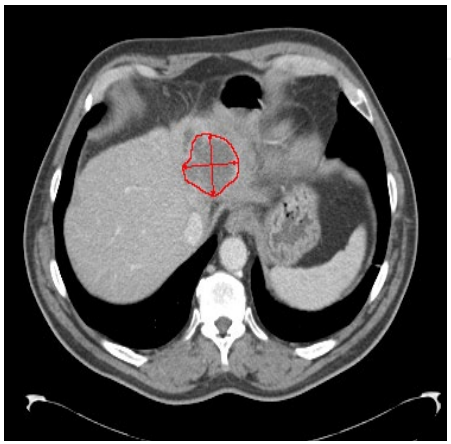
TP2 (+ 4 w):
- T stable,
- NLT ↑ ≥ 5mm
- **iCPD**

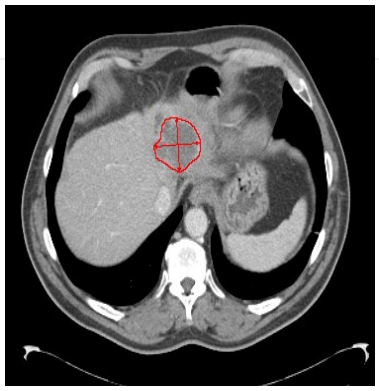
iCPD: New lesion then ≥ 5mm ↑iSOM of NLT

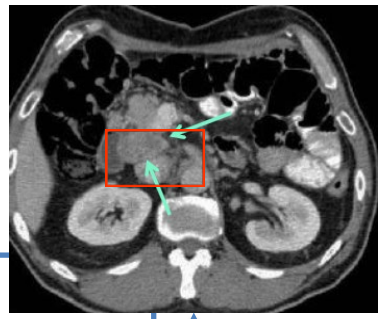
RECIST

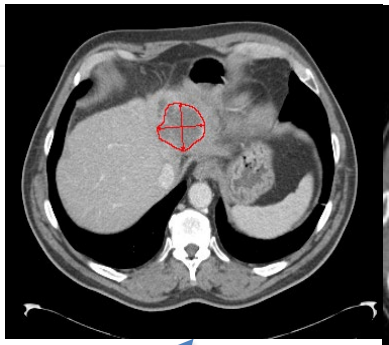
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

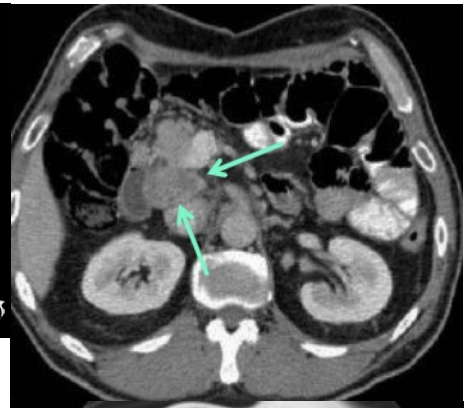
Scenarios: Imaging Examples # 3

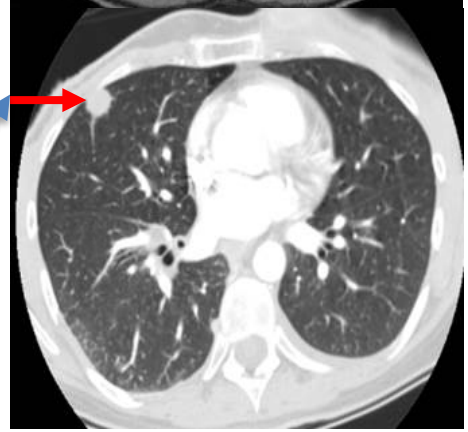












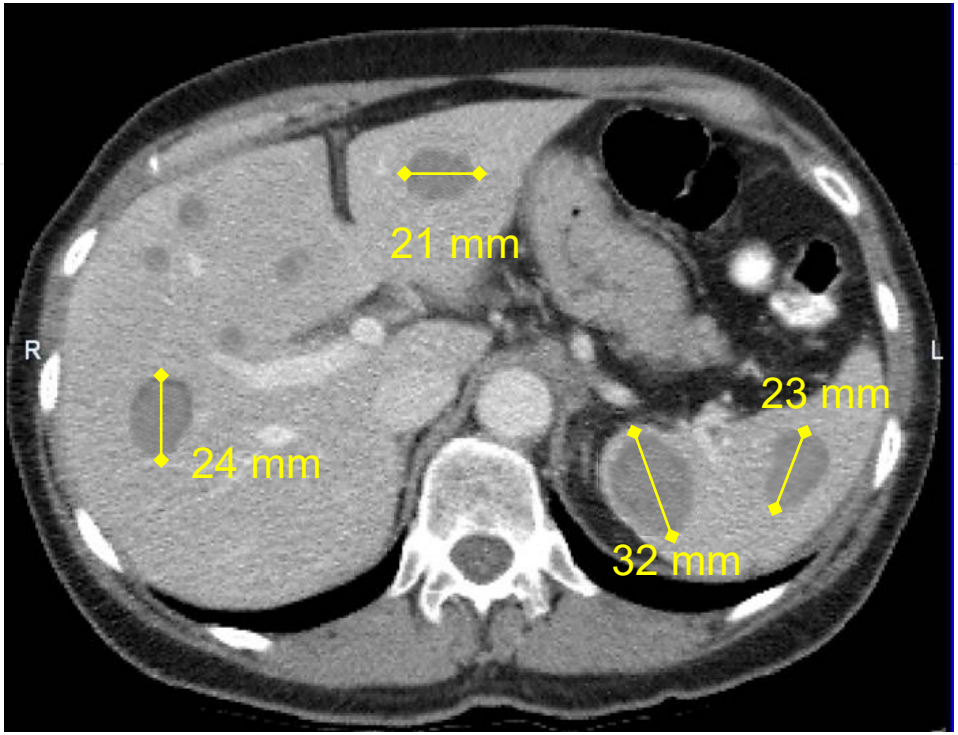
Baseline:
T - liver

TP1:
- New Lesion
- PD / iUPD
- Clinically stable.

TP 2 (+ 4w)
- TL and NLT no change
- Additional NL
- iCPD

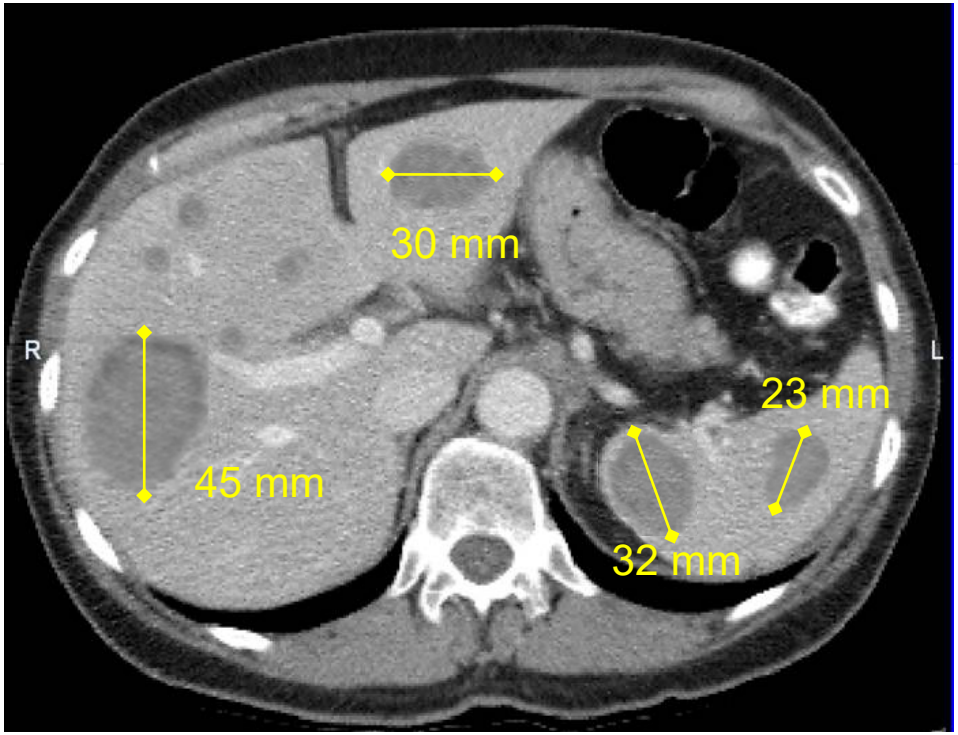
iCPD: New lesion followed by an additional NL

RECIST Scenarios: Imaging Examples # 4a



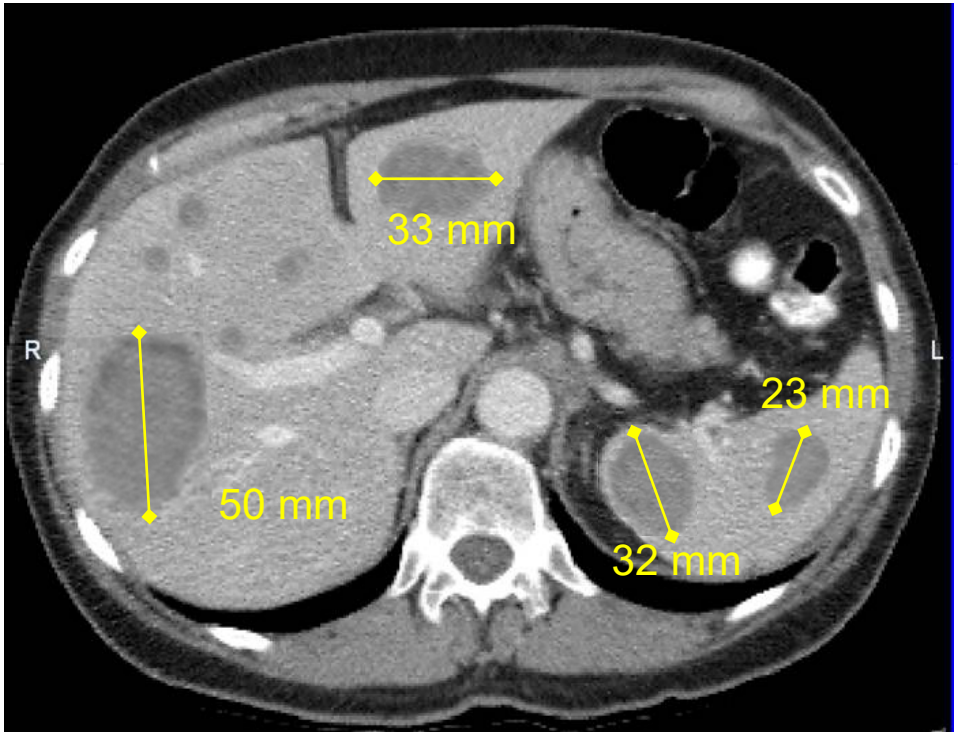
	BL
SOM (mm)	100
TL Resp	N/A

RECIST Scenarios: Imaging Examples # 4b



	BL	V1
SOM (mm)	100	130
TL Resp	N/A	iUPD

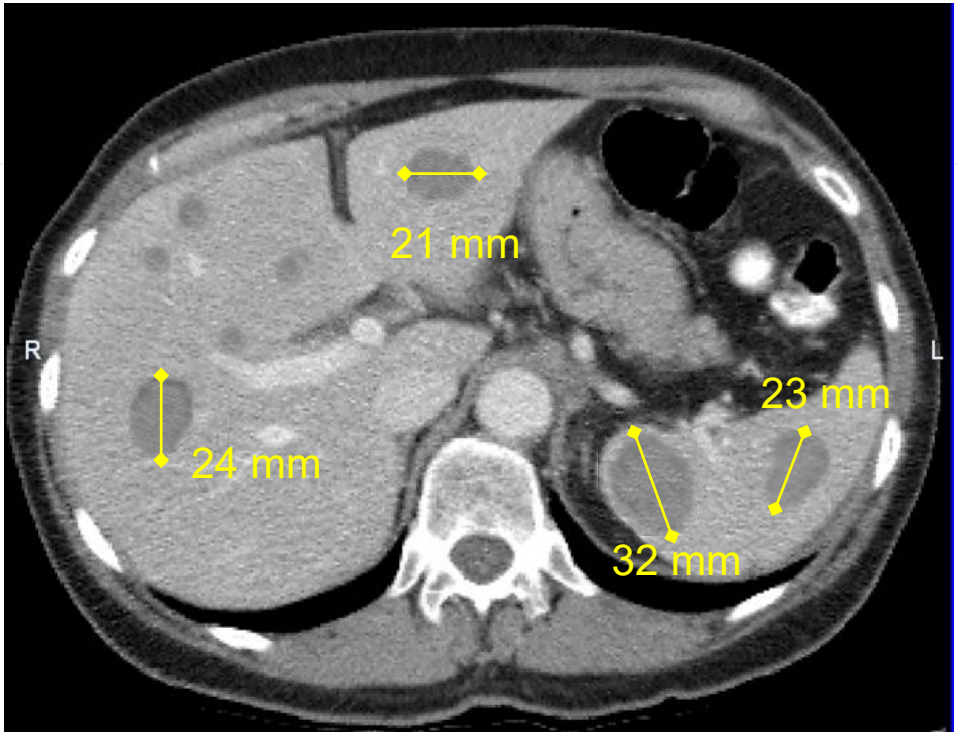
RECIST Scenarios: Imaging Examples # 4c



	BL	V1	V2
SOM (mm)	100	130	138
TL Resp	N/A	iUPD	iCPD

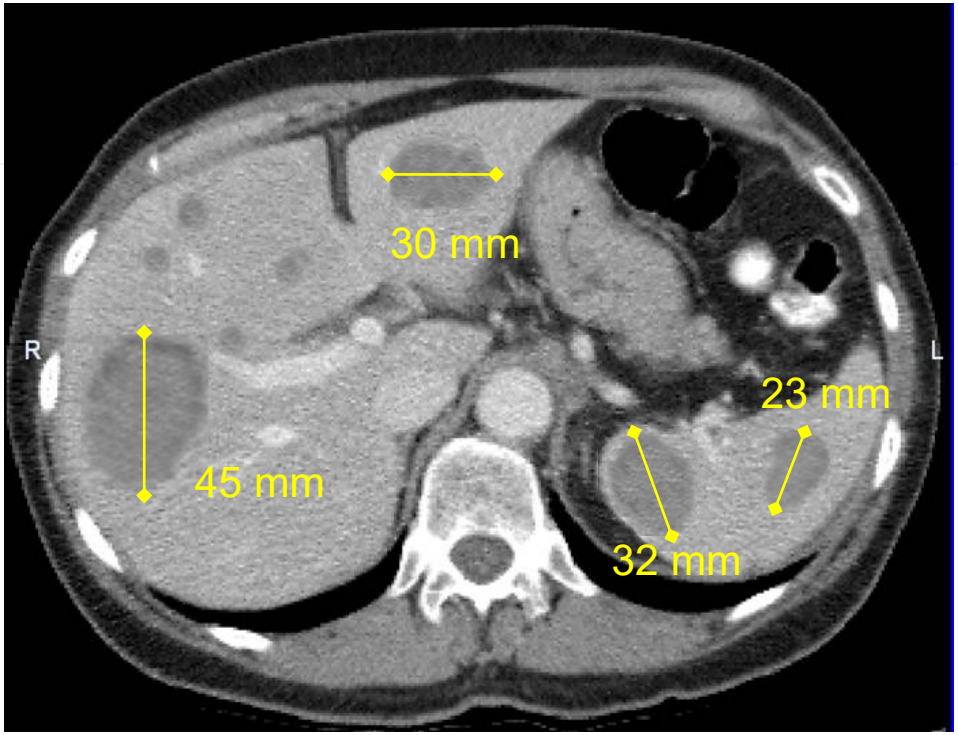
≥5 mm increase

RECIST Scenarios: Imaging Examples # 5a



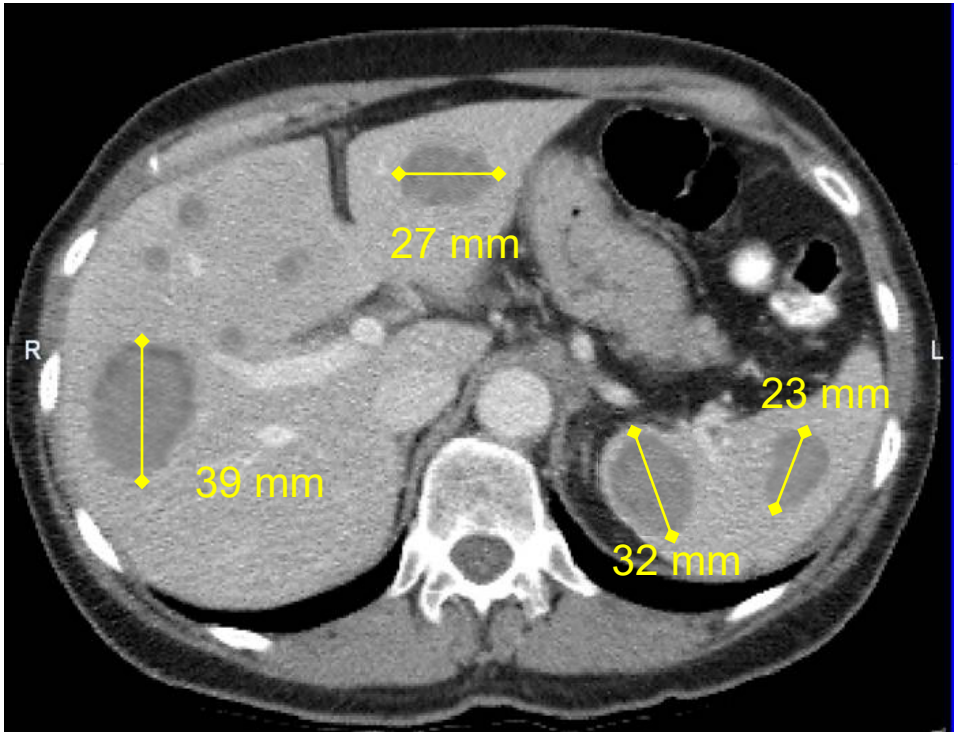
	BL
SOM (mm)	100
TL Resp	N/A

RECIST Scenarios: Imaging Examples # 5b



	BL	V1
SOM (mm)	100	130
TL Resp	N/A	iUPD

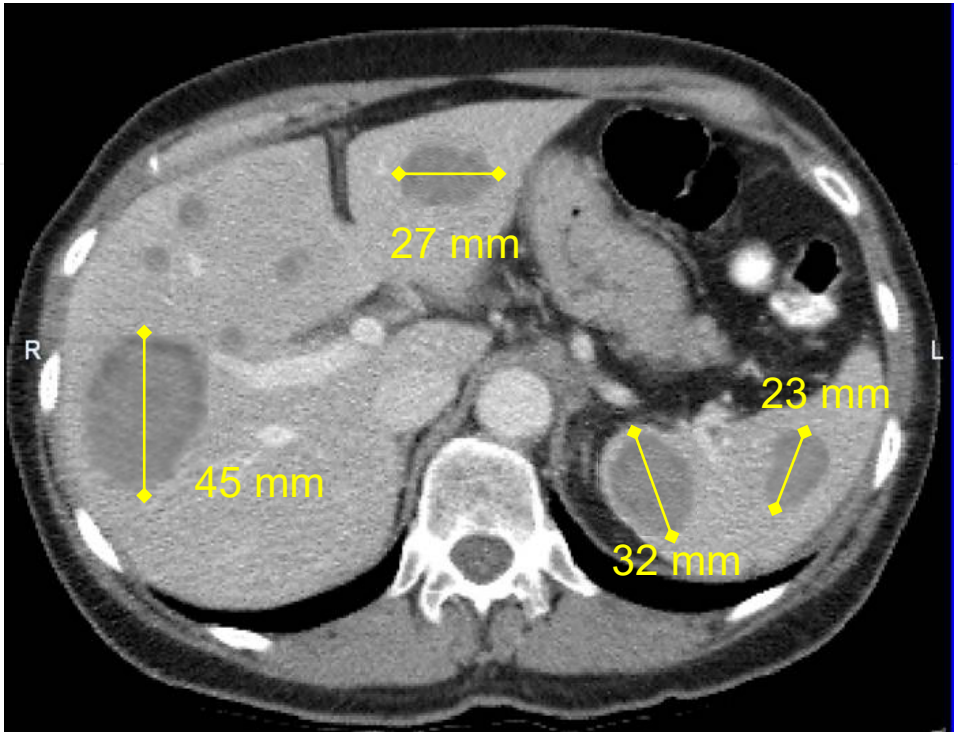
RECIST Scenarios: Imaging Examples # 5c



	BL	V1	V2
SOM (mm)	100	130	121
TL Resp	N/A	iUPD	iUPD

Decreased, still >PD threshold

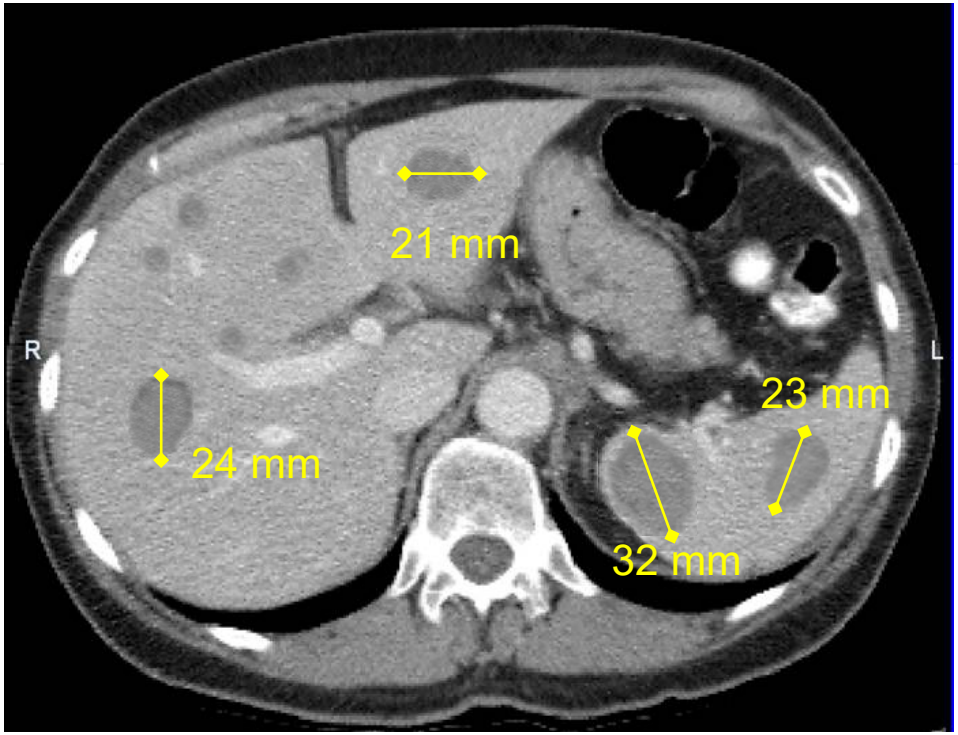
RECIST Scenarios: Imaging Examples # 5d



	BL	V1	V2	V3
SOM (mm)	100	130	121	127
TL Resp	N/A	iUPD	iUPD	iCPD

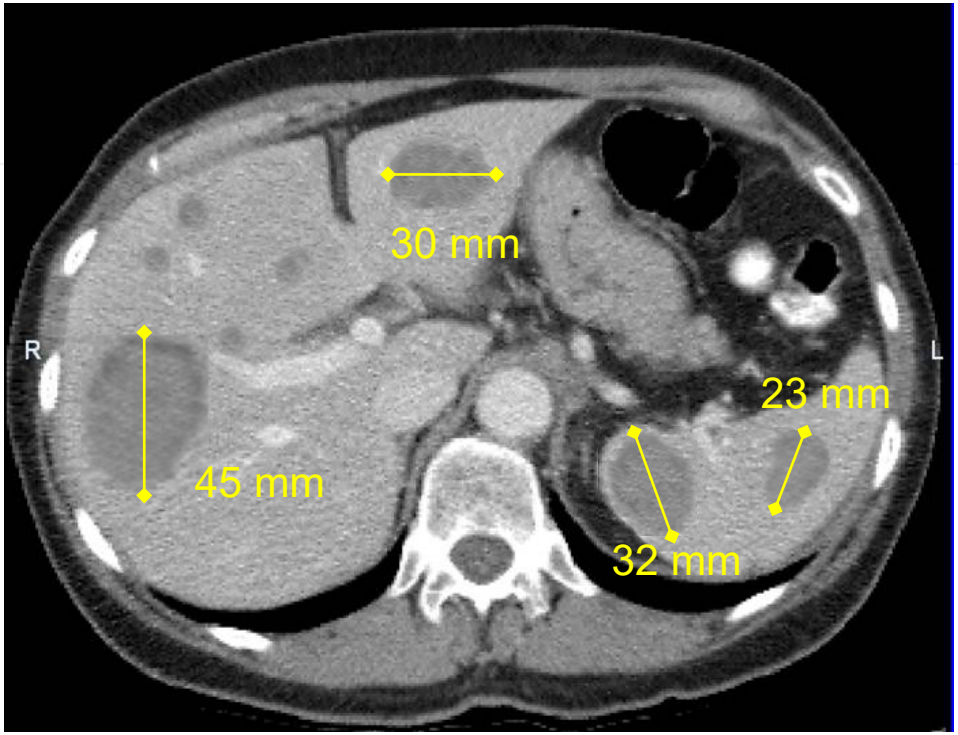
≥5 mm increase

RECIST Scenarios: Imaging Examples # 6a



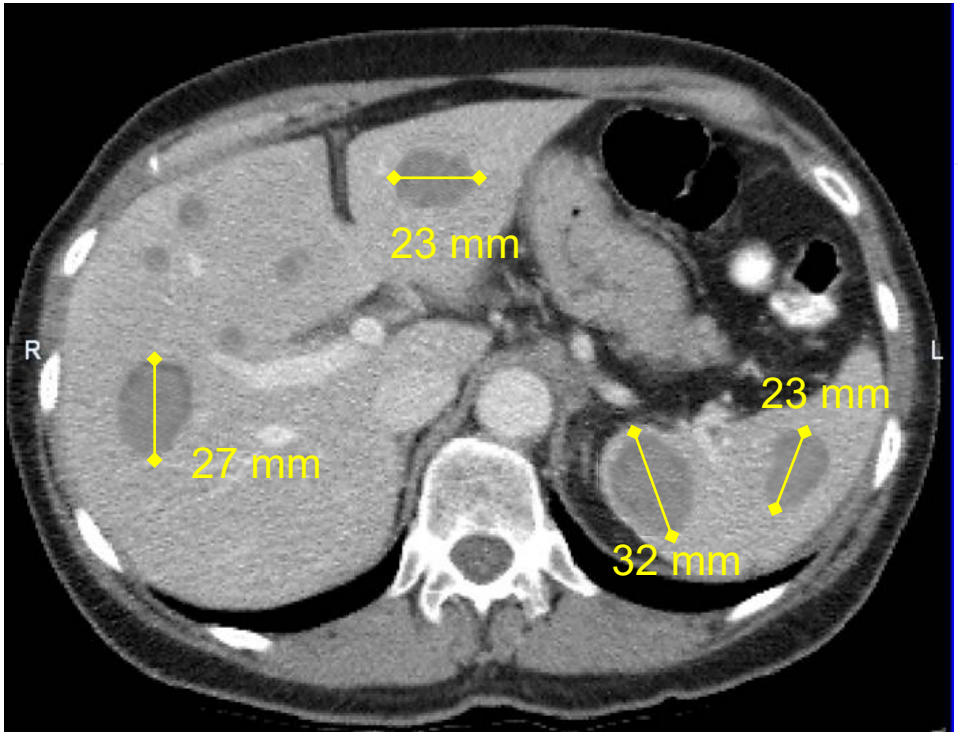
	BL
SOM (mm)	100
TL Resp	N/A

RECIST Scenarios: Imaging Examples # 6b



	BL	V1
SOM (mm)	100	130
TL Resp	N/A	iUPD

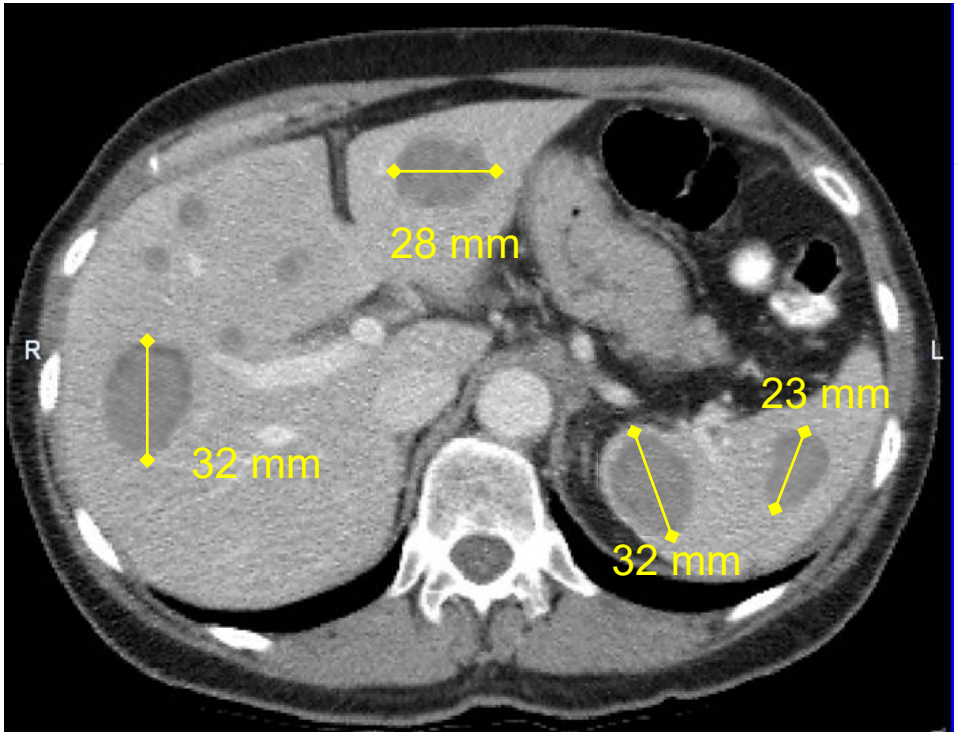
RECIST Scenarios: Imaging Examples # 6c



	BL	V1	V2
SOM (mm)	100	130	105
TL Resp	N/A	iUPD	iSD

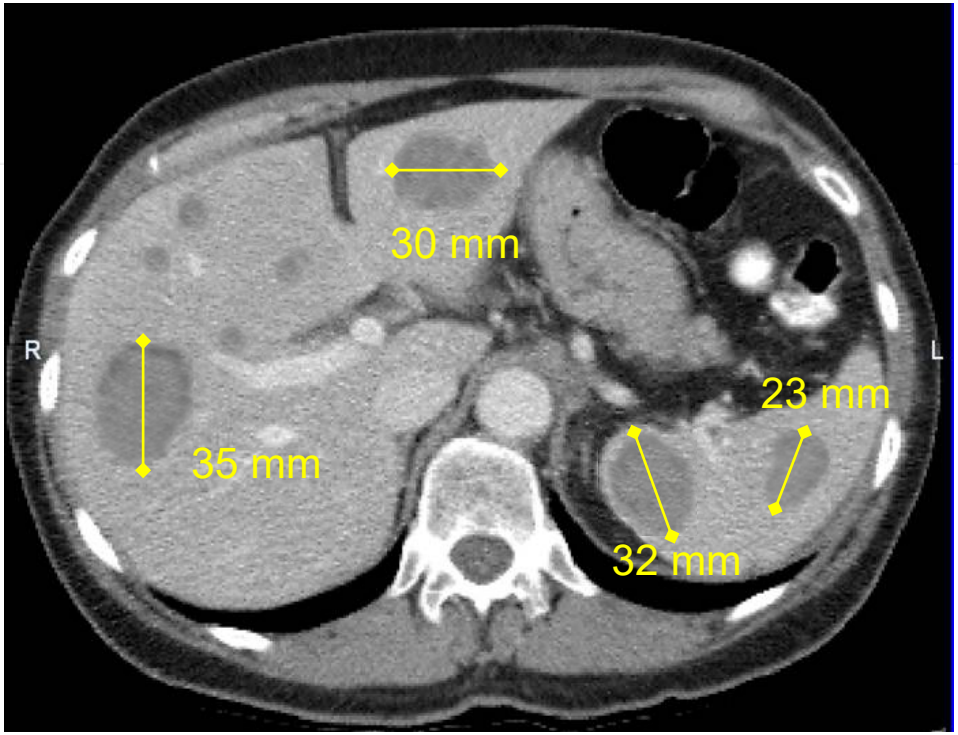
"reset bar"

RECIST Scenarios: Imaging Examples # 6d



	BL	V1	V2	V3
SOM (mm)	100	130	105	115
TL Resp	N/A	iUPD	iSD	iSD

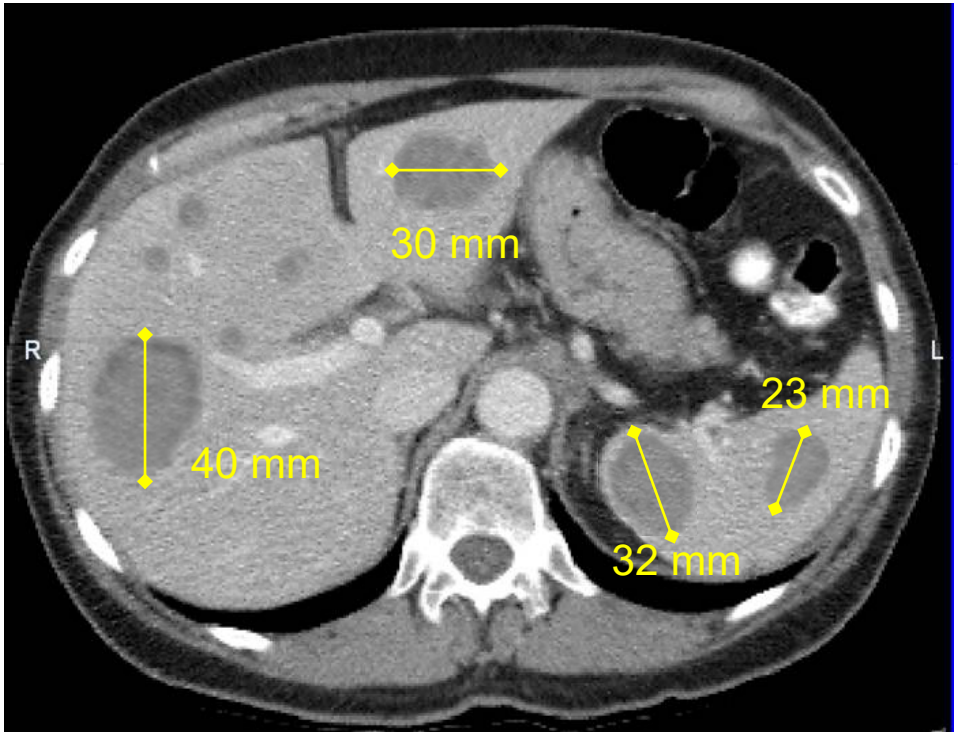
RECIST Scenarios: Imaging Examples # 6e



	BL	V1	V2	V3	V4
SOM (mm)	100	130	105	115	120
TL Resp	N/A	iUPD	iSD	iSD	iUPD

20% above nadir

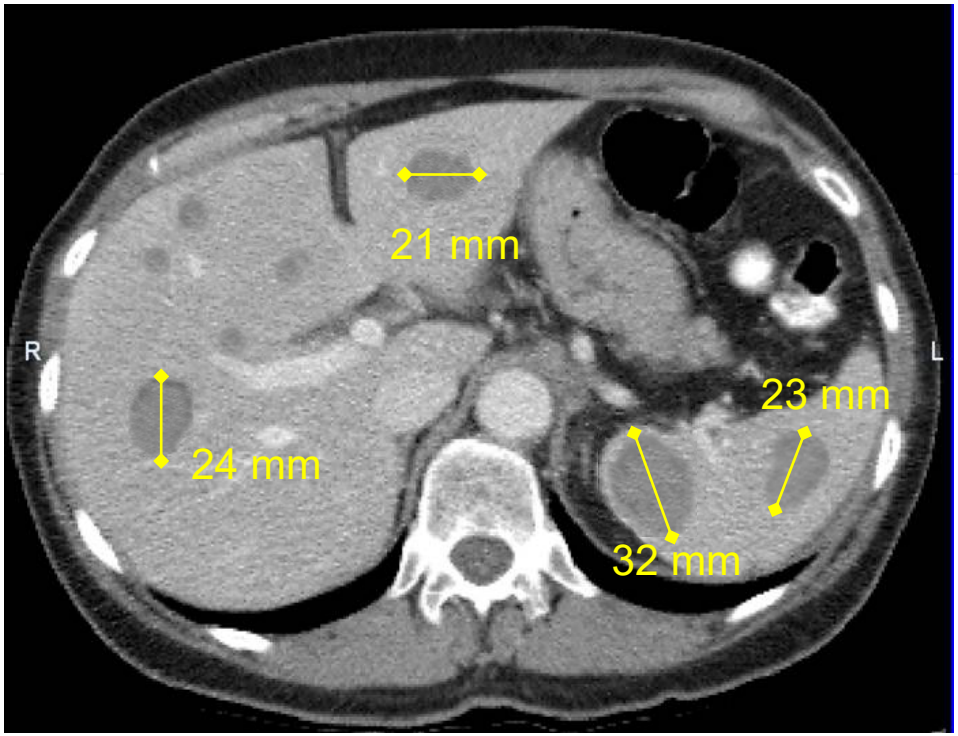
RECIST Scenarios: Imaging Examples # 6f



	BL	V1	V2	V3	V4	V5
SOM (mm)	100	130	105	115	120	125
TL Resp	N/A	iUPD	iSD	iSD	iUPD	iCPD

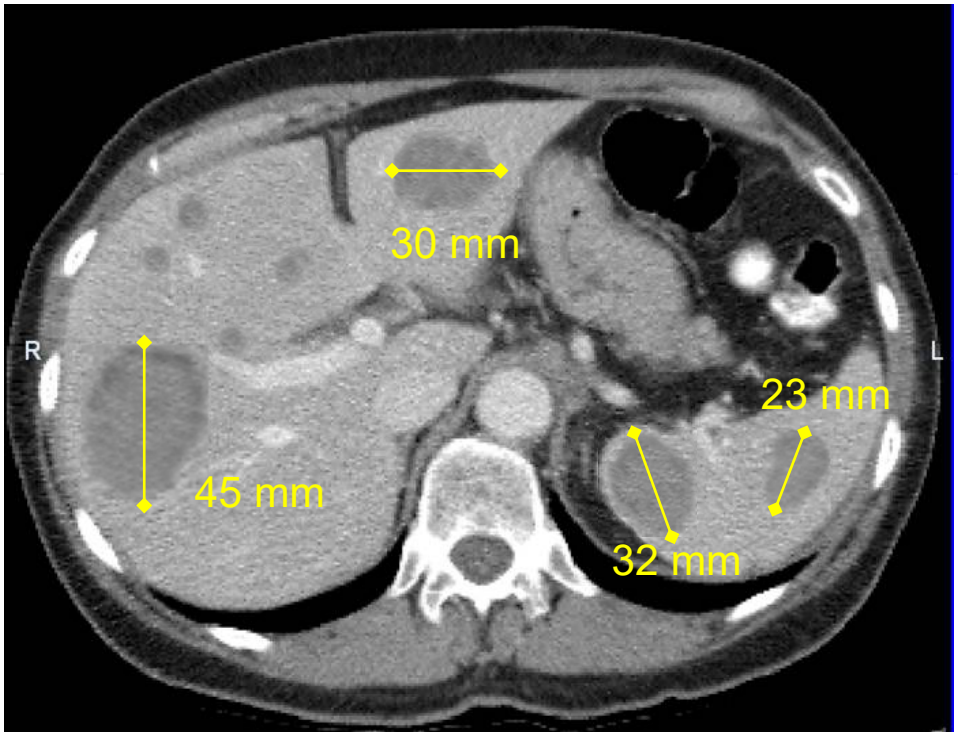
≥5 mm increase

RECIST Scenarios: Imaging Examples # 7a



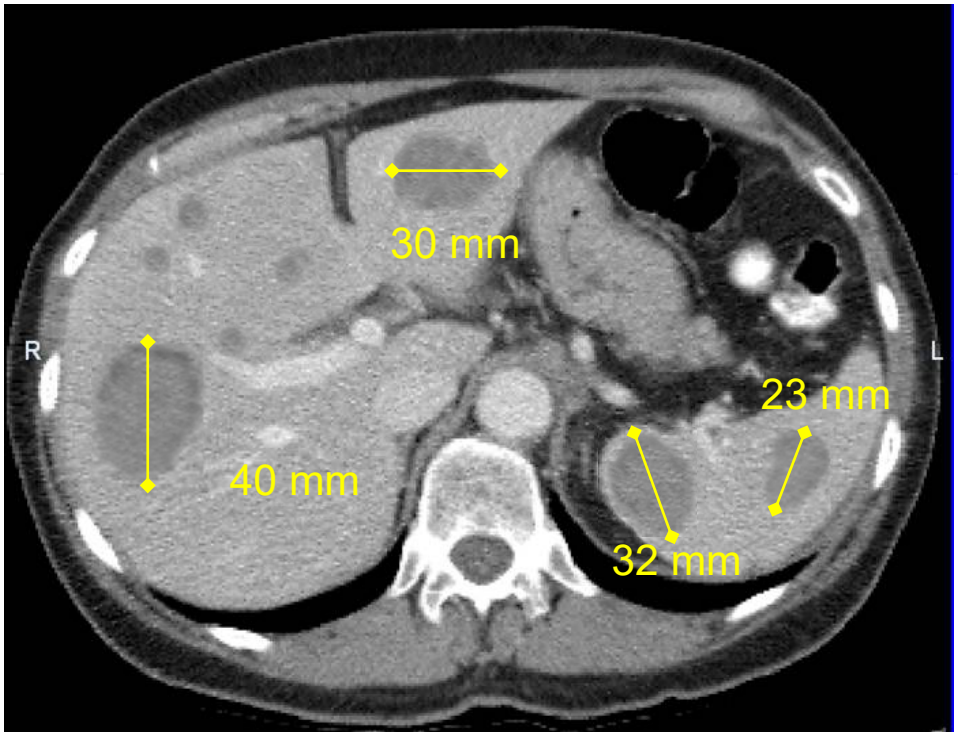
	BL
SOM (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

RECIST Scenarios: Imaging Examples # 7b



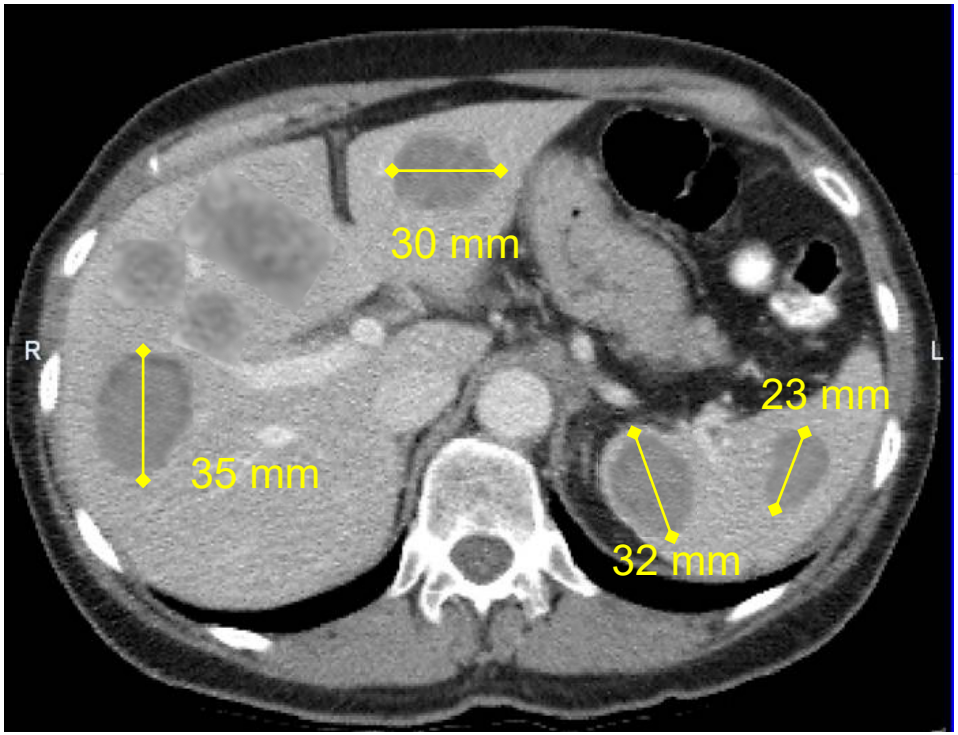
	BL	V1
SOM (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-CR/Non-PD
New		
Overall Resp		iUPD

RECIST Scenarios: Imaging Examples # 7c



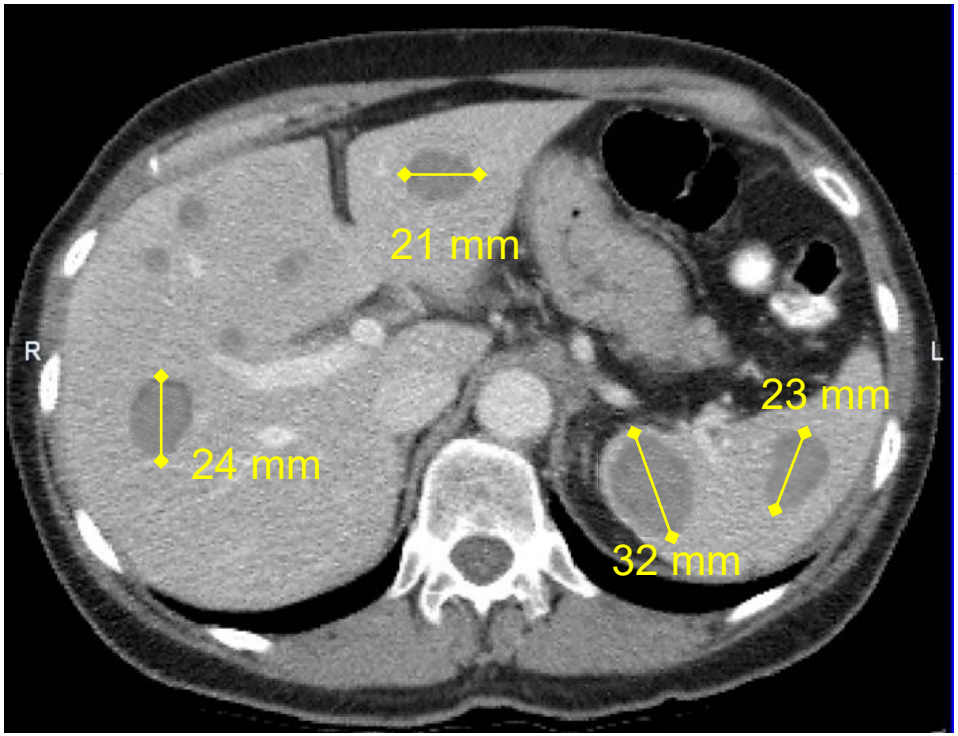
	BL	V1	V2
SOM (mm)	100	130	125
TL Resp		iUPD	iUPD
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD
New			
Overall Resp		iUPD	iUPD

RECIST Scenarios: Imaging Examples # 7d



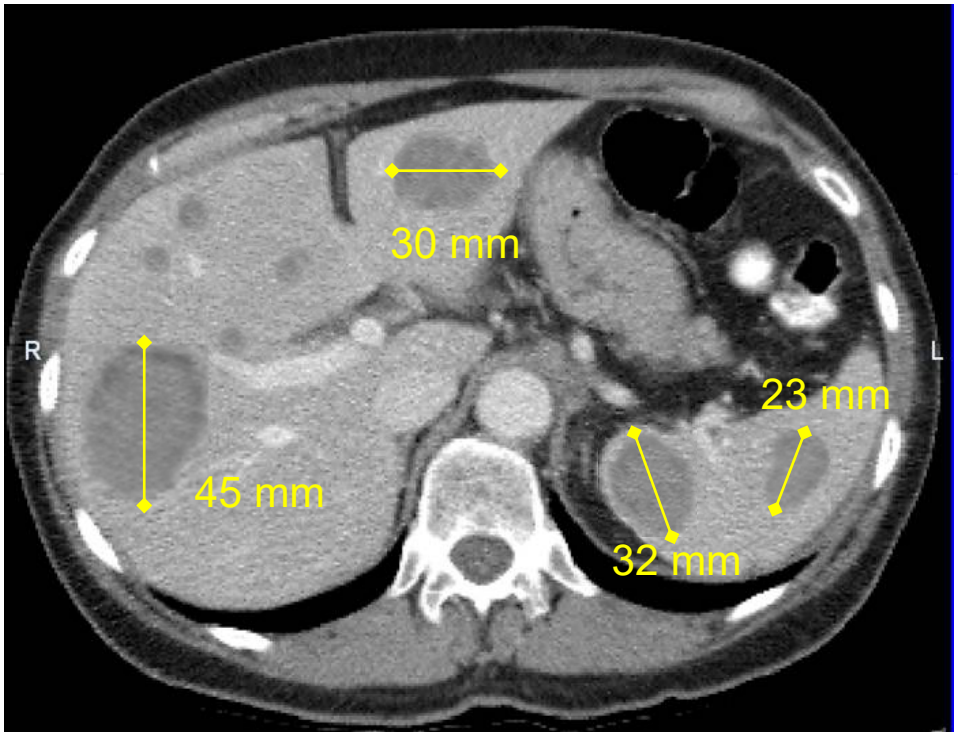
	BL	V1	V2	V3
SOM (mm)	100	130	125	120
TL Resp		iUPD	iUPD	iUPD
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD	PD
New				
Overall Resp		iUPD	iUPD	iCPD

RECIST Scenarios: Imaging Examples # 8a



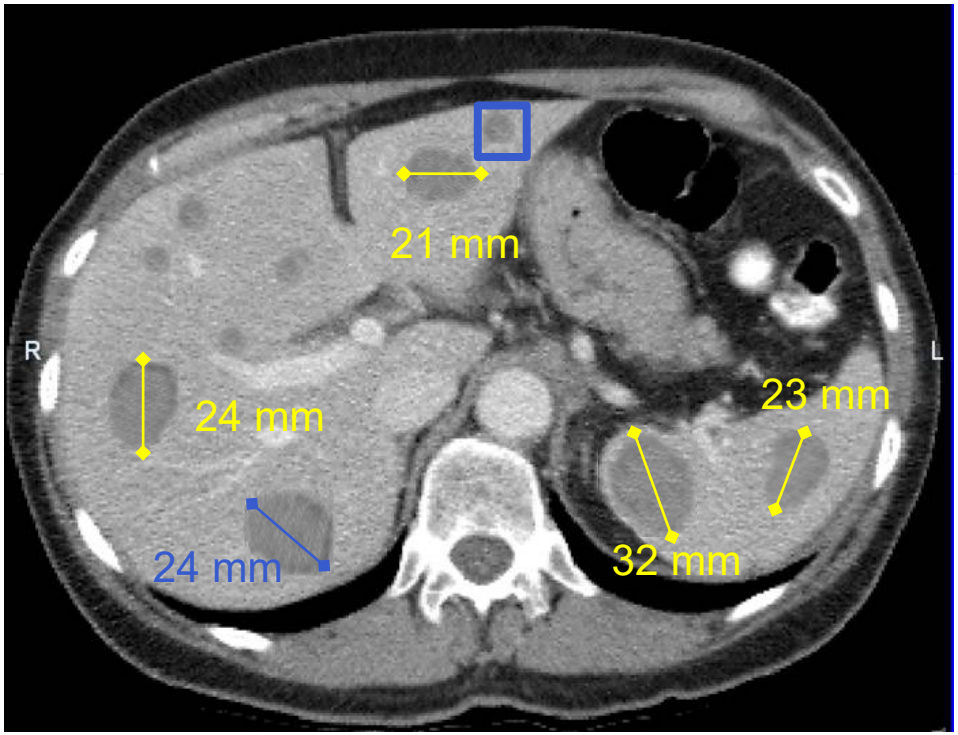
	BL
SOM (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

RECIST Scenarios: Imaging Examples # 8b



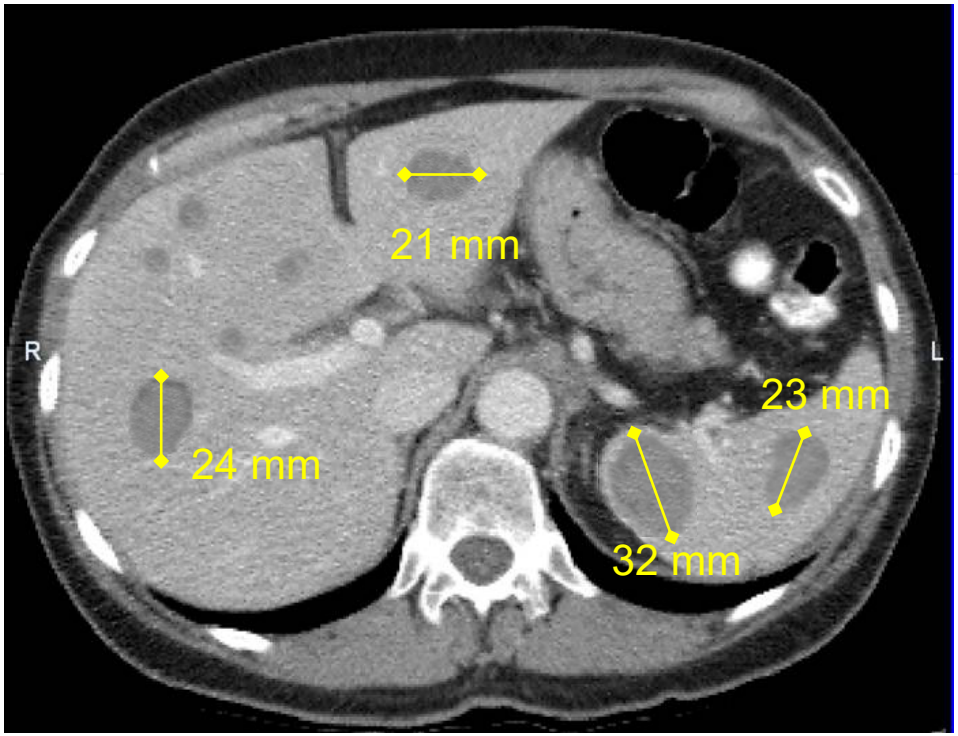
	BL	V1
SOM (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-CR/Non-PD
New		
Overall Resp		iUPD

RECIST Scenarios: Imaging Examples # 8c



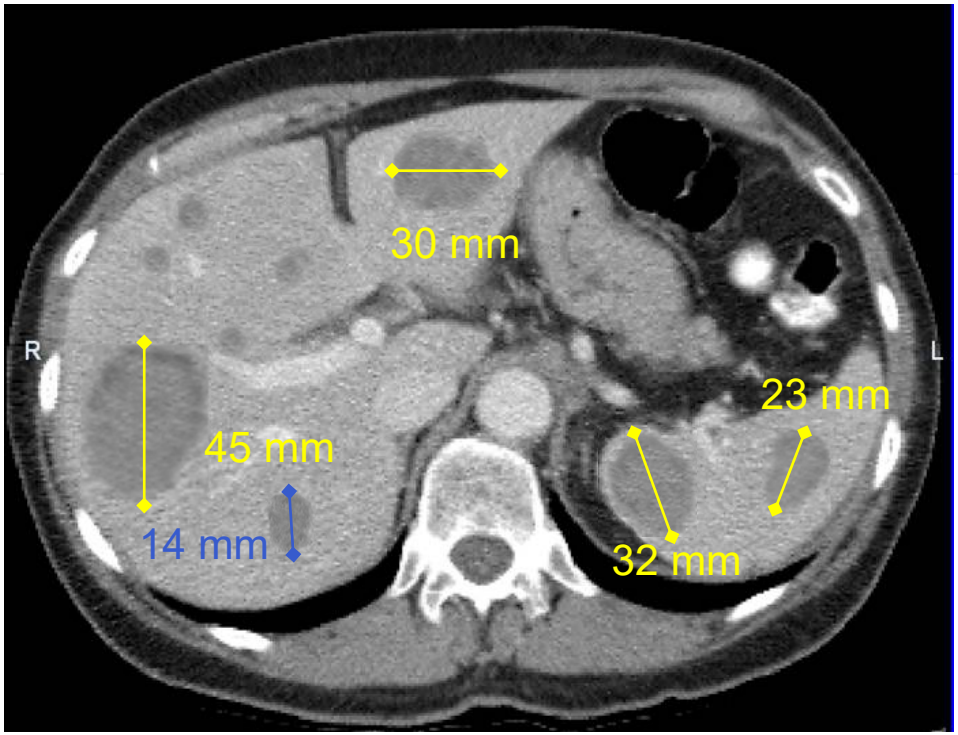
	BL	V1	V2
SOM (mm)	100	130	100
TL Resp		iUPD	iSD
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD
New			24 mm / NT +
Overall Resp		iUPD	iCPD

RECIST Scenarios: Imaging Examples # 9a



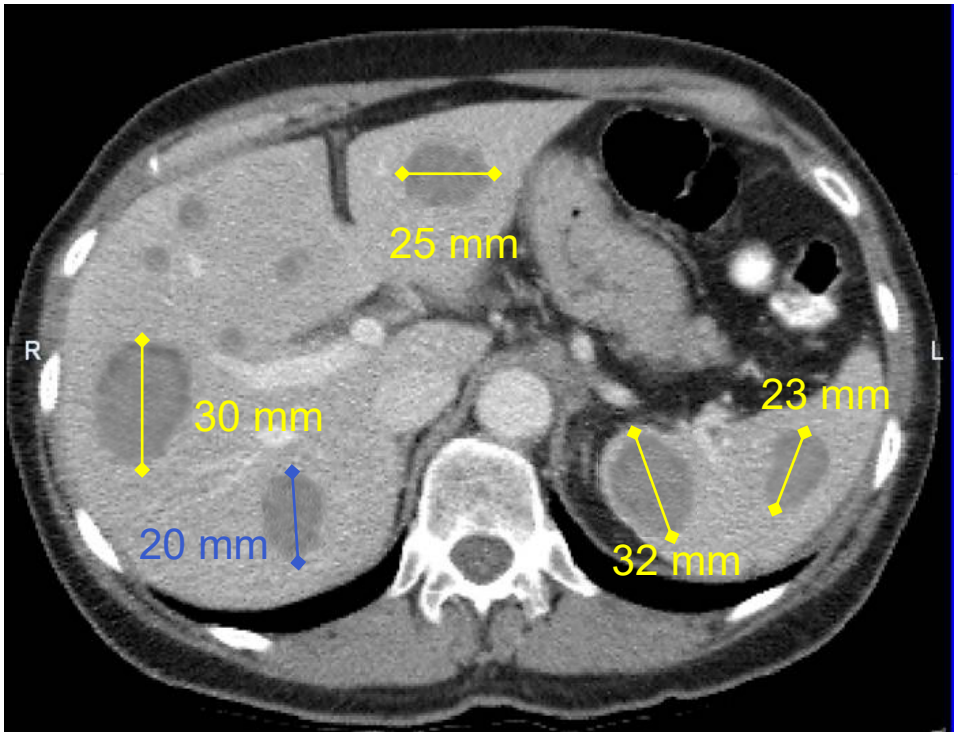
	BL
SOM (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

RECIST Scenarios: Imaging Examples # 9b



	BL	V1
SOM (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-CR/Non-PD
New		14 mm
Overall Resp		iUPD

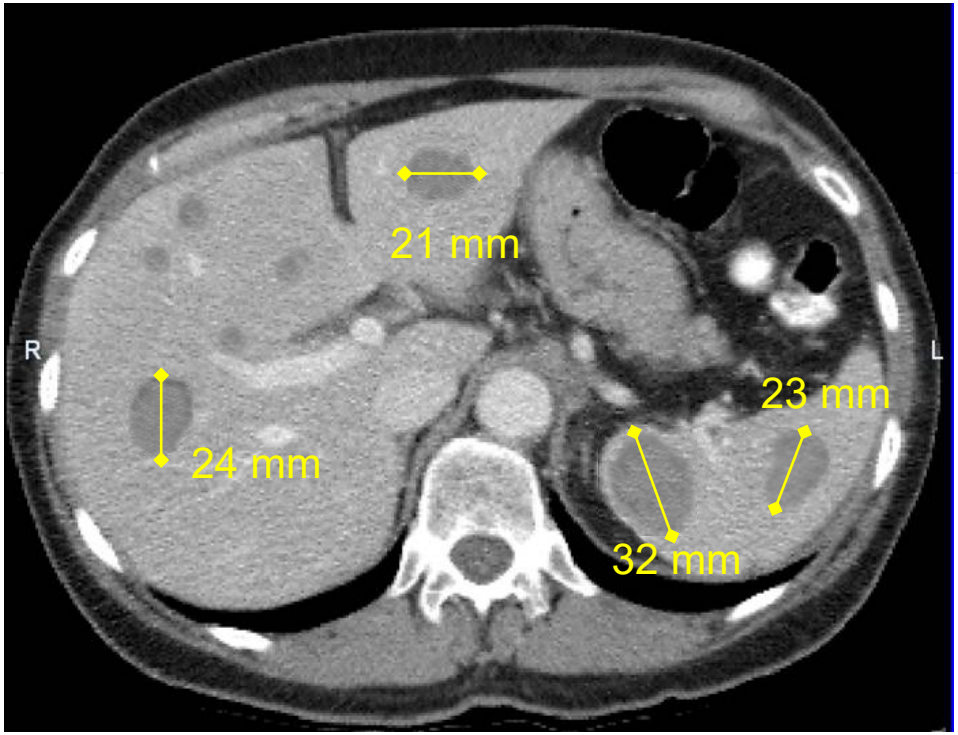
RECIST Scenarios: Imaging Examples # 9c



	BL	V1	V2
SOM (mm)	100	130	110
TL Resp		iUPD	iSD
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD
New		14 mm	20 mm
Overall Resp		iUPD	iCPD

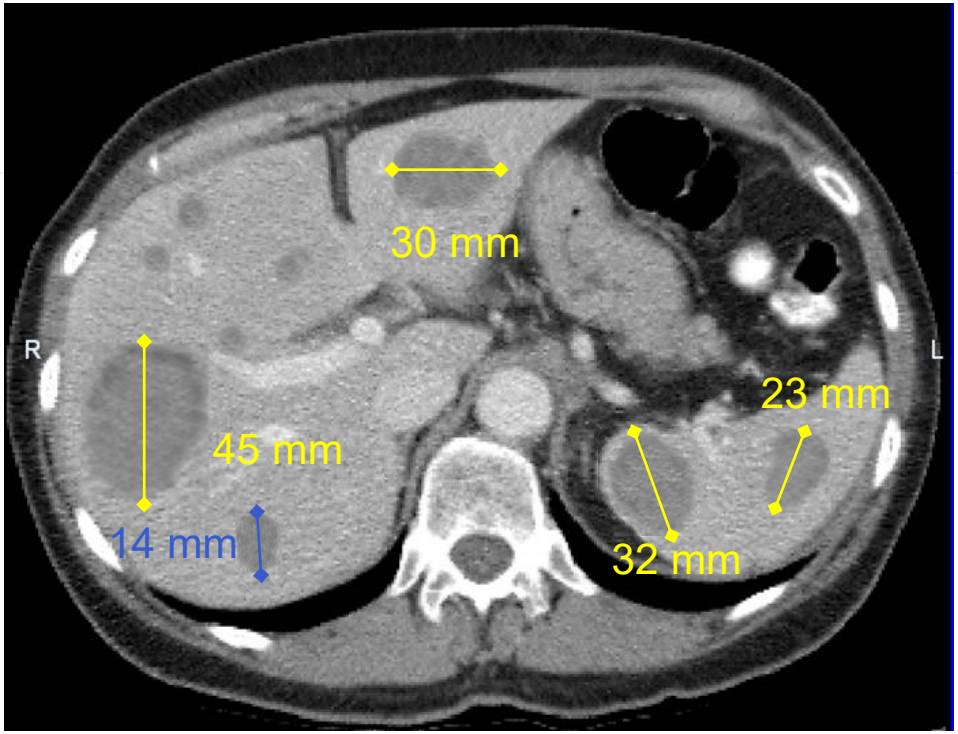
≥5 mm increase

RECIST Scenarios: Imaging Examples # 10a



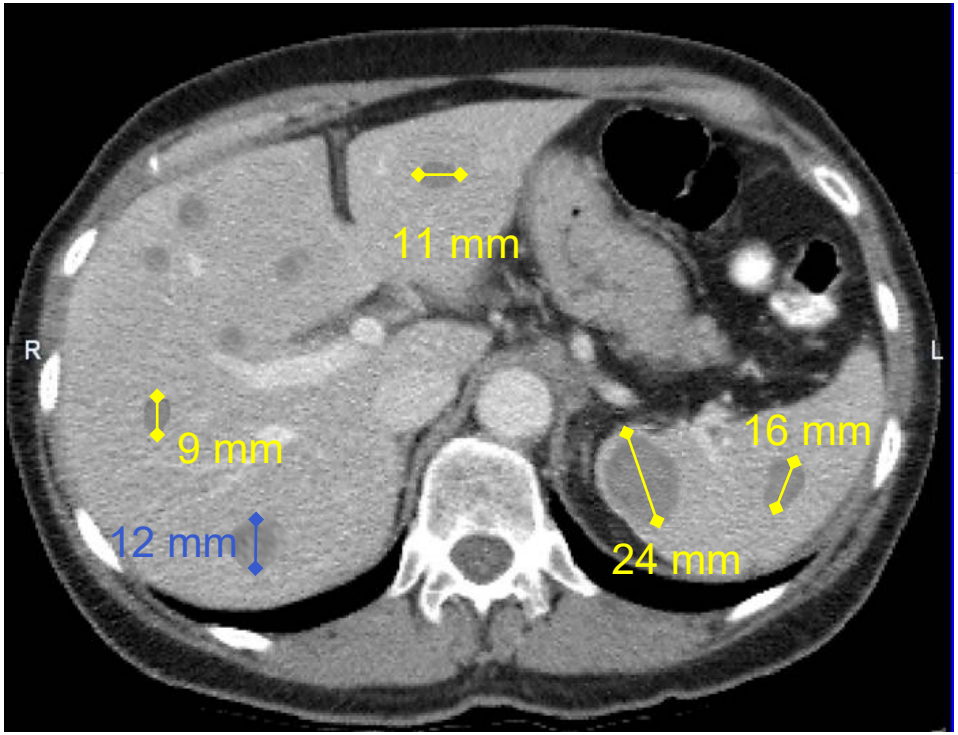
	BL
SOM (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

RECIST Scenarios: Imaging Examples # 10b



	BL	V1
SOM (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-CR/Non-PD
New		14 mm
Overall Resp		iUPD

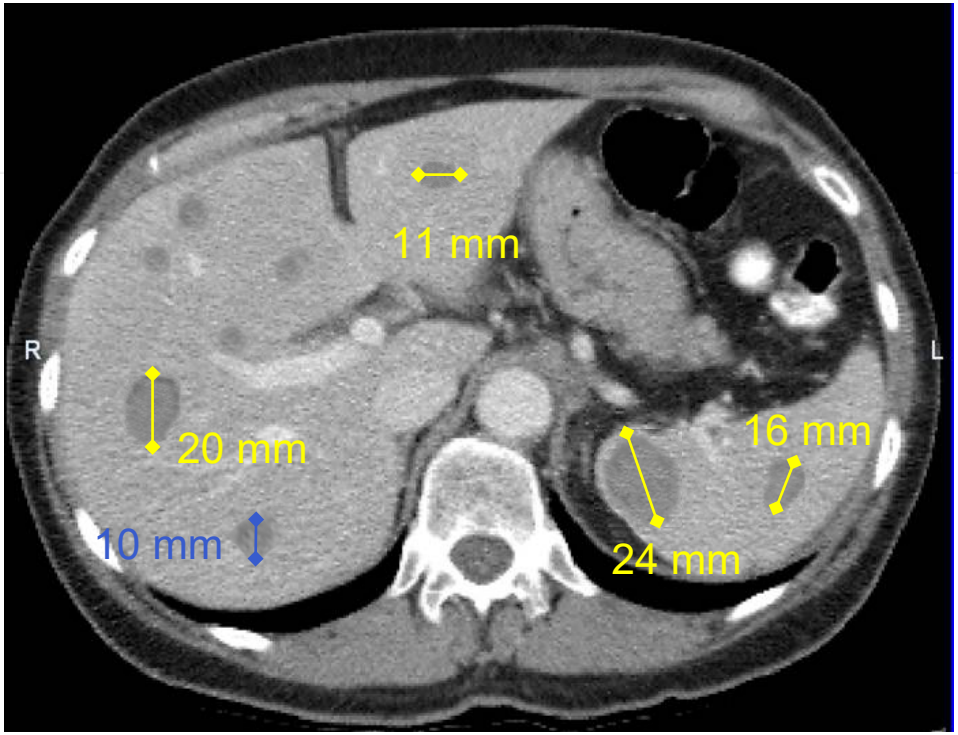
RECIST Scenarios: Imaging Examples # 10c



	BL	V1	V2
SOM (mm)	100	130	60
TL Resp		iUPD	iPR
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD
New		14 mm	12 mm
Overall Resp		iUPD	iPR

"reset bar"

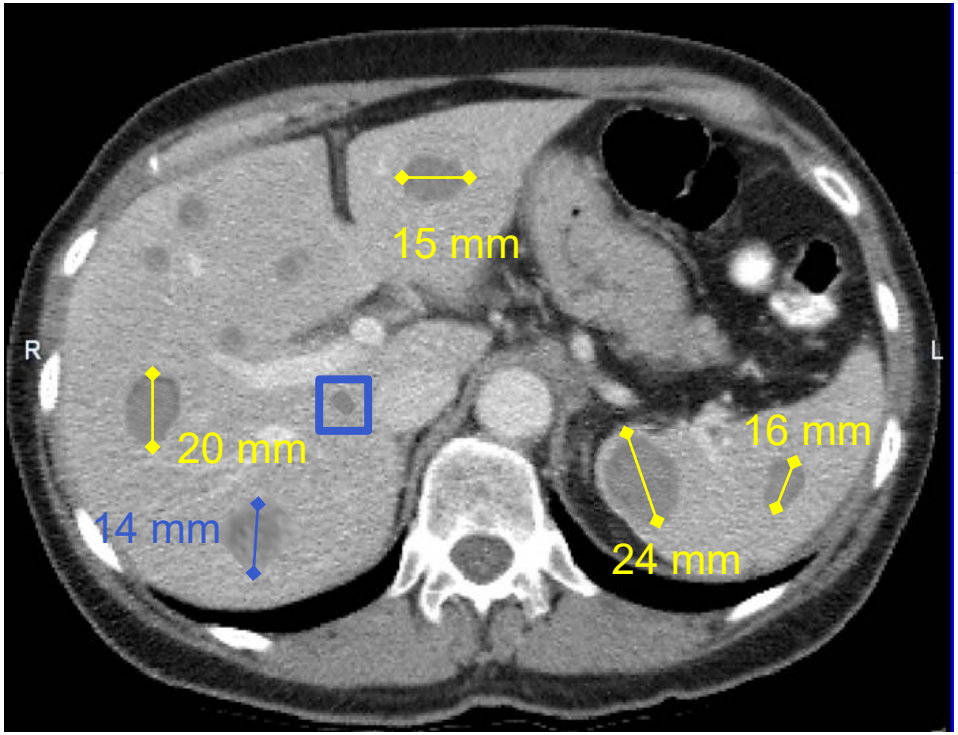
RECIST Scenarios: Imaging Examples # 10d



	BL	V1	V2	V3
SOM (mm)	100	130	60	71
TL Resp		iUPD	iPR	iPR
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD
New		14 mm	12 mm	10 mm
Overall Resp		iUPD	iPR	iPR

Note: there is variance in R1.1, as some users would code V3 as iSD

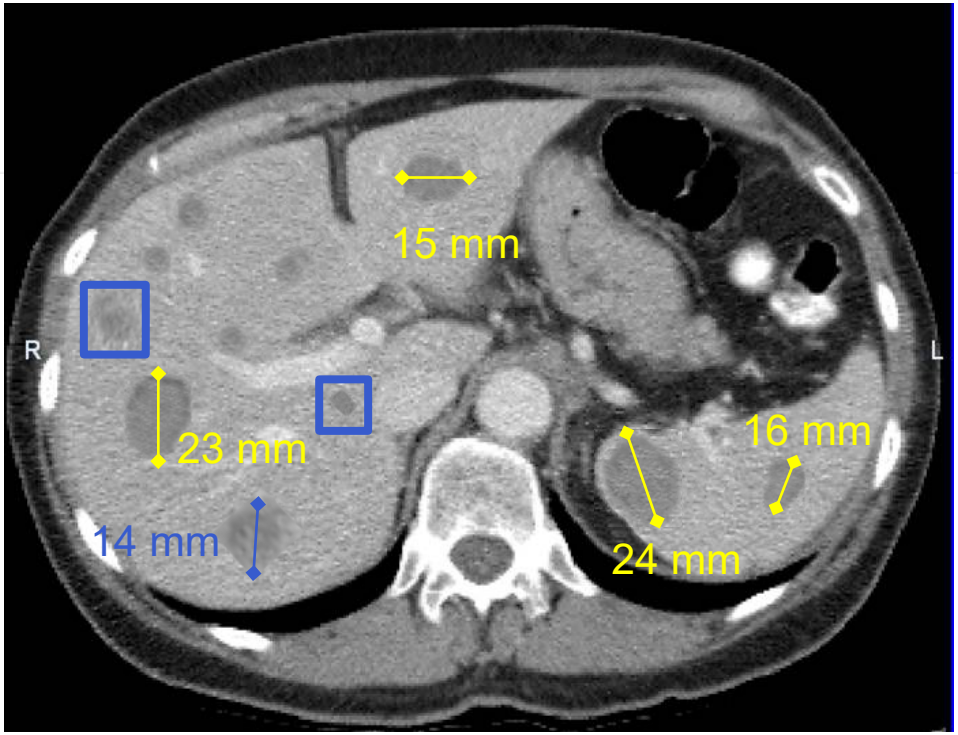
RECIST Scenarios: Imaging Examples # 10e



Note: there is variance in R1.1, as some users would code V3 as iSD

	BL	V1	V2	V3	V4
SOM (mm)	100	130	60	71	75
TL Resp		iUPD	iPR	iPR	iUPD
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD
New		14 mm	12 mm	10 mm	14 mm / NT+
Overall Resp		iUPD	iPR	iPR	iUPD

RECIST Scenarios: Imaging Examples # 10f



Note: there is variance in R1.1, as some users would code V3 as iSD

	BL	V1	V2	V3	V4	V5
SOM (mm)	100	130	60	71	75	78
TL Resp		iUPD	iPR	iPR	iUPD	iUPD
NTL Resp		Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD
New		14 mm	12 mm	10 mm	14 mm / NT+	14 mm / NT++
Overall Resp		iUPD	iPR	iPR	iUPD	iCPD

RECIST

Scenarios: Detailed Examples # 1

	Baseline	TP1	TP2	TP3
T lesions (sum)	100	125	125	125
NT lesions	PRES	No change	No change	UNE ↑
New lesions	-	-	-	-
TP response (R)	-	PD	PD	PD
TP response (iR)	-	iUPD	iUPD	iCPD

- RECIST (R) PD at TP 1 based on target disease, best RECIST response is PD
- PD not confirmed at TP 2 but is confirmed at TP3 based on new RECIST PD in NT
- iRECIST (iR) PD date is TP1, best iRECIST response is PD

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

Scenarios: Detailed Examples # 2

—	Baseline	TP1	TP2	TP3	TP4	TP5
T lesions (sum)	100	125	50	50	50	120
NT lesions	PRES	UC	UC	UC	UC	UC
New lesions		1 lesion	No change	No change	Extra NL	No change
TP response (R)		PD	PD	PD	PD	PD
TP response (iR)		iUPD	iPR	iPR	iUPD	iCPD

- RECIST (R) PD at TP1 (based on target lesions and a new lesion); best RECIST response is PD
- iPR assigned at TP 2 and 3 even though the new lesions do not resolve
- iUPD at TP4 based on an additional new lesion
- Confirmed at TP 5 because of RECIST defined PD in target lesions (from nadir) ; date of iPD is TP4
- Best iRECIST (iR) response is iPR

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

Scenarios: Detailed Examples # 3

	Baseline	TP1	TP2	TP3	TP4	TP5
T lesions (sum)	100	50	50	75	50	50
NT lesions	PRES	No change	No change	No change	No change	No change
New lesions		-	-	+	-	-
TP response (R)		PR	PR	PD	PD	PD
TP response (iR)		iPR	iPR	iUPD	iPR	iPR

- RECIST (R) and iRECIST (iR) PR/iPR at TP1 and 2
- RECIST PD at TP3 based on target disease and a new lesion; best RECIST response is PR with duration BL-TP3
- Second iPR occurs with no further progression. For iRECIST no PD date and remains in iPR.
- Best iRECIST response is iPR with duration BL-TP5+

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

RECIST

Scenarios: Detailed Examples # 4

	Baseline	TP1	TP2	TP3	TP4	TP5
T lesions (sum)	100	50	50	75	NE	NE
NT lesions	PRES	UC	UC	UC	NE	NE
New lesions		-	-	+	NE	NE
TP response (R)		PR	PR	PD	NE	NE
TP response (iR)		iPR	iPR	iUPD	NE	NE

- RECIST (R) PD at TP3, best response of PR
- iRECIST (iR) best response is iPR; TP3 is iUPD and never confirmed. As no iSD, iPR or iCR, date of iPD is TP3

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point
UNE: unequivocal increase

RECIST

STATISTICAL AND DATA CONSIDERATIONS

Primary and Exploratory Response Criteria

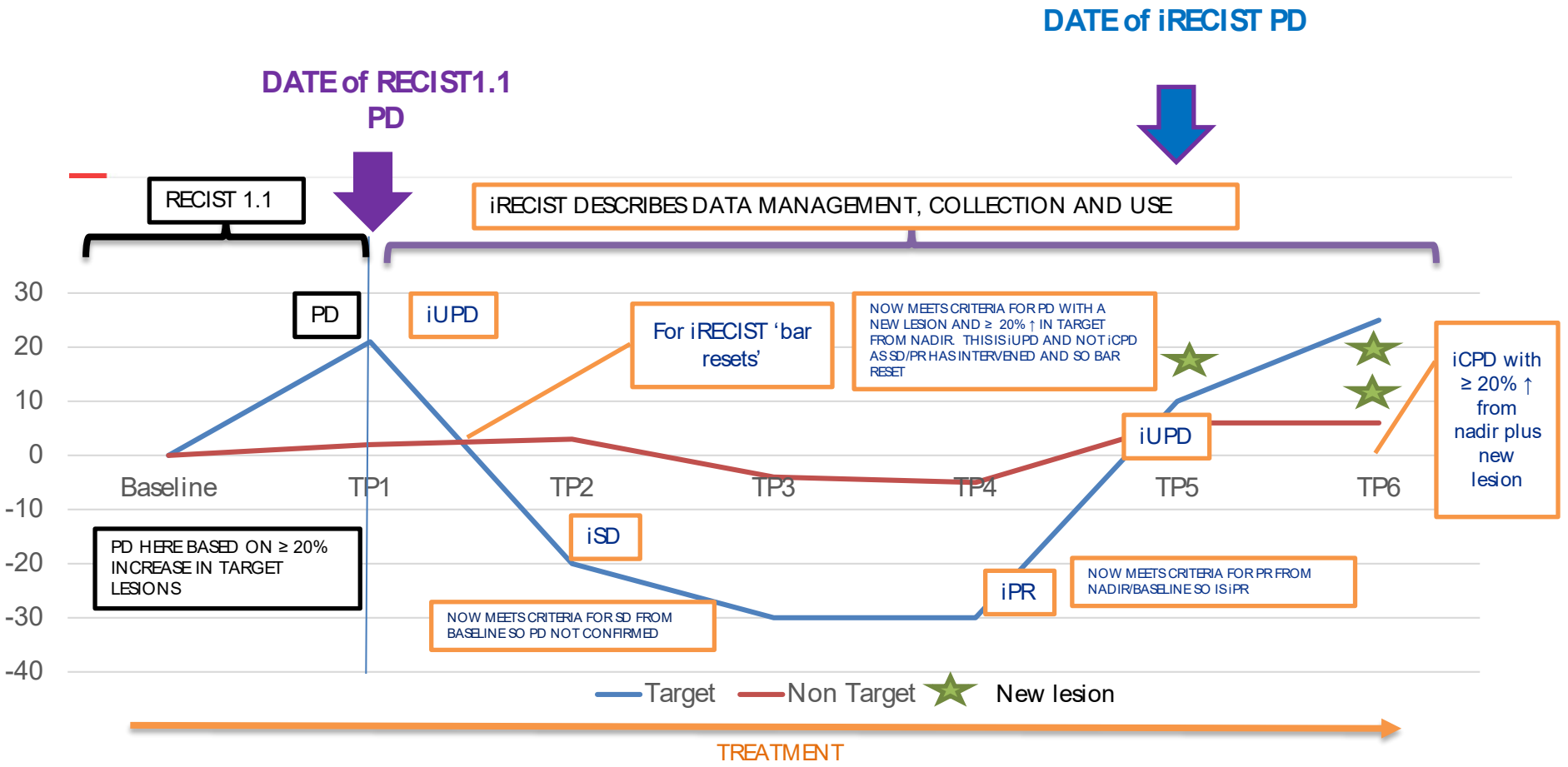
- RECIST 1.1 should remain primary criteria
  - iRECIST exploratory

Date of i-Progression

- Will be the same as RECIST 1.1 date (i.e. first iUPD date) ***UNLESS*** iSD, iPR or iCR intervenes
- Will be the UPD date which has been subsequently confirmed
  - The date used is the first UPD date
- If iUPD never confirmed
  - If a subsequent iSD, iPR or iCR is seen with no later iUPD or iCPD then the initial iUPD is ignored
  - Otherwise the iUPD date is used
    - 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.
    - The patient dies of cancer

RECIST

PD: progression
iSD: stable disease
iPR: partial response
iUPD: unconfirmed progression
TP: time point

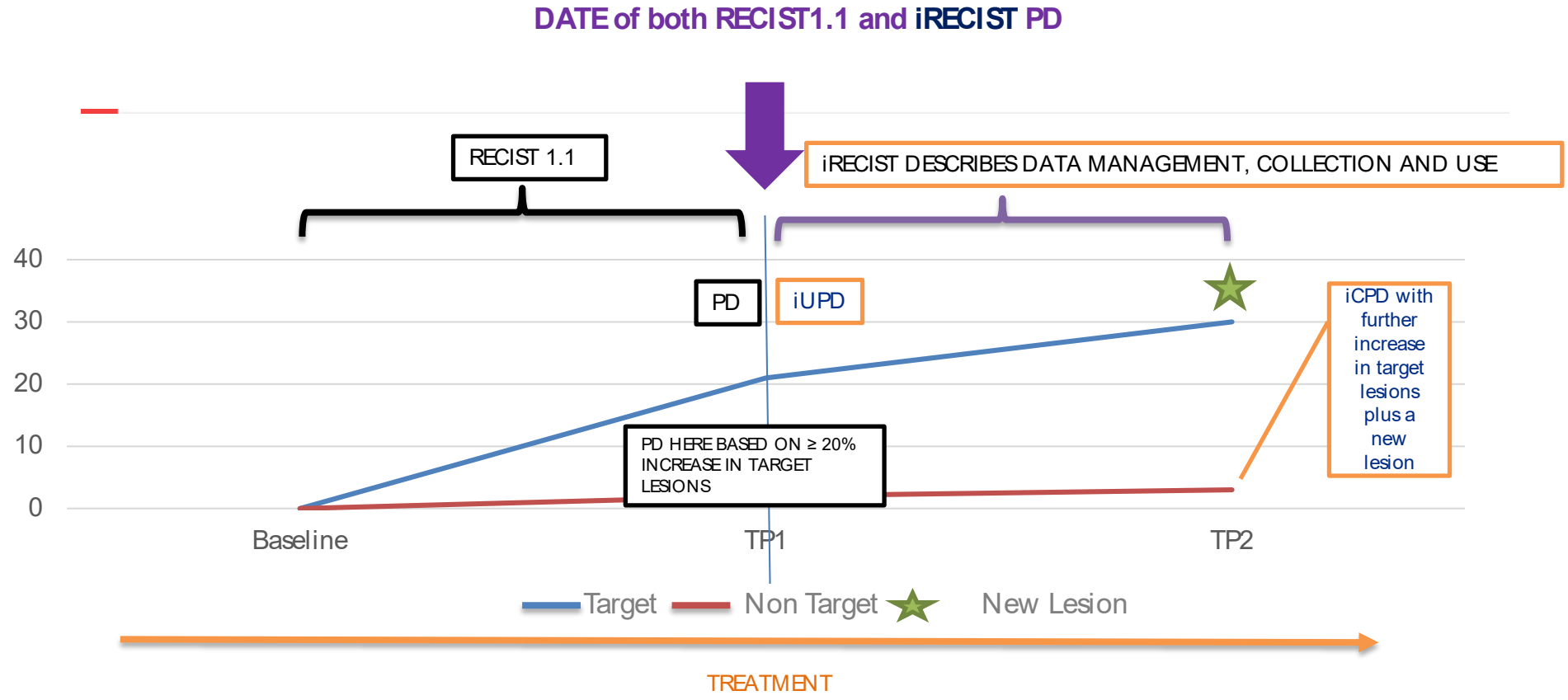


Progression: RECIST 1.1 vs. iRECIST:

with intervening response

PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
TP: time point

RECIST



Progression: RECIST 1.1 vs. iRECIST

***no* intervening response**

Data Collection

- Investigator/site assessment is the primary method of evaluation for RECIST and iRECIST in keeping with RWG principles
- Record time-point and best overall response for both
  - RECIST 1.1
  - iRECIST
- Record reasons
  - Treatment discontinued when iUPD
  - iCPD not confirmed
- Independent imaging review can occur in parallel if indicated
- We recommend CT images be collected if feasible

RECIST

SUMMARY

Summary: RECIST 1.1 vs. iRECIST (1)

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10mm in long diameter (15mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease considered not-target (must be 10mm of longer in short axis for nodal disease)	No change; however, • NEW lesions assessed per RECIST 1.1 • Recorded separately on the CRF • NOT included in the SOM for target lesions identified at baseline
CR, PR or SD	Cannot have met criteria for PD prior to CR, PR or SD	May have had iUPD (1 or more instances), but not iCPD, prior to iCR, iPR or iSD
Confirmation of CR, PR	Only required for non-randomized trials	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1

Summary: RECIST 1.1 vs iRECIST (2)

	RECIST 1.1	iRECIST
New lesions	Results in PD. Recorded but not measured	Results in iUPD but iCPD is only assigned based on this category if at next assessment • Additional NL appear or • Increase in size of NLs (≥5mm for SOM of NLT or any increase in NLNT) Remember NLs can also confirm iCPD if iUPD was only in T or NT disease
Independent blinded review and central collection of scans	Recommended in some circumstances	Collection of scans (but not independent review) recommended for all trials
Confirmation of PD	Not required (unless equivocal)	Always required
Consideration of clinical status	Not included in assessment	Clinical stability is always considered and collected on case record form

RECIST

iRECIST in a Nutshell # 1

- RECIST 1.1 – primary criteria
- iRECIST exploratory and applicable only after RECIST1.1 progression occurs
  - Most patients will not have ‘pseudoprogression’
- Principles of iRECIST follow RECIST 1.1 very closely
  - RECIST 1.1 principles are generally are the default except:
    - Management of new lesions
    - What constitutes confirmation of progression
- Assess RECIST 1.1 and iRECIST separately but in parallel at each time point

RECIST

iRECIST in a Nutshell # 2

- Progression must be confirmed
  - Consider treatment past progression only in carefully defined scenarios
  - Confirmation requires some worsening of disease bulk
    - Must be **next** evaluable assessment after iUPD
    - Lesion category with existing iUPD just needs to get a little bit worse *OR*
    - Lesion category without prior iUPD has to meet RECIST 1.1 criteria for progression
- New lesions
  - Managed using RECIST 1.1 principles
  - NOT added to SOM (but included in separate iSOM)
- Unconfirmed progression does not preclude a later i-response

RECIST

iRECIST in a Nutshell # 3

- Response after iUPD is driven by TARGET disease (as long as iCPD not confirmed)
- This means that can have subsequent iSD or iPR in target lesions (compared to baseline) EVEN IF
  - The new lesion seen at the time of iUPD is still there
  - The unequivocal increase in non-target lesions at the time of iUPD hasn't improved

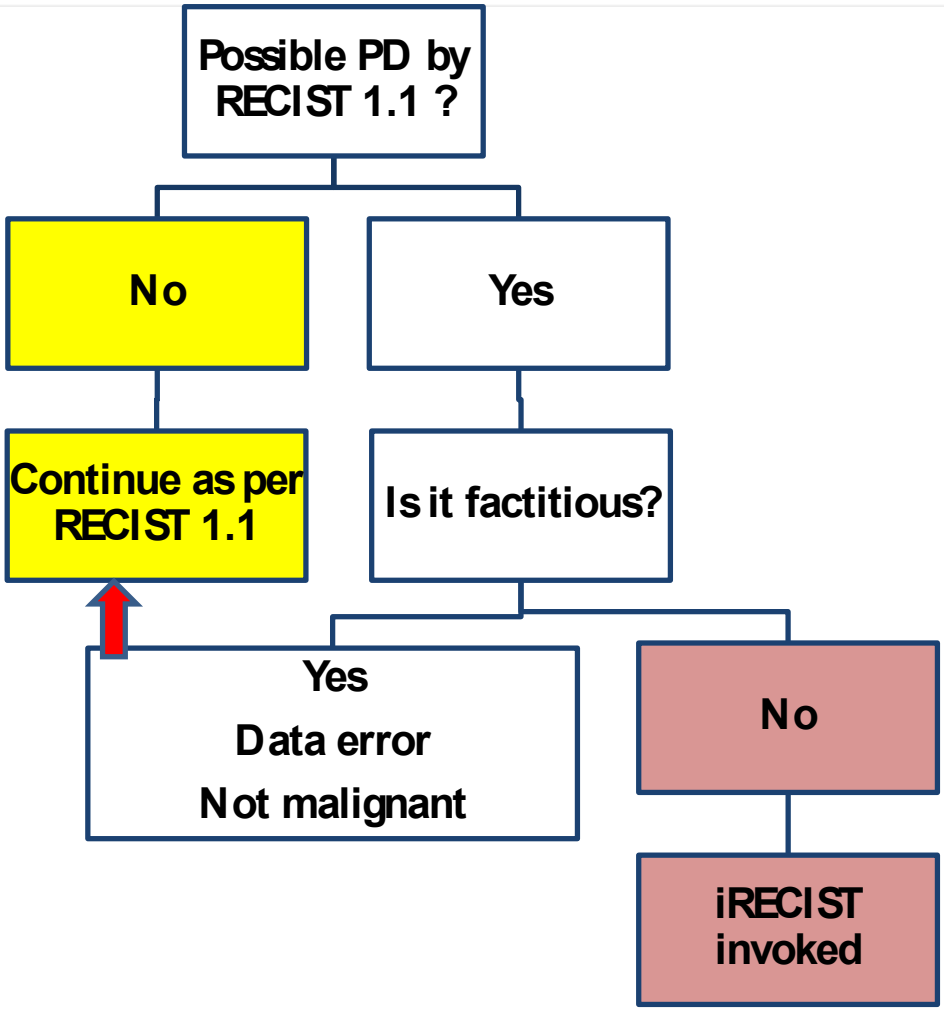
THIS IS THE SAME AS RECIST 1.1 WHERE TARGET DISEASE TRUMPS OTHER DISEASE

iRECIST in a Nutshell # 4

- "Bar reset" does mean that:
  - a previously observed iUPD can be ignored if there is an intervening response (i.e. if criteria for iPR, iCR, or iSD are met)

- "Bar reset" does not mean that:
  - the baseline or the nadir are re-set
    - iCR/iPR/iSD still calculated from BASELINE
    - i progression date still calculated from NADIR (which may or may not be the same as baseline – and could be before or after any iUPD)

iRECIST is only relevant at and after the time progression is suspected



CONCLUSIONS

RECIST

Conclusions

- Recommendations on terminology, collection and response definitions for trials including immunotherapeutics
- They are not recommendations for treatment decisions
  - How to manage the clinical trial data if treatment is continued past RECIST 1.1 progression
- RECIST 1.1 should continue to be used to define response based endpoints for late stage trials planned for marketing authorisations
- Data collection for testing and validation is ongoing
  - May result in a formal update to RECIST
- The RWG is always happy to address any questions

RESOURCES

RECIST Working Group

RECIST (Response Evaluation Criteria in Solid Tumours) provides a simple and pragmatic methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumors, using validated and consistent criteria to assess changes in tumor burden. The RECIST Working Group comprises representatives of the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States and Canadian Cancer Trials Group (CCTG), as well as several pharmaceutical companies. Its mission is to ensures that RECIST undergoes

http://www.eortc.org/recist/contact-us/

References and Resources

http://www.eortc.org/recist

http://www.eortc.org/recist/irecist/

THE LANCET Oncology

http://thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30074-8/fulltext

- This presentation
- Protocol sections
- CRF examples

- FAQ http://www.eortc.org/recist/contact-us/
- A WORD version of the manuscript

RECIST

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Institution/Agency	Participants
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Amgen	Roger Sidhu
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