iRECIST

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

Lesley Seymour MD, PhD
Canadian Cancer Trials Group, Kingston, Ontario

On behalf of the RECIST Working Group (RWG) and Immunotherapy Subcommittee

RECIST

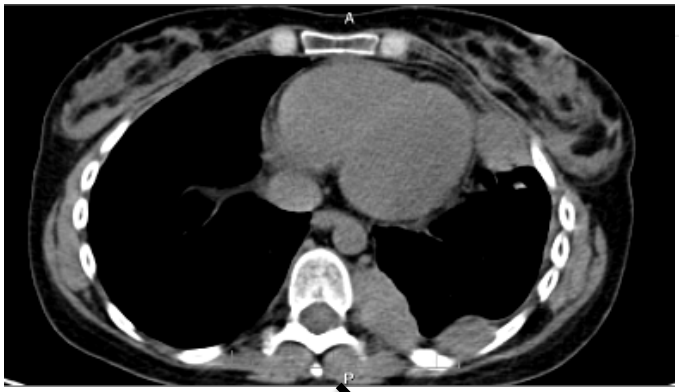
Response and Immunotherapy

- We know
  - Progression based endpoints are increasingly used for marketing approvals
  - Immune based therapies are a major advancement in patient care
  - Unusual response patterns well described especially in melanoma
- We don't know
  - True frequency
  - Optimal response criteria or how to implement them

RECIST

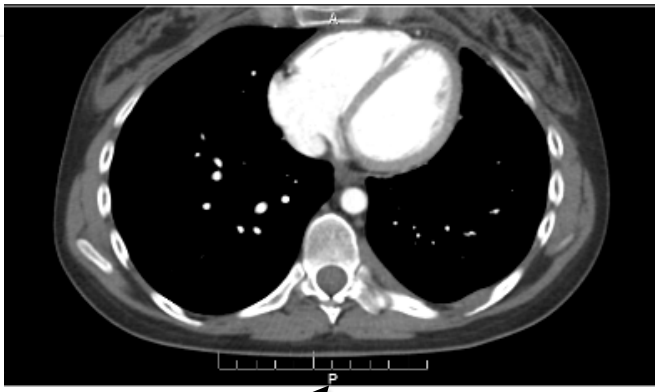
Unusual Response Patterns

What has been seen- durable partial or even complete response

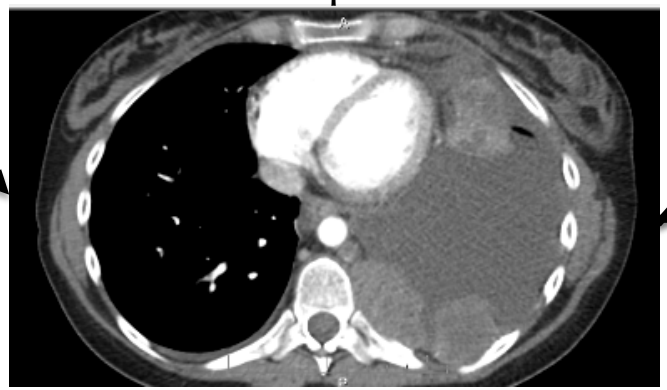


Baseline

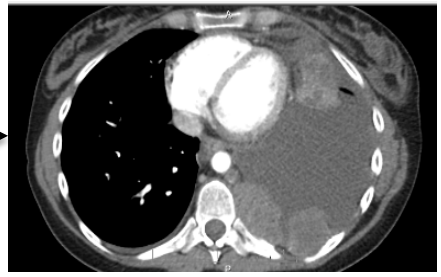
TP3



Time point 2



TP3

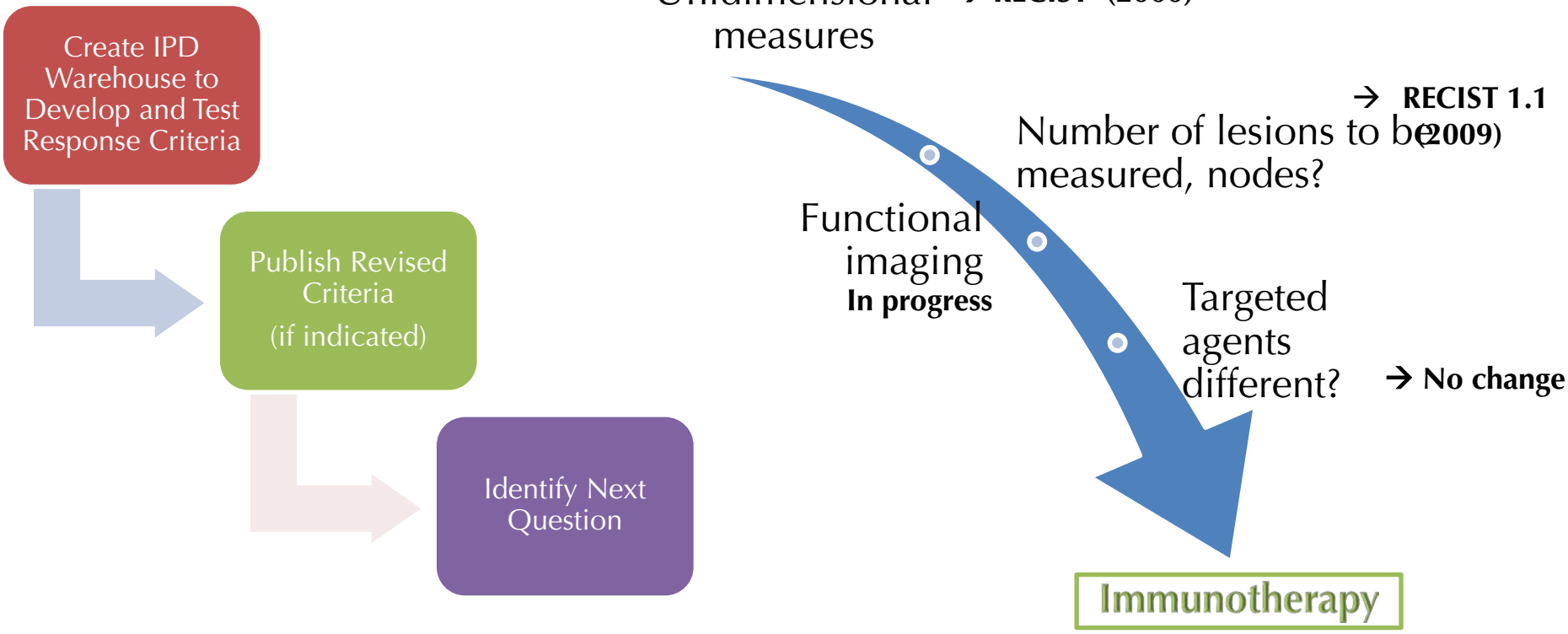


What we would expect

RECIST

How should we assess response and progression for trials which include at least one immunotherapy?

RECIST Working Group Strategy and Activity



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

Background: Immune Response Criteria

- 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. *J Clin Oncol* **2016;34:1510–7.**

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

RECIST

Response Criteria Summarised

	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?

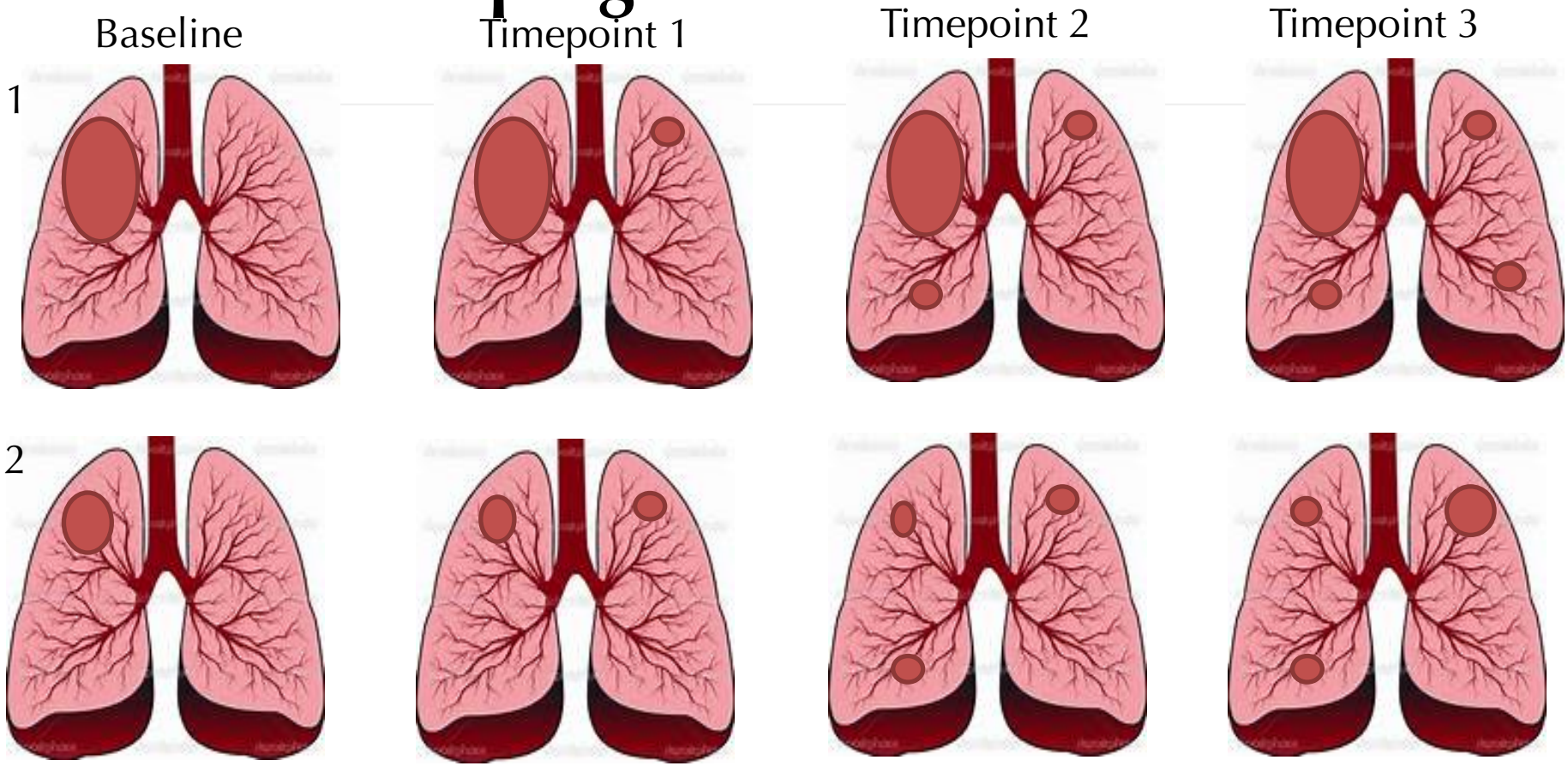
Validating RECIST for Immunotherapy Trials

Concerns

- Multiple variations used across trials
- Comparability
- Response data /measures not always collected after RECIST defined progression
- May not be applicable to other tumour types
- Delays in switch in therapy

RECIST

True or Pseudoprogression ?



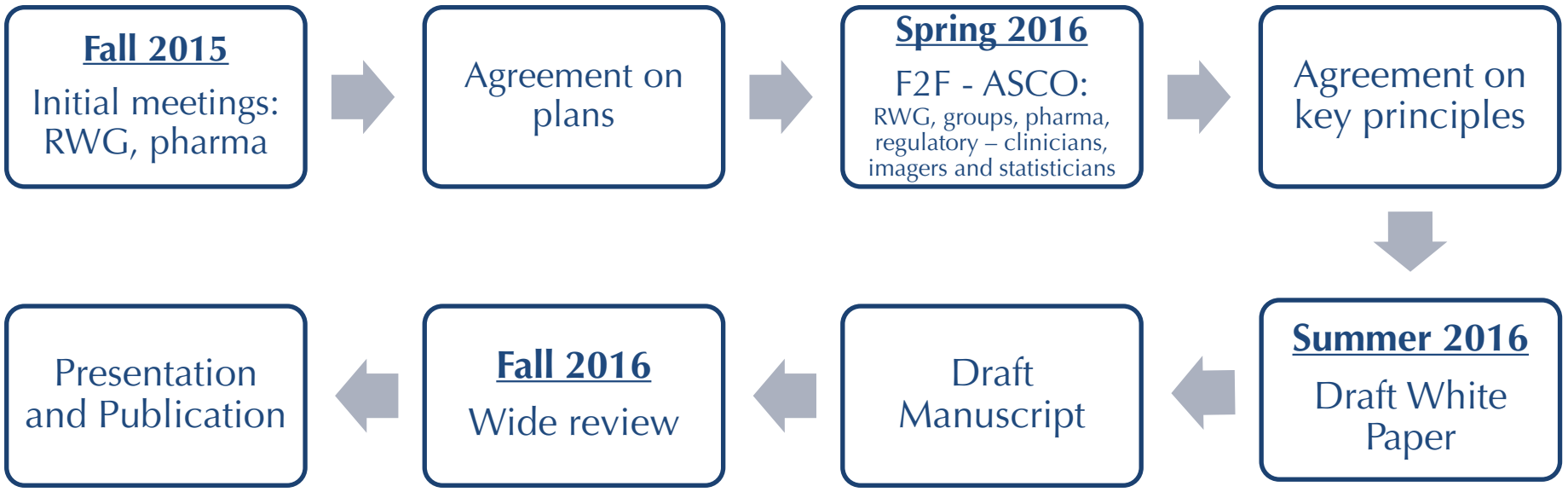
SOME CURRENT CRITERIA MAY ACCEPT THIS AS PSEUDOPROGRESSION - BUT IF TRUE PROGRESSION THEN THE START OF EFFECTIVE SALVAGE THERAPY WOULD HAVE BEEN DELAYED FOR MANY WEEKS

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

RECIST

iRECIST Addresses

- Recommendations on
  - Terminology ("i" prefix)
  - Data to be collected after RECIST 1.1 defined PD
  - Definition of "events"
  - Primary endpoints versus exploratory endpoints
- **They are not treatment decision guidelines**
- These are **not (yet) validated response criteria**
- They **are** internationally agreed data recommendations from academia, pharma and regulatory authorities

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 CR, PR, SD and their duration	√
Confirmation of CR and PR	√
Definition of progression in T and NT (iRECIST terms i-unconfirmed progression (iUPD))	√

iRECIST vs RECIST 1.1: **Changes**

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

Prior iUPD does not preclude subsequent iCR, iPR or iSD

iRECIST vs RECIST 1.1: **Changes**

- New lesions (NL) - assessed using RECIST 1.1 principles
  - Up to 5 (2 per site) measured (NL-T) are included in iSOM
    - Not included in SOM of target lesions identified at baseline
  - Other NLs (measurable/non-measurable) are recorded as 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

RECIST

Prior iUPD does not preclude subsequent iCR, iPR or iSD

iRECIST vs RECIST 1.1: **Changes**

- Time point (TP) response after RECIST 1.1 PD.
  - Once a PD always a PD is no longer the case
  - First RECIST 1.1 PD is "unconfirmed" - iUPD
  - iUPD must be confirmed at the next assessment (4-8 weeks)
- TP response is dynamic and based on
  - Change from baseline (iCR, iPR, iSD) or change from nadir (PD)
  - The last i-response

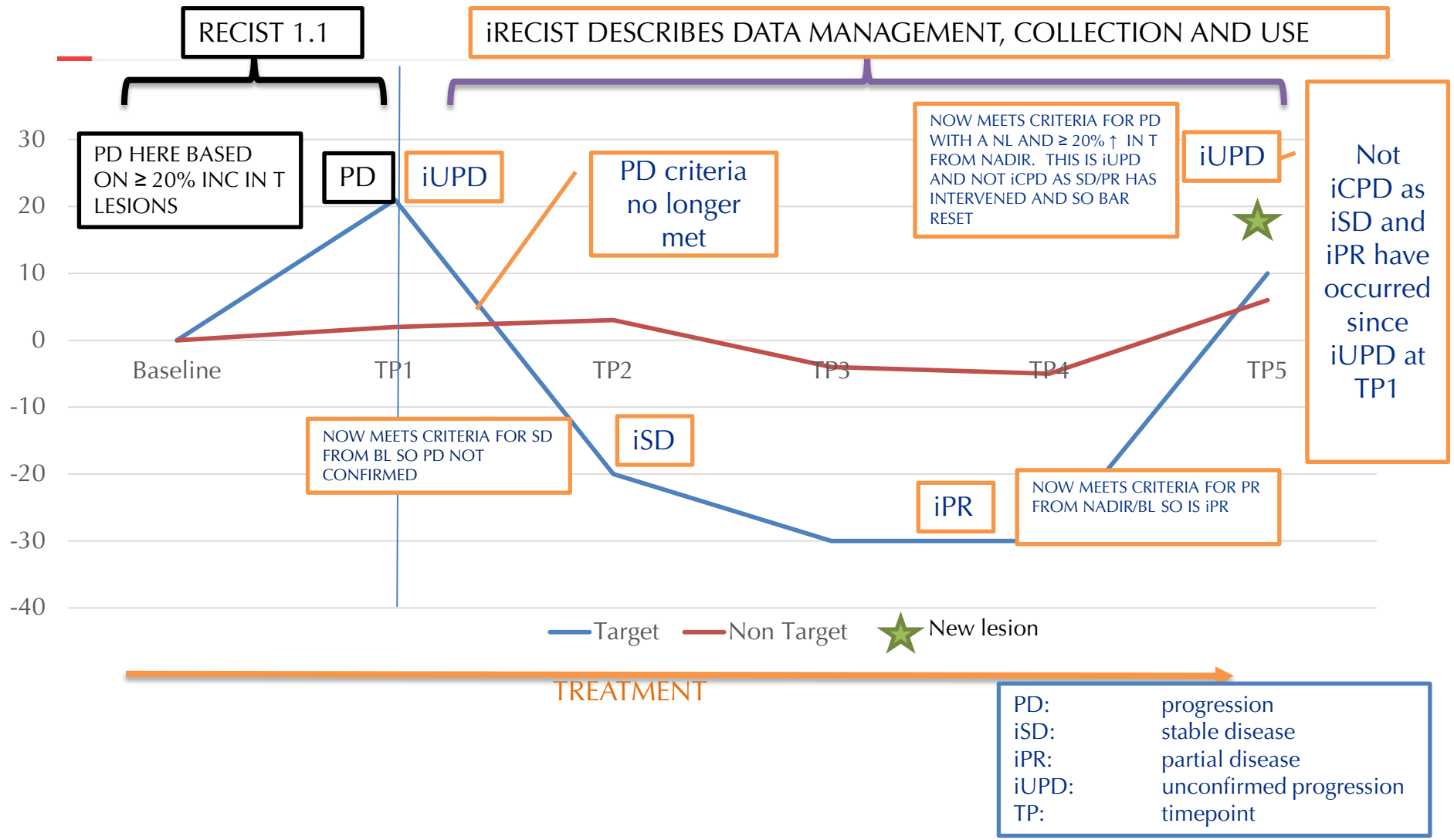
iRECIST vs RECIST 1.1: **Changes**

- Treatment past 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

RECIST

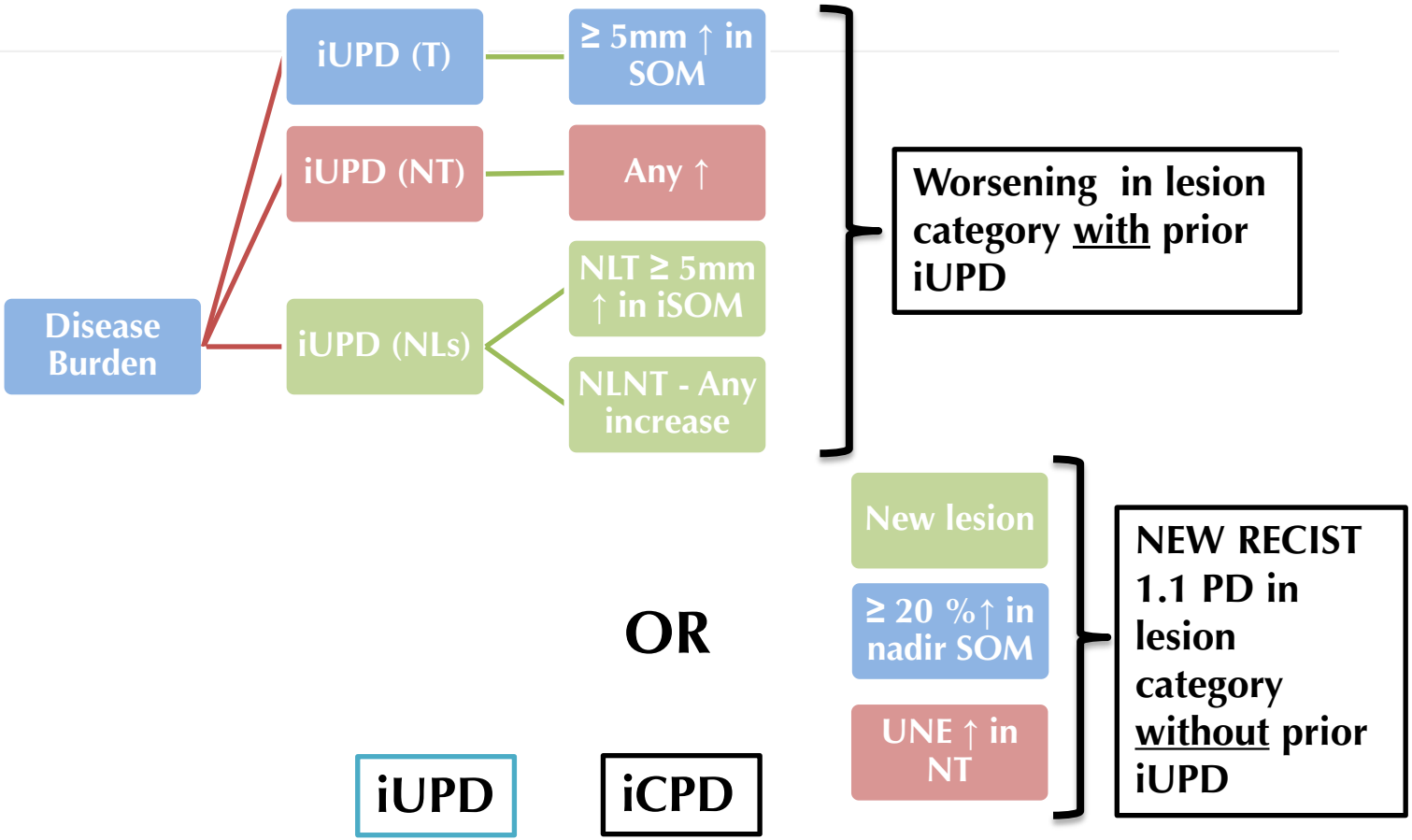
* iSD and iPR occur AFTER iUPD
* iUPD occurs again and must be confirmed



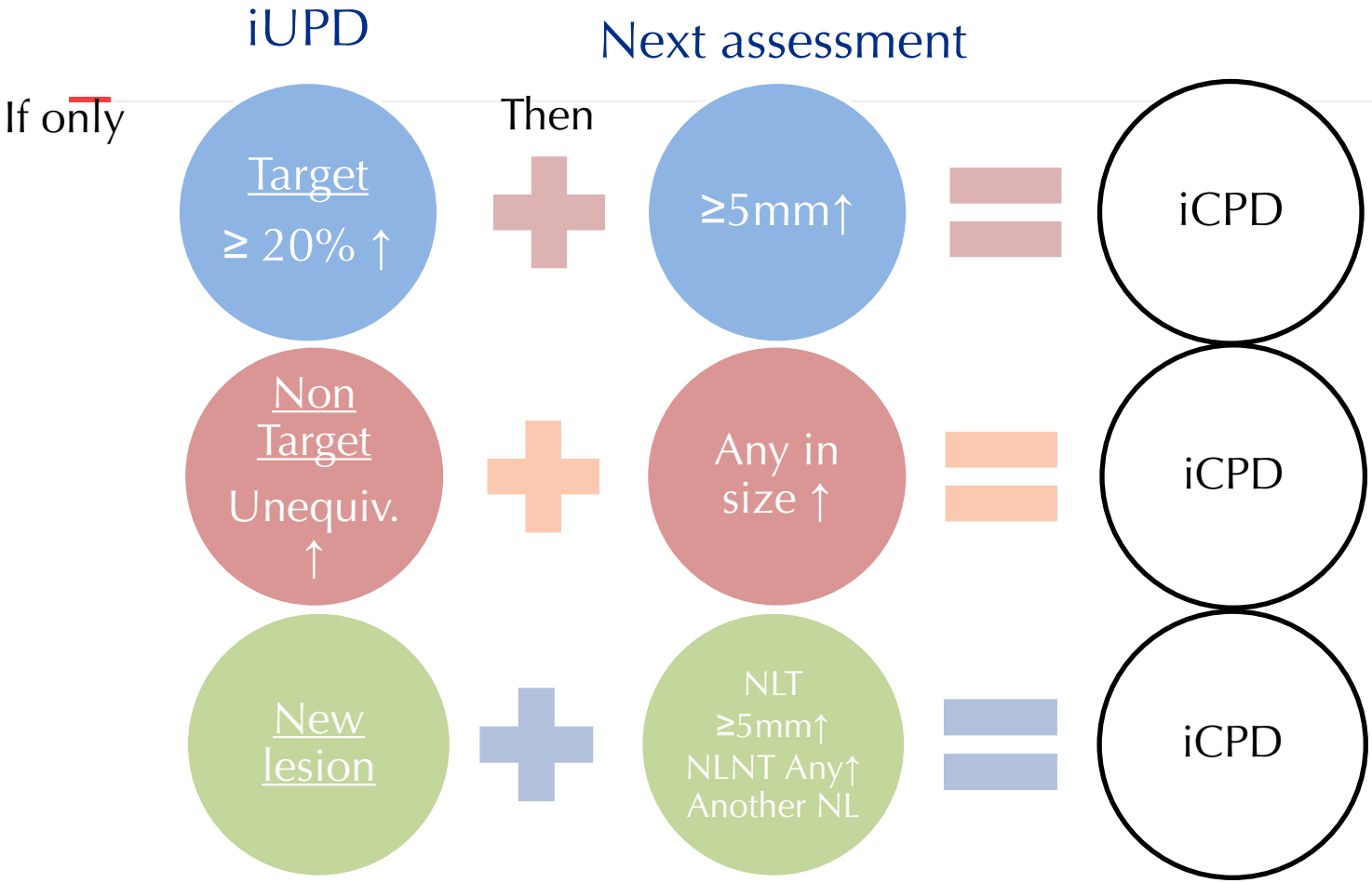
PD:	progression
iSD:	stable disease
iPR:	partial disease
iUPD:	unconfirmed progression
TP:	timepoint

RECIST

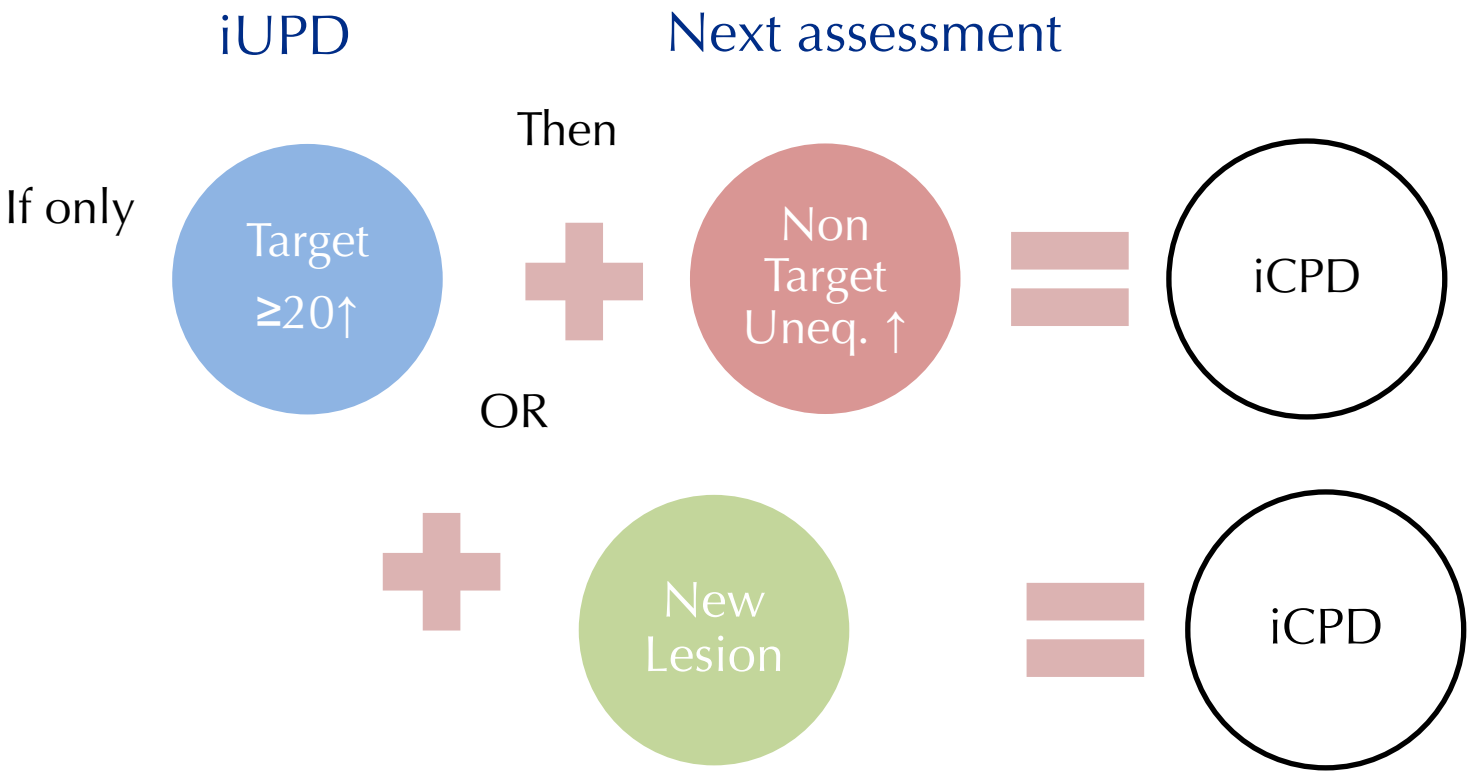
Means of Confirming Progression (iCPD)



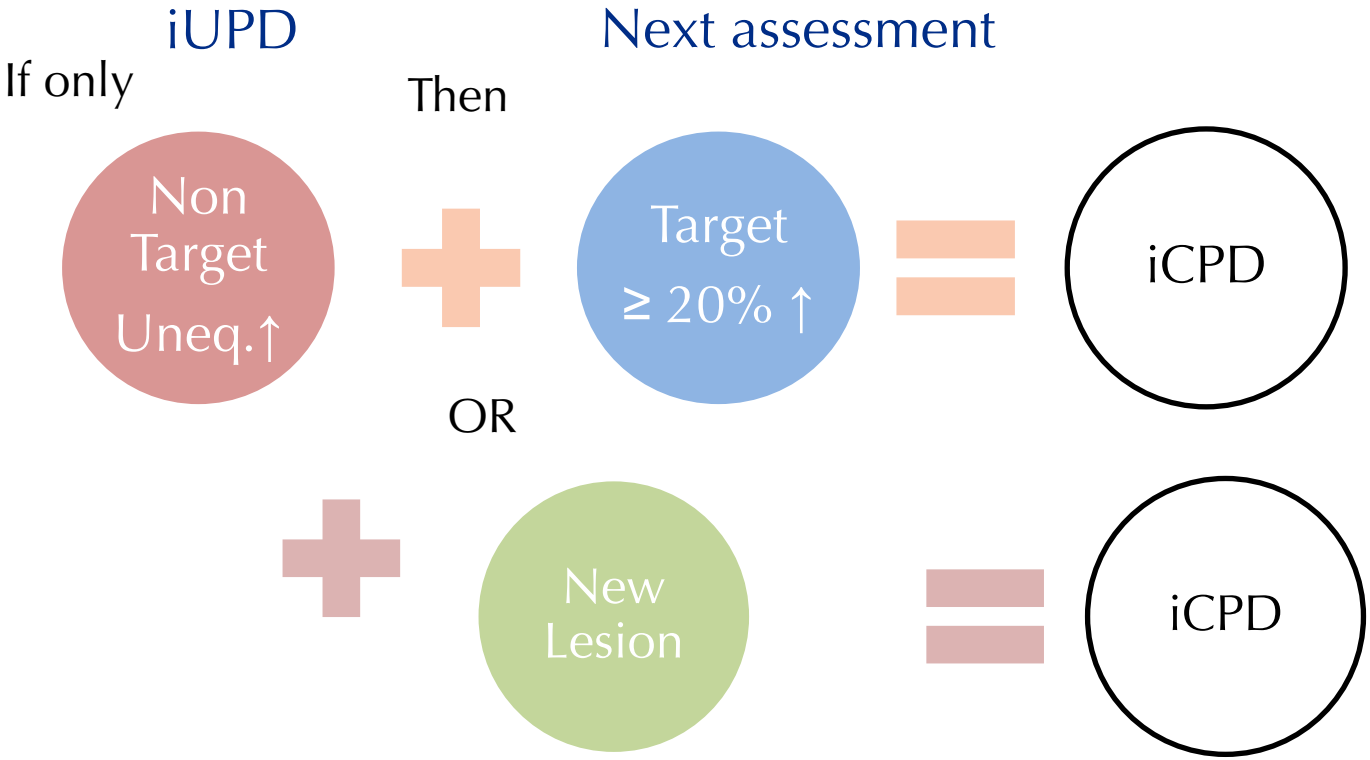
iCPD in Lesion Category with iUPD



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



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

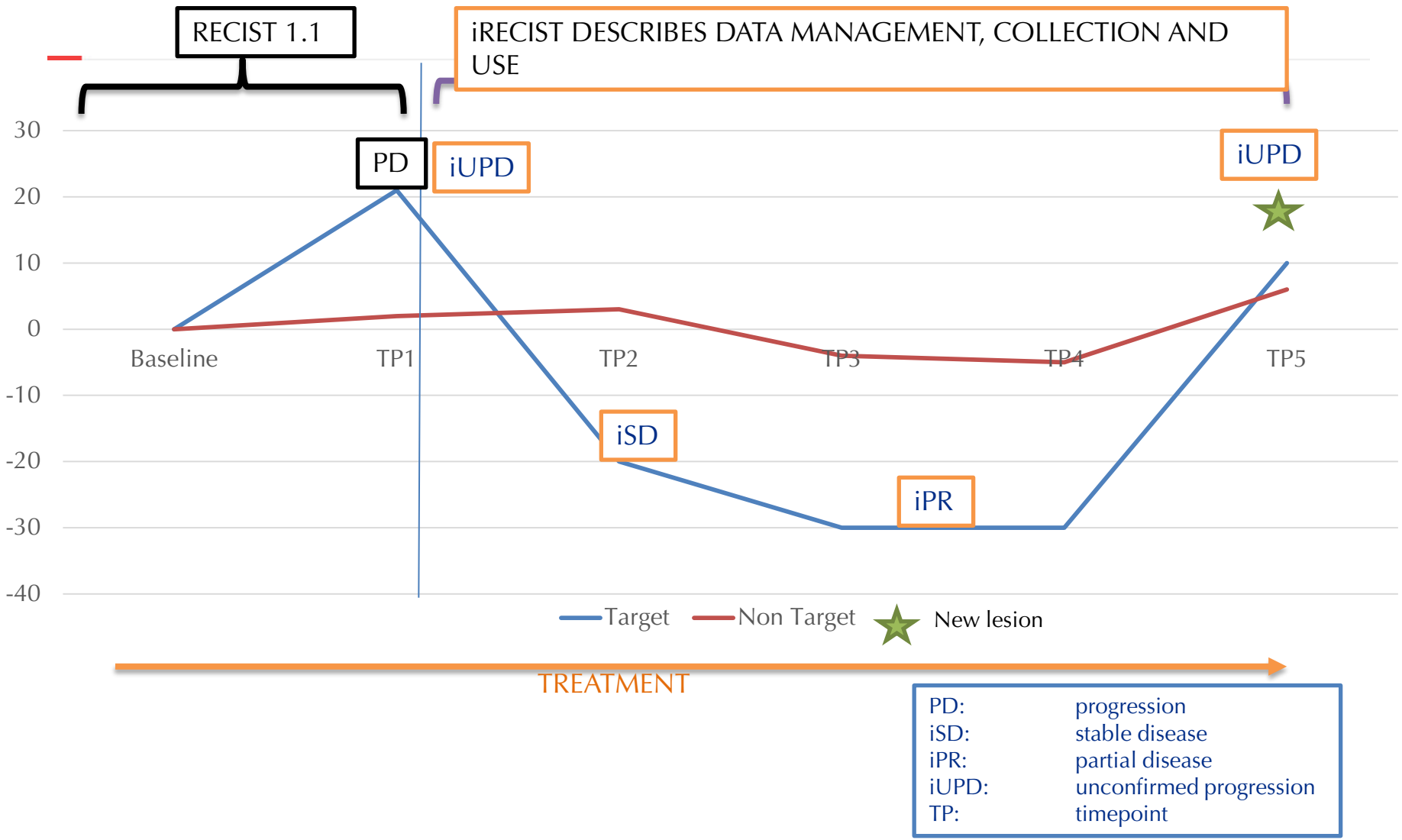


RECIST

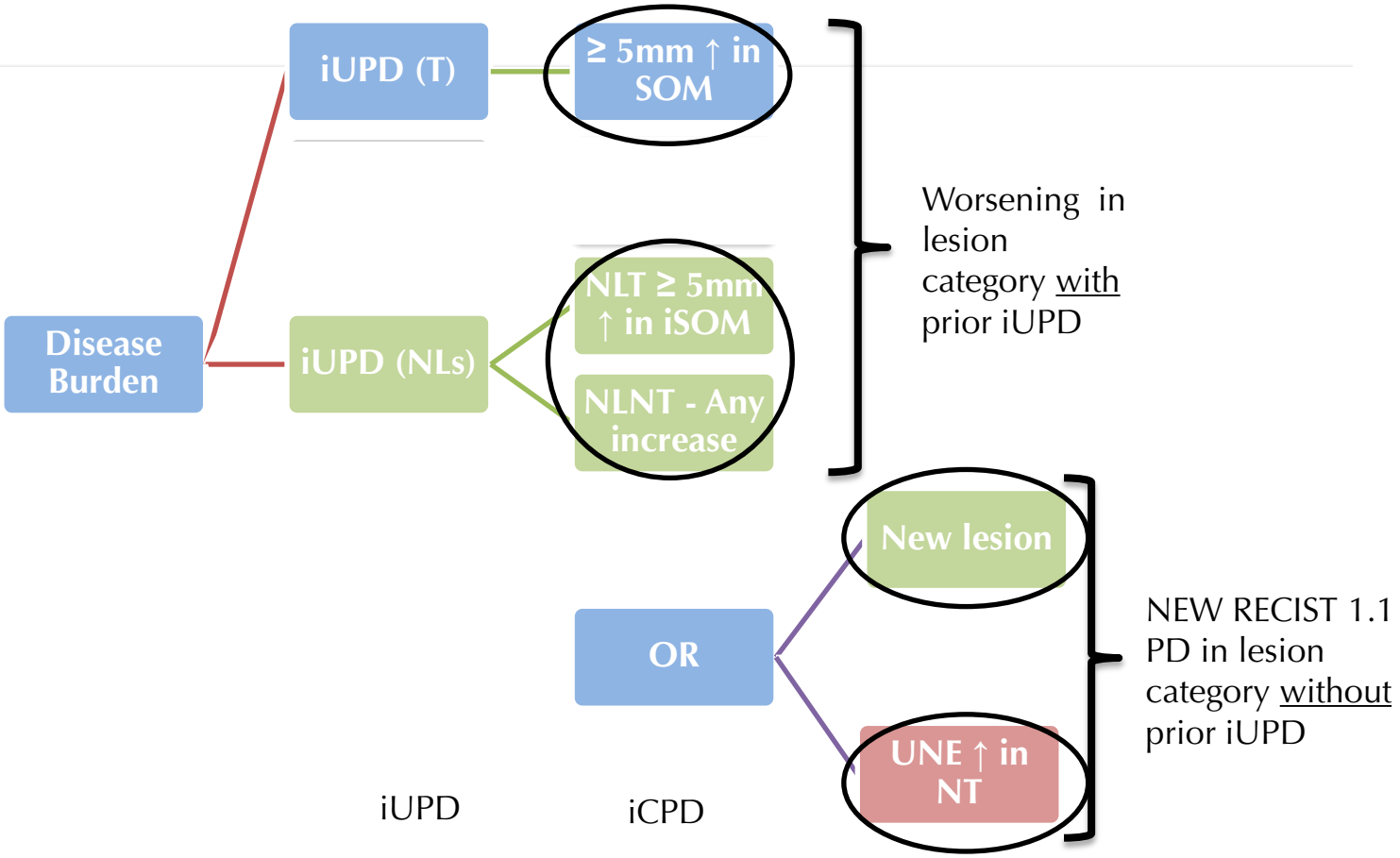
Notes: assigning PD in iRECIST:

- 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

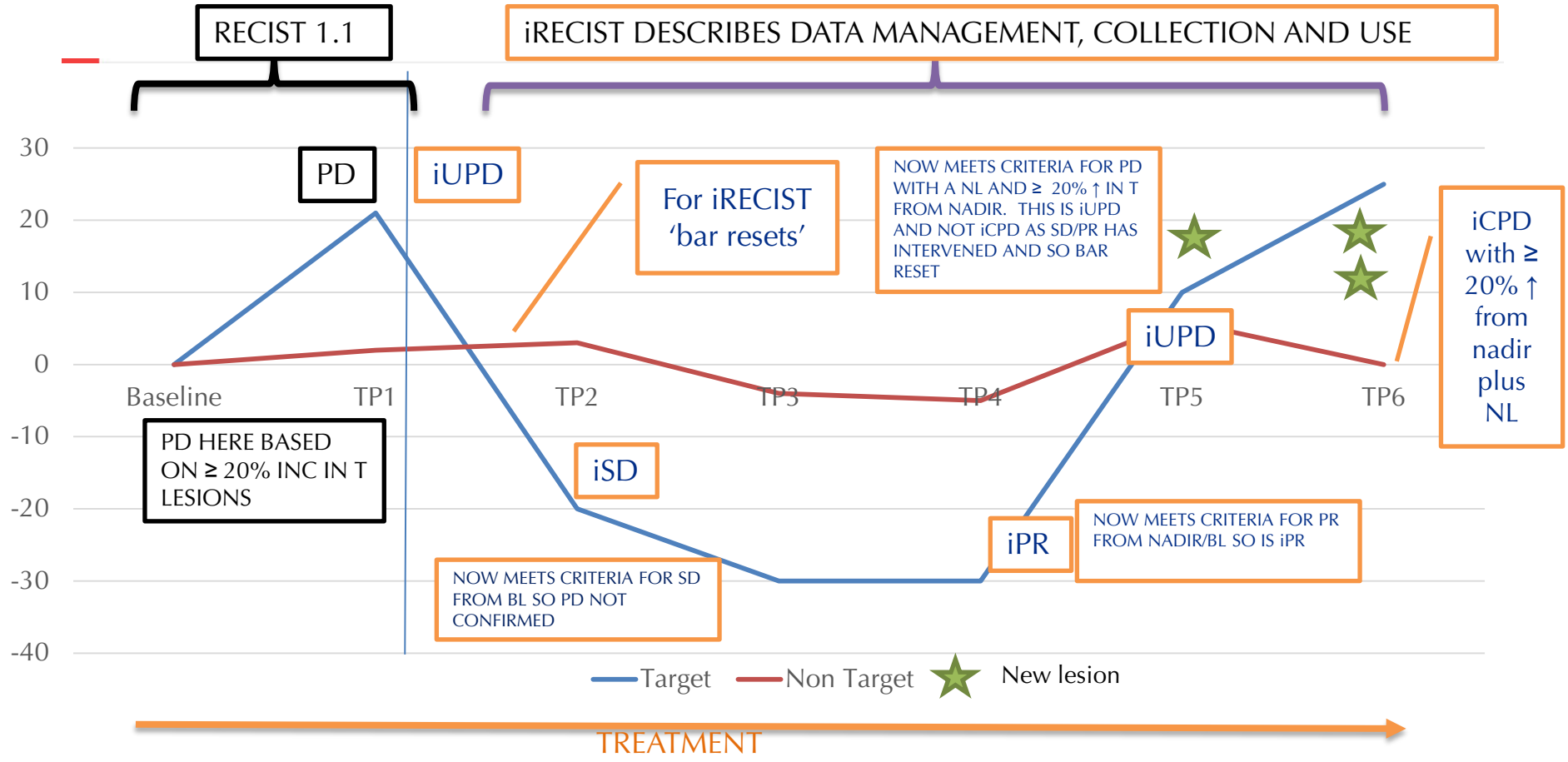
Example : iUPD in T lesion plus a new lesion



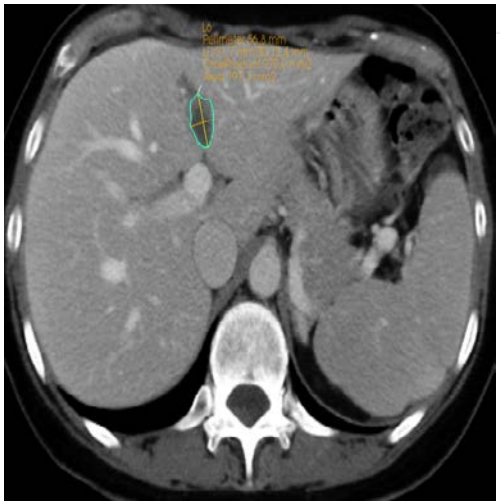
Four ways to confirm progression (iCPD)



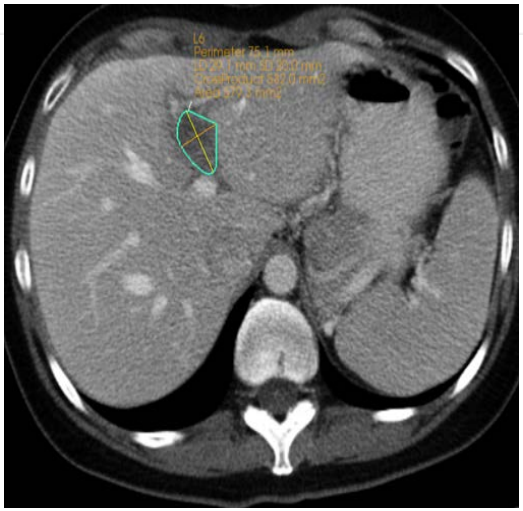
Progression confirmed at timepoint 6



iCPD: Target PD followed by ≥ 5mm↑

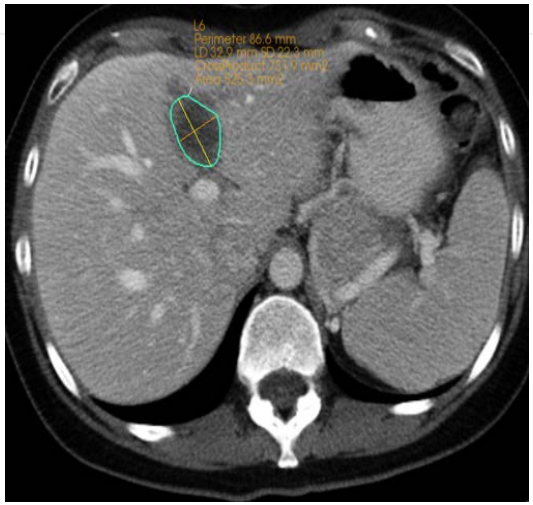


Baseline



TP 1:

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

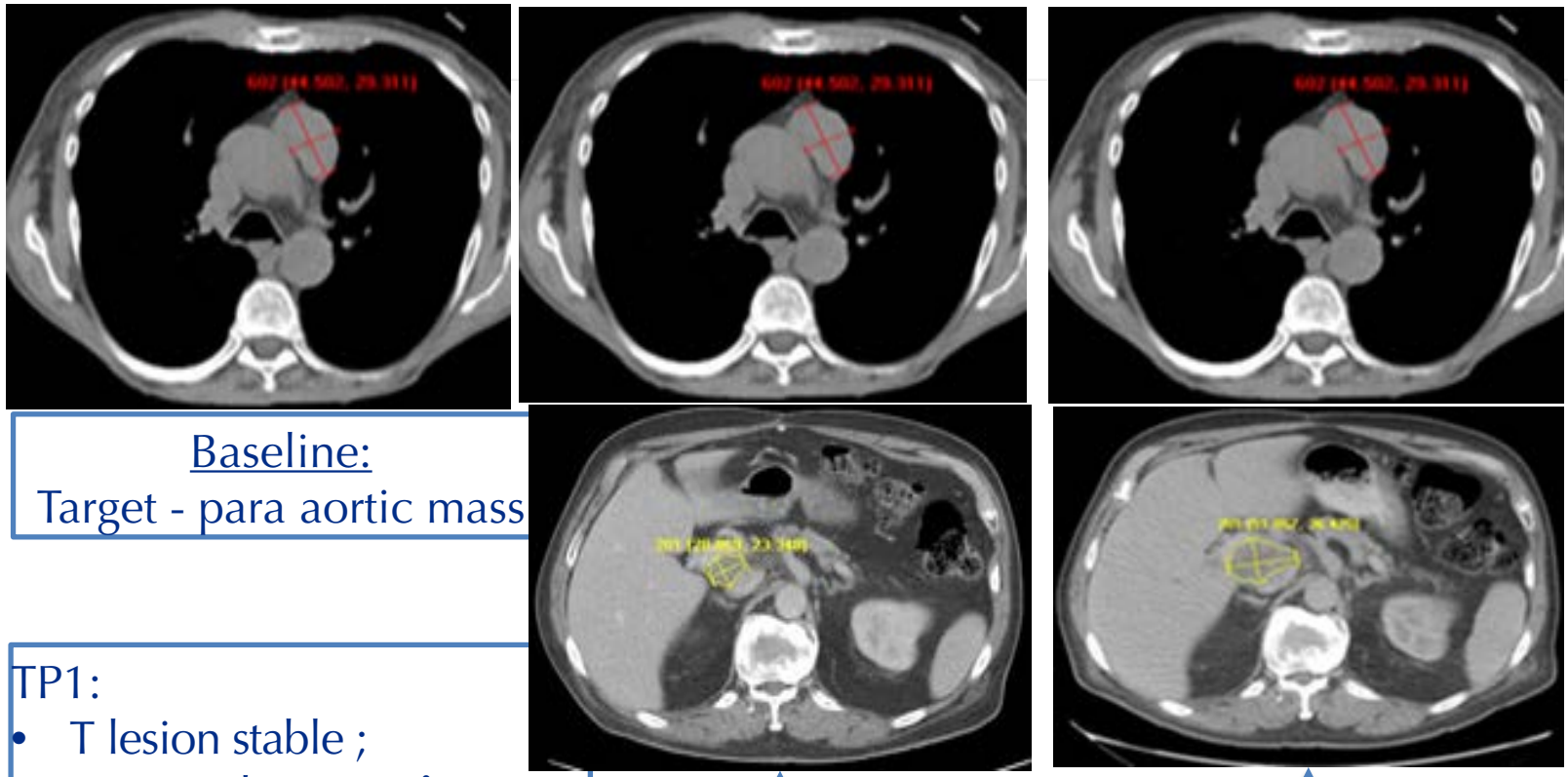


TP 2 (4 wks later):

- SOM ↑ ≥ 5mm above iUPD
- **iCPD**

RECIST

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



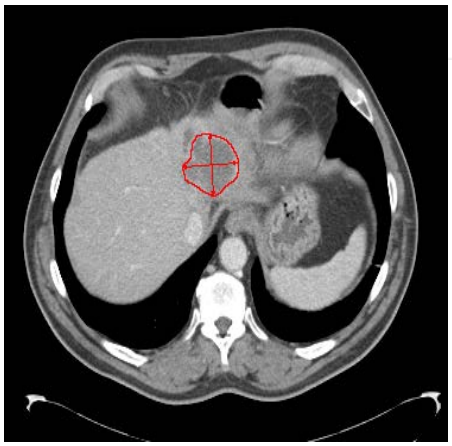
Baseline:
Target - para aortic mass

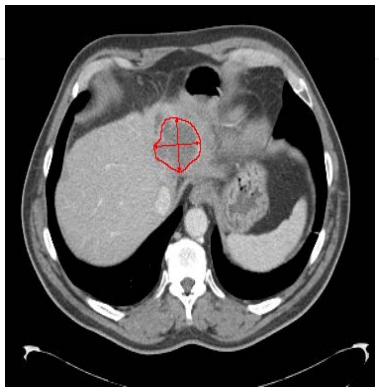
TP1:
- T lesion stable ;
- New node = PD / **iUPD**
- Clinically stable.

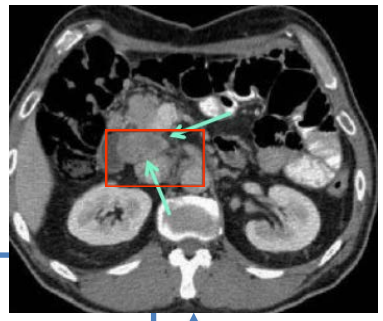
TP2 (+ 4 w):
- T stable,
- NLT ↑ ≥ 5mm
- **iCPD**

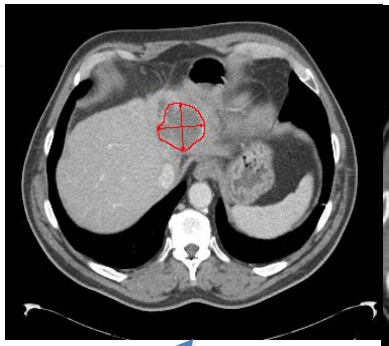
RECIST

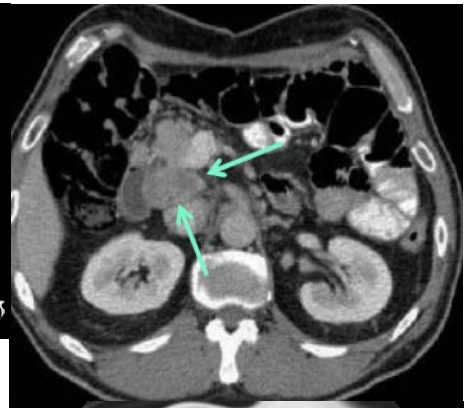
iCPD: New lesion followed by an additional NL

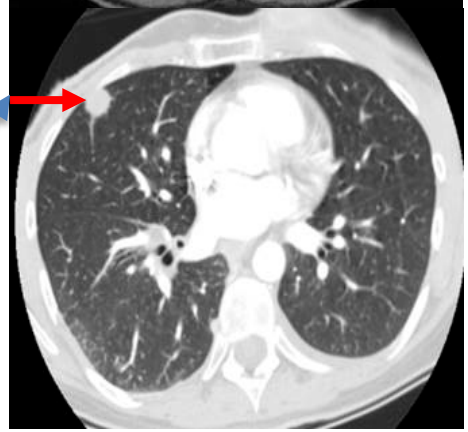












Baseline:
T - liver

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

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

RECIST

More Scenarios

RECIST

	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 PD at TP 1 based on target disease, best RECIST response is PD
- PD not confirmed at TP 1 but is confirmed at TP2 based on new RECIST PD in NT
- iRECIST PD date is TP1, best iRECIST response is PD

RECIST

	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 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 response is iPR

RECIST

	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 and iRECIST PR/iPR at TP2 and 3
- 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+

RECIST

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

RECIST

Statistical Considerations

- RECIST 1.1 should remain primary criteria
  - iRECIST exploratory
- iRECIST Event (progression)
  - iUPD 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

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

Summary: RECIST 1.1 vs. iRECIST

	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

	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

iRECIST in a Nutshell

- RECIST 1.1 – primary criteria
- Progression must be confirmed
  - Consider treatment past progression only in carefully defined scenarios
  - Confirmation requires some worsening of disease bulk
    - RECIST 1.1 PD criteria if the lesion category was previously stable disease or better
- 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

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

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

In Press

THE LANCET Oncology

- This presentation
- Protocol sections
- CRF examples
- FAQ
- A WORD version of the manuscript (after publication)

Acknowledgments

Institution/Agency	Participants
RECIST Working Group	Elisabeth de Vries, Jan Bogaerts, Saskia Litière, Alice Chen, Robert Ford, Sumithra Mandrekar, Nancy Lin, Janet Dancey, Lesley Seymour, Stephen Hodi, Larry Schwartz, Patrick Therasse, Eric Huang, Otto Hoekstra, Lalitha Shankar, Jedd Wolchok, Yan Liu, Stephen Gwyther
European Medicines Agency	Francesco Pignatti, Sigrid Klaar, Jorge Martinalbo
Food and Drug Agency, USA	Patricia Keegan, Sirisha Mushti, Gideon Blumenthal
AstraZeneca	Ted Pellas, Ramy Ibrahim**, Rob Iannone, Renee Iacona
Merck	Andrea Perrone*, Eric Rubin, Roy Baynes, Roger Dansey
Bristol Myers Squibb	David Leung, Wendy Hayes*
Genentech	Marcus Ballinger, Daniel S Chen, Benjamin Lyons, Alex de Crispigny
Gustave Roussy Cancer Campus	Caroline Caramella
Amgen	Roger Sidhu
* RECIST Working Group Member ** Currently Parker Institute	

RECIST

Acknowledgements

We also received written comments from:

Darragh Halpenny, Jean-Yves Blay, Florian Lordick, Silke Gillessen, Hirokazu Watanabe, Jose Pablo Maroto Rey, Pietro Quaglino, Howard Kaufman, Denis Lacombe, Corneel Coens, Catherine Fortpied, Jessica Menis, Francisco Vera-Badillo, Jean Powers, Michail Ignatiadis, Eric Gauthier, Michael O'Neal, Caroline Malhaire, Laure Fournier, Glen Laird.

Supported by

- Canadian Cancer Society Research Institute (grant #021039)
- EORTC Cancer Research Fund
- NCI (grant number 5U10-CA11488-45)