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iRECIST

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

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

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RECIST

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Disclosures

I have no conflicts to declare

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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

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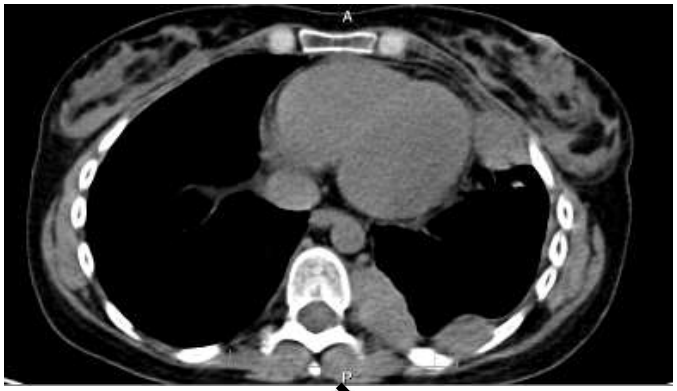
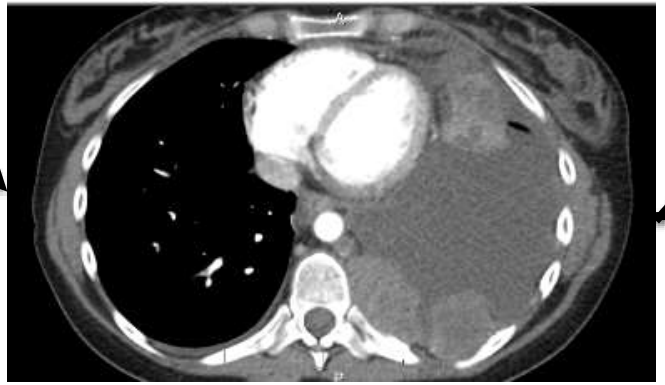
Unusual Response Patterns

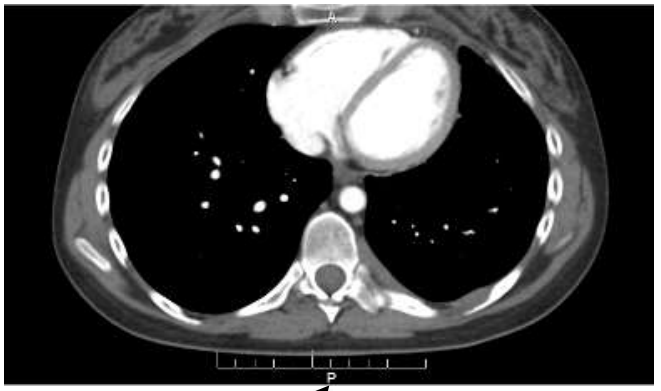


Baseline

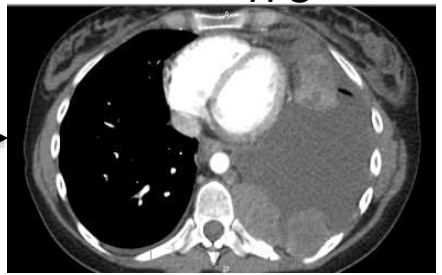


Time point 2

TP3



TP3



How should we assess response and progression for trials of immunotherapies?

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Plan

- RECIST Working Group
- Overview of current criteria & concerns
- Development of iRECIST
- Overview of iRECIST with examples
- Using iRECIST in your trials

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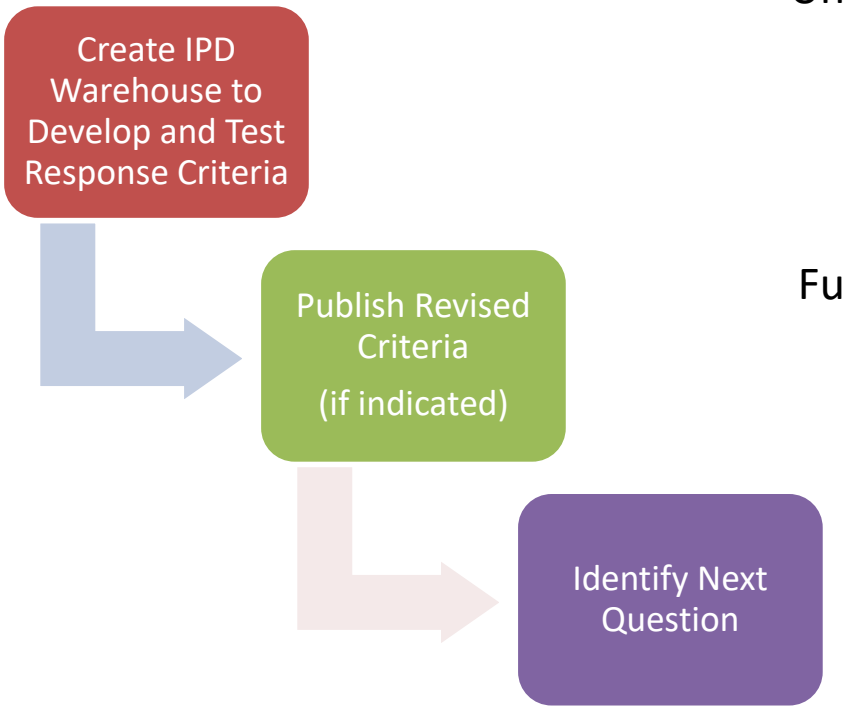
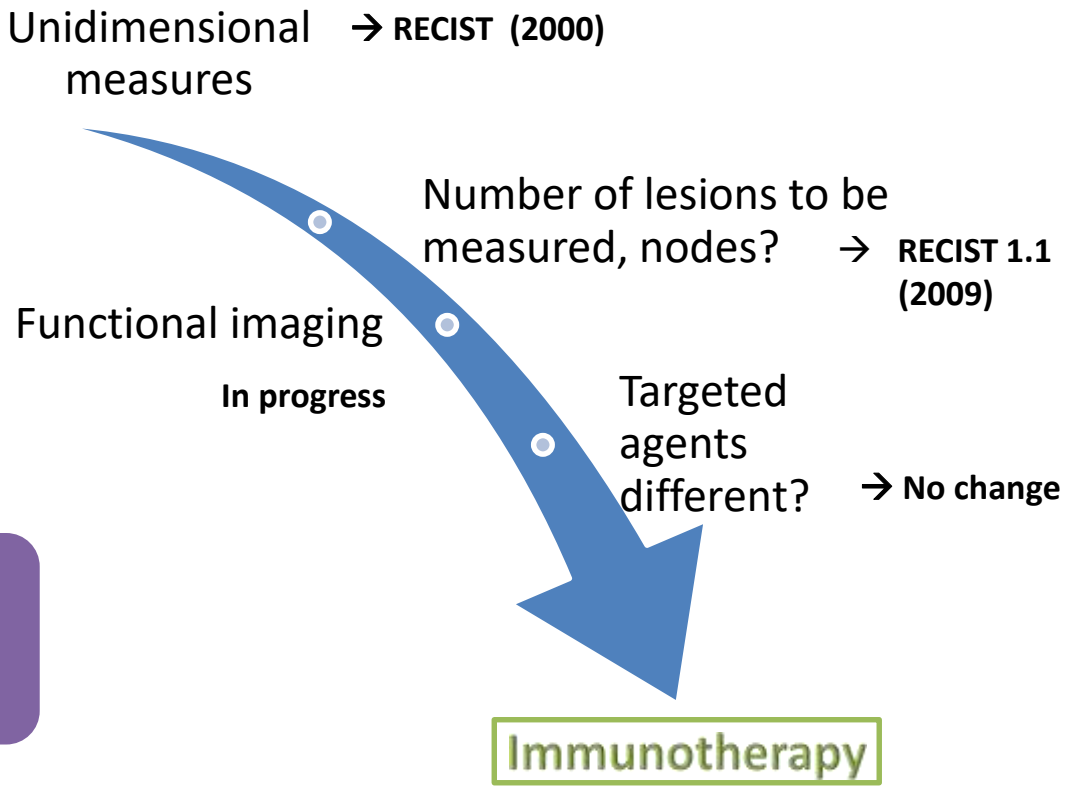
RECIST Working Group





Testing and Validating RECIST for Trials of Immunotherapy

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

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Response and Immunotherapy

- 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.

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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?

Testing and Validating RECIST for Trials of Immunotherapy

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

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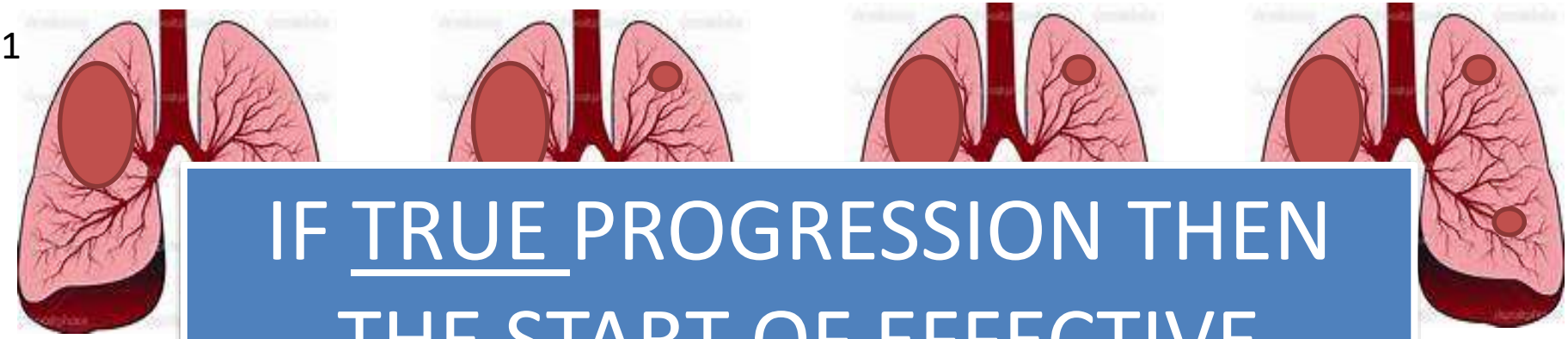
True or Pseudoprogression ?

1



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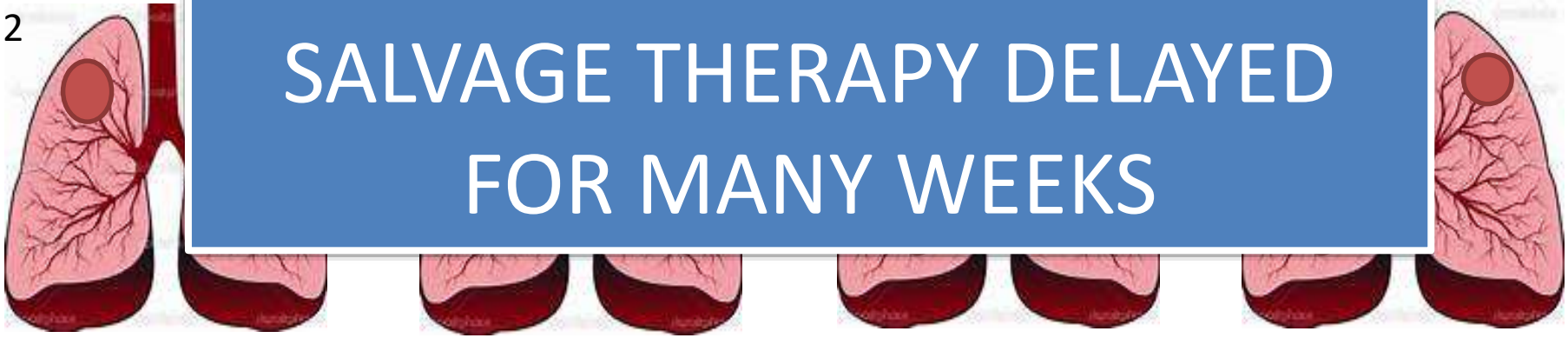

IF TRUE PROGRESSION THEN THE START OF EFFECTIVE SALVAGE THERAPY DELAYED FOR MANY WEEKS

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?)

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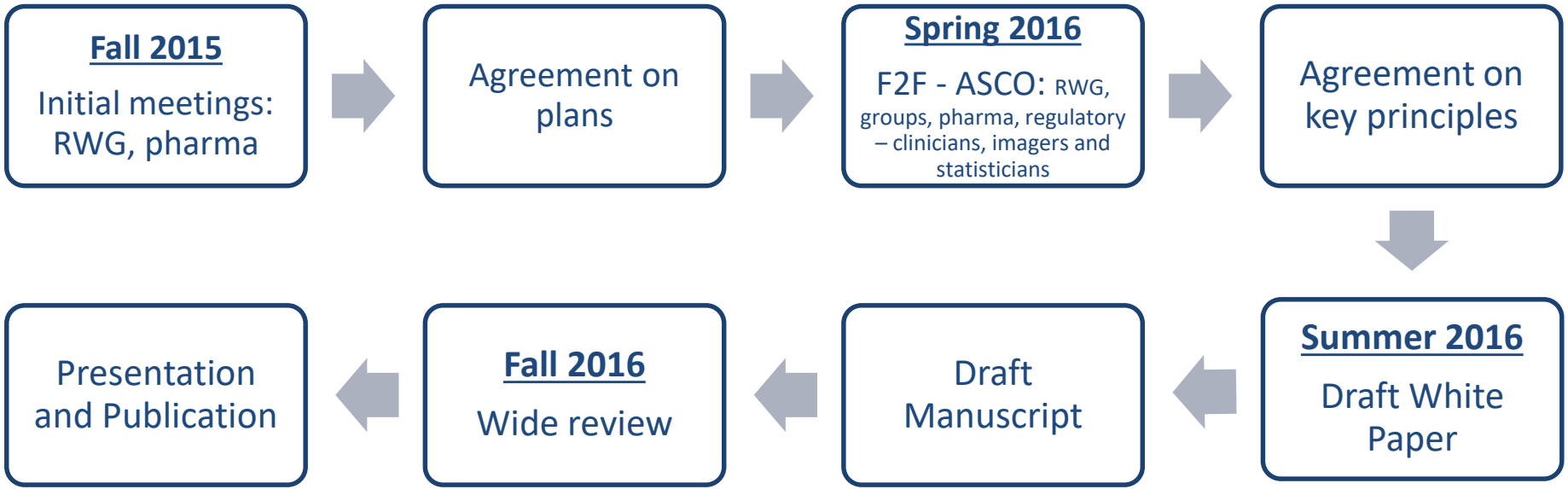
Development of iRECIST Guideline



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

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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

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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))	√

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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**

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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)
- 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
- TP response is dynamic and based on
  - Change from baseline (iCR, iPR, iSD) or change from
  - The last i-response

Prior iUPD does not preclude subsequent iCR, iPR or iSD

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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

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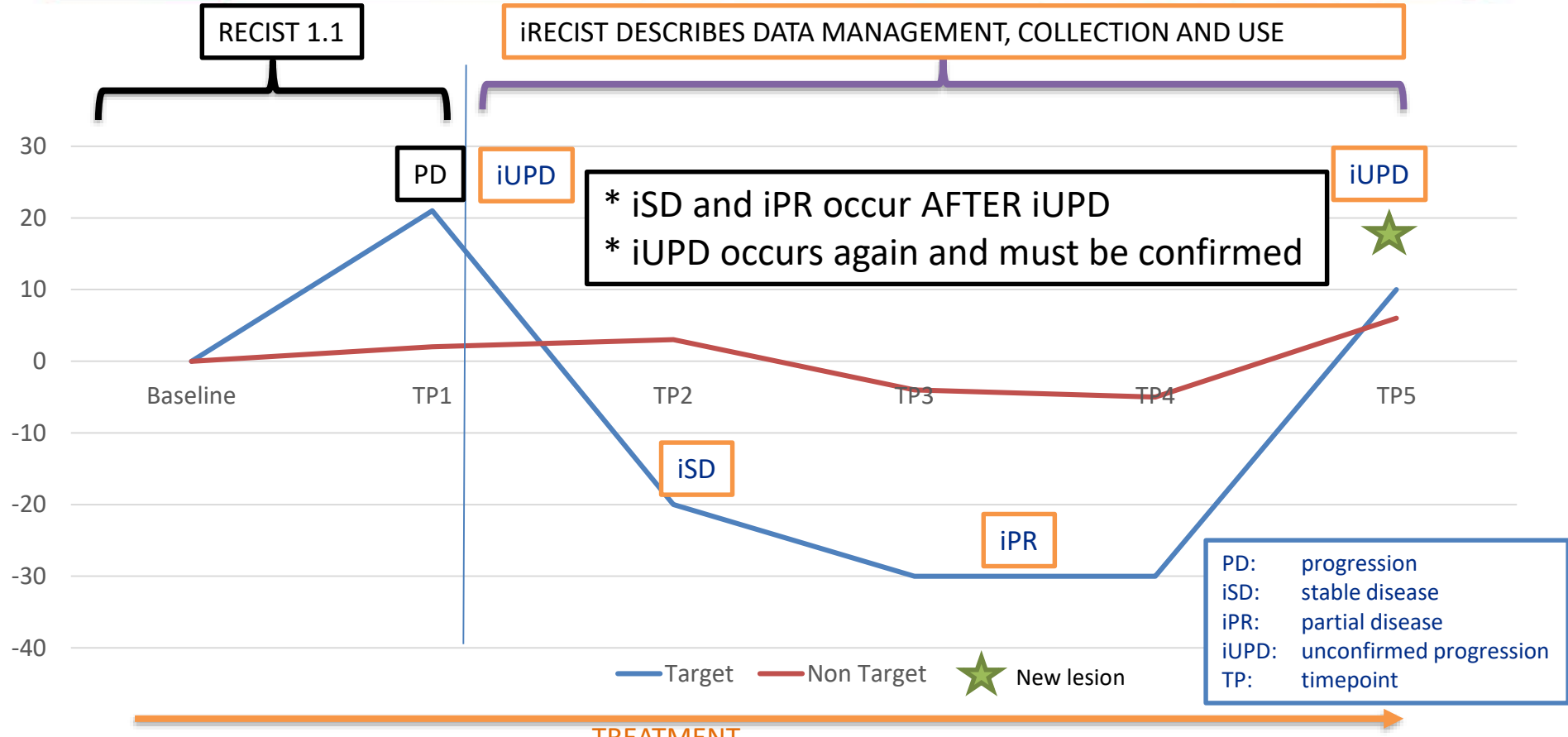
Summary



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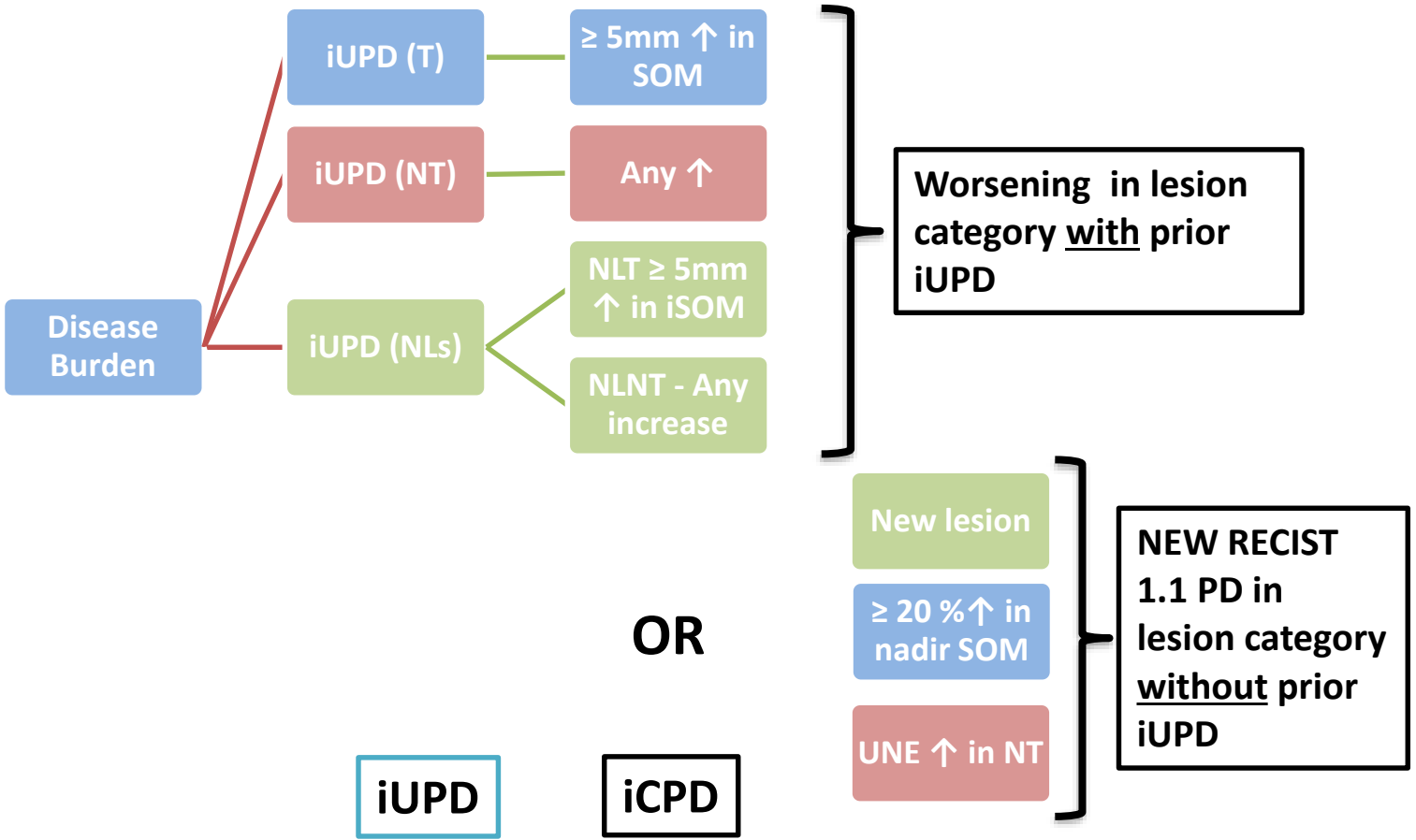
Confirming Progression (iCPD)



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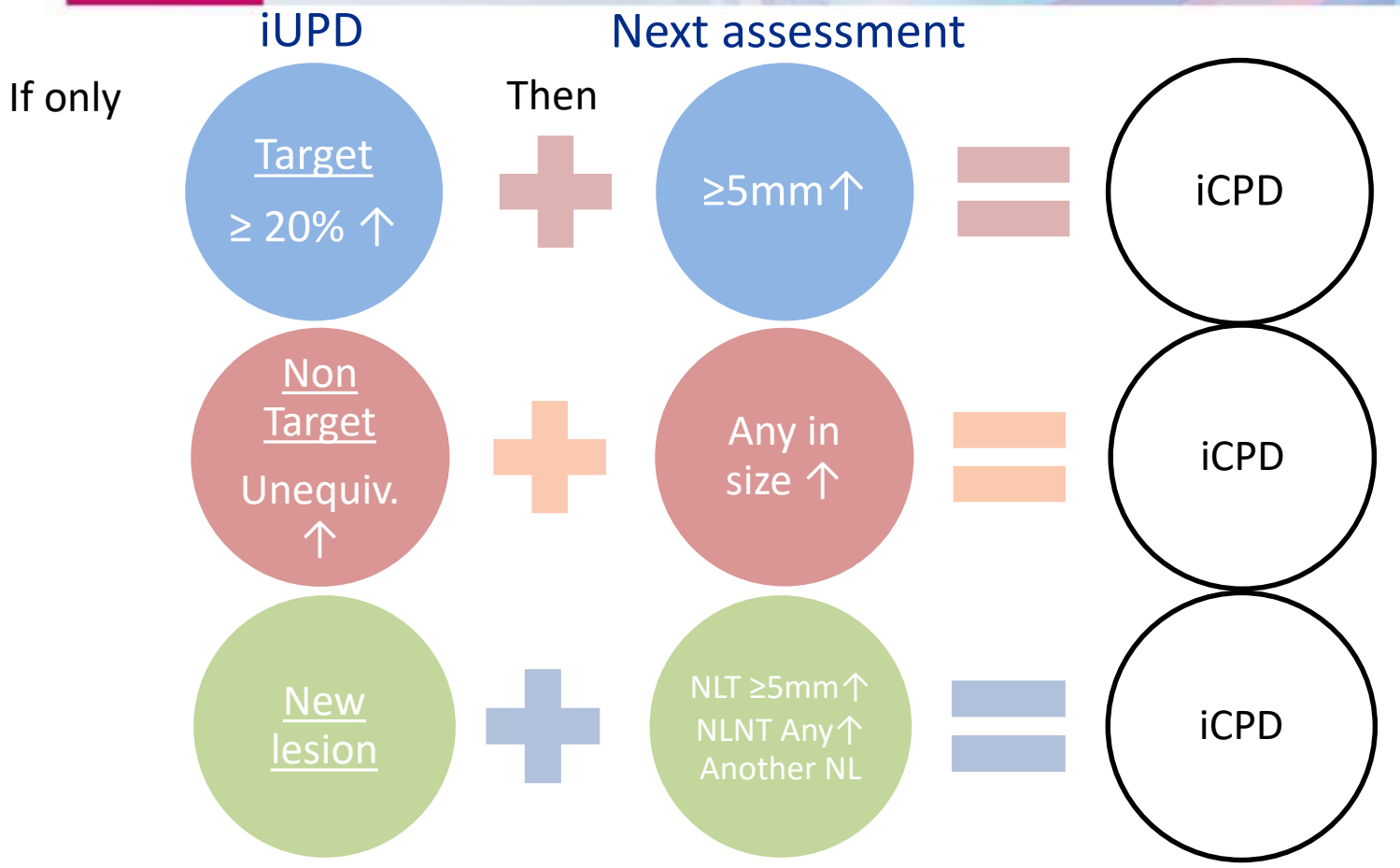
iCPD in Lesion Category with iUPD



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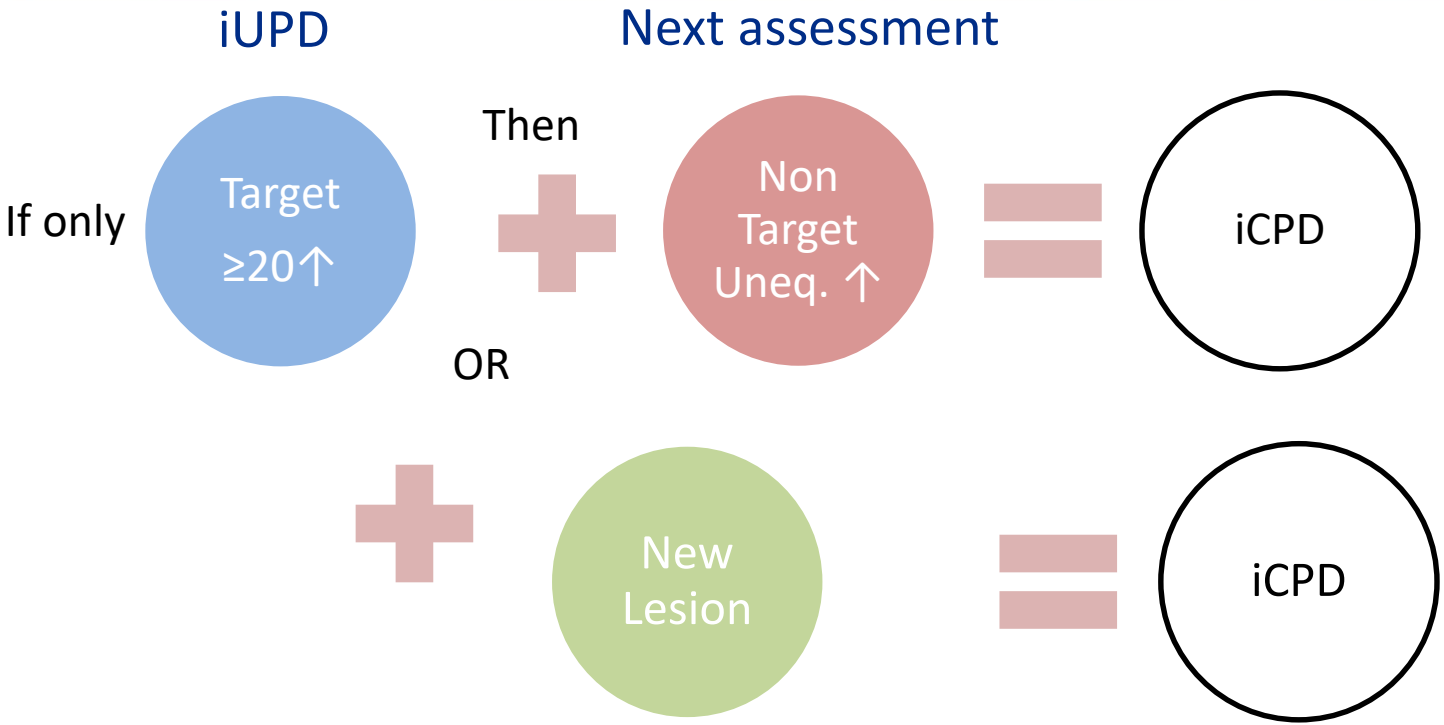
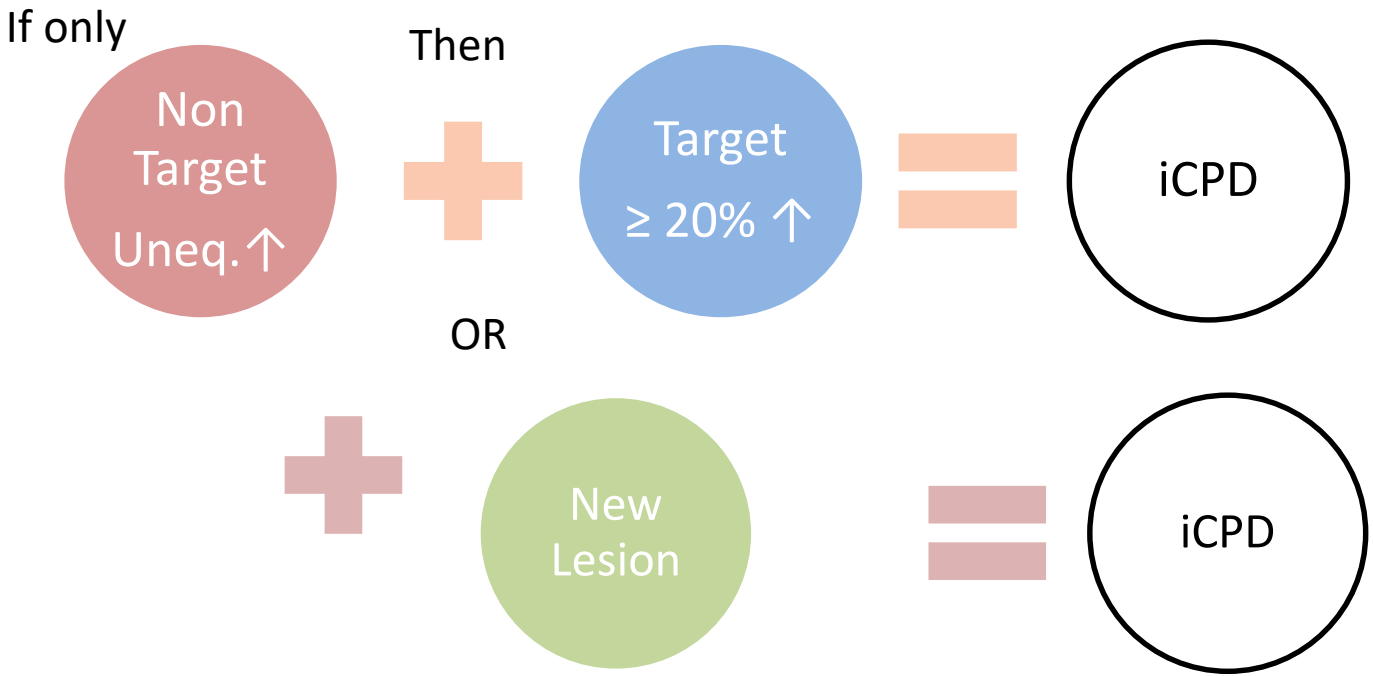
New RECIST PD in another Lesion Category



New RECIST PD in another Lesion Category

iUPD

Next assessment



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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

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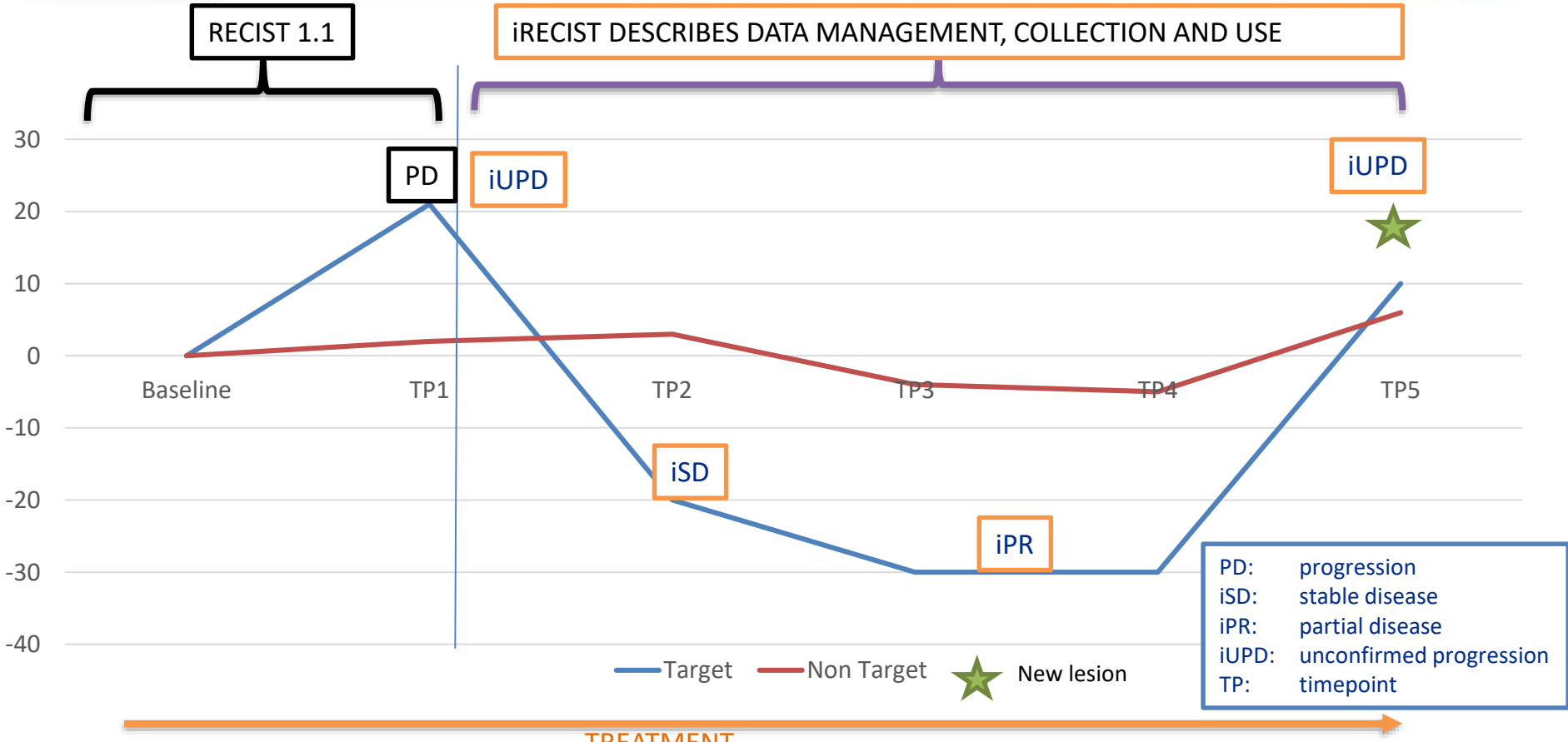
Summary: iUPD – T and NL



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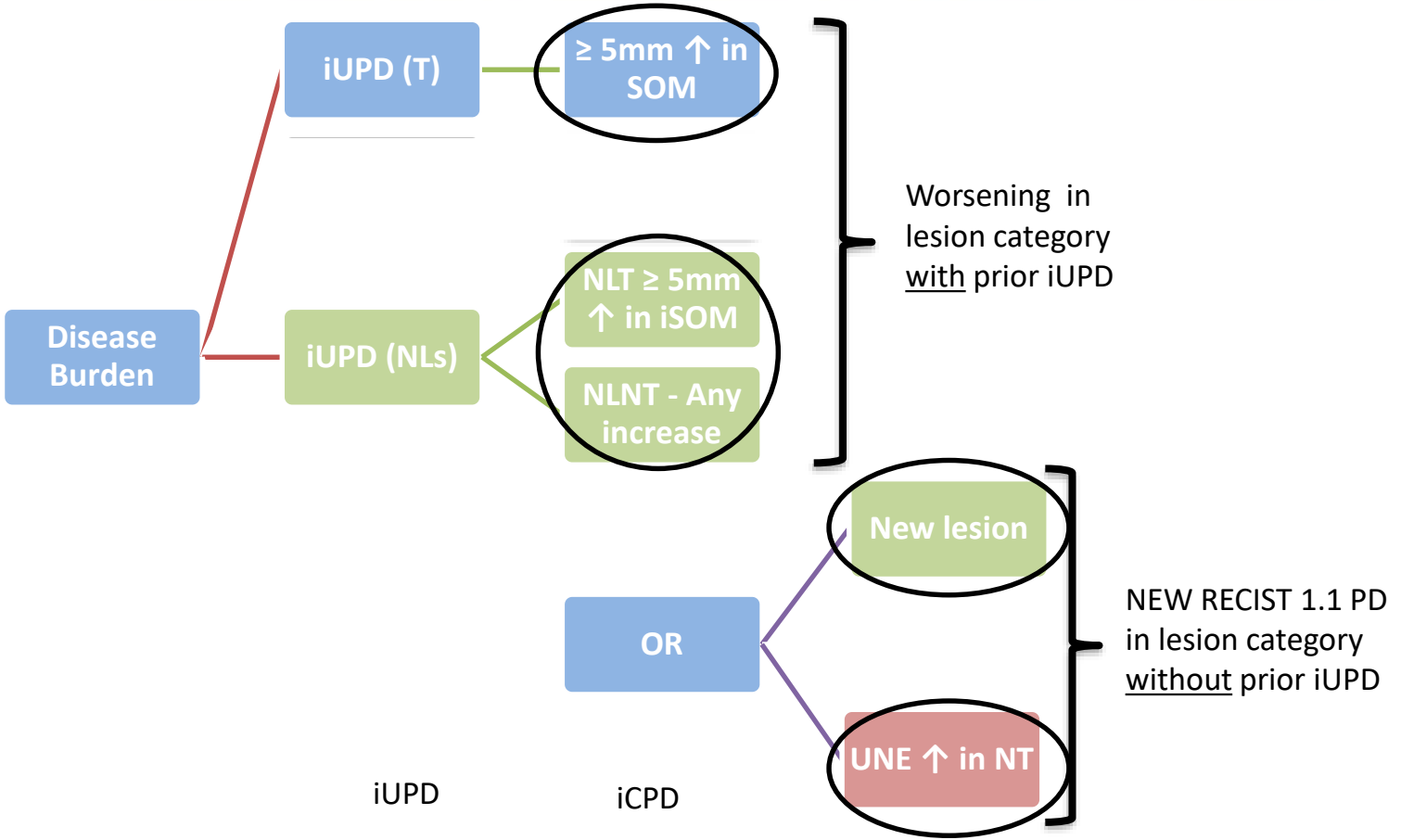
Confirming Progression (iCPD)



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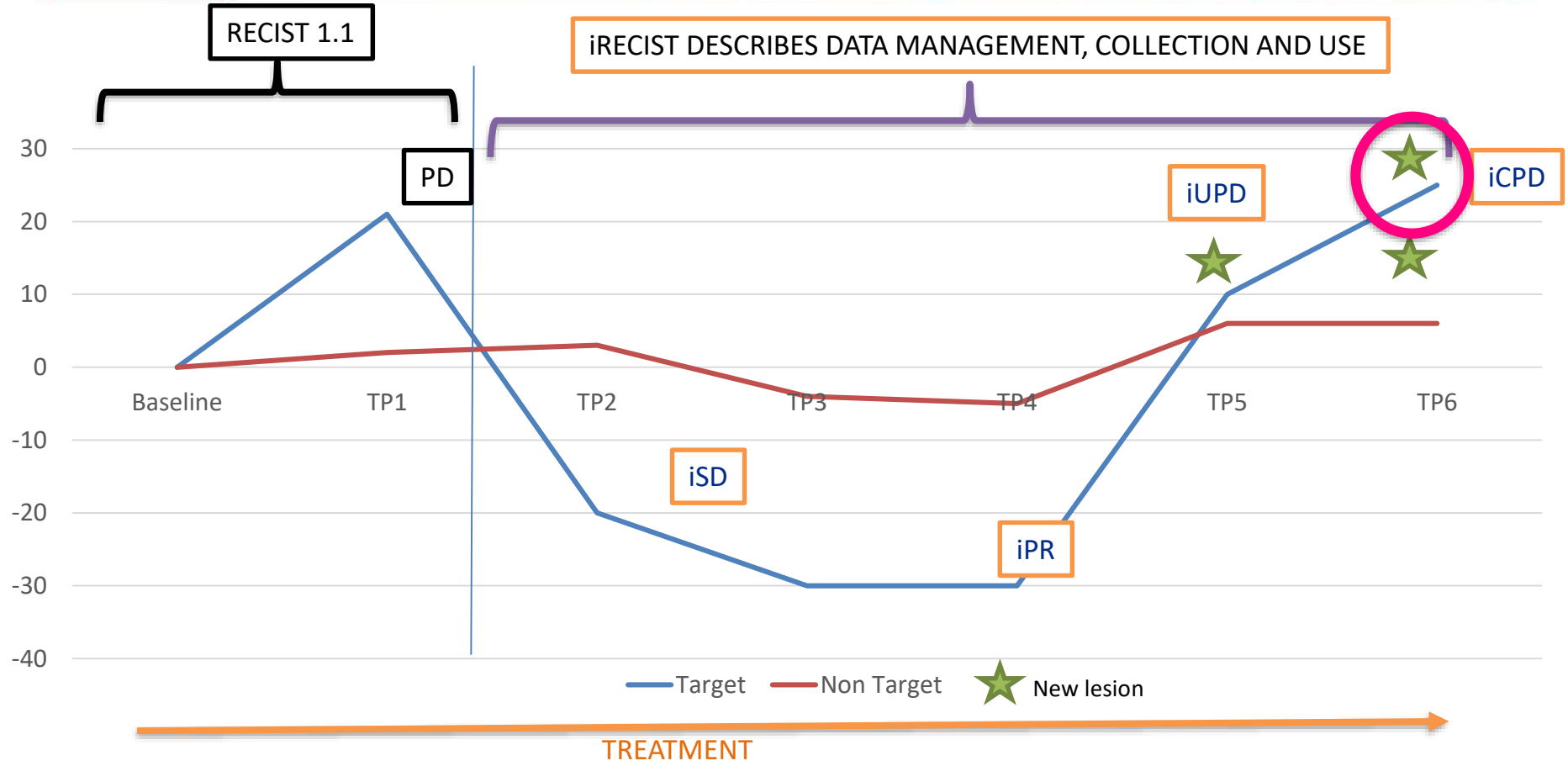
Summary



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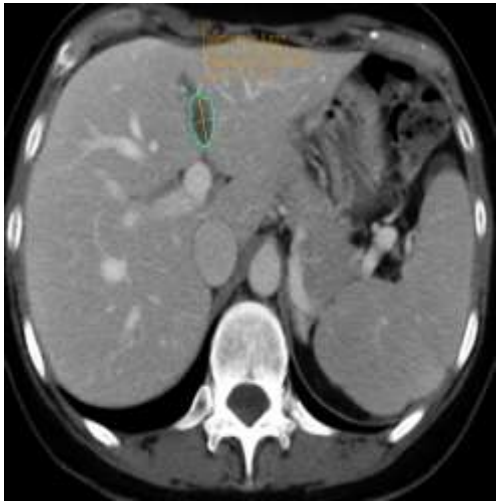
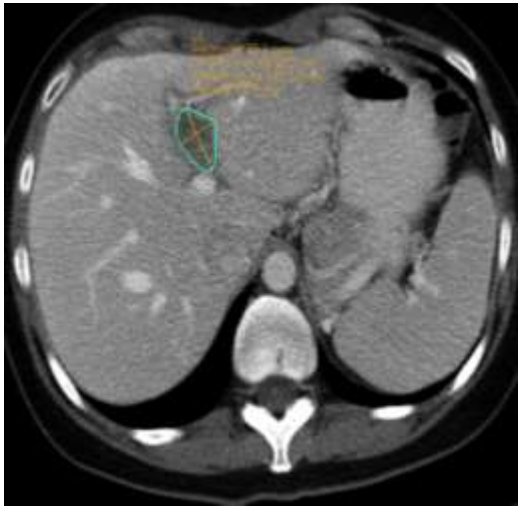
iCPD: Target PD followed by ≥ 5mm↑

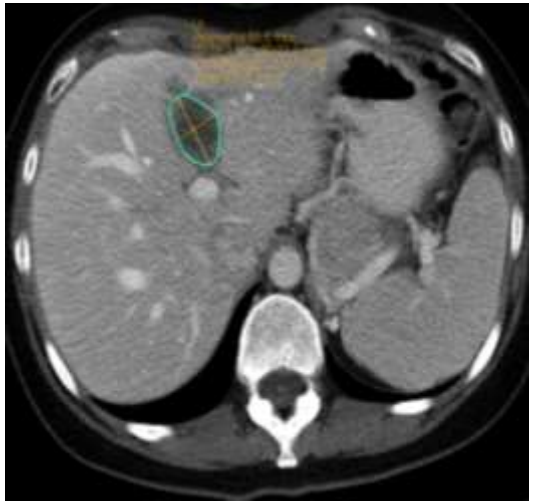


Baseline



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**

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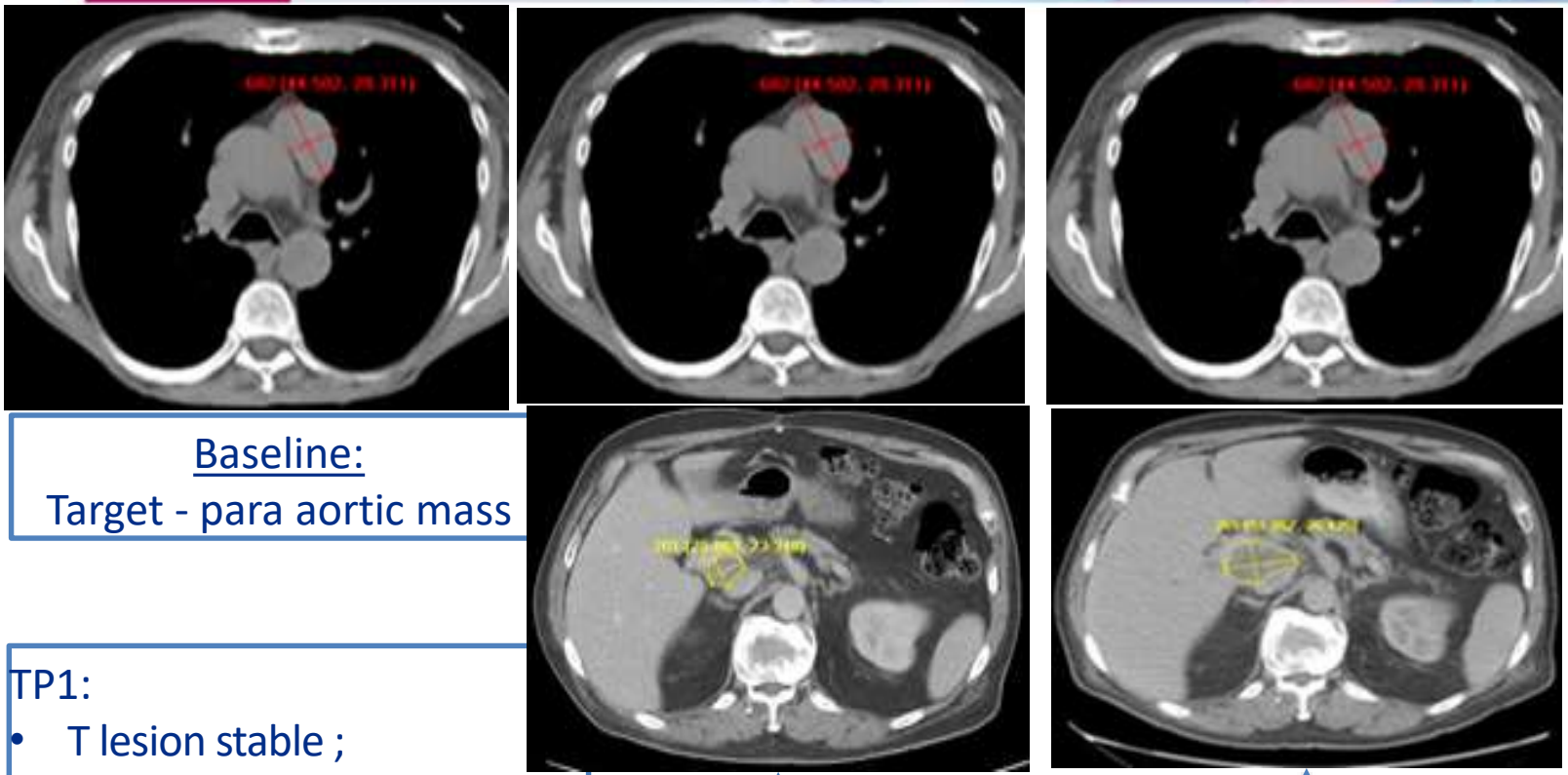
iCPD: NL then ≥ 5mm ↑iSOM



Baseline:
Target - para aortic mass

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

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

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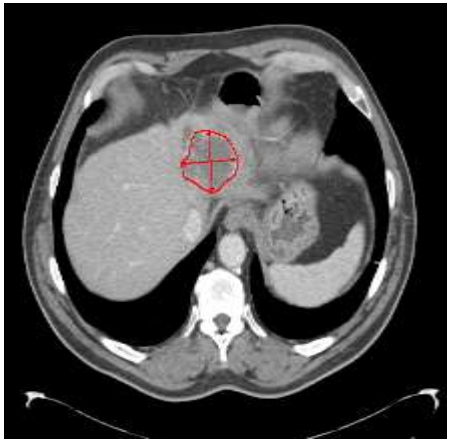
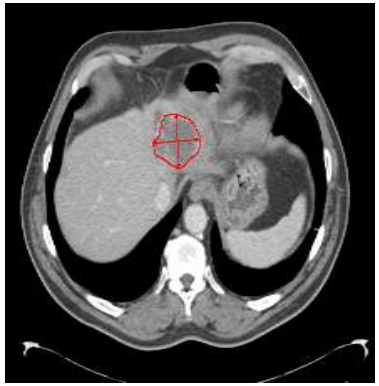
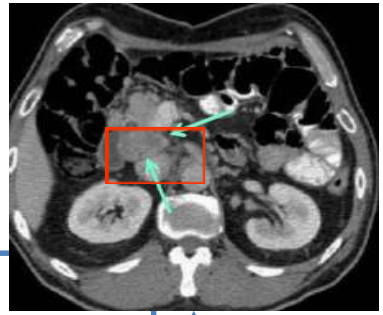
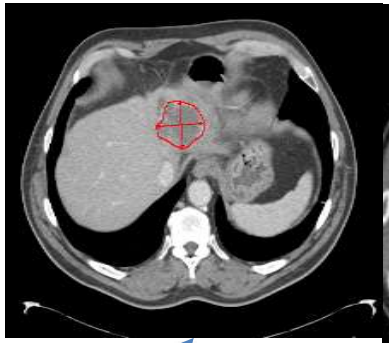
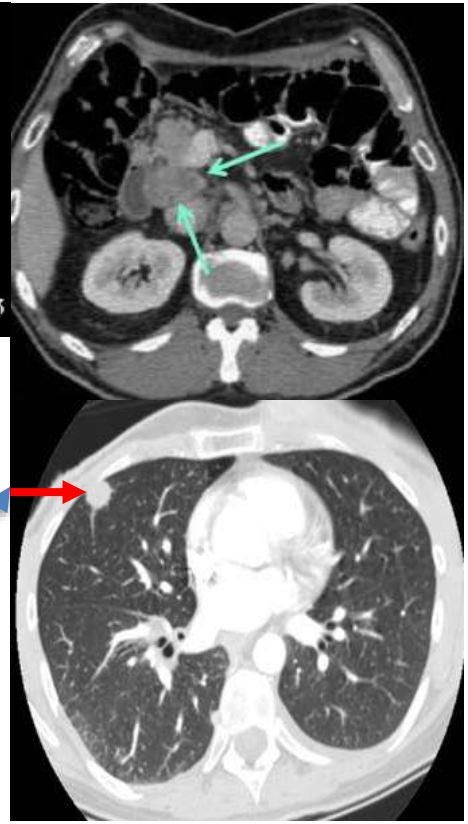
iCPD: NL then additional NL











Baseline:
T - liver

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

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

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Statistical Considerations

- RECIST 1.1 should remain primary criteria
  - iRECIST exploratory
- iRECIST Event (progression)
  - iUPD date which has been subsequently confirmed
  - 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

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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

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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
- 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

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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

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

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RECIST Working Group

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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)

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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
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Amgen	Roger Sidhu
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