iRECIST

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

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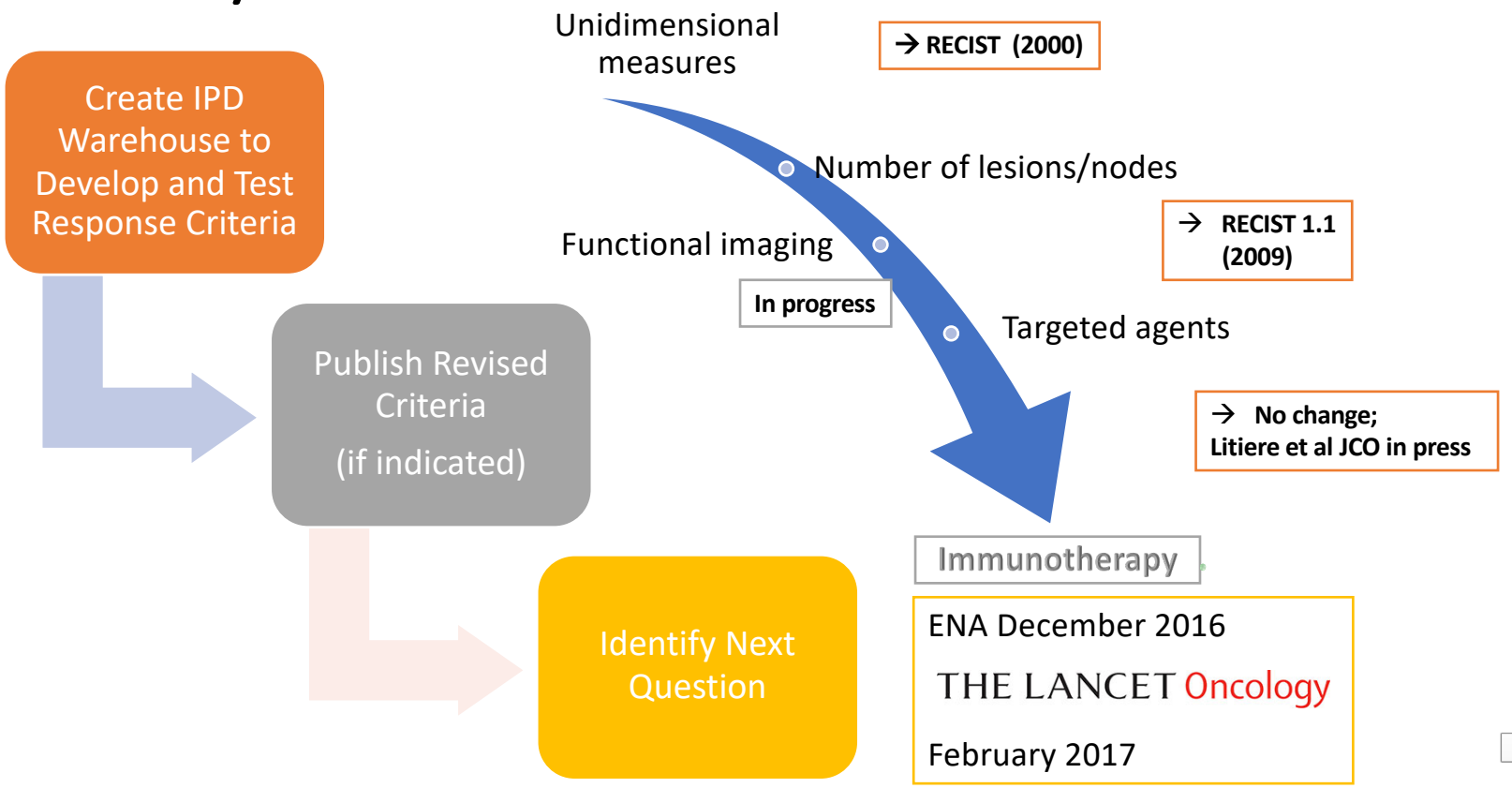
Background

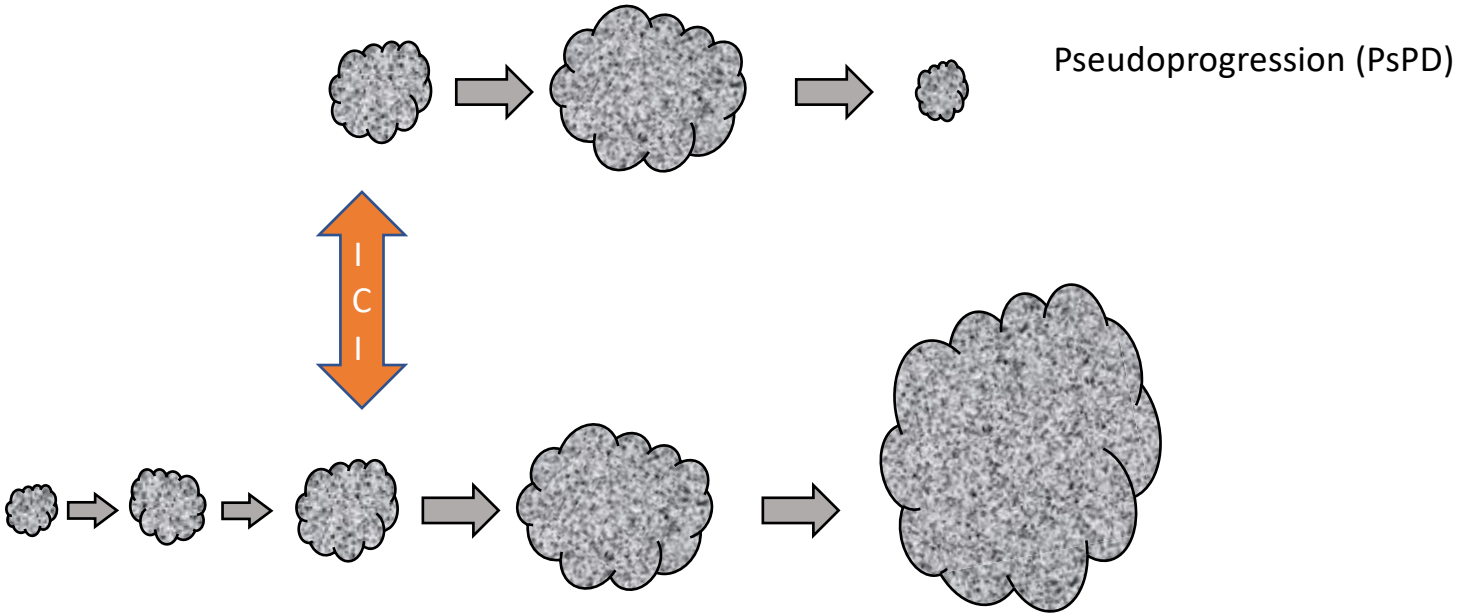
Response Criteria

- Gold standard for evaluating new therapies remains improvement in survival or quality of life
- Response based endpoints needed
  - Early clinical trials – making development decisions
  - Effective salvage therapies necessitate using response based endpoints such as progression or relapse free survivalo

RECIST Working Group Strategy and Activity



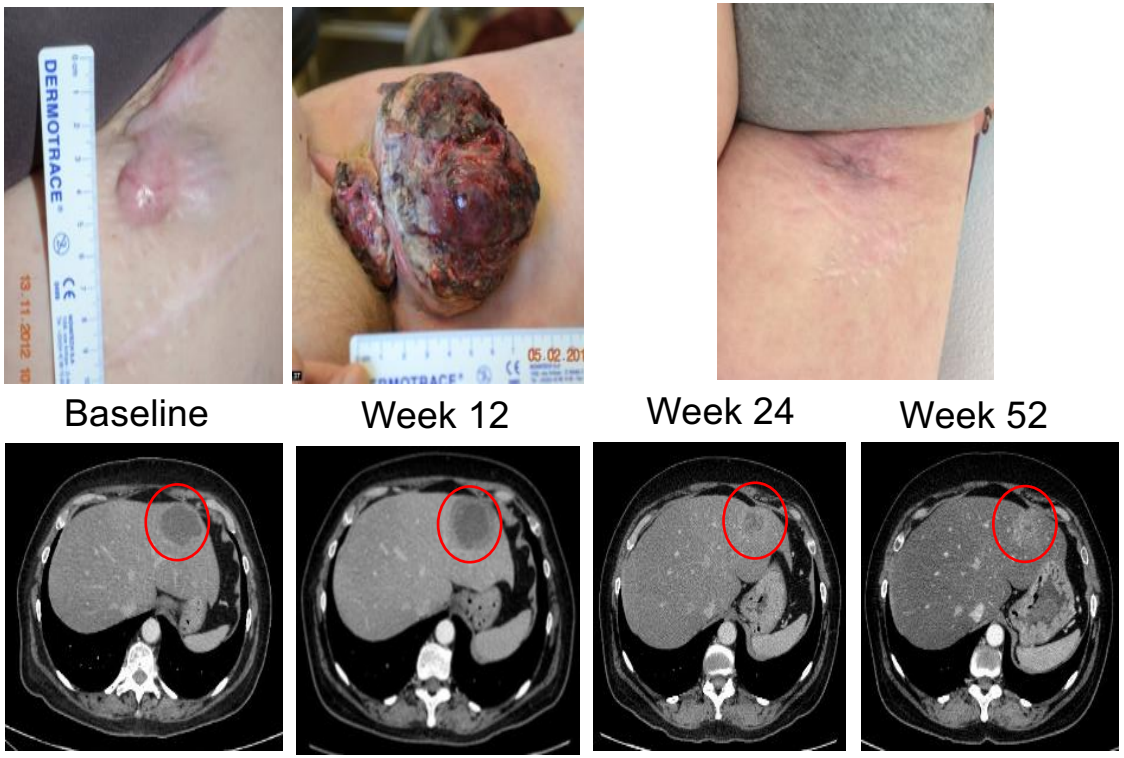
Rationale for iRECIST



Pseudoprogression (PsPD)

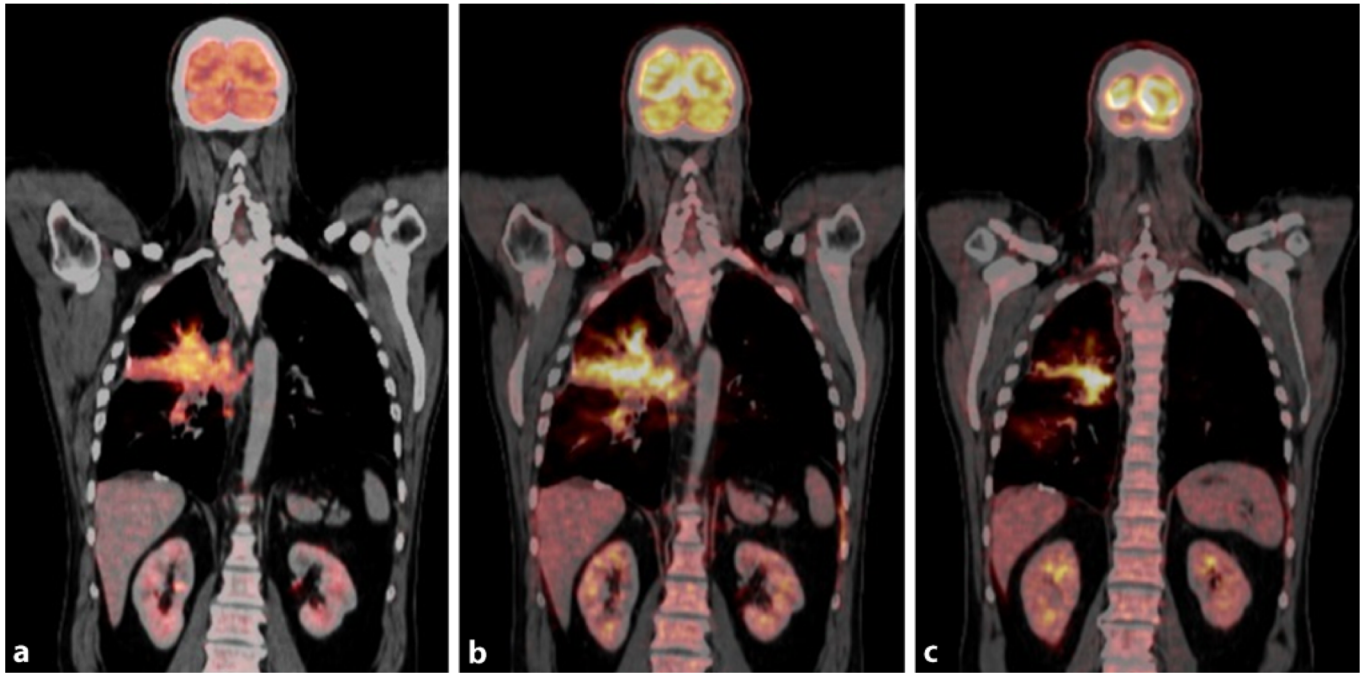
Hyperprogression (HPD)

Early PsPD: Advanced melanoma



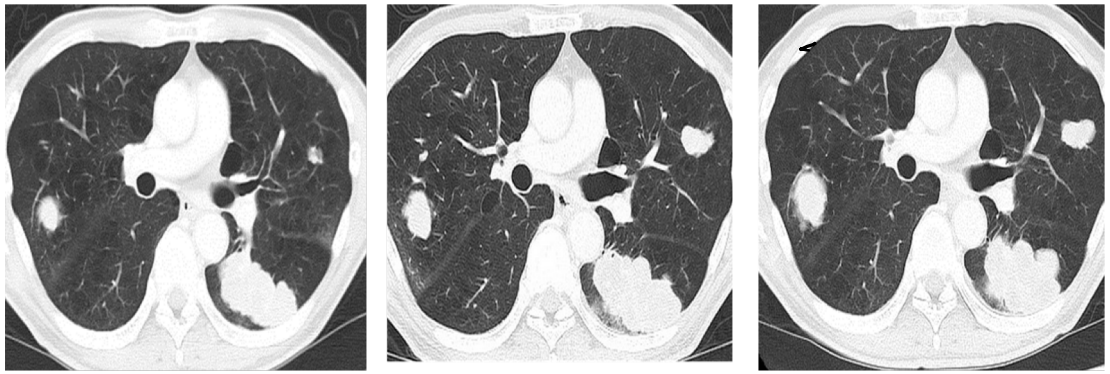
Presented by: F. Stephen Hodi ASCO 2014

Early PsPD: NSCLC

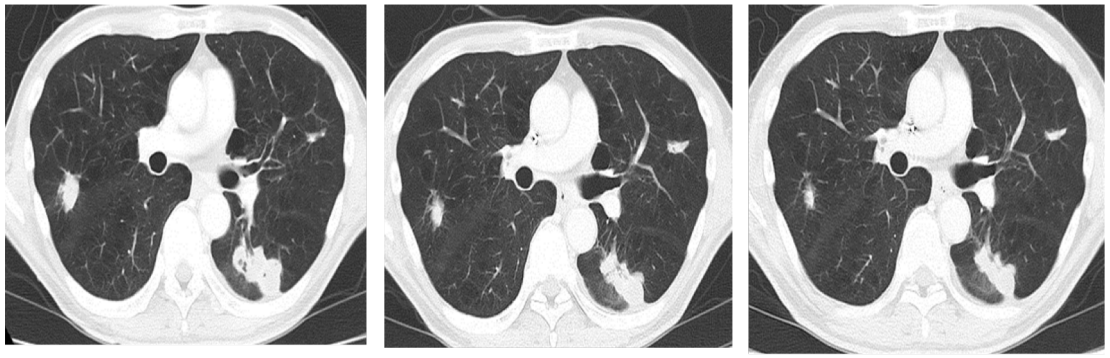


Beer et al: memo (2018) 11:138–143

Delayed PsPD



Baseline | Week 8 SD | Week 16 PD due to non target progression



Week 24 Tumor Burden ↓ 29.3% | Week 28 Tumor Burden↓ 37.3% | Week 32 Tumor Burden↓ 37.3%

PD at week 16 (central review)

PR achieved at week 28, confirmed at week 32

Both target and non-target lesions improved

Cannot be captured by RECIST 1.1

Case presented by K Muro at 2015 Gastrointestinal Cancer Symposium (abstract 03).

PRESENTED AT: ASCO Annual '15 Meeting

8

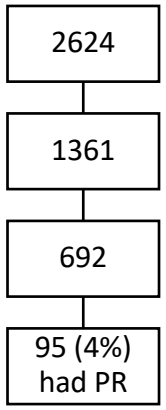
PsPD Incidence

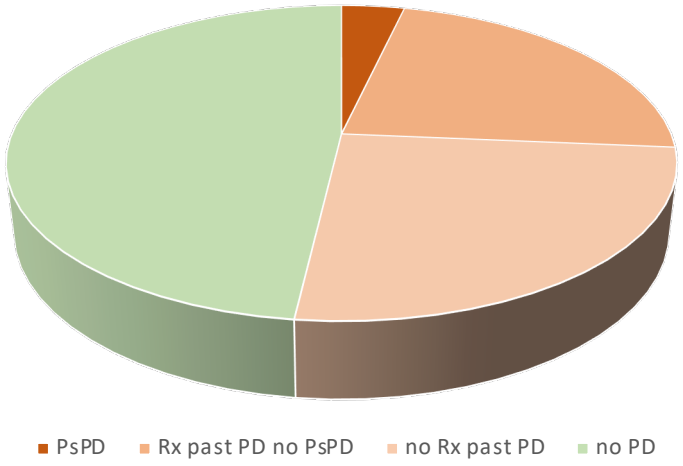
- Relatively uncommon phenomenon
- Reported incidence
  - Melanoma : 4 to 10%
  - NSCLC : 1 to 5%
  - Bladder: 2-17%
  - Renal: 5-15%

Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis

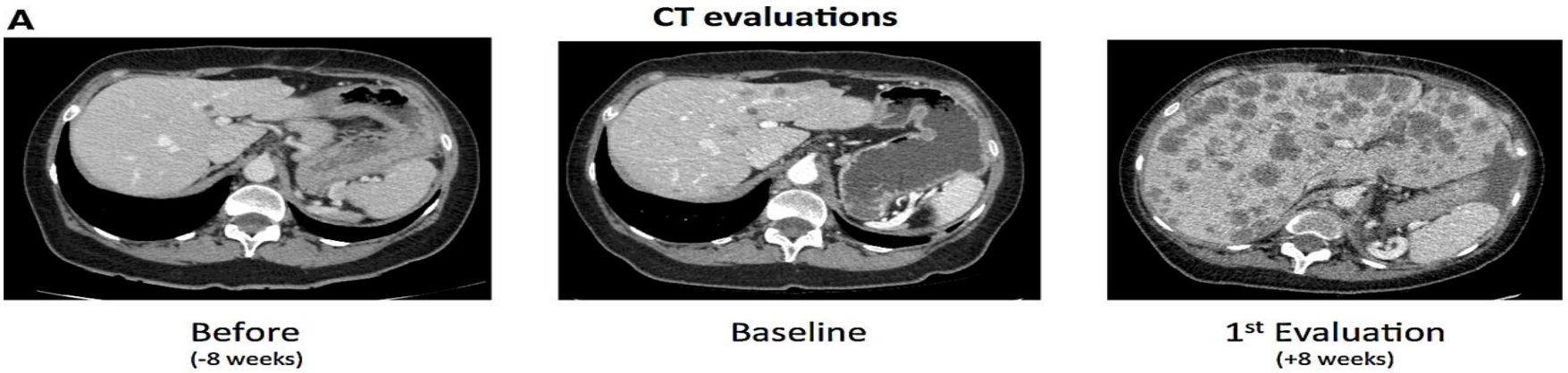
Julia A Beaver, Maitreyee Hazarika*, Flora Mulkey*, Sirisha Mushti, Huanyu Chen, Kun He, Rajeshwari Sridhara, Kirsten B Goldberg, Meredith K Chuk, Dow-Chung Chi, Jennie Chang, Amy Barone, Sanjeeve Balasubramaniam, Gideon M Blumenthal, Patricia Keegan, Richard Pazdur, Marc R Theoret*

The Lancet, 2018





Case study of patient with hyper progressing disease on PD-L1 inhibitor.



Stéphane Champiat et al. Clin Cancer Res 2017;23:1920-1928

Clinical Cancer Research
AACR American Association for Cancer Research

HPD

- Definition:
  - Time-to-treatment failure < 2 months, >50% tumor burden, and >2x pace? (Kato et al)
  - TGR $\geq$ 2? (Champiat et al)
  - TGKr $\geq$ 2? (Saâda-Bouzid et al)
- Frequency:
  - 9% (Champiat et al,), 29% (SCCHN, Saada-Bouzid et al), 16% (NSCLC, Ferrara et al)

Why iRECIST?

Why iRECIST ?

- Unusual response patterns described, but
  - Multiple, often protocol specific response criteria being used
  - Judgement calls made on what was iPD and iPR or not that were inconsistent
  - Most trials were only using immune criteria in BCIR scenarios
  - Most are for-profit organisations
    - Too costly for academic research
  - → Desire for consistency, and to bring back response assessment to investigators
- Also real concerns
  - Patients being treated past PD without informed consent
  - Patients removed from protocols with PsPD
  - How to deal with trials compared IO to non-IO drugs if the rules are different

Multiple 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?**

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.

Multidisciplinary Working Group

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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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
Plus multiple reviewers from academia around the world	

RWG Immunotherapy Sub Committee
Academia, Pharma, Health Authorities
Clinicians, Biostatisticians, Radiologists

iRECIST
The Key Principles

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** - to be used as exploratory endpoint
- iRECIST is **based on RECIST 1.1**
- Nomenclature: responses assigned using iRECIST have “i” pre-fix

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

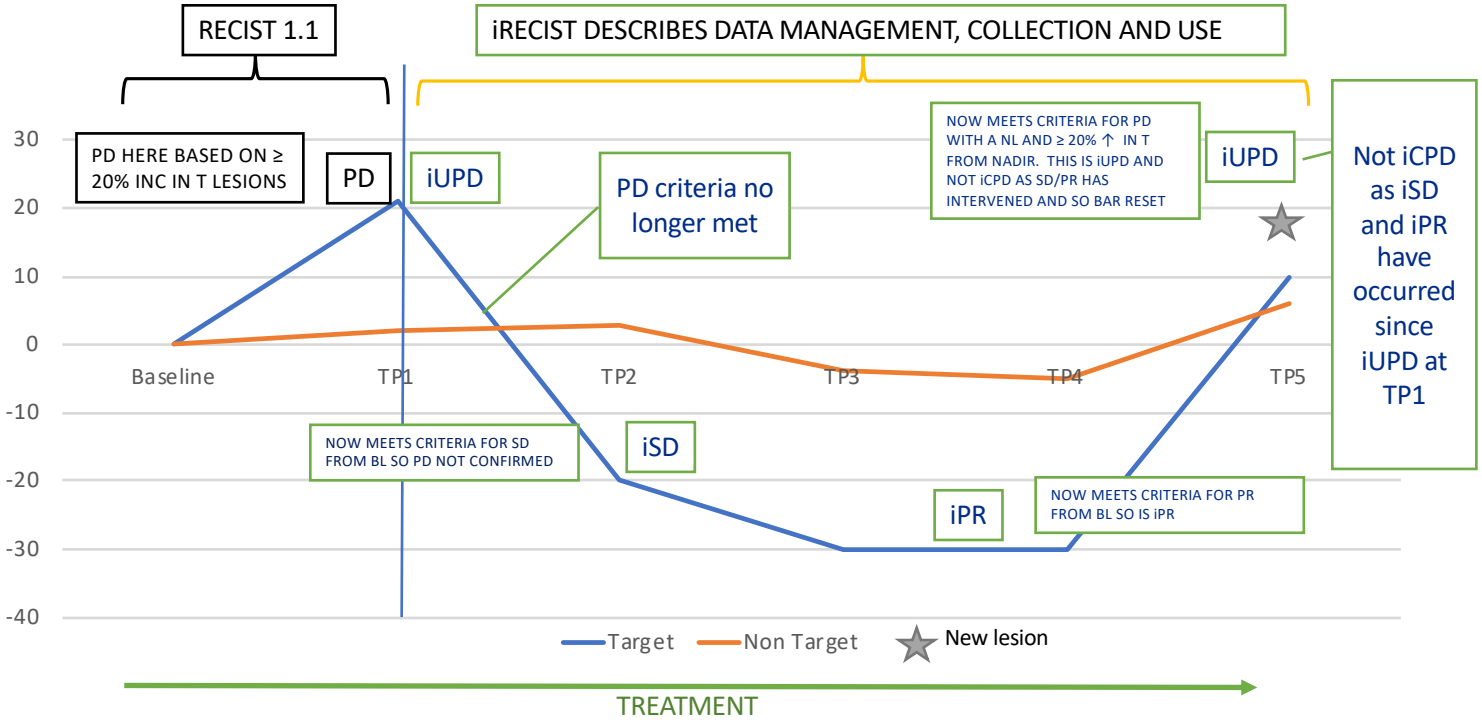
- In iRECIST there can be iSD, iPR or iCR after RECIST 1.1 PD
  - 'Once a PD always a PD' is no longer the case
  - First RECIST 1.1 PD is "unconfirmed" for iRECIST – termed iUPD
  - iUPD must be confirmed at the next assessment (4-8 weeks)
  - If confirmed, termed iCPD
- Time point response is dynamic 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



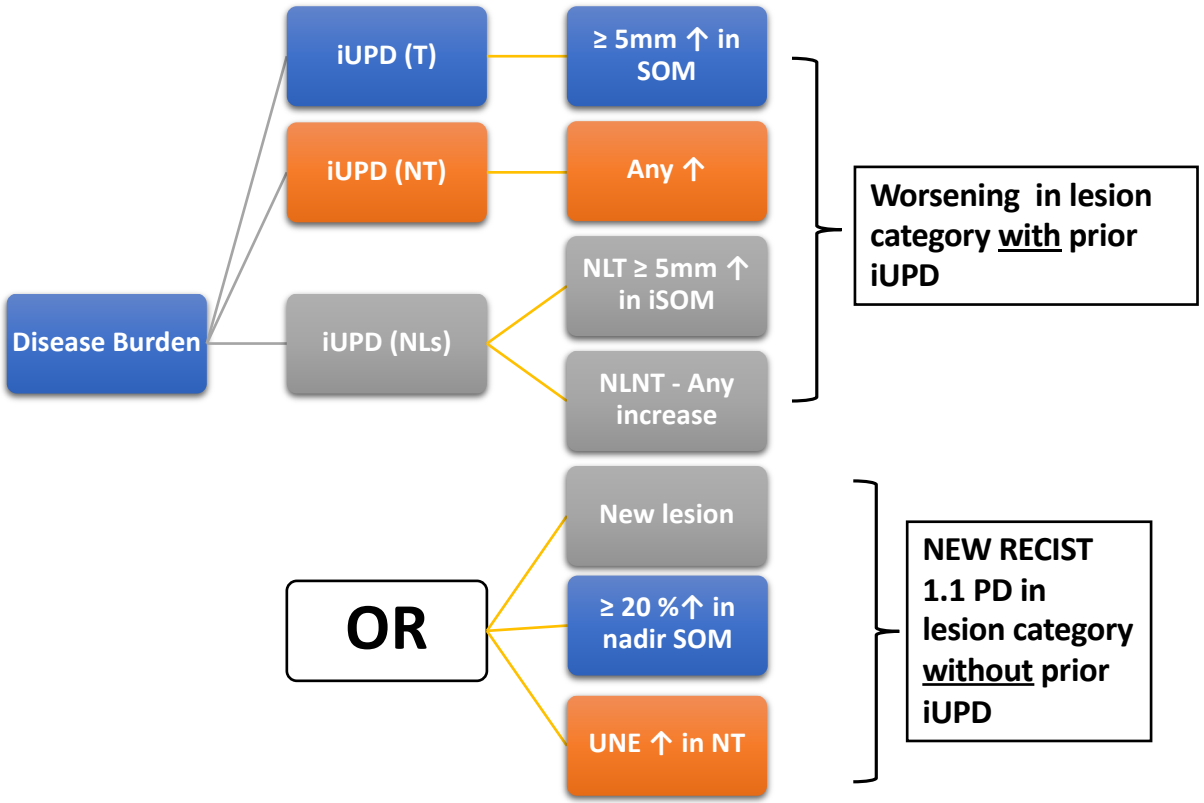
* iSD and iPR occur AFTER iUPD
* iUPD occurs again and must be confirmed

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

iRECIST: Confirming Progression (iCPD)

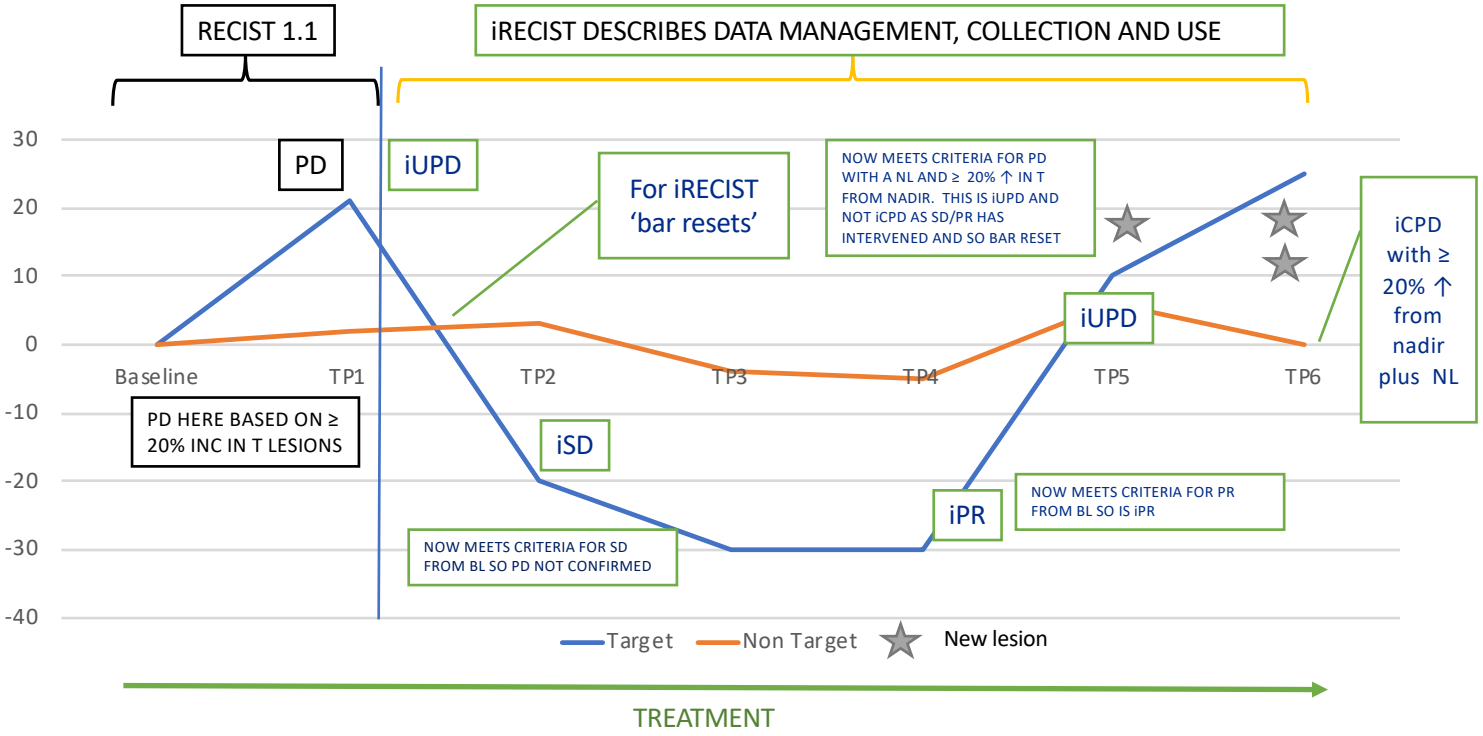
- There are two ways:
  - Existing iUPD “gets worse”
  - Lesion category without iUPD previously now meets the (RECIST 1.1) criteria for PD

Confirming Progression (iCPD)

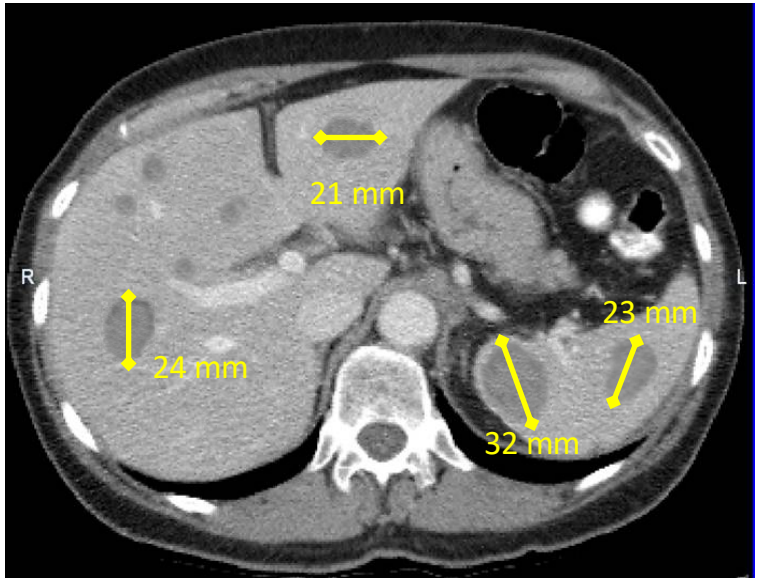


T: target lesions
NT: non-target lesions
NL: new lesions
NLT: new lesions – target
NLNT: new lesion – non target
PD: progression
iUPD: unconfirmed progression
iCPD: confirmed progression
SOM: sum of measurements
UNE: unequivocal

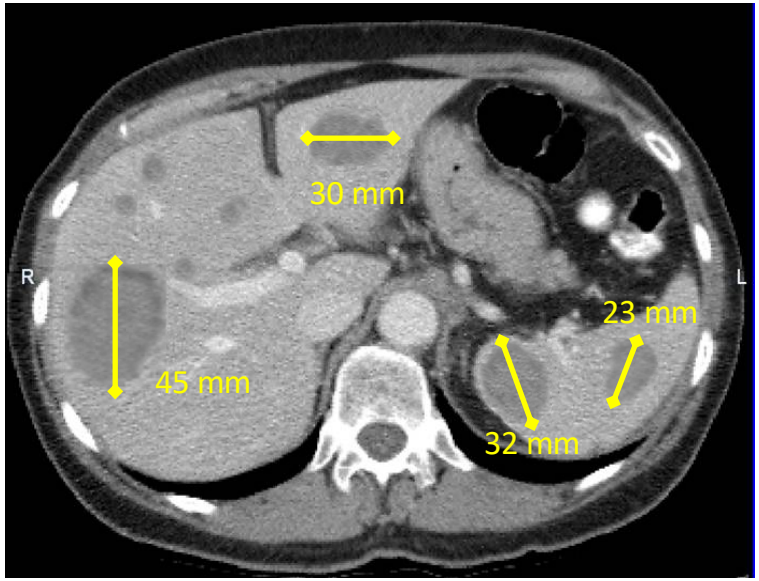
Confirming Progression (iCPD)



Progression confirmed at time point 6

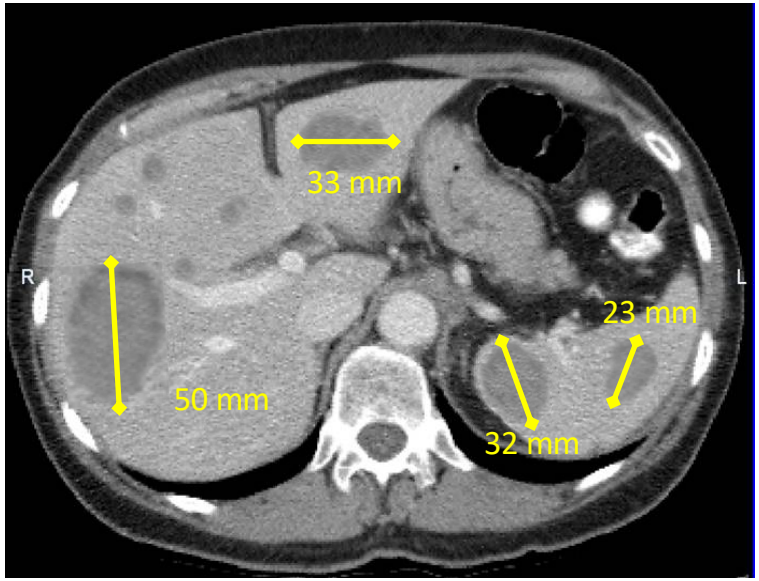


	BL
SOM (mm)	100
NT	Pres
TP Resp	N/A



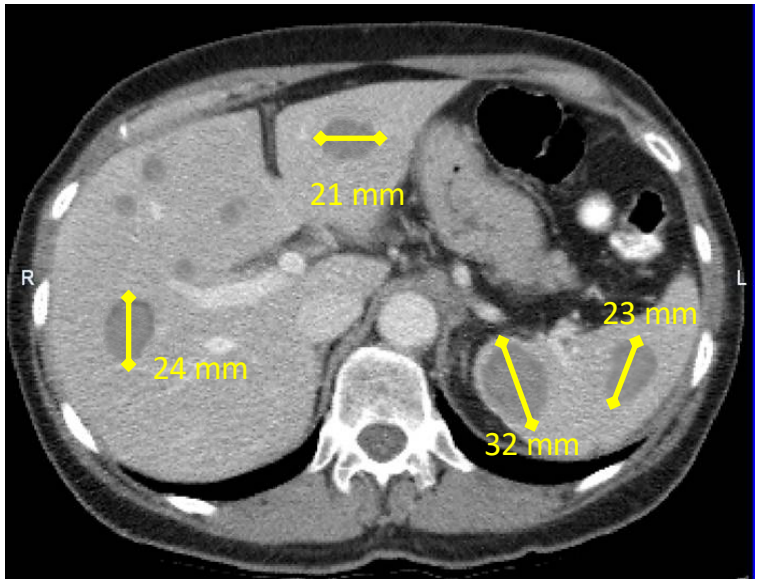
	BL	TP1
SOM (mm)	100	130
NT	Pres	Pres
TP Resp	N/A	iUPD

Date of iPD is TP1



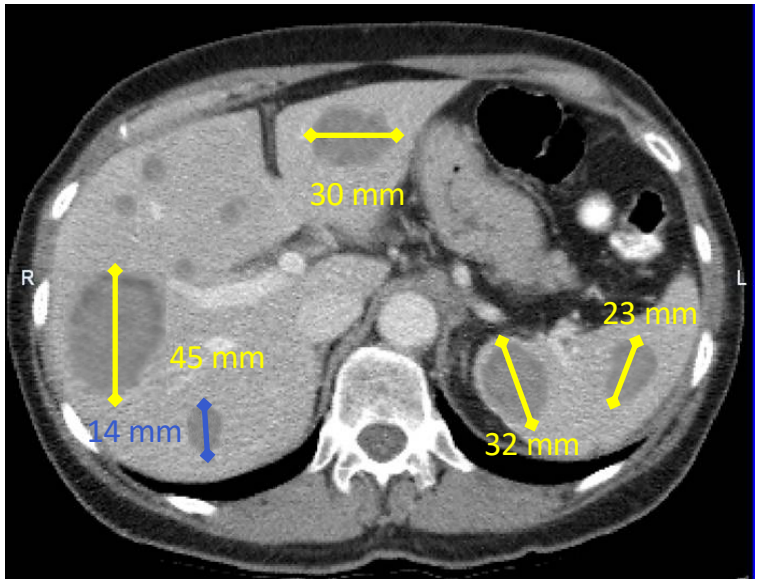
	BL	TP1	TP2
SOM (mm)	100	130	138
NT	Pres	Pres	Pres
TP Resp	N/A	iUPD	iCPD

≥5 mm increase



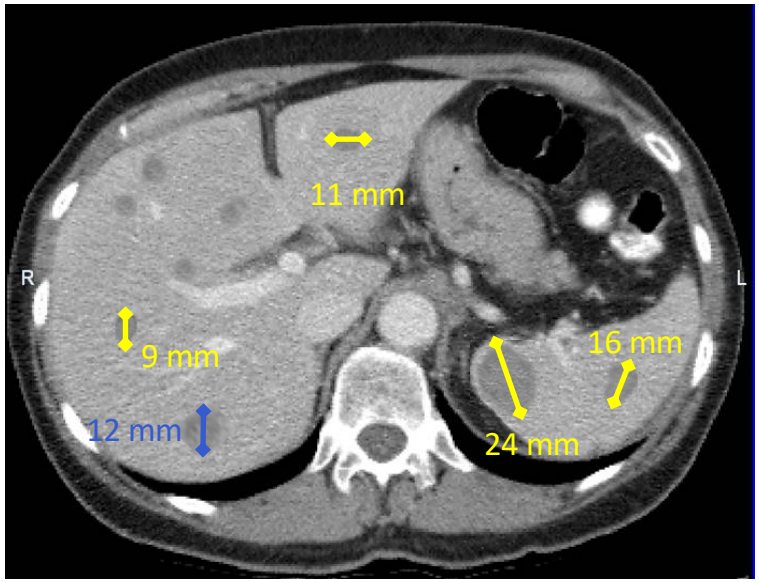
	BL
SOM (mm)	100
NT	Pres
New	
TP response	

31



	BL	TP1
SOM (mm)	100	130
NT	Pres	Pres
New		14
TP response		iUPD

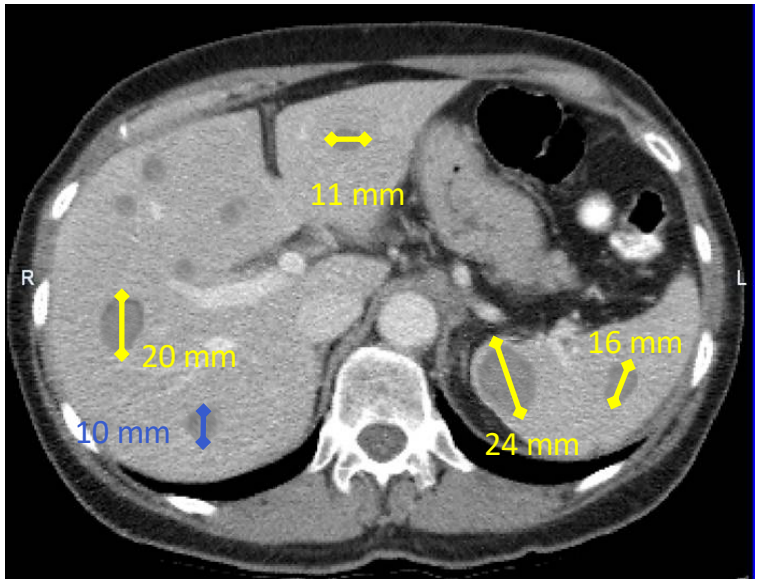
32



	BL	TP1	TP2
SOM (mm)	100	130	60
NT	Pres	Pres	Pres
New		14	12
TP response		iUPD	iPR

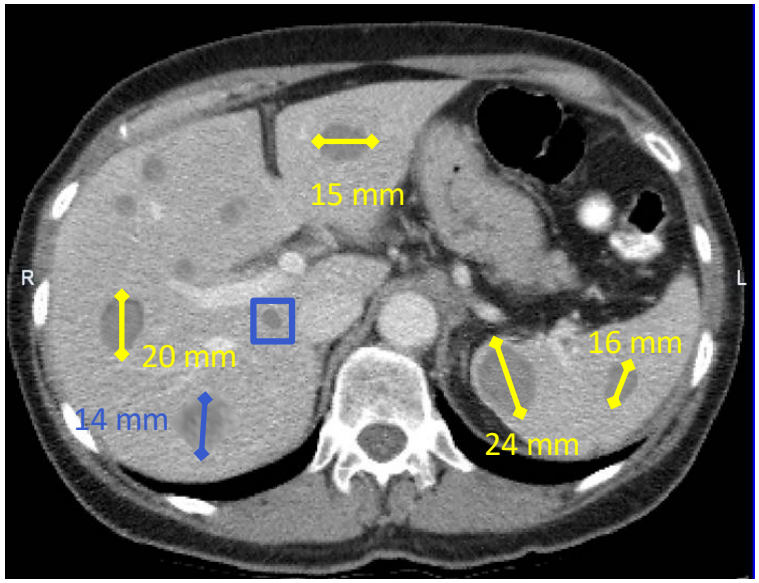
"reset bar"

33



	BL	TP1	TP2	TP3
SOM (mm)	100	130	60	71
NT	Pres	Pres	Pres	Pres
New		14	12	10
TP response		iUPD	iPR	iPR

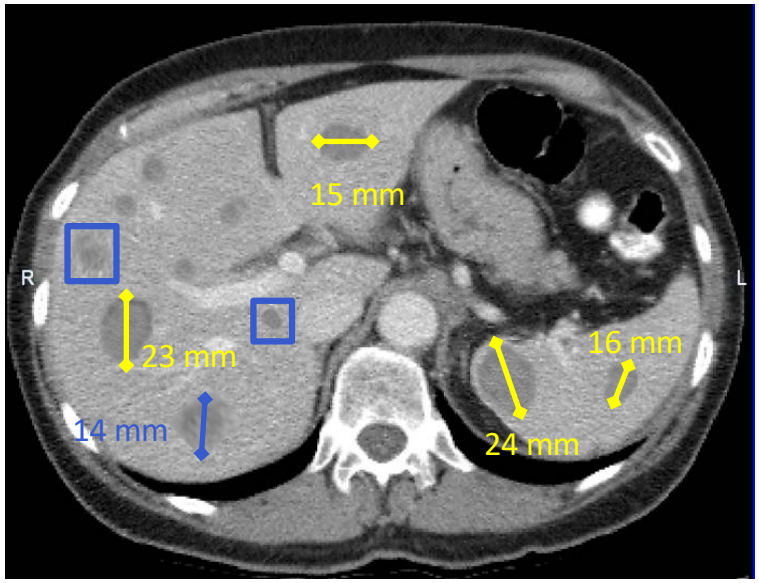
34



	BL	TP1	TP2	TP3	TP4
SOM (mm)	100	130	60	71	78
NT	Pres	Pres	Pres	Pres	Pres
New		14	12	10	14 + NL
TP response		iUPD	iPR	iPR	iUPD

35

Date of iPD is TP4

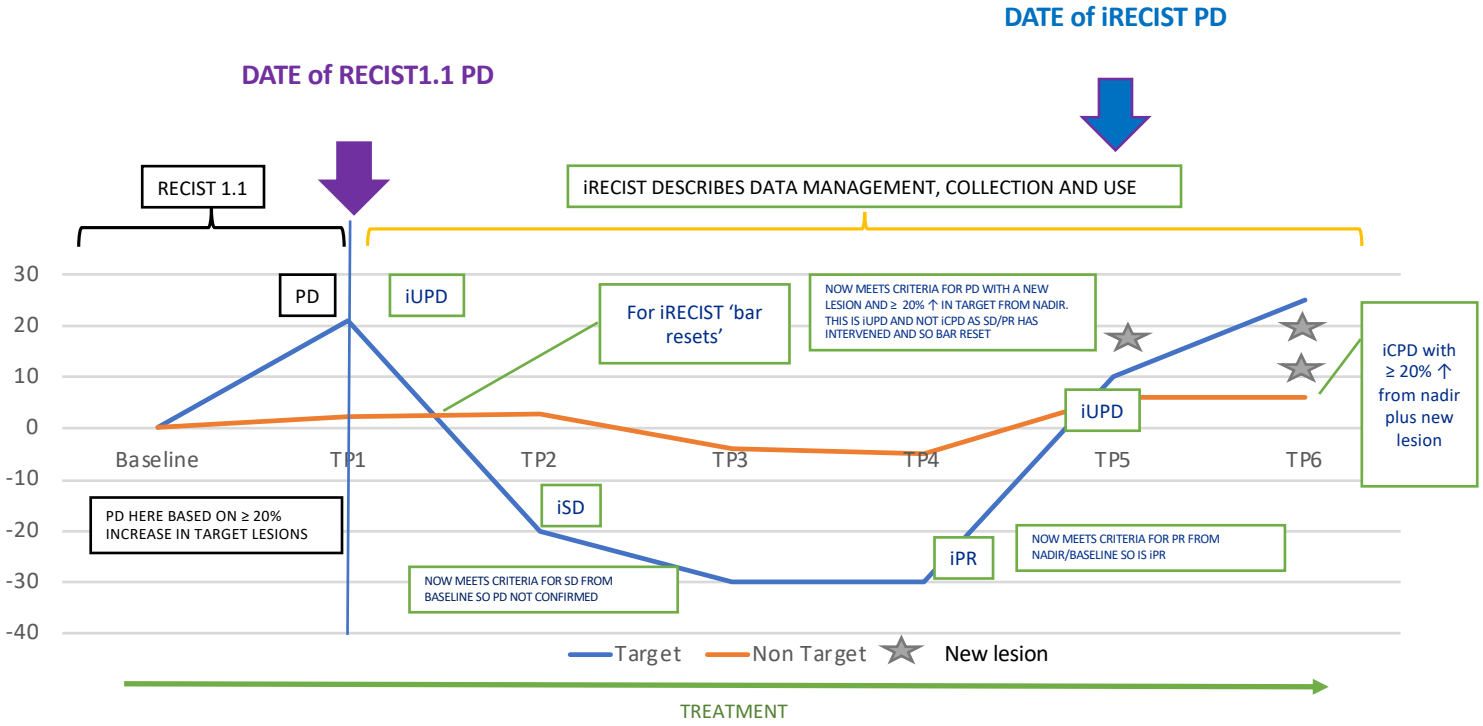


	BL	TP1	TP2	TP3	TP4	TP5
SOM (mm)	100	130	60	71	78	78
NT	Pres	Pres	Pres	Pres	Pres	Pres
New		14	12	10	14 + NL	14+NL+NL
TP response		iUPD	iPR	iPR	iUPD	iCPD

Statistical and data considerations

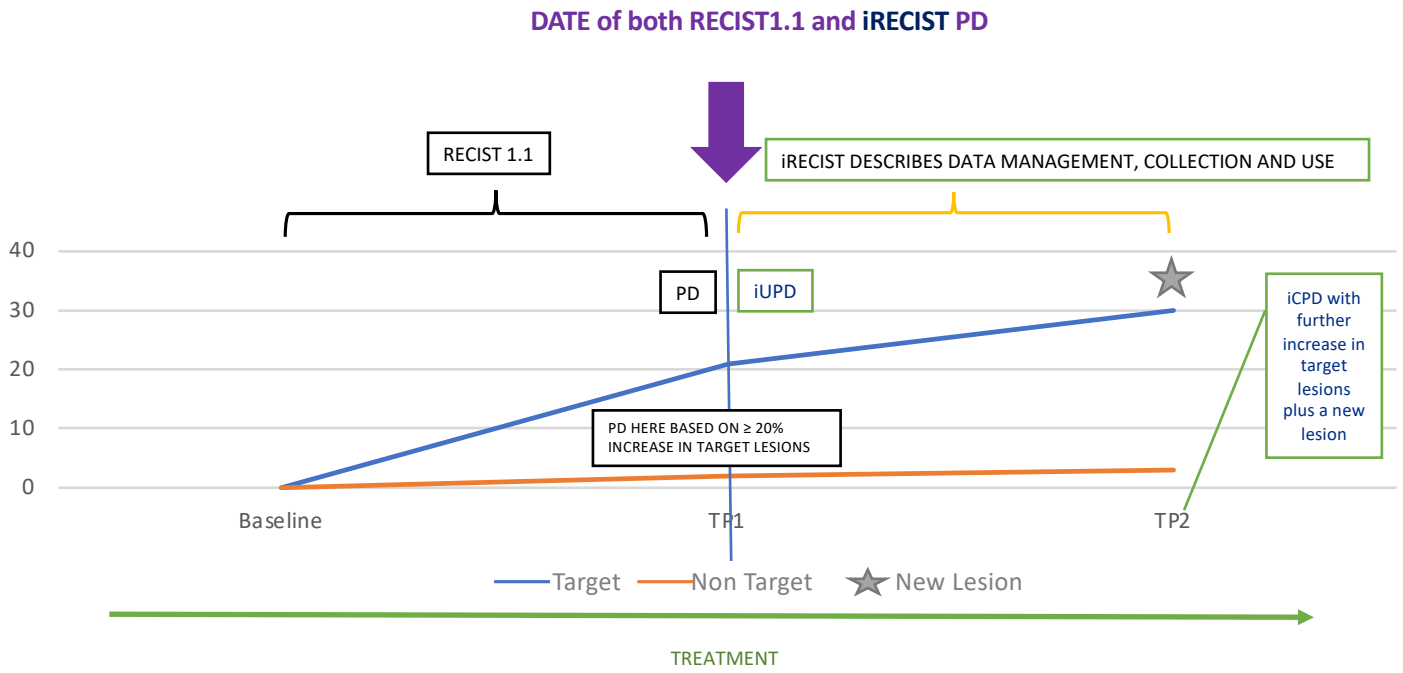
Date of i-Progression

- Will be the same as RECIST 1.1 date (i.e. first iUPD date) UNLESS iSD, iPR or iCR intervenes
- Will be the iUPD date which has been subsequently confirmed
- If iUPD never confirmed
    - First occurrence of iUPD date is used UNLESS subsequent iSD, iPR or iCR



Progression: RECIST 1.1 vs. iRECIST:
with intervening response

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



Progression: RECIST 1.1 vs. iRECIST

no intervening response

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

Primary and Exploratory Response Criteria

- RECIST 1.1 should remain primary criteria
    - iRECIST exploratory

Summary

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

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
- Unconfirmed progression does not preclude a later i-response

iRECIST in a Nutshell # 3

- Response after iUPD is driven by TARGET disease
- 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

CONCLUSIONS

Remember

- iRECIST is just a simple set of rules to deal with data to allow a true pseudoprogression followed by true response to be captured
- iRECIST will only invoked when RECIST 1.1 PD has been met AND the patient is clinically stable AND does not start salvage therapy
- While the rules are simple, application is more complex than for RECIST1.1 where a mixed or late response was just categorized as PD

Conclusions

- 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

resources

References and Resources

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

THE LANCET Oncology

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