Assessment of Efficacy and Immune Related RECIST criteria

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History of RECIST (Response Evaluation Criteria in Solid Tumors

1960s	**Early attempts to standardize tumor response to oncologic agents**
1979	**World Health Organization (WHO) standardized criteria for response assessment; published in 1981**
Mid-1990s	**International Working Party simplified response criteria**
1999-2000	**New criteria was presented at the American Society for Clinical Oncology meeting; RECIST 1.0 criteria published in 2000**
2009	**RECIST updated, latest version - RECIST 1.1, was published**

RECIST allows clinicians to determine whether a patient responds to therapy, whether they are stable, or whether their disease has progressed

RECIST 1.1 - Response Criteria

Target Lesions - includes all measurable lesions*; max 2 per organ, 5 lesions total

Evaluation of Target Lesions	RECIST Guideline
CR	Disappearance of all target lesions; confirmed at ≥ 4 weeks
PR	≥ 30% decrease of SoD from baseline, confirmed at ≥ 4 weeks
PD	≥ 20% increase from smallest sum of diameters recorded and 5 mm absolute increase over lowest sum
SD	Neither PR or PD

Non-Target Lesions – all other lesions not classified as a target lesion or sites of disease

Evaluation of non-target lesions	RECIST Guideline
CR	Disappearance of all non-target lesions; normalization of tumor markers
PD	Appearance of ≥ 1 new lesions and/or progression of existing non-target lesions
SD	Persistence of ≥ 1 non-target lesion; tumor marker level above normal

CR (Complete Response); PR (Partial Response); PD (Progressive Disease); SD (Stable Disease)

*measurable lesion = ≥ 10 mm in longest diameter by CT Scan; ≥ 20 mm in longest diameter by x-ray

sources: Eisenhauer et al., 2009; Nishino et al, 2010; and RECIST, Applying the Rules, National Cancer Institute, https://ccrod.cancer.gov/confluence/download/attachments/71041052/RECIST6.pdf?version=1&modificationDate=1317305352430

RECIST 1.1 – Time Point Response

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

- ***Tumor evaluation should occur every 6-8 weeks where the benefit of the therapy is not known***
  - ***Repetitive tumor evaluations depend on whether the trial has a goal of response rate or the time to an event (e.g. Progression- Free Survival (PFS))***

source: Eisenhauer et al., 2009

RECIST for Determining Tumor Response is Applicable to Cytotoxic and Targeted Therapy Agents

- Cytotoxic agents directly kill a tumor cell or prevent tumor cells from dividing (e.g. chemotherapy); therefore, response of cytotoxic agents can be easily measured from the start of therapy

- Early increase in tumor burden and/or an early increase in tumor size signifies progressive disease

- – Once progression is detected, drug cessation is recommended

- ***Response after initial treatment of a cytotoxic agent can often predict remission and survival***

Immuno-oncology agents differ from cytotoxic agents in that they stimulate an innate immune response against the tumor

- ***Vaccines***: trigger the immune system to initiate an anti-tumor response against an existing cancer
- ***Monoclonal Antibodies***: antibodies directed against tumor cells; they can block signaling pathways needed for tumor growth and trigger an immune-mediated cytotoxic response
- ***Checkpoint inhibitors***: tumors escape detection by the immune system through expression of "checkpoint" proteins on their cell surface. CTLA-4 and PD-1 receptors are examples of "checkpoint" receptors; targeted inhibition towards these receptors enhances T cell response towards the tumor
- ***Cytokines***: stimulates a broad-based immune response (e.g. interleukin-2 and interferon-α)

Source:
http://www.fightcancerwithimmunotherapy.com/immunotherapyandcancer/typesofcancerimmunotherapy.aspx

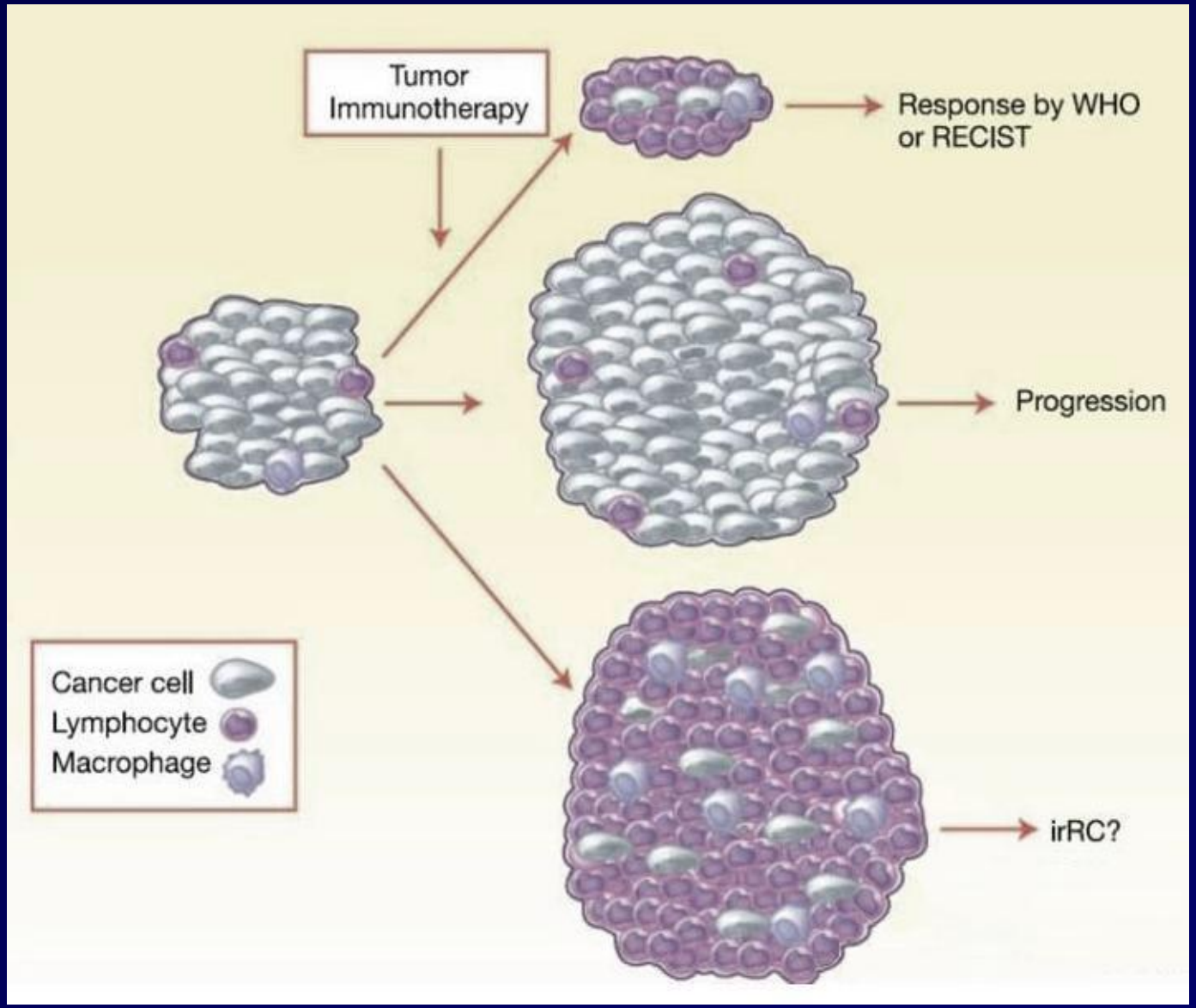
The unique mechanism of action of immuno- oncology agents requires modified tumor response criteria

RECIST may not provide a complete assessment of immunotherapeutics

- Anti-tumor response to immunotherapy may take longer compared to cytotoxic agent response
- Clinical response to immune therapies can manifest after conventional progressive disease (PD)
  - "Pseudnoprogression
- Discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed
- Allowance for "clinically insignificant" PD (e.g., small new lesions in the presence of other responsive lesions) is recommended
- Durable stable disease may represent antitumor activity

source: Wolchock et al., 2009

Differing mechanism of immunotherapy



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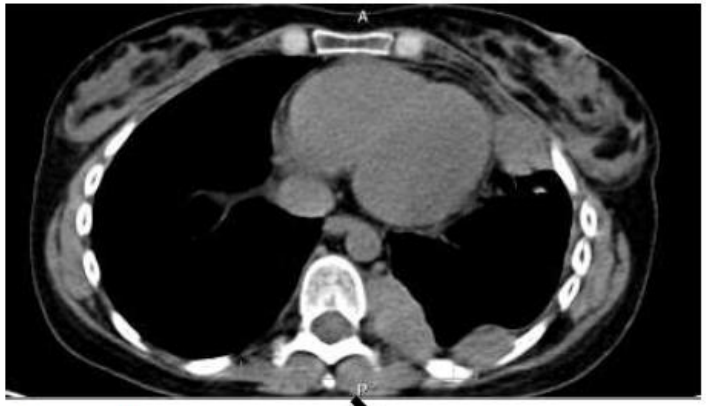
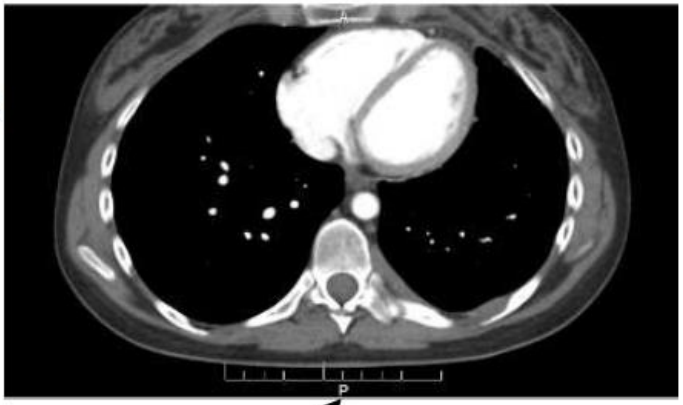
Unusual Response Patterns

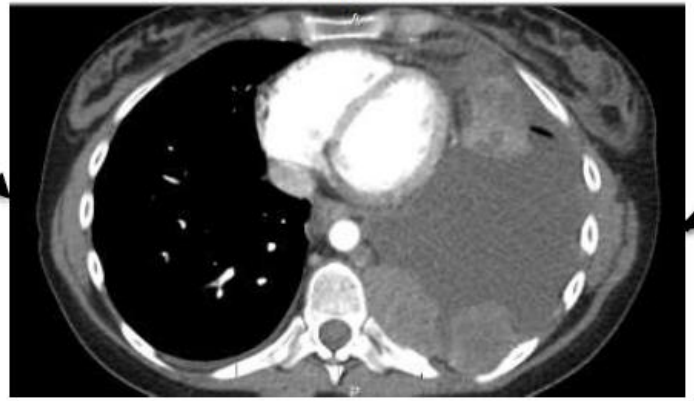


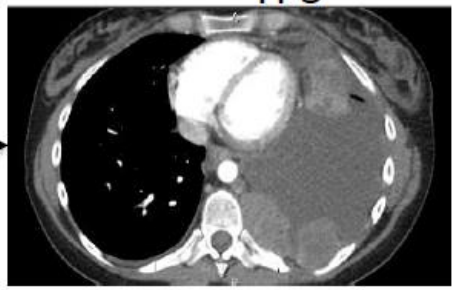
Baseline



TP3

Time point 2





TP3

Ipilimumab – clinical observations and evaluation of a novel set of response criteria

- Ipilimumab: human, monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cells. Blocking CTLA-4 from interacting with its ligands augments a T cell immune response to tumor cells

- Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma

- Ipilimumab was studied in three multicenter phase II trials evaluating 487 patients with unresectable stage III or IV melanoma

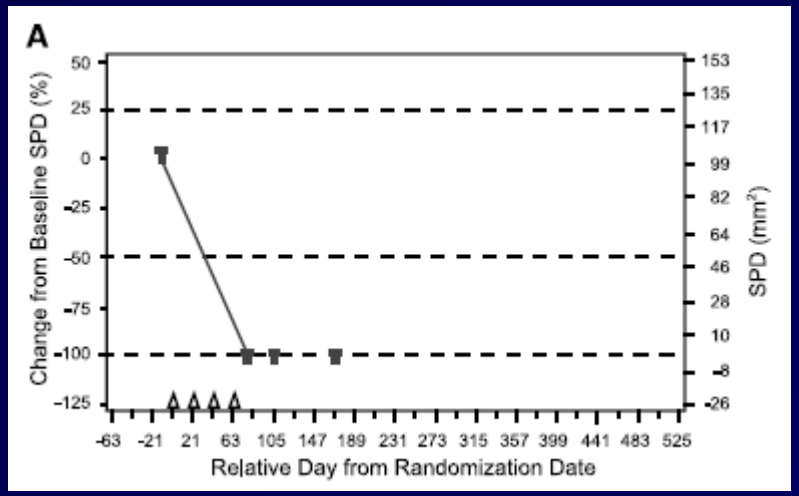
- Activity was categorized using a novel set of criteria
  - Tumor assessments carried out at week 12 following the end of the induction dosing period (ipilimumab 10 mg/kg every three weeks times x4)

source: Wolchock et al., 2009

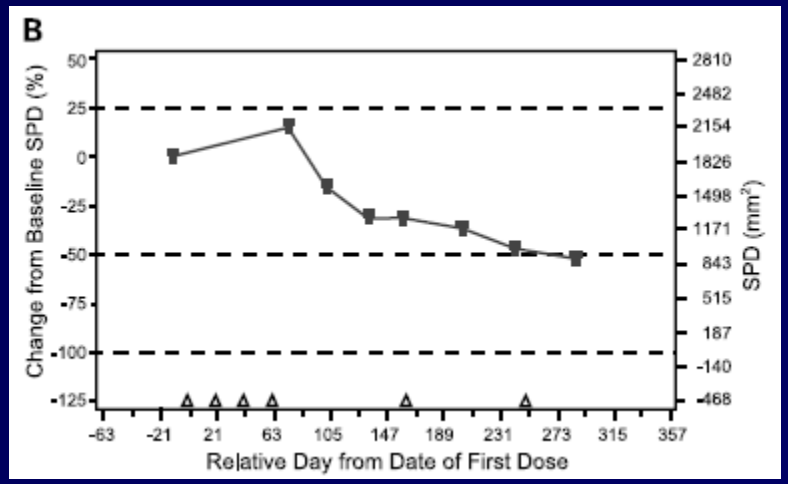
Four patterns of response were observed in patients treated with ipilimumab

- **Overall, ~30% of patients had disease control (CR, PR, or SD)**
- **Of the 4 patterns of response observed two met conventional criteria for tumor response:**

Response in baseline lesions



"stable disease" with slow, steady decline in total tumor volume



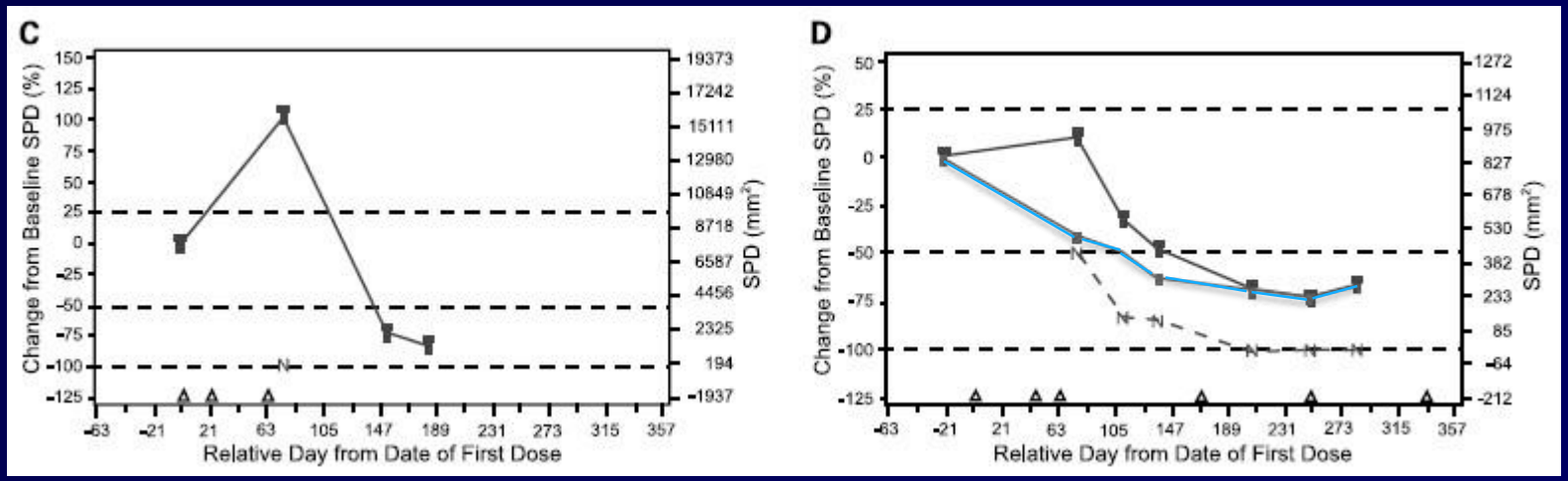
SPD = sum of the product of perpendicular diameters
Triangles = ipilimumab dosing time points

source: Wolchock et al., 2009

The other two response patterns observed go against the standard criteria for tumor response

Responses after an initial increase in total tumor burden

Reduction in total tumor burden during or after the appearance of new lesions



SPD = sum of the product of perpendicular diameters (used in WHO criteria)
Triangles = ipilimumab dosing time points
N=tumor burden of new lesions

A number of ipilimumab treated patients initially characterized as PD, are considered PR or SD using the irRC Guideline

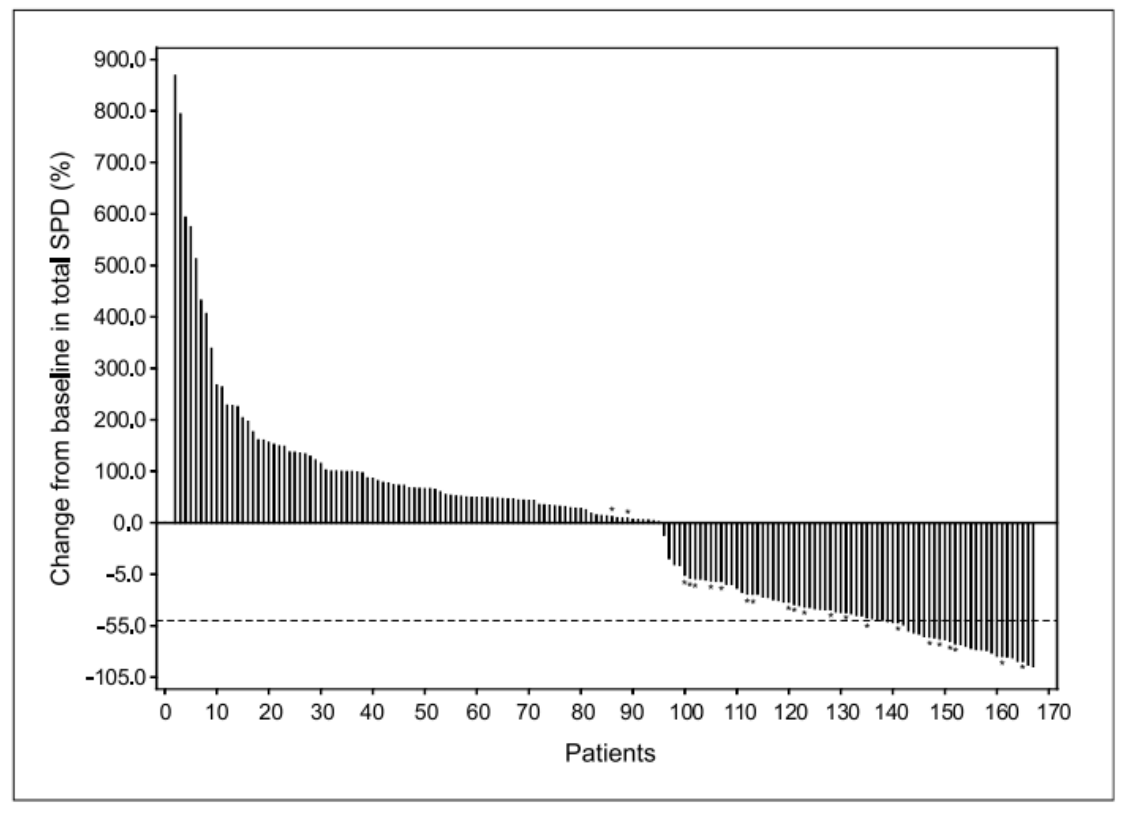
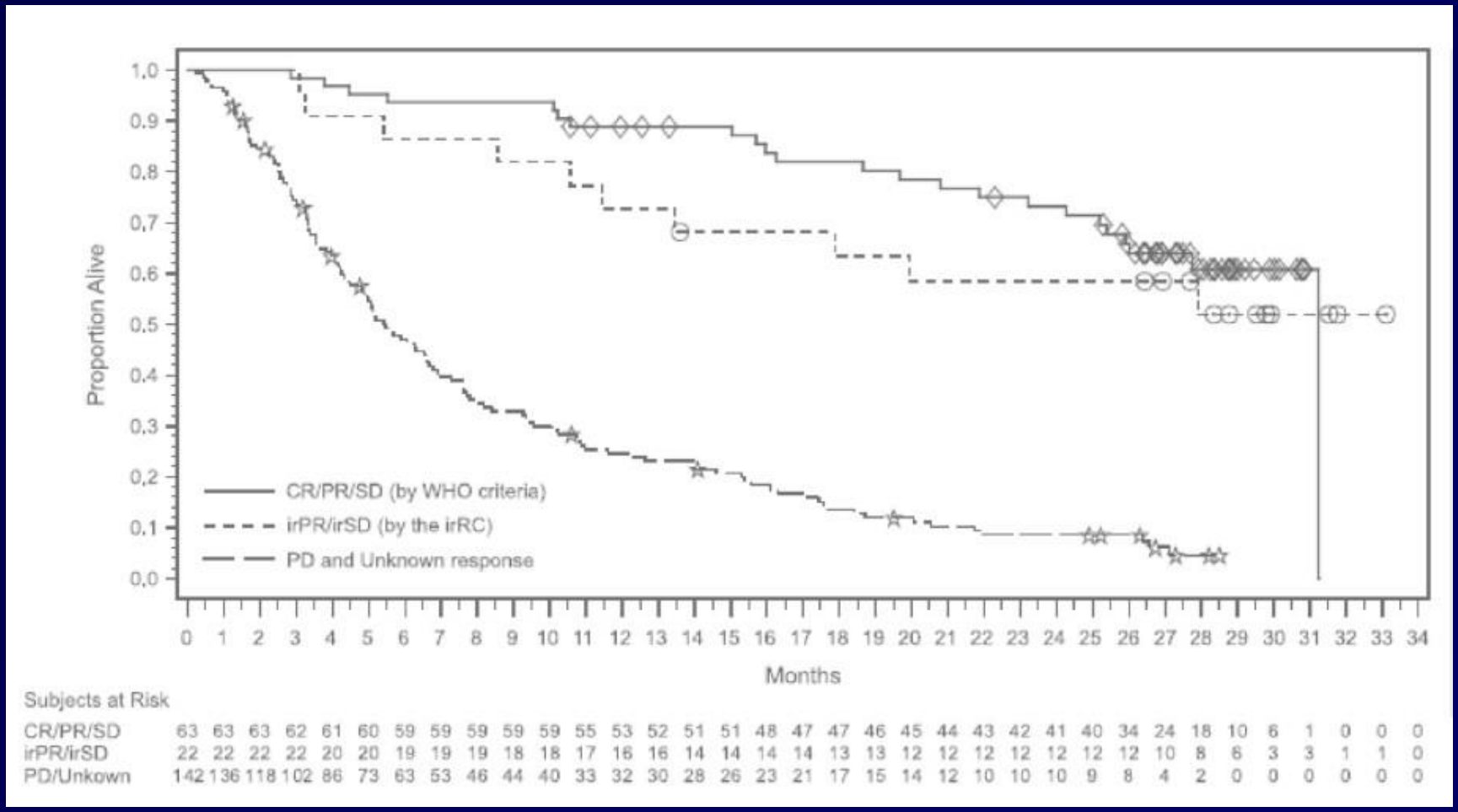


Fig. 2. Waterfall plot of maximum percentage reduction from baseline in total tumor burden. Included are advanced melanoma patients treated with, or randomized to, ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies; the tumor responses of 167 evaluable patients were assessed using the irRC. Twenty-two patients were characterized as irPR (n = 5) or irSD (n = 17), who otherwise would have been labeled "PD" by conventional WHO criteria. These patients are indicated by an asterisk. In addition, one patient characterized as SD by WHO criteria was evaluated as irPR (patient #148).

source: Wolchock et al., 2009

Association of response withsurvival



Clinical trials utilizing both irRC and RECIST 1.1 to measure tumor response

Evaluation of immune-related response criteria (irRC) in patients (pts) with advanced melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.

Citation:
J Clin Oncol 32:5s, 2014 (suppl; abstr 3006^)

- 411 pts, 192 were on MK-3475 (pembrolizumab) ≥ 28 weeks
- 215 patients had either a CR, PR, or SD by RECIST and irRC
- 51 patients had PD by RECIST, but had either a CR, PR, or SD by irRC

Authors concluded:

"conventional criteria such as RECIST may underestimate the benefit of MK-3475 in approximately 10% of treated pts."

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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

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Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer

RECIST

- 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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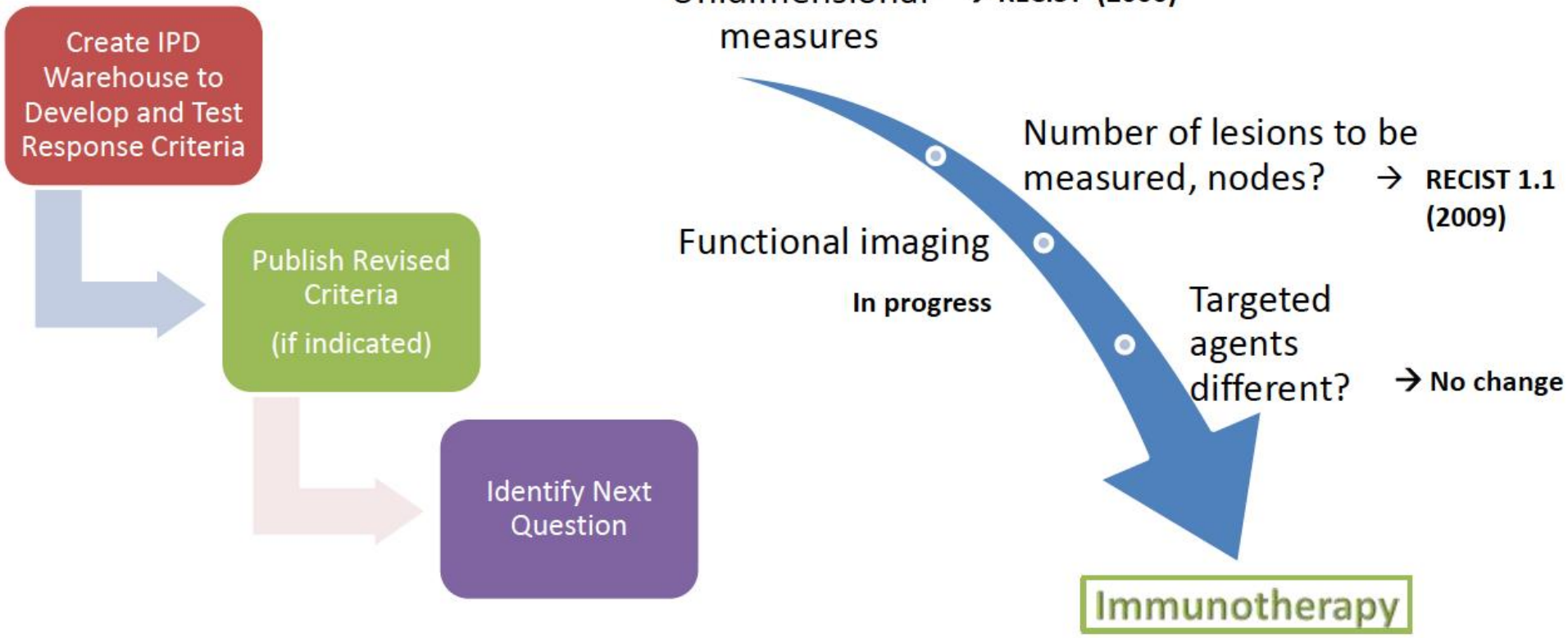
RECIST Working Group



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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.

Differences between WHO classification and irRC

	WHO	**irRC**
New Measurable lesions (> 5 x 5 mm)	Always represent PD	Incorporated into total tumor burden
New non-measurable lesions (<5 x 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining best overall response	Contribute to defining ir CR

Using the irRC

- irCR: Complete disappearance of all lesions (whether measurable or not, and no new lesions, and confirmation by a repeat consecutive assessment no less than 4 weeks from date first documented

- irPR: decrease in tumor burden ≥50% relative to baseline confirmed by repeat consecutive assessment at least 4 weeks later

- irSD: not meeting criteria for irCR or irPR in absence of ir PD

- irPD: increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmed by repeat consecutive assessment at least 4 weeks later

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Response Criteria

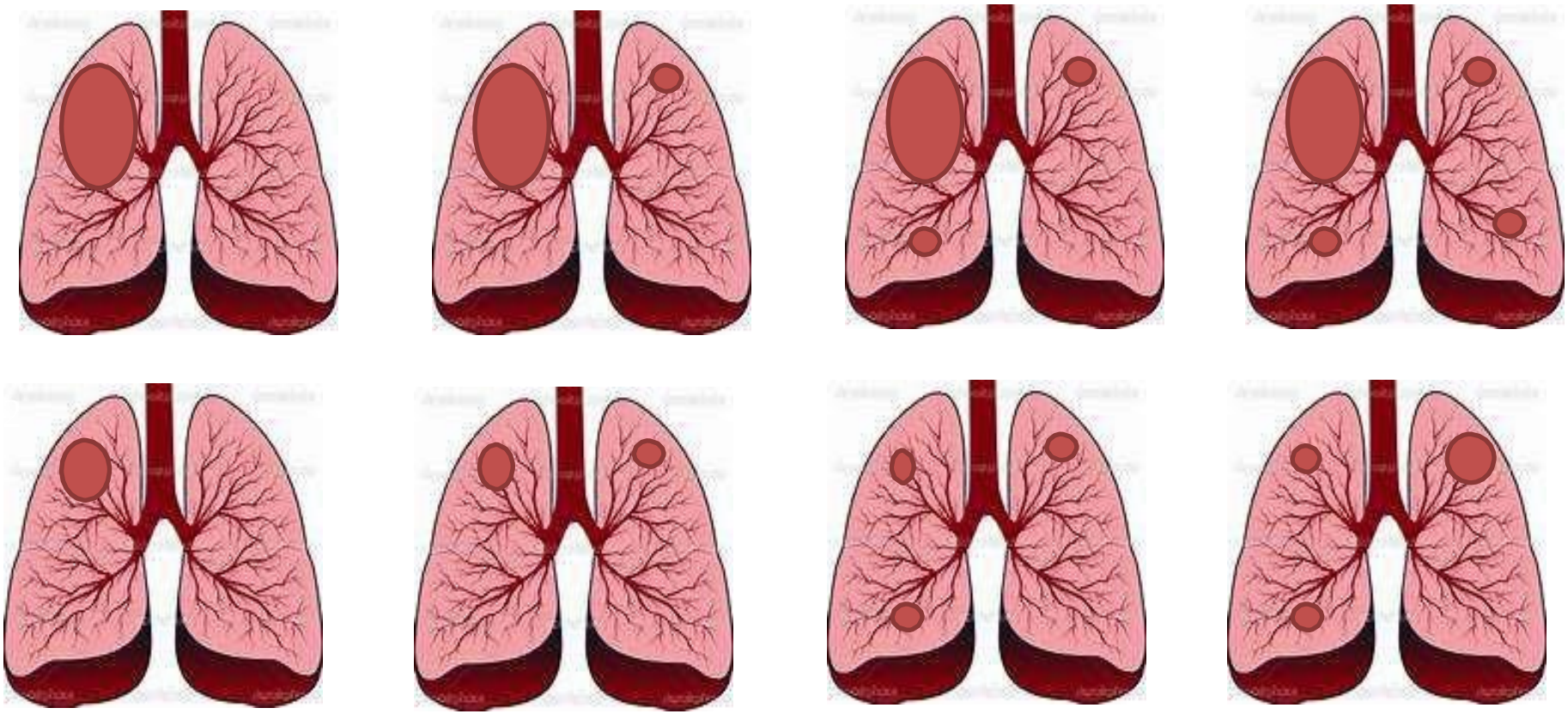
	RECIST 1.1	irRC (+ unidimensional variant)	"irRECIST /irRECIST1.1" variants
Bi/unidimen.?	Unidimensional	**Bidimensional**	Unidimensional
N Target	5	**15; (≥5 × 5mm)**	10 / 5 (≥10mm/ ≥10mm (15 for nodes))
New target lesions added to sum or measures (SOM)?	No	(≥5 × 5mm); **Yes** - does not automatically 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

True or Pseudoprogression ?



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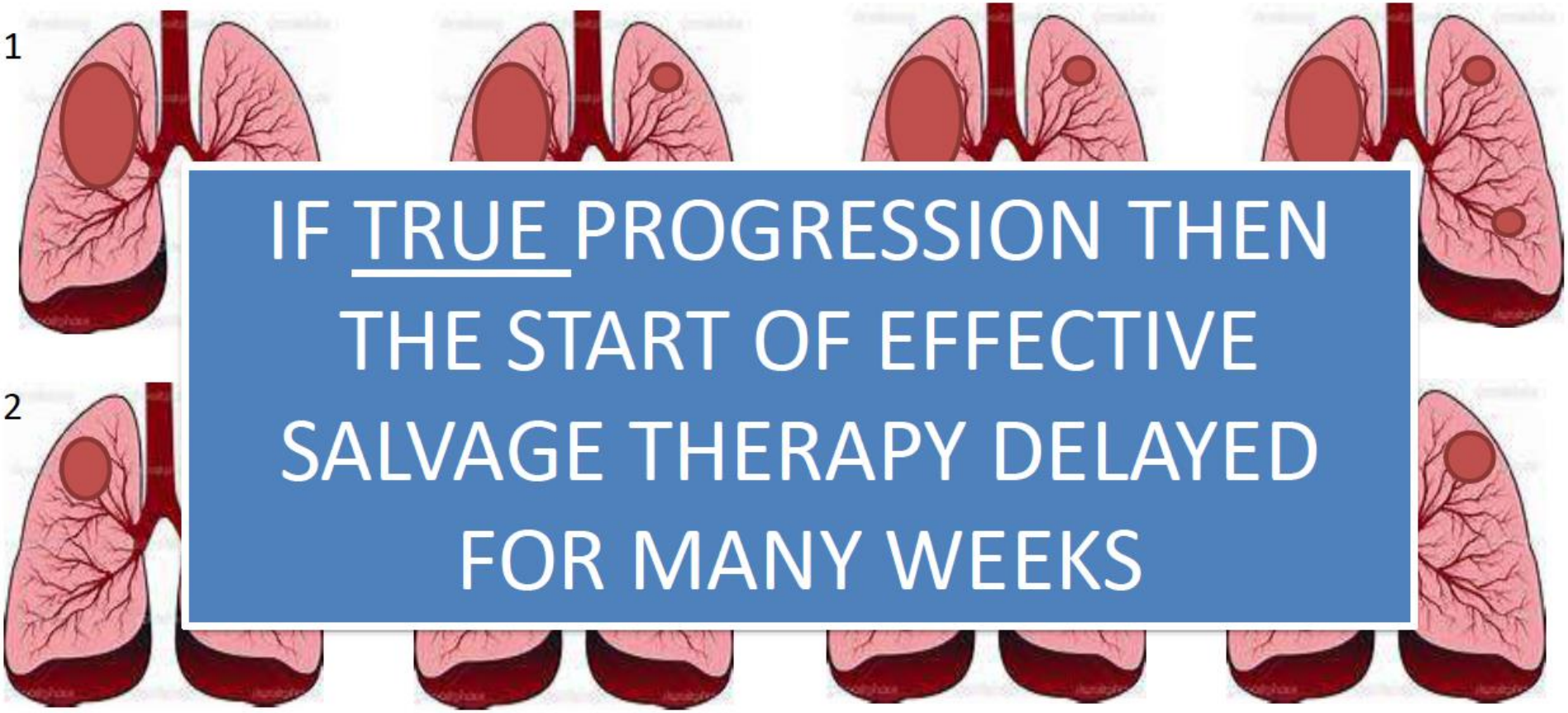
True or Pseudoprogression ?



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

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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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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

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

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iRECIST vs RECIST 1.1: Changes

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  - 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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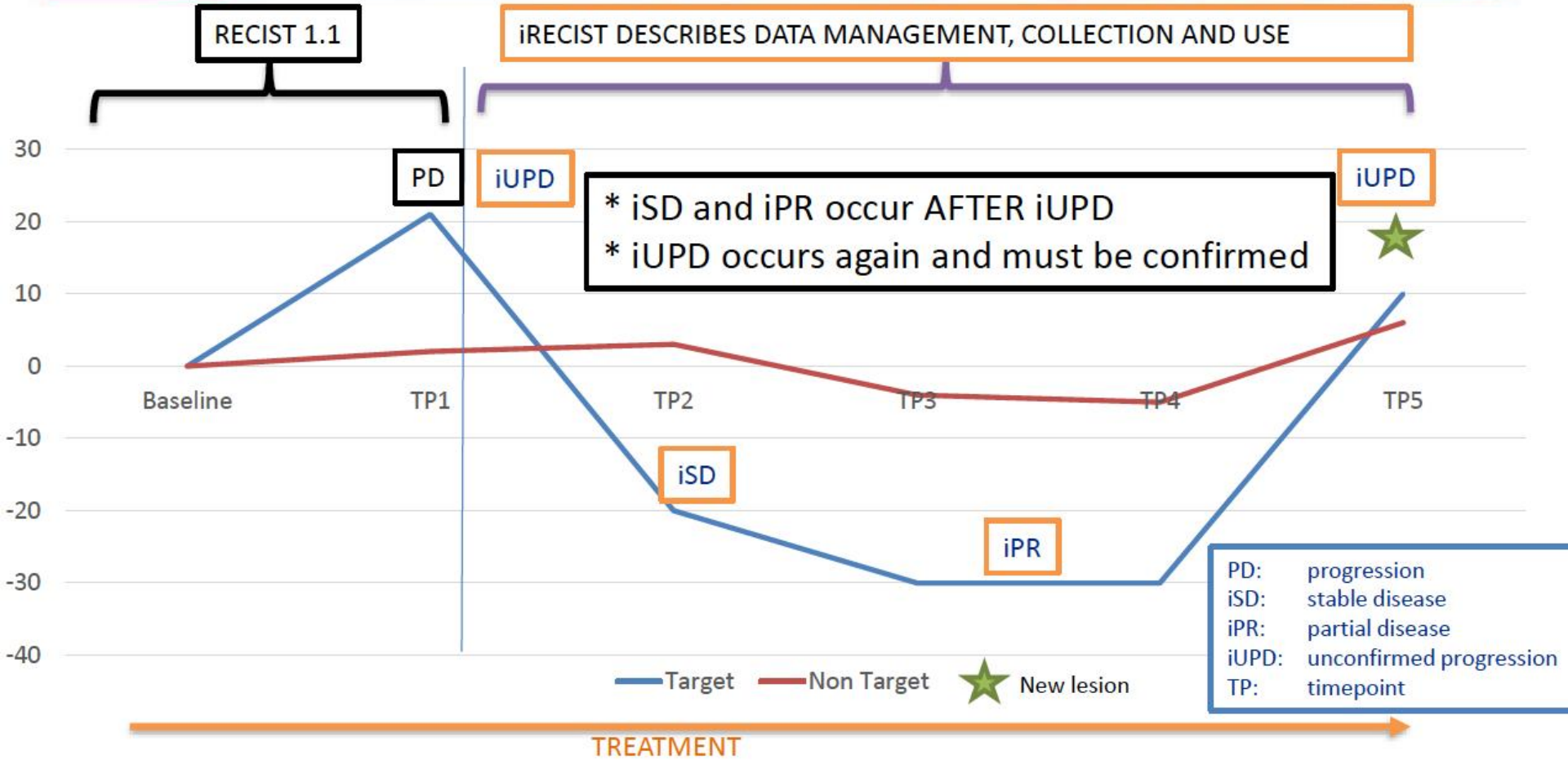
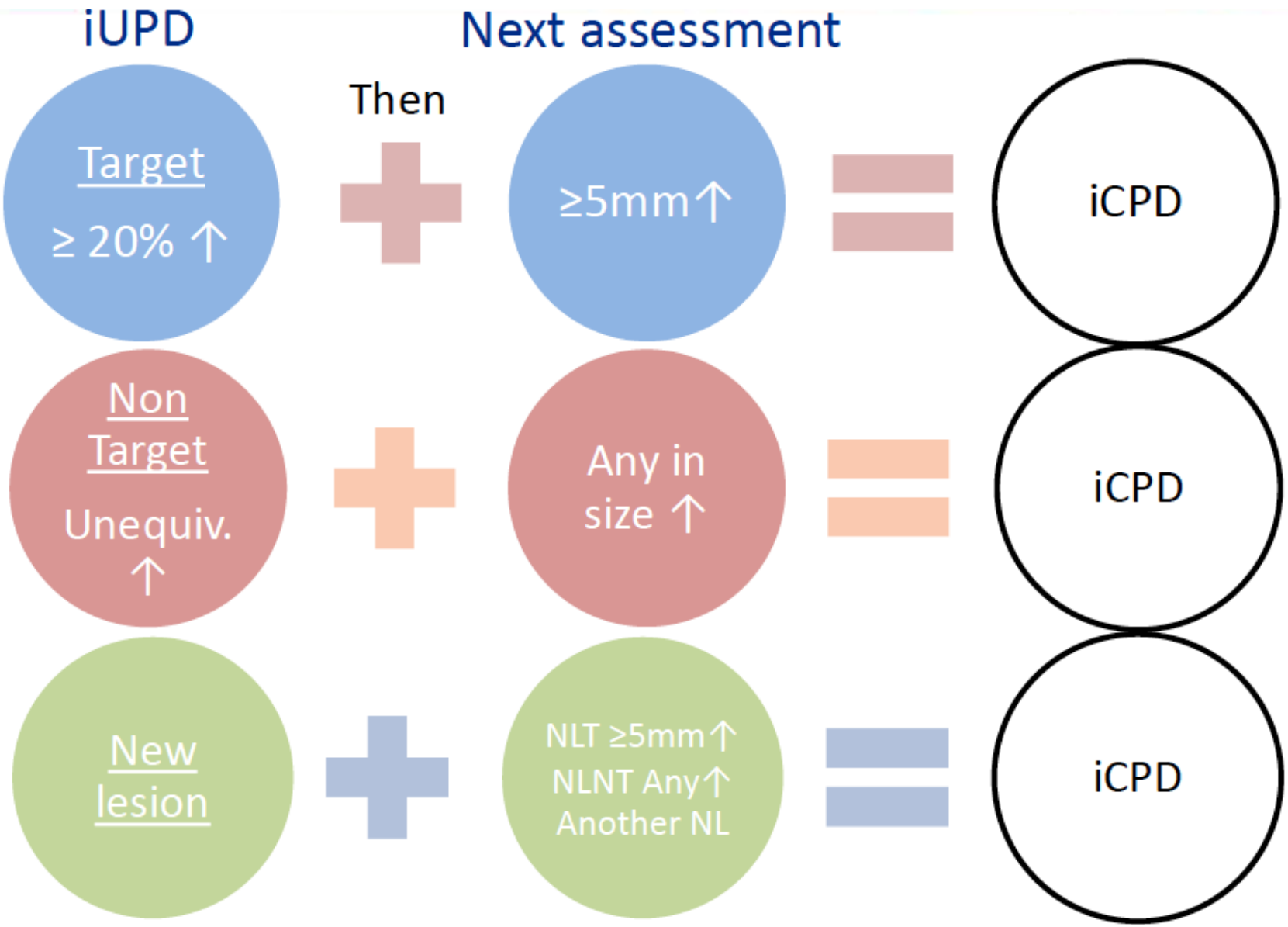
Summary




iUPD
Next assessment
Then
Target
≥ 20% ↑
≥5mm↑
iCPD
Non Target
Unequiv. ↑
Any in size ↑
iCPD
New lesion
NLT ≥5mm↑
NLNT Any↑
Another NL
iCPD

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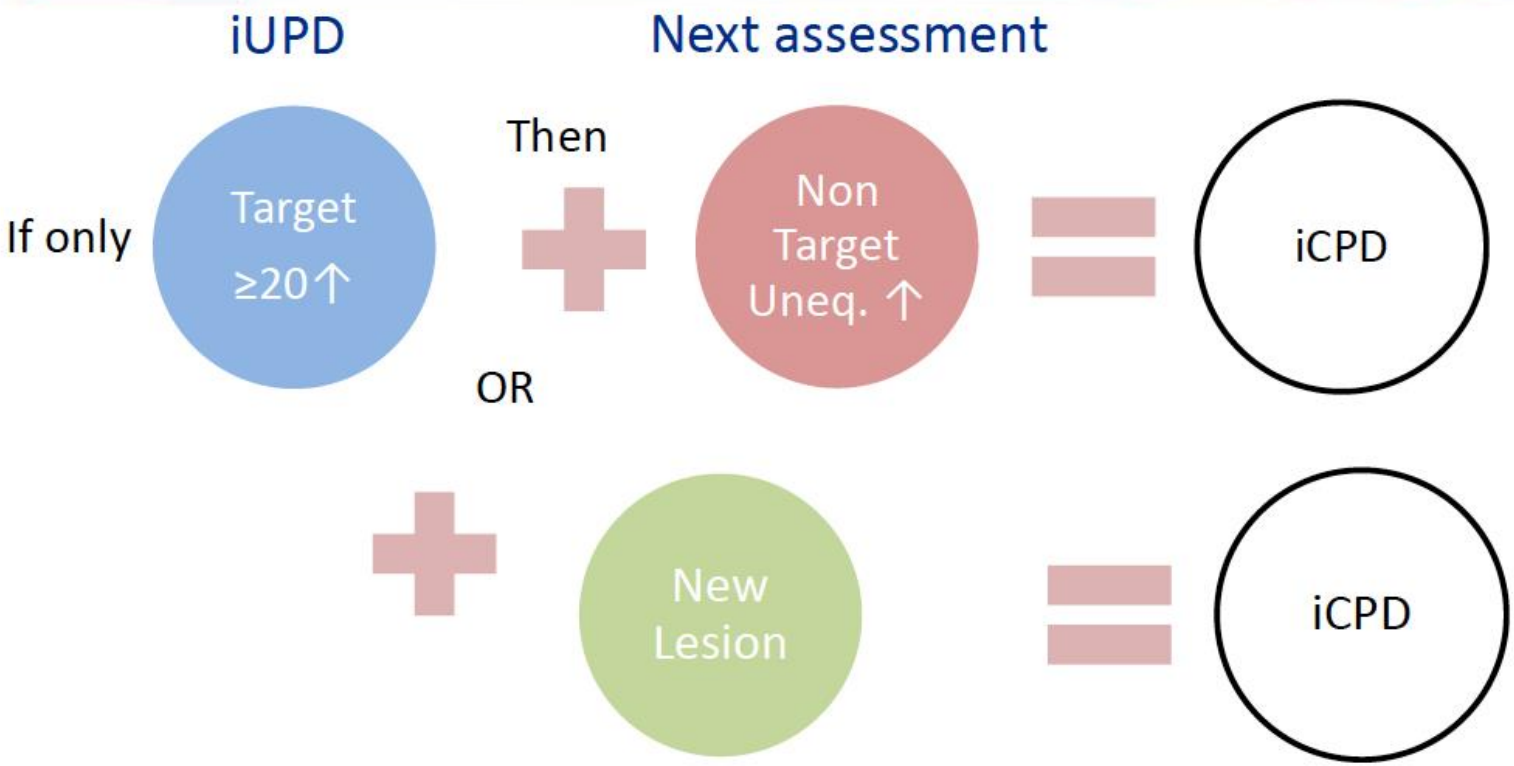
New RECIST PD in another Lesion Category



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New RECIST PD in another Lesion Category

iUPD

Next assessment

If only

Non Target Uneq.↑

Then

Target ≥ 20% ↑

iCPD

OR

New Lesion

iCPD

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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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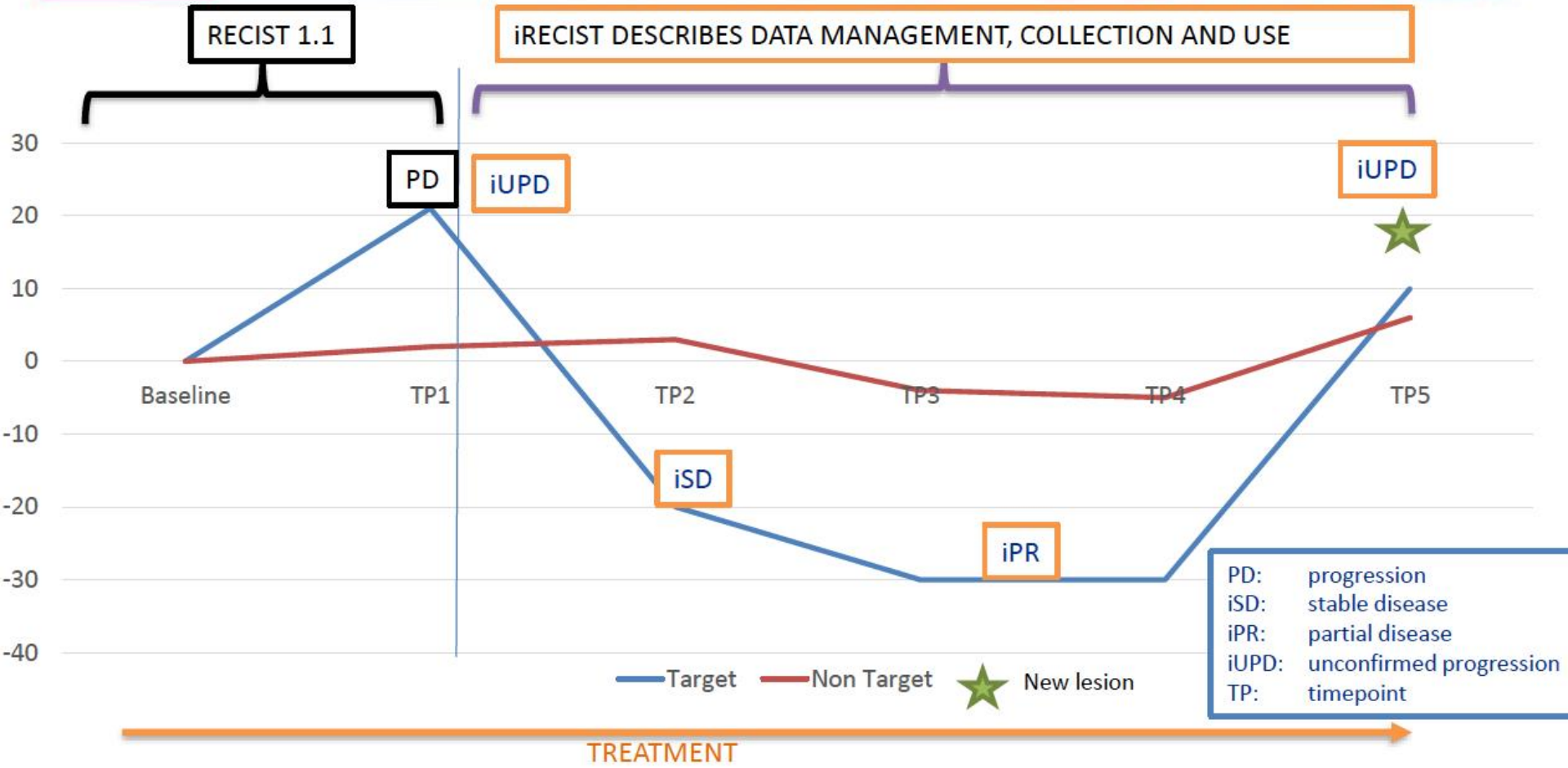
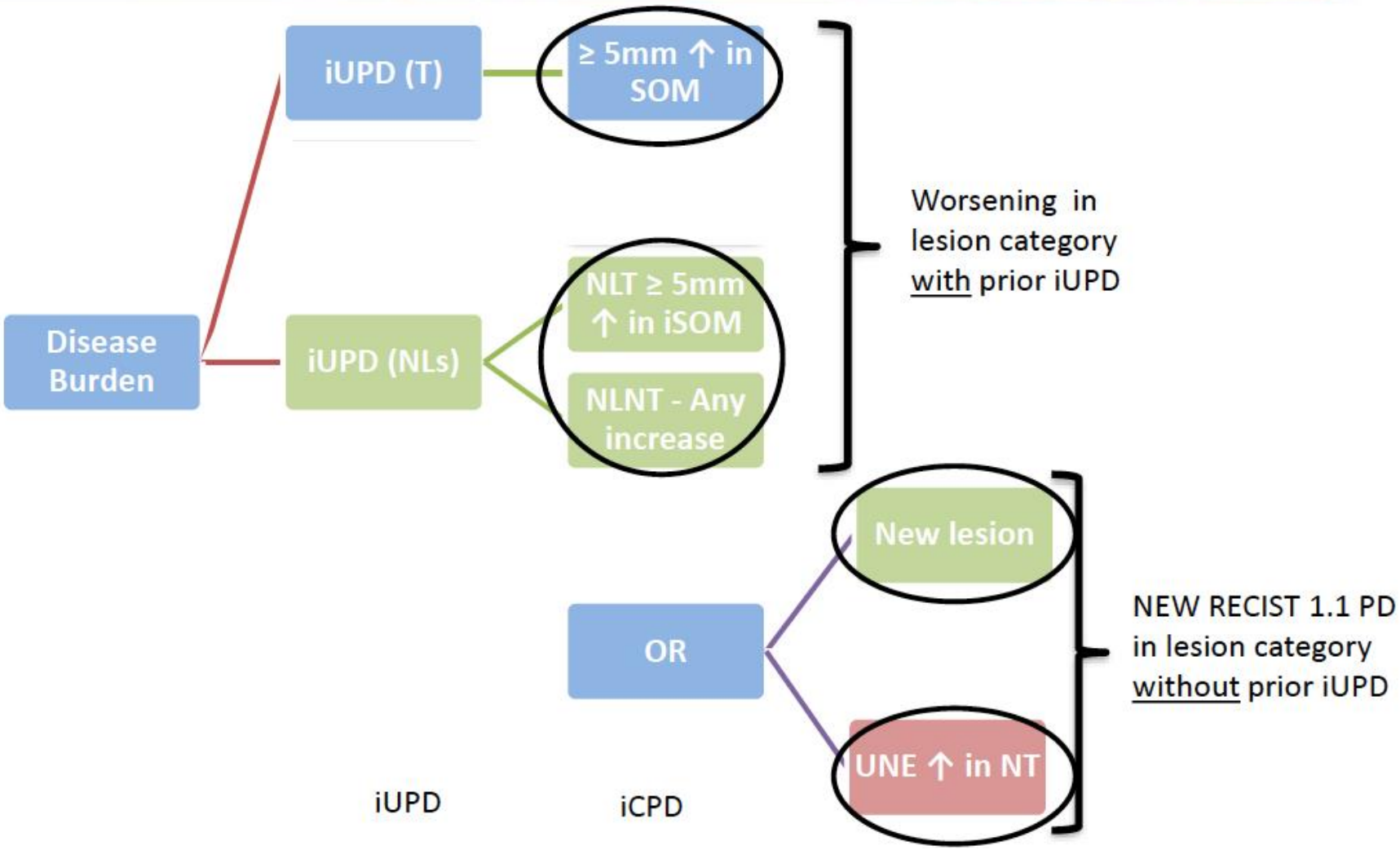
Summary: iUPD – T and NL



Confirming Progression (iCPD)



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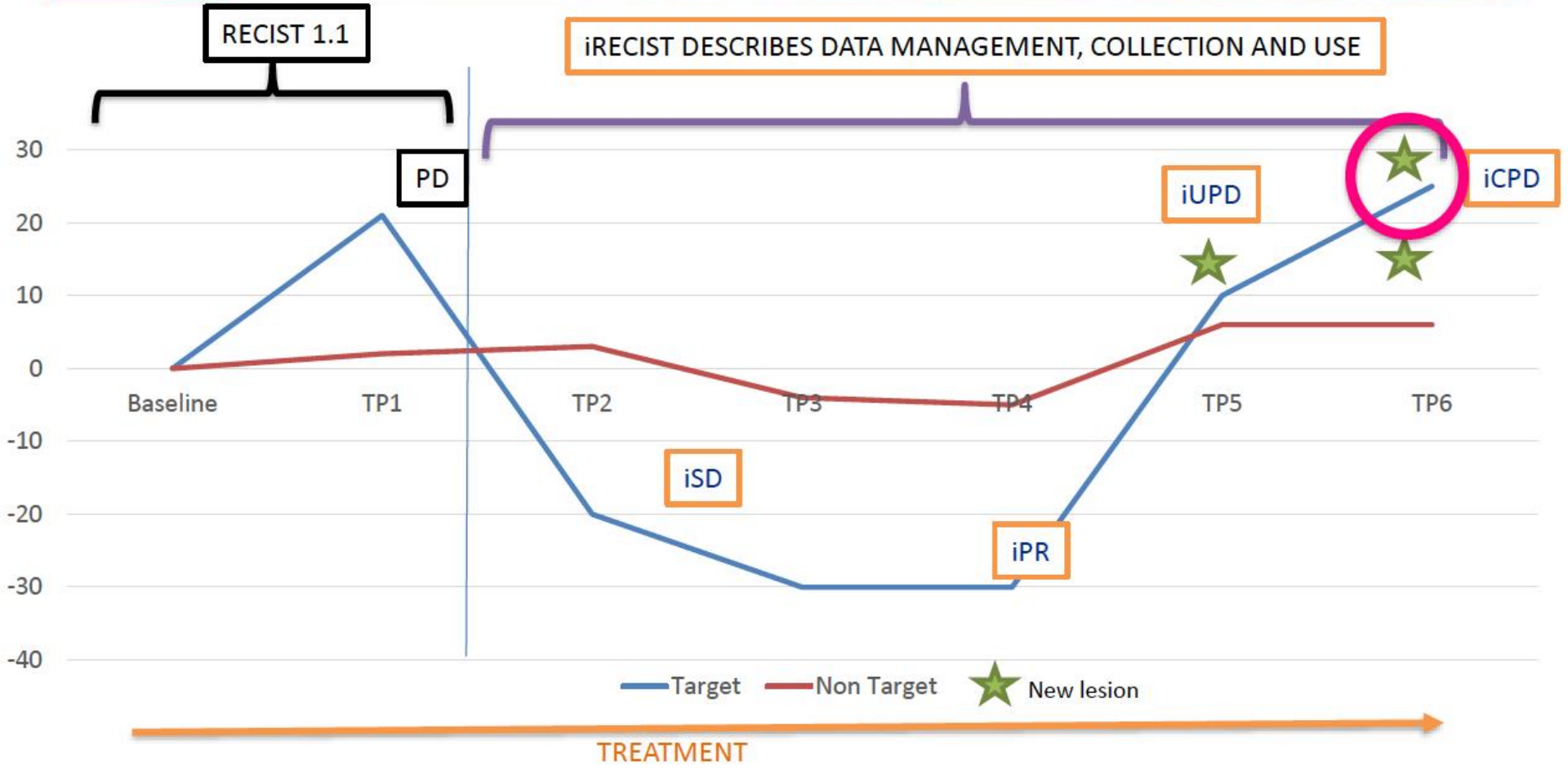
Summary



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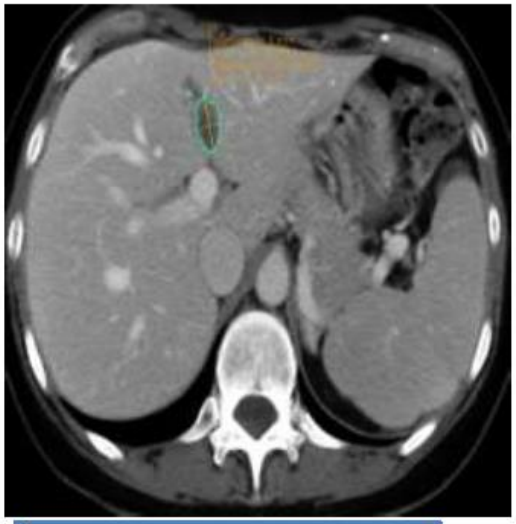
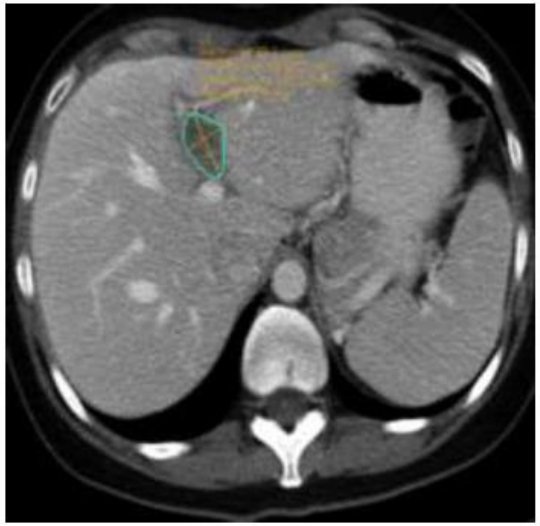
iCPD: Target PD followed by ≥ 5mm↑

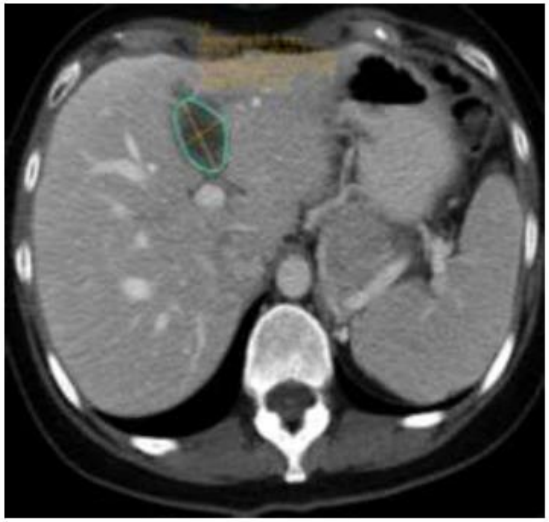


Baseline



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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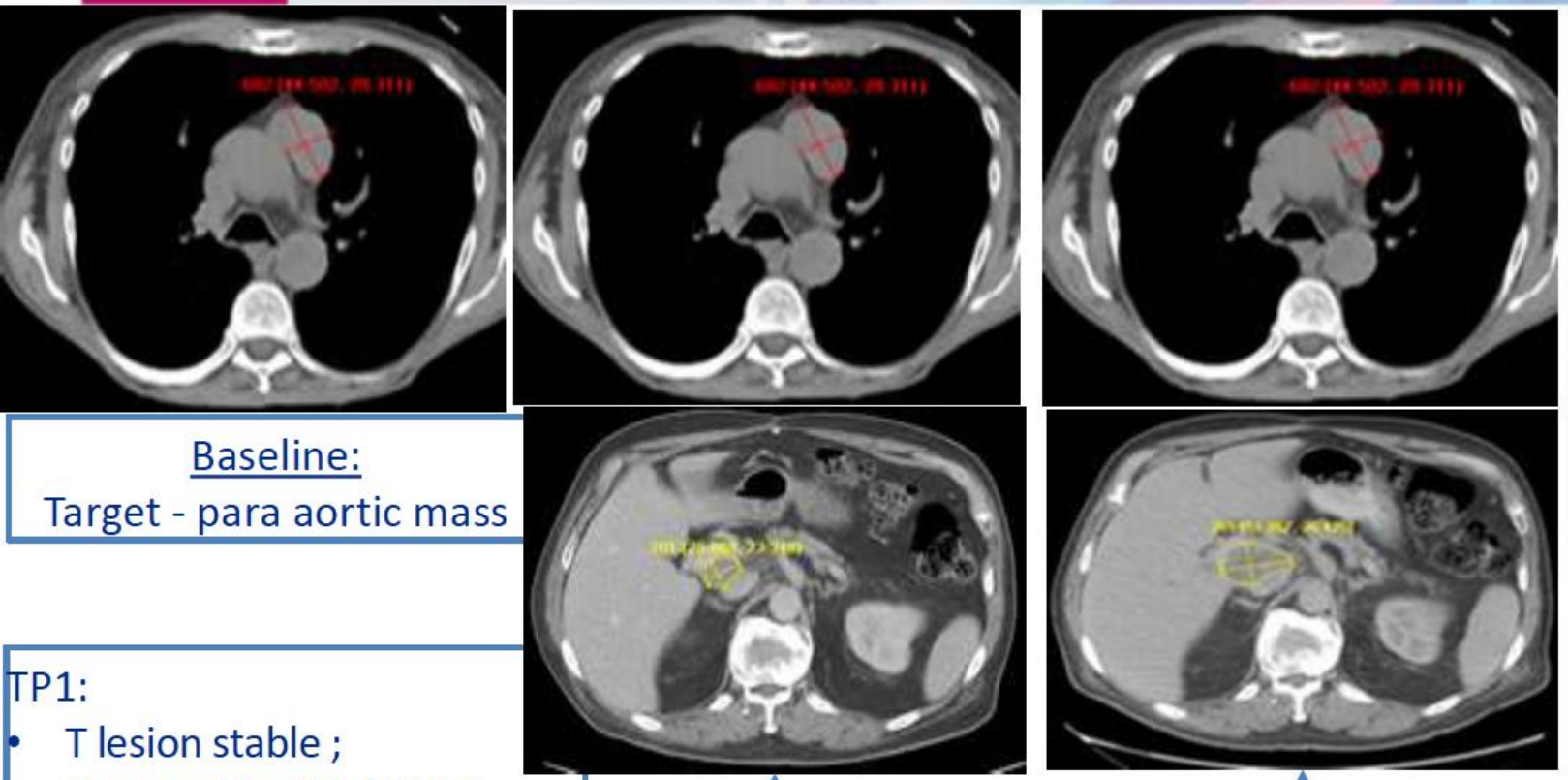
iCPD: NL then ≥ 5mm ↑iSOM



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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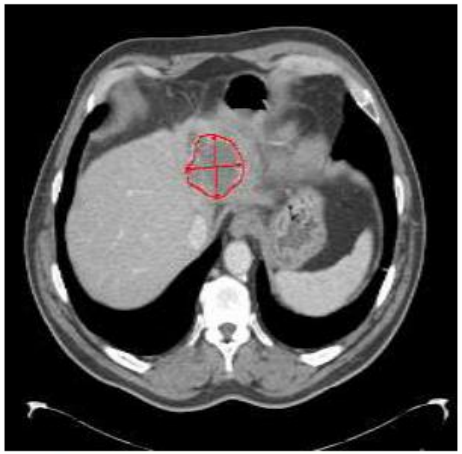
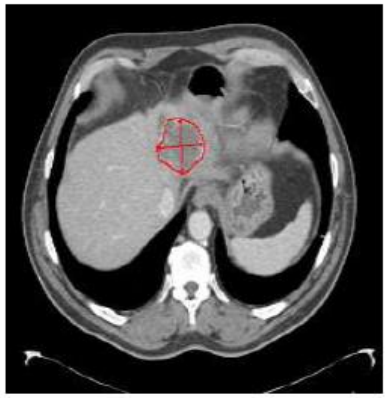
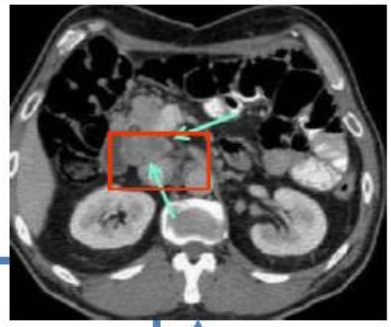
iCPD: NL then additional NL

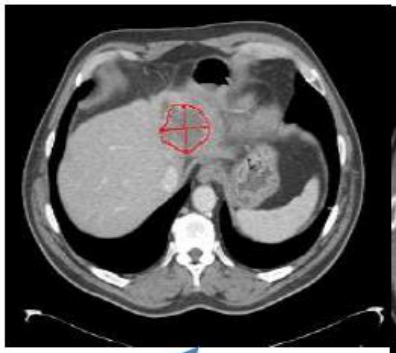




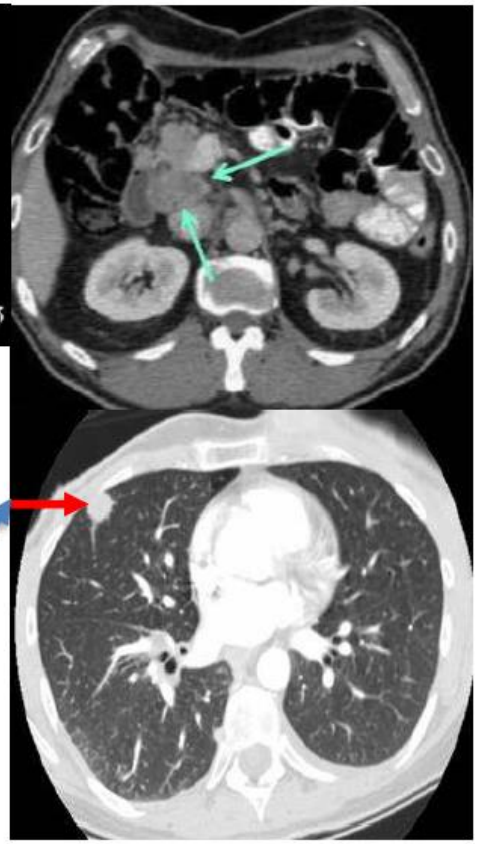


Baseline:
T - liver

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



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



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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/

Pseudo-progression

- Clinical trials have reported the presence of patients with distinct immune-related patterns of response that did not meet RECIST criteria (44 of 1,126 total patients; an approximate overall incidence of 4%)
- Immune response distinct from RECIST response has been reported in melanoma (6.6%; 31 of 471 patients)
- Lung Cancer appears less than 5%

Immune Related Response Criteria

- irRC RECIST 1.0
  - Presence of new lesion does not define progression
  - The measurement(s) of the new lesion(s) are included in the sum of the measurements
  - Up to 5 new lesions per organ and 10 new lesions in total can be added to measurements
- irRC RECIST 1.1
  - Presence of new lesion does not define progression
  - The measurement(s) of the new lesion(s) are included in the sum of the measurements (LN must be ≥ 15 mm)
  - Up to 2 new lesions per organ and 5 new lesions in total can be added to measurements

Implications for Patient Care

- Pragmatism
  - If patient well with RECIST 1.1 PD reasonable to continue therapy but restage early
  - If patient unwell with RECIST 1.1 – stop therapy and consider alternative treatments
- Continuation after progression being explored
  - OAK/Atezolizumab data suggest that, in selected well patients, maintenance may improve survival
  - Randomised phase III data required to confirm this observation and should not be used in routine care