Tumor Response Assessment

− Evolving Paradigms and Clinical Challenges

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- Background and Basic Principles
- Immune Response Patterns
- Real-world Challenges
- Molecular Assessment & Future Directions

Background & Basic Principles

History of Criteria

Criteria, years	Measurement	Target Lesions	Key Features
WHO, 1979	Bidimensional measurement (2D) = Longest diameter × Longest perpendicular diameter	No strict limit	Detailed but complex
RECIST 1.0, 2000	Unidimensional measurement (1D) = Only the longest diameter	10 lesions (max 5 per organ)	Simplified
RECIST 1.1, 2009	Unidimensional measurement (1D) = Only the longest diameter	5 lesions (max 2 per organ)	Improved reproducibility
iRECIST, 2017	Unidimensional measurement (1D) = Only the longest diameter	Same as RECIST 1.1	Accounts for pseudoprogression

Cancer. 1981 Jan 1;47(1):207-14.
J Natl Cancer Inst. 2000 Feb 2;92(3):205-16.
Eur J Cancer. 2009 Jan;45(2):228-47.
Lancet Oncol. 2017 Mar;18(3):e143-e152.

RECIST 1.1 – Measurable Lesions

Lesions	Measurable lesions	Non-measurable lesions
Tumor	• Longest diameter with a minimum size of 10mm by CT scan* • 20mm by chest X-ray • 10mm caliper measurement by clinical exam 	• <10mm by CT scan* • Lesions which cannot be accurately measured with calipers • Ascites, pleural or pericardial effusion • Leptomeningeal disease, lymphangitic involvement of skin or lung • Abdominal masses or organomegaly identified by physical exam
LN	• LN must be ≥ 15mm in short axis when assessed by CT scan*	• LN with ≥10 to <15mm short axis

*CT scan slice thickness no greater than 5 mm

Eur J Cancer. 2009 Jan;45(2):228-47.

RECIST 1.1 – Lymph nodes

- **Measurable/Target Lesions**

  : Only the short axis of LNs is measured and Included in the baseline sum.

  : Measurable lesions: Short axis ≥ 15 mm by CT scan.

- **Non-Target Lesions**

  : Pathological nodes with short axis ≥ 10 mm but < 15 mm.

  : Do not require measurements and should be recorded as: 'Present', 'Absent', or in rare cases 'Unequivocal Progression'.

- **Non-Pathological Nodes**

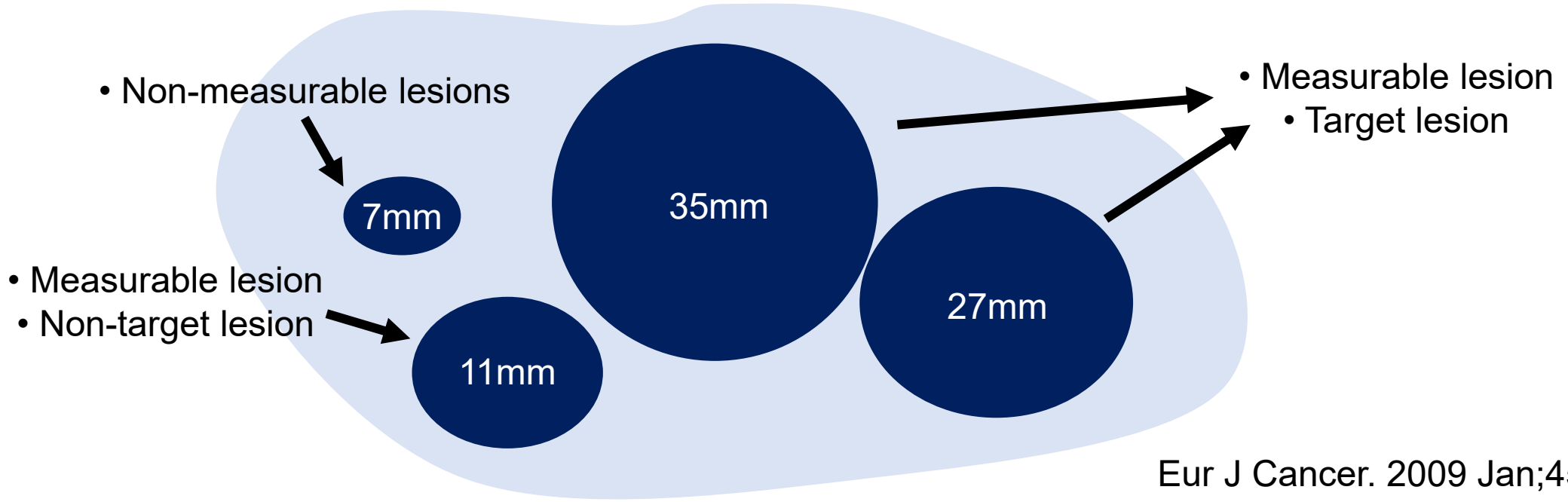
  : Nodes with a short axis < 10 mm.

  : Considered non-pathological and do not record or follow these nodes.

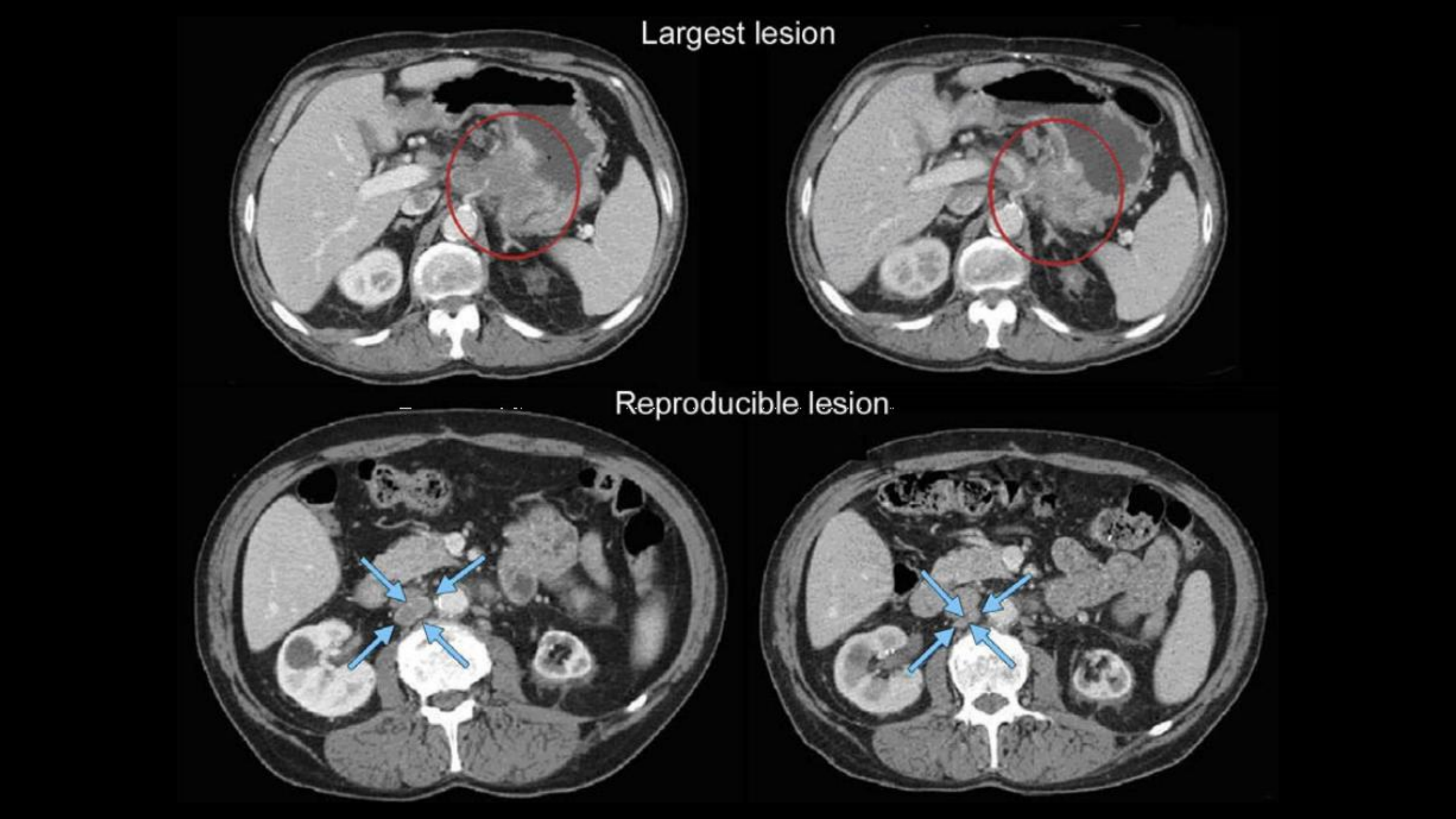
Eur J Cancer. 2009 Jan;45(2):228-47.

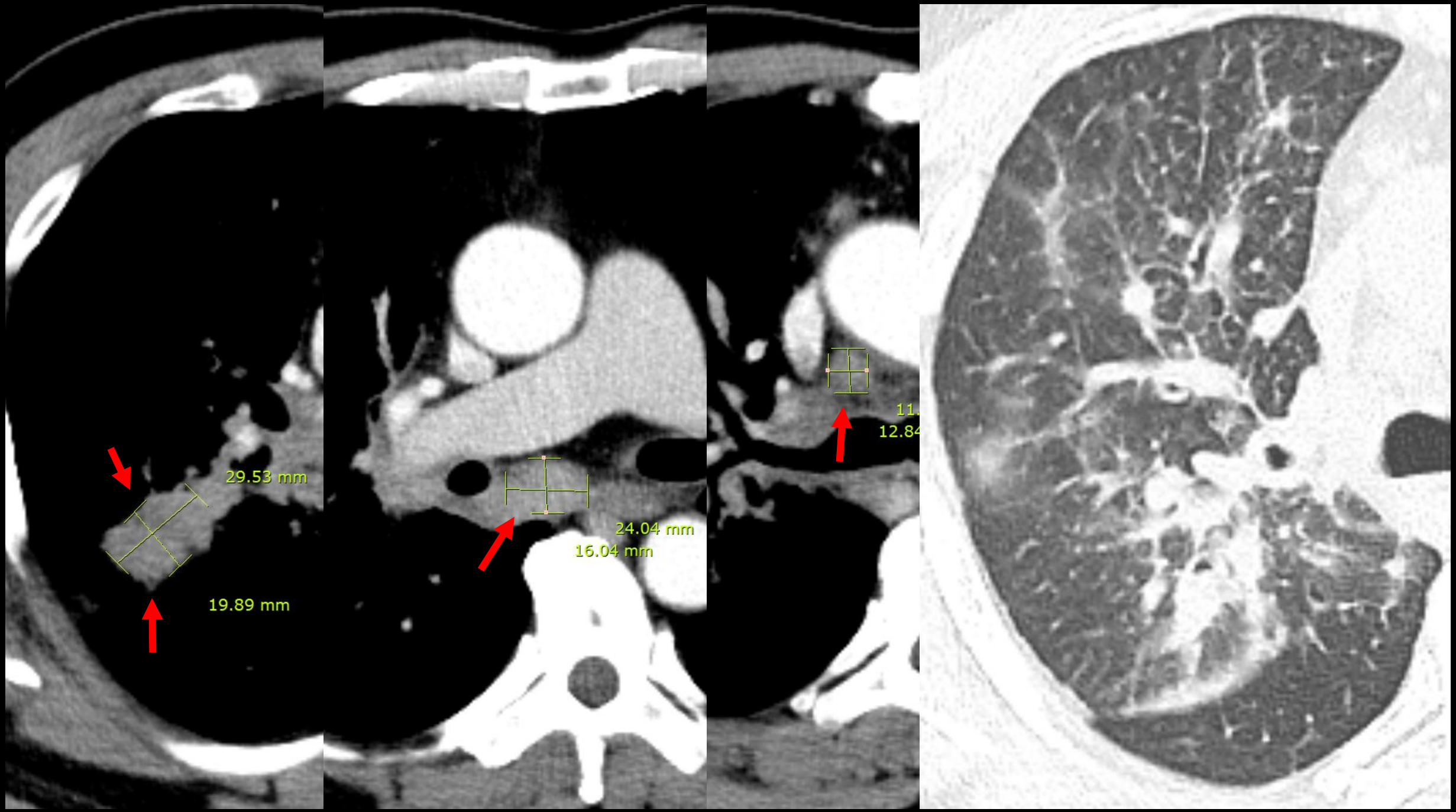
Measurable Lesions vs. Target Lesions

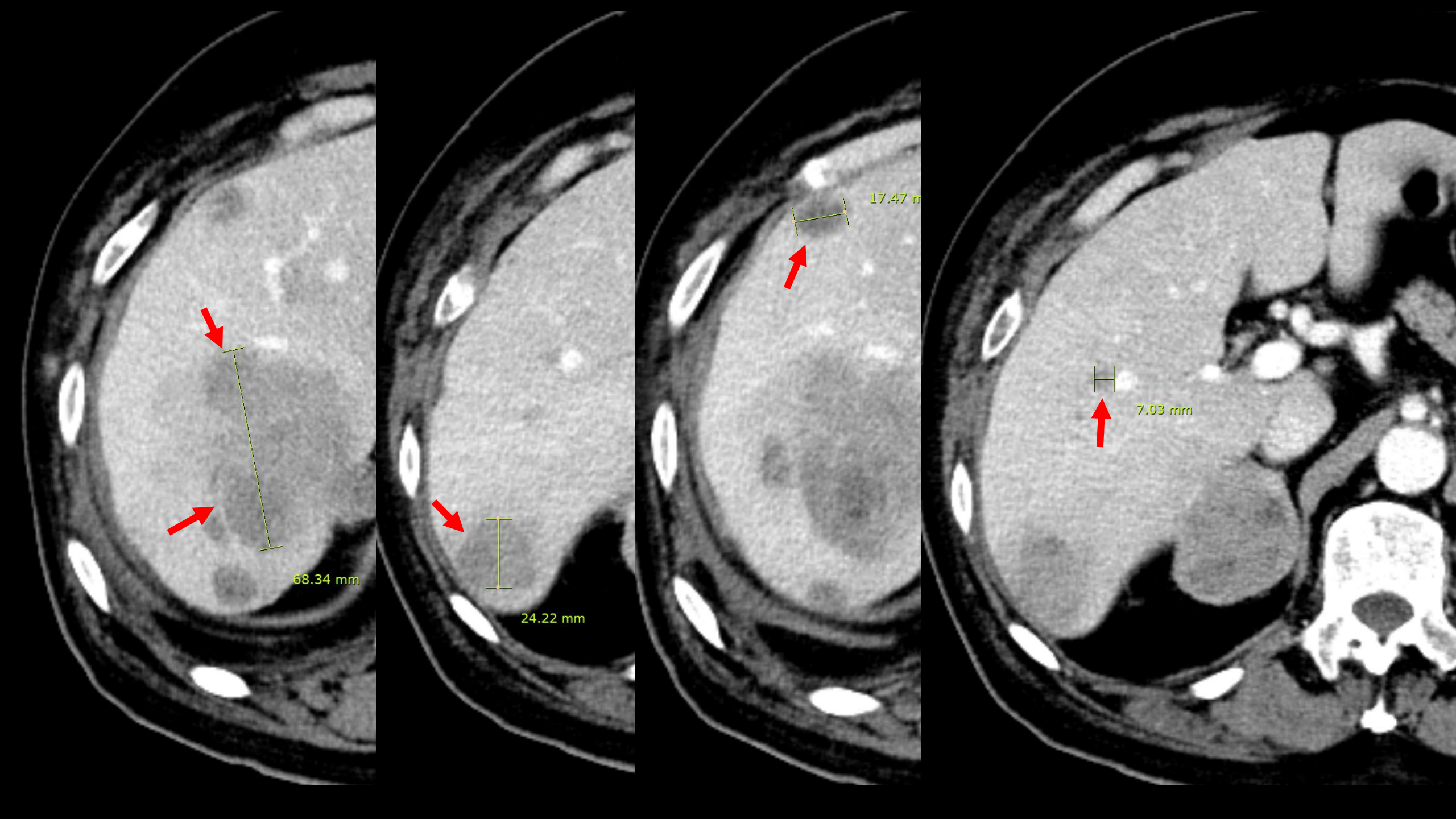
Measurable lesions	Target lesions
• All lesions that meets RECIST criteria • All may NOT become target lesions	• Selected from measurable lesion • Up to 2 lesions per organ, 5 in total • Used for response assessment • Reproducible repeated measurements



Eur J Cancer. 2009 Jan;45(2):228-47.


Largest lesion
Reproducible lesion


29.53 mm
19.89 mm
24.04 mm
16.04 mm


68.34 mm
24.22 mm
17.47 m
7.03 mm

RECIST 1.1 – CR, PR

- **Complete Response (CR)**

  : Disappearance of all target lesions.

  : Any pathological LNs (whether target or non-target) must have reduction in short axis to <10 mm.

- **Partial Response (PR)**

  : At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Eur J Cancer. 2009 Jan;45(2):228-47.

RECIST 1.1 – PD

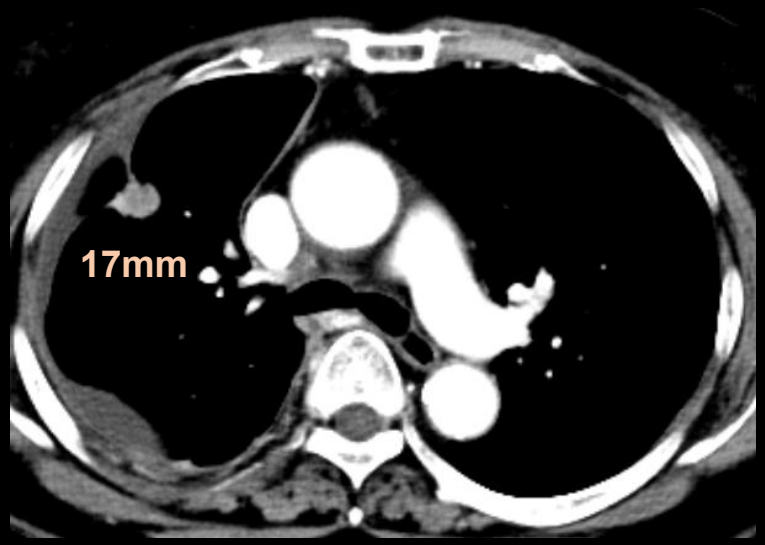
- **Progressive Disease (PD)**

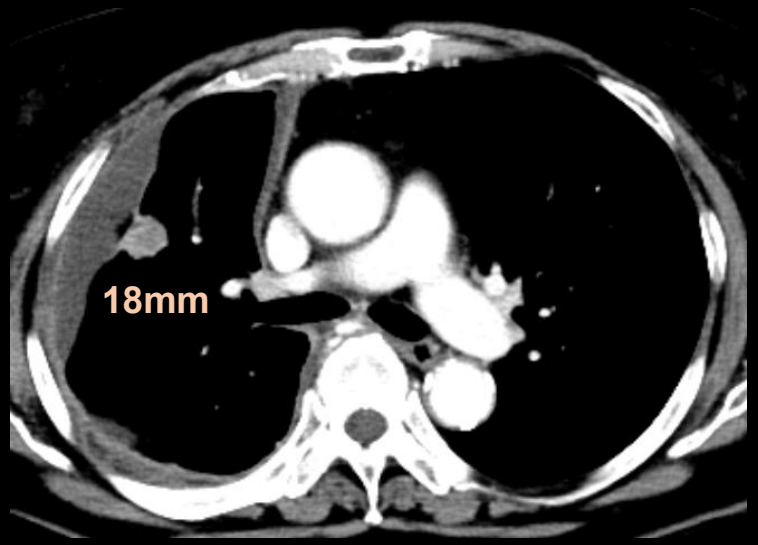
  : At least a 20% increase in the sum of diameters of target lesions, taking as referencethe smallest sum on study.

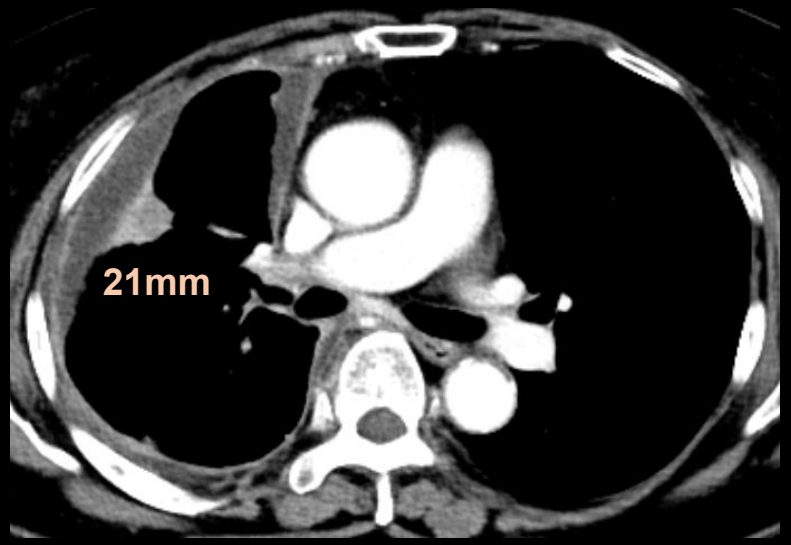
  : In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  : The appearance of one or more new lesions is also considered progression.

Eur J Cancer. 2009 Jan;45(2):228-47.







Initial CT scan → After C2 → After C4

New Lesions

- **Key Principles**

  : Appearance of new malignant lesions → **Progressive Disease (PD)**

  : Not due to imaging technique differences

  : Not a flare or healing of pre-existing lesions

- **Special Considerations**

  : Lesions found in previously unscanned areas → **New lesions**

  (*Example*: Brain metastases found on follow-up MRI without baseline brain imaging → **PD**)

  : If a new lesion is **equivocal** (small or unclear)

  - Continue therapy and follow-up.
  - If confirmed as new → Use the **initial scan date** for PD.

Eur J Cancer. 2009 Jan;45(2):228-47.

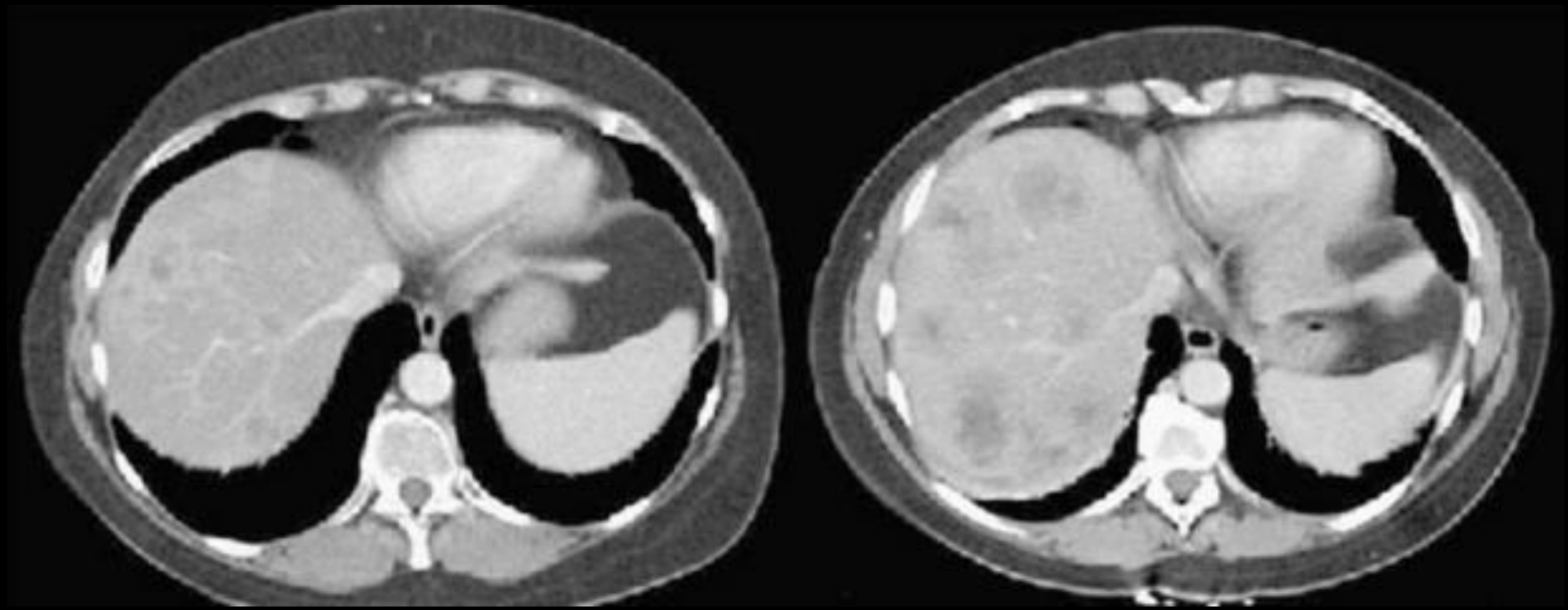
Progression of Non-Target Lesions

- **Definition of Unequivocal Progression**

  : Unequivocal progression refers to a clear and substantial worsening of non-target lesions.

  : This progression must be clinically significant enough to warrant a change in therapy, even if target lesions are SD or PR.

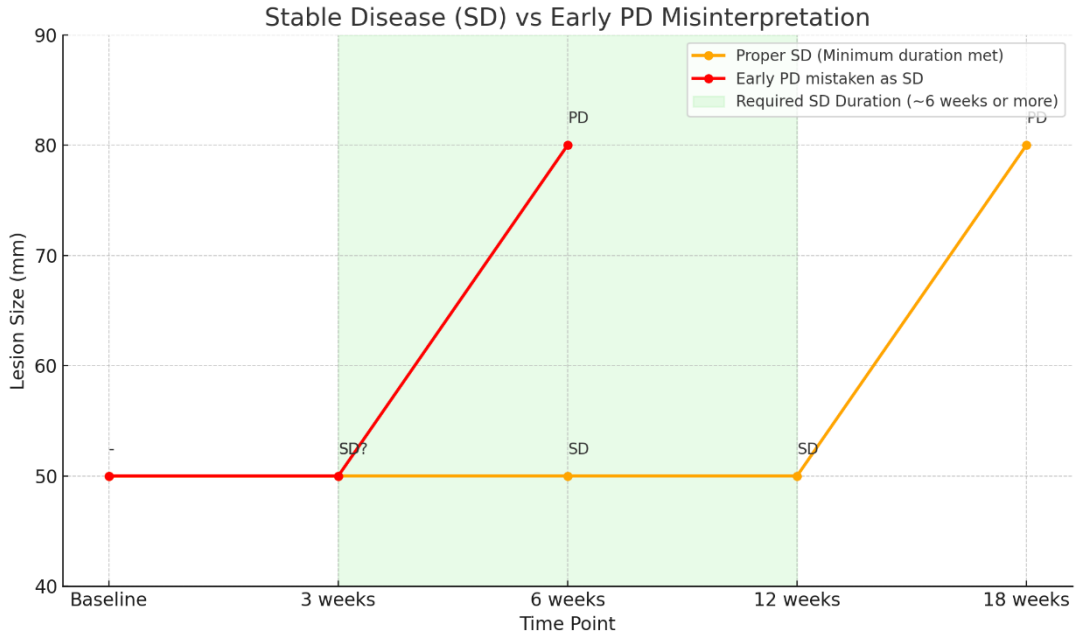
Eur J Cancer. 2009 Jan;45(2):228-47.



RECIST 1.1 – SD

- **Stable Disease (SD)**

  : Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.



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

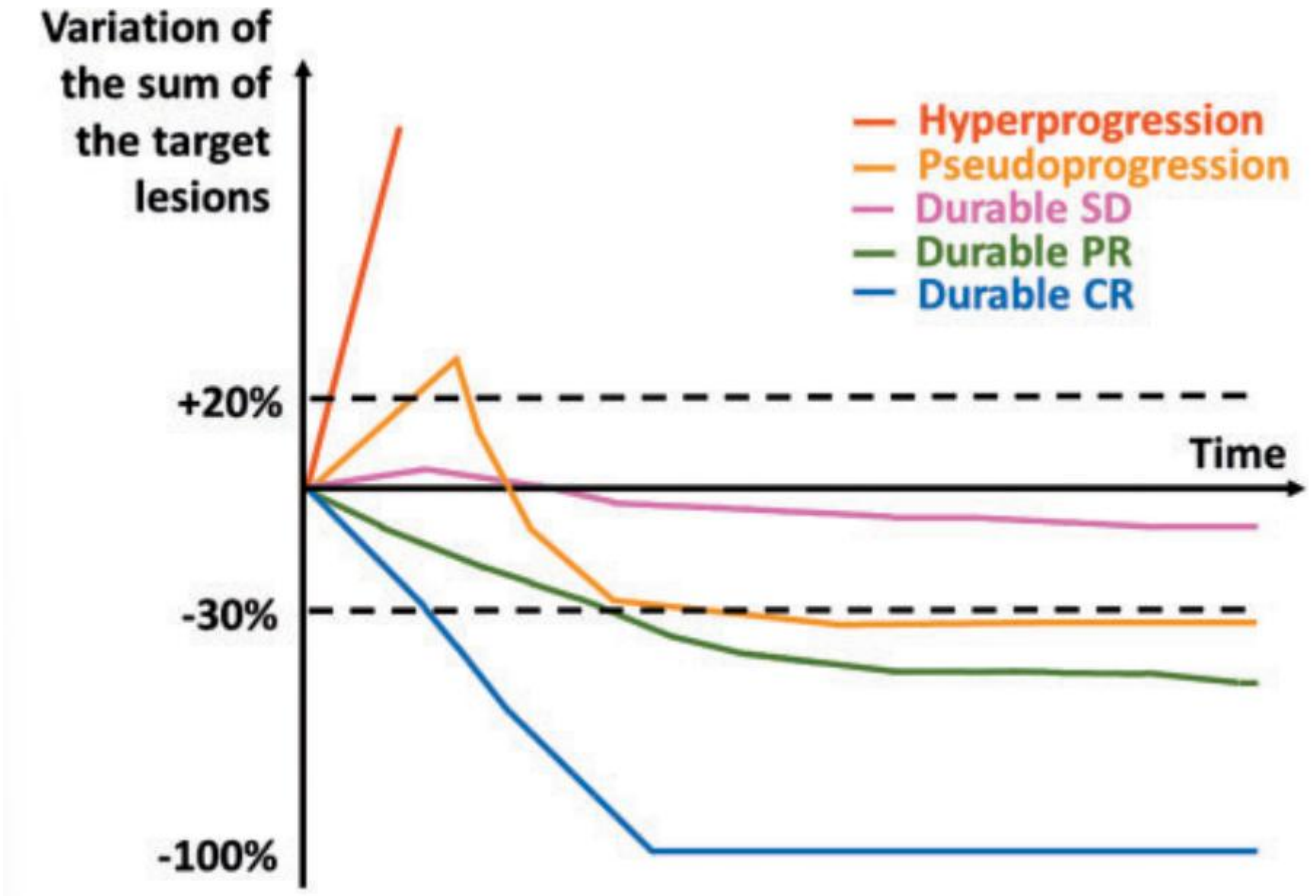
CR = complete response, PD = progressive disease, and NE = inevaluable.

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.

Eur J Cancer. 2009 Jan;45(2):228-47.

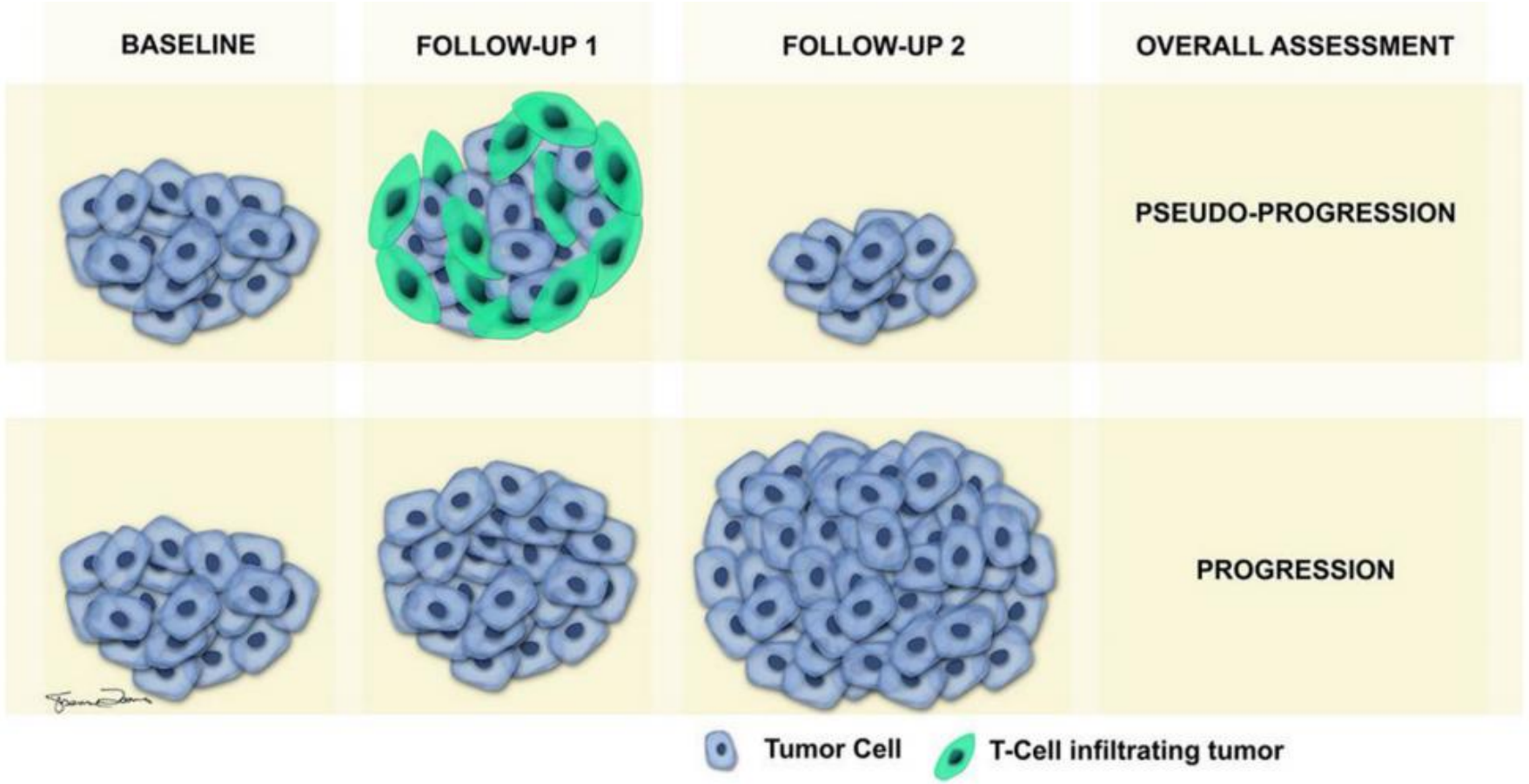
Immune Response Patterns

Immune Response Patterns



Ann Oncol. 2019 Mar 1;30(3):385-396.

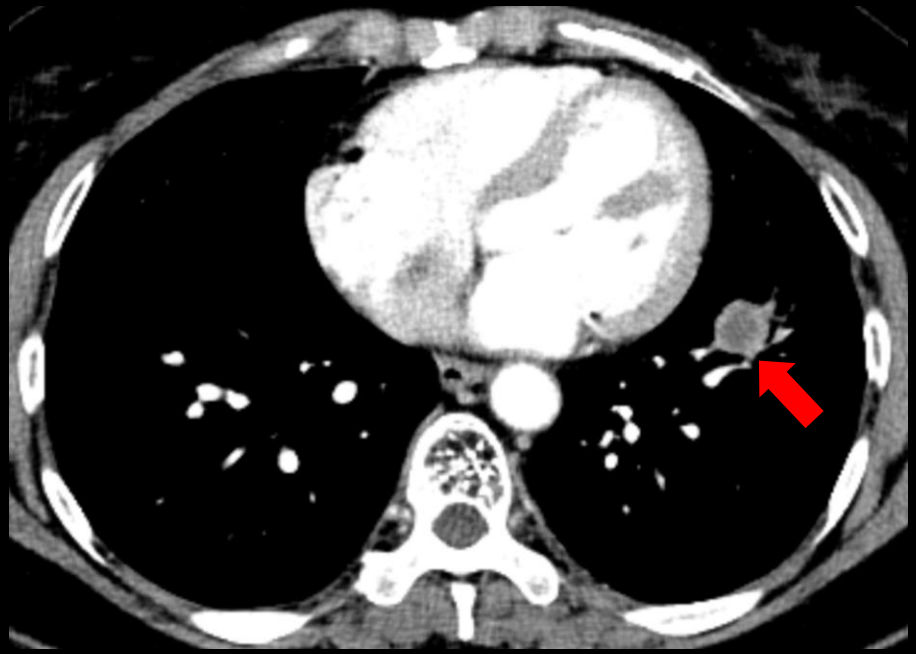
True vs Pseudo-progression

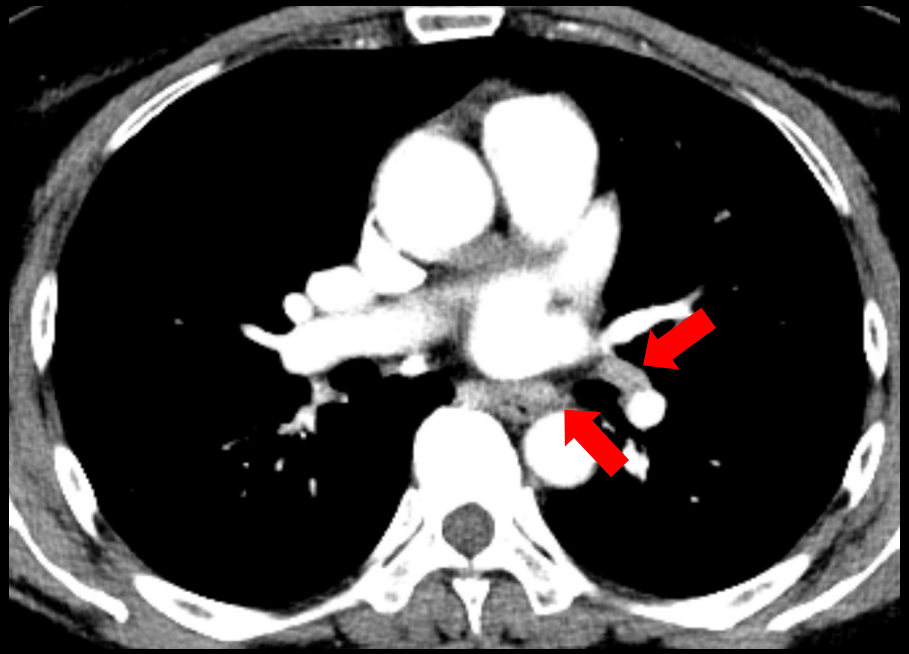


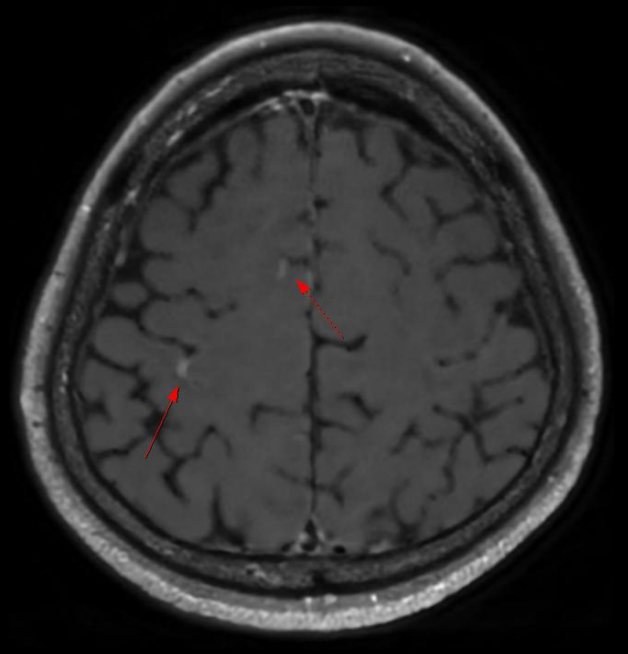
Br J Radiol. 2018 Apr;91(1084):20170457.

Case

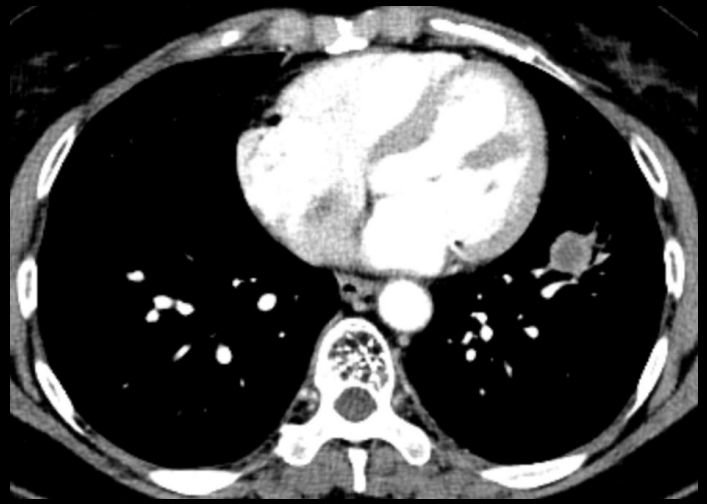
- Female/64
- Lung mass in left lower lobe with multiple brain metastases

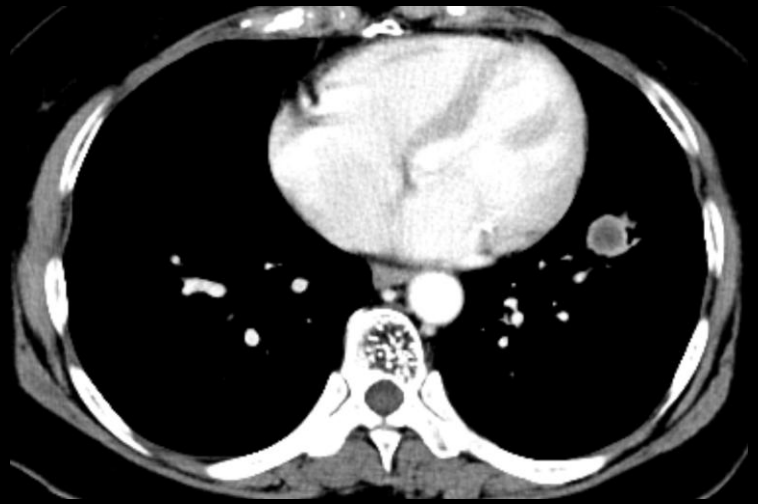


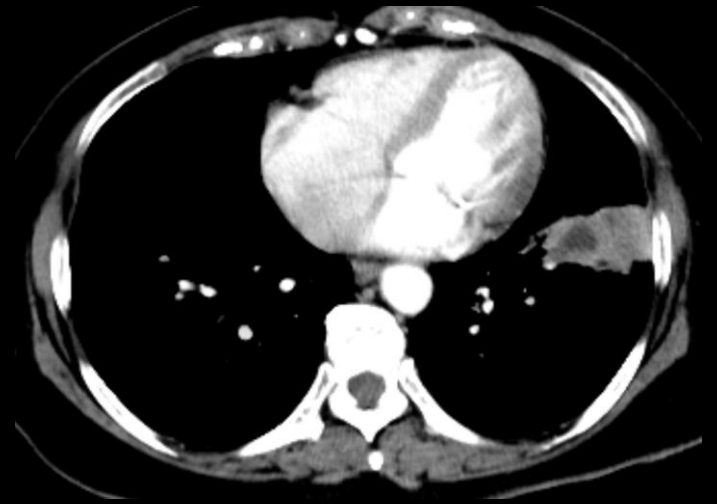




- **Adenocarcinoma, No driver mutation, PD-L1 SP263: 10%**







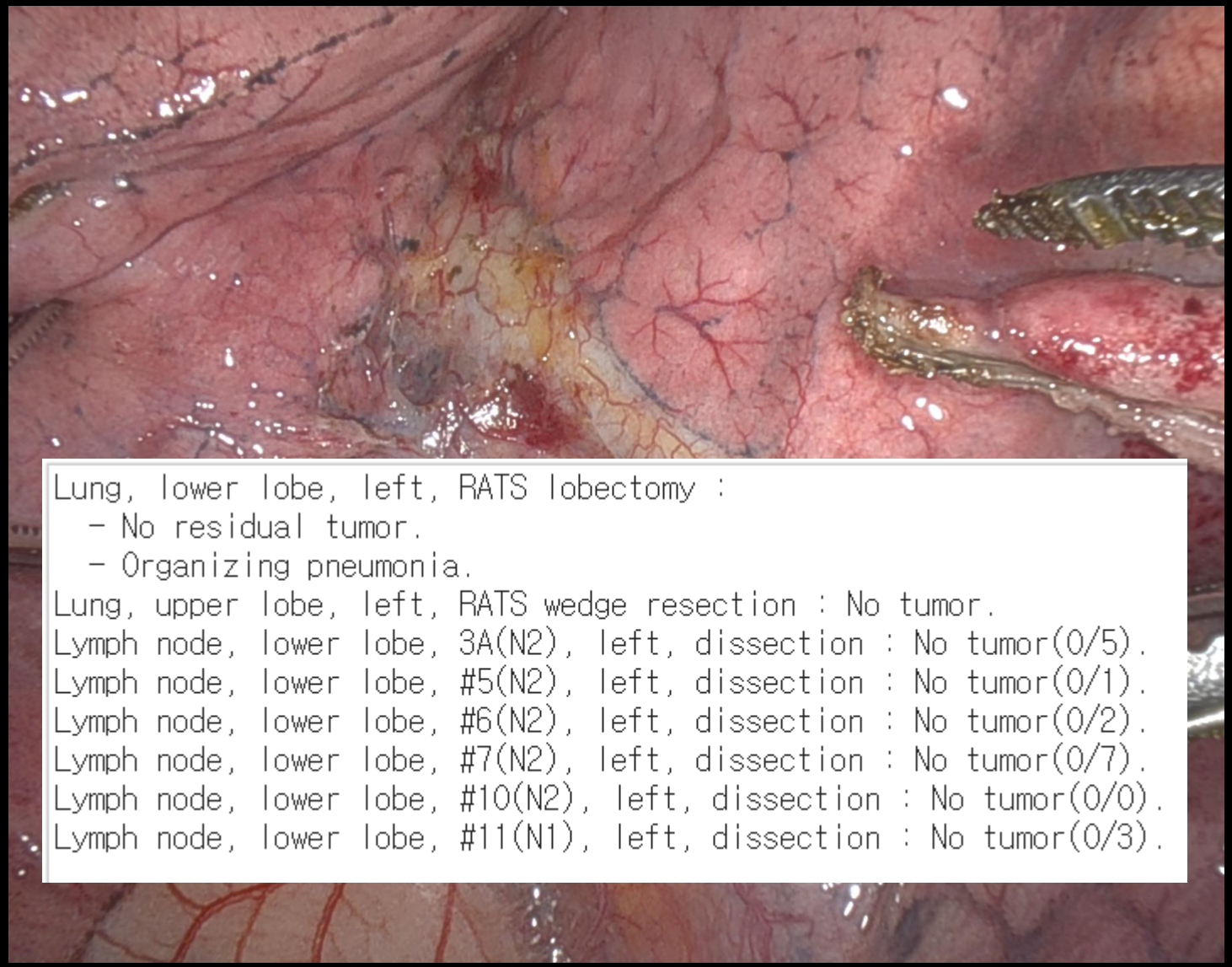
Initial CT scan

Pembrolizumab + Chemotherapy (After C2)

CONCLUSION
compared with previous MR, interval decreased and faint visualization state of previous multifocal small enhancement at both F,P,O lobe - improveing process of brain metastasis, more likely rec) clinical correalation, F/U

Pembrolizumab + Chemotherapy (After C4)

CONCLUSION
Compared to previous MRI taken 2025-02-07, No more visible multifocal small enhancement at both F,P,O lobe. - improveing process of brain metastasis, more likely. No newly appearing enhancing lesion. Microangiopathy.



Lung, lower lobe, left, RATS lobectomy :
- No residual tumor.
- Organizing pneumonia.

Lung, upper lobe, left, RATS wedge resection : No tumor.
Lymph node, lower lobe, 3A(N2), left, dissection : No tumor(0/5).
Lymph node, lower lobe, #5(N2), left, dissection : No tumor(0/1).
Lymph node, lower lobe, #6(N2), left, dissection : No tumor(0/2).
Lymph node, lower lobe, #7(N2), left, dissection : No tumor(0/7).
Lymph node, lower lobe, #10(N2), left, dissection : No tumor(0/0).
Lymph node, lower lobe, #11(N1), left, dissection : No tumor(0/3).

▪ RATS LLLobectomy with MLND

Case Summary

- Female/64, ECOG 0
- Stage IV ADC without driver mutation, PD-L1 SP263 10%

- 2025.01.10 Pembrolizumab/Pemetrexed/Carboplatin C1
- 2025.01.31 Pembrolizumab/Pemetrexed/Carboplatin C2

  RECIST − SD, iRECIST − iSD
- 2025.02.24 Pembrolizumab/Pemetrexed/Carboplatin C3
- 2025.03.18 Pembrolizumab/Pemetrexed/Carboplatin C4

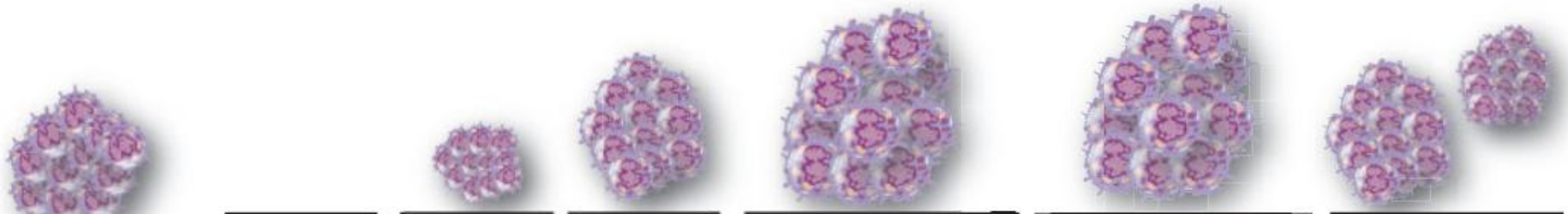
  RECIST − PD, iRECIST − iUPD

- 2025.04.16 Salvage surgery: pCR

Types of Atypical Immune Responses

Response Type	Definition	Incidence
Pseudoprogression	Initial progression → Tumor shrinkage or stabilization	5%
Dissociated Response	Some lesions shrink while others grow	7−8%

Eur J Cancer. 2018 Jan:88:38-47.
Clin Cancer Res. 2009 Dec 1;15(23):7412-20.
Lancet Oncol. 2017 Mar;18(3):e143-e152.



	CR	PR	SD	PD	Confirmation of PD	New lesions
RECIST1.1 [34] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	Not applicable	PD
irRC [74] Bi-dimensional 5mm x 5mm 15 lesions in total, 5 per organ	Disappearance of all lesions	≥ 50% decrease from baseline	Neither CR nor PD	≥ 25% increase in the nadir of the sum of target lesions	At least 4 weeks later	Incorporated in the sum of measurements
irRECIST [75] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks after and up to 12 weeks	Incorporated in the sum of measurements
iRECIST [76] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks after and up to 8 weeks	iUPD; not incorporated in the sum becomes iCPD if confirmed
imRECIST [77] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks later	Incorporated in the sum of measurements

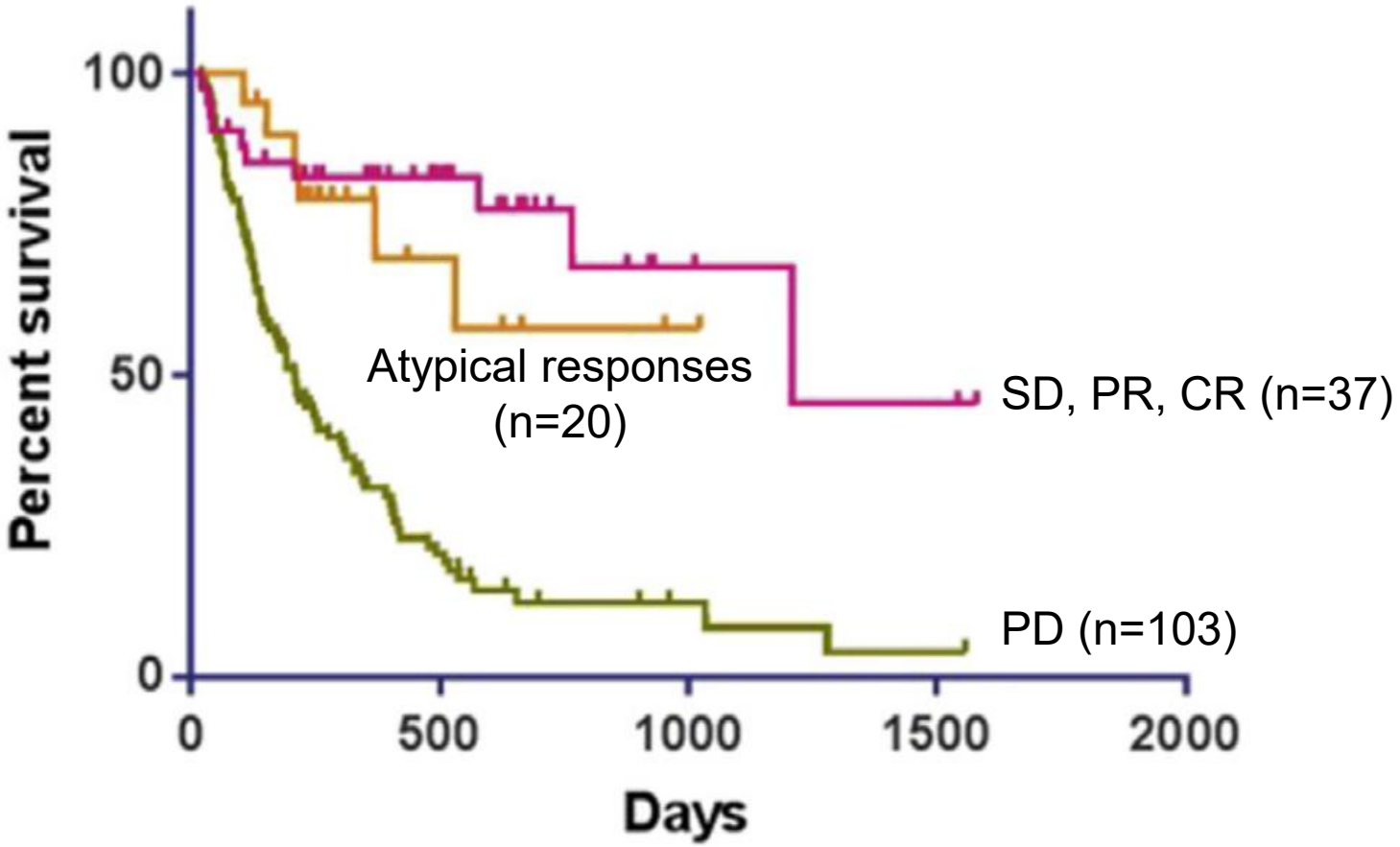
Ann Oncol. 2019 Mar 1;30(3):385-396.
Clin Cancer Res. 2009 Dec 1;15(23):7412-20.

irRC, irRECIST, iRECIST and imRECIST

Category	irRC (immune-related Response Criteria)	irRECIST (immunotherapy-related RECIST)	iRECIST (immune-related RECIST)	imRECIST (immune-modified RECIST)
Origin	Immune-related response in melanoma (2009)	Early immunotherapy trials (non-official)	Developed by RECIST working group (official, 2017)	Modified from RECIST for ICI studies (non-official)
Foundation	WHO 2D tumor measurement (bi-dimensional)	RECIST 1.0	RECIST 1.1	RECIST 1.1
Regulatory Acceptance	Not accepted	Limited, non-standardized	Increasingly accepted by FDA/EMA for immunotherapy trials	Not officially endorsed
Clinical Use	Historical use in early ICI trials	Obsolete; used in early immunotherapy trials	Widely used for immunotherapy trials	Used in real-world data & pharma trials

Lancet Oncol. 2017 Mar;18(3):e143-e152.
Ann Oncol. 2019 Mar 1;30(3):385-396.

OS in Atypical Response



Eur J Cancer. 2018 Jan:88:38-47.

RECIST *vs*. iRECIST

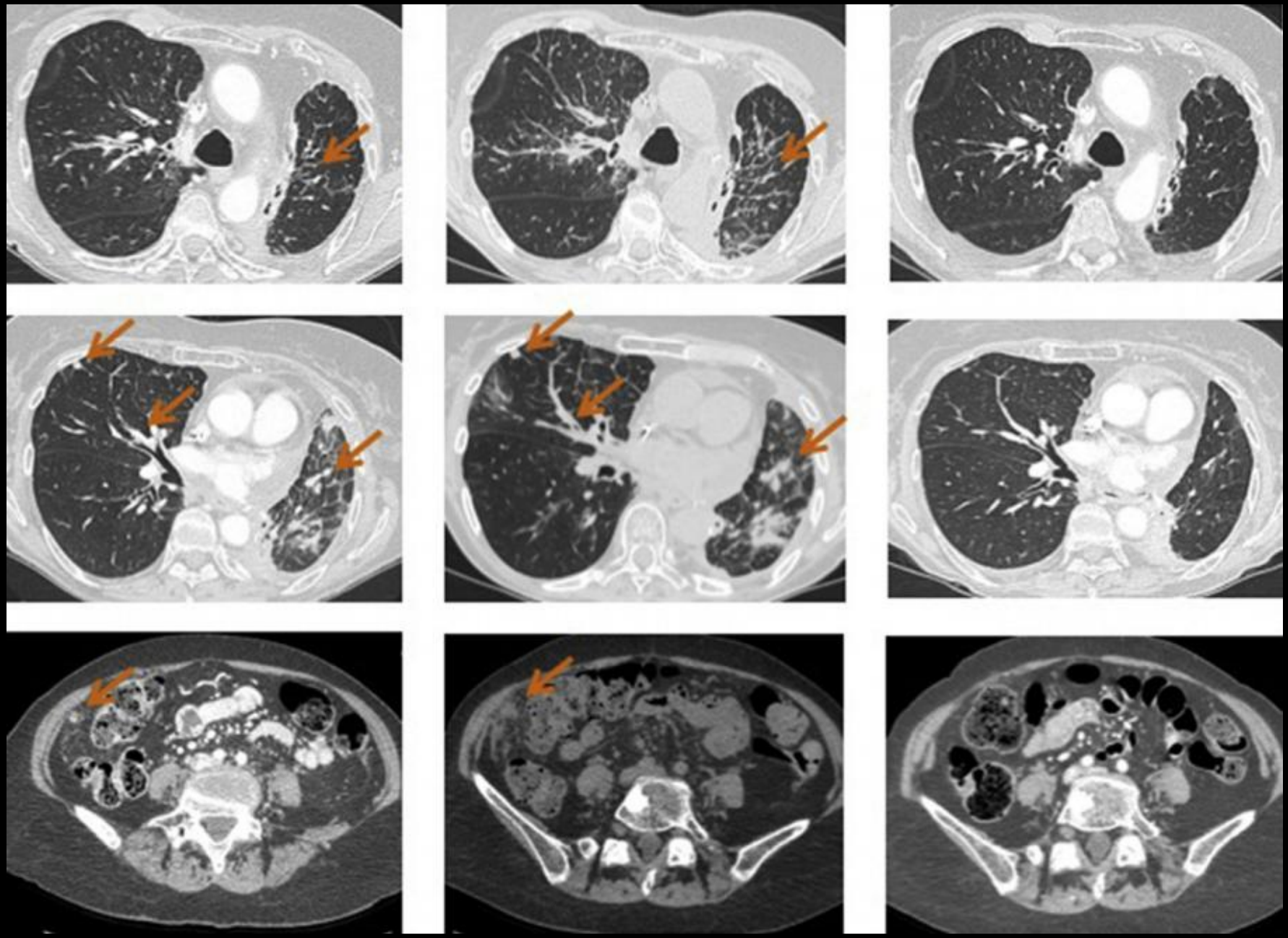
Category	RECIST 1.1	iRECIST
Confirmation of PD	Not required	Required (iUPD → iCPD)
Treatment beyond PD	Limited or not recommended	Permitted after iUPD
Response Categories	CR, PR, SD, PD	iCR, iPR, iSD, iUPD, iCPD
Overall Response Rate	28.5%	34.1%
Disease Control Rate	67.4%	74.6%
Time to Progression	538.1 days	618.3 days ($p < 0.05$)
Atypical Responses	May misclassify pseudoprogression as PD	Better captures atypical responses

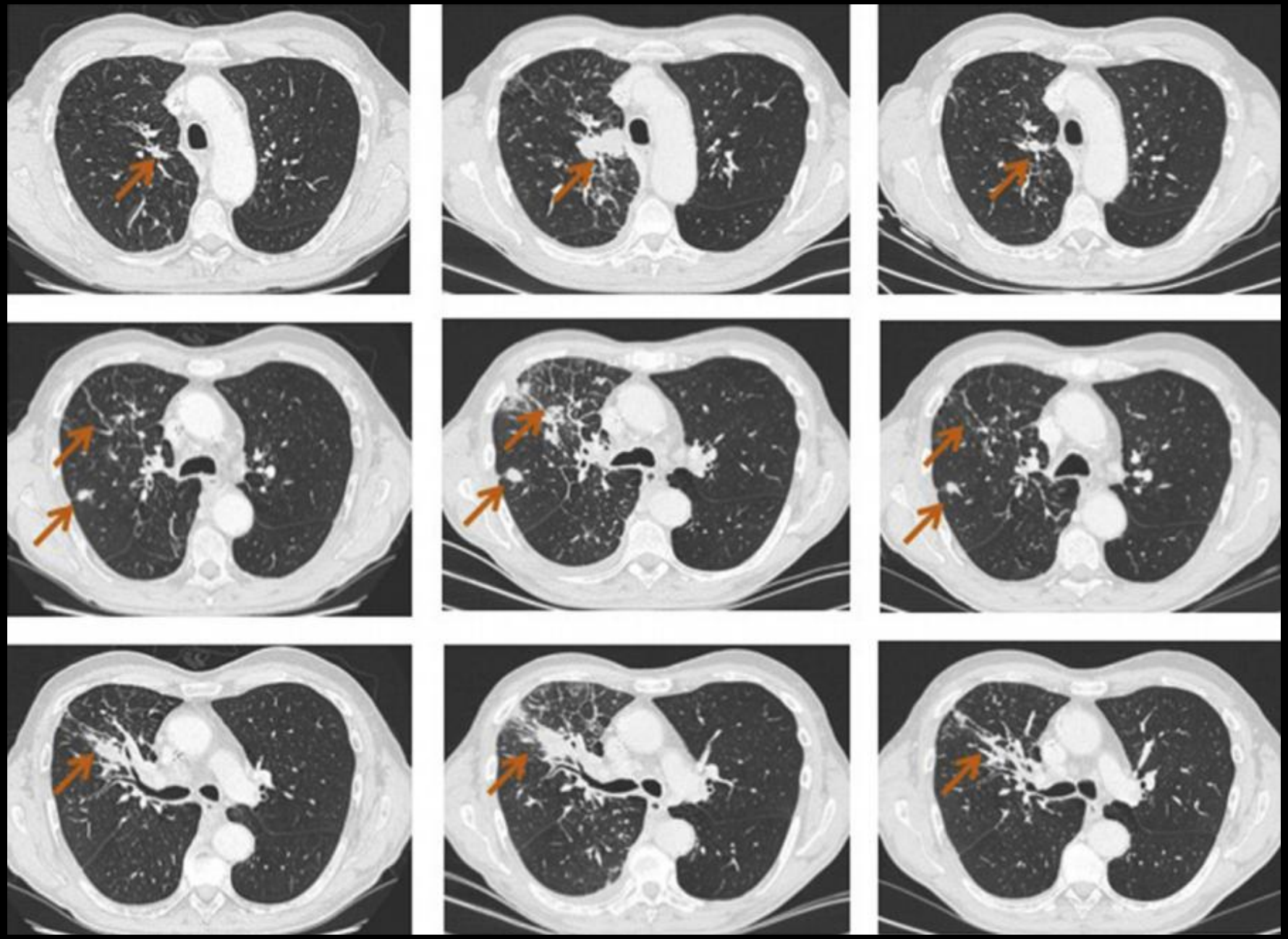
Eur Radiol. 2025 Apr;35(4):2084-2093.

Definition of PD in iRECIST

Feature	Description
New Lesion Handling	• Not immediately considered PD • Recorded separately
Initial PD Term	**iUPD** – Unconfirmed Progressive Disease
Confirmation Required	PD must be confirmed at ≥4 weeks with FU scan
Confirmed PD Term	**iCPD** – Confirmed Progressive Disease

Lancet Oncol. 2017 Mar;18(3):e143-e152.


Baseline
Week 6
Week 24


Baseline
Week 6
Week 24

Real-world Challenges

Bone Lesions

1. Imaging Techniques

: Bone scan, PET, or X-ray are NOT suitable for measuring bone lesions.

: These modalities may confirm the presence or disappearance, but not used for measurement.

2. Measurable Bone Lesions

: Lytic or mixed lytic-blastic lesions with a soft tissue component that can be evaluated by CT or MRI are considered measurable.

3. Non-Measurable Bone Lesions

: Blastic bone lesions are non-measurable.

: Lesions without a measurable soft tissue component cannot be target lesions.

Eur J Cancer. 2009 Jan;45(2):228-47.

Cystic Lesions

1. Definition

: 'Cystic lesions' suspected to be cystic metastases can be considered measurable if they fulfill standard RECIST measurability criteria.(e.g., longest diameter ≥ 10 mm on CT)

2. Preference in Lesion Selection

: If non-cystic lesions are also present in the same patient,
→ Non-cystic lesions are preferred for selection as target lesions.

3. Caution

: Cystic changes may reflect necrosis, treatment response, or non-malignant processes, so careful interpretation is needed..

Eur J Cancer. 2009 Jan;45(2):228-47.

Lesions with Prior Local Treatment

1. General Principle

: Lesions located in previously irradiated areas or areas treated with loco-regional therapy (e.g., RFA, surgery) are usually NOT considered measurable.

2. Exception

: These lesions may be considered measurable only if there is documented progression after local treatment.

→ Imaging must show clear evidence of tumor growth post-treatment.

Eur J Cancer. 2009 Jan;45(2):228-47.

Lesions that split or coalesce on treatment

1. Splitting of Lesions

: When a non-nodal lesion fragments into multiple parts,

→ Measure each visible fragment.

→ Sum the longest diameters of all fragments to calculate the total for that target lesion..

2. Coalescence of Lesions

: If two or more lesions begin to merge, assess as follows

1) If a clear plane between lesions remains → Measure each separately.

2) If fully coalesced with no separable boundary → Measure the longest diameter across the entire merged lesion.

Eur J Cancer. 2009 Jan;45(2):228-47.

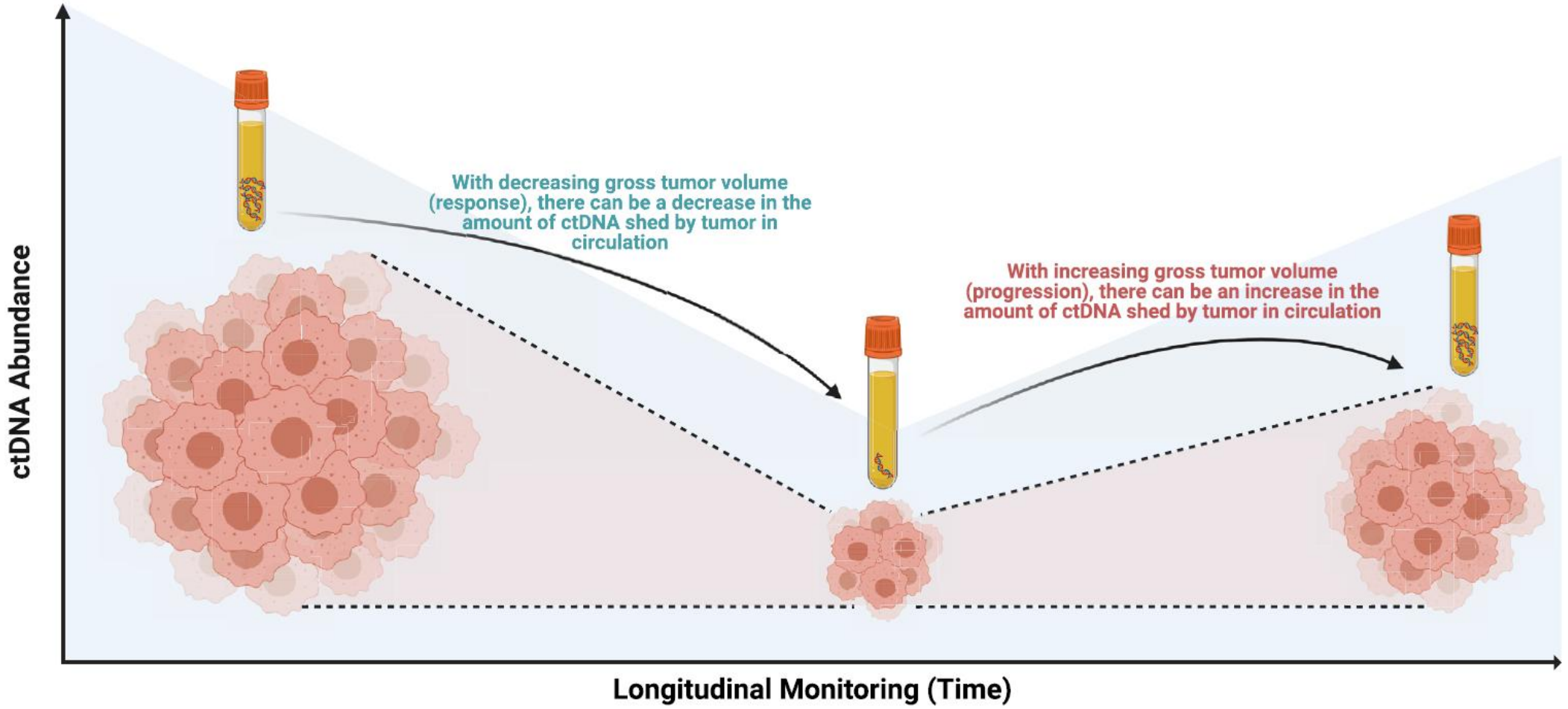
Molecular Assessment & Future Direction

Limitations of RECIST (Imaging-Based)

- Detects only gross tumor changes, not microscopic disease
- Cannot distinguish pseudoprogression *vs*. true progression
- Radiation exposure from repeated scans
- Measurement variability due to lesion selection and reader differences
- May miss early response or progression
- Dependent on imaging modality and expertise

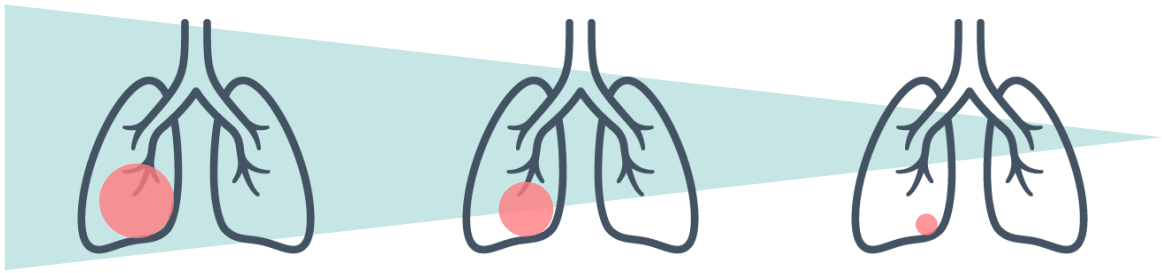
LB-RECIST

: Liquid Biopsy Response Evaluation Criteria in Solid Tumors



Ann Oncol. 2024 Mar;35(3):267-275.

Tumor burden *vs*. ctDNA

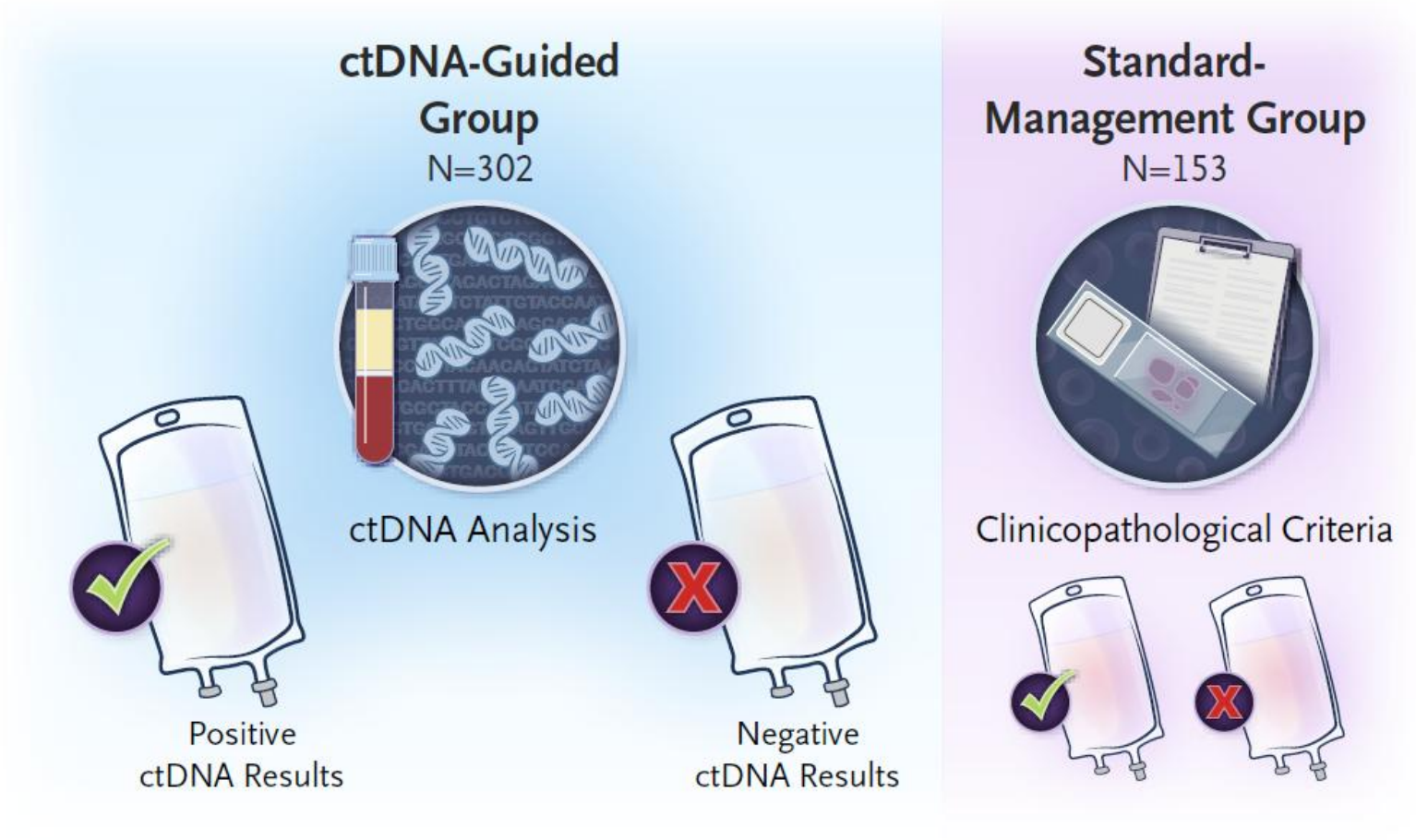


VAF	1.4% (0.62-3.1%)	0.1% (0.06-0.18%)	0.008% (0.002-0.03%)
Nodule diameter	5.8 cm	2.6 cm	1.2 cm
Nodule volume	100 cm^3	10 cm^3	1 cm^3
T stage	T3	T1c	T1b

- Limited ctDNA in early-stage disease or low tumor burden
- The amount of ctDNA is known to vary depending on
  1) Nodule diameter, 2) Nodule volume, and 3) Tumor stage

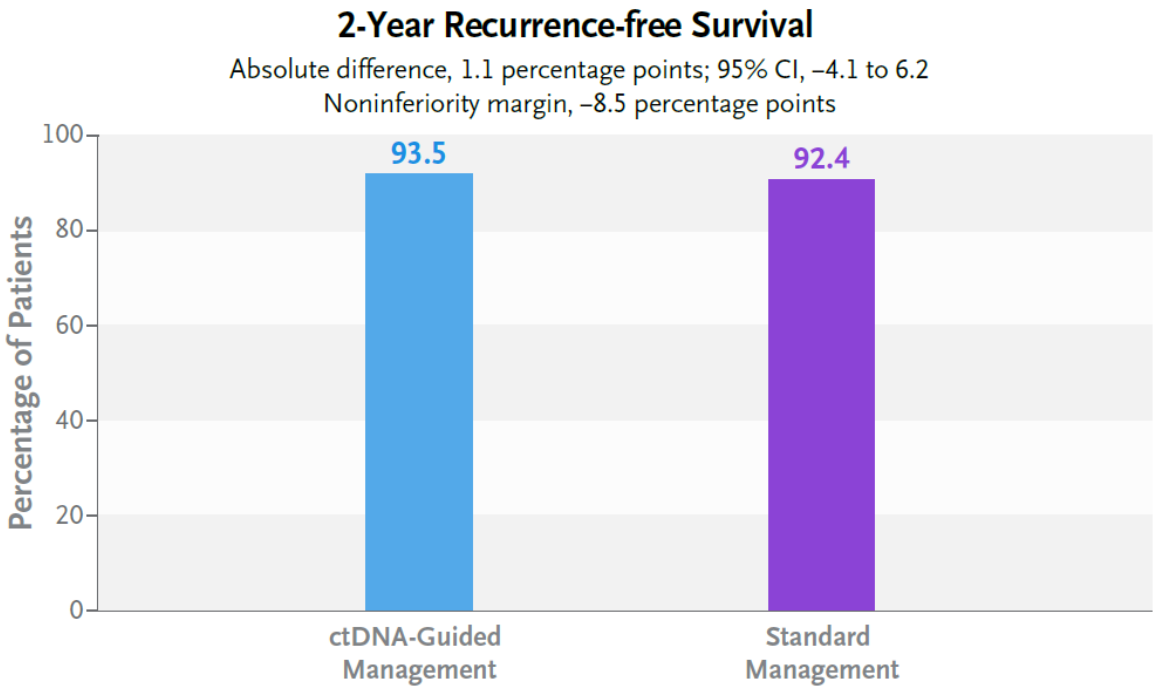
J Thorac Oncol. 2016 Jan;11(1):39-51.
Nat Rev Clin Oncol. 2018 Sep;15(9):577-586.

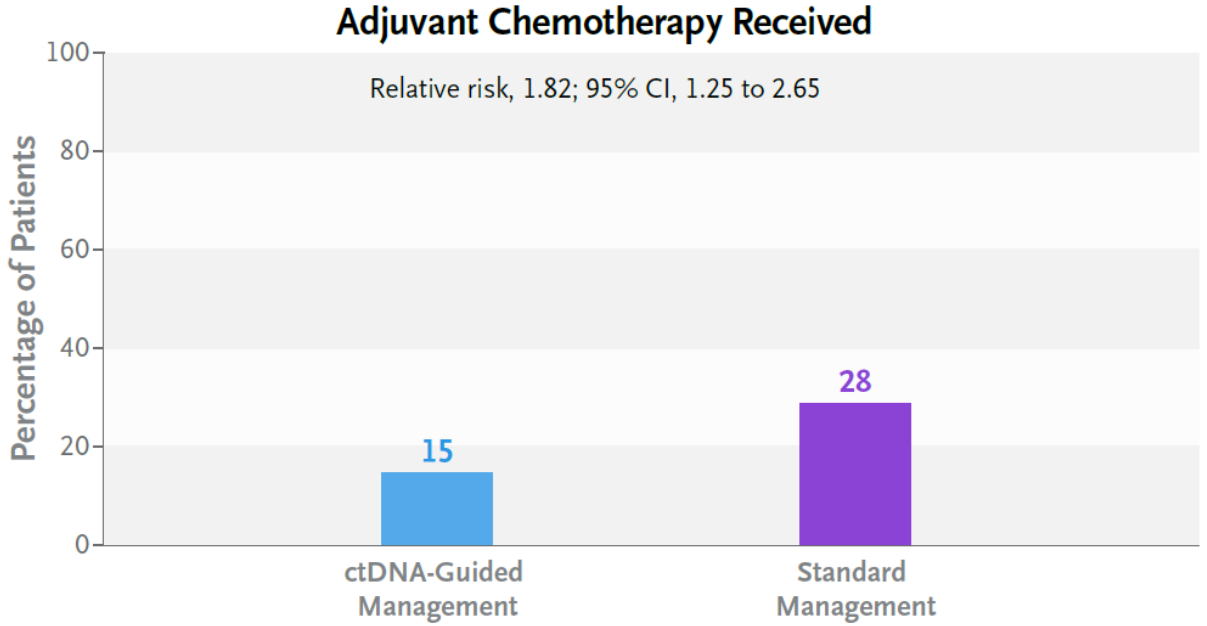
ctDNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer



N Engl J Med. 2022 Jun 16;386(24):2261-2272.

ctDNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer





N Engl J Med. 2022 Jun 16;386(24):2261-2272.

Criteria	Group	Definition
Qualitative response criteria	Group 1 (G1; D-D)	Patients with detectable ctDNA which remains detectable after therapy
	Group 2 (G2; D-U)	Patients with detectable ctDNA which becomes undetectable after therapy
	Group 3 (G3; U-D)	Patients with undetectable ctDNA which becomes detectable after therapy
	Group 4 (G4; U-U)	Patients with undetectable ctDNA which remains undetectable after therapy
Quantitative response criteria	ctDNA complete response (CCR)	ctDNA clearance after initial detectability
	ctDNA partial response (CPR)	Decrease of >10% in variant allele frequency
	ctDNA stable disease (CSD)	No increase or up to 10% increase or decrease in variant allele frequency
	ctDNA progressive disease (CPD)	Increase of >10% in variant allele frequency or *de novo* ctDNA detection
	ctDNA nonmeasurable disease (CND)	Undetectable ctDNA before and after treatment

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- **Example of ctDNA response criteria previously proposed**

Ann Oncol. 2024 Mar;35(3):267-275.

Future Direction

Proposed Update	Key Feature	Development Status
LB-RECIST	ctDNA-based response	Proposed 2024
AI/Radiomics	Qualitative tumor analysis	Ongoing
Non-target/New Lesion Criteria	Quantification and clarity	Ongoing

Ann Oncol. 2024 Mar;35(3):267-275.
Eur J Cancer. 2012 Mar;48(4):441-6.
Eur J Cancer. 2016 Jul:62:132-7.

Summary

- RECIST 1.1 remains the standard but has limitations in reflecting true biological response.
- Immune-related responses are assessed using iRECIST, introducing iUPD to distinguish true progression from delayed immune responses.
- Molecular approaches like ctDNA and LB-RECIST are emerging to complement imaging and improve accuracy.
- Future direction: Integrating radiologic, molecular, and pathologic data for a more comprehensive assessment.

감사합니다.