



INTEGO
GROUP

AS08

How has the immunotherapy era changed response criteria?

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Agenda

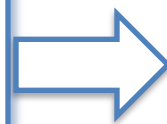
- ☐ What is Anti-Cancer Immunotherapy and how Immune Checkpoint Inhibitors work?
- ☐ Immunotherapy Response Pattern
- ☐ RECIST1.1 in Nutshell
- ☐ Why do we need iRECIST?
- ☐ iRECIST vs RECIST1.1
- ☐ i-Efficacy Endpoints
- ☐ Conclusions

What is Anti-Cancer Immunotherapy?

Traditional Chemotherapies: (Direct Killing of tumor cells)

Interferes with cell division

- ☐ DNA damaging alkylating
- ☐ DNA intercalating agents
- ☐ DNA synthesis-blocking antimetabolites



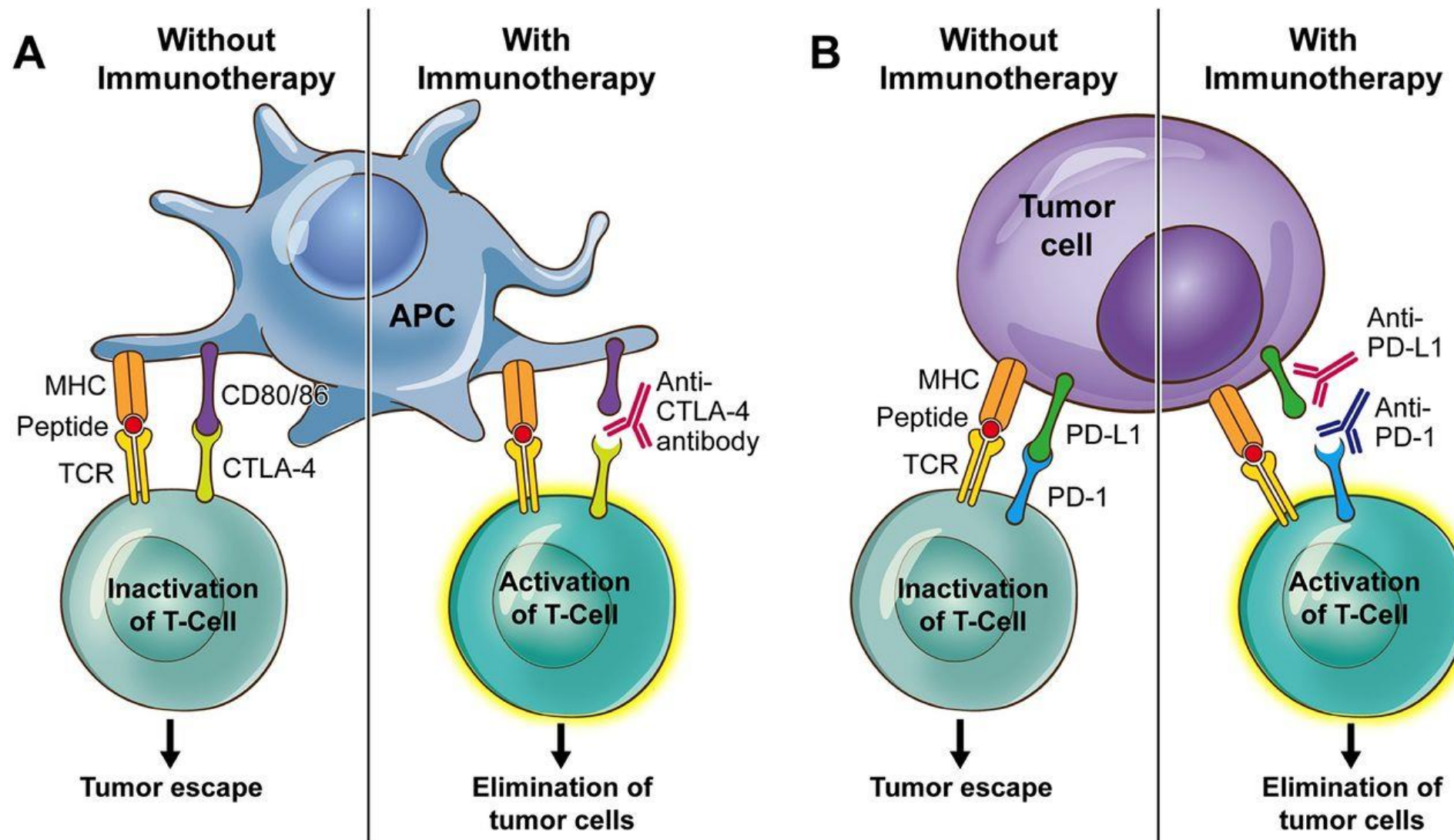
Immunotherapies: (Immune-mediated cell killing)

Activate immune system to detect and eliminate tumor cell

- ☐ Non-specific Immune stimulation
- ☐ Vaccination strategies
- ☐ Adoptive cell transfer
- ☐ **Immuno-checkpoint blockades**

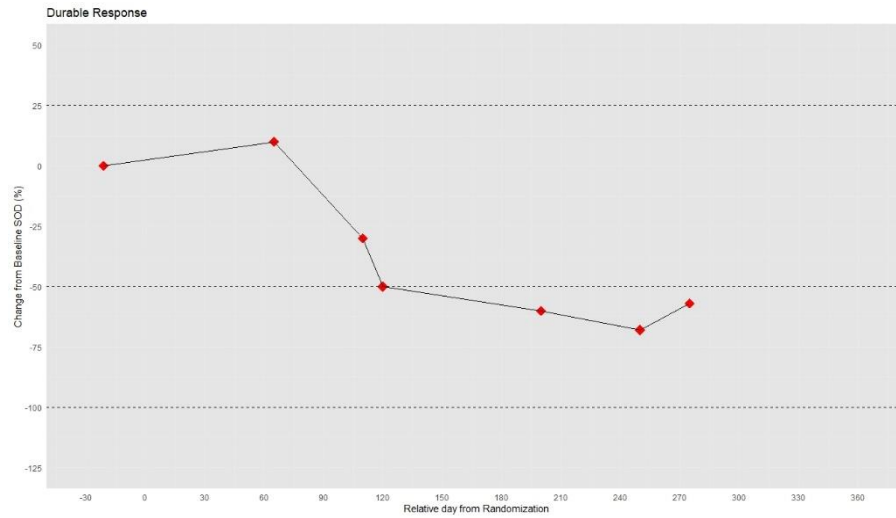


Immune-checkpoint inhibitors (ICIs)

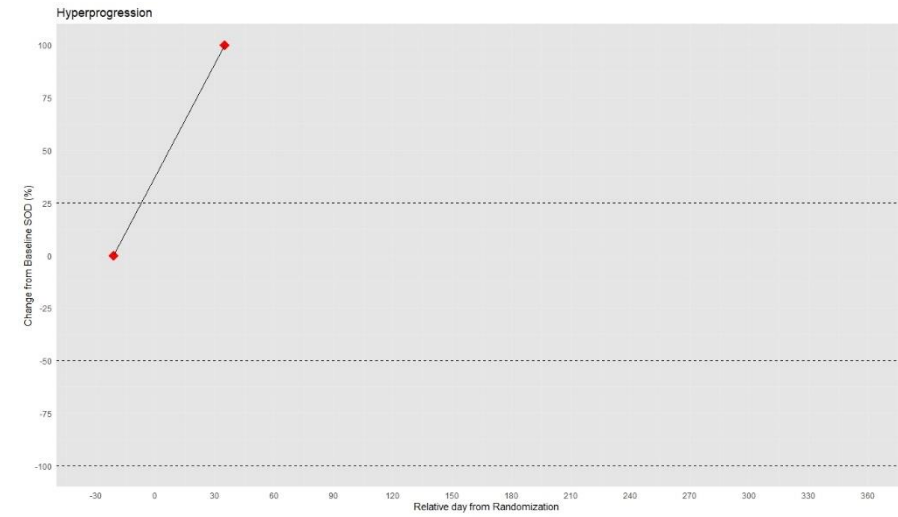


Novel Response Pattern

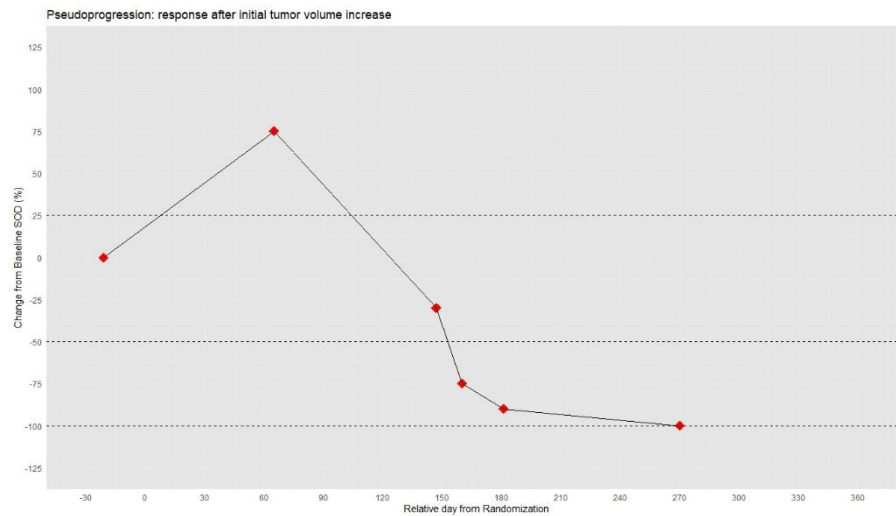
Durable Response



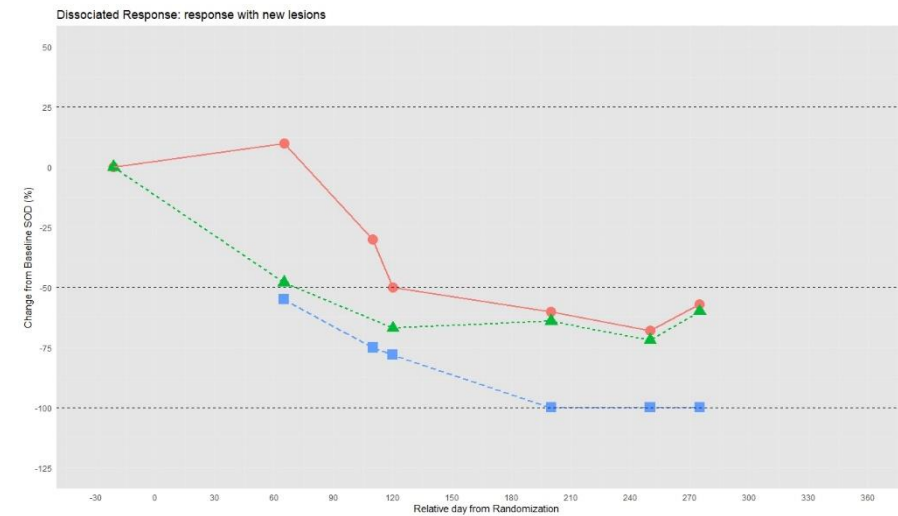
Hyperprogression



Pseudoprogression



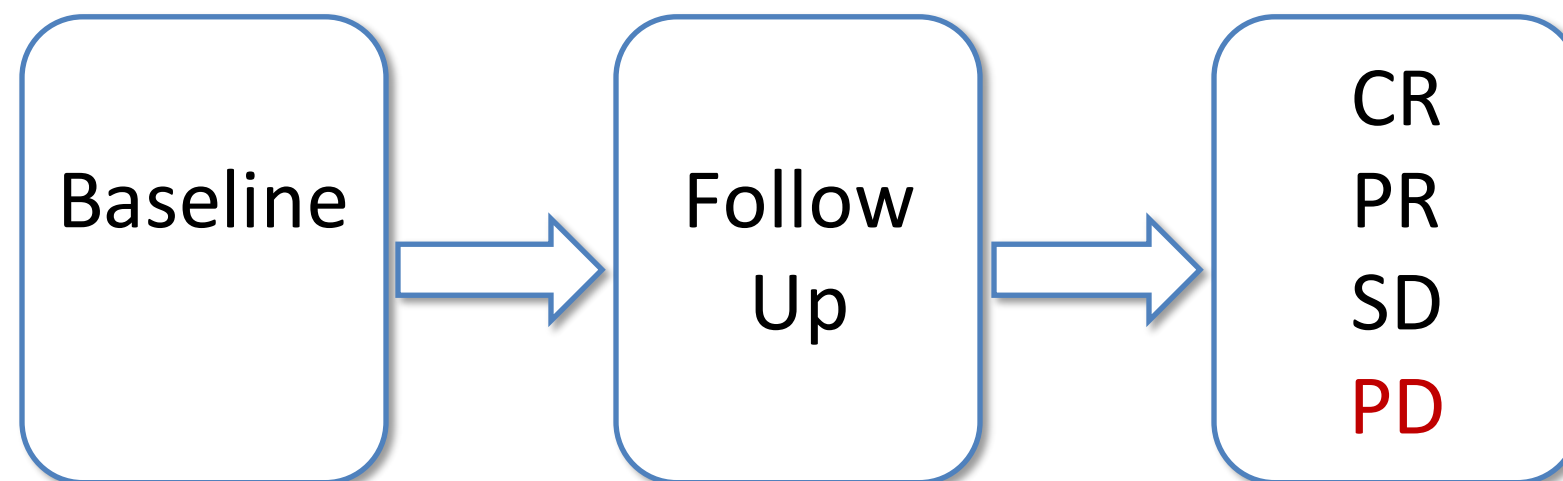
Dissociated Response



RECIST 1.1 in Nutshell

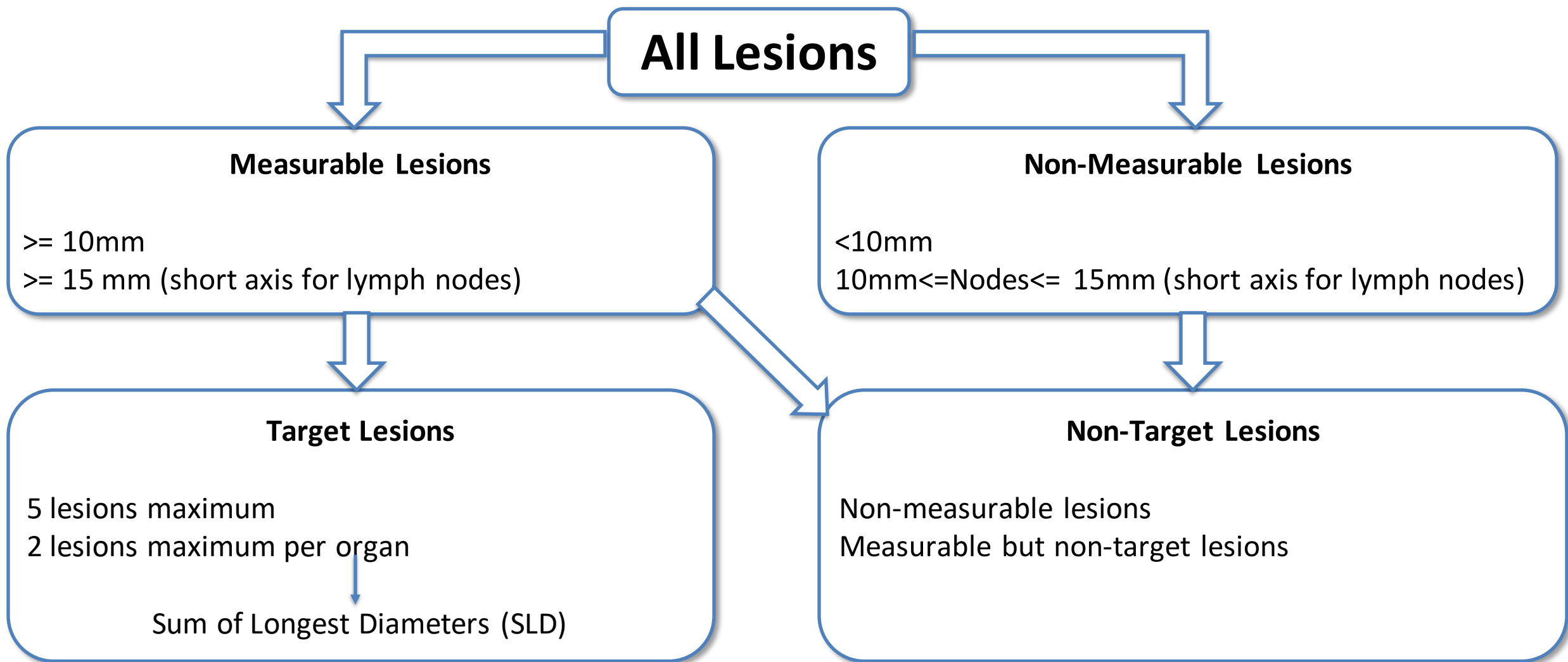
Response Evaluation Criteria In Solid Tumors*

- ❑ standard way to measure the response of a tumor to treatment
- ❑ the main subject - assessment of change in tumor burden
- ❑ CT is the preferred modality for the baseline study
- ❑ the criteria to determine whether a tumor disappears, shrinks, stays the same or gets bigger are complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)
- ❑ Disease Progression leads to termination of the treatment



(*) Developed by European Organization for Research and Treatment of Cancer (EORTC), originally published in 2000, revised in 2009

RECIST1.1: Baseline Disease Assessments



RECIST1.1: Assessing Target Response

Complete Response (CR)	all target lesions disappeared. CR can be observed with SLD not equal to 0. Nodal lesion can exist, but <10mm
Partial Response (PR)	at least 30% reduction of sum compared to baseline
Progressive Disease (PD)	increase of disease of at least 20% compared to the smallest sum recorded (nadir) + increase of at least 5mm in absolute value.
Stable disease (SD)	No PR, no PD



RECIST1.1 Assessing Non-Target Response

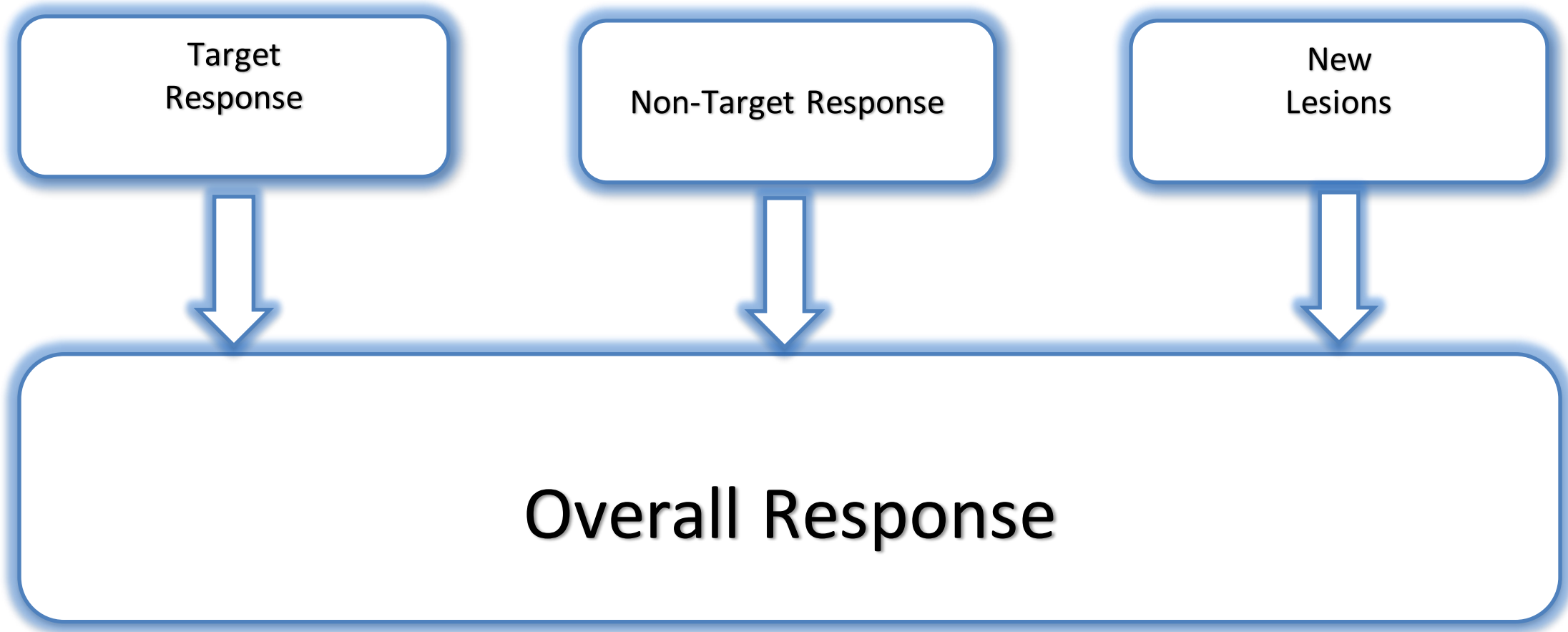
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR / Non PD	Presence of at least one non target lesion.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions.



RECIST1.1 New Lesions

- ☐ Lesion seen in anatomical region which was not imaged at baseline = **New Lesion**
- ☐ Appearance of new lesions denotes **Progressive Disease (PD)**

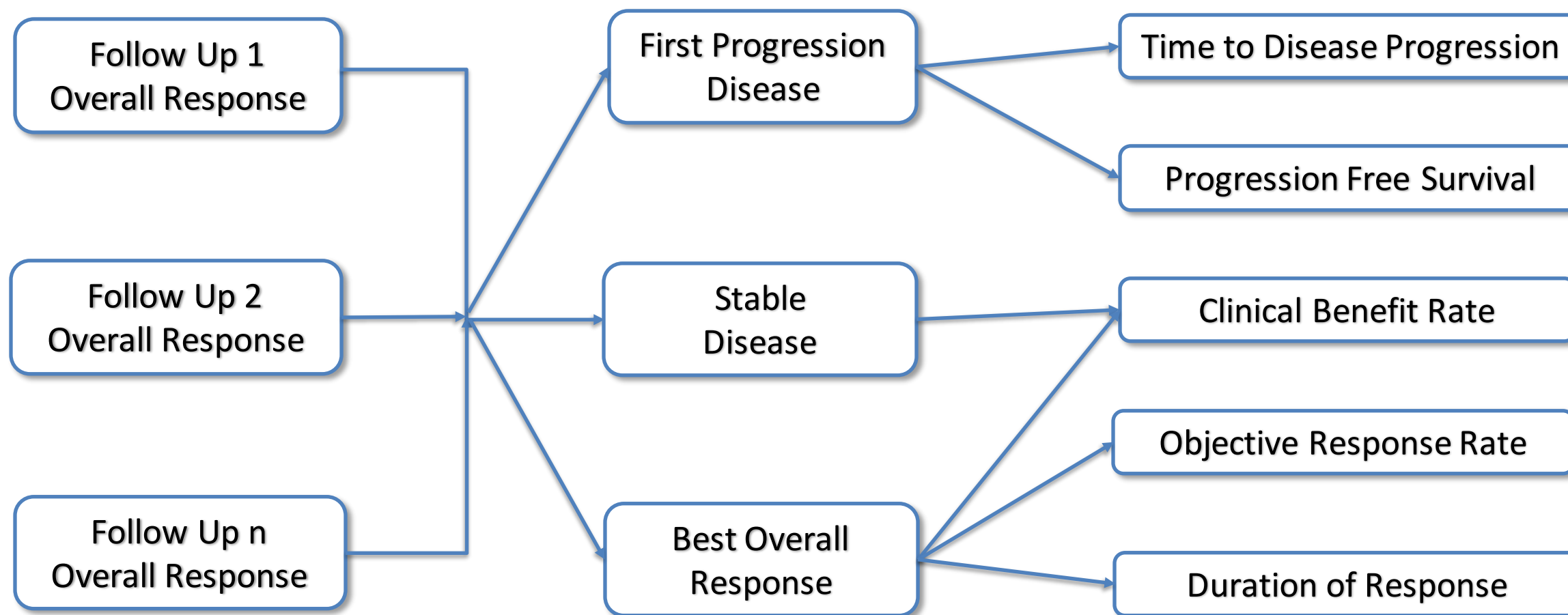
RECIST1.1: Follow Up Tumor Assessments



RECIST1.1: Assessing Overall Response

	Target Lesion	Non-Target lesion	New Lesion	Overall Response
Measurable Disease	CR	CR	No	CR
	CR	Non CR / Non PD	No	PR
	CR	NE	No	PR
	PR	Non PD or NE	No	PR
	SD	Non PD or NE	No	SD
	NE	Non PD	No	NE
	PD	CR, PD, Non CR/ Non PD, or NE	Yes or No	PD
	CR, PR, SD, PD, or NE	Unequivocal PD	Yes or No	PD
	CR, PR, SD, PD, or NE	CR, PD, Non CR/ Non PD, or NE	Yes	PD
Non-Measurable Disease			CR	CR
			Non CR / Non PD	Non CR/Non PD
			NE	NE
			Unequivocal PD	PD
			CR, PD, Non CR/ Non PD, or NE	PD

RECIST1.1: Efficacy Endpoints



Modified RECIST criteria for Immunotherapy (iRECIST)

RECIST1.1 **remains** the gold standard for evaluating treatment response in solid tumors

- ❑ However, new lesions or flare equals progressive disease under RECIST1.1 guidelines
- ❑ Inaccurate interpretation of response can result in premature termination of therapy and patient removal from a trial;

Need **new** response criteria

- ❑ Immune-related response criteria (irRC), 2009
 - Based on WHO criteria
- ❑ Immune-related RECIST (irRECIST), 2013
 - Combines elements of irRC and RECIST1.1
- ❑ iRECIST, 2017
 - Standardize and validate immune response criteria
- ❑ All account for novel response pattern seen with immunotherapies

Nomenclature: responses assigned using iRECIST have “i” prefix: iCR, iPR, iSD, iUPD, iCPD

iRECIST vs RECIST1.1: Unchanged

RECIST1.1	iRECIST
Definition of measurable, non-measurable disease	✓
Definition of target (T) and non-target (NT) lesions	✓
Measurement and management of nodal disease	✓
Calculation of the sum of measurement (SoM)	✓
Definition 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 RECIST1.1: Changes (1)

	iRECIST	RECIST1.1
Management of new lesions	New	✗
Timepoint response after RECIST1.1 progression	New	✗
Confirmation of progression required	New	✗
Collection of reasons why progression cannot be confirmed	New	✗
Inclusion and recording of clinical status	New	✗



iRECIST vs RECIST1.1: Changes (2)

- ☐ New lesions (NL) assessed using RECIST1.1 principles
 - up to 5 (2 per site) measured (NL-T) are included in iSoM, but not included in SoM of target lesions identified at baseline;
 - other NLs are recorded as non-target (NL-NT)

- ☐ Timepoint response after RECIST1.1 PD
 - first RECIST1.1 PD is “unconfirmed” – iUPD
 - iUPD must be confirmed at the next assessment (4-8 weeks)

- ☐ Timepoint response is based on
 - change from baseline (iCR, iPR, iSD) or from nadir (PD)
 - the last i-response

- ☐ Prior iUPD doesn't exclude subsequent iCR, iPR or iSD



iRECIST vs RECIST1.1: Changes (3)

- ☐ Treatment past PD should only be considered if patient clinically stable (*)
 - No worsening of performance status;
 - No clinically relevant increase in disease related symptoms
 - No requirements for intensified management of disease related symptoms

- ☐ Record the reason iUPD not confirmed
 - Not stable
 - Treatment stopped but patient not reassessed/imaging not performed
 - iCPD never occurs
 - Patient has died

Note: clinical stability may be protocol specific

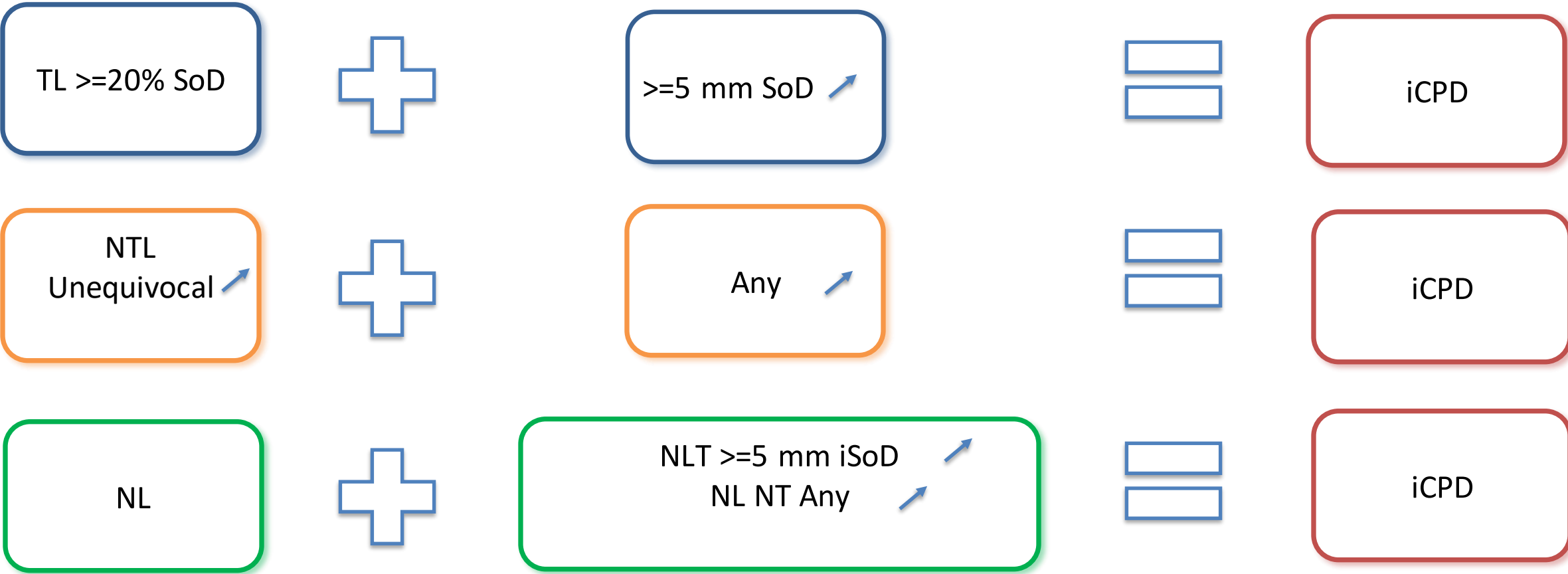


Confirming Progression (iCPD) (1)

❑ Worsening in the lesion category

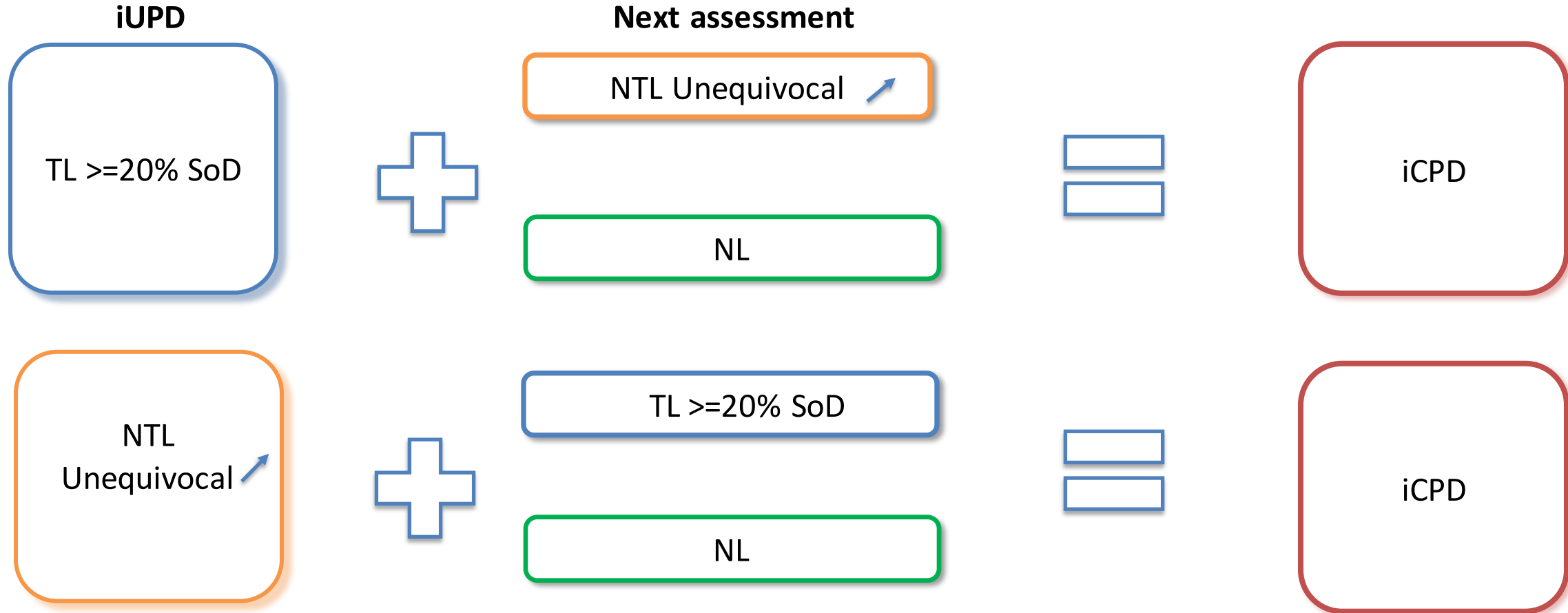
iUPD

Next assessment

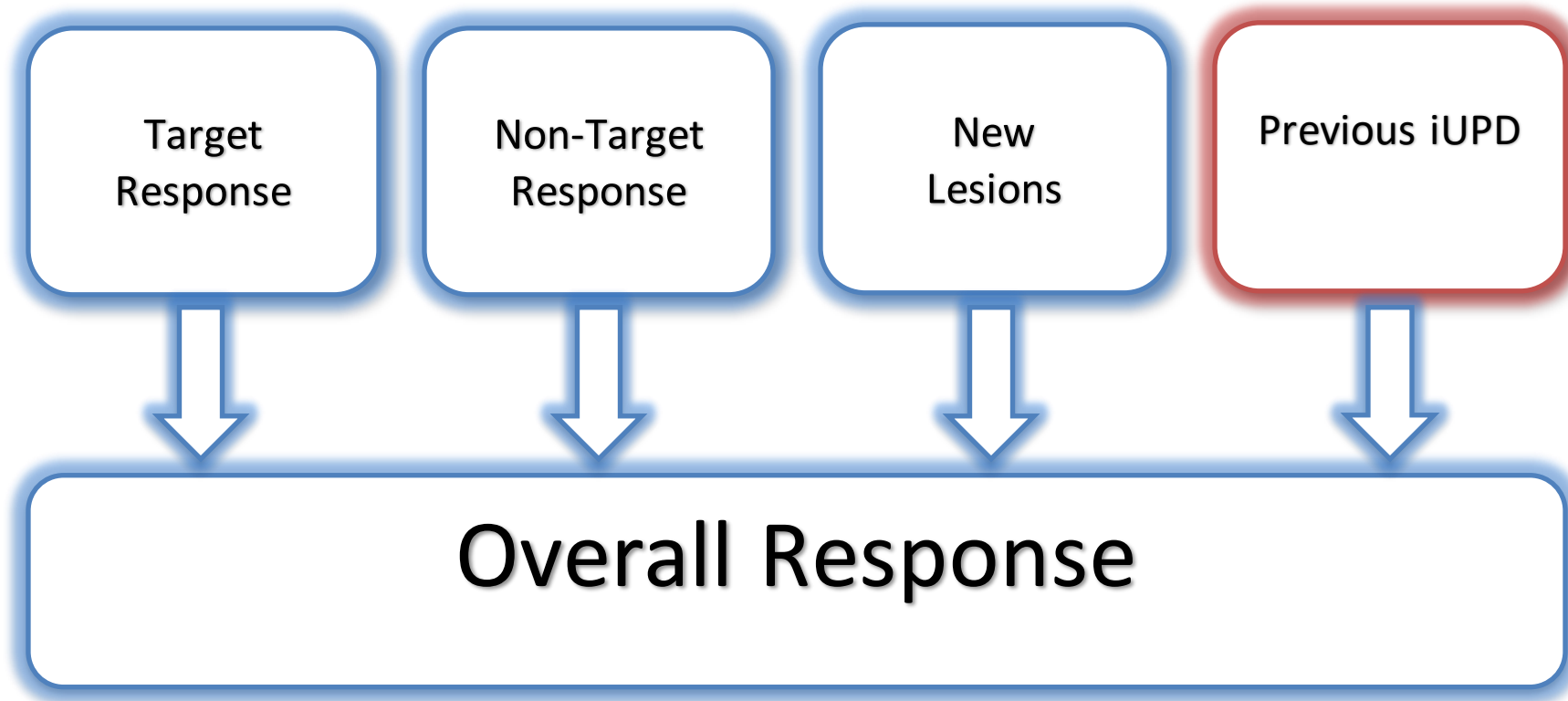


Confirming Progression (iCPD)(2)

❑ Worsening in other lesions categories



iRECIST1.1: Assessing Overall Response(1)



iRECIST1.1: Assessing Overall Response (2)

Target Lesions*	Non-Target Lesions*	New Lesions*	Overall Response	
			No prior iUPD**	Prior iUPD**, ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non iUPD	No	iPR	iPR
iPR	Non-iCR/Non iUPD	No	iPR	iPR
iSD	Non-iCR/Non iUPD	No	iSD	iSD
iUPD with no change OR ↓ from the last TP	iUPD with no change OR ↓ from the last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD SOM ≥5 mm and / or - NT lesion iUPD (prior assessment- need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD ≥5 mm and / or - previously identified NT lesion iUPD (need not be unequivocal) and /or - size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this timepoint.



i-Efficacy Endpoints

Commonly used Efficacy Endpoints in Oncology Studies:

- ☐ Best Overall Response
- ☐ Objective Response Rate
- ☐ Clinical Benefit Rate

Response rates

- ☐ Duration of Response
- ☐ Duration of Stable Disease
- ☐ Progressive Free Survival
- ☐ Overall Survival

Time-To-Event endpoints



Immune Best Overall Response (iBOR)

iBOR – the best response across all overall response timepoints up to treatment study end or start of new anti-cancer therapy

- iUPD **will not override** a subsequent iSD, iPR or iCR
- iSD or iPR can be assigned even if new lesions have not regressed or unequivocal progression remains unchanged, providing that **iCPD are not met**
- Confirmation of iCR/iPR, as in RECIST 1.1, is necessary for non-randomized trials but not for randomized trials.
- The definitive duration for iCR/iPR should be specified in the protocol.
- The protocol should specify what to do if assessments are not performed or cannot be assessed following iUPD:
 - NE included in the assessment or not.
 - NE excluded from iBOR calculations or not.

Order of iBOR : $iCR > iPR > iSD = \text{Non-}iCR/\text{non-}iUPD > iCPD > iUPD > NE$



Immune Objective Response Rate (iORR)

$$\text{iORR} = \frac{\text{Number of Responders}^*}{\text{Total Number of Patients}^{**}}$$

* Number of Responders = iBOR in (iCR, iPR)

** Total number of patients = all treated/ all eligible



Immune Clinical Benefit Rate (iCBR)

$$\text{iCBR} = \frac{\text{Number of Responders}^*}{\text{Total Number of Patients}^{**}}$$

* Number of Responders = iBOR in (iCR, iPR, iSD)

** Total number of patients = all treated/ all eligible



Time to Event Endpoints

TTE = (Date of Event/Censoring Date - Start Date) + 1

Endpoint	Start Date	Date of Event	Censoring Date
Duration of Stable Disease	Randomization Date (*)	First PD Date (**)	Last Tumor Assessment Date
Duration of Response (iDOR)	First iPR/iCR date	First PD Date (**)	Last Tumor Assessment Date
Progressive Free Survival (iPFS)	Randomization Date (*)	First PD Date (**) or Death Date	Last Tumor Assessment Date
Overall Survival (OS)	Randomization Date (*)	Death Date	Last Known to be Alive

* Not all trials are randomized. In nonrandomized trials, time from study enrolment is commonly used.

** First Progressive Disease Date (First PD Date):

If progression is confirmed (iCPD) after iUPD, the date of first iUPD is considered as the progression date.

If iUPD occurs but subsequently becomes iSD, iPR, or iCR, that iUPD date is not used as the event date for progression.

If iUPD occurs but progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios:

- Withdrawal of protocol therapy because patient is not clinically stable (deterioration of PS, onset or increase of disease-related clinical symptoms such as dyspnea & cancer pain, etc.);
- Continuous iUPD and no iCPD;
- Death of the patient;



Conclusions

- ❑ Fundamental principles of iRECIST are similar to those of RECIST 1.1.
- ❑ To distinguish between true progression or pseudoprogression, classifications were added for new lesions (new lesion target, new lesion non-target) and confirmed/unconfirmed PD (iCPD/iUPD).
- ❑ To determine iCPD overall response, there must be progression of the same or different lesion category.
- ❑ iRECIST defines data collection in immunotherapy clinical trials but is not a guideline for deciding treatment.
- ❑ RECIST 1.1 will continue to be used as the primary endpoint, and iRECIST will be used as the exploratory endpoint.
- ❑ In early phase trials, iRECIST may also be used as the primary endpoint.



THANK YOU

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