RESPONSE EVALUATION AND END POINTS IN ONCOLOGY

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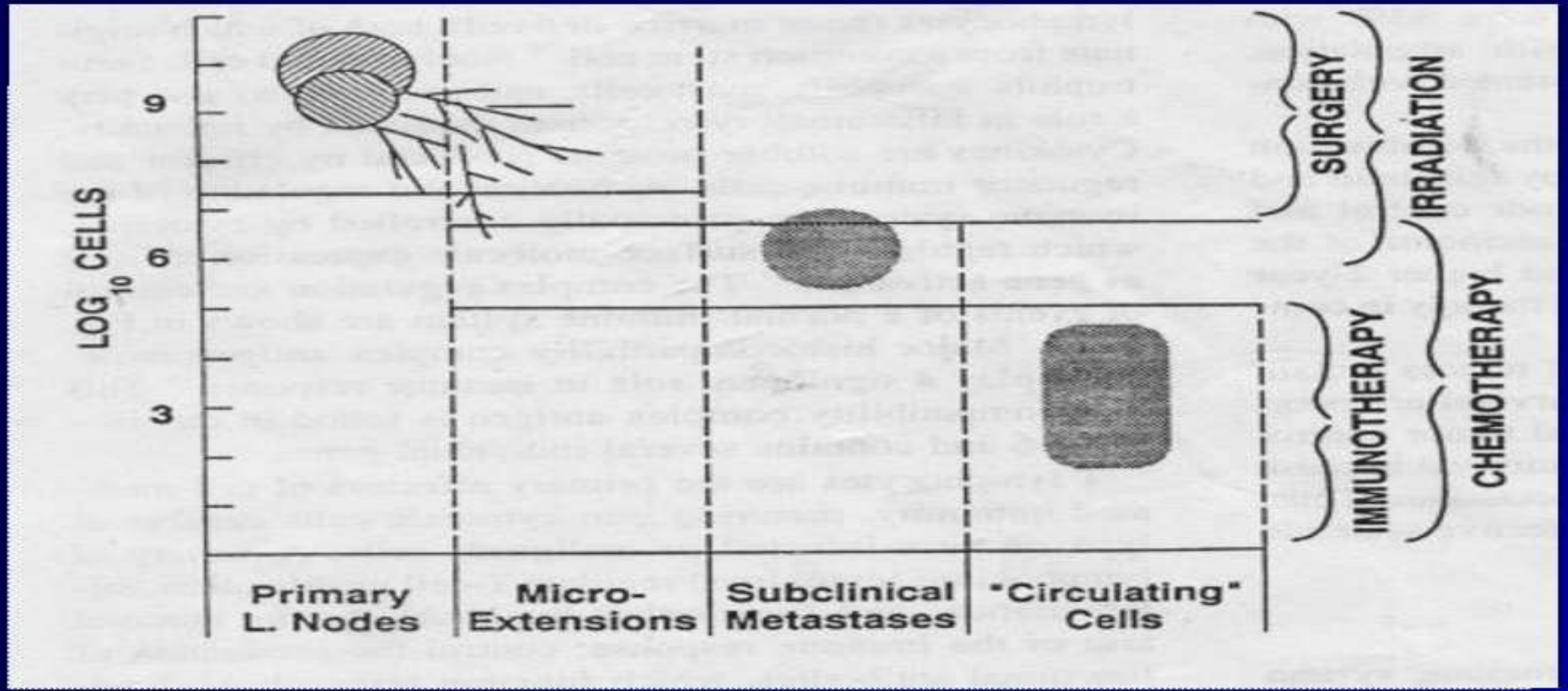
MULTIDISCIPLINARY APPROACH



RESPONSE EVALUATION

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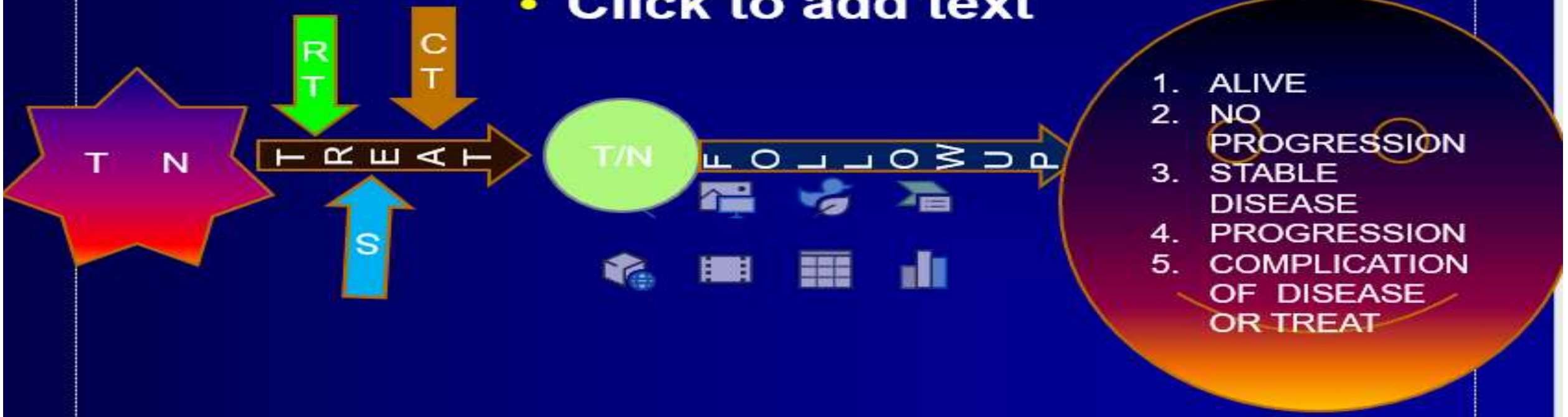


RESPONSE EVALUATION

1. **WHO TUMOUR RESPONSE CRITERIA**
2. **RECIST (RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS),**
3. **PERCIST CRITERIA**
4. **DEAUVILLES RESPONSE CRITERIA**
5. **MRD**
6. **pCR**
7. **IMMUNE-RELATED RESPONSE CRITERIA (irRC)**

REPORTING OF RESPONSE

- Objective response can be determined clinically, radiologically, biochemically, or by surgico-pathologic restaging.
- Measurable disease:

✓ Complete response (CR) - The disappearance of all known disease, determined by two observations not less than four weeks apart.

✓ Partial response (PR) - 50% or more decrease in total tumor load of the lesions that have been measured and maintained for 4 weeks

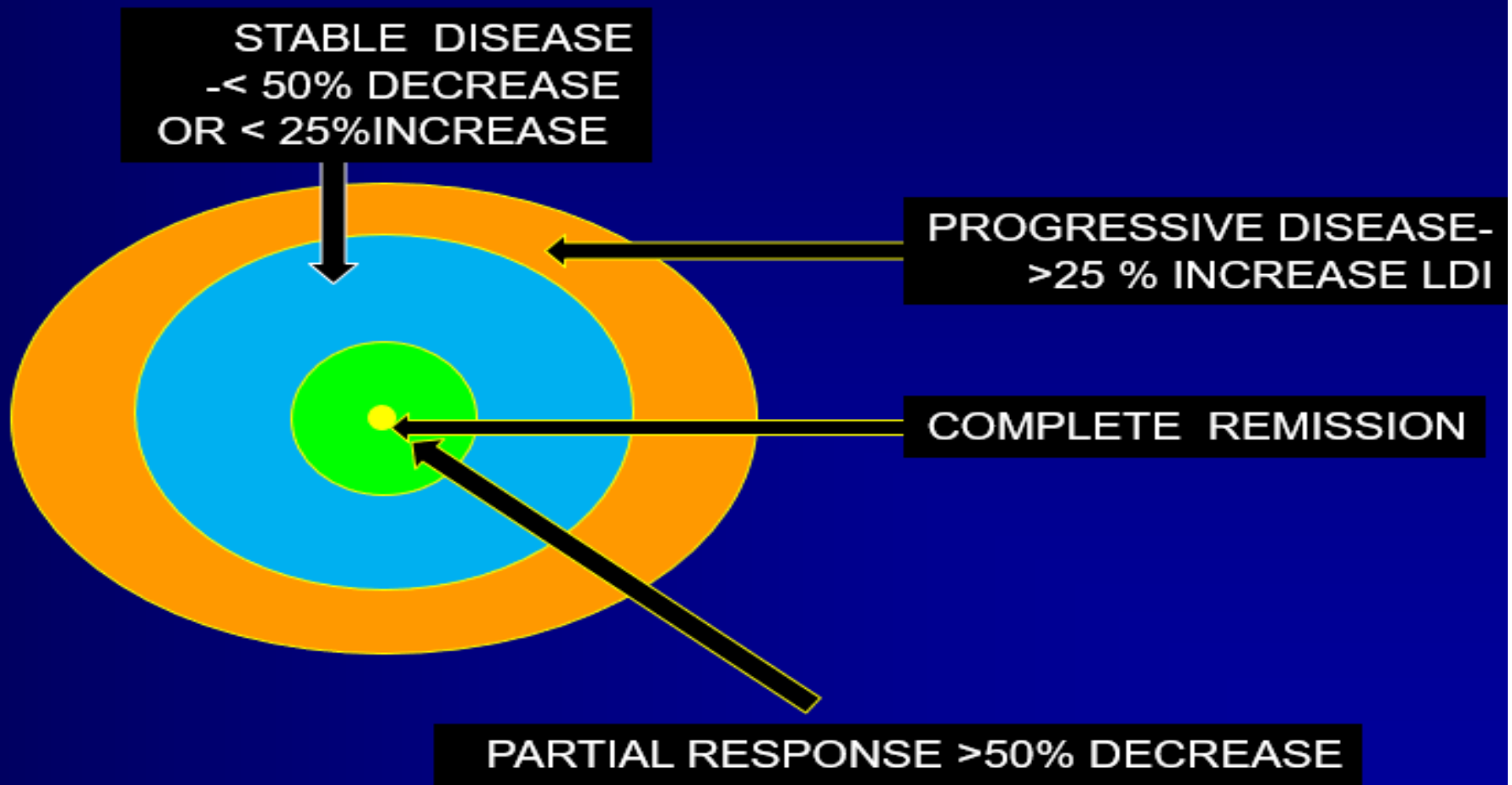
✓ No change (NC) -

- ❖ 50% decrease in total tumor size cannot be established.
- ❖ < 25% increase in the size of one or more measurable lesions.

✓ Progressive disease (PD) –

- ❖ 25% or more increase in the size of one or more measurable lesions.
- ❖ Appearance of new lesions

WHO CRITERIA



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REPORTING OF RESPONSE

- **Non-measurable disease:**

✓ **Complete response (CR)** - Complete disappearance of all known disease for at least four weeks.

✓ **Partial response (PR)** - Estimated decrease in tumor size of 50% or more for at least four weeks.

✓ **No change (NC)** -

- No significant change for at least four weeks.
- **Stable disease.**
- Estimated decrease of less than 50%.
- Lesions with estimated increase of less than 25%.

✓ **Progressive disease (PD)** -

- Appearance of any new lesions not previously identified.
- Estimated increase of 25% or more in existent lesions.

DRAW BACK OF WHO CRITERIA

1. ***Minimum lesion size*** **and** ***number of lesions*** **not reflected.**
2. ***Newer technologies*** **[CT & MRI] have added concept of three-dimensional measurement.**

Implementation issues with RECIST

Minimum number of lesions

RECIST in randomized trials

Imaging with CT ,MRI and PET

Response Evaluation Criteria in Solid Tumors(RECIST 1.1)

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SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

Journal of the National Cancer Institute, Vol. 92, No. 3, February 2, 2000

RECIST CRITERIA .. METHODS OF MEASUREMENT

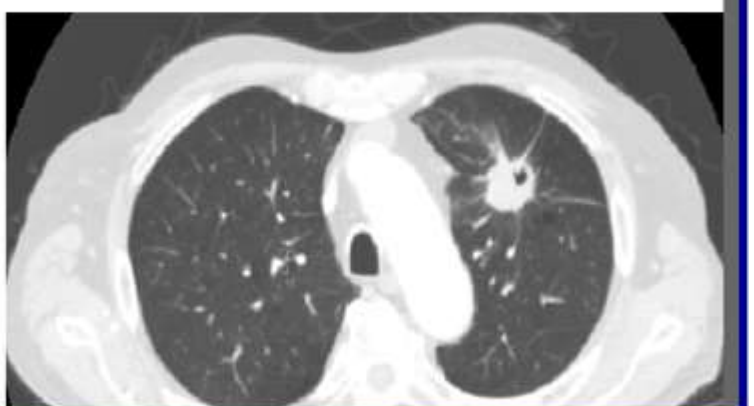
- **CLINICAL EXAMINATION** : For superficial lesions.
- **CHEST X-RAY** :
  - Full inspiration with PA view.
  - Constant film to tube distance.
  - Clearly defined lesions with surrounding aerated lung.
- **C.T SCAN :-STANDARD**
  - The minimum size of the lesion should be no less than double the slice thickness to avoid "partial volume" effects.
  - The longest diameter of each target lesion should be selected in the axial plane only.
  - Intravenous &/ oral contrast agents should also be given,
  - The same windows should be used on subsequent examinations to measure any lesion.
- **MRI:- NOT CONSISTENT,NOT IN THORAX**
- **ULTRASOUND (US) :- not be used to measure tumor lesions.**
  - (possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules..)
- **ENDOSCOPY AND LAPAROSCOPY** :- not yet been fully and widely validated.
- **TUMOR MARKERS**:- alone cannot be used to assess response.

  (If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.)
- **CYTOLOGY AND HISTOLOGY** can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

TIME POINT FOR EVALUATION

- **Baseline / Screening:**
  - within 21 days prior to treatment
- **Follow-Up:**
  - every 6 weeks (± 3 days)
- **End of Treatment/ early discontinuation:**
  - After 4 weeks (discontinuation due to PD, or early discontinuation)

All baseline evaluations should be performed as closely as possible, *never more than 4 weeks before the beginning of treatment,IDEALY 3 WKS*.



RECIST : Response Evaluation

➢ **Baseline Evaluation :**

- **Baseline documentation of "TARGET" AND "NON TARGET" LESIONS :**

✓ **Measurable lesions up to a MAXIMUM OF TWO LESIONS PER ORGAN,5 LESIONS IN TOTAL, representative of all involved organs**

✓ **A sum of the longest diameter for all target lesions will be calculated and reported as the baseline SUM LONGEST DIAMETER(SLD).**

✓ **All other lesions / sites should be identified as non target lesions and recorded. Measurements of these lesions are not required.**

RECIST Criteria .. Measurability

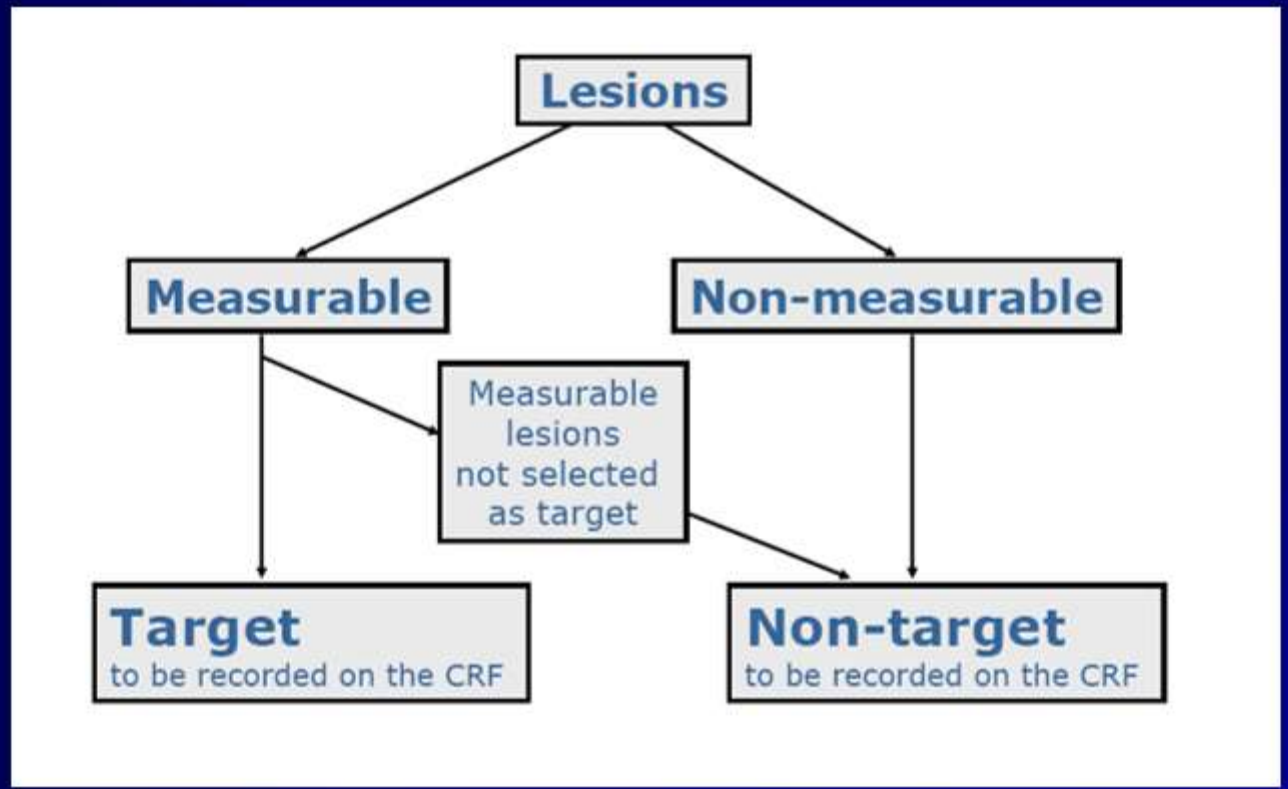
➢ Measurable Lesions :

- Lesions that can be accurately measured in at least one dimension in at least one site.
  - >20 mm with X-RAY
  - >10 mm with spiral CT scan (LONGEST DIAMETER)
  - LYMPH NODE> 15 MM (SHORT AXIS)
  - CLINICALEXAMINATION:- 10MM

➢ Nonmeasurable Lesions :

- All other lesions
- Smaller lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan]

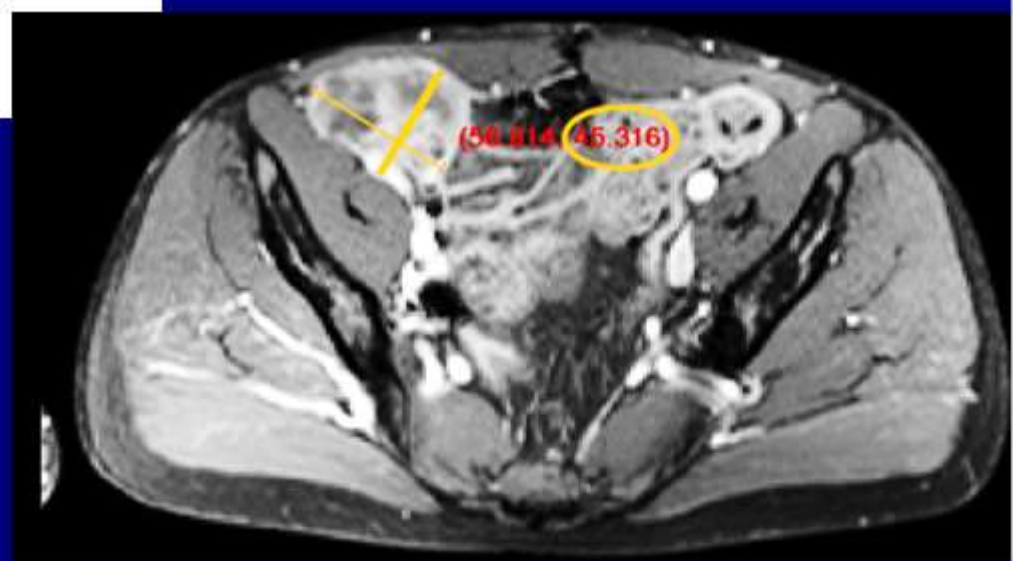
TYPE OF LESION



LYMPH NODE

Assessment of Lymph Nodes:

- **Normal**: short axis **<10mm**
- **Non measurable** = non-target: short axis **>10mm - <15mm**
- **Measurable** (possible target): short axis **≥15 mm**
  - Target nodes measured in the SHORT axis (perpendicular to longest diameter)
    - More reproducible and predictive of malignancy
  - Short axes of target nodes to be added to the SOD



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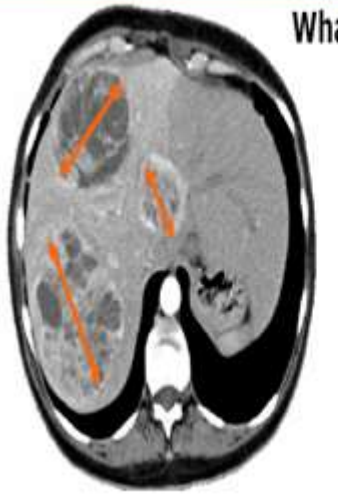
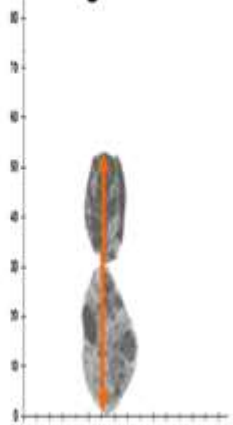
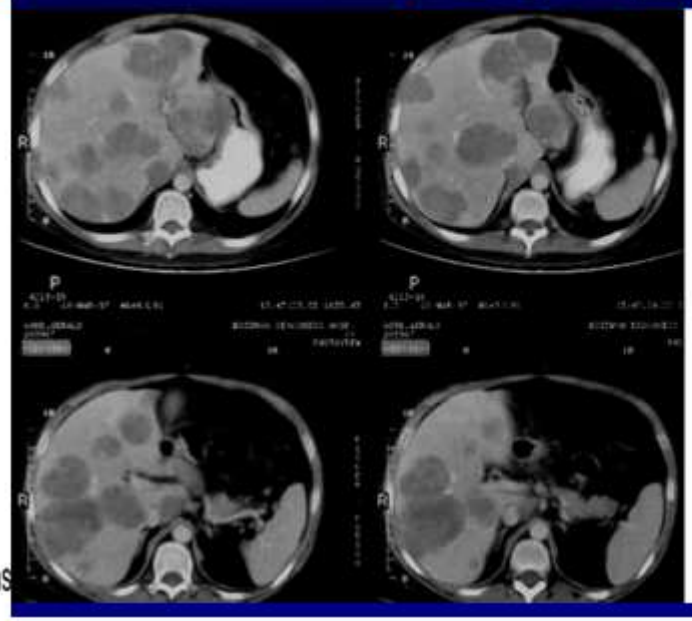
What HAS changed



Unidimensional measurements used to assess target lesions

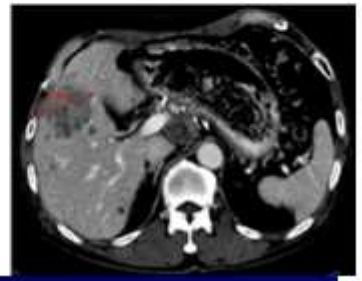


Tumor burden based on the sum of diameters of target lesions



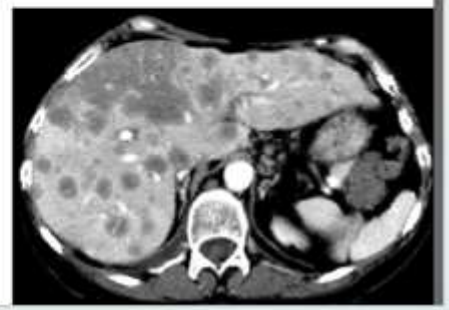
Select lesions that can be accurately measured throughout all follow-up scans

- Choose the slice where the target lesion is largest
- Always measure the longest diameter of the target lesion
- Target nodes measured in the SHORT axis
- → SOD (no longer SLD)
- Liver lesions by CT should be preferably measured on **portal venous phase** images

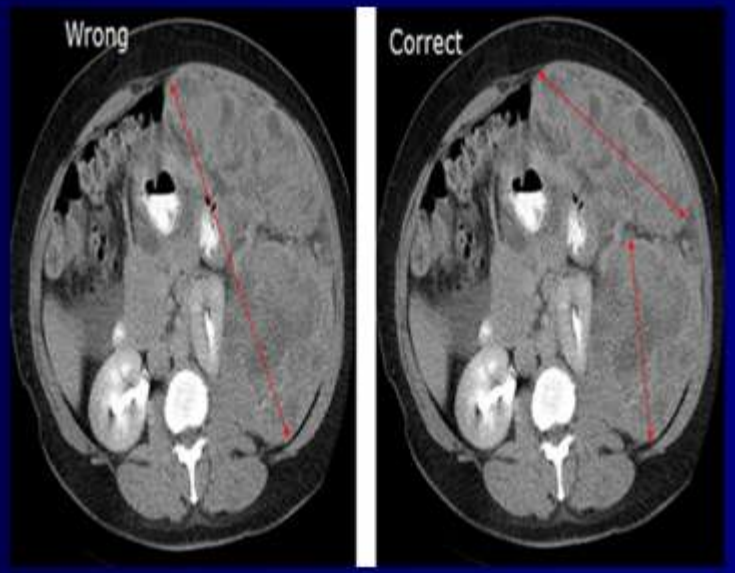


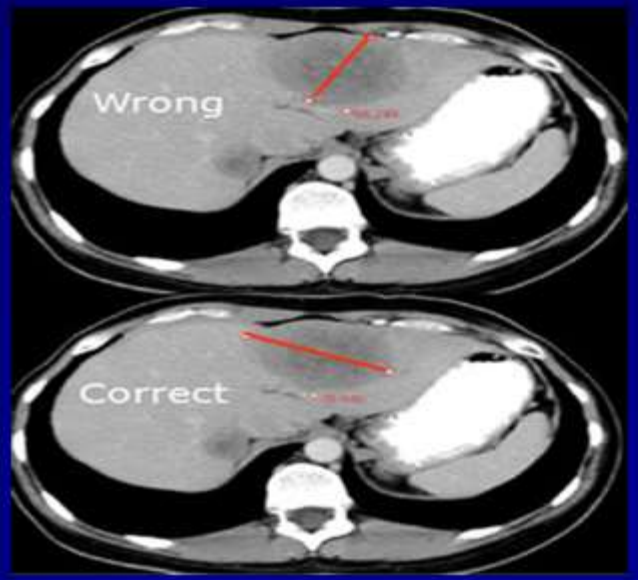
Baseline selection of target lesions:

All lesions up to a maximum of **five lesions total** and a maximum of **two lesions per organ** representative of all involved organs should be identified as target lesions



DO NOT MEASURE LESIONS ACROSS NORMAL, NON-TUMOR TISSUE





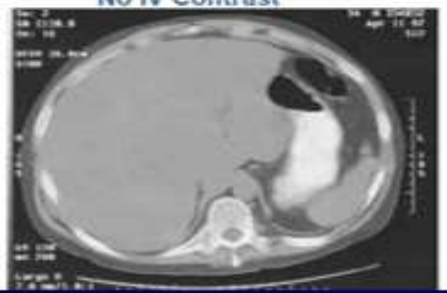
MEASURE WHERE THE TARGET LESION IS LARGEST, EVEN WHEN THE SLICE AND ORIENTATION ARE DIFFERENT COMPARED TO BASELINE

IV CONTRAST

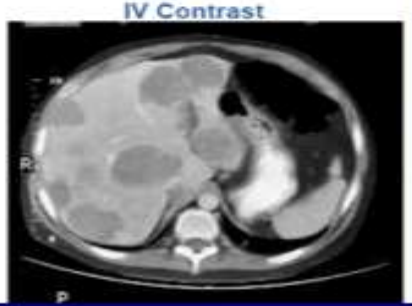
IV contrast should be consistently administered

- If no IV contrast, lesion assessments may not be possible or may be inaccurate
- Enter a comment on Image Transmittal Form (ITF) noting contraindications to IV contrast

No IV Contrast



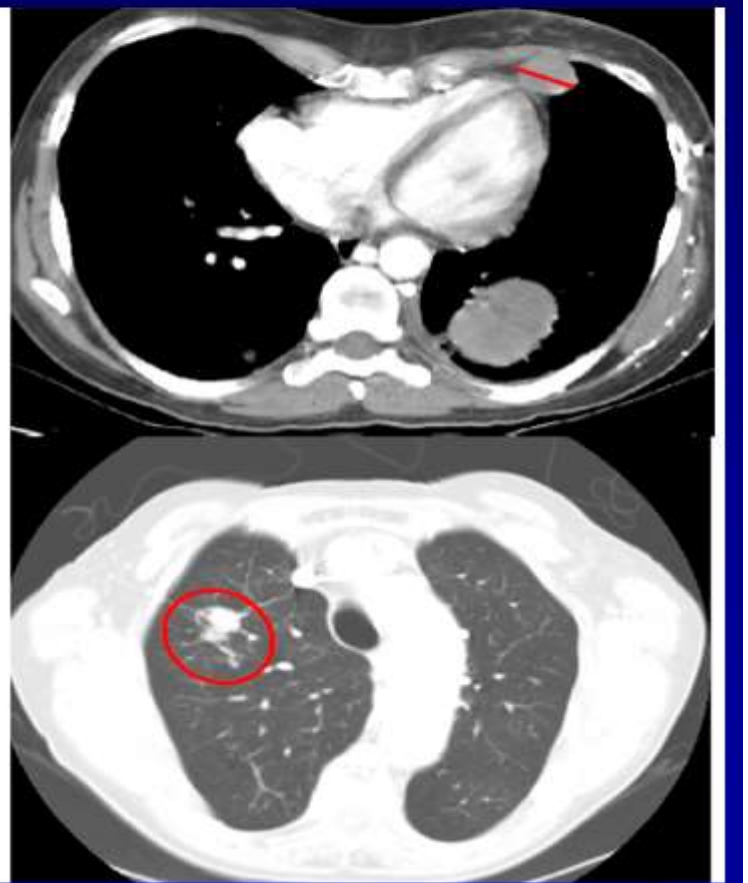
IV Contrast



- Include the hypervascular "enhancing rim", if present, in the longest diameter measurement

CT THORAX LUNG WINDOW SETTING

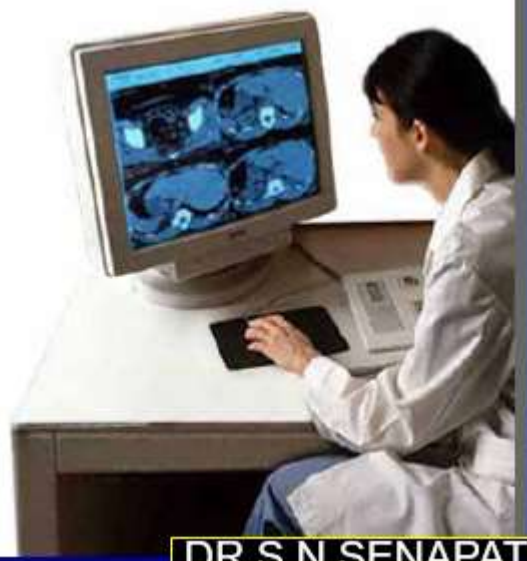
- Use the same Baseline Window Level at all follow up visits. Tumors cannot be measured accurately if window levels are not kept consistent.
  - Prefer soft tissue windows for peripheral or central nodules
  - Prefer lung windows for lesions surrounded by lung



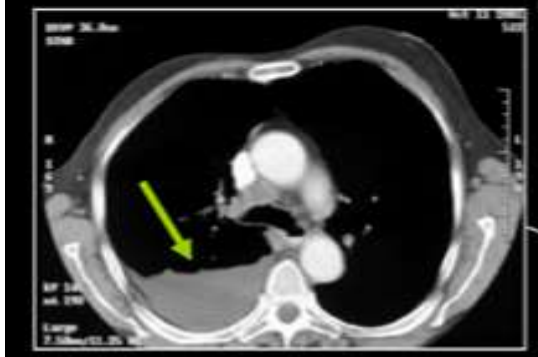
NON TARGET LESION

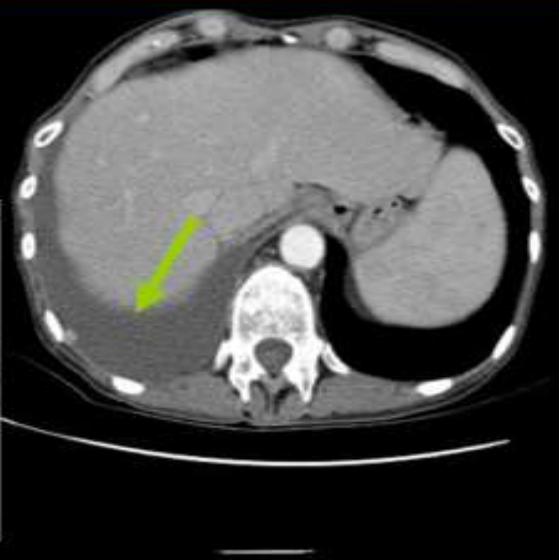
Non-Measurable Lesions

- Lesions too small to qualify as targets (<10mm)
- Lymph nodes smaller than measurable size (short axis 10 to <15mm)
- All other lesions including:
  - Leptomeningeal disease
  - Ascites
  - Pleural or pericardial effusions
  - Inflammatory breast disease
  - Lymphangitis cutis, -pulmonis
  - Abdominal masses
  - Abdominal organomegaly

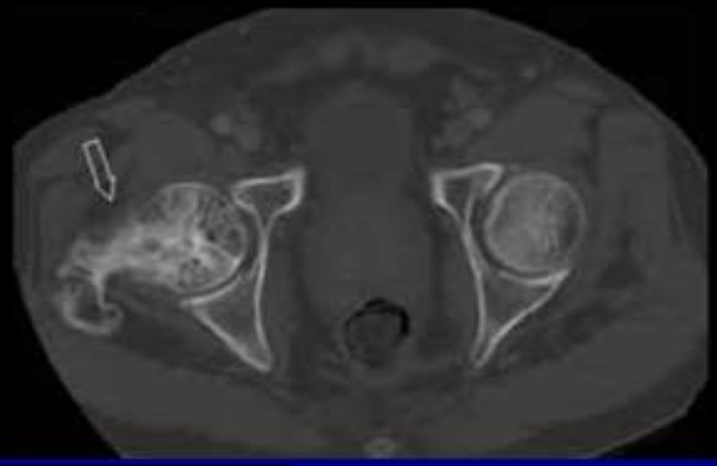


Pleural effusion, ascites are **non-measurable**

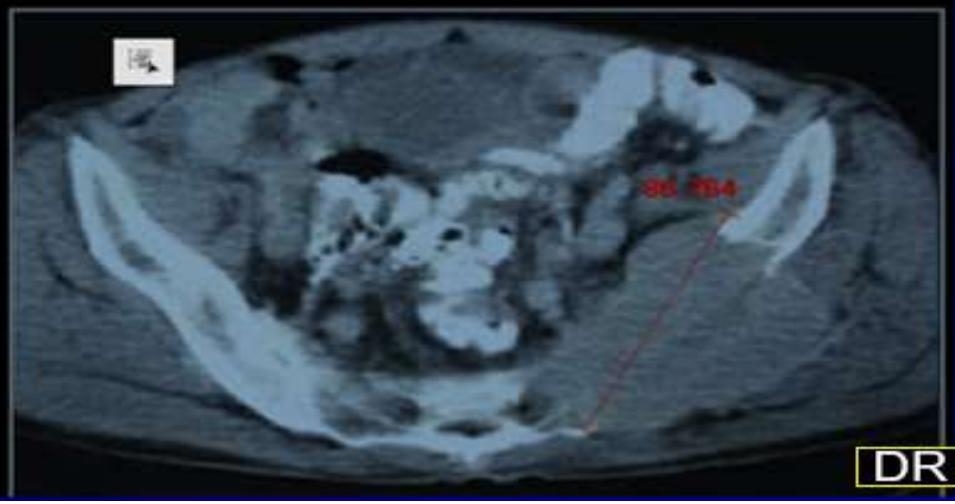




Blastic, sclerotic bone lesion is **non-measurable**



Lytic bone lesion with soft tissue mass is **measurable**



RECIST : Response Evaluation

- Response Criteria

1. Evaluation of *target lesions* :

✓ Measurement of the longest diameter only for all target lesions.

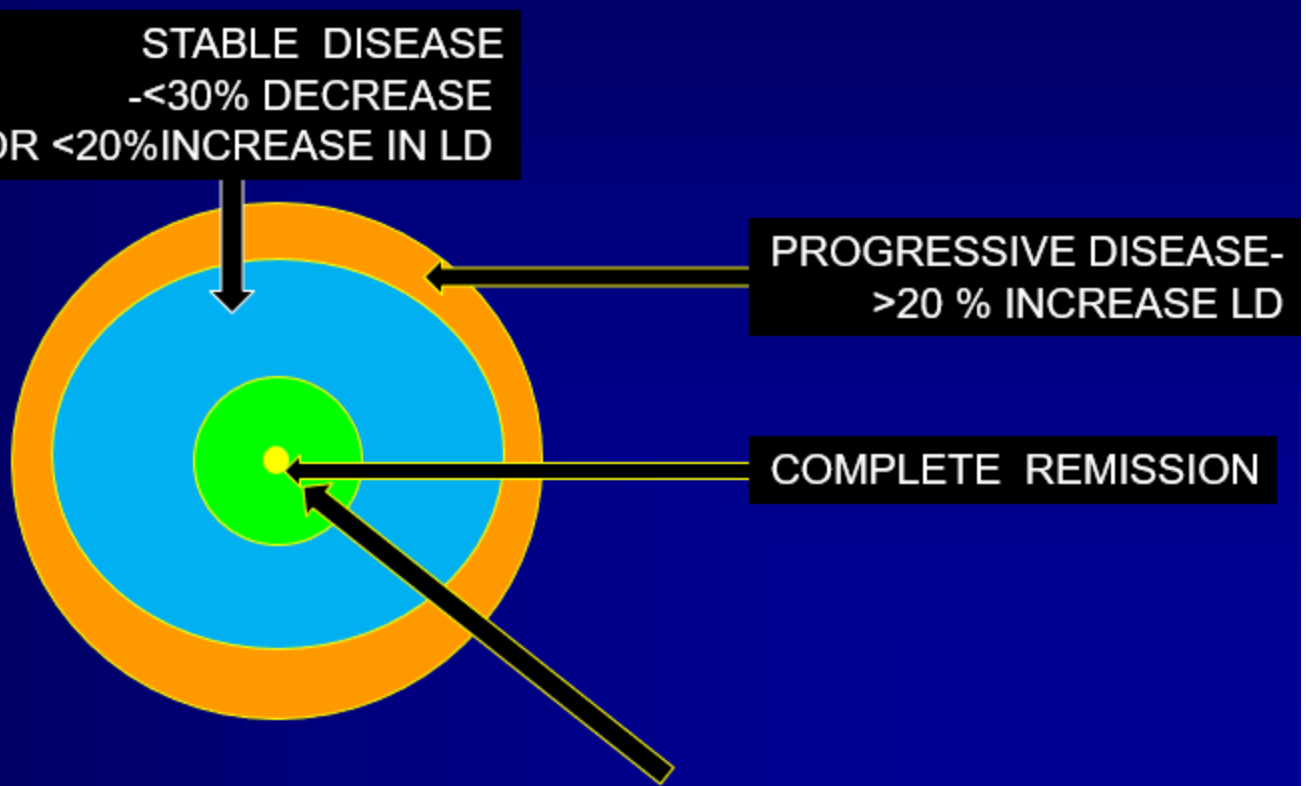
✓ **COMPLETE RESPONSE** : Disappearance of all target lesions.

✓ **PARTIAL RESPONSE** : At least a **30%** decrease in the sum of the longest diameter of target lesions

✓ **STABLE DISEASE** : Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

✓ **PROGRESSIVE DISEASE** : At least a **20%** increase in longest diameter of target lesions. (ref. smallest sum longest diameter)

RECIST 1.1



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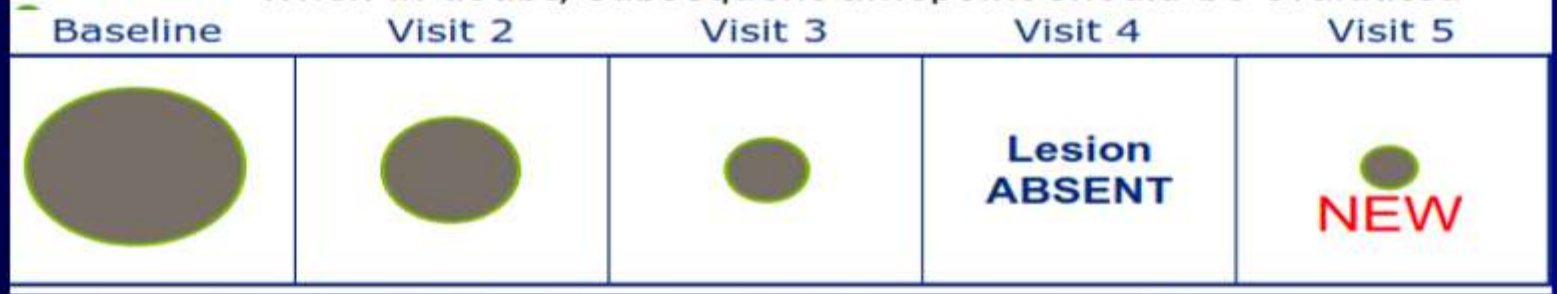
Tumor Response Evaluation

➢ ***Evaluation of non target lesions*** :

- **COMPLETE RESPONSE :**
- **Disappearance of all non target lesions.**
- **Normalization of tumor marker level.**
- **INCOMPLETE RESPONSE/STABLE DISEASE:**
- **Persistence of one or more lesion (s).**
- **Elevated tumor marker level above the normal limits.**
- **PROGRESSIVE DISEASE :**
- **Appearance of one or more new lesions.**
- **Unequivocal progression of existing non target lesions.**

NEW LESION

- Lesions that appear after BL = new lesion.
  Irrespective of size, in the same organ or different organ, which was not imaged at BL = new lesion.
- Lesions that re-appear after CR assessment are considered new = PD
- In the setting of PR or SD, if a lesion disappears and reappears at a subsequent time point it should continue to be measured. Response will depend upon the status of other lesions. The lesion should simply be added into the sum.
- Lymph nodes that were normal size at prior time point and grow or regrow are considered new lesions (>10mm)
  - 5mm⇧ absolute!
- Finding of a new lesion should be unequivocal:
  - i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than a tumor. This is particularly important when patient was SD, PR or CR.
    - When in doubt, subsequent timepoint should be evaluated



Response : WHO Vs RECIST

Best response	WHO change in sum of products	RECIST change in sums longest diameters
CR	Disappearance; confirmed at 4 wks†	Disappearance; confirmed at 4 wks†
PR	50% decrease; confirmed at 4 wks†	30% decrease; confirmed at 4 wks†
SD	Neither PR nor PD criteria met	Neither PR nor PD criteria met
PD	25% increase; no CR, PR, or SD documented before increased disease	20% increase; no CR, PR, or SD documented before increased disease

RECIST Criteria .. Disadvantages

- RECIST makes no provision for total volume of disease.
- RECIST excludes bone and mediastinal structures, and hematologic malignancies.
- Number of target lesions may not account for the full burden of disease.
- The edges of irregular or infiltrating lesions are often difficult to identify.
- Its difficult to distinguish peritumoral fibrosis from tumour spread at times.

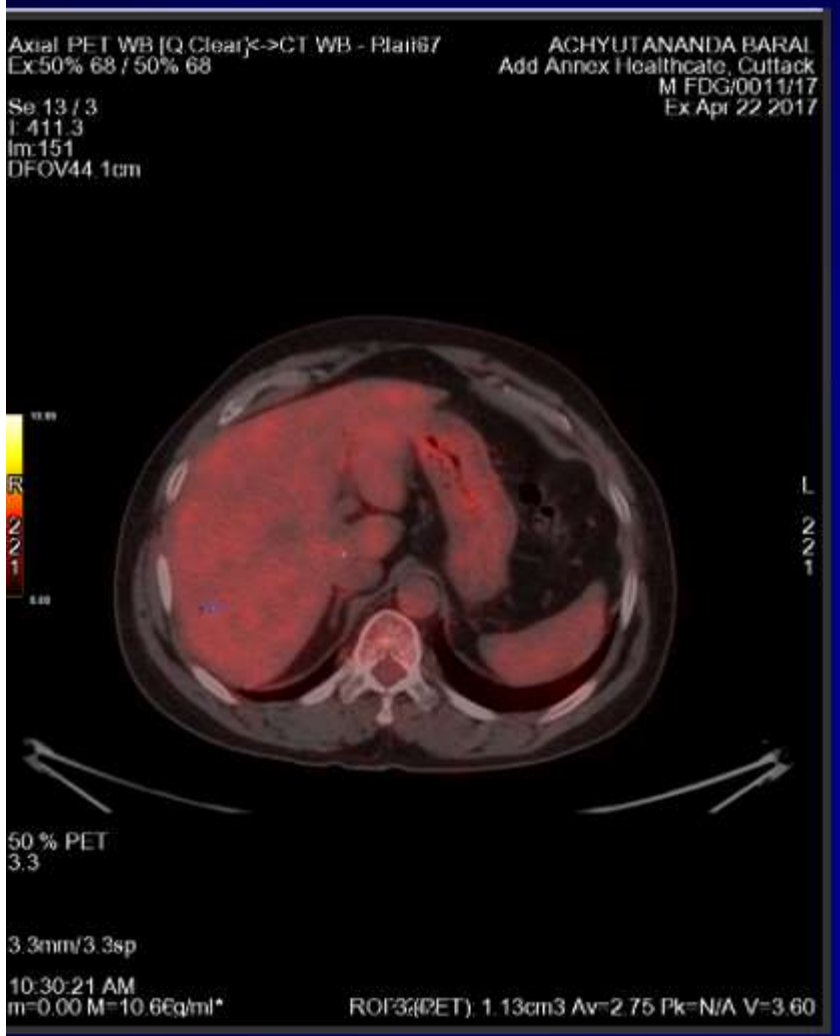
Overview: RECIST vs. RECIST 1.1

	RECIST	RECIST 1.1
Measurable Disease at BL	Required, MTLS	When required then MTLS, Pats. with non-measurable disease only are allowed
Minimum Target Lesion Size	≥10 mm (Spiral CT) ≥20 mm (Conventional CT, MRI)	≥10 mm (CT + MRI) ≥15 mm Lymph nodes ≥20 mm Chest X-Ray
No. of measurable Lesions, per organ	1-10 5	1-5 2
Measurement	Uni-Dimensional	Uni-Dimensional Lymph nodes = short axis
PD	20 % increase in SLD from Nadir	20 % increase in SOD + min. 5mm increase from Nadir
Confirmation of CR and PR	After at least 28 days	Only required, if response is primary endpoint and not randomized
Non Measurable Assessment	Unequivocal progression	… substantial worsening, … tumor burden has increased sufficiently
Lymph node Measurements	None	Specific instructions ≥15mm, 10-14mm, <10mm
PET	Not available	May be considered to support CT; for PD and confirmation of CR

PERSIST CRITERIA

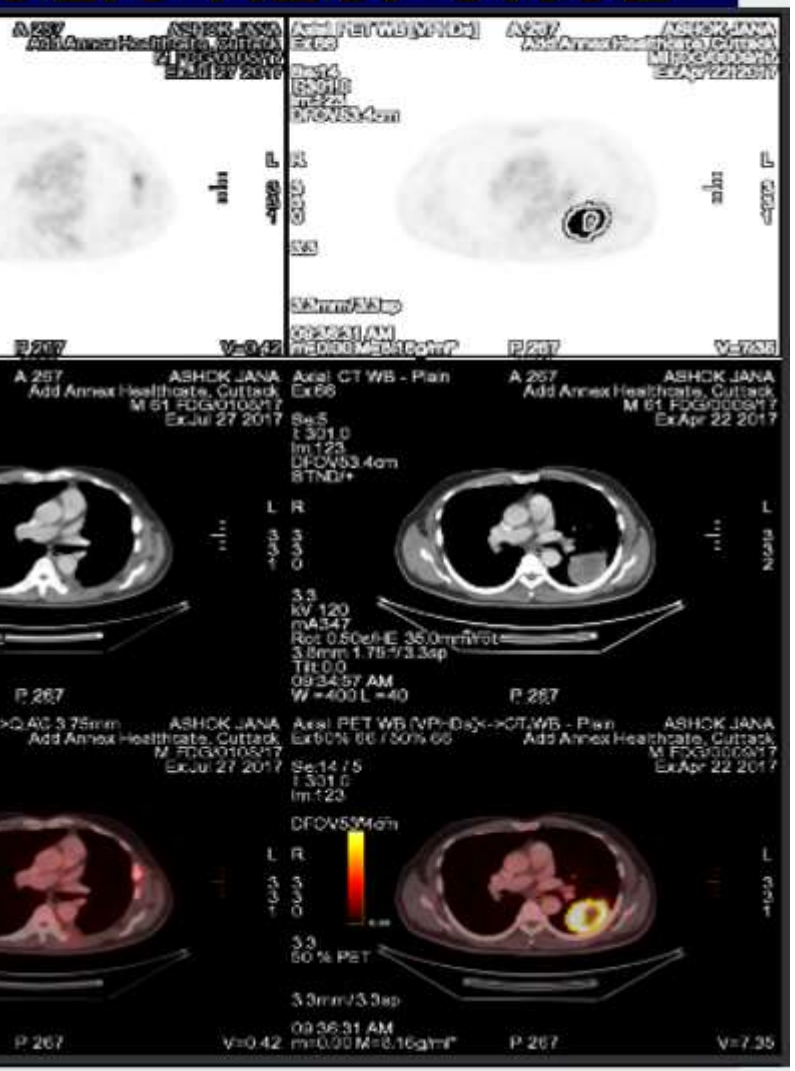
- Click to add text

DEFINING ROI IN PET



COMPLETE METABOLIC RESPONSE

- Complete metabolic response (CMR) complete resolution of [18F]-FDG uptake within the measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood pool levels .



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Partial Response

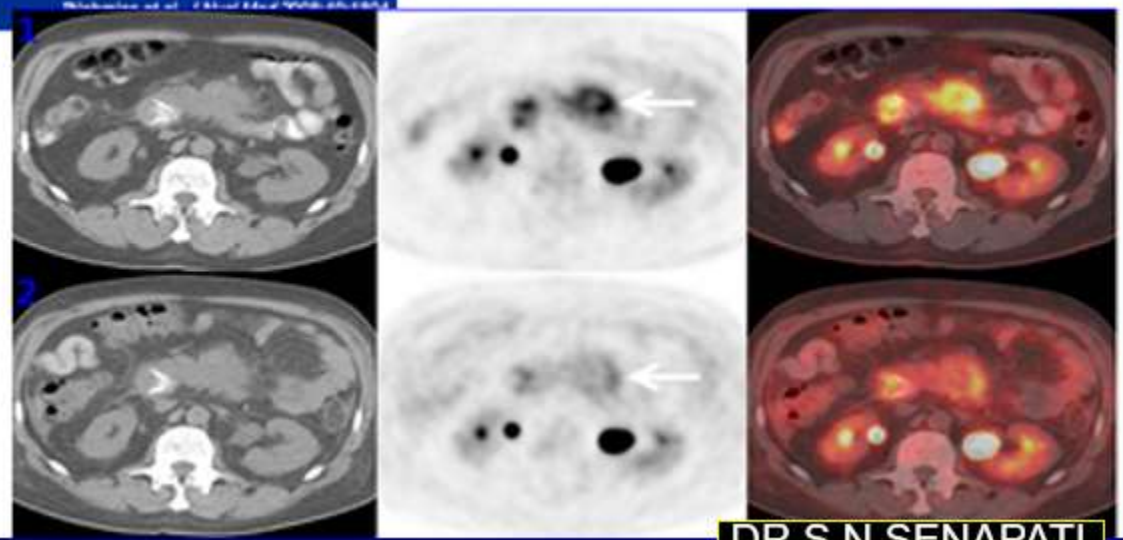
↓30% SUL peak

- EORTC: 15-25%
- 10-20% variability of SUV
- Lower thresholds, medically relevant
- 25% of a low number not much change

↓0.8 SUL units

- 0.9 and 0.5 SUV units previously proposed*

*Weber et al. *J Nucl Med* 1999;40:1771



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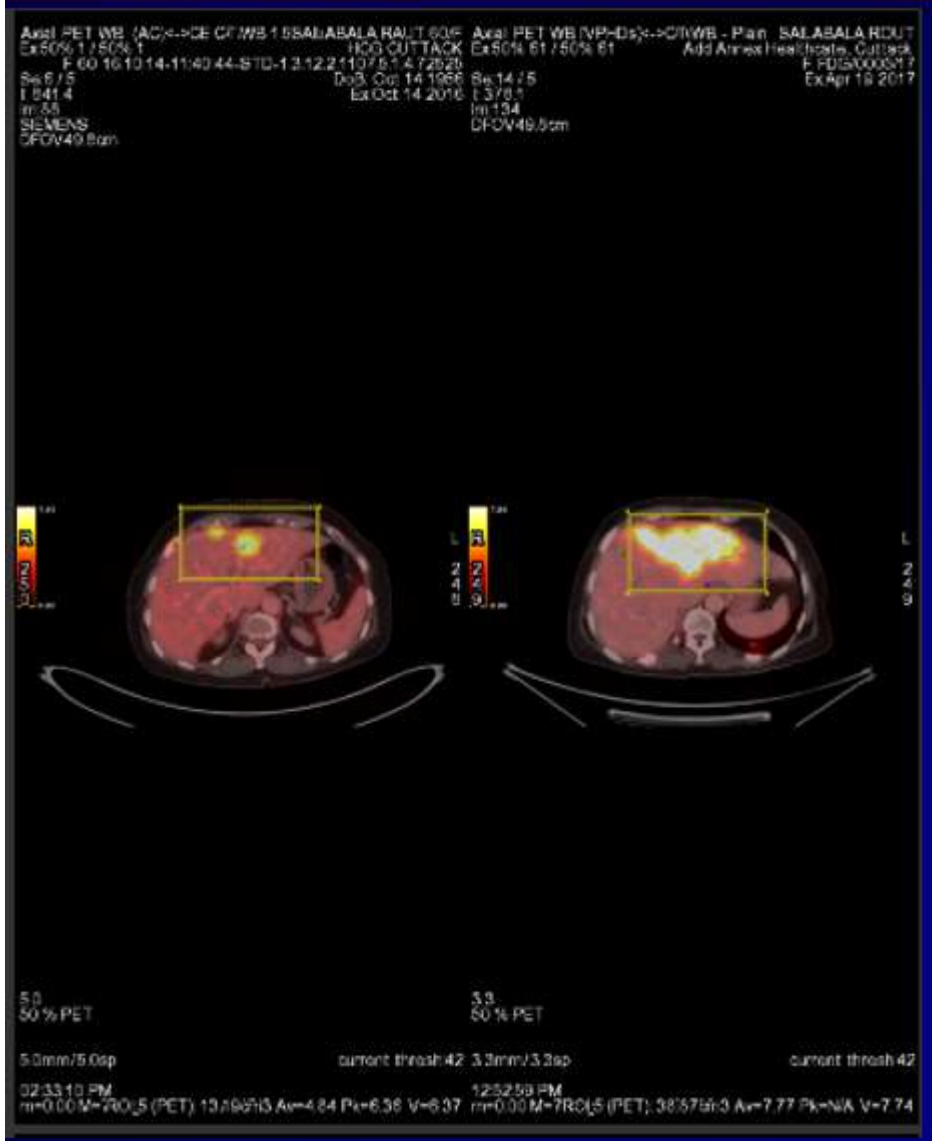

Progressive metabolic disease

- >30% increase in FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from the baseline scan in pattern typical of tumor and not of infection/treatment effect.

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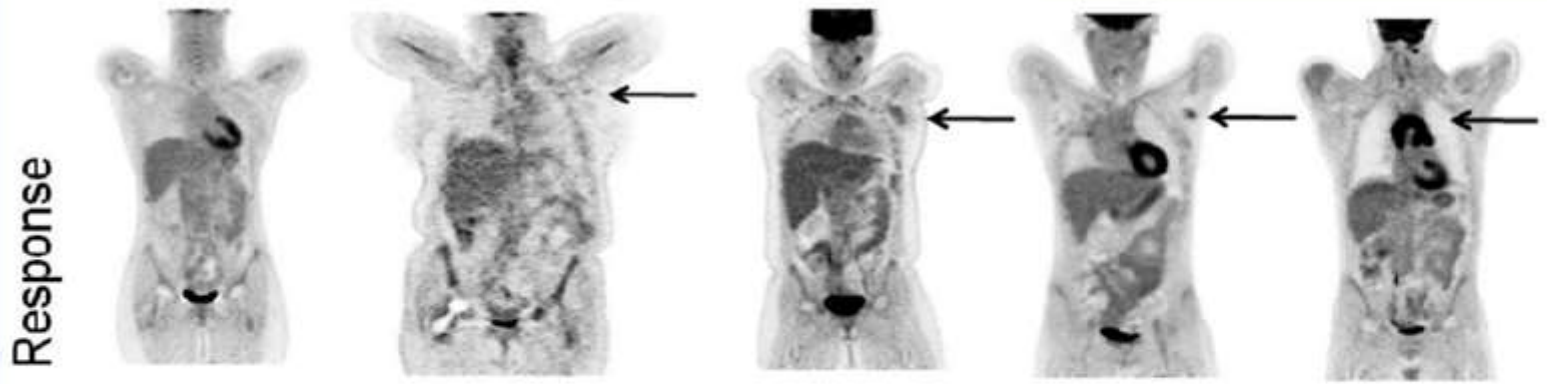
Deauville Criteria (5-point score)

Score	Residuals in Interim-PET/CT	
1	No Uptake over background	negative
2	Uptake ≤ Mediastinum	
3	Uptake > Mediastinum but ≤ Liver	
4	Uptake moderately > Liver	positive
5	Uptake strongly > Liver	



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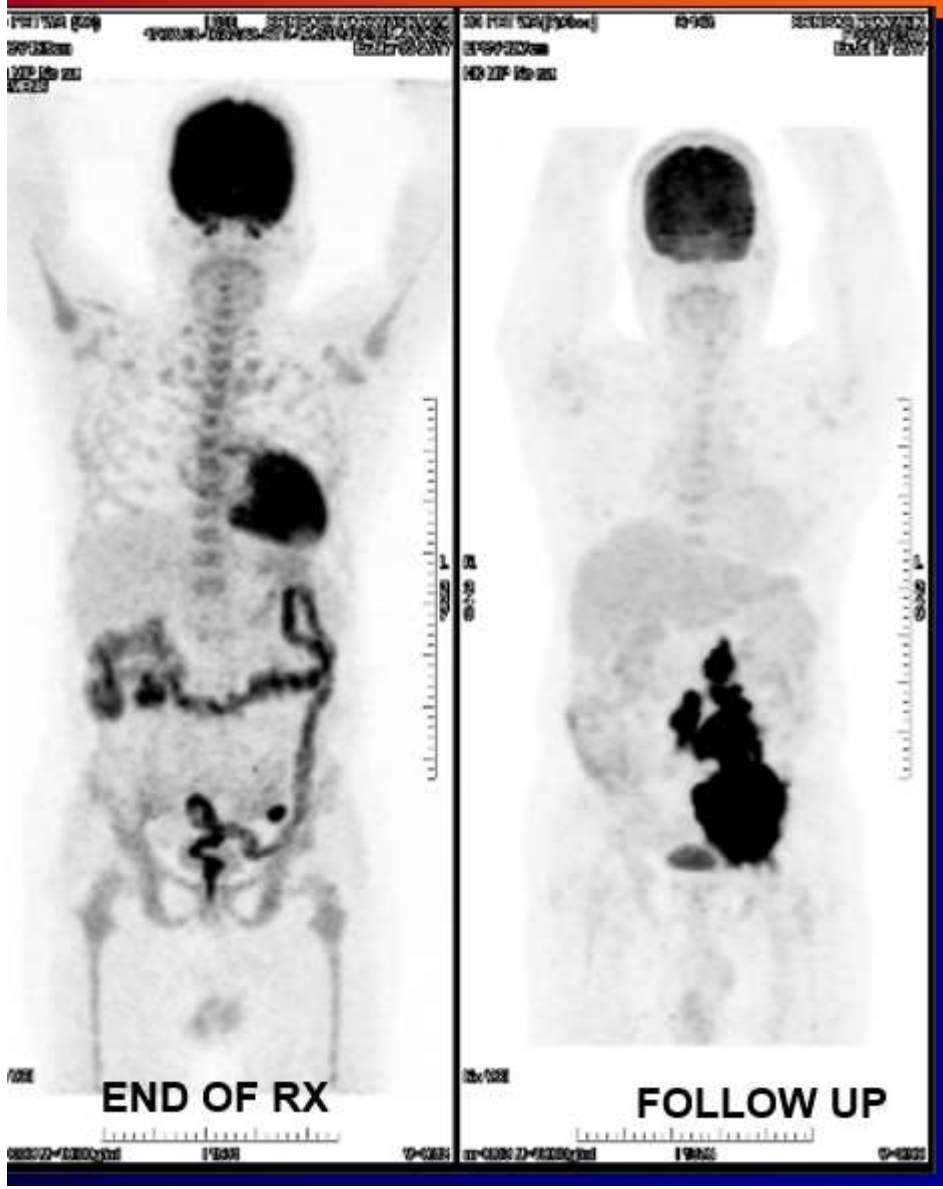

PROGRESSIVE DISEASE-
DEAUVILLE - 5

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LUGANO CRITERIA PET- CT BASED CHESON-2014

Modality	Complete Response	Partial Response	Stable Disease	Progressive Disease
FDG PET-CT	Scores 1, 2 ,3 in nodal or extranodal sites with or without a residual mass	Scores 4 or 5 with ↓ uptake compared with baseline and residual mass(es)	Scores 4 or 5 with no obvious change in FDG uptake	Scores 4 or 5 in any lesion with ↑ uptake from baseline and/or New FDG-avid foci

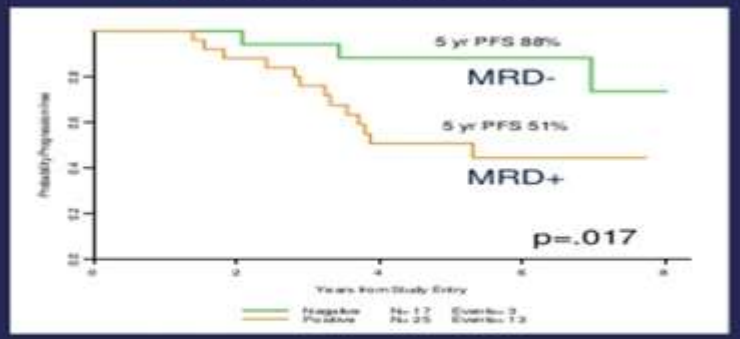
Ldi = longest transverse diameter; Sdi = shortest transverse diameter; PPD = product of perpendicular diameters; SPD = sum of the product of the perpendicular diameters of multiple lesions; ↑ = increase; ↓ = decrease

MRD

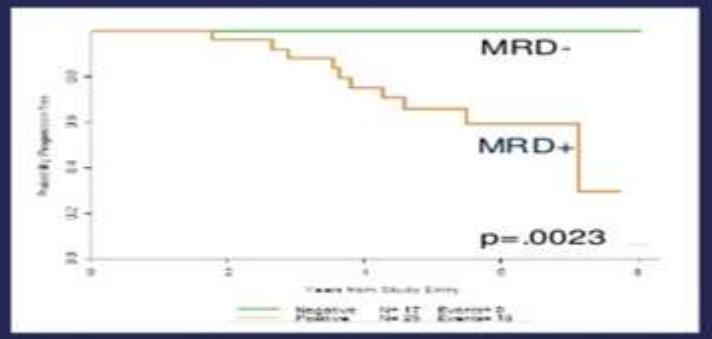
- .
- MRD NEGATIVITY MAY BE AN IMPORTANT CRITERION TO EVALUATE TREATMENT EFFICACY IN HEMATOLOGIC TUMORS
- IT HAS BEEN SHOWN TO CORRELATE WITH SURVIVAL IN MULTIPLE CLINICAL STUDIES.

Progression free and Overall survival by MRD post-induction (Median Follow-up 5.5yr)

Progression-free survival



Overall Survival



MRD- : n=17 MRD+ : n=25

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pCR

- **FDA DEFINITIONS OF PCR :**

- **ABSENCE OF RESIDUAL INVASIVE AND IN SITU CANCER ON HEMATOXYLIN AND EOSIN EVALUATION OF THE COMPLETE RESECTED TISSUE SPECIMEN AND ALL SAMPLED REGIONAL LYMPH NODES FOLLOWING COMPLETION OF NEOADJUVANT SYSTEMIC THERAPY.**

Immune-related response criteria (irRC)

- . The irRC utilize an important concept: the overall tumor burden.

- THE OVERALL TUMOR BURDEN EMBRACES THE COMBINED SIZE OF INDEX LESIONS PRESENT AT BASELINE PLUS ANY NEW TUMORS DETECTED AFTER TREATMENT BEGINS (HOOS 2010). UNDER RECIST, THESE NEW TUMORS WOULD BE REGARDED AS DISEASE PROGRESSION—INDICATING TREATMENT FAILURE—BUT IRRC TREATS NEW TUMORS AS PART OF THE TUMOR BURDEN INSTEAD OF CONSIDERING THEM AS NOTIFICATION THAT THE DISEASE HAS WORSENED (HOOS 2012).

- THE IRRC TYPICALLY INCLUDE 4 DIFFERENT KINDS OF RESPONSE:
- IMMUNE-RELATED COMPLETE RESPONSE (IRCR);
  - IMMUNE-RELATED PARTIAL RESPONSE (IRPR);
  - IMMUNE-RELATED STABLE DISEASE (IRSD);
- IMMUNE-RELATED PROGRESSIVE DISEASE (IRPD) (HOOS 2010)

ONCOLOGY END POINTS

PATIENT CENTRED END POINT

- OVER ALLSURVIVAL
- HEALTH RELATED QUALITY OF LIFE

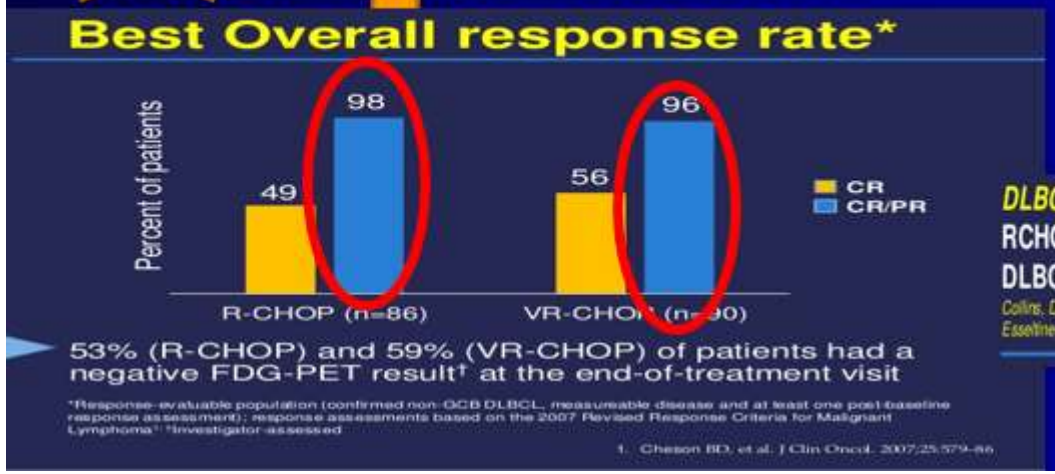
TUMOR CENTERED END POINT

- OVER ALL RESPONSE RATE
- DISEASE CONTROL RATE
- PROGRESSION FREE SURVIVL
- TIME TO TUMOR PROGRESSION
- DISEASE FREE SURVIVAL
- DURATION OF RESPONSE
- TIME TO TREATMENT FAILURE

OVER ALL RESPONSE RATE (ORR)

(ORR) IS DEFINED AS THE PROPORTION OF PATIENTS WHO HAVE A PARTIAL OR COMPLETE RESPONSE TO THERAPY

PROPORTION OF PATIENTS WHO HAVE A PARTIAL OR COMPLETE RESPONSE TO THERAPY



DLBCL - ABSTRACT 811: Randomized phase 2 study of RCHOP ± Bortezomib in Untreated Non-Germinal Center type DLBCL: PYRAMID TRIAL *Leonard, Kolibaba, Reeves, Tulpule, Flinn, Lolevska, Robles, Flower Collins, DiBella, Papish, Venugopal, Horodner, Tabatabai, Hajdenberg, Mulligan, Neuwirth, Suryanaramyan, Esseltine, de Vos*

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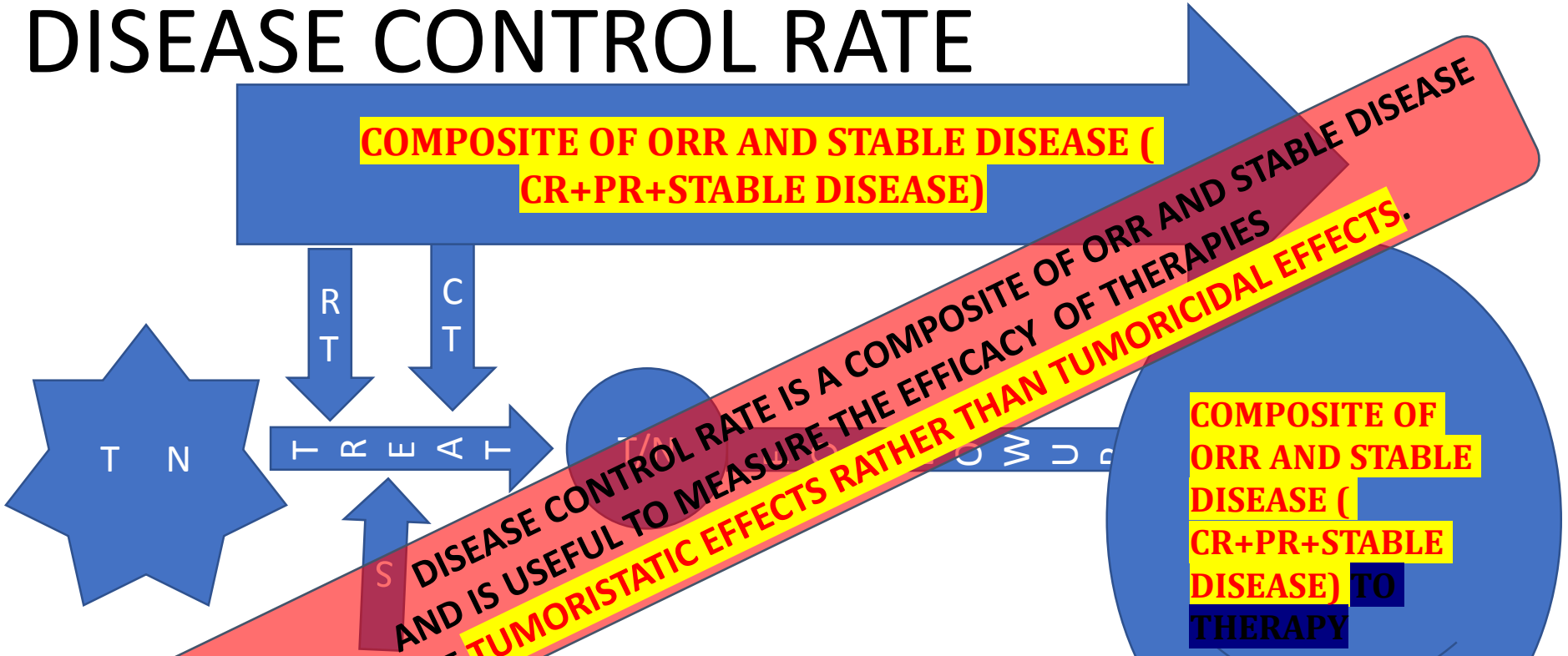
DISEASE CONTROL RATE



Response	Overall Population *n* (%)	Oxaliplatin-Based Doublet *n* (%)	Irinotecan-Based Do *n* (%)
ORR	18 (10.5)	7 (13.7)	11 (9.6)
PR	16 (9.3)	7 (13.7)	9 (7.8)
CR	2 (1.2)	0	2 (1.7)
DCR	56 (32.3)	18 (35.2)	35 (30.7)
SD	38 (22.0)	11 (21.5)	24 (21.1)
PR	16 (9.3)	7 (13.7)	9 (7.8)
CR	2 (1.2)	0	2 (1.7)

OVERALL SURVIVAL (OS)

TIME FROM RANDOMIZATION UNTIL DEATH FROM ANY CAUSE

T N

RT

CT

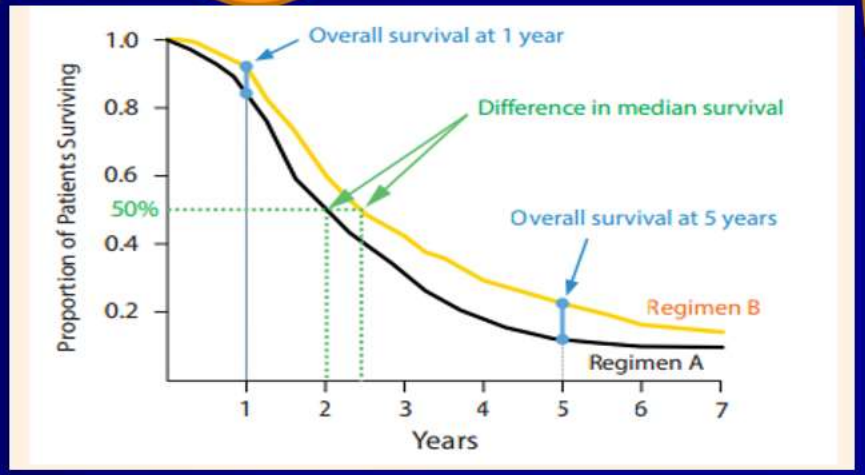
S

TREAT

T/N

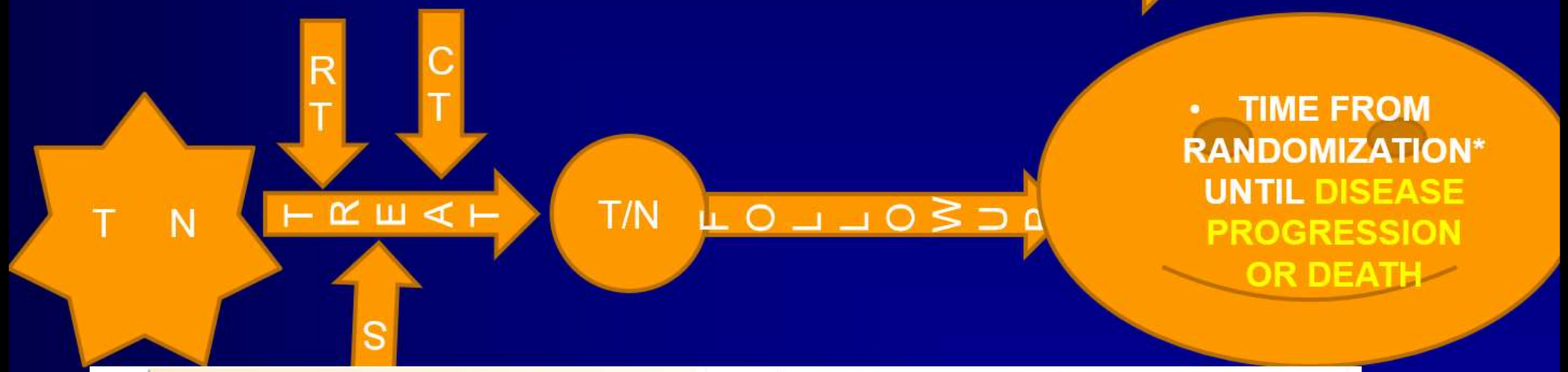
FOLLOWUP

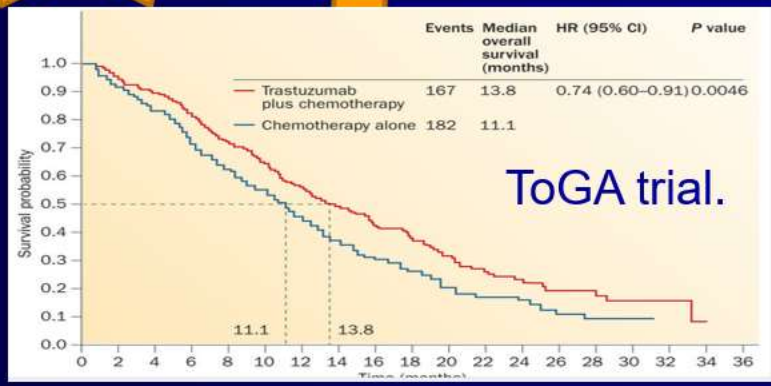
- DEATH FROM ANY CAUSE

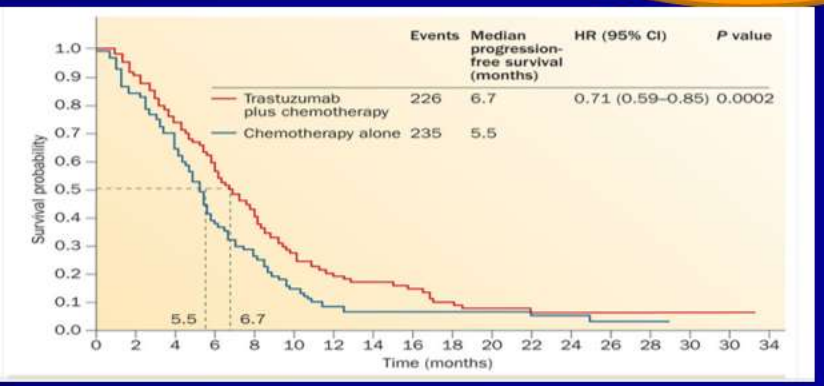


PROGRESSION-FREE SURVIVAL (PFS)

TIME FROM RANDOMIZATION UNTIL **DISEASE PROGRESSION** OR DEATH







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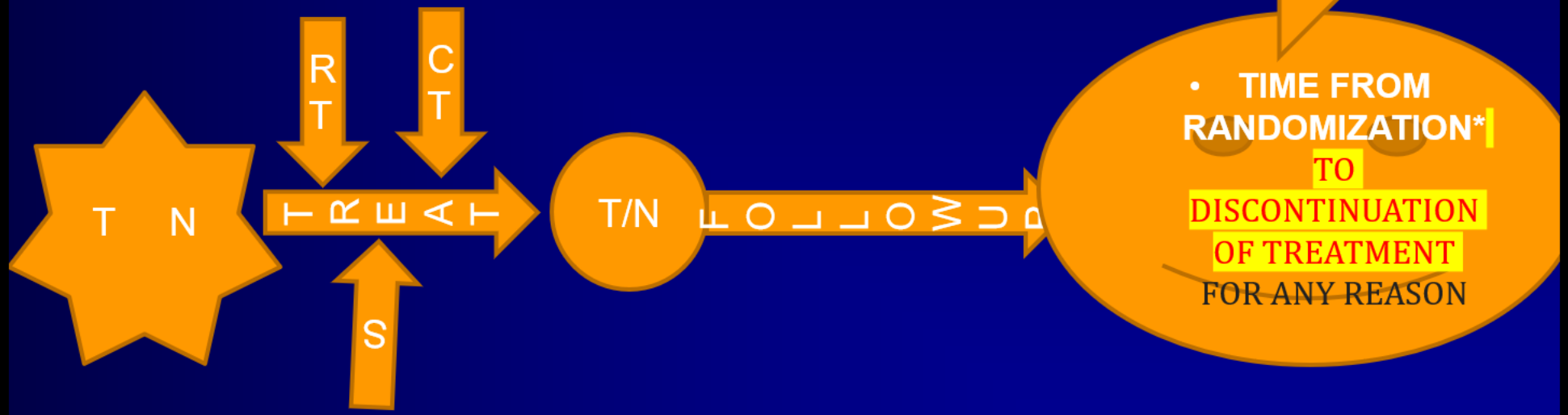
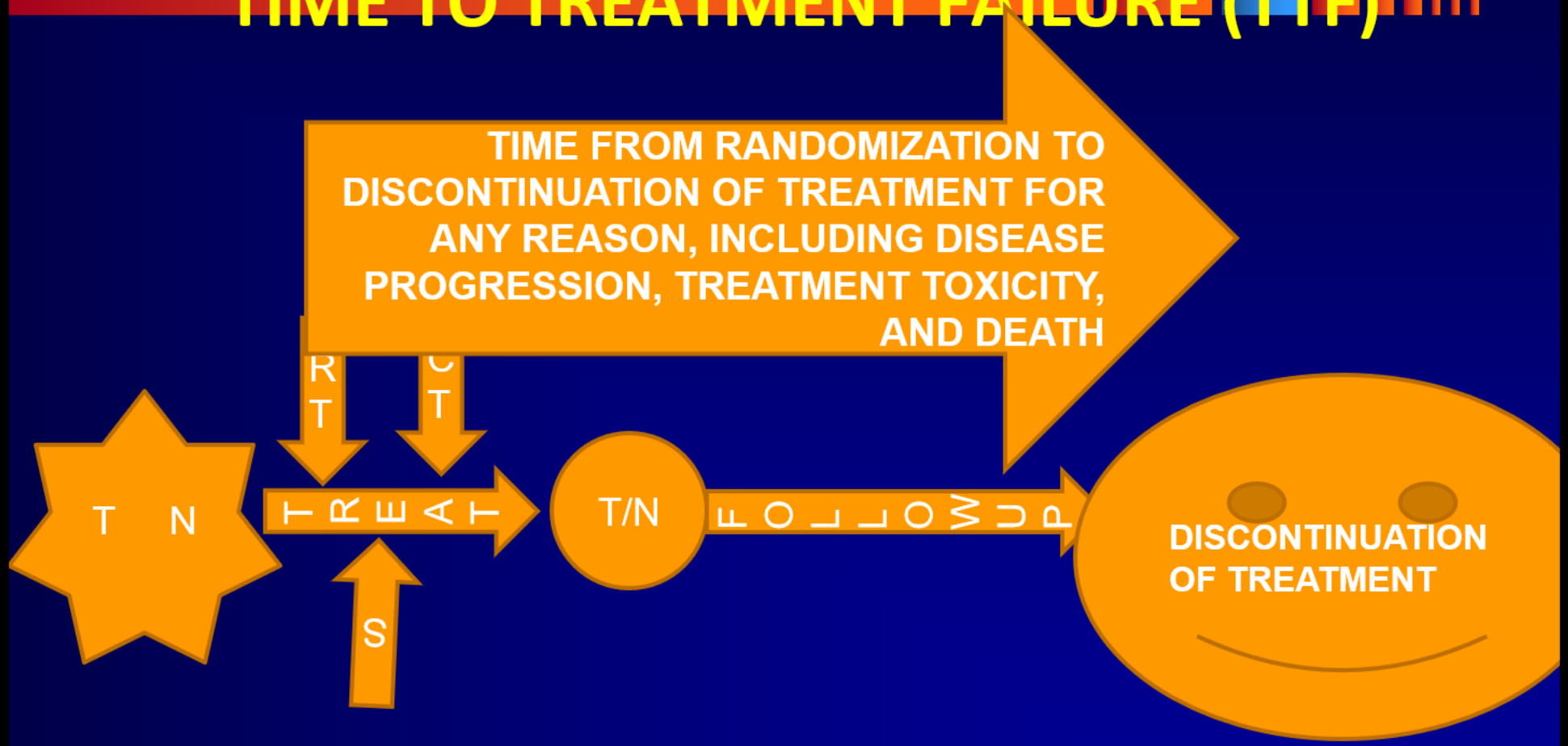
TIME TO TREATMENT FAILURE

TIME FROM RANDOMIZATION TO DISCONTINUATION OF TREATMENT FOR ANY REASON, INCLUDING PROGRESSIVE DISEASE, TREATMENT TOXICITY AND DEATH

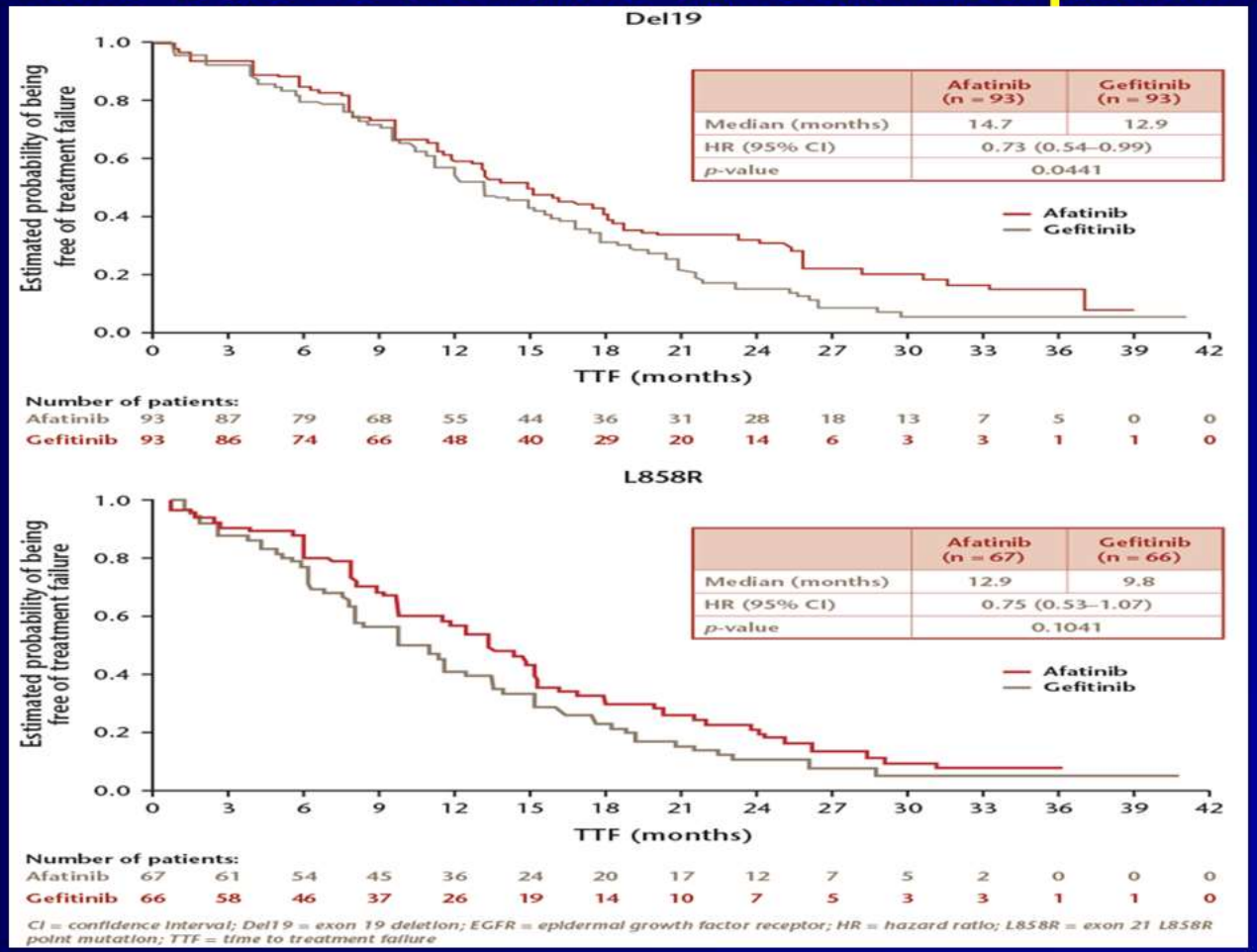


ToGA trial.

TIME TO TREATMENT FAILURE (TTF)



Time to treatment failure with first-line afatinib versus gefitinib in patients with EGFR mutation-positive advanced NSCLC from the randomized phase IIb LUX-

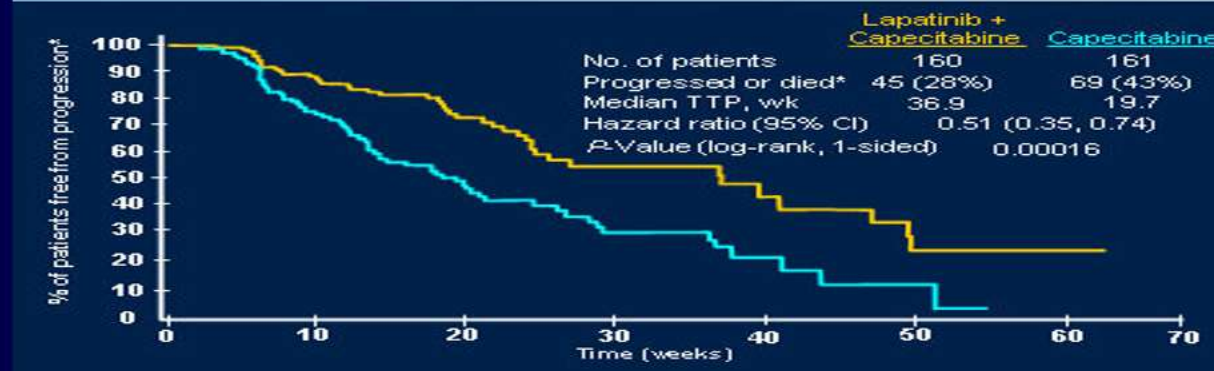


TTF stratified by EGFR mutation type (exon 19 deletions and exon 21 L858R point mutation) was longer for afatinib vs. gefitinib.

TIME TO PROGRESSION (TTP)

TIME FROM RANDOMIZATION UNTIL OBJECTIVE TUMOR PROGRESSION; DOES NOT INCLUDE DEATHS

Time to Progression: ITT Population



* Censors 4 patients who died due to causes other than breast cancer

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EVENT-FREE SURVIVAL (EFS)

TIME FROM RANDOMIZATION* TO DISEASE PROGRESSION, DEATH, OR DISCONTINUATION OF TREATMENT FOR ANY REASON (EG, TOXICITY, PATIENT PREFERENCE, OR INITIATION OF A NEW TREATMENT WITHOUT DOCUMENTED PROGRESSION)

T N

T T

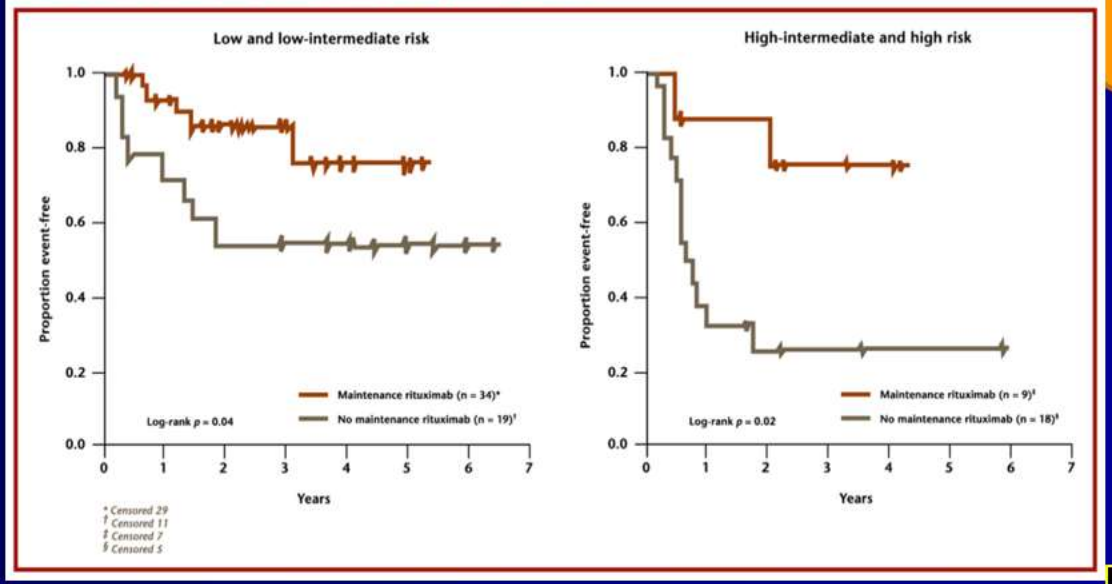
TREAT

T/N

FOLLOWUP

- DISEASE PROGRESSION, DEATH, OR DISCONTINUATION OF TREATMENT FOR ANY REASON

Figure 3: Event-free survival by International Prognostic Index (IPI)



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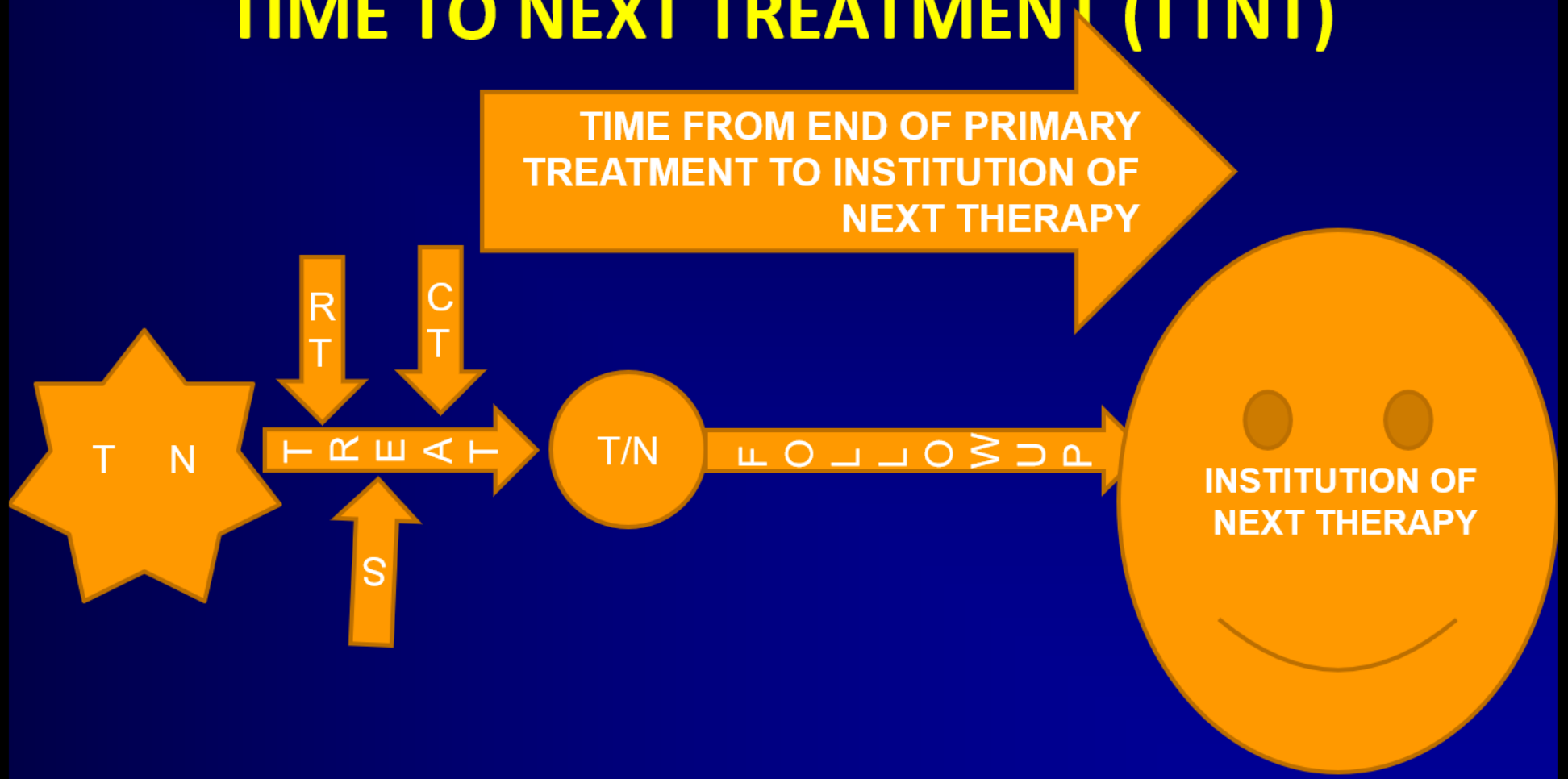
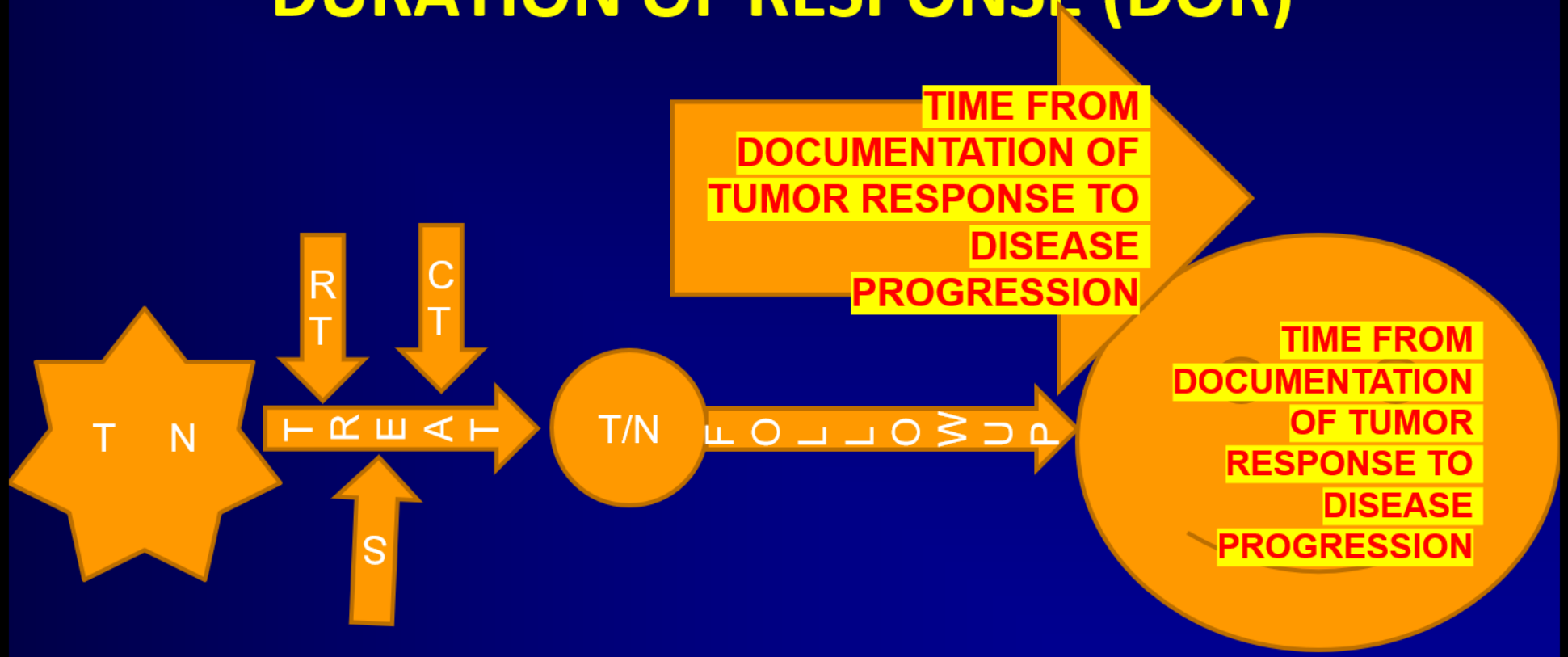
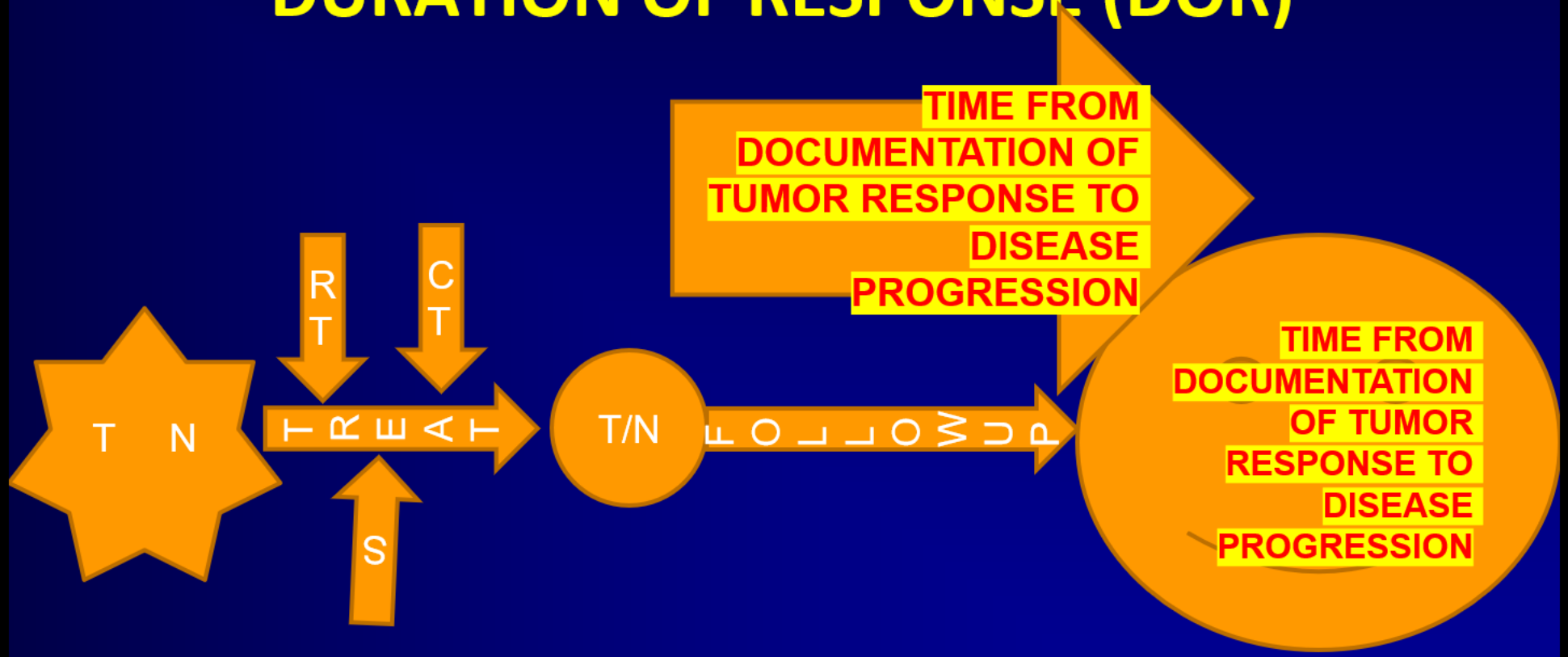
TIME TO NEXT TREATMENT (TTNT)



DURATION OF RESPONSE (DOR)



DURATION OF RESPONSE (DOR)



TAKE HOME MESSAGE

- **RESPONSE EVALUATION:-**

  WHO,RECIST,PERCIST, DEAUVILLES RESPONSE CRITERIA

  MRD,PCR,IMMUNE-RELATED RESPONSE CRITERIA (irRC),

- **RECIST:-**
  - CT preffered over X-Ray chest .
  - Measurable tumor lesions must be accurately measured at least one dimension with a minimum size of
  - 10mm by CT Scan where slice thickness 5mm
  - 10 mm caliper measurement
  - 20mm by chest x-ray
  - >/ 15 mm lymphnodes in short axis as target lesions.
  - When more than one measurable lesions present at baseline,all lesions up to maximum 5 lesions total and maxm.2 les ion per organ to be identified

TAKE HOME MESSAGE

- Target lesions should be based on longest diameter,Lymph nodes measured based on short axis diameter,Lumph node >15 mm :- pathological
- CR;-COMPLETE DISSSAPEARANCE,PR:- ATLEAST 30%, STABLE DISEASE <30% DECREASE OR <20%INCREASE IN LD ,PROGRESSION:-PROGRESSIVE DISEASE->20 % INCREASE LD
- PERSIST:- METABOLIC RESPONSE BASED ON SUL
- CR:-COMPLETE RESPOSE,PR:-AT LEAST 30% OR 0.8% DECREASE OF SUL,STABLE DISEASE,PROGRESSIVE:-30% INCREASE OR .8% OF SUL INCREASE .
- DEAUVILLES RESPONSE CRITERIA:- IN LYMPHOMA ON COMPARISION OF SWITH MEDIASTINUM/LIVER.D 1,2,3 ARE NEGATIVE,45 ARE POSITIVE
- HEMATOLOGICAL MALIGNANCIES:- MRD