



INTEGO
GROUP

Step-by-Step Guide to Efficacy Analysis in Solid Tumors Oncology Clinical Trials

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Introduction

Cancer is no longer a death sentence!



R - Response

E - Evaluation

C - Criteria

I - In

S - Solid

T - Tumors

European Organization Research and Treatment for Cancer (EORTC) and others, 2000 (V1.0) and 2009 (V1.1)

RECIST Criteria Features

- ☐ Widely accepted and readily applied
- ☐ Subject of interest – assessment of a change in the tumor burden
- ☐ Covers the whole analysis process: data collection → efficacy conclusion
- ☐ Required for all the clinical trials where ORR or PFS are study endpoints
- ☐ RECIST 1.1 currently in use

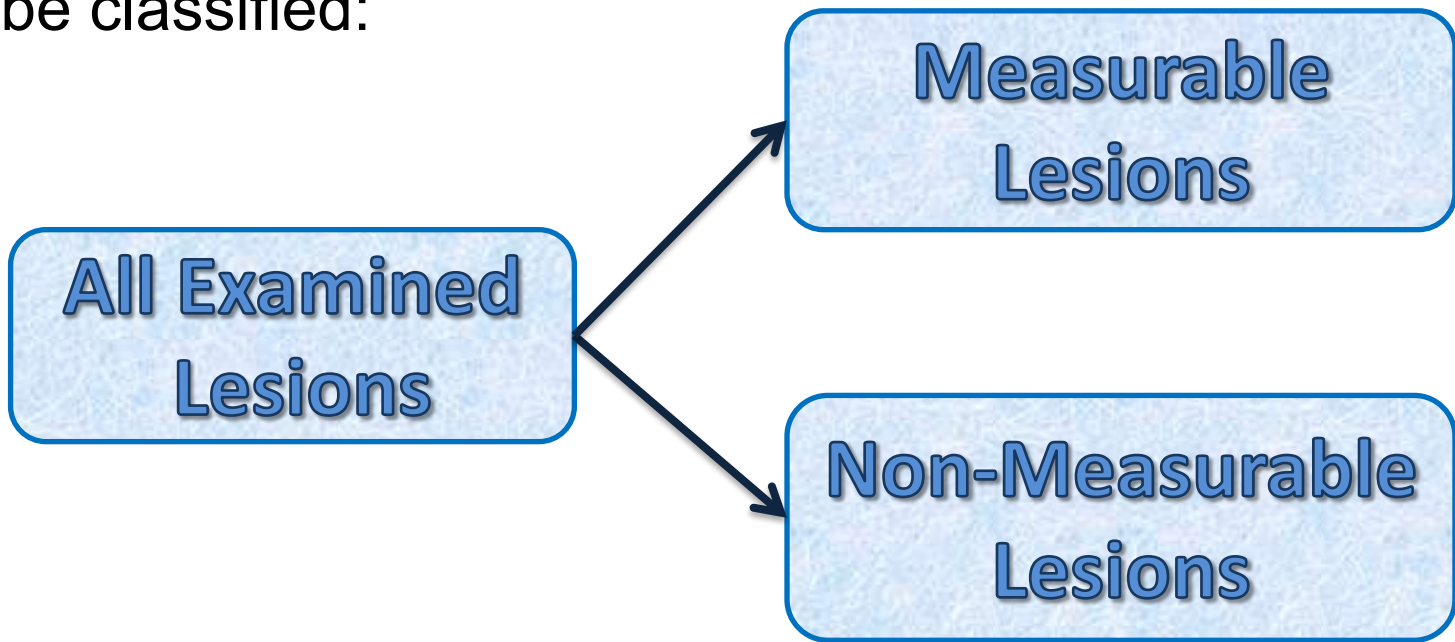


Baseline Tumor Documentation



Screening Requirements

- ☐ Evaluation within 4 weeks before TX start
- ☐ As many lesions as possible to be documented
- ☐ ≥ 1 measurement for the lesion
- ☐ All the tumors to be classified:



Study Eligibility

Measurable disease is required if ORR is a primary efficacy endpoint (typical for Phase II studies)

Non-measurable disease only can be accepted if Time to Progression is a primary efficacy endpoint (typical for Phase III studies).
Progression Disease Definition to be clarified!

Methods of Tumor Assessment

Main

- ☐ CT and MRI ← the best currently available
- ☐ Chest X-Ray
- ☐ Clinical Examination (CE)

Supportive

- ☐ Ultrasound
- ☐ Endoscopy & Laparoscopy
- ☐ Tumor Markers
- ☐ Cytology & Histology

Methods of Tumor Assessment

The **same technique** to be used to one lesion **at baseline and** during the **follow-up!**



Lesions Measurability. Tumor Lesions

Measurement Characteristic - **Longest Diameter (LD)**

Lesion is **Measurable** if LD has min size of:

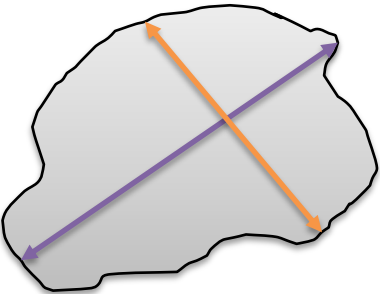
- 10 mm by CT scan / calipers
- 20 mm by chest X-ray

Lesion is **Non-measurable** if:

- $LD < 10$ mm by CT / calipers or $LD < 20$ mm by X-ray
- Truly non-measurable

Lesions Measurability. Malignant Lymph Nodes

Measurement Characteristic – **Short Axis (SA)** because of normal anatomical structure



Longest Diameter
Short Axis

- **Measurable:** SA $\geq$ 15 mm by CT scan
- **Non-measurable:** 10 mm $\leq$ SA < 15 mm by CT scan
- **Non-pathological:** SA < 10 mm – should not be followed

Tumor Categorization

- ☐ Two separate tumor groups: **Target** and **Non-target**
- ☐ Different follow-up approaches
- ☐ Valid until the end of the study

Target Lesions

- The largest & the most reproducible
- Measurable by definition
- Representatives of all cancer-affected organs
- Max 5 in total & max 2 per organ

Tumor Number	Location	Method of Assessment	LD or SA (mm)
T001	Lung	Chest X-Ray	25
T002	Lymph Node	CT Scan	15
T003	Skin	Calipers	18

Documentation: LD (SA) of each lesion & Sum of Diameters.

Baseline Sum of Diameters (BSD) = 25 + 15 + 18 = 58 mm

Non-Target Lesions

- All lesions excluded from the target
- Not required to be measurable
- Number is not limited
- Multiple lesions in the same organ in one item - Okay

Documentation: the fact of the presence is enough

Non-Target Lesions. Examples

Tumor Number	Location	Method of Assessment	LD or SA (mm)	Why Non-Target
T001	Lung	CT Scan	7	Non-measurable, LD < 10mm
T002	Lung	Chest X-Ray	18	Non-measurable, LD < 20mm
T003	Lymph Node	CT Scan	13	Non-measurable, 10 < SA < 15mm
T004	Lymph Node	CT Scan	9	Non-pathological, should not be followed
T005	Kidney (previously irradiated)	CT Scan	25	Located in previously irradiated area
T006	Liver (Cystic Lesion)	CT Scan	30	Non-cystic lesions are present
T007	Brain	MRI	7	Non-measurable, LD < 10mm
T008	Brain	MRI	5	Non-measurable, LD < 10mm

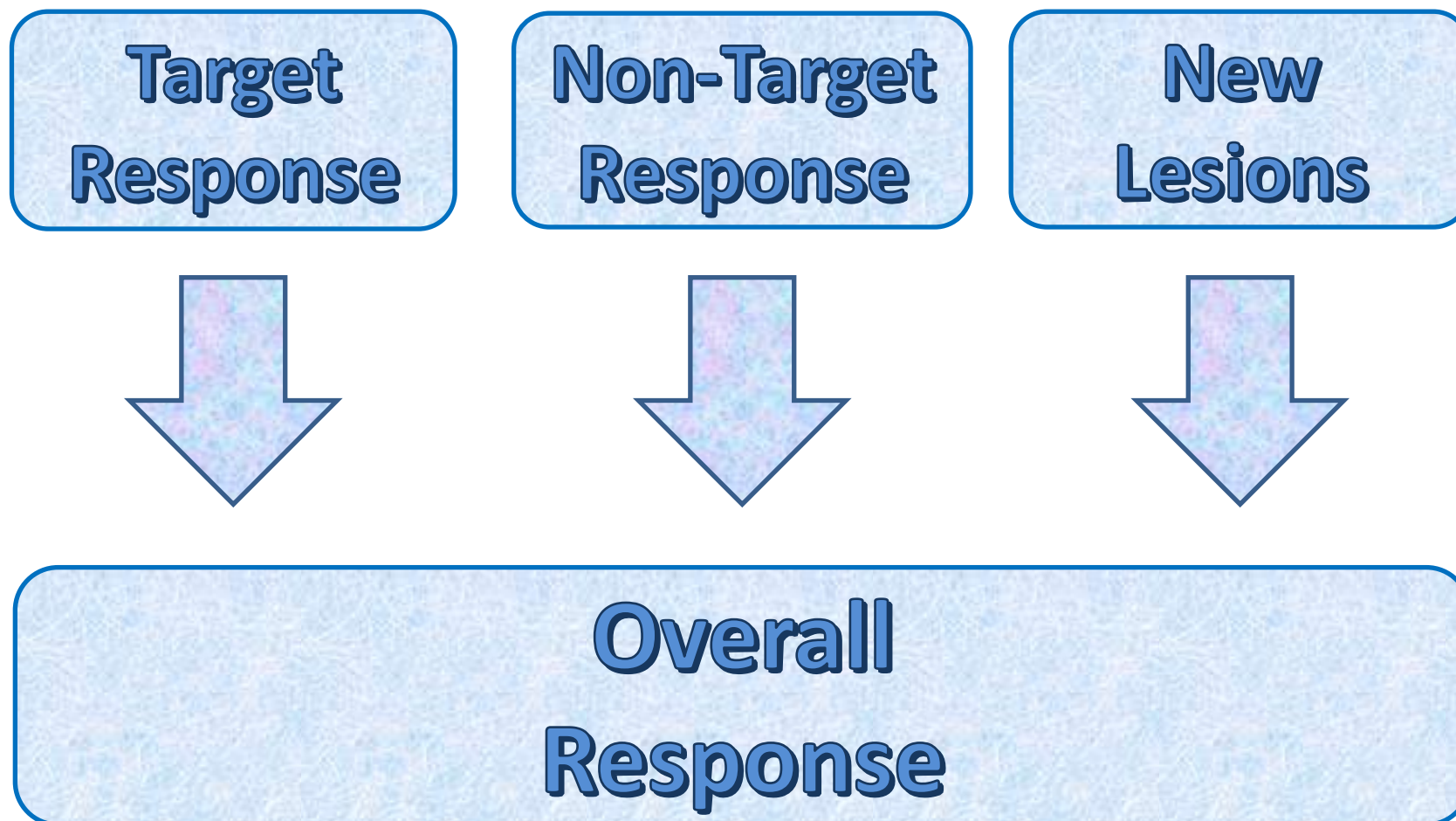
Can be reported as a single item



Post-Baseline Tumor Evaluation



Time Point Response



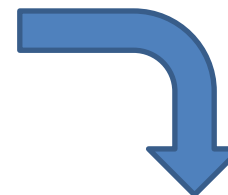
Frequency of the tumor assessments

- ❑ Based on the treatment schedule and study phase
- ❑ Independent of a study drug delay & omission & interruption
- ❑ Tumor evaluation after the TX end? Depends on the study primary endpoints



Target Response

Sum of Diameters
calculated



	Criteria to be met
Complete Response (CR)	All the target lesions disappeared and the lymph nodes are non-pathological
Partial Response (PR)	$\geq 30\%$ ↓ in the Sum of Diameters compared to the BSD
Progressive disease (PD)	$\geq 20\%$ ($\geq 5\text{mm}$) ↑ in the Sum of Diameters compared to NADIR
Stable Disease (SD)	No significant changes in the target lesions size

NADIR - the smallest sum of diameters reported at prior study visits

Target Response

Special lesions occasions

- **'too small to measure'**

disappeared → LD = 0 mm, faintly seen → LD = 5 mm

- **split up**

LD of fragmented portions → to Sum of Diameters

- **coalesce**

a plane between lesions → to Sum of Diameters

Example of Target Response Derivation

Subject ID	Visit	Study Day	Sum of Diameters (mm)
001	Screening	-1	110
001	Week 8	56	99
001	Week 16	112	68
001	Week 24	168	73
001	Week 32	224	89

BSD = 110 mm

NADIR = 110 mm
 → 11% Decrease from BSD
 → Target Response is **SD**

NADIR = 99 mm
 → 38% Decrease from BSD
 → Target Response is **PR**

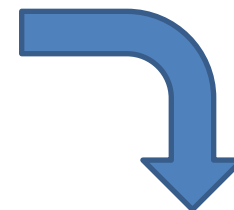
NADIR = 68 mm
 → 34% Decrease from BSD
 → 7% Increase from NADIR
 → Target Response is **PR**

NADIR = 68 mm
 → 19% Decrease from BSD
 → 31% Increase from NADIR
 → Target Response is **PD**

NADIR - the smallest sum of diameters reported at prior study visits

Non-Target Response

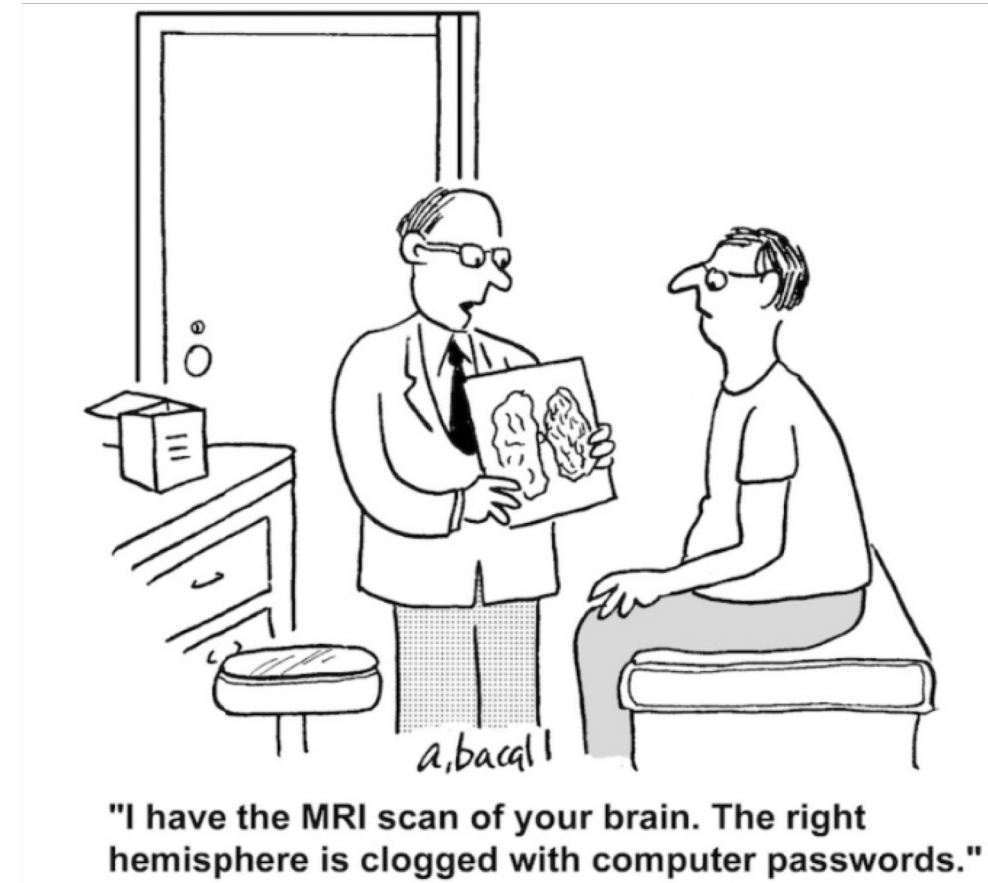
No quantitative
result available



	Criteria to be met
Complete Response (CR)	▪ All the non-target lesions disappeared ▪ All the lymph nodes are non-pathological ▪ The tumor-marker level is normal
Non-CR/Non-PD	At least one non-target lesion is persistent OR the tumor marker level is above normal
Progressive disease (PD)	Unequivocal progression

New Lesion Appearance

- ❑ Always means PD
- ❑ Must be unequivocal.
Otherwise – **additional evaluation!**



Overall Response. Measurable Disease

Target Response	Non-target Response	New Lesion	Overall Response
CR	CR	No	Complete Response
CR	Non-CR/non-PD	No	Partial Response
CR	NE*	No	Partial Response
PR	Non-PD or NE*	No	Partial Response
SD	Non-PD or NE*	No	Stable Disease
NE*	Non-PD	No	Unevaluable
PD	Any	Yes or No	Progressive Disease
Any	PD	Yes or No	Progressive Disease
Any	Any	Yes	Progressive Disease

* NE - Not All Evaluated

Overall Response.

Non-Measurable Disease only

Non-target Response	New Lesion	Overall Response
CR	No	Complete Response
Non-CR/non-PD	No	Non-CR/non-PD
NE*	No	Unevaluable
Unequivocal PD	Yes or No	Progressive Disease
Any	Yes	Progressive Disease

* NE - Not All Evaluated



Best Overall Response



Best Overall Response (BOR)

the best response across all the time points up to the treatment/study end or the start of the new therapy

- **Complete Response** → to be confirmed?
- **Partial Response** → to be confirmed?
- **Stable Disease** → min time from baseline!
- **Progressive Disease**
- **Unevaluable**

Complete Response Confirmation

First Time Point Response	Subsequent Time Point Response	Best Overall Response (BOR)
CR	CR	Complete Response
	PR	Stable Disease or Progressive Disease or Partial Response
	SD	Stable Disease* or Progressive Disease**
	PD	
	NE	Stable Disease* or Unevaluable**

Min time from baseline criterion: * - met, ** - not met.

Partial Response Confirmation

First Time Point Response	Subsequent Time Point Response	Best Overall Response (BOR)
PR	CR	Partial Response
	PR	Partial Response
	SD	Stable Disease
	PD	Stable Disease* or Progressive Disease**
	NE	Stable Disease* or Unevaluable**

Min time from baseline criterion: * - met, ** - not met.

Best Overall Response. Example 1

	Subject ID	Visit	Study Day	Parameter Name	Analysis Value, Character
1	001	Week 8	56	Overall Response	SD
2	001	Week 16	112	Overall Response	PR
3	001	Week 24	168	Overall Response	PR
4	001	Week 32	224	Overall Response	PR
5	001	Week 40	280	Overall Response	CR

Requirements:

- min SD duration - 7 weeks
- min 4 weeks between assessments to confirm BOR

Unconfirmed BOR is **CR**

Confirmed BOR is **PR**

Best Overall Response. Example 2

	Subject ID	Visit	Study Day	Parameter Name	Analysis Value, Character
1	002	Week 8	56	Overall Response	PR
2	002	Week 16	112	Overall Response	NE
3	002	Week 24	168	Overall Response	PD

Requirements:

- min SD duration - 7 weeks
- min 4 weeks between assessments to confirm BOR

Unconfirmed BOR is **PR**

Confirmed BOR is **SD**



Other Efficacy Endpoints



$$\text{Objective Response Rate (ORR)} = \frac{\text{Number of Responders}}{\text{Total Number of Patients}}$$

$$\text{Clinical Benefit Rate (CBR)} = \frac{\text{Number of Responders} + \text{SD}}{\text{Total Number of Patients}}$$

Responders = BOR is CR/PR

Responders + SD = BOR is CR/PR/SD

Total number of patients = All treated / all eligible

Time to Event Endpoints

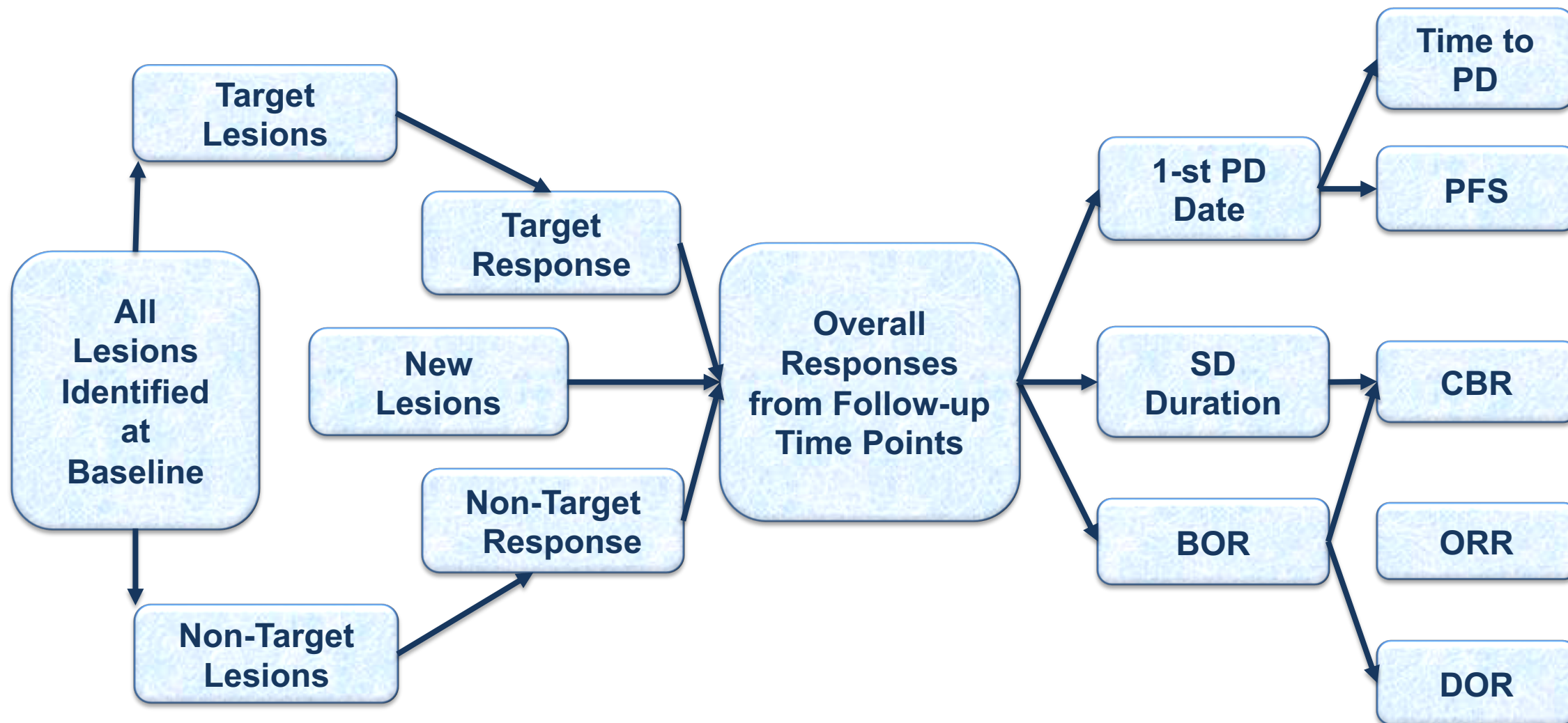
Endpoint Name	Start Time Point	Event of Interest	Censoring Date
Duration of Response (DOR)	First PR/CR Date	First PD Date	Last non-PD Tumor Assessment Date
Duration of Stable Disease	First Treatment / Randomization Date	First PD Date	Last non-PD Tumor Assessment Date
Progression Free Survival (PFS)	First Treatment / Randomization Date	First PD or Death Date	Last non-PD Tumor Assessment Date



Conclusion



Efficacy Analysis Process





THANK YOU

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