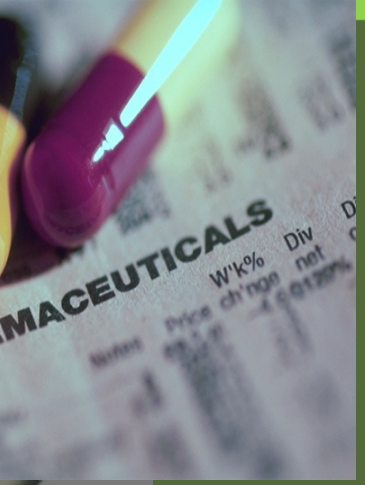

FMD

Programming Practice in Oncology Study with RECIST 1.1 and iRECIST

Li Chen, FMD

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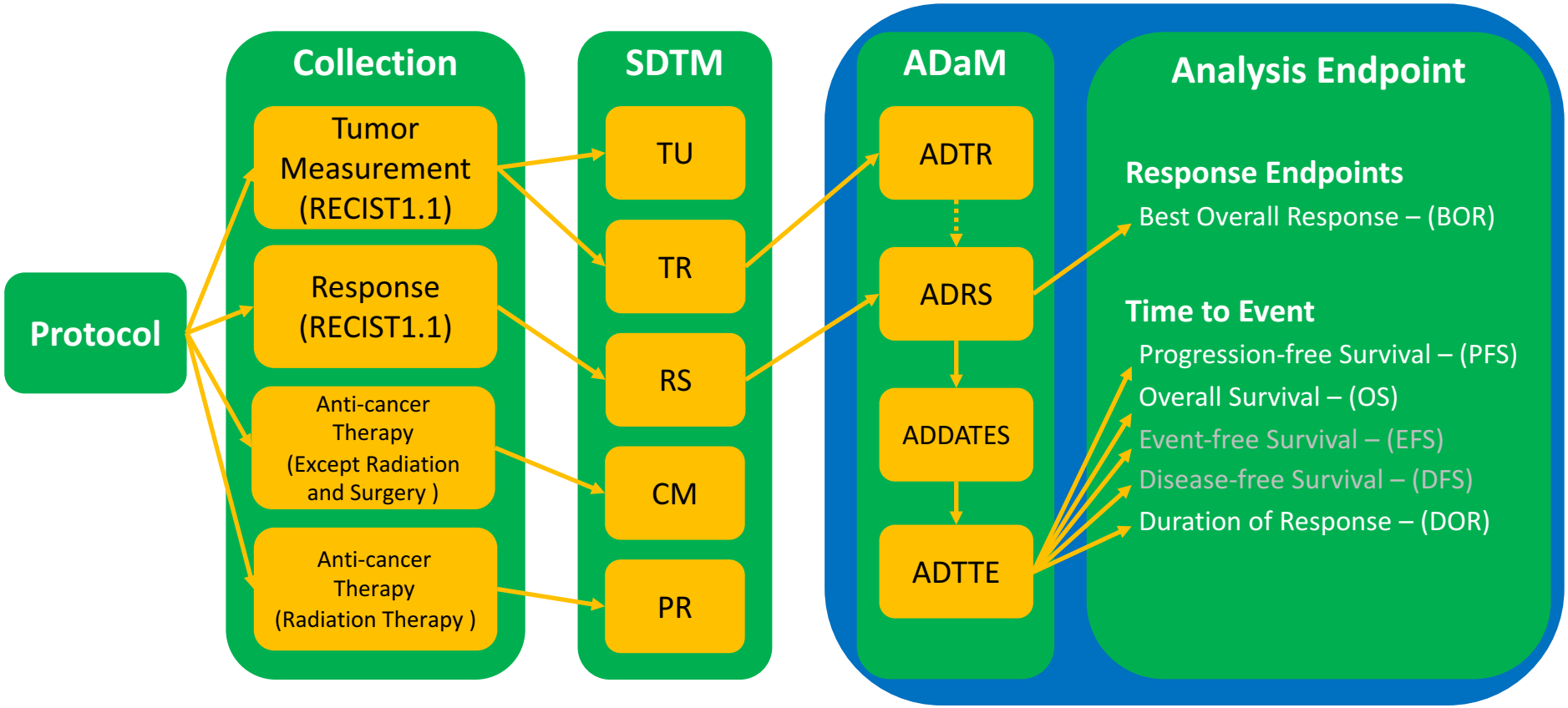
03Nov2017

End to End


Protocol
Collection
Tumor Measurement (RECIST1.1)
Response (RECIST1.1)
Anti-cancer Therapy (Except Radiation and Surgery)
Anti-cancer Therapy (Radiation Therapy)
SDTM
TU
TR
RS
CM
PR
ADaM
ADTR
ADRS
ADDATES
ADTTE
Analysis Endpoint
Response Endpoints
Best Overall Response – (BOR)
Time to Event
Progression-free Survival – (PFS)
Overall Survival – (OS)
Event-free Survival – (EFS)
Disease-free Survival – (DFS)
Duration of Response – (DOR)

Brief Introduction to RECIST 1.1 and iRECIST

Measurement of Tumor

Method	CT/MRI (preferred), Ultrasound, etc.
Measurability	Measurable vs. Non-measurable
Identification	Target (5 lesions (2 per organ)), Non-target, New
Time Point	Baseline, Post-baseline

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.

Versions of "Immune Response Criteria"

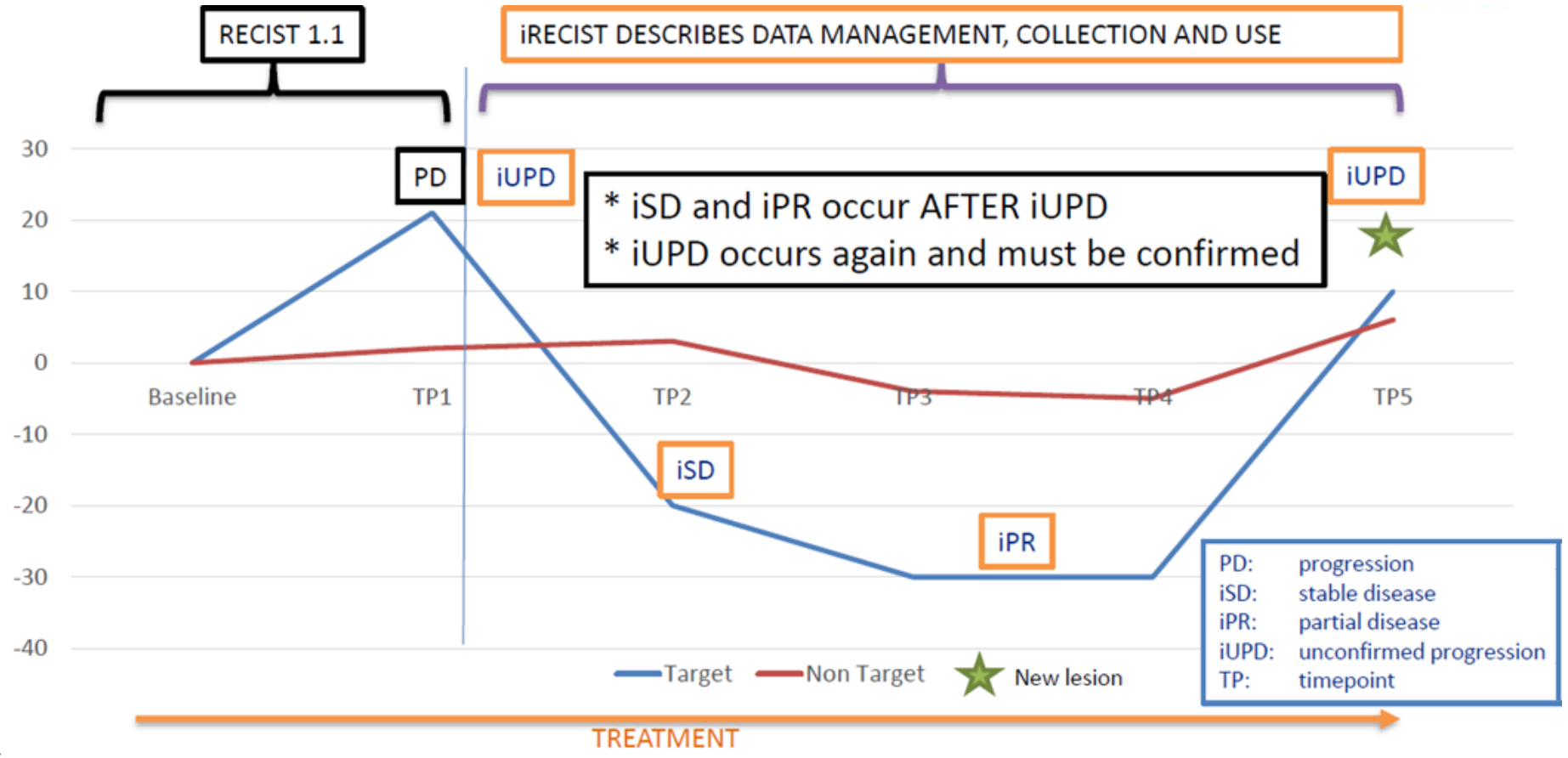
	RECIST 1.1	irRC (+ unidimensional variant)	"irRECIST /irRECIST1.1" variants
Bi/unidimen.?	Unidimensional	**Bidimensional**	Unidimensional
N Target	5	**15; (≥5 × 5mm)**	10 / 5 (≥10mm/ ≥10mm (15 for nodes))
New target lesions added to sum or measures (SOM)?	No	(≥5 × 5mm); **Yes** - does not automatically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

http://recist.eortc.org/wp-content/uploads/2017/03/Final-ENA-slides.pdf

iRECIST vs RECIST 1.1 - Changes

	RECIST 1.1	iRECIST
Management of new lesions	X	New
Time point response after RECIST 1.1 progression	X	New
Confirmation of progression required	X	New
Collection of reason why progression cannot be confirmed	X	New
Inclusion and recording of clinical status	X	New

Summary



http://recist.eortc.org/wp-content/uploads/2017/03/Final-ENA-slides.pdf

Data Collection and Mapping Consideration

Tumor Identification/Results – TU/TR

Target TUTESTCD=TUMIDENT and TUORRES=TARGET

Response Criteria: *Pre-specified*	RECIST 1.1
Were tumors identified? TUYN*	☐ Yes ☐ No
Tumor ID: TULNKID	
Location: TULOC	<*Select appropri*
Laterality: TULAT	☐ Left ☐ Right ☐ Bilateral <*Select appropri*
Directionality: TUDIR	☐ Distal ☐ Intermediate ☐ Proximal ☐ Inner ☐ Outer <*Select appropriate values from DIR CT*>
Location Detail: TULOCDTL* SUPPTU.LOCDTL	(A200)
Changes to Tumor Identified: TUCHANGE*	☐ Split TUTESTCD=TUSPLIT ☐ Merged TUTESTCD=TUMERGE
Method of Evaluation: TUMETHOD	☐ Clinical Exam ☐ CT Scan ☐ MRI ☐ Ultrasound ☐ X-Ray <*Select appropriate values from METHOD CT*>

Date of Evaluation: (DD-MMM-YYYY) TUDAT* TUDTC	__/___/____
Evaluator TUEVAL	☐ Investigator ☐ Independent Assessor
Evaluator Identifier: TUEVALID	☐ Radiologist 1 ☐ Radiologist 2 ☐ Radiologist 3 ...
Diameter: TRTESTCD=DIAMETER TRORRES	
Diameter Unit: TRDIAMU* TRORRESU	mm
Diameter Too Small to Measure: TRTOOSM* TRORRES	☐ Yes
Tumor Inevaluable? TRINEVAL* TRTESTCD=TUMSTATE TRSTAT=NOT DONE	☐ Inevaluable
If Tumor Is Inevaluable, Reason Not Done: TRREASND	☐ Lesion or Background Change that Prevents Evaluation ☐ Focal Intervention ☐ Poor Scan Quality ☐ Insufficient Images/Anatomy ☐ Inconsistent Modality ☐ Site Error ☐ Other
Lymph Node State: TRLNSTAT* TRTESTCD=LNSTATE TRORRES	☐ Pathological ☐ Non-Pathological

Tumor Identification -- TU

TU Definition

– Represents data that uniquely identifies tumors. The tumors are usually tracked during the course of a study and will contribute to an assessment of response to therapy.

– Contain only one record for each unique tumor identified by an assessor.

– The initial identification of a tumor is done once, usually at baseline.

– The identification information, including the location description, must not be repeated for every visit.

Post-baseline records might be included

– New Tumor is identified in post-baseline assessment;

– A tumor identified at baseline subsequently splits into separate distinct tumors;

– One or more tumors identified at baseline subsequently merge together;

– In situations where a re-baseline of Targets and Non-Targets is required.

Tumor Identification -- TU

Lesion Split

- **Data Mapping Rule:**

TU: For “new” lesions, add records with new lesion ID, TUORRES = “TARGET” where TUTESTCD = “TUSPLIT”.

Lesion Merged

- **Data Mapping Rule:**

TU: Add a record for the merged lesion with new lesion ID, TUORRES = “TARGET” where TUTESTCD = “TUMERGE”.

Tumor Results -- TR

Tips #1

– The TR domain does **not include anatomical location information on each measurement record** because this would be a duplication of information already represented in TU.

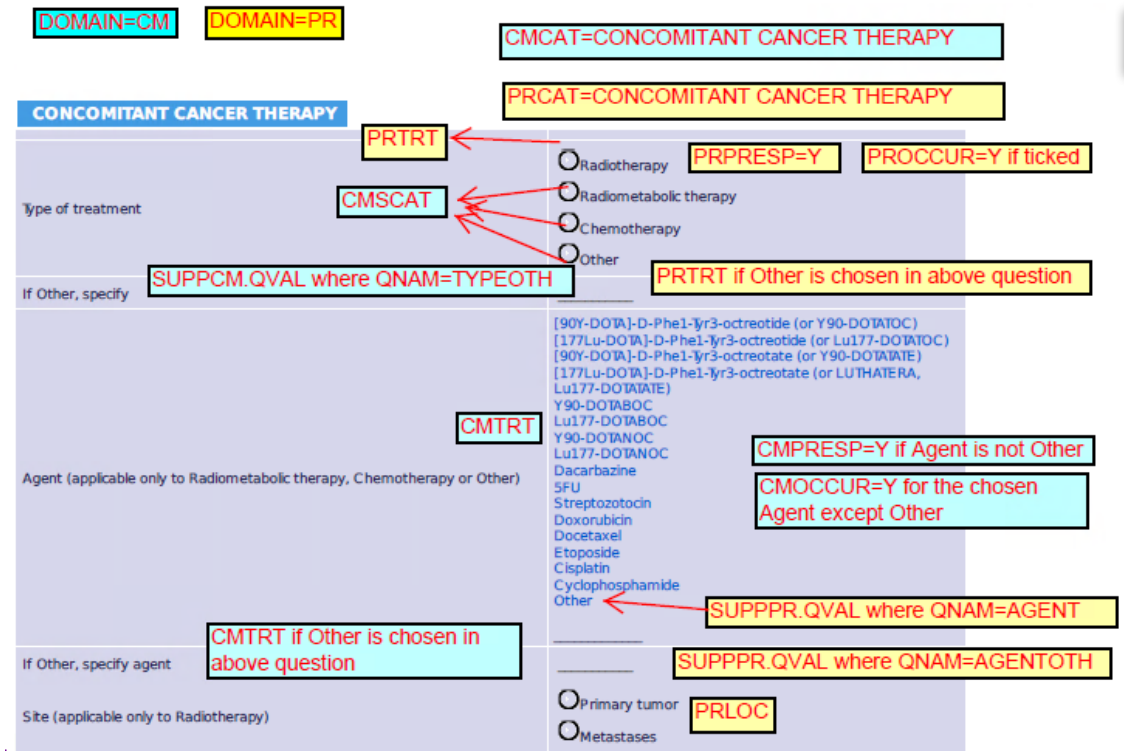
Tips #2

– **Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer.** It is not intended that the sponsor would create derived records to supply those values in the TR domain. Derived records/results should be provided in the analysis dataset.

Disease Response -- RS

Response Criteria: *Pre-specified* RSCAT	**RECIST 1.1**
Was the response assessment performed? RSYN	☐ Yes ☐ No RSSTAT=NOT DONE where RSTESTCD=OVRLRESP
Reason Response Assessment Not Performed: RSREASND* RSREASND where RSTESTCD=OVRLRESP	☐ Not Imaged ☐ Patient Refusal ☐ Site Error ☐ Other
Evaluator RSEVAL	☐ Investigator ☐ Independent Assessor
Evaluator Identifier: RSEVALID	☐ Radiologist 1 ☐ Radiologist 2 ☐ Radiologist 3
Overall Response: OVRLRESP* RSTESTCD=OVRLRESP RSTEST=Overall Response	RSORRES (RSSTRESC) ☐ Complete Response (CR) ☐ Partial Response (PR) ☐ Stable Disease (SD) ☐ Non Complete Response/Non Progressive Disease (NON-CR/NON-PD) ☐ Progressive Disease (PD) ☐ Not Evaluable (NE)
Date of Procedure for Overall Response (e.g., scan date): (DD-MMM-YYYY) OVRLDAT* RSDTC	__/___/____
Target Response: TRGRESP* RSTESTCD=TRGRESP RSTEST=Target Response	RSORRES (RSSTRESC) ☐ Complete Response (CR) ☐ Partial Response (PR) ☐ Stable Disease (SD) ☐ Progressive Disease (PD) ☐ Not Evaluable (NE) ☐ Not All Evaluated
Date of Procedure for Target Response (e.g., scan date): (DD-MMM-YYYY) TRGDAT* RSDTC	__/___/____

Concomitant Anti-Cancer Therapy



Maybe better to split as 3 forms in CRF

- **Concomitant Radiation Therapy**
- **Concomitant Anti-Cancer Medication**
- **Concomitant Cancer Surgery**

Concerning of FDA -- Missing Data

Why most of the tumor assessment records are missing?

Method of Identification

TUMETHOD	Frequency	Percent	Cumulative Frequency	Cumulative Percent
	21494	86.53	21494	86.53
CT SCAN	1263	5.08	22757	91.61
MRI	204	0.82	22961	92.44
OCTREOSCAN	1873	7.54	24834	99.98
OTHER	6	0.02	24840	100.00

Concerning of FDA -- Special Mapping Rule

Why TRGRPID was classified as EN, ET, IRC, and TE. Please note, the IRC vs. INV assessment should be grouped by variable TREVAL and TREVALID.

Permitted Value (Code)	Display Value (Decode)
EN	Evaluation of non target lesions
ET	Evaluation of target lesions
IRC	Keosys
TE	Overall tumor evaluation

Concerning of FDA -- “Inconsistent” Data

In the SDTM.PR domain, the procedure data only included 2 treatment procedures, which is inconsistent with your PRSTDY. Please verify that your data is accurate. In general, PR data has post randomization procedures records including radiotherapy.

EPOCH	Frequency	Percent	Cumulative Frequency	Cumulative Percent
	4	0.41	4	0.41
LONG-TERM FOLLOW-UP	12	1.22	16	1.63
SCREENING	962	98.16	978	99.80
TREATMENT	2	0.20	980	100.00

Category

PRCAT	Frequency	Percent
CONCOMITANT CANCER THERAPY	18	1.84
OTHER PREVIOUS TREATMENTS OF DISEASE	40	4.08
PRIOR CANCER SURGERY	922	94.08

The SAS System

18 in total

The SAS System

The FREQ Procedure

Study Day of Start of Procedure

PRSTDY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
-157	1	0.10	962	98.16
129	1	0.10	963	98.27
136	1	0.10	964	98.37
152	1	0.10	965	98.47
261	1	0.10	966	98.57
269	1	0.10	967	98.67
274	1	0.10	968	98.78
325	1	0.10	969	98.88
365	1	0.10	970	98.98
400	1	0.10	971	99.08
447	1	0.10	972	99.18
449	1	0.10	973	99.29
517	1	0.10	974	99.39
544	1	0.10	975	99.49
549	1	0.10	976	99.59
561	1	0.10	977	99.69
620	1	0.10	978	99.80
807	1	0.10	979	99.90
1031	1	0.10	980	100.00

Analysis Endpoints

Response Endpoint -- ADRS

Definition

– Best overall response (BOR) is defined as the best response recorded from the start of the trial, normally the date of randomization, until disease progression occurs, evidenced by either RECIST assessment or death, or the patient discontinues treatment.

– When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline.

– Protocols should be clear if post-treatment assessments are to be considered in determination of best overall response.

Confirmation

– Confirmation of **PR and CR** is required in non-randomized trials where response is the primary endpoint;

– Confirmation of response is not required in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints.

BOR and confirmation

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Time to Event -- ADDATES, ADTTE

Start Date

- PFS, OS, EFS, DFS:
  - the date of randomization;
  - the start date of therapy.
- DOR:
  - the date on which that subject achieves either CR or PR after the start of the study.

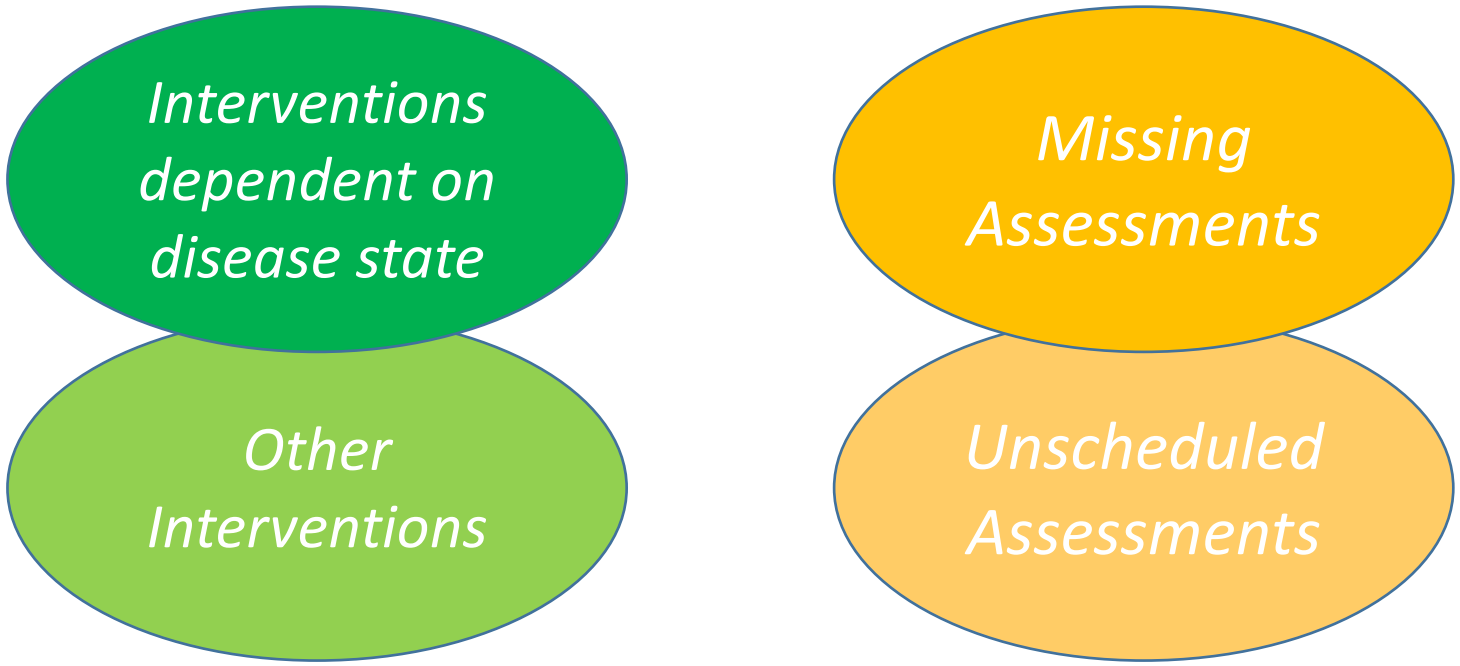
Date of Event

- PFS: date of PD or death without PD.
- OS: date of death.
- EFS: date of death or PD or some pre-defined complication(s) that precludes surgery.
- DFS: date of death or any further PD is detected.
- DOR: first date that recurrent or progressive disease .

Date of Censor

- PFS, DOR:
  - last radiological assessment prior to initiation of new anti-cancer therapy
  - last radiological assessment
  - last radiological assessment prior to PD
  - Day 1
  - analysis cutoff date.
- OS:
  - last known alive date.
  - analysis cutoff date.

Key Point for Analysis -- Special Consideration



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THANKS