

RECIST 1.1: Was bringt's? - Bringt's was ?

RECIST 1.1: Credits and Debits

A short review

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slides available at www.cesar.or.at



New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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Why do we need response criteria?

..... to assess the change in tumor burden for the clinical endpoints

- response
- time-to-progression
- progression-free-survival
- ...more?

.....to assess the effect of treatment

for the individual patient (reliably, standardized...)

in Phase II trials

as surrogate for overall survival



What happened in the year 2000?

3rd January:

The last "**Peanuts**" comic strip is created by **Charles Schulz**.



What had happened in the year 2000?

January 03:

The last "Peanuts" comic strip is created by Charles Schulz.

February 02:

J Natl Cancer Inst 2000;92:205–16

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

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What happened in the year 2008/2009?

RECIST version 1.0 Therasse et al. 2000: JNCI

RECIST version 1.1 Eisenhauer et al. 2009: EJC
January 2009 Special Issue (7 more papers)

RECIST Working Group

Database of 6500 patients with 18 000 lesions (data warehouse)

i.e. approx 3 lesions/pt on average

these data led to change from 10 to 5 target/lesions /pt and from
5 to 2 lesions/organ

announced already on 22 October 2008 by EORTC-NCI-AACR: a pdf of talk in [www](#)



Who wrote, who gave data and who commented?

clinic, industry, imaging

NCI, NCRN UK

EORTC

NCI CTG

Amgen, AstraZeneca, BMS,
Genentech,
Pfizer, RadPharm
Roche, Sanofi Aventis
BCURG, EORTC Erasmus

providing helpful comments on an earlier draft of these revised guidelines: Ohad Amit, Phil Murphy, Teri Crofts and Janet Begun, GlaxoSmithKline, USA; Laurence H. Baker, Southwest Oncology Group, USA; Karla Ballman, Mayo Clinic, USA; Charles Baum, Darrel Cohen, and Mary Ashford Collier, Pfizer, USA; Gary J. Becker, American Board of Radiology, Tucson, USA; Jean-Yves Blay, University Claude Pertrand, Lyon France; Renzo Canetta, Bristol-Myers Squibb, USA; David Chang, Amgen Inc., USA; Sandra Chica, Perceptive Informations Inc. (PAR-EXEL), USA; Martin Edelman, University of Maryland Greenbaum Cancer Centre, USA; Gwendolyn Fyfe, Genentech, USA; Bruce Giantonio, Eastern Cooperative Oncology Group, USA; Gary Gordon, Abbott Pharmaceuticals, USA; Ronald Gottlieb, Roswell Park Cancer Institute, USA; Simon Kao, University of Iowa College of Medicine, USA; Wasaburo Koizumi, Kitasato University, Japan; Alessandro Riva, Novartis Pharmaceuticals, USA; Wayne Rackhoff, Ortho Biotech Oncology Research and Development, USA; Nagahiro Saijo, President Japanese Society of Medical Oncology, Japan; Mitchell Schnall American College of Radiology Imaging Network, USA; Yoshik Shimamura, PAR-EXEL International Inc., Japan; Rajeshwari Sridhara, Centre for Drug Evaluation and Research, Food and Drug Administration, USA; Andrew Stone, Alan Barge, AstraZeneca, United Kingdom; Orhan Suleiman, Centre for Drug Evaluation and Research, Food and Drug Administration, USA; Daniel C. Sullivan, Duke University Medical Centre, USA; Masakazu Toi, Kyoto University, Japan; Cindy Welsh, Centre for Drug Evaluation and Research, Food and Drug Administration, USA.



What's New?

- **Measuring tumor burden:** rules revisited
 - e.g. definition of target CR based on sum of diameters and assessment of single lymph nodes
- **Lymph node assessment rules**
- **PD revisited**
 - definition of target PD based on relative and absolute changes
 - new definition of non-target PD
- **Need of confirmation:** relaxed for randomized studies
- **New lesions:**
 - Criteria for identification of new lesions using FDG-PET

What else?

- more criteria for measurement at baseline
- specification of methods of measurement
 - clinical caliper,ruler,photo,..
 - Xray but CT is preferred
 - CT „the best“
 - MRI acceptable in certain situations
 - US not
 - endoscopy/lapar. not
 - tumor markers not alone but CA-125, PSA allowed
 - cytology/histol. rarely

All changes summarized in a table which shows what is new

... lets look at details next....

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral Clinical: 20 mm Lymph node: not mentioned	CT 10 mm; delete reference to spiral scan Clinical: 10 mm (must be measurable with calipers) CT: >15 mm short axis for target >10- <15 mm for non-target <10 mm is non-pathological	Most scans used have 5 mm or less slice thickness. Clearer to give instruction based on slice interval if it is greater than 5 mm. Caliper measurement will make this reliable Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al. ¹⁵
Special considerations on lesion measurability	-	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al. ²⁰
Response criteria target disease	CR lymph node not mentioned PD 20% increase over smallest sum on study or new lesions	CR lymph nodes must be <10 mm short axis PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	In keeping with normal size of nodes Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	Schwartz et al. ¹⁵
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	

Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Frequently asked questions on these topics Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al. ²⁰
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al. ²¹
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		



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<u>Overall tumour burden</u>	10 lesions (5 per organ)	5 lesions (2 per organ)

10 or 5 or 3 lesions?

- Number of lesions
 - no appreciable loss of information from 10 to 5 lesions
 - 5 lesions less affected by random error than 3 lesions
 - for 1 or 2 lesions exists a higher proportion of discordance and differing ORRs
 - select largest, most reproducible target lesions

Lymph node assessment

- measure short axis
- add short axis length to sum

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<u>Response criteria non-target disease</u>	<p>'unequivocal progression' considered as PD</p>	<p>More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, <u>not a single lesion increase</u></p>
<u>New lesions</u>	<p>–</p>	<p>New section on New lesions</p>
<u>Overall response</u>	<p>Table integrated target and non-target lesions</p>	<p><u>Two tables: one integrating target and non-target and the other of non-target only</u></p>

PD

- requires still 20% increase but absolute increase of 5 mm minimum
- expanded definition of non-measurable disease
 - „unequivocal progression“
 - overall status of PD at that time which should stop therapy
 - overall increase should be substantial
 - modest increase is usually not sufficient

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<u>Reporting of response results</u>	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response
<u>Response in phase III trials</u>	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III

Confirmation

stances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

RECIST 1.1

- stays with one-dimensional and summing up of the lengths
- stays with former response categories and algorithms
 - to combine target and non-target
 - assess patients with non-target lesions only
-

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.

RECIST 1.1

- stays with one-dimensional and summing up of the lengths
- stays with former response categories and algorithms
 - to combine target and non-target
 - assess patients with non-target lesions only
- keeps the inconsistency between CR/PR and PD:
 - Response endpoint only possible when lesions measurable at baseline
 - Progression endpoints allow non-measurable lesions at baseline
- spends no efforts to
 - link response definition with evaluation of ORR
 - resolve dilemma with brain metastases not scanned at baseline
 - guide the selection of lesions --> unequivocal
 - discuss reference assessment and repeated measurement

RECIST 1.1 has deficits when

- target lesions can become non-measurable
 - likely disappeared size = 0 mm diameter
 - present but faintly seen size = 5 mm diameter
 - but some are measurable also below 5 mm
- non-target lesions are assessed
 - must not be measured even if measurable, but if not measured they are classified like non-measurable ones
 - their progression criterion remain vaguely; refuge taken in the term „unequivocal“

RECIST 1.1 has deficits when

- when missing values may cause bias
 - evaluation is allowed in some cases when a decision can be made even in absence of information
 - 3 lesions:1 unknown 2 highly progressive; the 2 progressive may overrule the unknown
 - bias is only excluded when one assumes that missing information happens at random
- when lymph nodes are among the target lesions
 -

Impact of lymph nodes on the response

- potentially larger impact of lymph nodes on the response when using the default cut-off size of 15 mm

- Example:

Baseline

1 non-nodal lesion: 17 mm
2 nodal lesions: 15 mm each

Sum: $17+15+15=47\text{mm}$

Time point of tumor assessment

1 non-nodal lesion: 22 mm
2 nodal lesions: „too low to measure“

Sum: $22+5+5=32\text{mm}$

This implies PR (30% decrease=>32.9mm) according to RECIST 1.1, even though ~ 30% increase (17 mm -->22 mm) in main target lesion

RECIST 1.1 leaves problems unsolved

- number of lesions assessed in patients often vary largely
- PFS assessment in case of non-measurable lesions
- new practices may be needed with new imaging techniques
- logistic problems with treatment schedules and schedules necessary to assess response /progression for PFS
- evaluation of non-cytotoxic drugs
- and statistical issues: e.g.
 - waterfall plot is not an endpoint but a descriptive statistical graphic
 - guidance for interval censored data when analyzing PFS

There is a some sort dilemma with RECIST:

The second paper in the Special EJC Issue Bogaerts et al. say in the abstract:

“Assessment of 5 lesions per patient led to a difference in best overall response assignment for an estimated 209 (3.2%) patients as compared to RECIST version 1.0. However, these changes did not affect the overall response rate. Progression-free survival was only minimally affected by measuring fewer lesions.”

BUT: If the validation of the new version is such that one wants show that by using the new criteria the resulting ORRs do not change, then why do we change the criteria?

Now RECIST 1.1 is out

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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... and RECIST 2.0 has been already mentioned.

Danke für Ihre Aufmerksamkeit
slides available at www.cesar.or.at





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.

