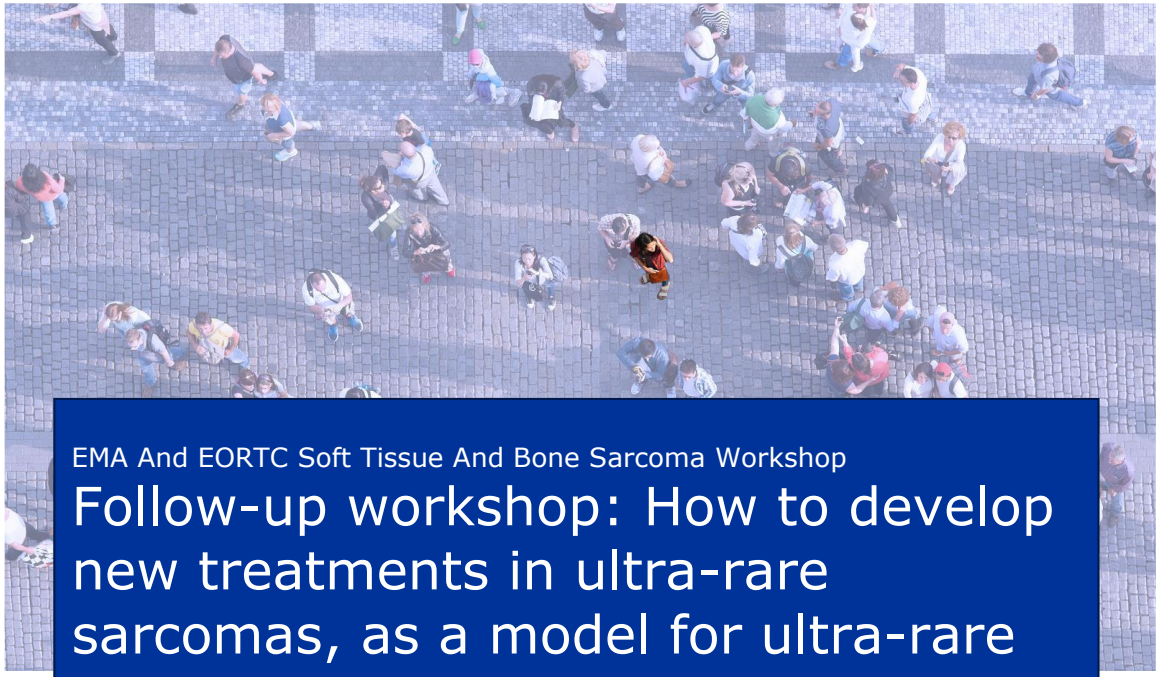


EMA And EORTC Soft Tissue And Bone Sarcoma Workshop

Follow-up workshop: How to develop new treatments in ultra-rare sarcomas, as a model for ultra-rare tumours?

24 May 2024

Developing new criteria for response assessment: Case example of epithelioid haemangioendothelioma

Lorenzo D'Ambrosio MD PhD
Department of Oncology
University of Turin
AOU San Luigi Gonzaga

COIs last 2 years

Advisory Board: PSI CRO Italy, GSK, AstraZeneca, Boehringer Ingelheim

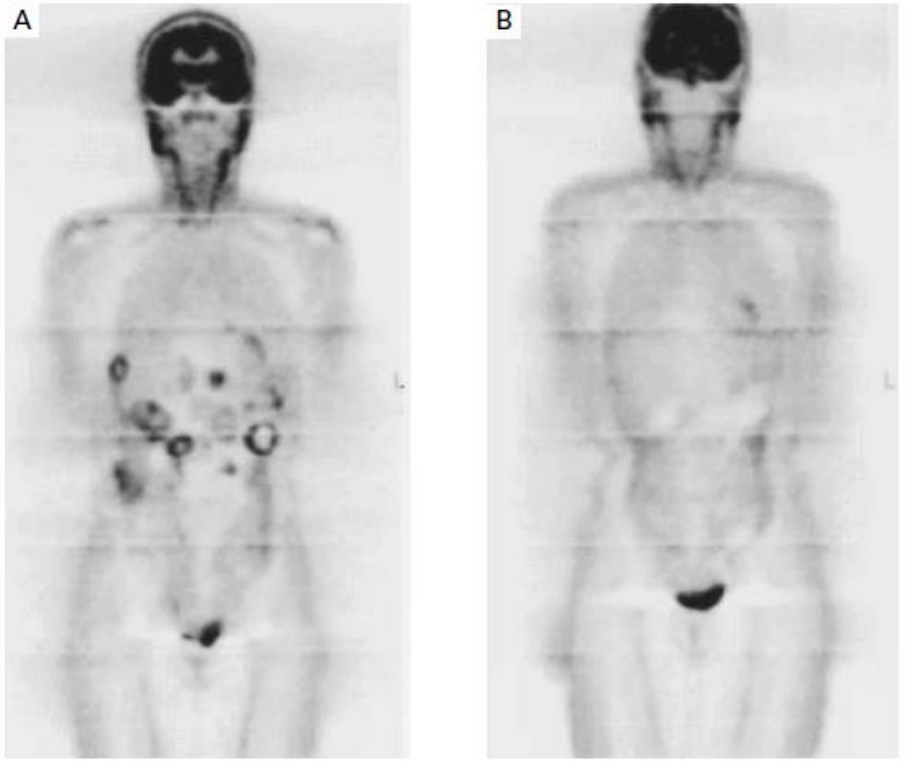
Meeting participation: GSK, AstraZeneca, PharmaMar, Amgen

The aim

Improve response assessment in rare tumors in which RECIST 1.1 criteria do not mirror clinical treatment effect and RCT are unfeasible

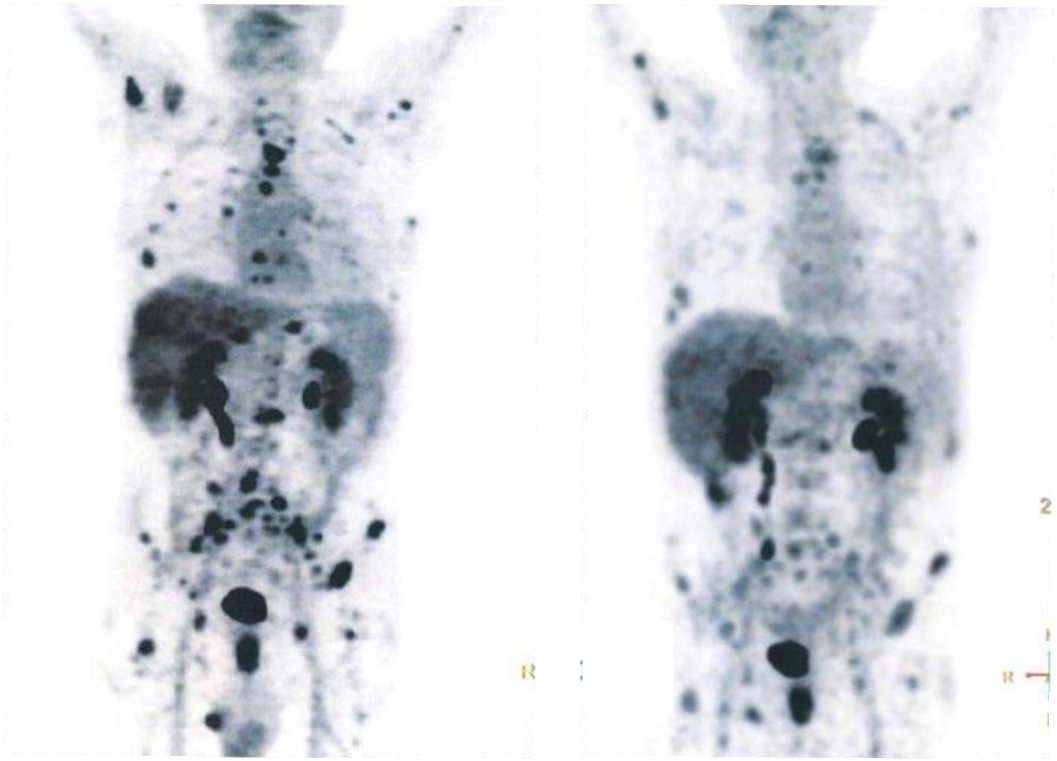
Is this drug active?

GIST patient «zero» treated with imatinib



baseline +4 weeks

EHE patient treated with off-label sirolimus



baseline +3 weeks

"It is the obvious that is so difficult to prove." George Bernard Shaw

Sirolimus in EHE

Original Article

Activity of Sirolimus in Patients With Progressive Epithelioid Hemangioendothelioma: A Case-Series Analysis Within the Italian Rare Cancer Network

Silvia Stacchiotti, MD [1]; Noemi Simeone, MD [1]; Salvatore Lo Vullo [2]; Giacomo G. Baldi, MD [3]; Antonella Brunello, MD [4]; Bruno Vincenzi, MD [5]; Elena Palassini, MD [1]; GianPaolo Dagrada, PhD [6]; Paola Collini, MD [6]; Carlo Morosi, MD [7]; Francesca G. Greco, MD [7]; Marta Sbaraglia, MD [8]; Angelo P. Dei Tos, MD [8,9]; Luigi Mariani, MD [2]; Anna Maria Frezza, MD [1]; and Paolo G. Casali, MD [1,2,3,4,5,6,7,8,9,10]

ORR (RECIST 1.1)	**4/37 (10.8%)**
PR+SD RECIST 1.1	**32/37 (86.5%)**
mPFS (months)	**13 (95%CI 3.7-NE)**
Clinical progression w/o RECIST progression	**3 (11%)**

Cancer February 15, 2021

RECIST 1.1 – still the standard

OPINION

RECIST — learning from the past to build the future

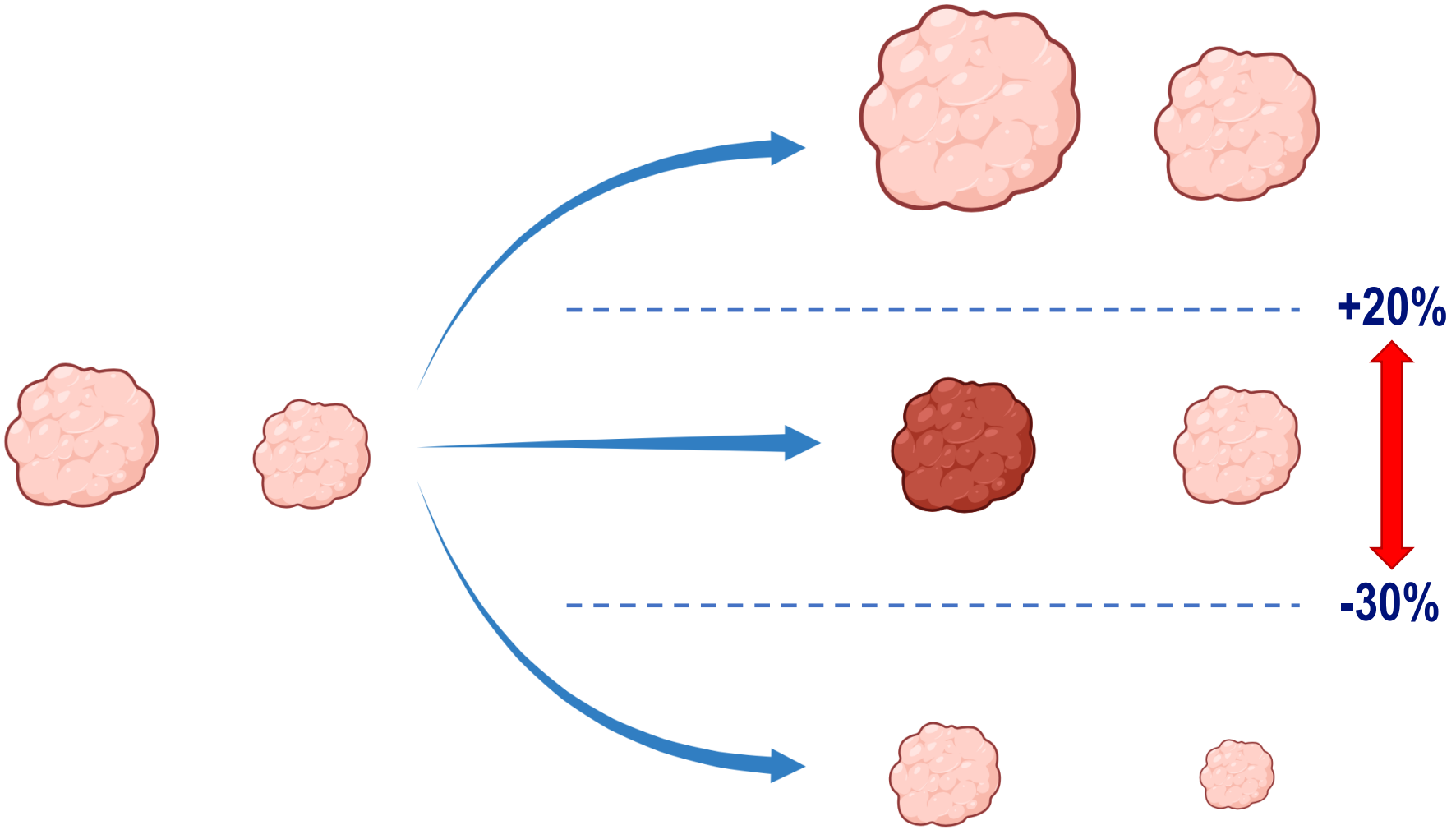
Saskia Litière, Sandra Collette, Elisabeth G. E. de Vries, Lesley Seymour and Jan Bogaerts

Table 1 | **Summary of major changes to RECIST 1.0** (REF. 2) **and 1.1** (REF. 3)

Parameter	WHO[1]	RECIST 1.0 (REF. 2)	RECIST 1.1 (REF. 3)	Comments
Measurements				
Method	Product of longest diameter and greatest perpendicular diameter	Longest diameter in axial plane	Longest diameter in axial plane Short axis for lymph nodes	• Comparisons between bi-dimensional and uni-dimensional methods showed minimal impact on response rate • Short axis for lymph nodes is most sensitive
Measurable lesion	No minimal size	• ≥10 mm spiral CT ≥20 mm non-spiral CT	CT: • 10 mm (when slice thickness is ≤5 mm); or • 2-fold slice thickness (when slice thickness is >5 mm) Lymph nodes: • ≥15 mm short axis for target • ≥10–<15 mm for non-target • <10 mm is non-pathological	• To update to more frequently used imaging methods and account for measurement error • To account for normal structure of lymph nodes
Response evaluation				
Number of lesions	No particular number specified	Max. ten lesions with max. of five per organ	Maximum five lesions with maximum of two per organ	Requires less time to assess, while showing minimal impact on outcome
Complete response (CR)	NA	Disappearance of all lesions; confirmed at 4 weeks	• Disappearance of all lesions • Lymph nodes must be <10 mm short axis	To account for normal structure of lymph nodes
Partial response (PR)	• ≥50% decrease in size of target lesions, without a 25% increase in any one target lesion • Confirmed at 4 weeks	• ≥30% decrease in the sum of the longest diameters of target lesions, with the baseline measurements taken as the reference • Confirmed at 4 weeks	≥30% decrease in the sum of the longest diameters of target lesions and short axis of target lymph nodes, with the baseline; measurements taken as the reference	Adjusted cut-off for unidimensional measurements
Stable disease (SD)	NA	Neither PR nor PD criteria are met	Neither PR nor PD criteria are met	NA
Progressive disease (PD)	• ≥25% increase in the size of any measurable lesion • Appearance of new lesions, or • Unequivocal progression of non-target lesions	• ≥20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum recorded, or • Appearance of one or more new lesions, or • Unequivocal progression of non-target lesions	• ≥20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum recorded AND absolute increase of at least 5 mm, or • Appearance of one or more new lesions, or • Unequivocal progression of non-target lesions	• Adjusted cut-off for unidimensional measurements • Correcting for measurement error that might lead to overcalling PD

NA, not applicable.

RECIST 1.1



RECIST 1.1 & Sons

Table 1. Comparison of imRECIST With RECIST v1.1 and irRC

Criterion	RECIST v1.1	irRC[6]	imRECIST*
Tumor burden	Unidimensional Up to five target lesions/two per organ	Bidimensional per WHO Up to 10 target lesions/ five per organ	Unidimensional, with other target lesion criteria (number, measurability) per RECIST v1.1
New lesions	Always represent PD	New lesions do not categorically define PD Measurable new lesions incorporated into the total tumor burden Nonmeasurable new lesions preclude CR	
Nontarget lesions	Can contribute to defining CR or PD (unequivocal progression)	Nontarget progression does not define PD Can only contribute to defining CR (complete disappearance required)	
PD	≥ 20% increase in the SLD (RECIST) and ≥ 5 mm increase compared with nadir, unequivocal progression in nontarget lesions, and/or appearance of new lesions	Determined only on the basis of measurable disease Negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented (lack of confirmation) ≥ 25% increase in the SLD compared with baseline/ nadir	≥ 20% increase in SLD (RECIST) compared with baseline/nadir
	Confirmation of PD not required	Best response may occur before confirmed PD	Best response may occur after any number of PD assessments

Abbreviations: CR, complete response; imRECIST, immune-modified RECIST; irRC, immune-related response criteria; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SLD, sum of longest diameters.
*imRECIST follows RECIST v1.1 conventions unless otherwise stated.

imRECIST

Table 3. Modified CT Response Evaluation Criteria

Response	Definition
CR	Disappearance of all lesions No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT No new lesions No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.[10]

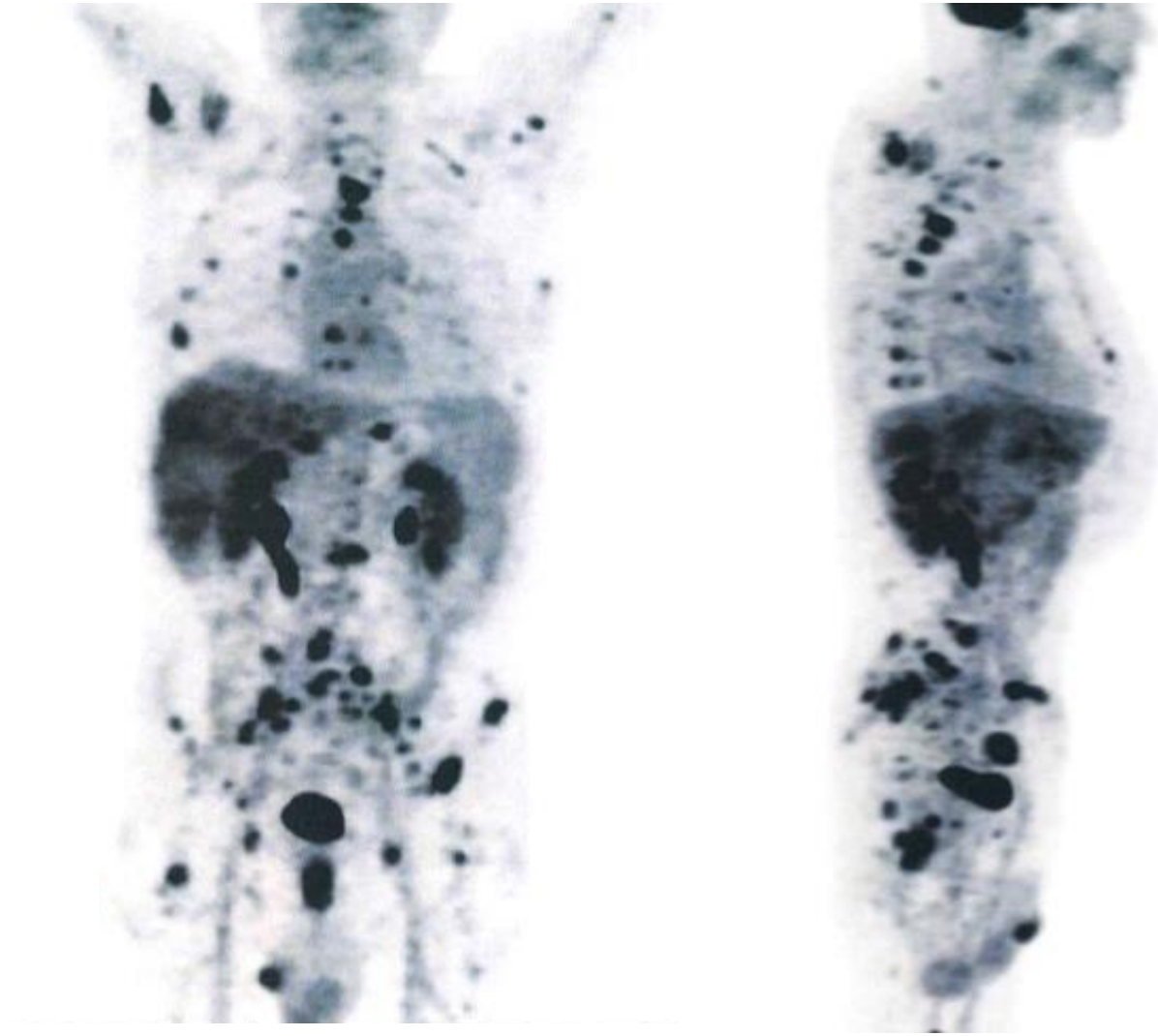
Choi criteria

PERCIST 1.0 Metabolic response	
Progressive metabolic disease (PMD)	**Increase of at least 30% in SULpeak and an absolute increase of 0.8SULpeak units or a new FDG avid lesion**
Stable metabolic disease (SMD)	**Response between PMR and PMD**
Partial metabolic response (PMR)	**Reduction of at least 30% in SUL peak and an absolute drop of at least 0.8 in SUL peak units**
Complete metabolic response (CMR)	**Complete resolution of FDG uptake within all lesions to a level less than or equal to mean liver activity**

PERCIST

Lancet Oncol 2017; 18: e143–52, J Clin Oncol 2007 May 1;25(13):1753-9; J Nucl Med. 2009 May;50 Suppl 1(Suppl 1):122S-50S

And now choose 5 target lesions…



The challenge of response assessment in STS

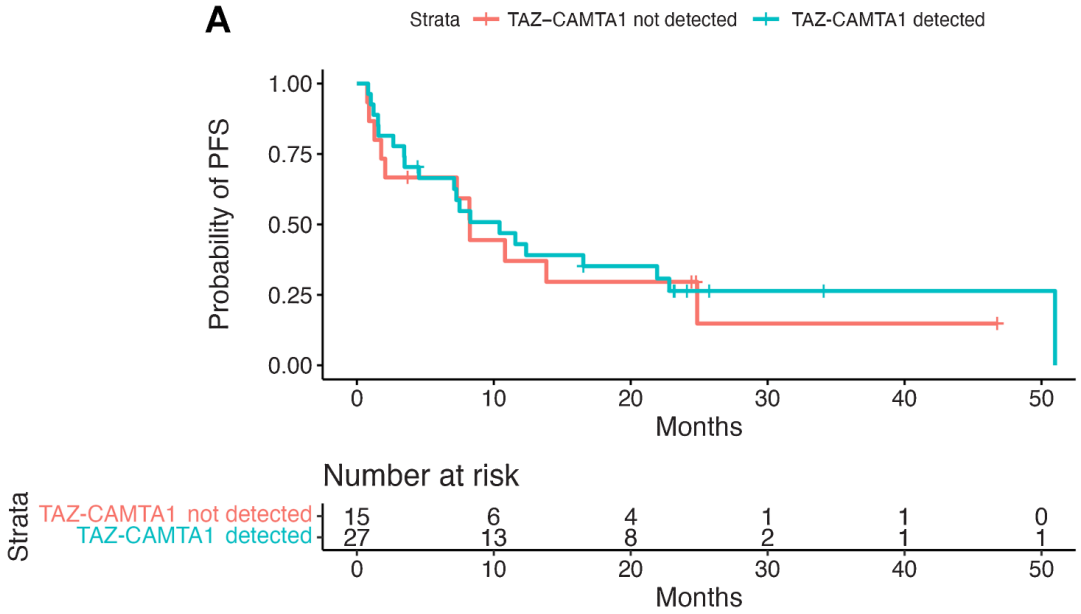
- Sarcomas may not shrink
- Sarcomas can become fibrotic, cystic, or myxoid without substantial changes in overall size
- Inaccurate response definitions may partially explain why prognostic factors for response and survival are still different and to be improved

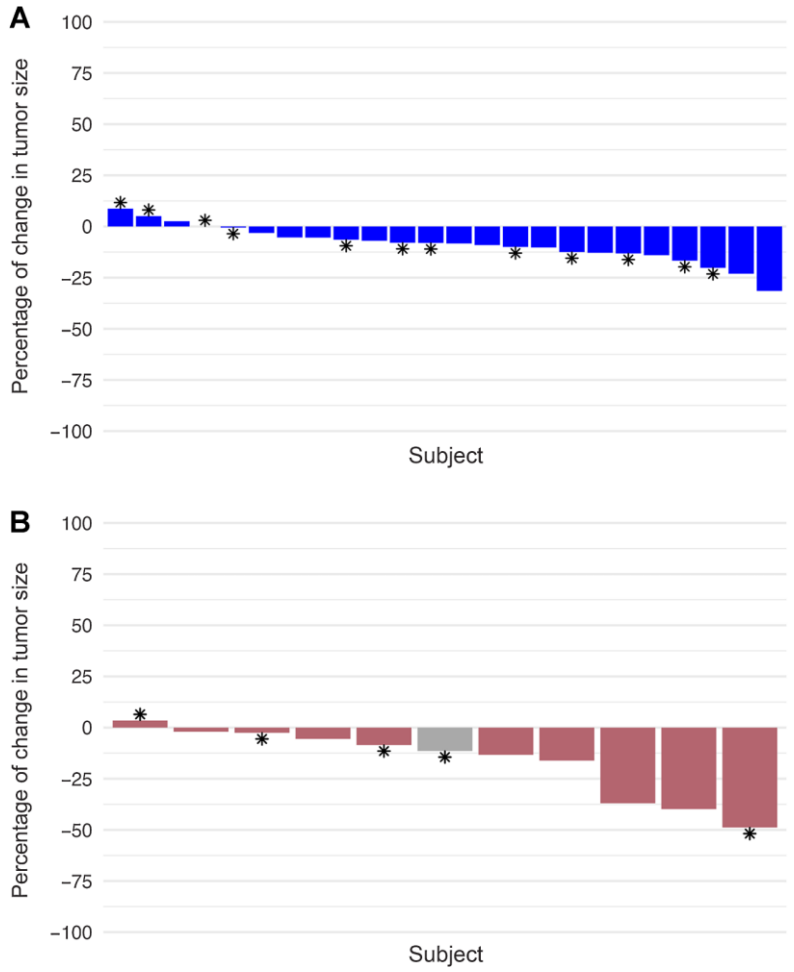
The challenge of response assessment in EHE

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

A Single-Arm Phase 2 Trial of Trametinib in Patients with Locally Advanced or Metastatic Epithelioid Hemangioendothelioma

Scott M. Schuetze[1], Karla V. Ballman[2], Rachel Heise[3], Kristen N. Ganjoo[4], Elizabeth J. Davis[5], Suzanne George[6], Melissa A. Burgess[7], Edwin Choy[8], Dale R. Shepard[9], Gabriel Tinoco[10], Angela Hirbe[11], Ciara M. Kelly[12], Steven Attia[13], Hari A. Deshpande[14], Gary K. Schwartz[15], Brittany L. Siontis[2], Richard F. Riedel[16], Margaret von Mehren[17], Erin Kozlowski[18], Helen X. Chen[19], Caroline Astbury[9], and Brian P. Rubin[9]





Clin Cancer Res 2024

To shrink or not to shrink? Lessons from GISTs

VOLUME 27 · NUMBER 24 · AUGUST 20 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Absence of Progression As Assessed by Response Evaluation Criteria in Solid Tumors Predicts Survival in Advanced GI Stromal Tumors Treated With Imatinib Mesylate: The Intergroup EORTC-ISG-AGITG Phase III Trial

Axel Le Cesne, Martine Van Glabbeke, Jaap Verweij, Paolo G. Casali, Michael Findlay, Peter Reichardt,

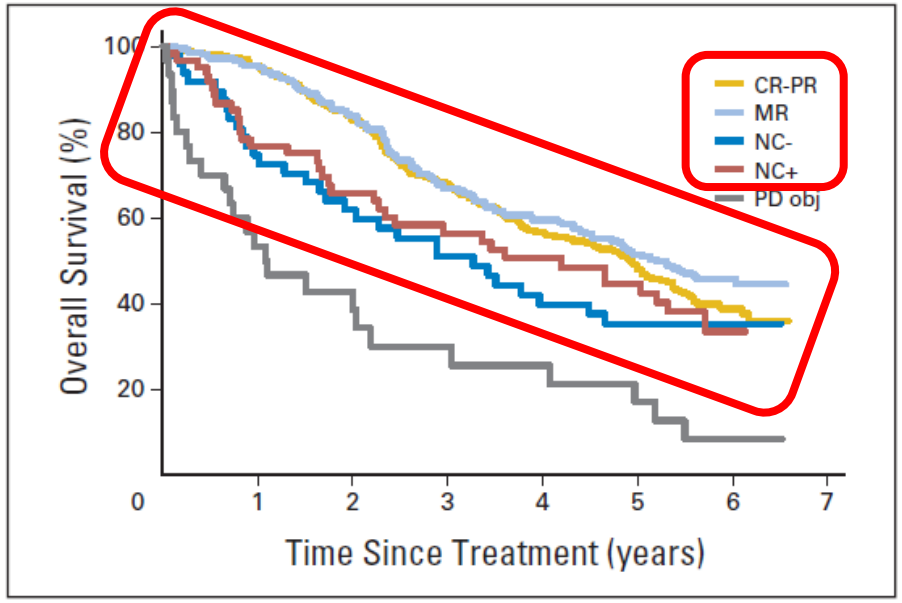


Fig 1. Overall survival according to response at 4 months of treatment with imatinib. CR, complete response; PR, partial response; MR, minor response; NC−, no change (0% to 10% reduction); NC+, no change (0% to 20% size increase); PD obj, objective progressive disease.

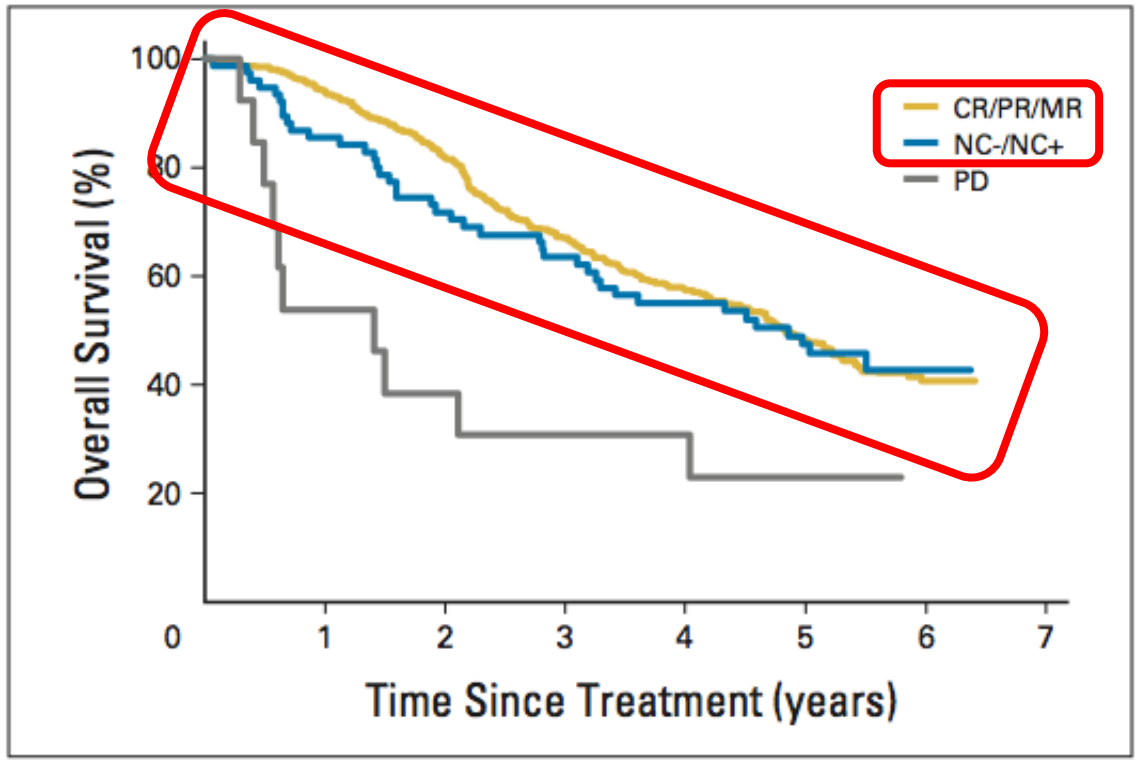
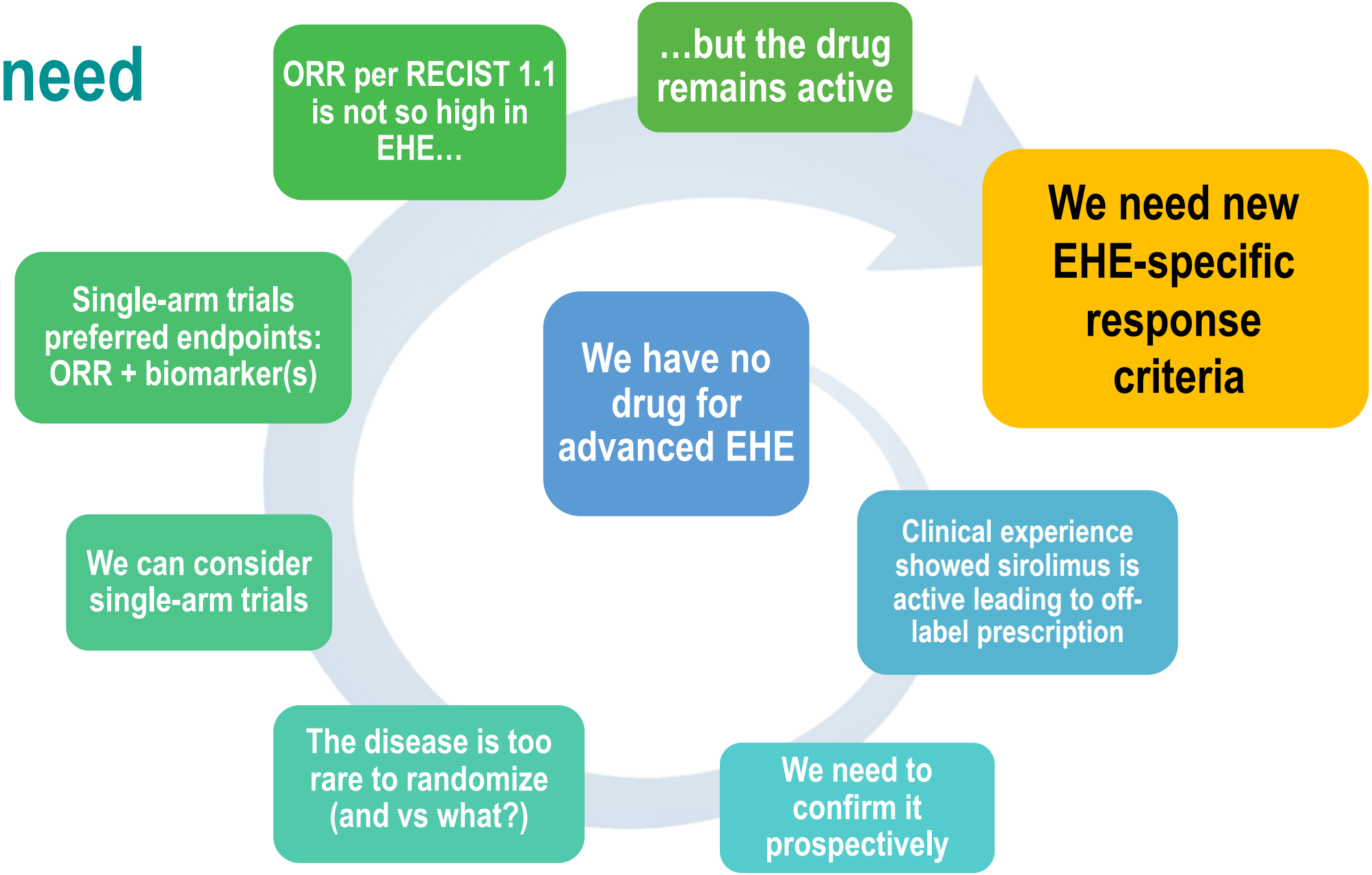


Fig 3. Overall survival according to grouped categories of response at 6 months of imatinib. CR, complete response; PR, partial response; MR, minor response; NC−, no change (0% to 10% reduction); NC+, no change (0% to 20% size increase); PD, progressive disease.

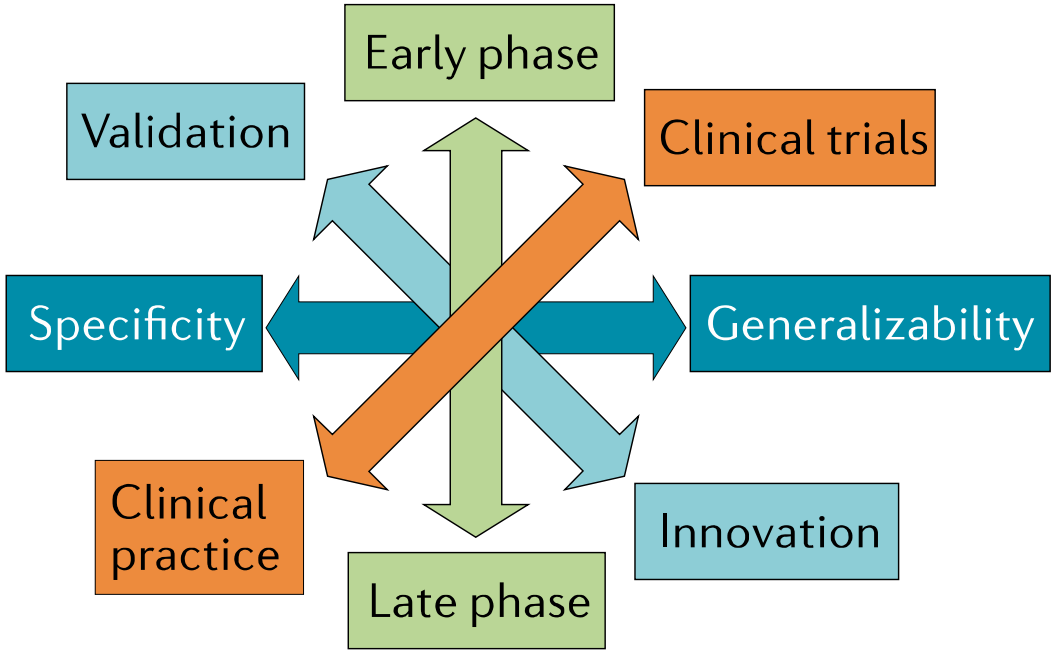
The need


ORR per RECIST 1.1 is not so high in EHE…
…but the drug remains active
We need new EHE-specific response criteria
Clinical experience showed sirolimus is active leading to off-label prescription
We need to confirm it prospectively
The disease is too rare to randomize (and vs what?)
We can consider single-arm trials
Single-arm trials preferred endpoints: ORR + biomarker(s)
We have no drug for advanced EHE

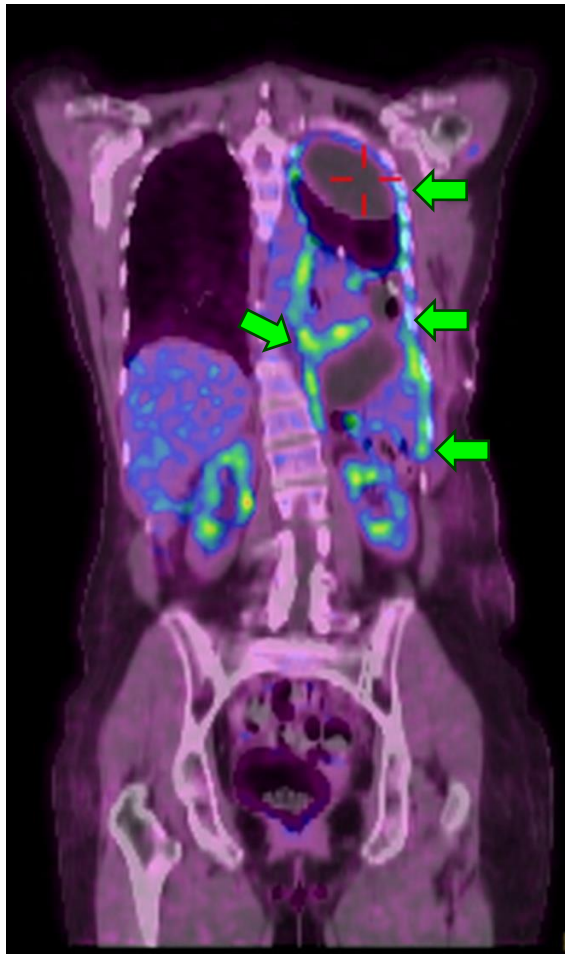
Challenges in introducing new response criteria

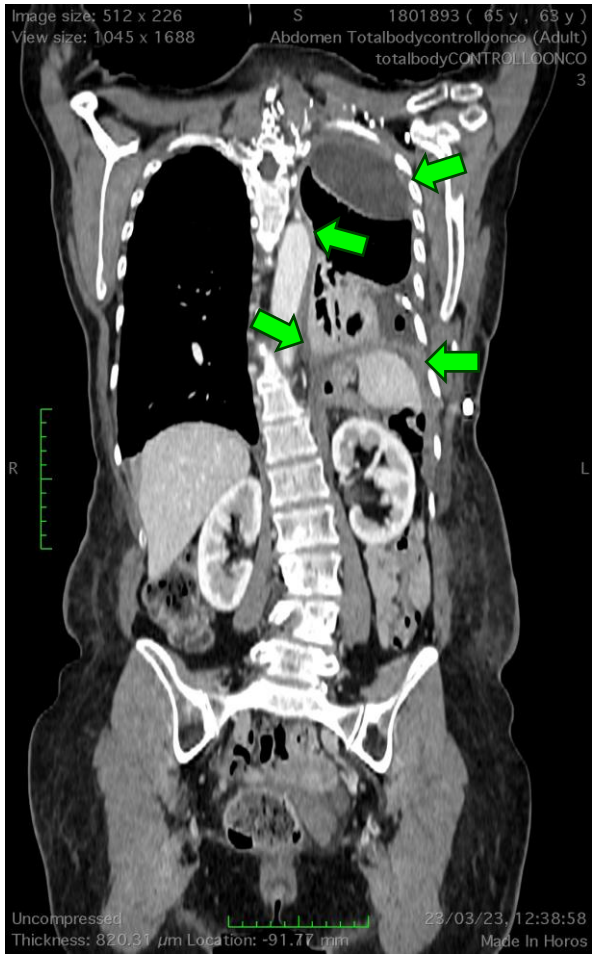
Box 1 | **End point validation criteria**

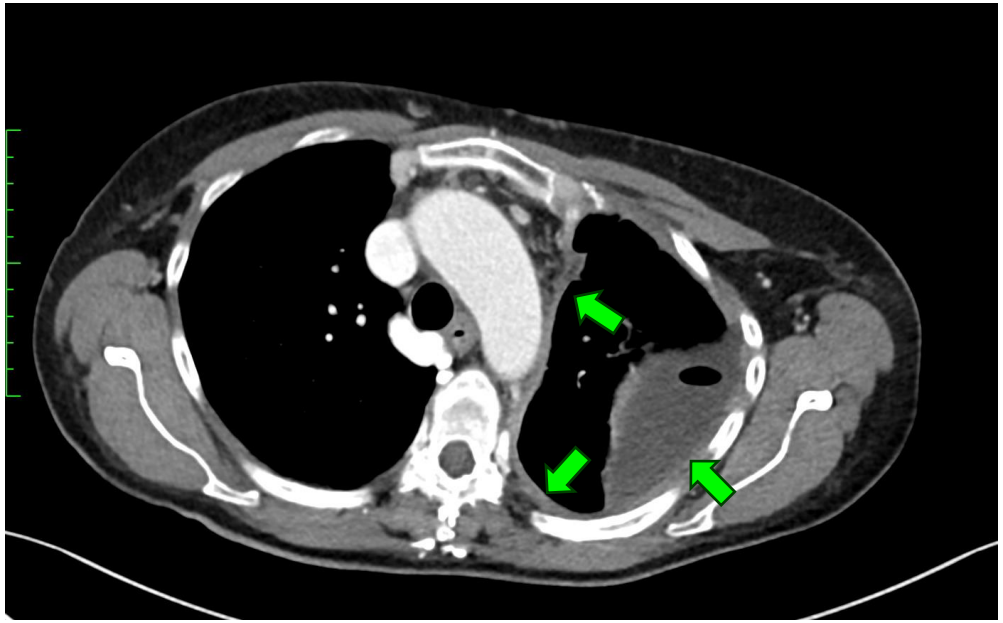
- Sound biological rationale
- Standardized protocol for interpreting measurements
- Understanding of the limitations associated with end point
- Evidence of correlation with a true patient-benefit end point



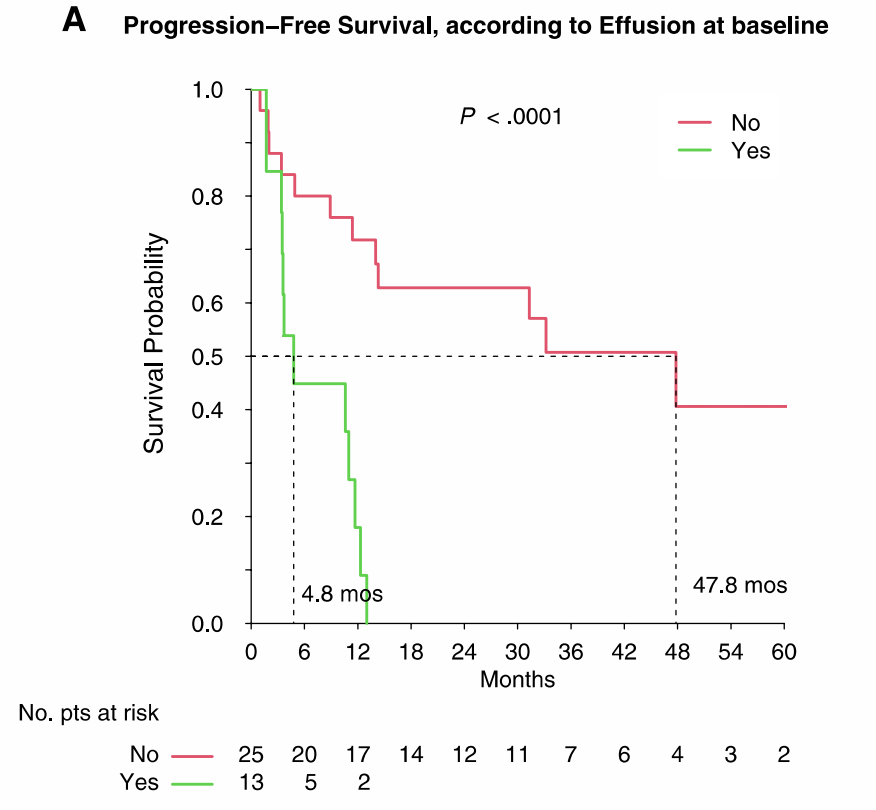
How to measure this disease?







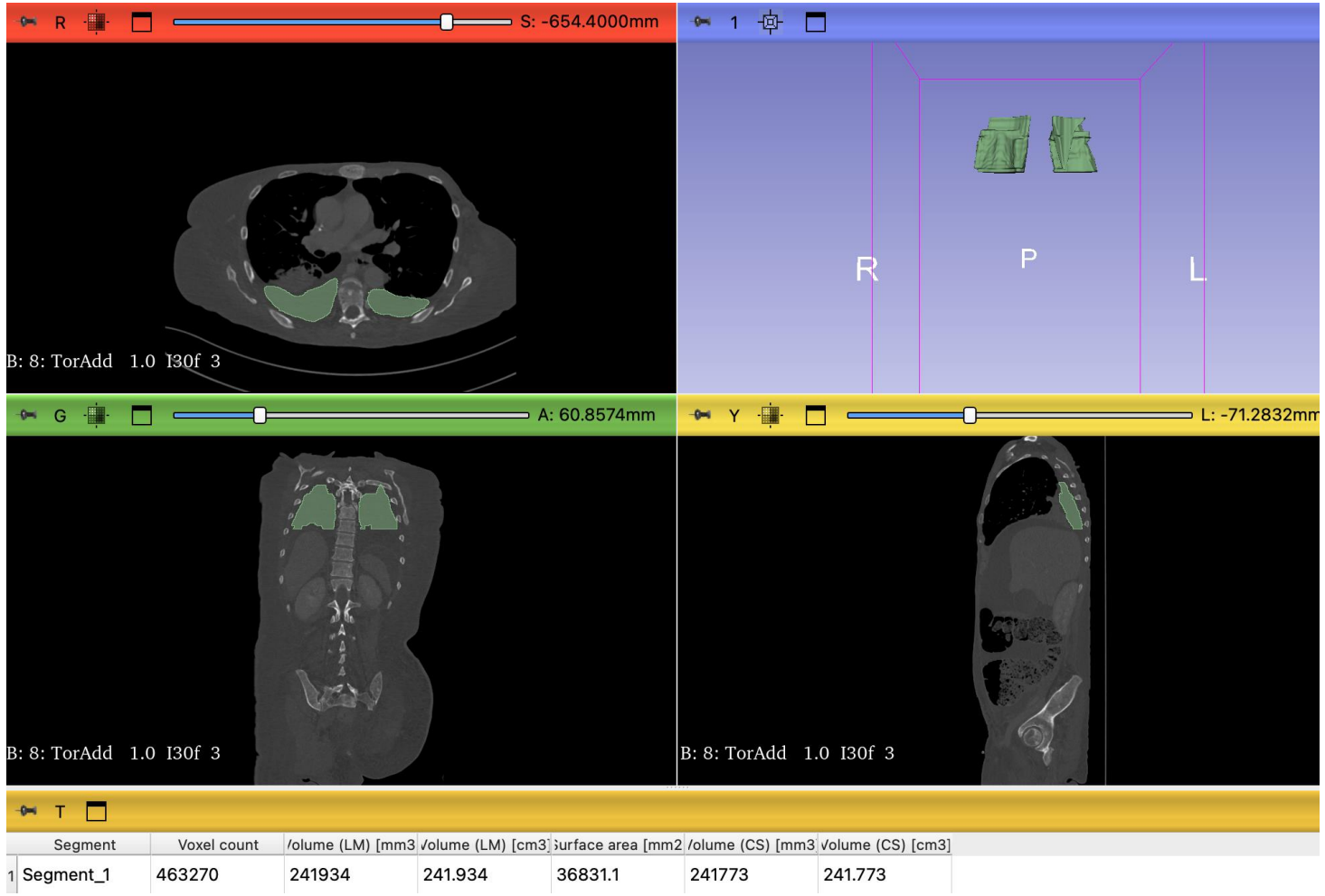
Serosal effusion in EHE



	Overall (38 pts)	No serosal effusion	Serosal effusion
ORR (RECIST 1.1)	10.8	16%	0%
mPFS (months)	13	47.8	4.8

Stacchiotti S, et al. Cancer. 2021 Feb 15;127(4):569–76.

Quantification of pleural effusion



	Segment	Voxel count	/olume (LM) [mm3	/olume (LM) [cm3]	urface area [mm2	/olume (CS) [mm3	/olume (CS) [cm3]
1	Segment_1	463270	241934	241.934	36831.1	241773	241.773

Courtesy of A. Vanzulli, C. Morosi

RESCORe CRITERIA

RESCORe Complete response (CR)

RECIST 1.1 for CR are satisfied and no pleural/peritoneal involvement (defined as either focal/diffuse serosal layers thickening, effusion or both) is observed (or has completely resolved if previously present).

RESCORe Partial response (PR)

RECIST 1.1 for PR are satisfied and no new pleural/peritoneal involvement (defined as either focal/diffuse serosal layers thickening or effusion) has appeared and existing effusion (if present) has not increased ≥ 40% at volumetric assessment and serosal localizations - if detectable - did not show unequivocal numerical and/or dimensional increase.
PR category is also assigned in case of a decrease in the SLD of target lesions per RECIST 1.1 10% < x < 30% and serosal effusion has reduced ≥ 66% at volumetric assessment and serosal localizations - if detectable - did not show unequivocal numerical and/or dimensional increase.

RESCORe CRITERIA

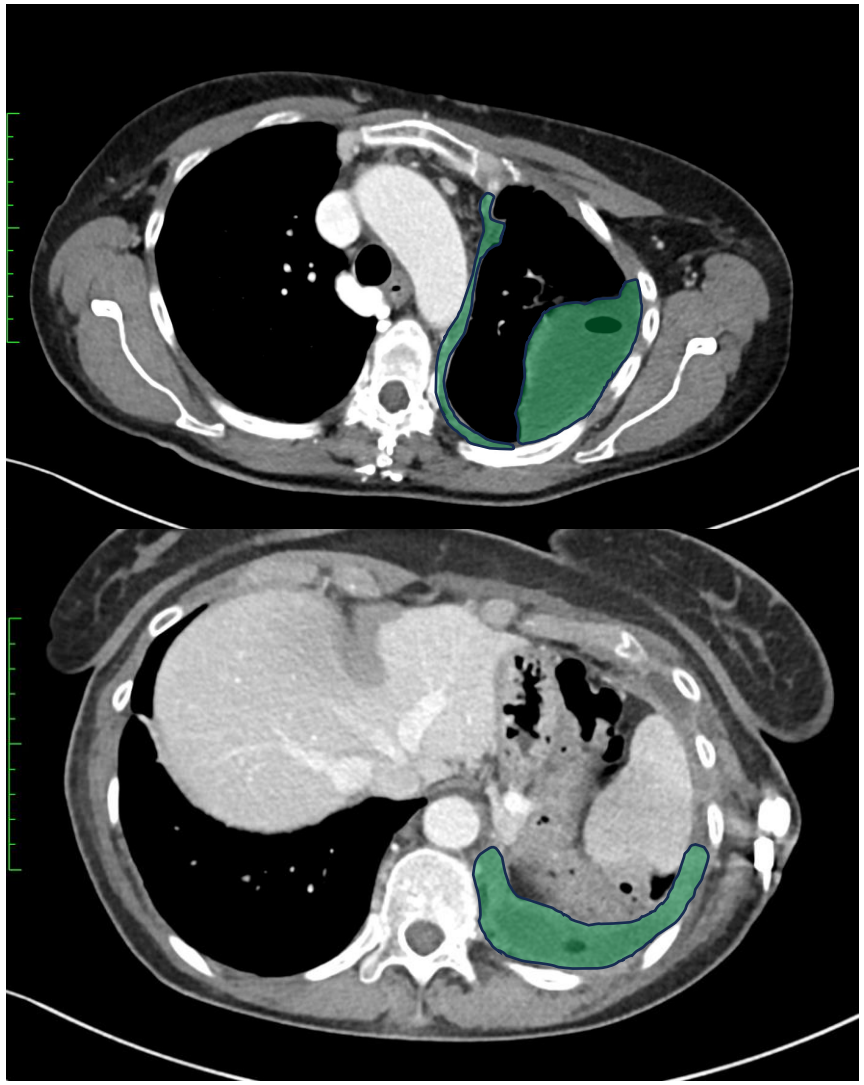
RESCORe Stable disease (SD)

assigned if RECIST 1.1 for SD are satisfied and no new pleural/peritoneal involvement (defined as either focal/diffuse serosal layers thickening or effusion) has appeared and serosal effusion has not modified beyond thresholds specified for PR and PD and serosal layers localizations did not show unequivocal numerical and/or dimensional increase.

RESCORe Progressive Disease (PD)

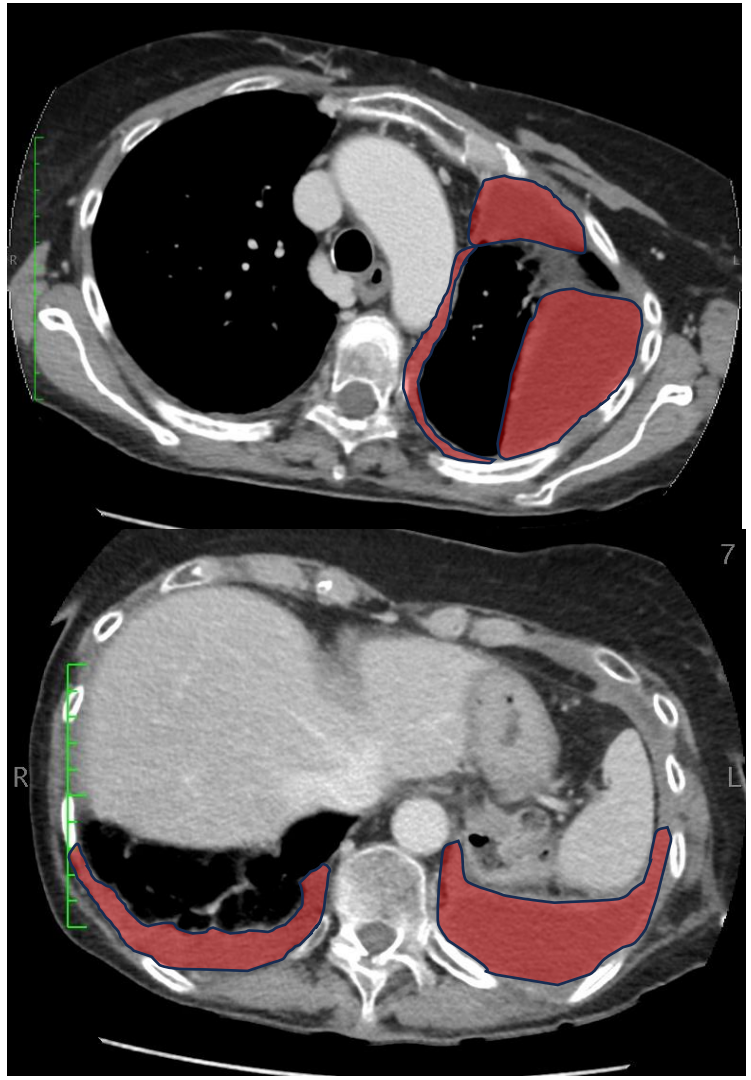
assigned if RECIST 1.1 for PD are satisfied or new pleural/peritoneal involvement (defined as either focal/diffuse serosal layers thickening or effusion) appears or existing effusion (if present) has increased ≥ 40% at volumetric assessment or serosal layers localizations - if detectable - showed unequivocal numerical and/or dimensional increase.

RECIST SD vs RESCORe PD



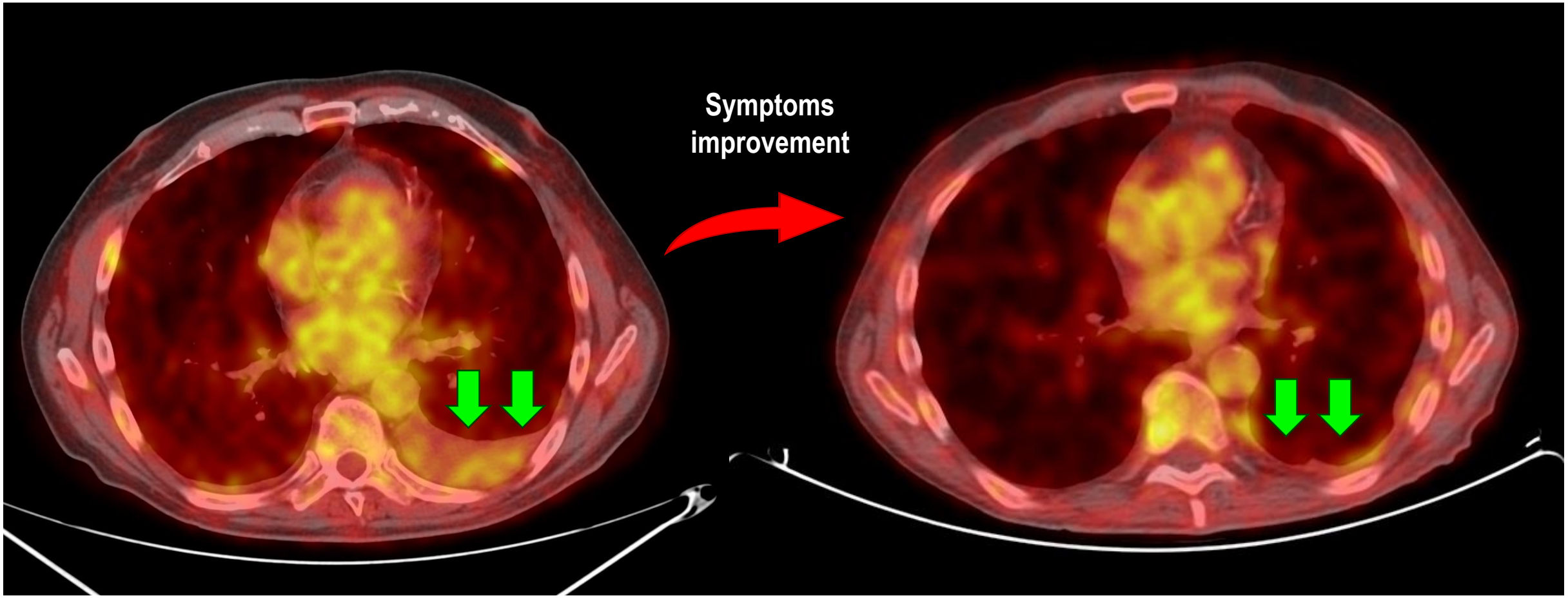
baseline

symptoms worsening

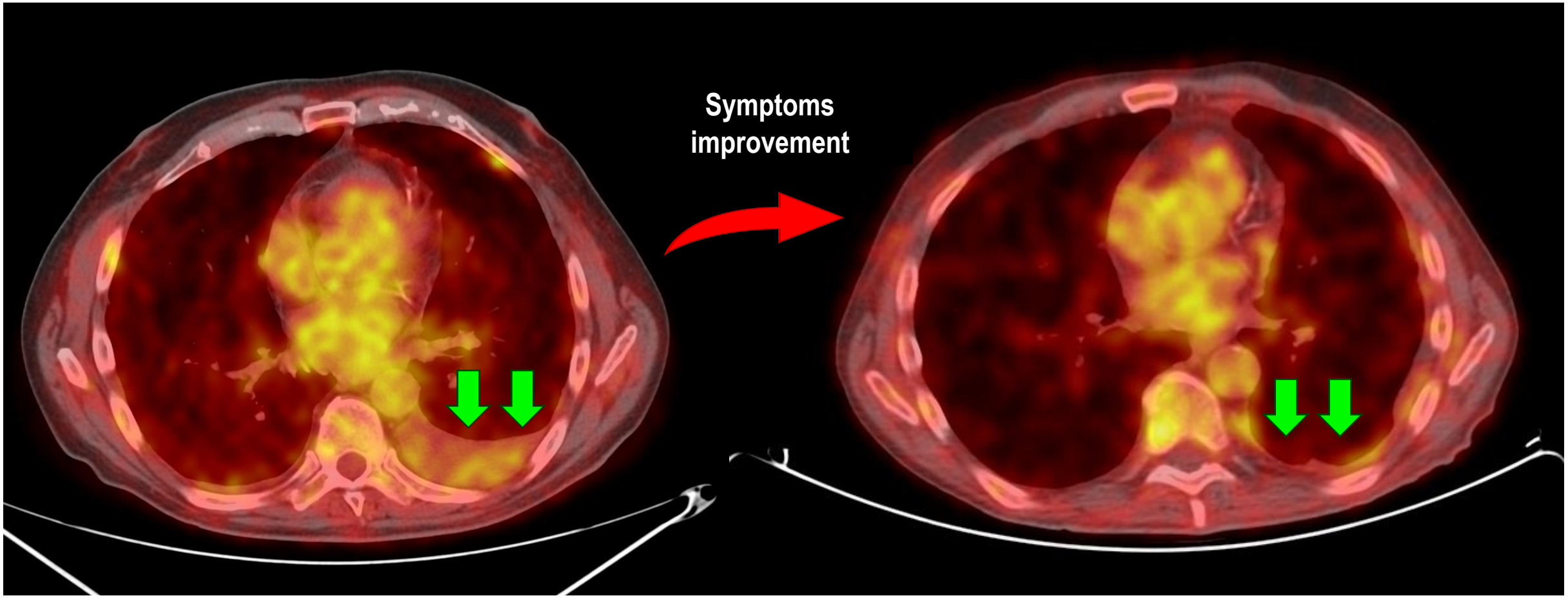


+4 months

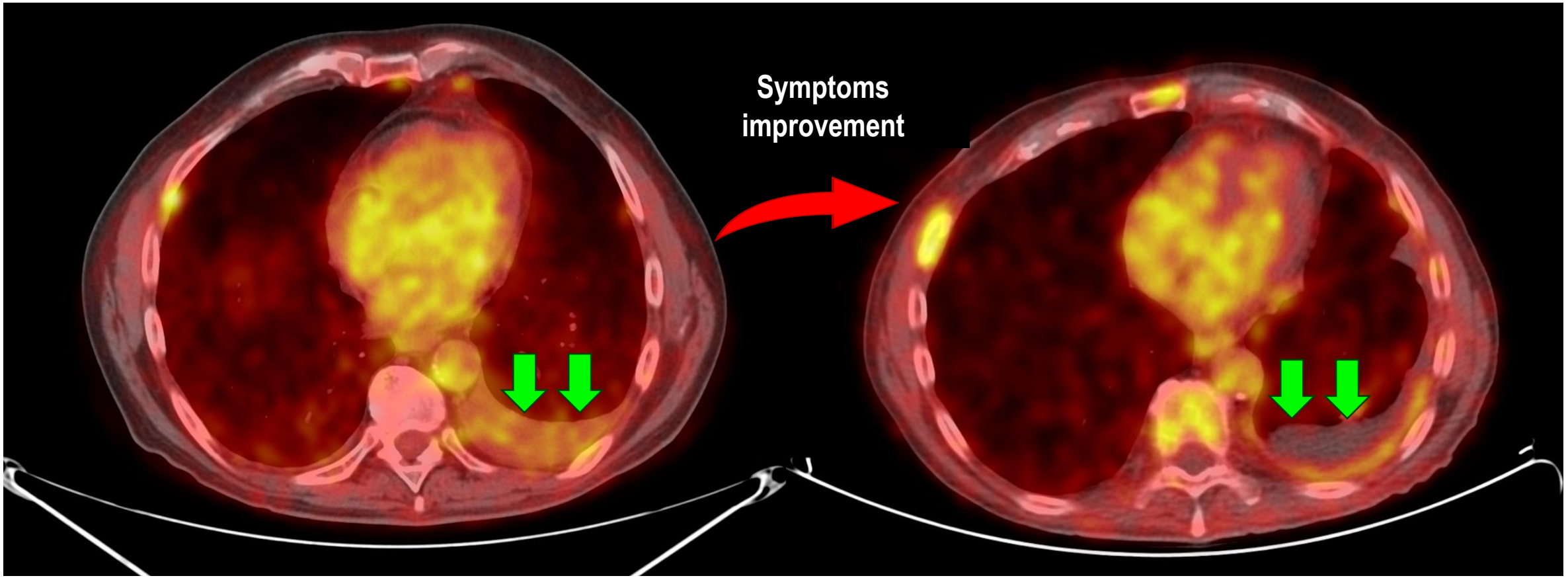
RECIST SD vs RESCORe PR



RECIST SD vs RESCORe PR



RECIST SD vs RESCORe PR



baseline

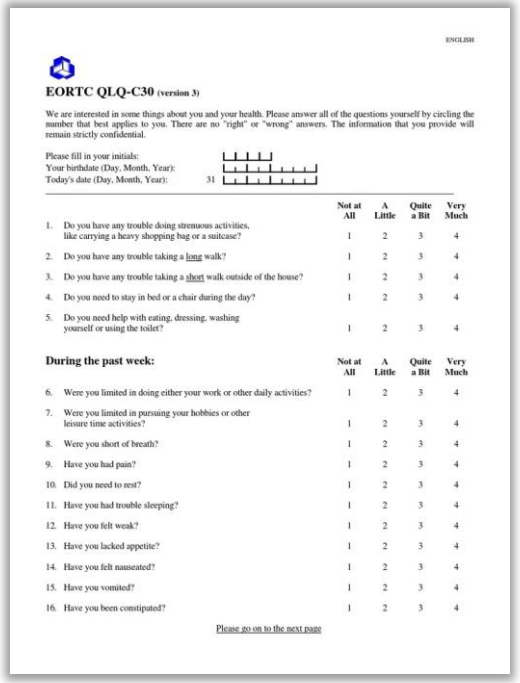
+3 weeks

RESCORe PAIN CRITERIA

WPI = Worst Pain Intensity

Complete response (CR)	WPI=0 with no more than a 10% increase in opioid/NSAID daily dose
Partial response (PR)	At least a 30% decrease in WPI with no more than a 10% increase in opioid/NSAID daily dose, and/or at least a 30% reduction in opioid/NSAID daily dose with no more than a 1-point increase in WPI
Stable Disease (SD)	WPI and/or opioid/NSAID daily dose variations that do not meet PR or PD criteria
Progressive Disease (PD)	At least a 30% increase in WPI with no more than a 10% reduction in opioid/NSAID daily dose, and/or at least a 30% increase in opioid/NSAID daily dose with no more than a 1-point reduction in WPI and/or the development of new disease related pain with a WPI more than 4

RESCORe QoL



ENGLISH

EORTC QLQ-C30 (version 3)

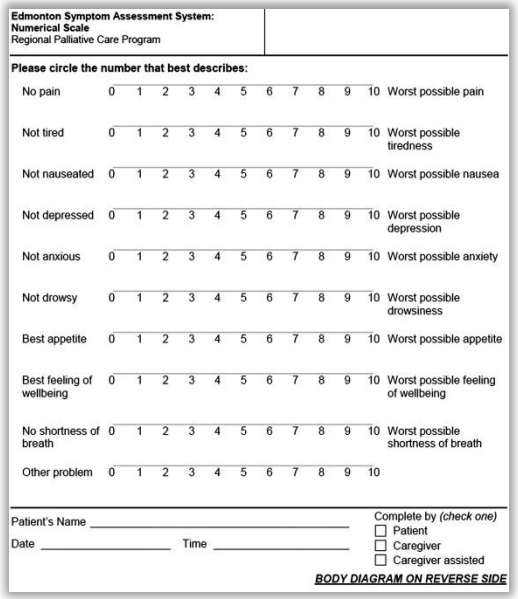
We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

EORTC QLQ-C30



Edmonton Symptom Assessment System:
Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Patient's Name _____
Date _____ Time _____

Complete by *(check one)*
☐ Patient
☐ Caregiver
☐ Caregiver assisted

BODY DIAGRAM ON REVERSE SIDE

ESAS-r

+

EORTC Quality of Life Group

THE EHE FOUNDATION

New EHE-specific QoL

RESCORe

Box 1 | **End point validation criteria**

- Sound biological rationale
- Standardized protocol for interpreting measurements
- Understanding of the limitations associated with end point
- Evidence of correlation with a true patient-benefit end point

Question to EMA

Are RESCORe criteria acceptable for EMA/FDA to evaluate drug activity in EHE?

Can we schedule regular meetings / scientific advice to discuss new response assessment criteria in ultra-rare tumors whenever RECIST 1.1 are not adequate?

Thanks!

Questions?