The basis of RECIST 1.1

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I have no conflicts of interest

In WHO criteria (1979)

- **Assessment of response is based on % change (from baseline) in sum of products of target lesions**

- **Increase in any individual target lesion results in progression**

> The use of a 25% increase in one or more measurable lesions or appearance of a new lesion is recommended for defining progression of disease. This percentage should not necessarily be regarded as influencing the management of the patient.

From '80 to 2000

- **Researchers made their own adjustments and versions: variations of the WHO criteria**
- **Fast forward to 2000**
    - **Response Evaluation Criteria in Solid Tumors (=RECIST "v 1.0", Therasse et al., JNCI 2000)**
    - **Next slide was used by E. Eisenhauer in 2009, Geneva**

Response Evaluation Criteria in Solid Tumors (RECIST)
Therasse et al JNCI 2000

- Intended for use in clinical trials with <u>primary endpoint of objective response</u>

- Measurable lesion >= 20 mm (10 if spiral CT)

- Unidimensional assessment: Tumor burden assessed by summing longest diameters of all measurable lesions up to 10 (5 per organ)

- Four categories of response: CR*, PR*, SD, PD

- RECIST widely adopted by cooperative groups, industry, academia

* Required confirmation

From 2004 onwards

- **Work was started to adjust the criteria**
- **Resulted in RECIST version 1.1 published in European Journal of Cancer 2009**
- **This time, revisions of the criteria were evaluated in a database of**
  - **16 clinical trials containing**
  - **detailed tumor assessments of > 6500 patients,**
  - **totaling > 18000 lesions**

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Issues since 2000

- RECIST Working Group committed to revisiting/updating criteria

- Several issues identified:

  - 10 lesions needed?

  - Confirmation needed?

  - Use in randomized trials with progression endpoint: how to assess PD in patients with non-measurable disease?

  - Lymph node assessment?

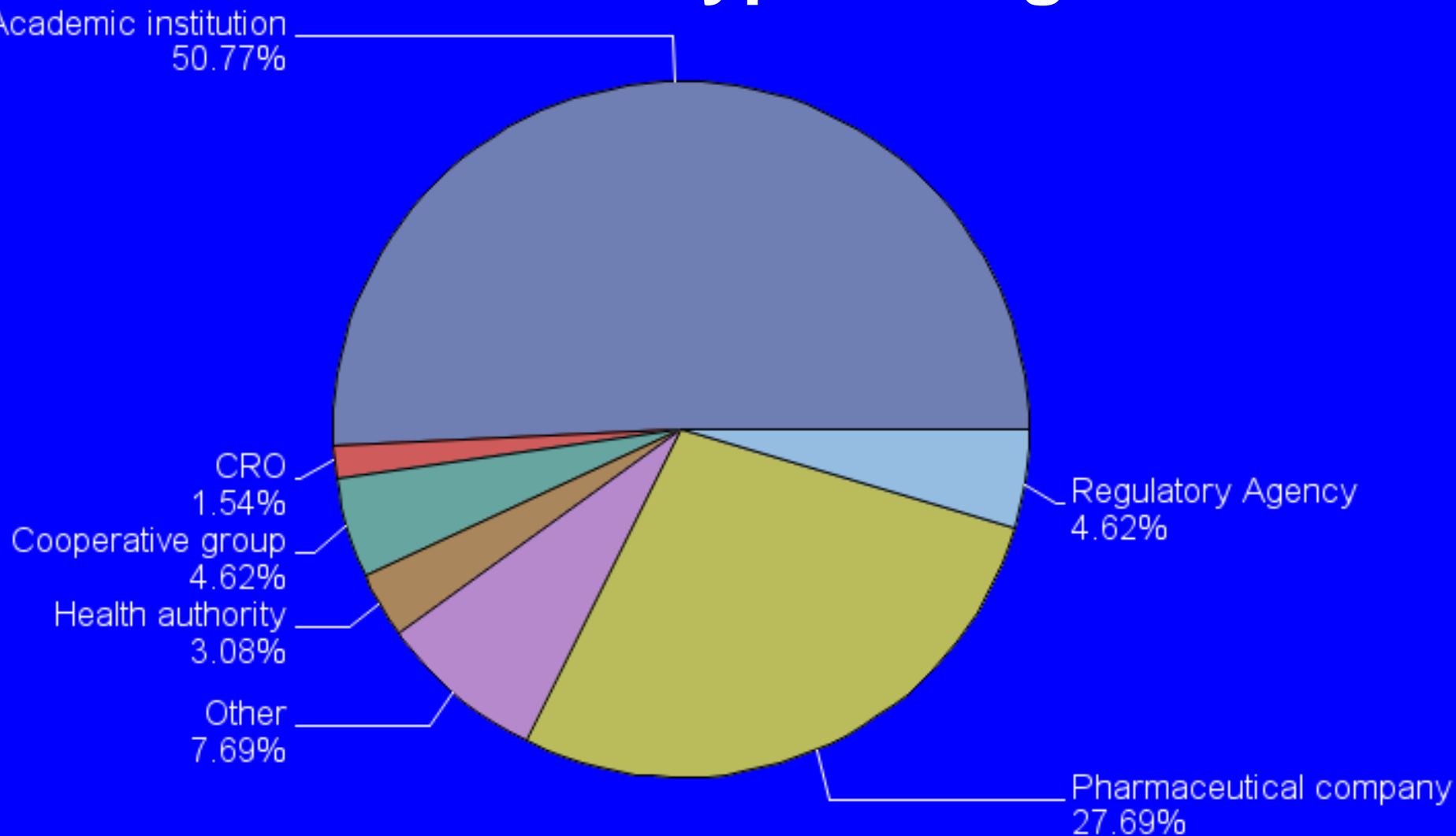 - Functional instead of anatomical imaging?

Summary:
What HAS changed in RECIST 1.1

	RECIST 1.0	RECIST 1.1
Measuring tumor burden	10 targets 5 per organ	For response: 5 targets (2 per organ)
Lymph node	Measure long axis as for other lesions. Silent on normal size	Measure short axis. Define normal size.
Progression definition	20% increase in sum	20% increase and at least 5 mm absolute increase
Non-measurable disease PD	"must be unequivocal"	Expanded definition to convey impact on overall burden of disease. Examples.
Confirmation	required	Required when response primary endpoint—but not PFS
New lesions	--	New section which includes comment on FDG PET interpretation

Background of survey participants (run up to end august 2012)

Country of participant	Total = 65
	N (%)
Country	
Austria	1 (1.5)
Belgium	5 (7.6)
Canada	2 (3.0)
France	5 (7.6)
Germany	1 (1.5)
Italy	1 (1.5)
Japan	1 (1.5)
Poland	1 (1.5)
Spain	1 (1.5)
Switzerland	2 (3.0)
The Netherlands	3 (4.5)
U.S.A.	32 (48.5)
United Kingdom	10 (15.2)

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Type of organisation

Academic institution 50.77%

Regulatory Agency 4.62%

Pharmaceutical company 27.69%

Other 7.69%

Health authority 3.08%

Cooperative group 4.62%

CRO 1.54%

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Function

Other: specify
Imaging Scientists (2)
Radiation Oncologist (3)
Imaging Advisor
Medical Physicist
Regulator
Surgical oncologist
Clinician
Head Translational medicine
Trials review and analysis

Medical Oncologist 45.31%
Statistician 23.44%
Radiologist 9.38%
Other 18.75%
Nuclear Medicine Physician 3.13%

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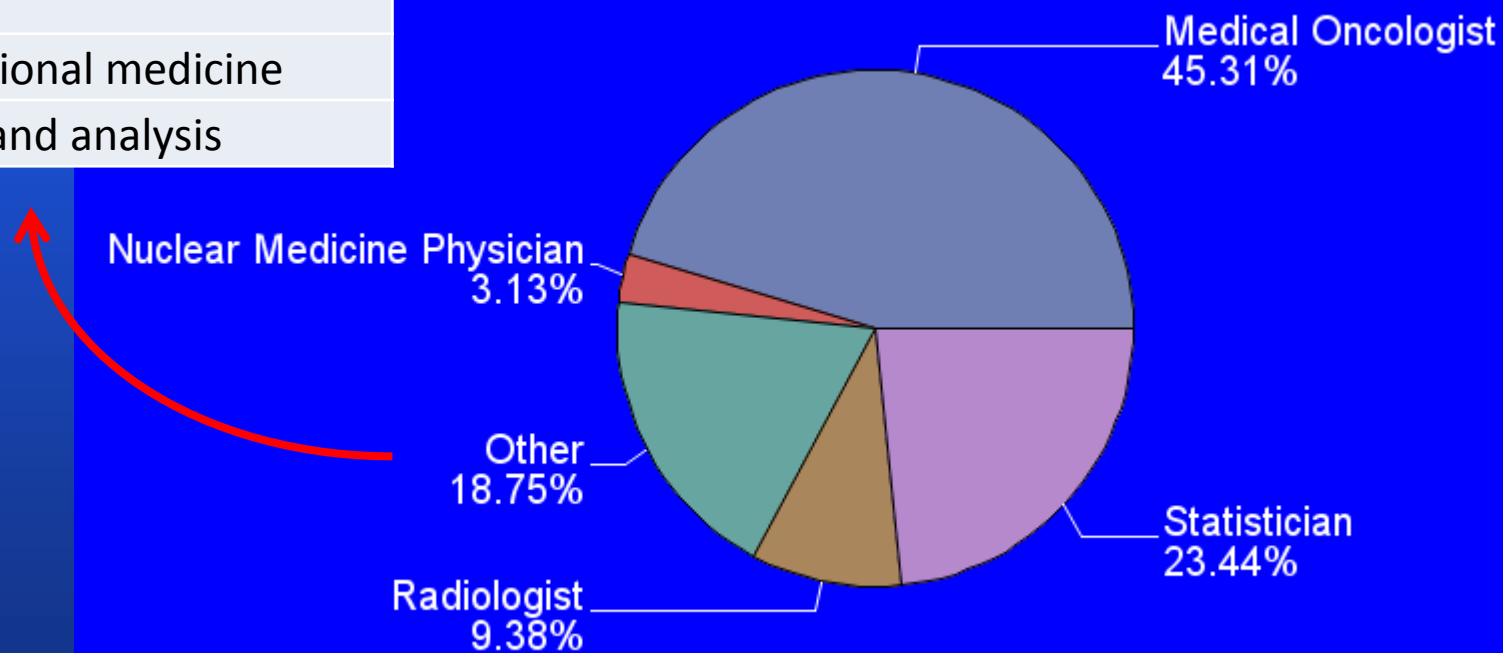
RECIST 1.1

What is your opinion regarding the use of RECIST 1.1?	N (%)
1. Should be used to evaluate activity (in Phase II)	17 (26.2)
2. Should be used to evaluate comparative efficacy (in Phase III)	4 (6.2)
3. Both 1. and 2.	36 (55.5)
4. Is no longer usable for clinical trials	7 (10.8)
Missing	1 (1.5)

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RECIST 1.1

Have you used a modification of RECIST 1.1?	Total = 65 N (%)
Yes	39 (60.0)
If yes, which of the following?	*% out of 39*
MacDonald Criteria/RANO criteria (Response assessment in Neuro-oncology	15 (38.5)
CHOI	15 (38.5)
PERCIST (PET Response Criteria in Solid Tumor)	14 (35.9)
WHO	8 (20.5)
irRC (Immune related Response Criteria)	6 (15.4)
Other	13 (33.3)

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RECIST 1.1

For which cancer type did you use a modification of RECIST 1.1?

	Total =65
	N (%)
I have not used a modification	19 (29.2)
Yes, Glioblastoma multiforme (GBM)	14 (21.5)
Yes, Lymphoma	11 (16.9)
Yes, Gastrointestinal stromal tumor (GIST)	9 (13.8)
Yes, Prostate Cancer	8 (12.3)
Yes, Renal Cell Cancer	6 (9.2)
Yes, other cancer types :	15 (23.1)
lung, ovary, colorectal, breast cancers	
Melanoma, HCC, BCC, Meduloblastoma	
Gyneacologic Oncology	
GBM	
GIST, soft tissue and bone sarcoma	

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RECIST V2

What do you think are the most important changes needed to RECIST (for V2)?

	Total = 37
	N (%)
Fine as it is	6 (9.2)
Develop disease specific variations for e.g. GIST, GBM or mesothelioma	32 (49.2)
FDG-PET/CT	32 (49.2)
3D imaging techniques (volumetric measurements)	22 (33.8)
Develop computer algorithm for assessment of response	18 (27.7)
FDG-PET	10 (15.4)
DCE-MRI	8 (12.3)
DCE-CT	1 (1.5)
Other	9 (13.8)

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Other recommendations (my bias)

- **Look at cut-offs / other approaches affecting predictiveness for OS?**
- **About the use of RECIST:**
  - **More discussion on what it is aiming for: to indicate (any activity)?**
  - **Needs clarification as a tool to assess biologic activity. Is being misused to inform potential for effectiveness**

Overall satisfaction

Overall, how satisfied are you with RECIST 1.1?	
	Total = 65
	N (%)
Satisfied	**34 (52.3)**
Neither	**18 (27.7)**
Dissatisfied	**7 (10.8)**
Missing	6 (9.2)

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RECIST V2

What are your major concerns (if any) with RECIST 1.1?

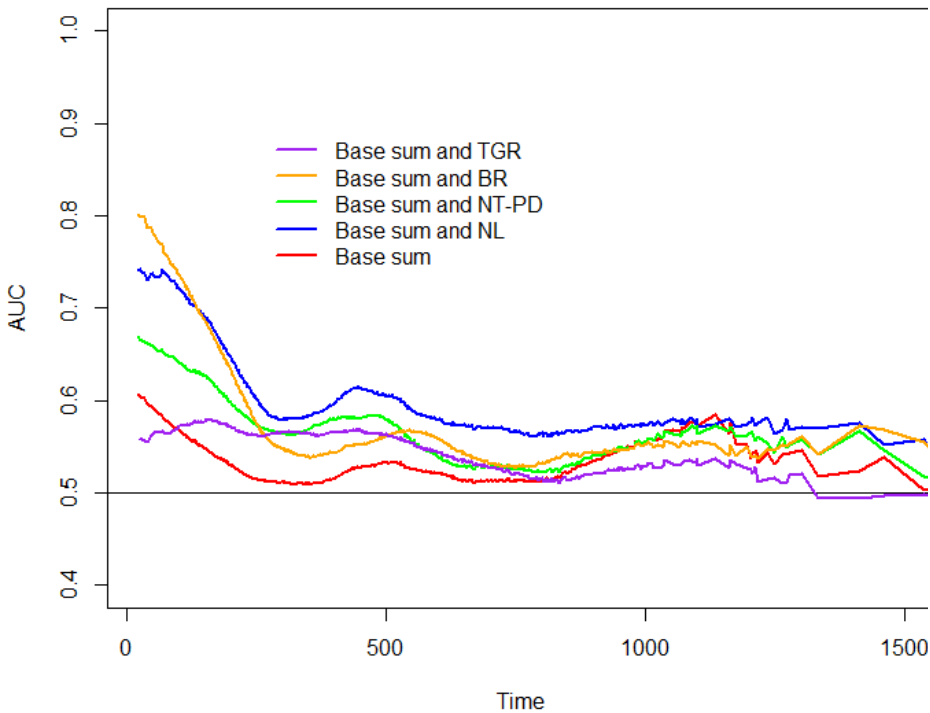|	Total = 37
	N (%)
Does not include functional imaging (e.g. FDG-PET, FDG-PET/CT, DW-MRI, DCE-MRI, DCE-CT)	29 (44.6)
Not easily applicable to certain tumour types	26 (40.0)
Difficult to compare non-measurable lesions	18 (27.7)
Does not assess early response to treatment	17 (26.2)
Uses tumor shrinkage only	19 (29.2)
I do not believe this to be relevant with novel agents	15 (23.1)
Concerns with number of lesions selected	12 (18.5)
Concerns with all nodes being considered one organ	8 (12.3)
Too complex	3 (4.6)
Prefer to use a nominated target lesion to assess response	2 (3.1)
Other	13 (20.0)

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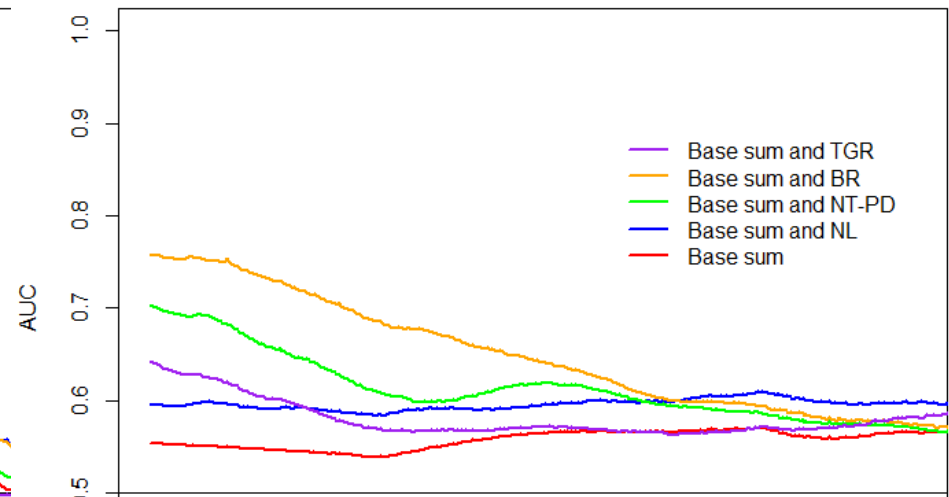
The components of progression free survival

- **We call an 'event':**
  - **Growth of target lesions (20% increase in sum from nadir, at least 5 mm) -> we modeled this in various ways**
  - **New lesions**
  - **"Unequivocal growth" of non-target lesions**
  - **Death in absence of any of the above**
- **If none of the above occur, censor at "last appropriate time" (a whole discussion …)**
- **Multivariate model to detect each contribution to OS**

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Parameter		Breast cancer (N = 1167) HR [95% CI]	NSCLC (N = 1855) HR [95% CI]	Colorectal cancer (N = 736) HR [95% CI]
Baseline sum	mm	1.001 [1.000; 1.002] (p = 0.009)	1.004 [1.003; 1.005] (p < 0.001)	1.001 [0.999; 1.003] (p = 0.336)
Best target response	0%	1.00	1.00	1.00
	]0,15[	0.69 [0.48; 0.99]	0.58 [0.48; 0.72]	0.80 [0.58; 1.10]
	[15,30[	0.79 [0.60; 1.05]	0.59 [0.49; 0.70]	0.48 [0.35; 0.66]
	[30,50[	0.69 [0.54; 0.88]	0.44 [0.37; 0.53]	0.31 [0.22; 0.44]
	[50,70[	0.63 [0.49; 0.81]	0.36 [0.30; 0.44]	0.39 [0.28; 0.54]
	[70,100[	0.60 [0.46; 0.78]	0.26 [0.20; 0.34]	0.23 [0.14; 0.36]
	100% (CR)	0.46 [0.36; 0.59] (p < 0.001)	0.32 [0.23; 0.44] (p < 0.001)	0.21 [0.12; 0.37] (p < 0.001)
Occurrence of new lesion	Yes vs No (ref)	1.97 [1.70; 2.29] (p < 0.001)	1.57 [1.38; 1.78] (p < 0.001)	2.22 [1.73; 2.85] (p < 0.001)
Non-target PD	PD vs No PD (ref)	1.50 [1.27; 1.76] (p < 0.001)	1.70 [1.49; 1.92] (p < 0.001)	1.57 [1.21; 2.04] (p < 0.001)
Tumor growth rate (TGR) in mm/week	0	1.00	1.00	1.00
	0 < TGR ≤ 2	0.94 [0.79; 1.13]	0.80 [0.69; 0.92]	0.84 [0.66; 1.06]
	2 < TGR ≤ 5	1.68 [1.32; 2.13]	1.31 [1.11; 1.55]	1.36 [1.01; 1.84]
	> 5	1.54 [1.07; 2.23] (p < 0.001)	1.48 [1.14; 1.90] (p < 0.001)	1.25 [0.78; 1.99] (p = 0.013)

Separate analysis for each tumor type

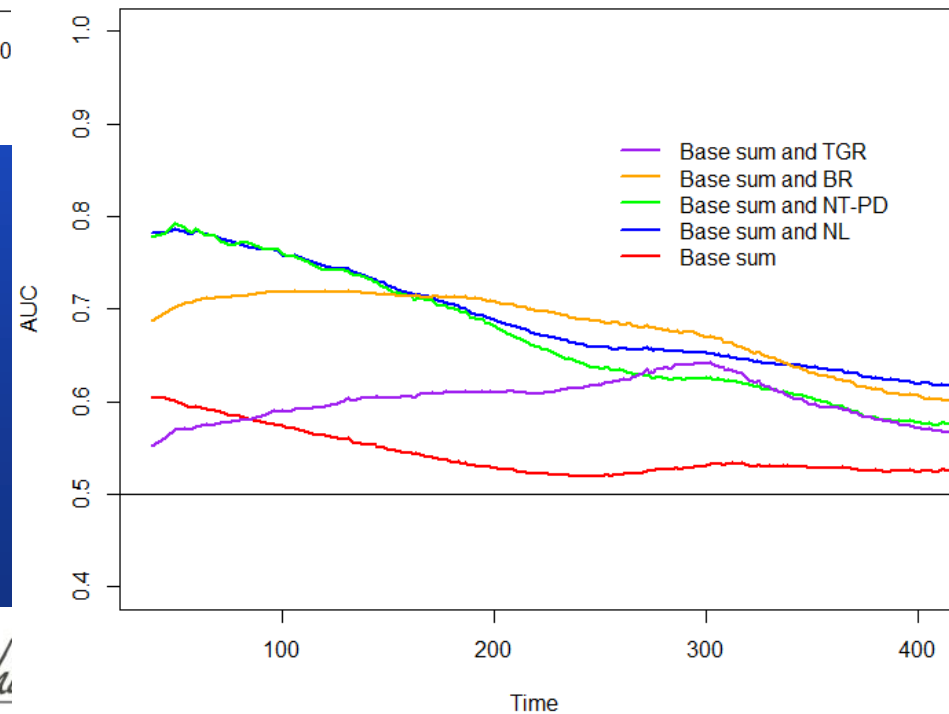EORTC — *The future of cancer therapy*

AUC plot - Breast Cancer

AUC plot - NSCLC Cancer

AUC plot - Colon Cancer

The purple line, which represents the contribution of PD on the basis of target measurements to the explanatory value for OS, is disappointingly low, as compared to other components of RECIST model.

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The future of RECIST

- **Should we consider**

  RECIST for proof of activity
  as opposed to
  RECIST for comparative trials

- **How to incorporate "new" techniques such as FDG-PET?**

- **Does RECIST function the same for newer targeted drugs as for cytotoxics? Should it?**
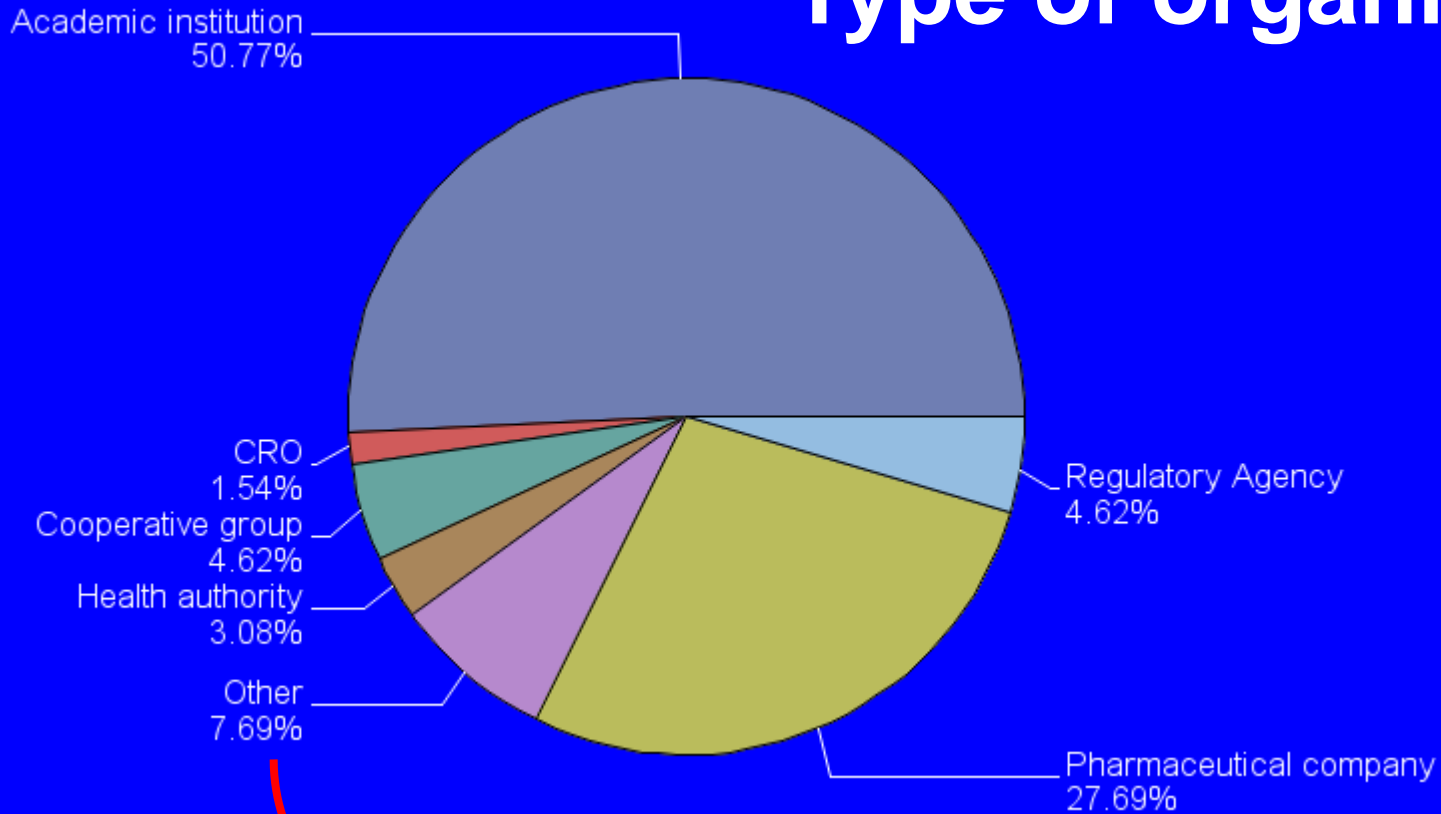
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Thank you

Back Up

Type of organisation

Pie chart: Type of organisation
- Academic institution 50.77%
- CRO 1.54%
- Cooperative group 4.62%
- Health authority 3.08%
- Other 7.69%
- Pharmaceutical company 27.69%
- Regulatory Agency 4.62%

Other: specify	Tumor institute
Cooperative group	Cancer Center
NHS hospital	Radiology
Oncology Institute	Patient organisation

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