Evaluating Responses in Solid Tumors & Future Trials

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- *Material freely available from internet has been used and acknowledged*

Agenda

- Introduction
- Changing Endpoints
- Response Evaluation Criteria In Solid Tumors (RECIST)
- Immune-Related Response Criteria (irRC)
- Next-generation clinical trials
- QA

Introduction

- Efficacy analyses are very specific in oncology
- Focus on the standard criteria used for assessing solid tumors
- Commonly used endpoints:
  - overall survival
  - progression free survival
  - response rates
- Response refers to the observed change in patient's tumors or lesions

Changing Endpoints

- 1960: Initial attempts to standardize assessing tumor response
- 1981: World Health Organisation (WHO) – first tumor response criteria
- Afterward: Direct evidence of clinical benefit
  - improvement in survival
  - improvement in Quality of Life (QOL)
  - improved physical functioning, or
  - improved tumor-related symptoms.

Survival improvement is considered an appropriate measure of clinical benefit.

Changing Endpoints

- 1990: Surrogate endpoints were introduced to support clinical benefits

  Objective Response Rate (ORR): most commonly used surrogate endpoint
  - Directly attributable to drug effect
  - Useful for single-arm trials in patients with refractory tumors

  Clinical benefit for regular approval
  - Overall Survival
  - Symptom Endpoints (patient-reported outcomes)

Changing Endpoints

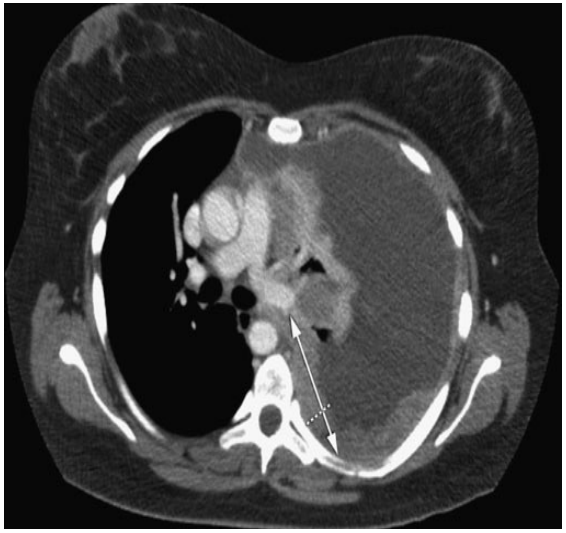
- Surrogate endpoints include overall survival, endpoints based on tumor assessments
  - Objective Response Rate (ORR)
  - Complete Response (CR)
  - Time to Progression (deaths before progression censored) (TTP)
  - Progression-Free Survival (includes all deaths) (PFS)
  - Endpoints based on symptom assessment

Response Evaluation Criteria In Solid Tumors (RECIST)

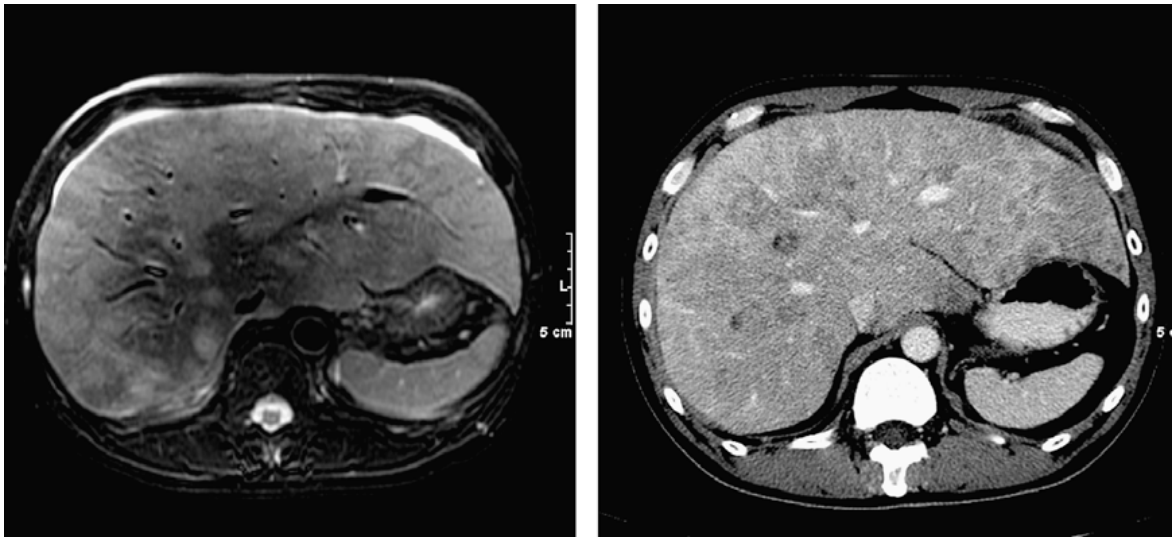
- RECIST - a set of rules: define patients improve (Respond), stay the same (Stable) or worsen (Progression) during treatments
- Internationally accepted simplified and standardized response definitions – 2000
- RECIST 1.1 – updated version , published in Jan, 2009

Challenges in using RECIST

- RECIST rules are highly dependent
  - Measurement of tumor size
  - Methods of measurements (CT/MRI)



CT image of chest of a patient with mesothelioma; longest diameter of the tumour is represented by the arrow[1]

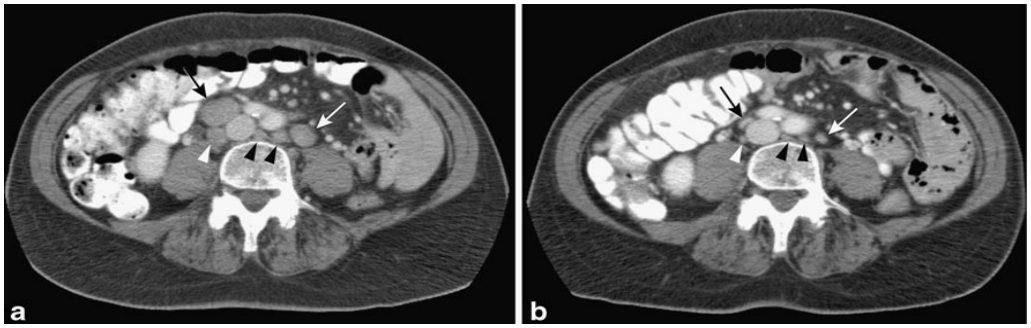


CT versus MRI of same lesions showing apparent 'progression' due to differing method of measurement[2]

[1] Els L. van Persijn van Meerten et al (2010), RECIST revised: implications for the radiologist. A review article on the modified RECIST guideline, Eur Radiol, 20: 1456–1467
[2] E.A. Eisenhauer et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1); EUROPEAN JOURNAL OF CANCER, 45, 228 –247

Challenges in using RECIST[3]

- Inconsistency in following imaging requirements



(a) At baseline (b) After chemotherapy.
(b) Lymph nodes are still visible, but of normal size, categorizing this patient as CR according to RECIST 1.1

CT image of target (arrows) and non-target (arrowheads) retroperitoneal lymph nodes of a patient with non-Hodgkin lymphoma[1]

- Missing measurements
- Tumor(s) might be split or merged
- Longest diameter might be very small
- Definition of Progression
  - ✓ 20% increase from the lowest preceding value (Nadir)
- Lesion might disappear and reappear
- Lesions might change the shape and may be un-evaluable.

[1] Els L. van Persijn van Meerten et al (2010), RECIST revised: implications for the radiologist. A review article on the modified RECIST guideline, Eur Radiol, 20: 456–1467
[3] G. Ruhnke, Overcoming Difficulties in Implementing RECIST criteria, PhUSE 2013

Nadir

- Nadir - The Smallest Sum Of Longest Diameter (SOLD) for all target lesions recorded based on all prior tumor assessments

  Nadir (visit) = min SOLD value from all pervious visits SOLD values
- Nadir is variable over time

Ex:[4]

Time Point	SOLD	Defining Nadir	Nadir	% Change from Nadir	Conclusion
Baseline	50				
T1	40	Min [50]	50	-20	SD
T2	25	Min[50, 40]	40	-37.5	PR
T3	27	Min[50, 40, 25]	25	8	PR
T4	35	Min[50, 40, 25, 27]	25	40	PD

[4] Angelo Tinazzi, EFFICACY ENDPOINTS IN ONCOLOGY, PhUSE 2013

More Challenges

- For cytotoxic agents - an early increase in tumor growth and/or the appearance of new lesions indicates progressive disease (PD)
- Progression becomes synonymous with drug failure
- Recommendation of cessation of current treatment once PD is detected.

Immune-Related Response Criteria (irRC)

- RECIST or WHO criteria detect early effects of cytotoxic agents
- Require criteria for the evaluation of antitumor responses with immunotherapeutic agents – irRC (2009)[2]
  - Capture the response patterns observed with some immunotherapeutic agents
  - irRC allows more comprehensive evaluation of immunotherapeutic agents
  - May offer guidance in clinical care
  - irRC - a tool for clinical investigation of immune therapy in cancer patients

[2] E.A. Eisenhauer et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1); EUROPEAN JOURNAL OF CANCER, 45, 228–247

More on irRC

- Identify four distinct response patterns[5]
  - Shrinkage in baseline lesions, without new lesions
  - Durable stable disease (in some patients followed by a slow, steady decline in total tumor burden)
  - Response after an increase in total tumor burden
  - Response in the presence of new lesions
- All the above patterns are associated with favorable survival.

[5] Wolchok JD, et al (2009), Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria; Clin Cancer Res,15(23), 7412-7420

Key Elements in Radiographic Assessment[2,5]

	mWHO*	RECIST 1.1	irRC
New, measurable lesions (i.e., ≥5x5 mm)	Represents PD	Represents PD	Incorporated in tumor burden
New, non-measurable lesions (i.e., <5x5 mm)	Represents PD	Represents PD	Do not define progression - preclude immune-related complete response
Non-index lesions	Changes contribute to - BOR of CR or PR and stable or PD	Changes contribute to - BOR of CR or PR and stable or PD	Contribute to defining immune-related CR - complete disappearance required
Complete Response (CR)	- Disappearance of all target /non-target lesions - Reduction in short axis to <10 mm for pathological lymph nodes	Disappearance of all lesions in two consecutive observations ≥ 4 weeks apart	Disappearance of all lesions in two consecutive observations ≥ 4 weeks apart

*mWHO: modified WHO

[2] E.A. Eisenhauer et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1); EUROPEAN JOURNAL OF CANCER, 45, 228 –247
[5] Wolchok JD, et al (2009), Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria; Clin Cancer Res,15(23), 7412-7420

Key Elements in Radiographic Assessment

	mWHO	RECIST 1.1	irRC
Partial Response (PR)	≥ 50% decrease in SPD* of all index lesions vs. baseline	At least a 30% decrease in sum of diameters of target lesions with respect to baseline	≥ 50% decrease in tumor burden vs. baseline in two observations at least 4 weeks apart
Stable Disease (SD)	50% decrease in SPD - Not 25 % increase vs. nadir	- Not sufficient shrinkage for PR nor sufficient increase for PD (ref. smallest sum diameters) - Persistence of one or more non-target lesion(s)**	50% decrease in tumor burden vs. baseline cannot be established - Not 25% increase vs. nadir
Progressive Disease (PD)	At least 25% increase in SPD vs. nadir and/or - progression of non-index lesions and/or appearance of new lesions (at any single time point)	- At least 20% increase in the sum of diameters of target lesions with respect to the smallest sum on study*** - Relative increase of 20% (absolute increase at least 5 mm)	At least 25% increase in tumor burden vs. nadir in two consecutive observations at least 4 weeks apart

*SPD = sum of products of the 2 largest perpendicular diameters
** Non-complete response/non-progressive disease is preferred over stable disease when assessing non-target lesion disease
*** includes the baseline sum if that is the smallest on study

Next-generation clinical trials

- Personalized Cancer Care - leads toward specific molecular aberrations for potential improvement of outcomes
- A few challenges here again:
  - Inter-patient heterogeneity - heterogeneity within any given tumor-type from patient to patient
  - Intra-patient heterogeneity - molecular evolution through space (primary tumor to metastasis) and time (after therapy)
  - Getting molecularly targeted agents
  - Classic trial design unable to test targeted therapeutics against low frequency genomic 'oncogenic driver' aberrations with adequate power.

Next-generation clinical trials

- Needs to have innovative clinical trial designs
- Strategic implementation of diagnostic biomarker technologies to account for interpatient molecular diversity
- Need for pre-defined treatment priority algorithms given numerous aberrations commonly observed within an individual
- Access multiple available therapeutic agents
- Serial biomarker assessment at the time of tumor progression that may address intra-patient heterogeneity

All these lead to biomarker-driven trial designs.

Concern of complex trial designs

- High number of variables embedded within the personalized strategy
- Biomarker subsets
- Pre-stated treatment algorithm
- Statistical analyses of pre-specified subset
- Pre-defined statistics to identify ineffective biomarker-drug groups

References

[1] Els L. van Persijn van Meerten et al (2010), RECIST revised: implications for the radiologist. A review article on the modified RECIST guideline, Eur Radiol, 20: 1456–1467

[2] E.A. Eisenhauer et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1); EUROPEAN JOURNAL OF CANCER, 45, 228 –247

[3] G. Ruhnke, Overcoming Difficulties in Implementing RECIST criteria, PhUSE 2013

[4] Angelo Tinazzi, EFFICACY ENDPOINTS IN ONCOLOGY, PhUSE 2013

[5] Wolchok JD, et al (2009), Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria; Clin Cancer Res,15(23), 7412-7420

Suggested reading

Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Cancer Drugs and Biologics, FDA, 2011

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/CancerDrugs/ucm094586.htm

Guidance for Industry Clinical Trail Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 **(***http://www.fda.gov/cber/guidelines.htm**)*

K. Lee, CDISC Journey on Solid Tumor Studies using RECIST 1.1., PhUSE 2013

Therasse and Arbuck et al. (2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

Daniel V.T. Catenacci (2015), Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity; MOLECULAR ONCOLOGY , 9, 967-996

Acknowledgement

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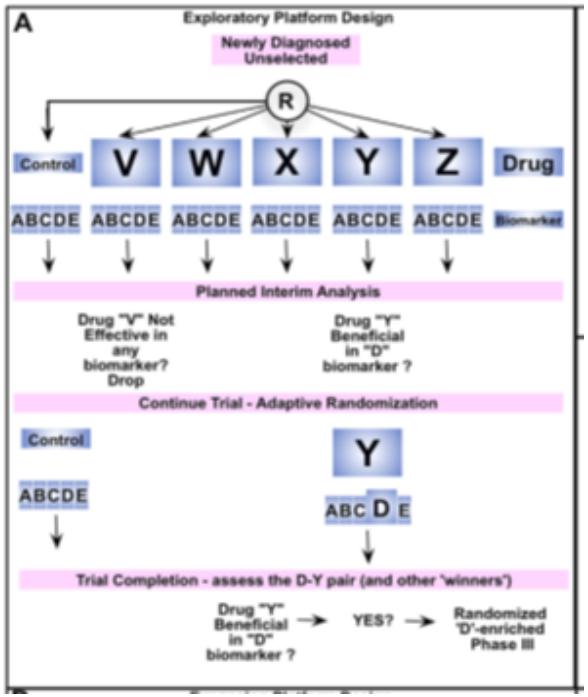
Thank you !!

Q&A

Back-up

Next-generation clinical trial design, an example



Exploratory Platform Design

Reference: Daniel V.T. Catenacci (2015) , Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity, MOLECULAR ONCOLOGY , 9, 967-996

Longest Target Lesion Diameter (cm)

Lesion	Baseline	T1	T2	T3	T4
Rt.Lung #1	3	2	2	2	3
Rt.Lung #2	2.5	2	2	2	3
Lt liver lobe	6	5	3	3	5
Rt Liver lobe	2.5	2	2	2	2
Total Length	14	11	9	9	13
% Change		-21%	-36%	-36%	+44%*
Disease Status		**SD**	**PR**	**PR**	**PD**

* Change from nadir