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The forest of methods in cancer research

Expert: **Dr Luca Bertolaccini**, IEO European Institute of Oncology IRCCS, Milan, Italy

Expert: **Dr Jessica Menis**, University Hospital of Verona, Verona, Italy

The forest of methods in cancer research

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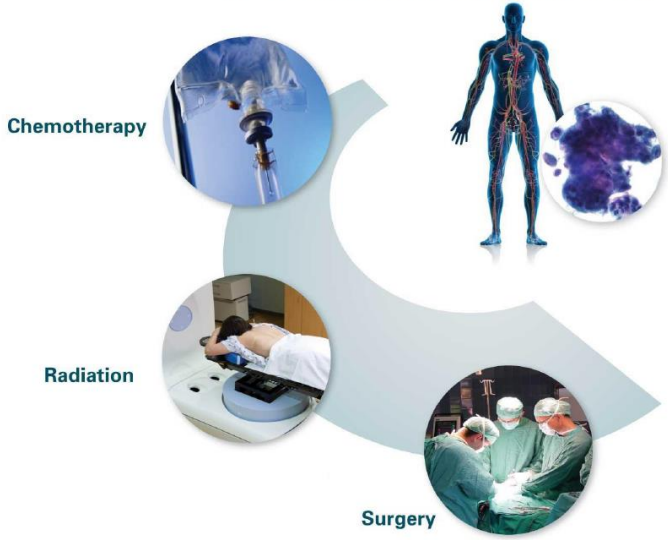
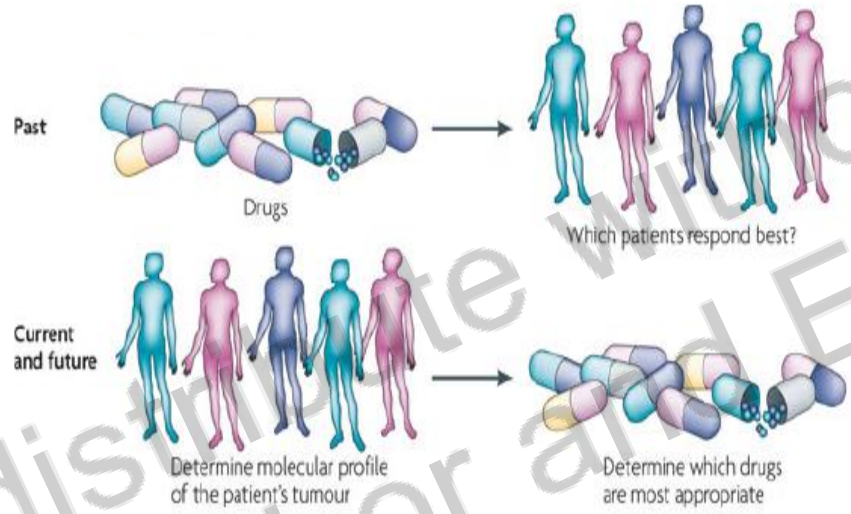
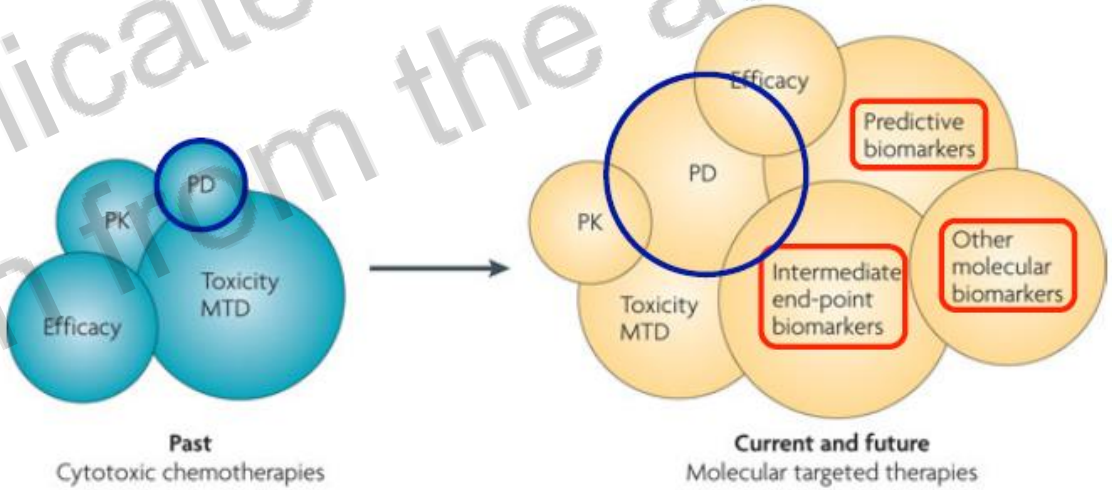
Standard anti-cancer therapy has reached a plateau

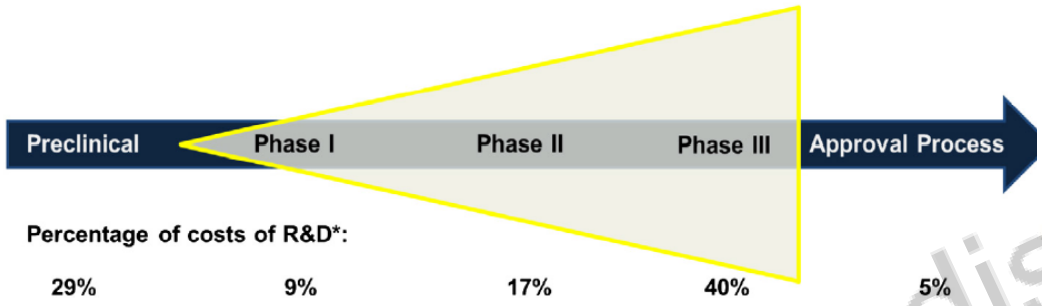


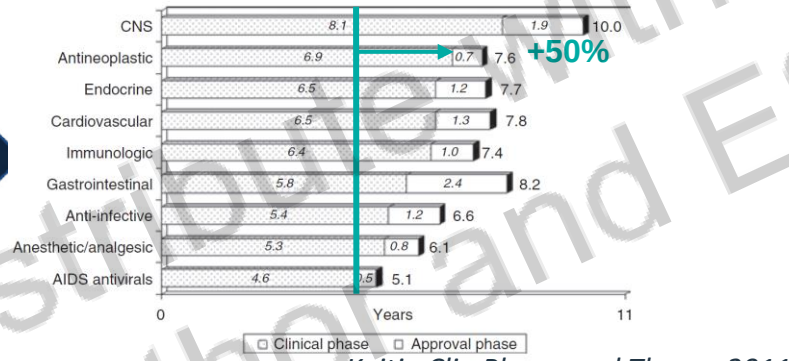




Yap et al. Nature Reviews Cancer 2010

Evolving clinical research landscape





Kaitin Clin Pharmacol Therap 2011

From studies designed to learn to subsequent studies conducted to conclude and to real life situation

Early clinical trials (R&D)
- Biology / imaging driven
- Integrated TR
- Screening platforms
- Quality Assurance programs
- Sophisticated trials

Pivotal trials
- Highly targeted
- Large differences

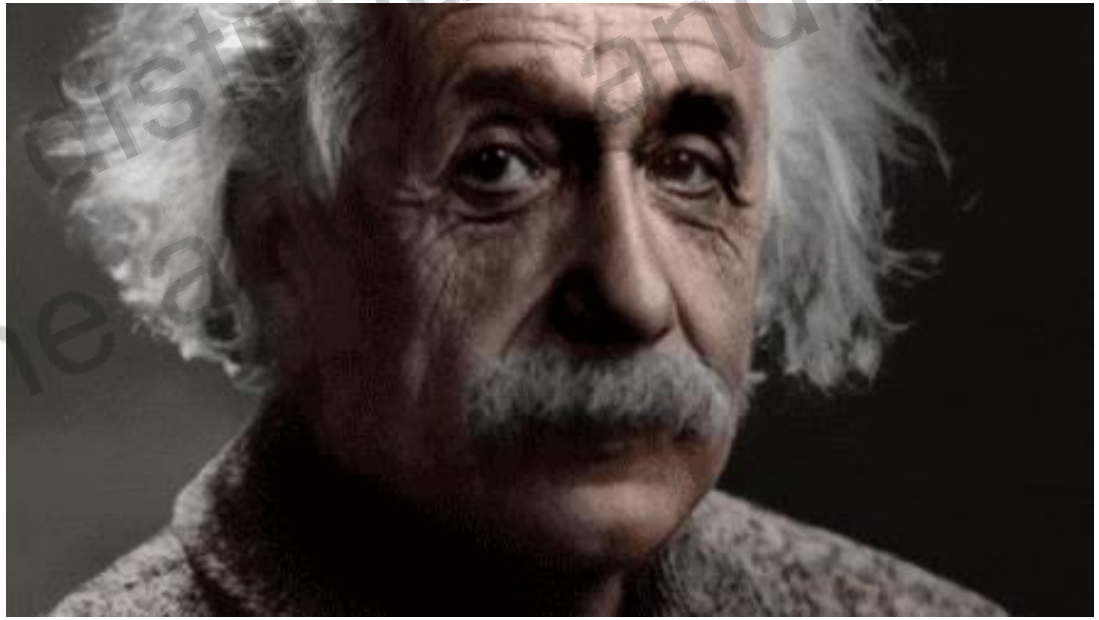
Population based studies
- Real world data
- QoL
- Outcomes research
- Health economics
- HTAs
- Pragmatic trials

Urgent need to re-shape interactions between stakeholders
New models of partnerships

Burock S, EJC 2013

If we knew what we were doing, it wouldn't be called research, would it?

Albert Einstein



Definitions of Research

- Merriam-Webster
  - Investigation or experimentation aimed at the discovery and interpretation of facts
- Redman and Mory
  - Systematic effort to gain new knowledge
- Clifford Woody
  - Defining and redefining problems, formulating hypothesis/objectives
  - Collecting, organizing and evaluating data
  - Making deductions and reaching conclusions
  - Testing conclusions to determine whether they fit formulating hypothesis/objectives

Why we do Research?

- Desire to get a research degree along with its consequential benefits
- Desire to face the challenge in solving the unsolved problems
- Desire to get intellectual joy of doing some creative work
- Desire to be of service to society
- Desire to get respectability
- Directives of government, employment conditions etc.
- Validate intuition
- Improve methods
- Demands of the Job
- For publication/patent

Developing Your Question

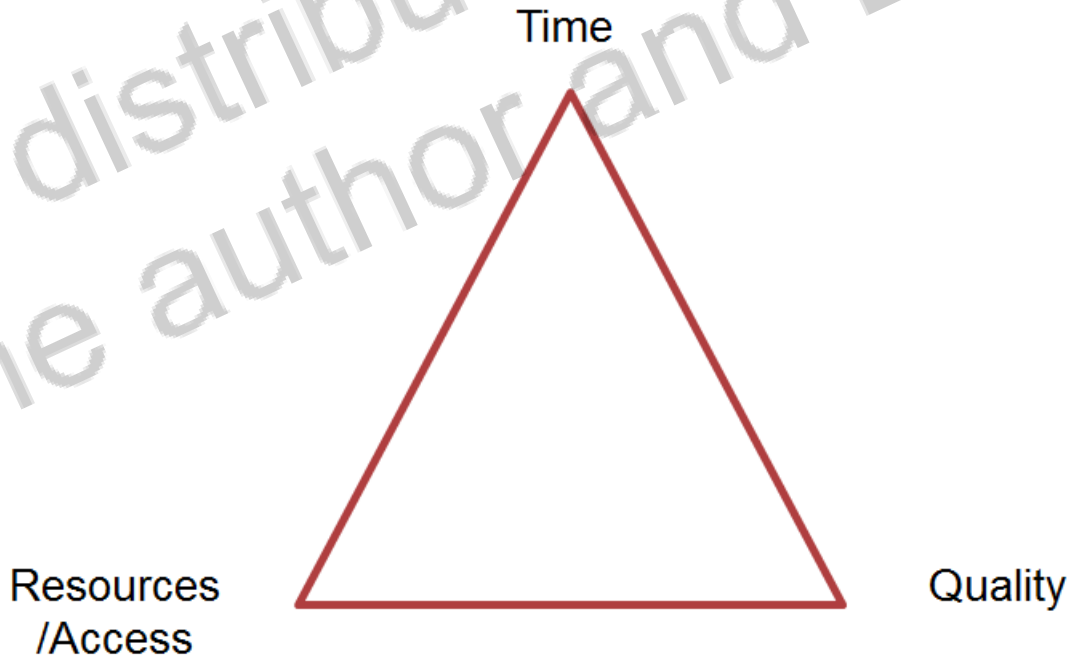
- Start with a clear purpose
- Know your literature
- Be iterative in your approach
- Try to specify the who, what, where and when of your purpose
- Ask yourself
  - What would the answer to this question add to the literature?

The Research Process

- Identification of general problem/question
- Literature review
- Specify questions/hypotheses
- Determination of design/methodology
- Data collection
- Data analysis/presentation
- Interpretation of findings

Selecting your research method

- What factors to consider when choosing one research method over another?
- Overall applicability to meet research objectives
- Time i.e., key planning and decision-making milestones to inform
- Resources available
  - Material resources
  - Financial resources
  - Human resources
- Access to population of interest



Agenda

- Clinical trials vs clinical reality

- Early stages & Oligometastatic
  - Endpoints
    - MPR, pCR, DFS, OS (Validated vs surrogate endpoints)
    - Feasibility and QOL endpoints
  - Design (WOO, ph I-II-I/II, ph III, basket/umbrella)
  - Quality assurance surgery (what about CT?)
  - Translational research

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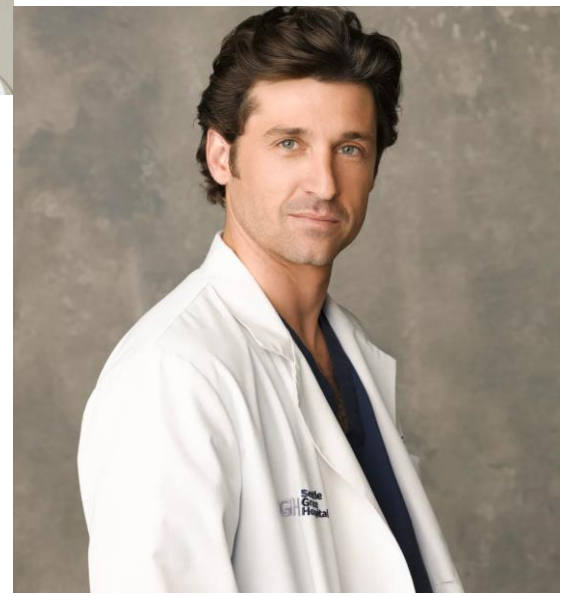
Clinical trial vs clinical reality

Real life patients vs patients in trial

Clinical trial vs clinical reality

Real life patients vs patients in trial

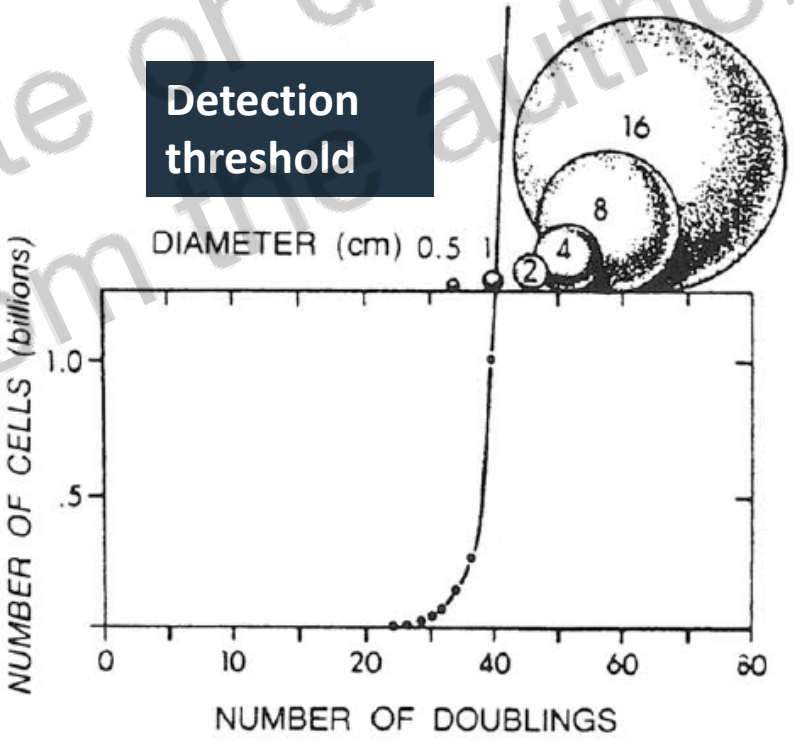


Clinical trial vs clinical reality

Staging procedures in clinical trials vs real life

"Suddenly a solitary horseman appeared on the horizon, then another, then another . . . in a few moments a whole crowd of horsemen swooped down upon him."—Leacock

Do we believe in an oligometastatic state?



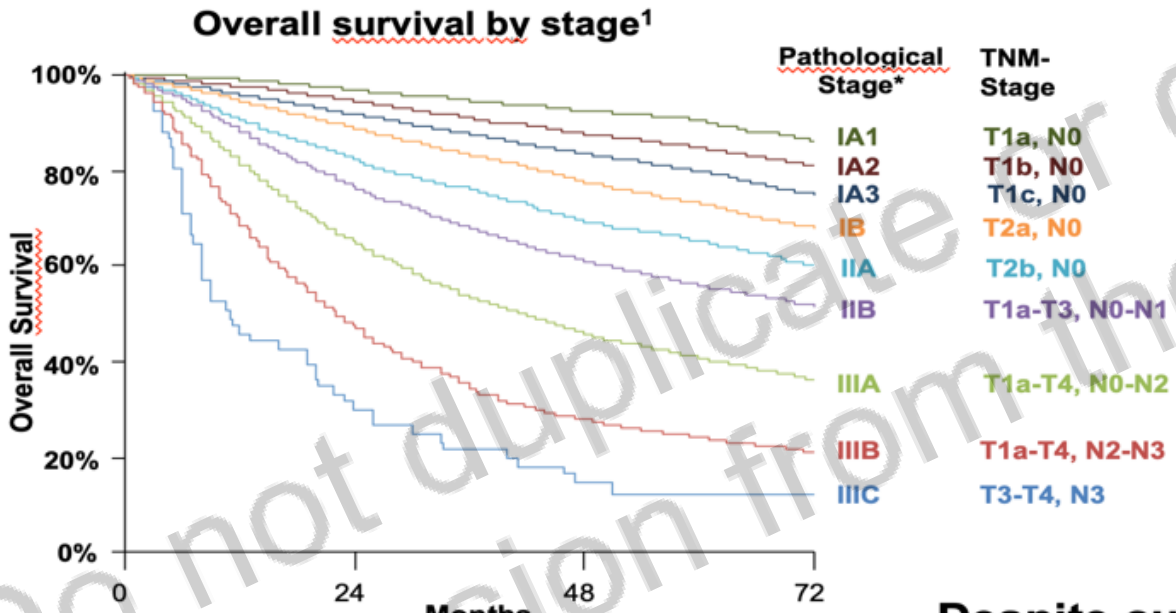
Courtesy of L Hendricks

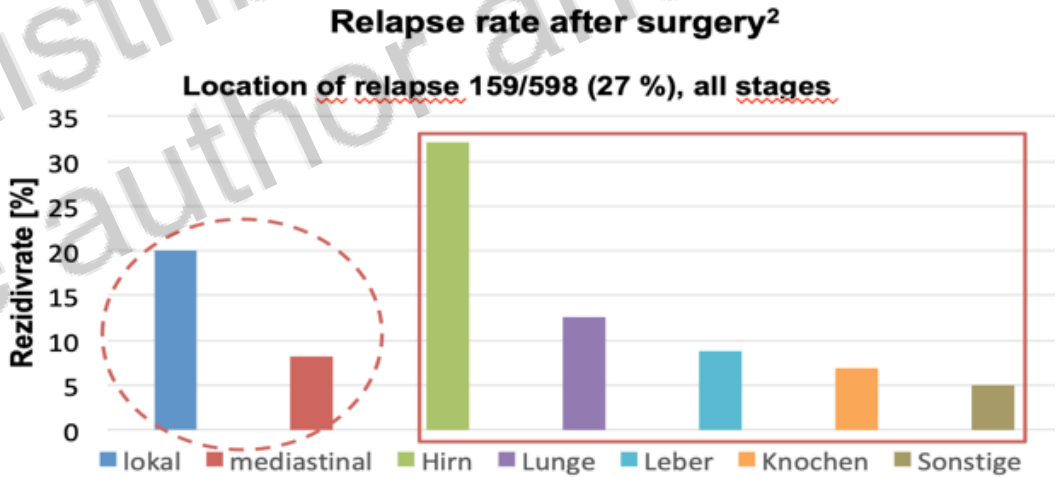
Rubin, Sem Rad Onco 2006

Clinical trial vs clinical reality

Treatment choices

We need to do something in perioperative Treatment of NSCLC!





Despite curative surgery relapse rate of 30-55% of patients with early stage NSCLC.³

*According to AJCC/UICC Version 8.

Modified: 1. Goldstraw P et al. *J Thorac Oncol*. 2016;11(1):39-51 | 2. Martini N et al. *J Thorac Card Sur*. 1995;109(1):120-129 | 3. Uramoto H, Tanaka F. *Transl Lung Cancer Res*. 2014;3:242-249.

Modified from Prof M. Reck

Clinical trial vs clinical reality

Treatment choices

YES: Oligometastases are “hot”!

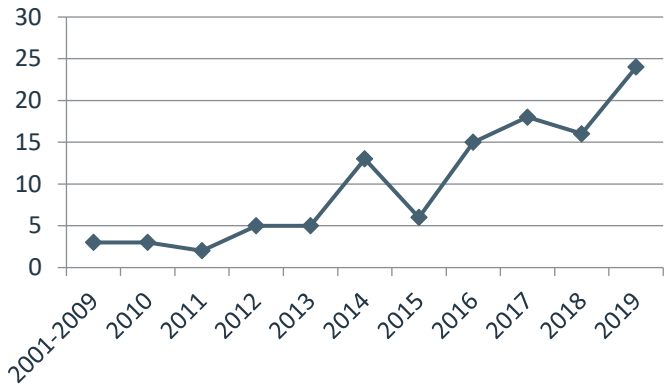
ASTRO 2018

Meeting Coverage > ASTRO

Aggressive RT, Surgery Doubles OS in NSCLC With Limited Mets

— If new drug produced such a response it would make "millions," said expert

Pubmed publications/year
Oligometastatic AND NSCLC



Clinicaltrials.gov

22 Studies found for **oligometastatic OR oligometastases OR oligo | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | NSCLC**

Also searched for **Nonsmall cell lung cancer**. See Search Details

Search date dec 29 2019
Courtesy of L Hendricks

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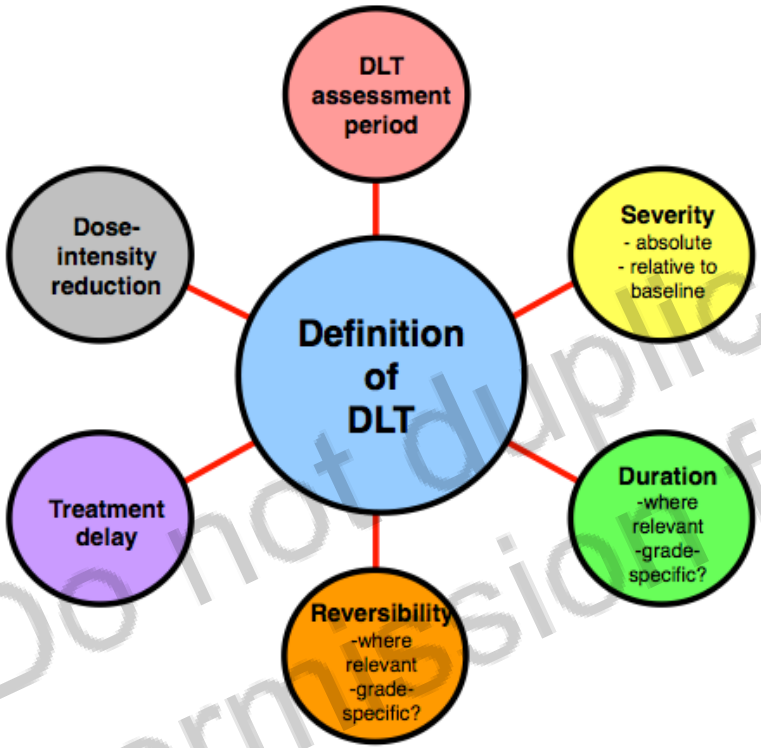
Endpoints

- Methodologically correct but clinically meaningful

- Validated vs Surrogate
  - Early stage
    - MPR
    - pCR
    - DFS
    - OS
  - Advanced stage - Oligometastatic
    - PFS
    - OS

- Feasibility and PROs/QOL endpoints

Trial design	Type of endpoint
I	DLT, MTD, RP2D
II	ORR, DFS/PFS rate
III	DFS, PFS, OS, QOL



Postel-Vinay S, et al. EJC 2014, 50:2040-9

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

ELSEVIER

EJC

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

E.A. Eisenhauer[a,*], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]

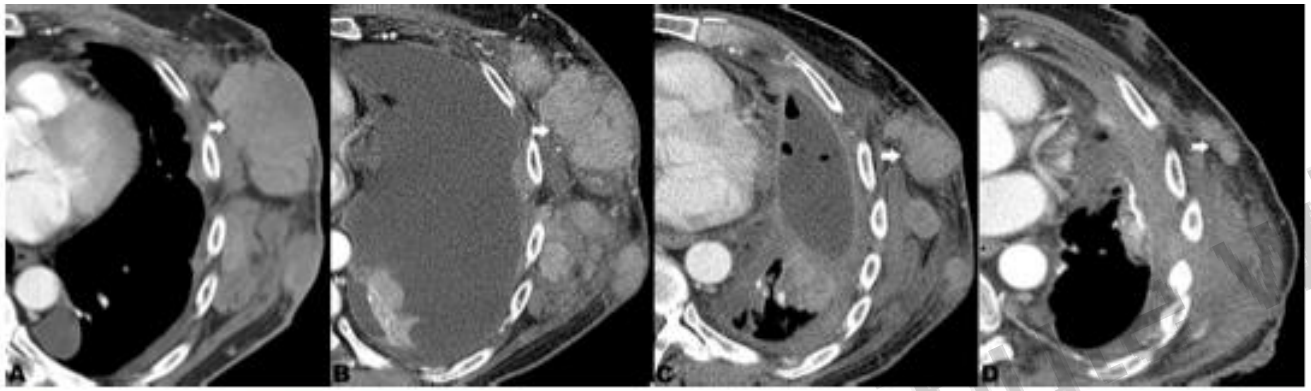
iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

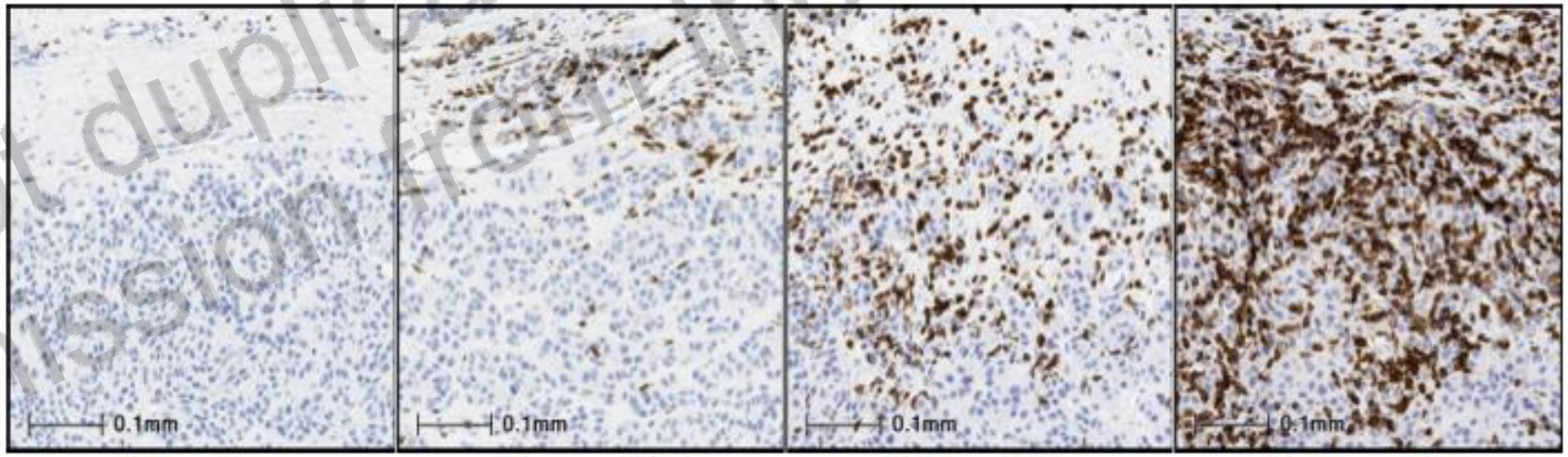
Lesley Seymour, Jan Bogaerts, Andrea Perrone, Robert Ford, Lawrence H Schwartz, Sumithra Mandrekar, Nancy U Lin, Saskia Litière, Janet Dancey, Alice Chen, F Stephen Hodi, Patrick Therasse, Otto S Hoekstra, Lalitha K Shankar, Jedd D Wolchok, Marcus Ballinger, Caroline Caramella, Elisabeth G E de Vries, on behalf of the RECIST working group

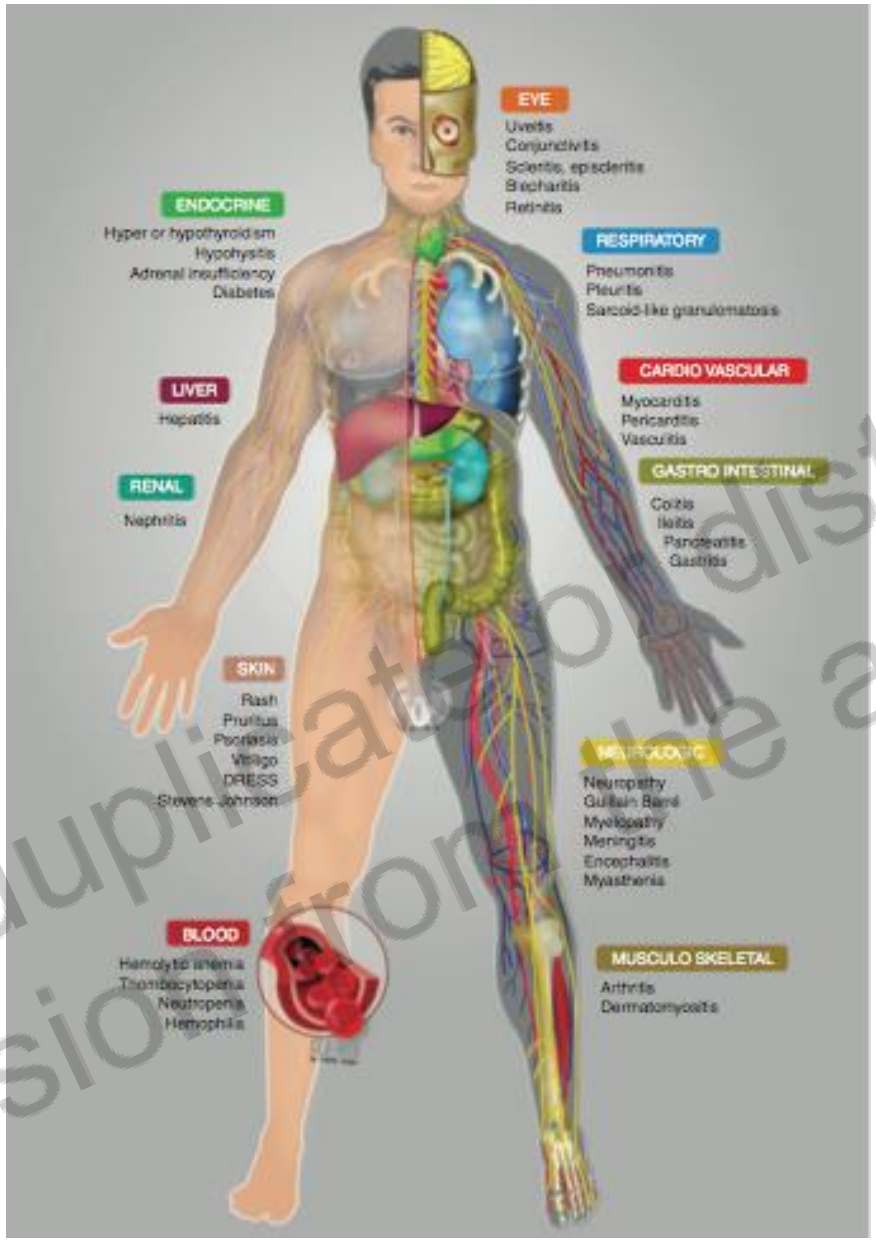
	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1: **Comparison of RECIST 1.1 and iRECIST**

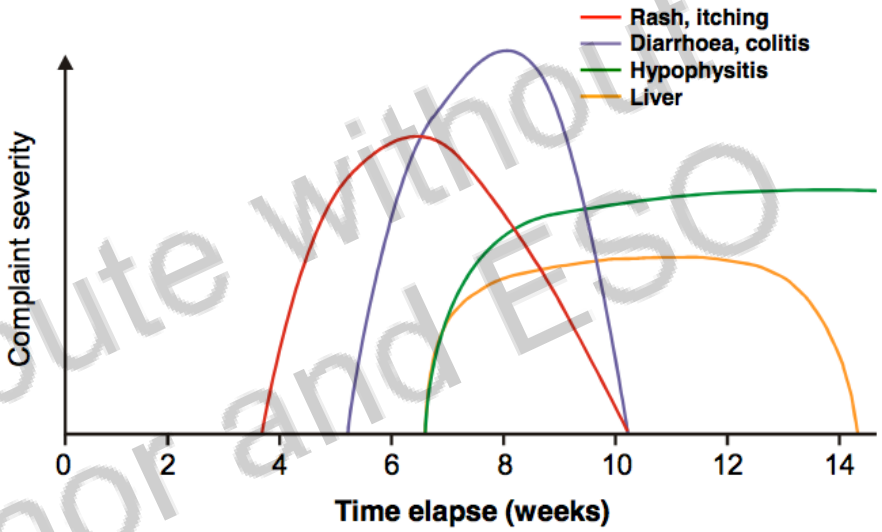




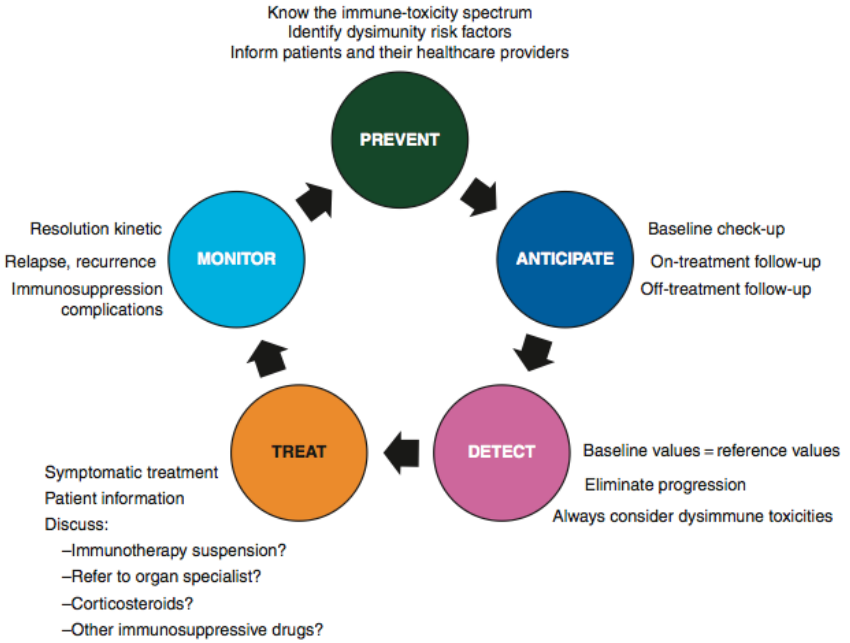


Champiat S, Annals of Oncol 2016

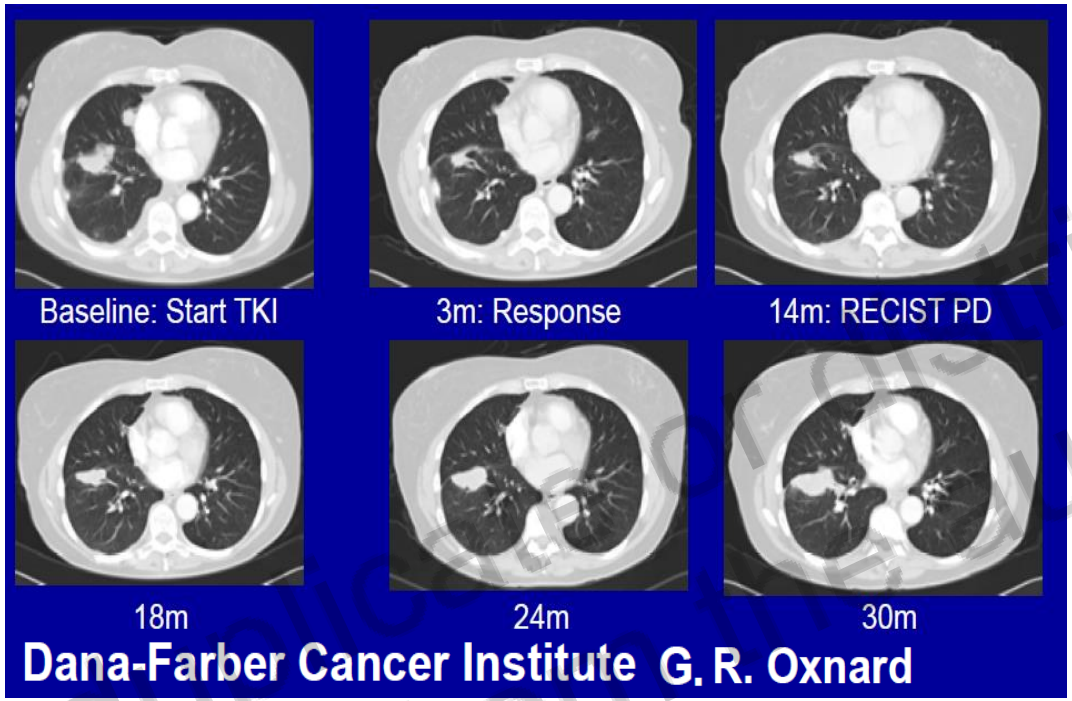
Chronological sequence of typical side effects



Kaehler, 2010

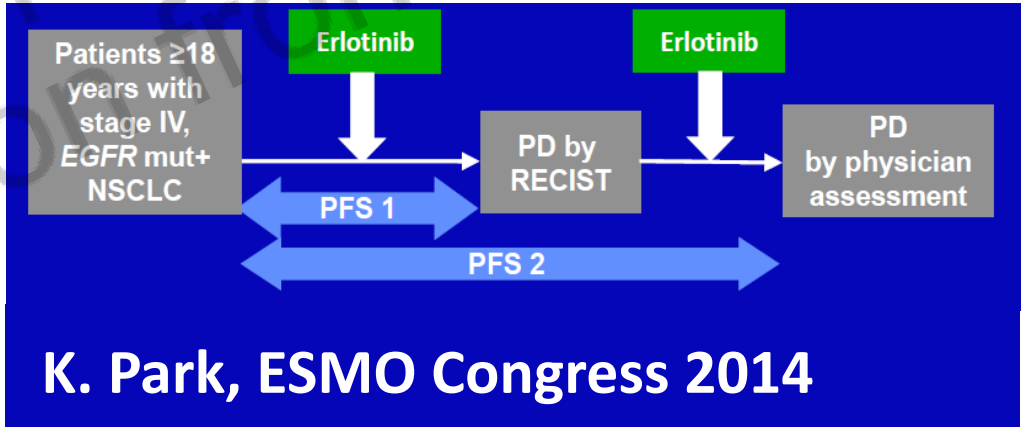


Assessing Progression: RECIST



Always RECIST?

Cave: disease flare!

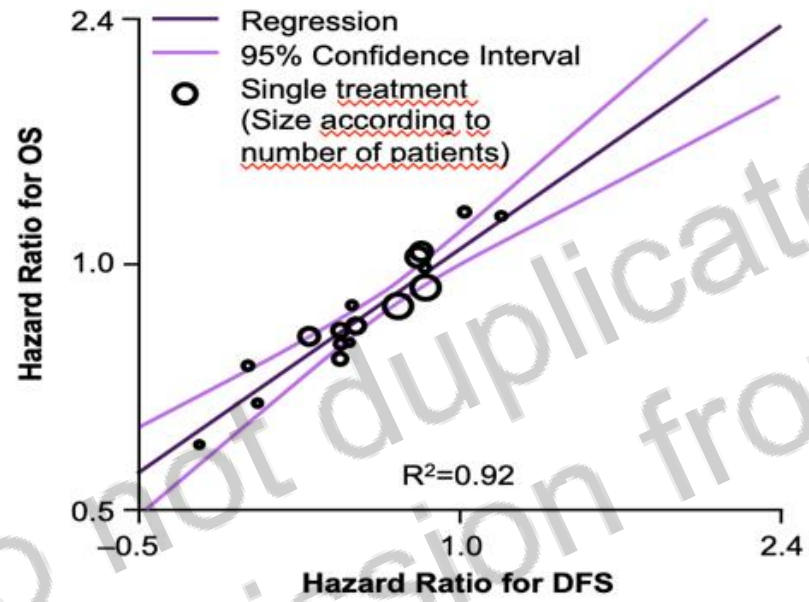


Courtesy of Prof M. Reck

DFS = OS?

Tibetanian Prayer Wheel

Correlation between DFS and OS in adjuvant Chemotherapy of NSCLC[1]



- Somewhat convincing data, that DFS might be a surrogate marker for OS
- However – so far only data for adjuvant chemotherapy, but not for *adjuvant immuno- or targeted therapies*
- In this early days of adjuvant immunotherapy assesment of more mature OS data essential

Mauguen A, et al. Lancet Oncol 2013

Approval Endpoints

Regular Approval - clinical benefit or effect on an established clinical endpoint

Accelerated Approval

- effect on an early clinical endpoint that is reasonably likely to predict clinical benefit
- requires verification of clinical benefit

Need validation that the early clinical endpoint is reasonably likely to predict clinical benefit

Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

Endpoints supporting regular approval

- Overall survival - ideal endpoint, requires extended f/u in neoadjuvant setting
- Event-free survival (EFS) defined as time from randomization to any of the following: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause
  (FDA guidance, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2018)
- Adjuvant approval based on disease-free survival (DFS), neoadjuvant approval based on event-free survival (EFS)

PRESENTED BY:
Erin Larkins, M.D., Division of Oncology 2, FDA

EFS as an Approval Endpoint for Neoadjuvant

- EFS may be supportive of regular approval if:
  - ❖ clinically meaningful (magnitude, statistically robust, across subgroups)
  - ❖ acceptable safety profile
  - ❖ no evidence of detriment in OS

- All factors taken into consideration as part of overall risk-benefit assessment
- Incorporate formal interim analysis of OS with EFS analysis
- Post-approval assessment of mature OS data (PMC)

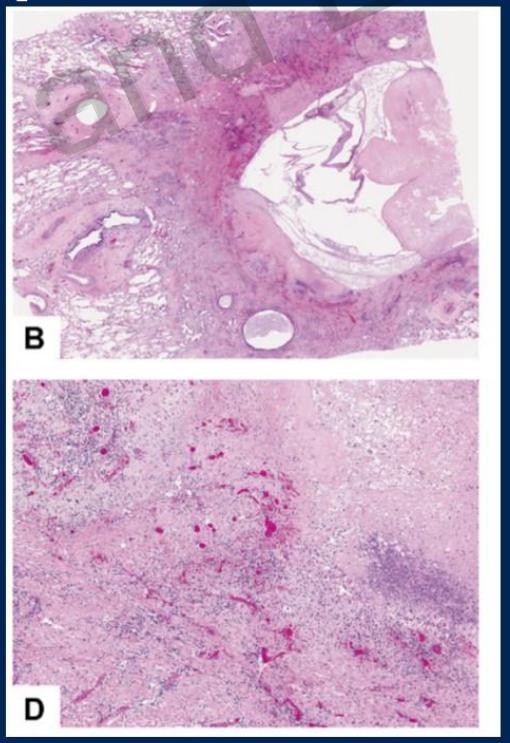
PRESENTED BY:
Erin Larkins, M.D., Division of Oncology 2, FDA

Endpoints – pathologic response

Need meta-analyses in NSCLC assessing correlation with EFS and OS

- Standards for processing and grossing of resection specimens
- Uniform definitions for pathologic response following neoadjuvant tx
- Uniform pathologic evaluation (blinded pathologic review)

IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy



Travis et al, J Thorac Oncol, 2020

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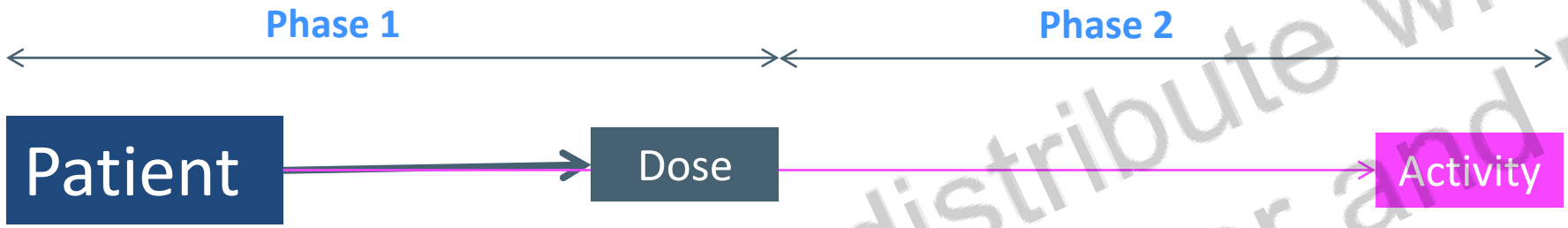
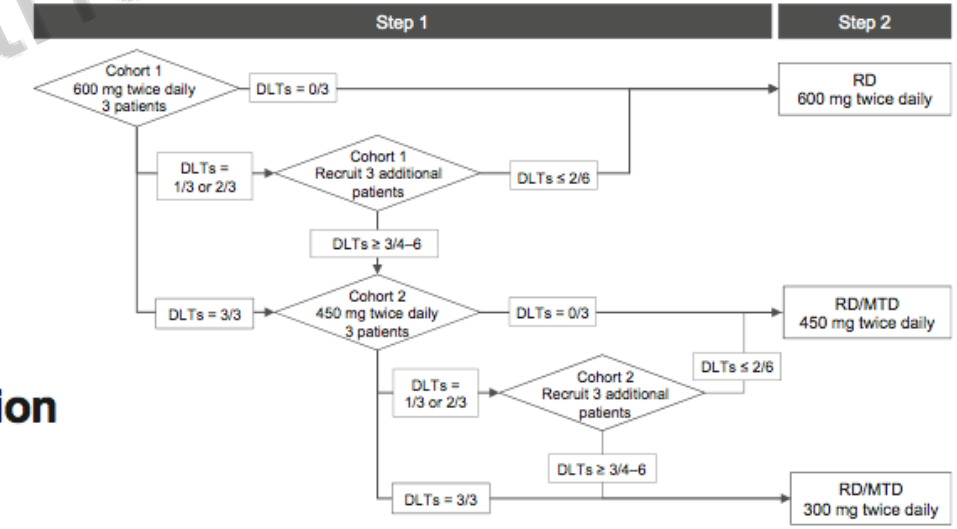
Design

- WOW
- Phase I/II
- Phase II/III
- Phase III – do we still need them?
- Basket trials
- Umbrella trials
- RWS

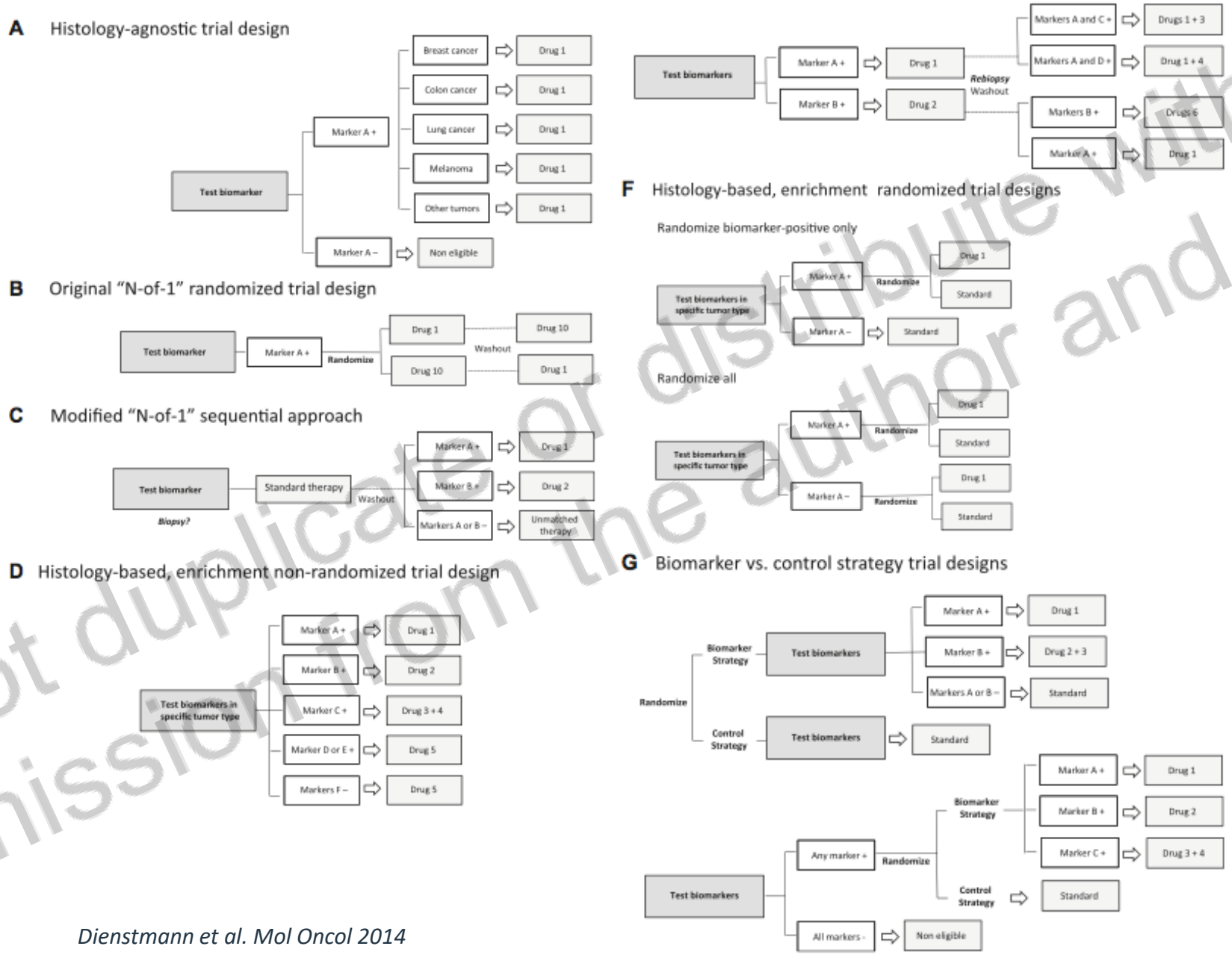
Phase I/II



Used more and more often to have an early signal of activity if the expected safety profile is acceptable



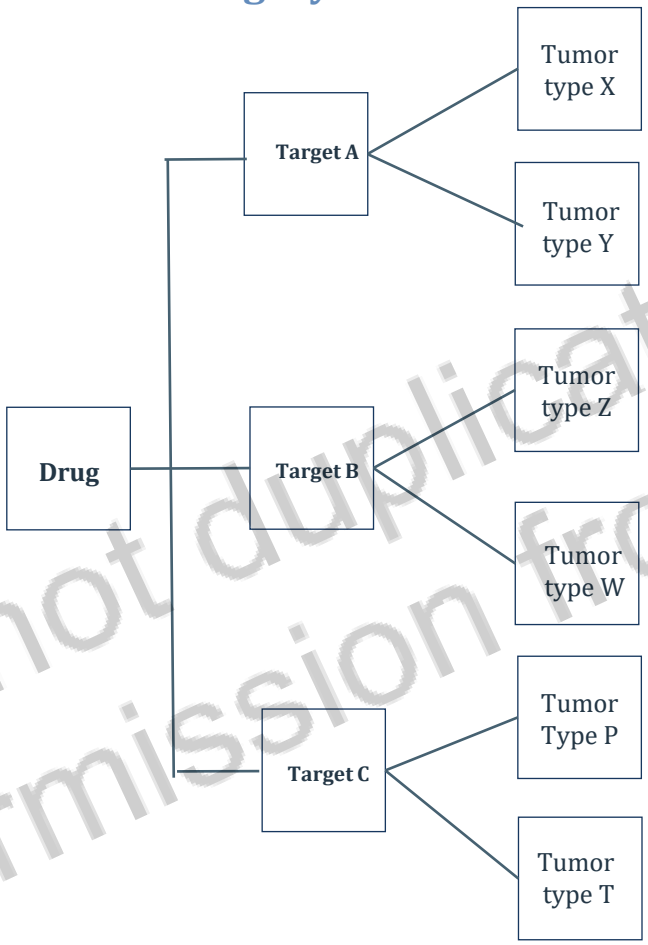
Phase I/II study of alectinib in lung cancer with *RET* fusion gene : study protocol



Dienstmann et al. Mol Oncol 2014

Basket studies

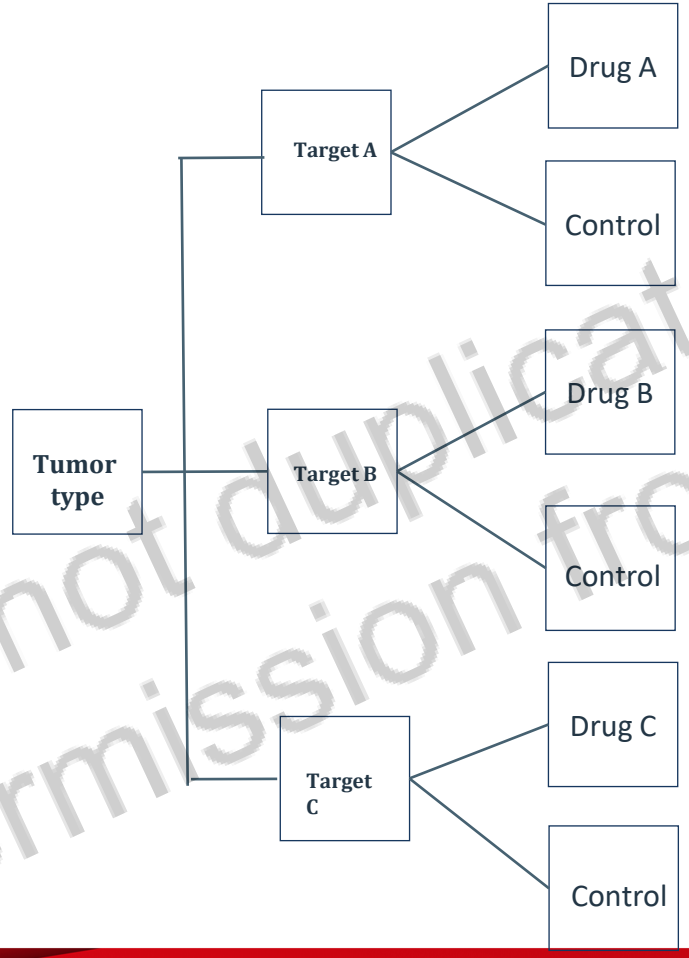
Parallel phase II trials for one drug, but within the same legal entity on the basis of a common denominator that can be the drug or the molecular alteration.
Most of them are histology-independent and aberration-specific clinical trial. These usually fall in the 'trial to learn' category.

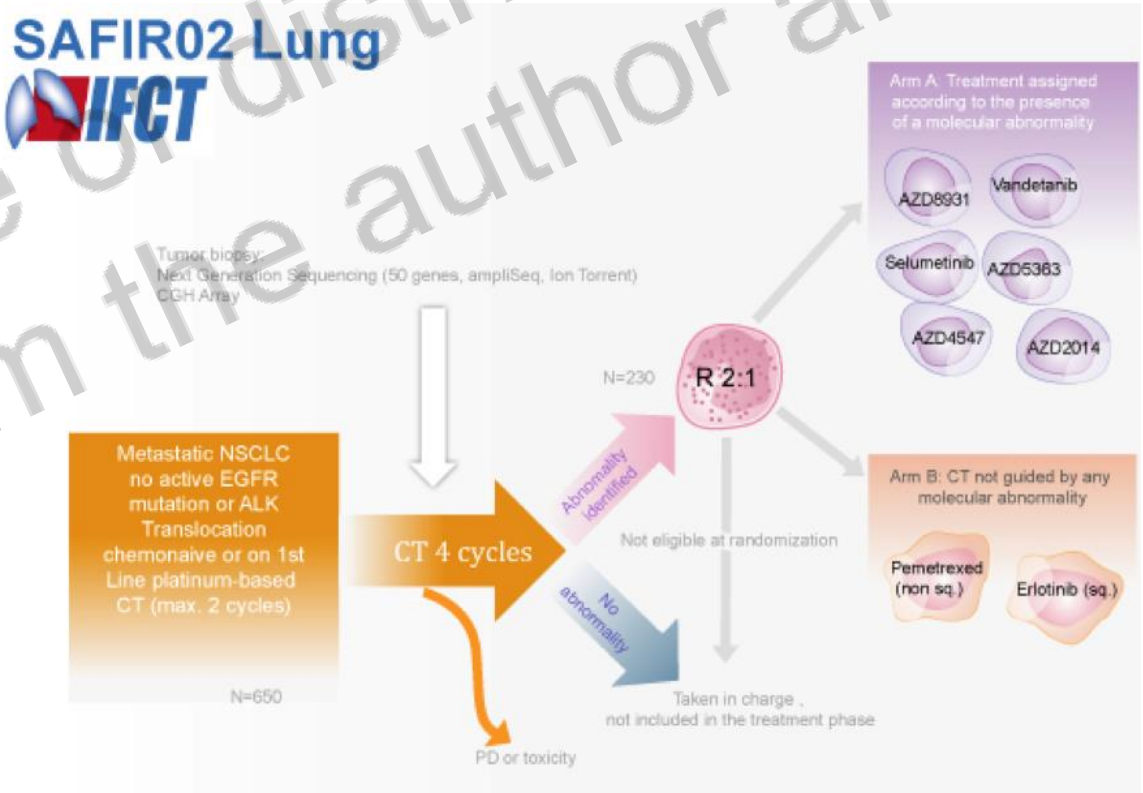


Menis, ERS 2014

Umbrella studies

They embrace both a centrally performed molecular portrait and molecularly selected cohorts with matched drug.
They may fall in the 'trial to conclude' category.





Menis, ERS 2014

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Oncologic Quality Indicators in Thoracic Surgery

Jessica Hudson, MD, MSc[a,1], Tara Semenkovich, MD[a,1], Varun Puri, MD, MSCI[b,*]

Fig. 1. A model for understanding quality of care in medicine as proposed by Donabedian. The 3 categories outlined provide a framework for discussion. (*Data from* Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q 1966;33(4):691–729.)

Thorac Surg Clin 27 (2017) 227–244
http://dx.doi.org/10.1016/j.thorsurg.2017.04.001

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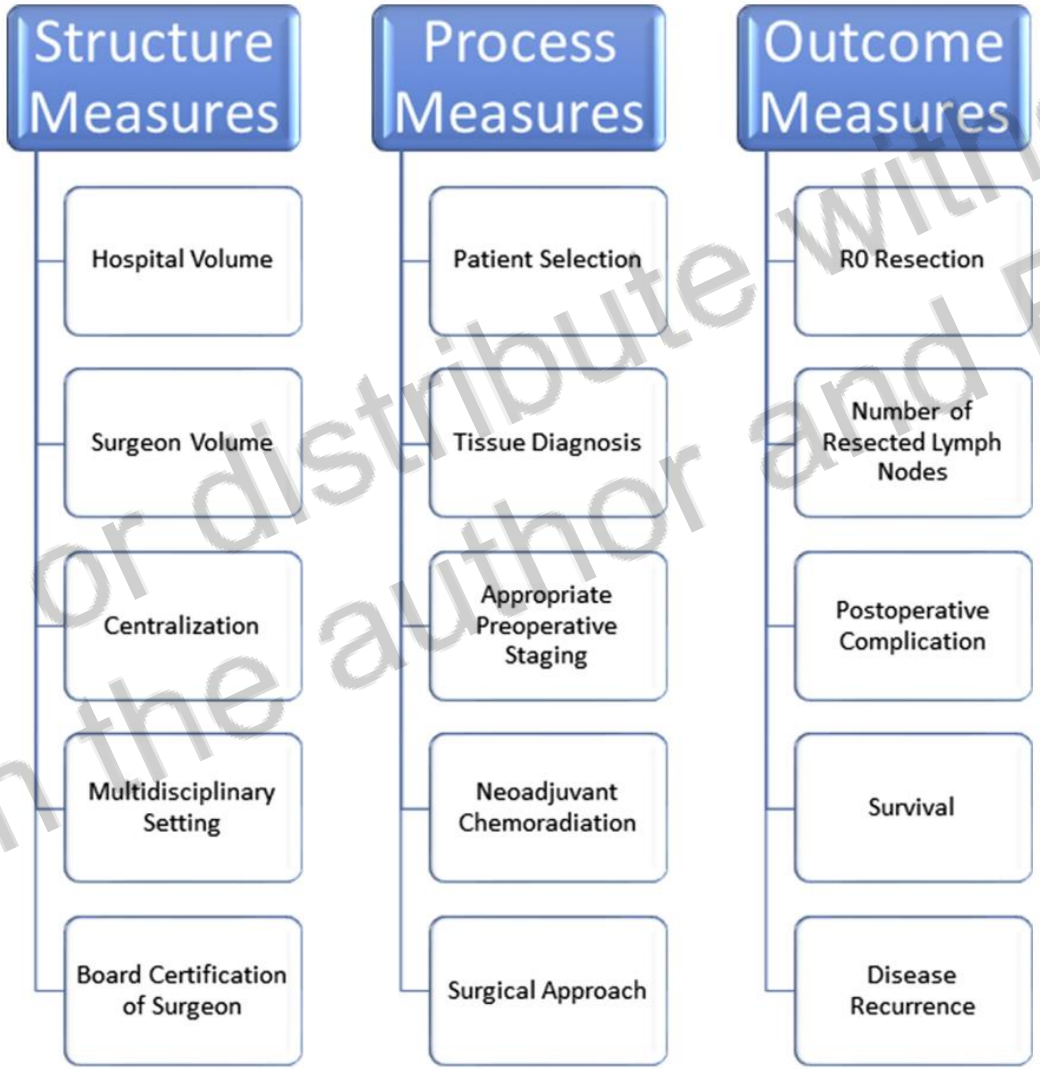

Fig. 2. Examples of quality measures for thoracic cancers. (*Data from* Courrech Staal EFW, Wouters MWJM, Boot H, et al. Quality-of-care indicators for esophageal cancer surgery: A review. Eur J Surg Oncol 2010;36(11): 1035–43.)

Thorac Surg Clin 27 (2017) 227–244
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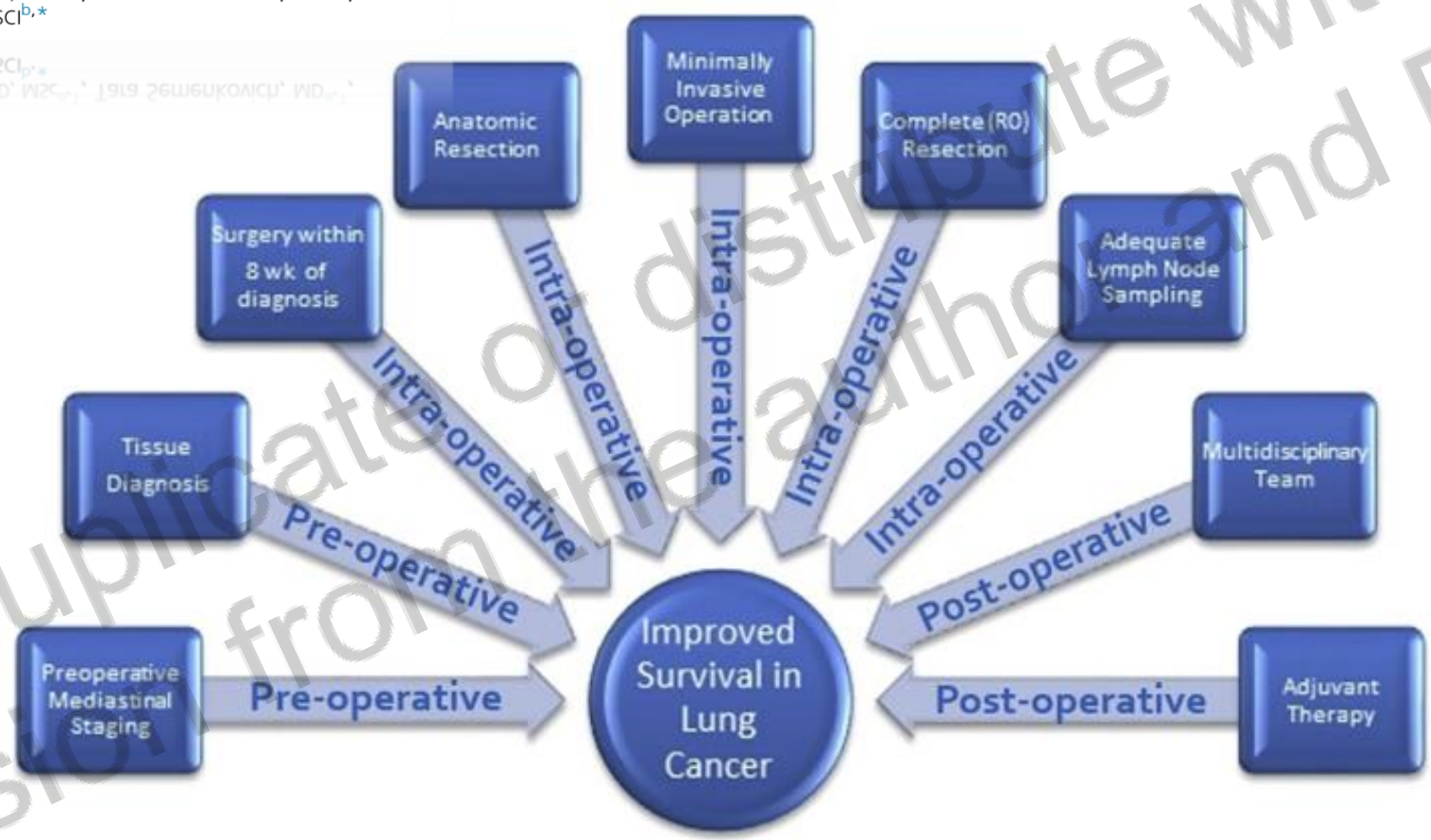

Fig. 3. Quality indicators in lung cancer.

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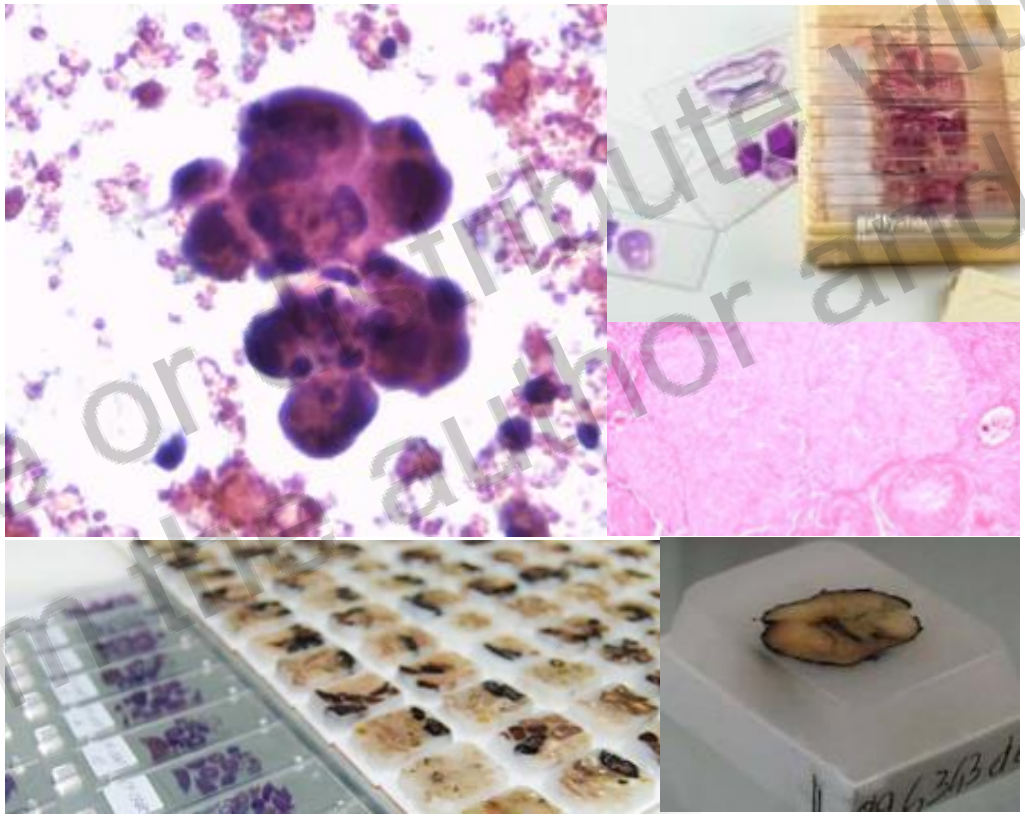
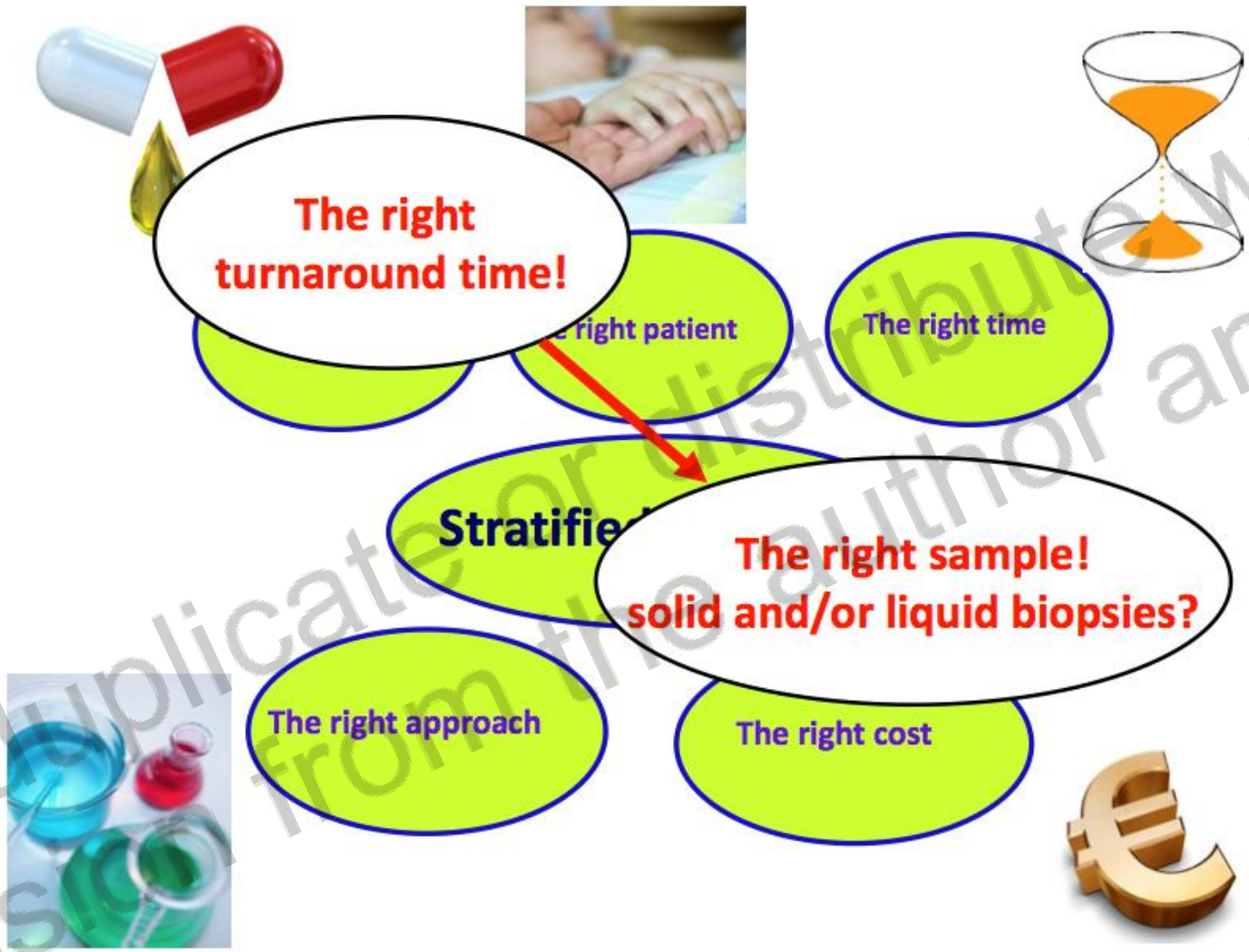
Translational research

- **Tissue is the issue**



- The role of liquid biopsy



Tissue is the issue

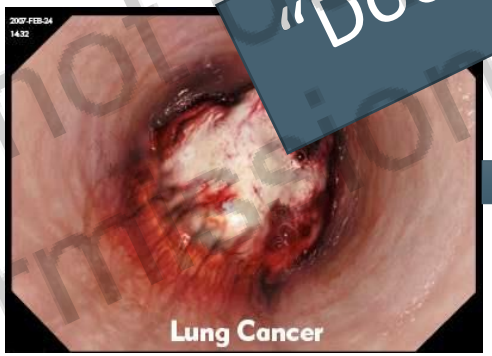
Timelines

TREATMENT

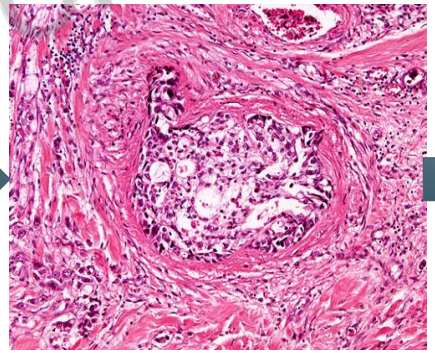
Oncologist

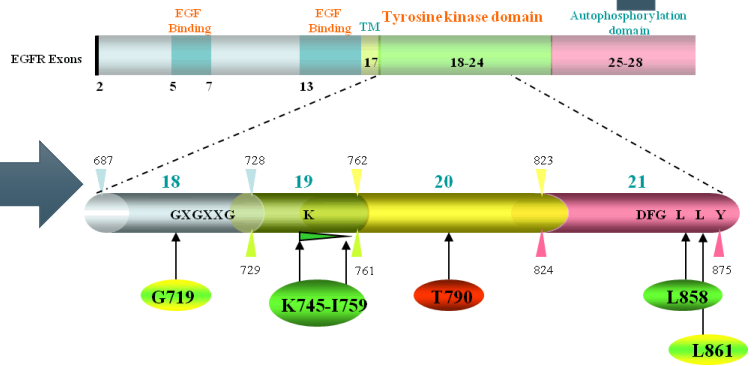
"Doctor how long is it going to take?"

Biops



IHC



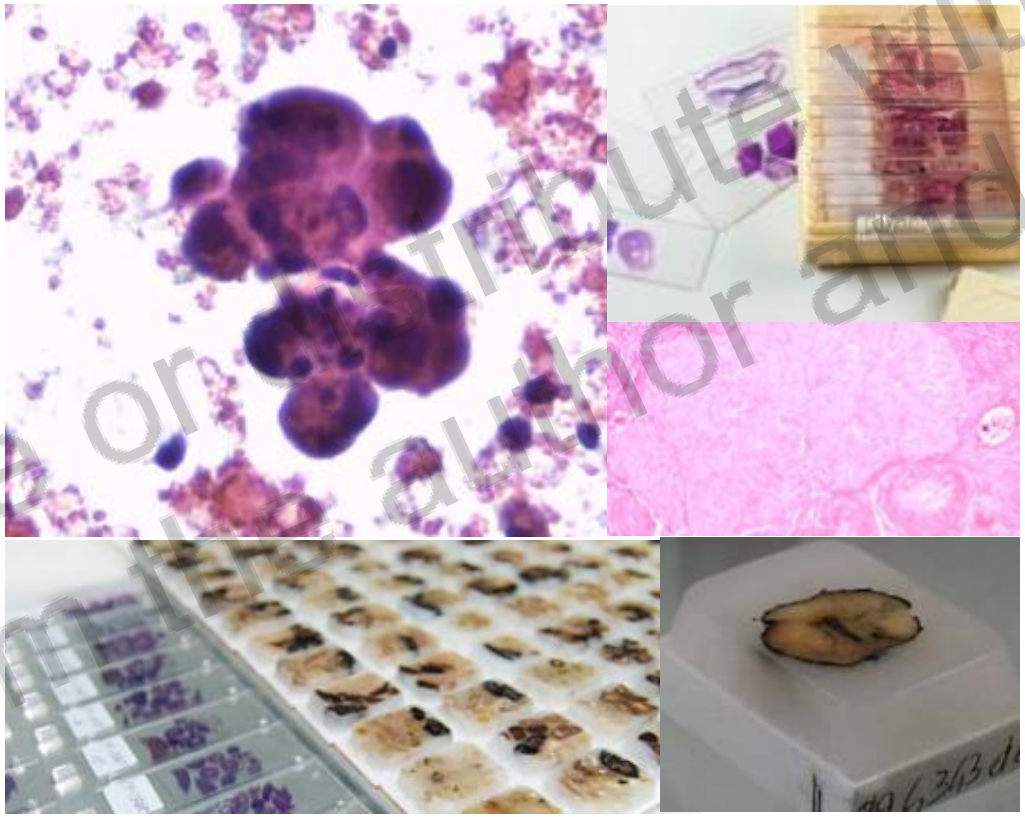


Molecular testing

Courtesy of O. Belvedere

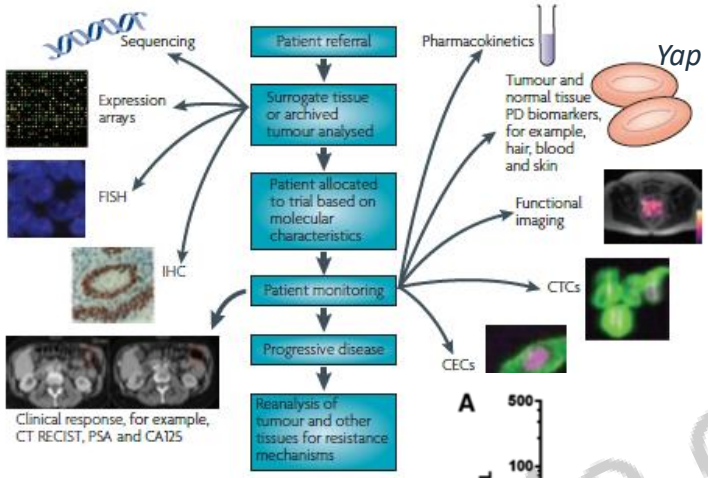
Translational research

- Tissue is the issue

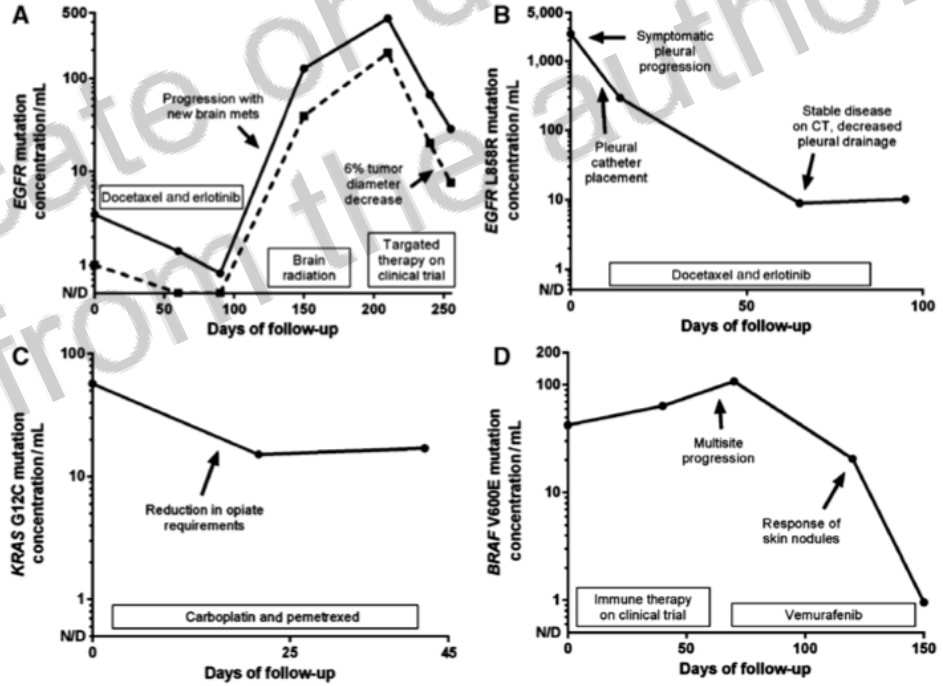


- **The role of liquid biopsy**

What seemed future is a reality

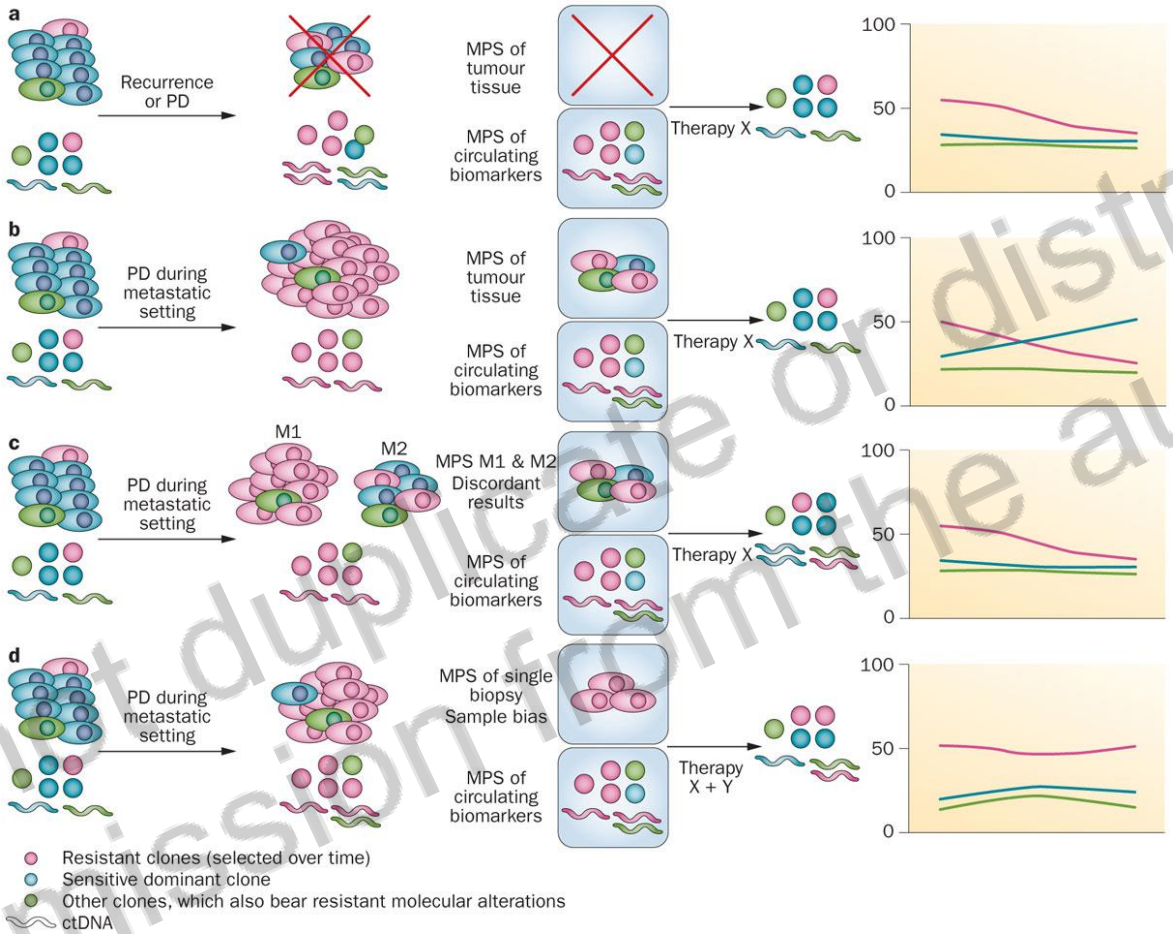


Yap et al. Nature Reviews Cancer 2010



Oxnard GR, et al. Clin Cancer Res; 20(6); 1698–705

Liquid biopsy vs Tissue biopsy



- Heterogeneity
- Accessibility
- Feasibility
- Costs

De Mattos-Arruda. et al. Nat. Rev. Clin. Oncol. 2013

Pitfalls and temptations

- Try to solve all the questions at once
- Base the assumptions only on expert opinion
- Using the easier methodology
- Consider the disease as a uniquum
- Disease-center vs patient-centered

The main rules

The main rules

COLLABORATE

DISCUSS

Pass information as much as possible