Evidence, from a scientific point of view

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27 Definitions of “Evidence”

The internet already provides 27 different versions of the definition of ”Evidence”

Most common ingredients:

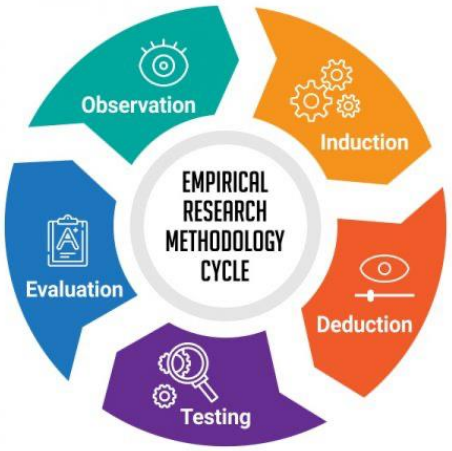
- Something that gives proof or leads to a conclusion
- The available body of facts or information indicating whether a belief or proposition is true or valid
- That, which tends to prove or disprove something
- A sign which shows that something exists or is true

Non-debatable certainty ⟷ Belief, proposition, or expectation

”Scientific Evidence”

- Scientific evidence, is evidence that serves to either **support or refute a scientific theory or hypothesis**.
- Such evidence is expected to be **objective** empirical evidence and interpretable in accordance with **scientific methods**.
- Standards for scientific evidence vary according to the field of inquiry, but the strength of scientific evidence is generally based on the results of **statistical analysis** and the rigor of **scientific controls**.

◎ **Exclude the possibility of an observation by chance**



CLINICAL PARAMETERS USED FOR SCIENTIFIC EVIDENCE IN ONCOLOGY

- Survival
- Tumor burden change (Response/Remission)
- Symptom change
- Quality of Life change

OVERALL SURVIVAL

- Requires availability of the date of death
- ”Overall survival” = time from start of the observation until the date of death

Overall Survival (in weeks, or months)

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Overall Survival (in weeks, or months)

PROGRESSION FREE SURVIVAL

- Requires evidence for growth of the tumor
- ”Progression survival” = time from start of the observation until the evidence of the first progression of disease

Progression Free Survival (in weeks, or months)

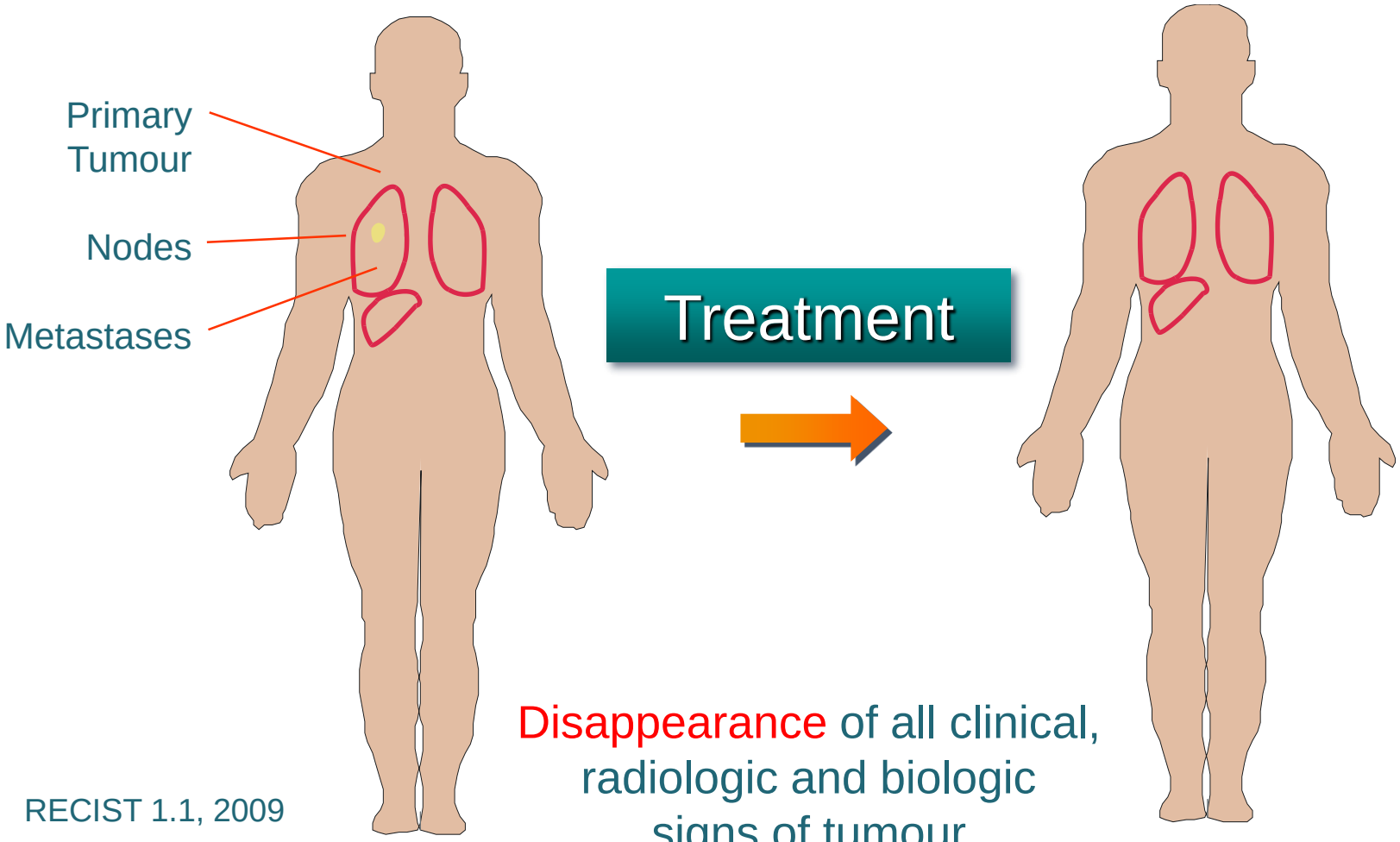
➥ **Assessing “Progression of Disease”, requires measuring tumor extent/size**

IMPORTANCE OF SPEAKING THE SAME LANGUAGE, WHEN MEASURING TUMOR EXTENT/SIZE

REsponse Criteria In Solid Tumors (RECIST)

NCI-NCIC-EORTC

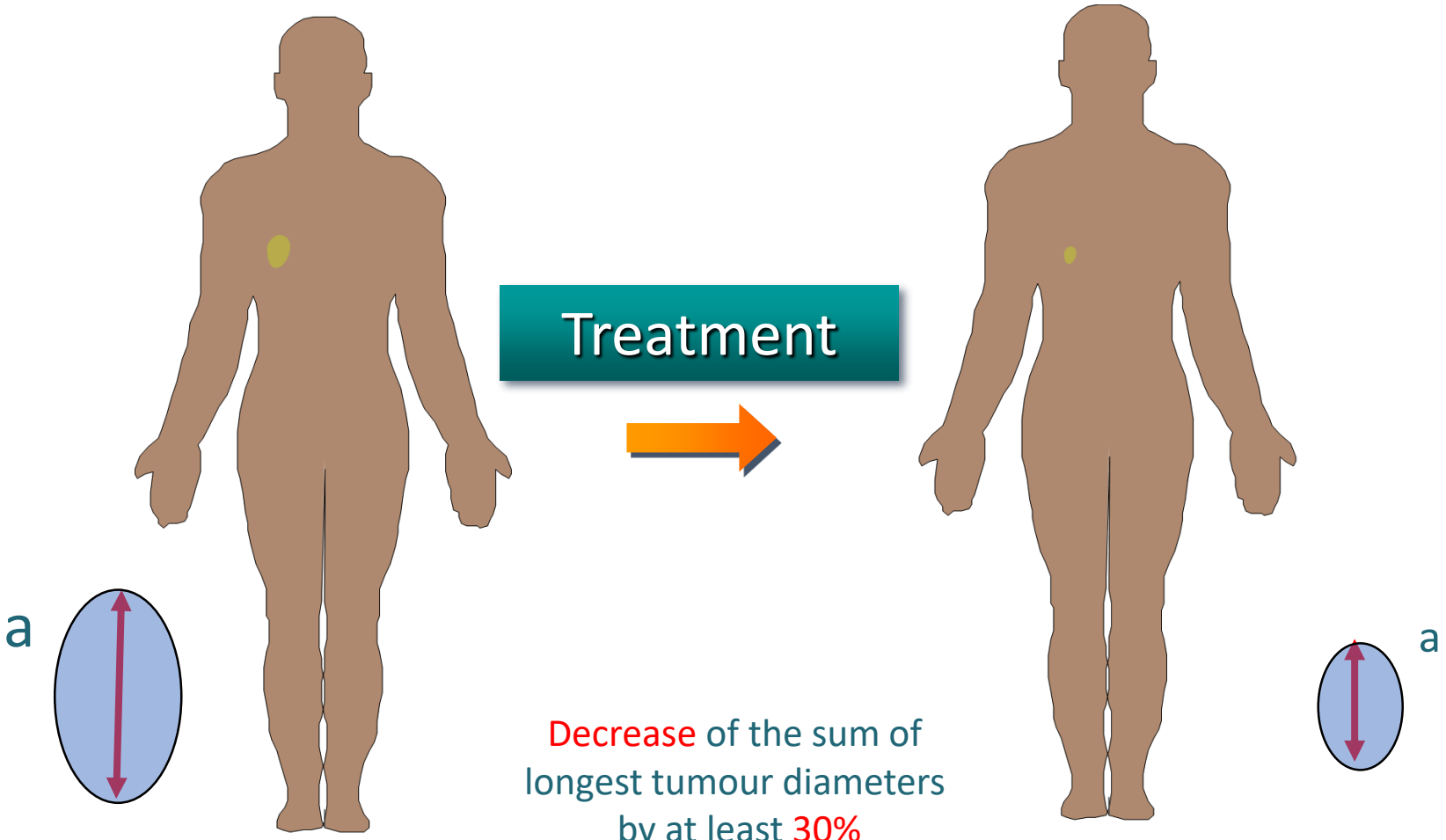
COMPLETE REMISSION



Disappearance of all clinical, radiologic and biologic signs of tumour

RECIST 1.1, 2009

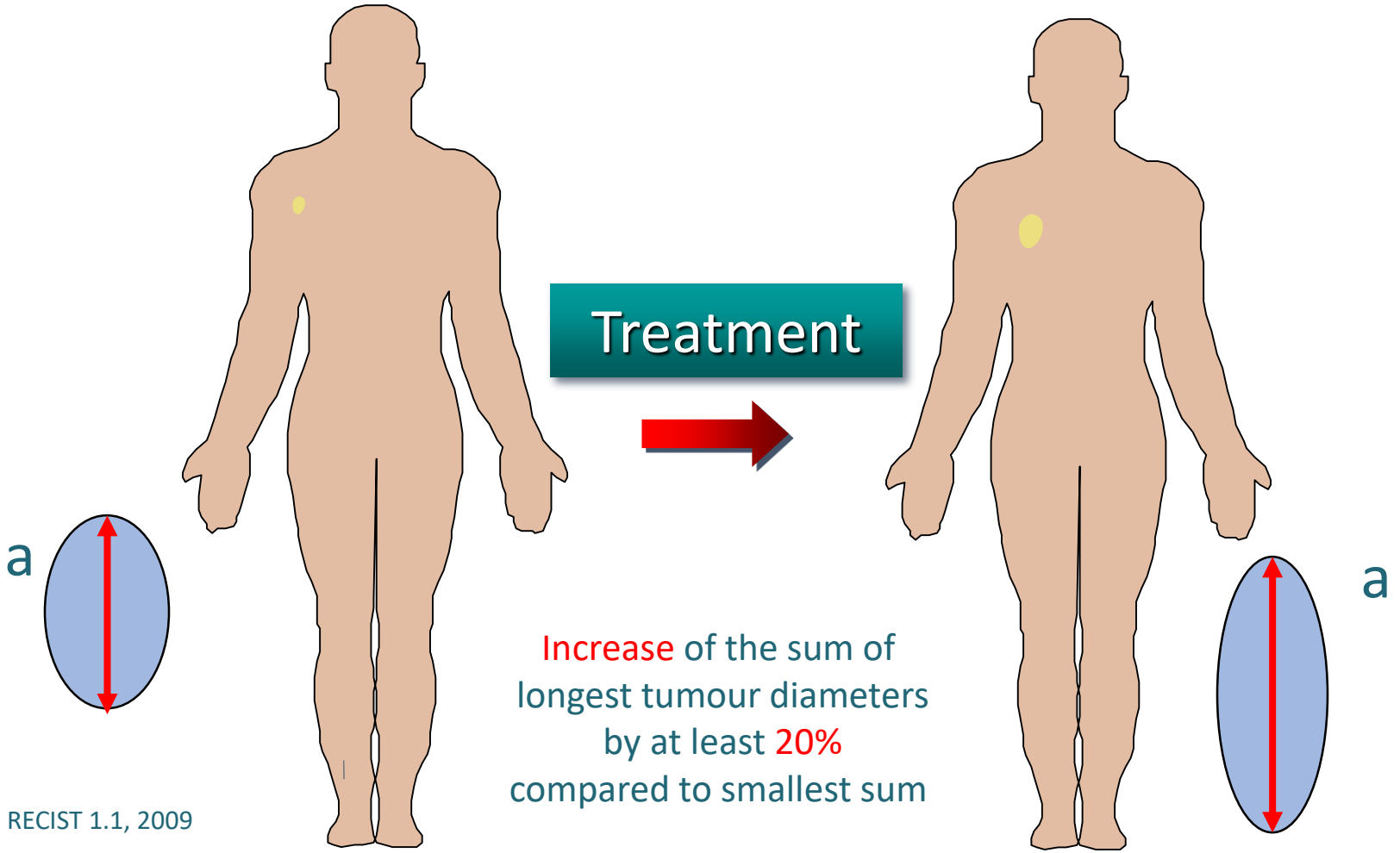
PARTIAL REMISSION



Decrease of the sum of longest tumour diameters by at least 30% compared to baseline

RECIST 1.1, 2009

PROGRESSION



Increase of the sum of longest tumour diameters by at least 20% compared to smallest sum

RECIST 1.1, 2009

IMPORTANCE OF SPEAKING THE SAME LANGUAGE, WHEN MEASURING TUMOR EXTENT/SIZE

REsponse Criteria In Solid Tumors (RECIST)

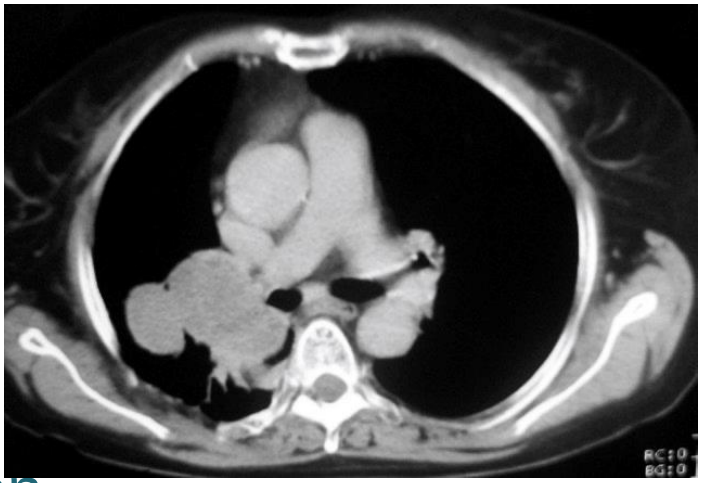
NCI-NCIC-EORTC

! **Scientifically validated based upon a huge set of databases** !

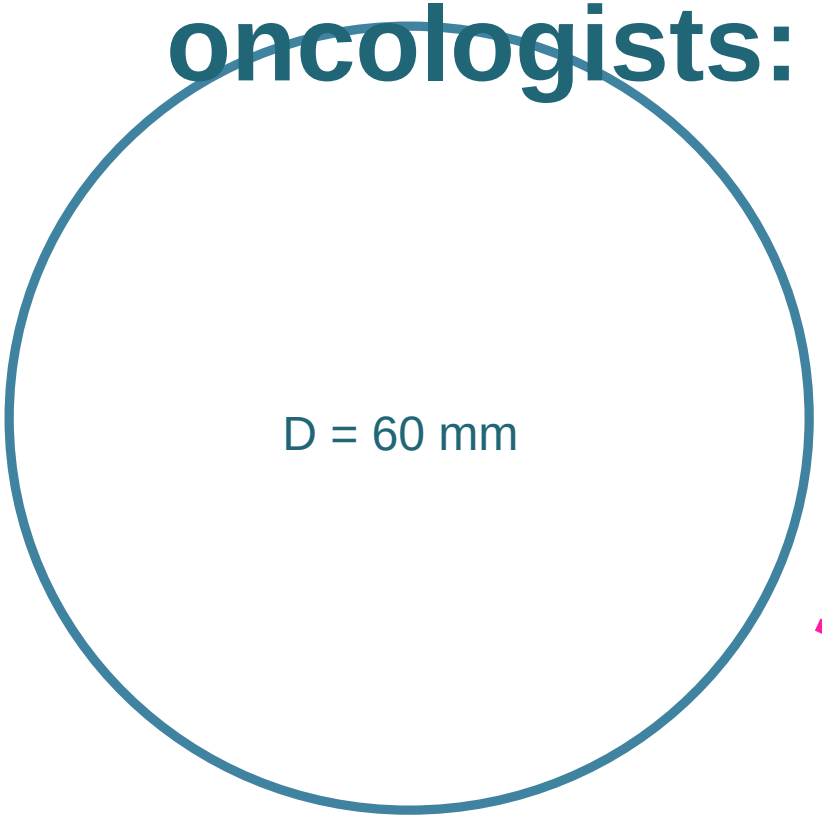
Measuring tumors

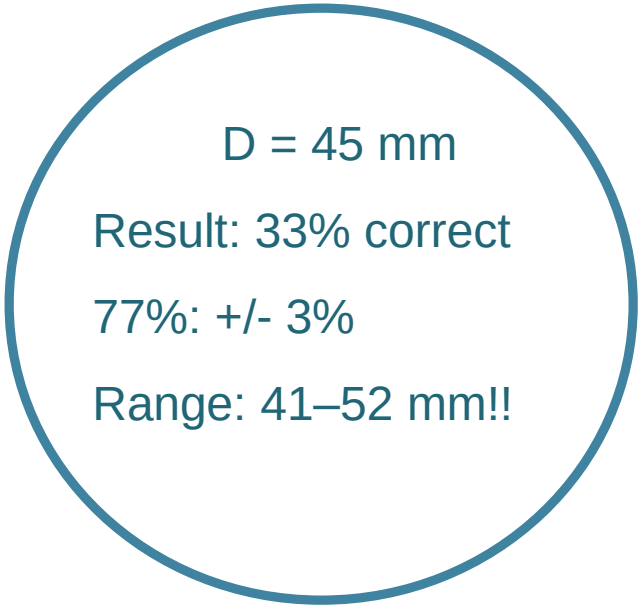
Not easy !!!!!!!!!!

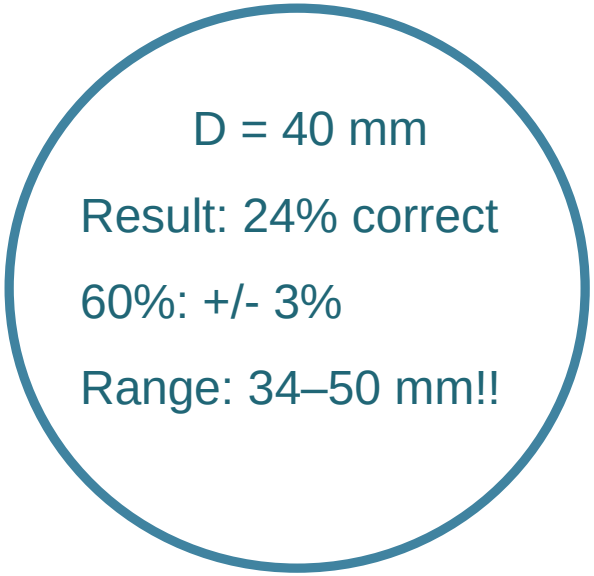
- Selecting suitable lesion(s)
- Finding largest size
- Finding margins
- Being precise
- Selecting equivalent image on subsequent examinations



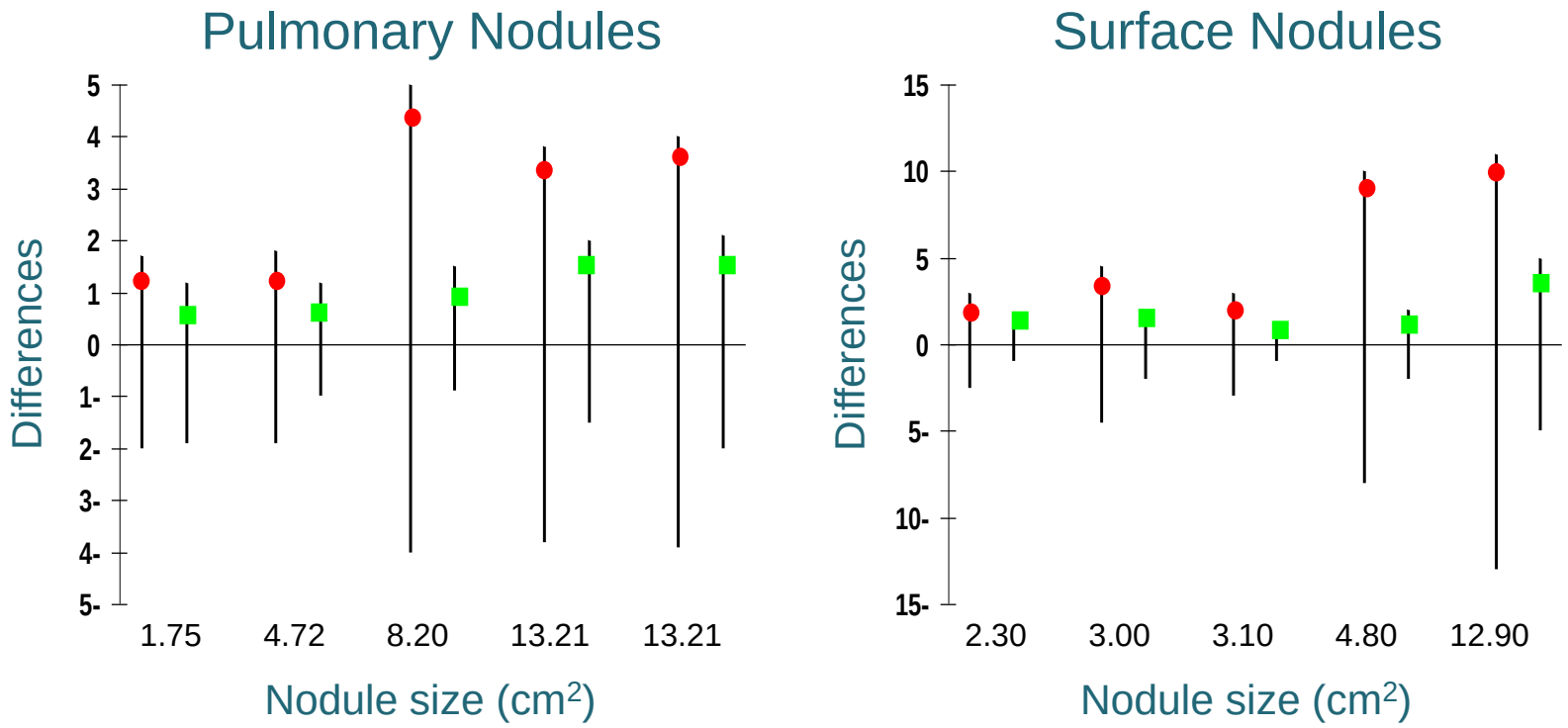
Test with 60 medical oncologists:







Mean differences between replicate radiologic measurements (in cm^2)



From: Monsky et al., JCO 18: 437, 2000

CLINICAL PARAMETERS USED FOR SCIENTIFIC EVIDENCE IN ONCOLOGY

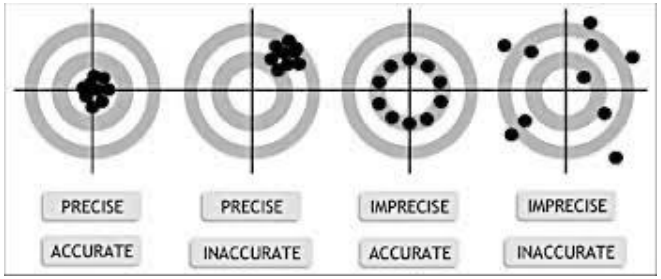
- Survival
- Tumor burden change (Response/Remission)
- Symptom change
- Quality of Life change

◎ Very subjective
◎ Require tools to create objectivity

Alternative “surrogate” endpoints of drug-activity

- Serum marker change
- Measures of target inhibition
  - Tumor tissues
  - Normal tissues
- Change in metabolism at PET-scanning

- No alternative endpoint has truly been validated. To be a valid substitute for response: measure must be able to select drugs later proven to be effective in randomised trials



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IN ONCOLOGY, OBTAINING OBJECTIVE CLINICAL EVIDENCE OF EFFECT, IS A SCIENTIFIC ART

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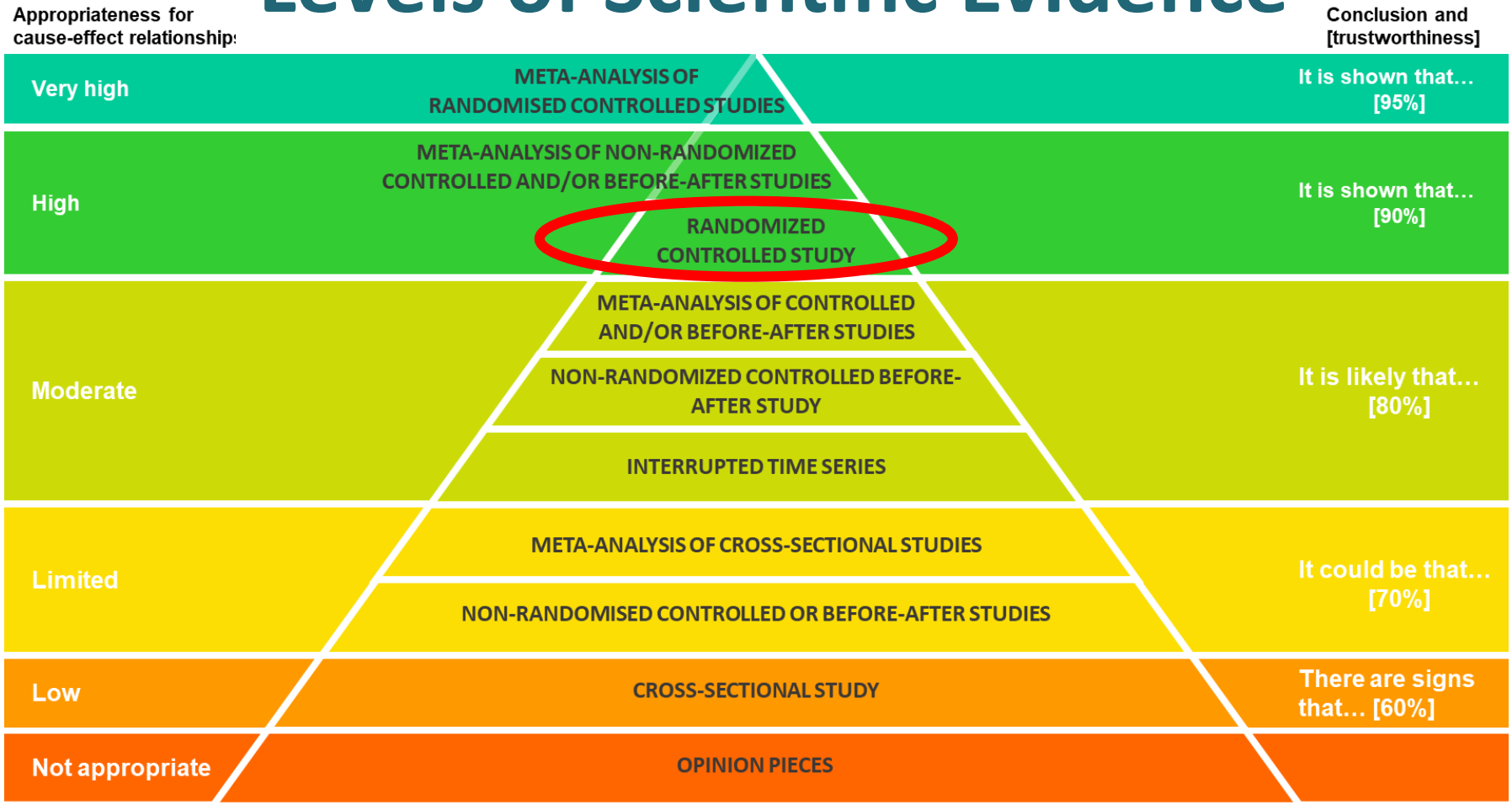
Levels of Scientific Evidence

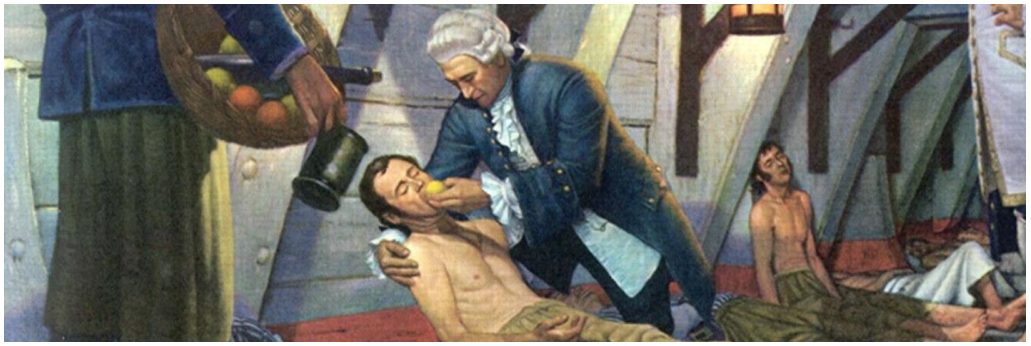


SCIENCE FOR WORK

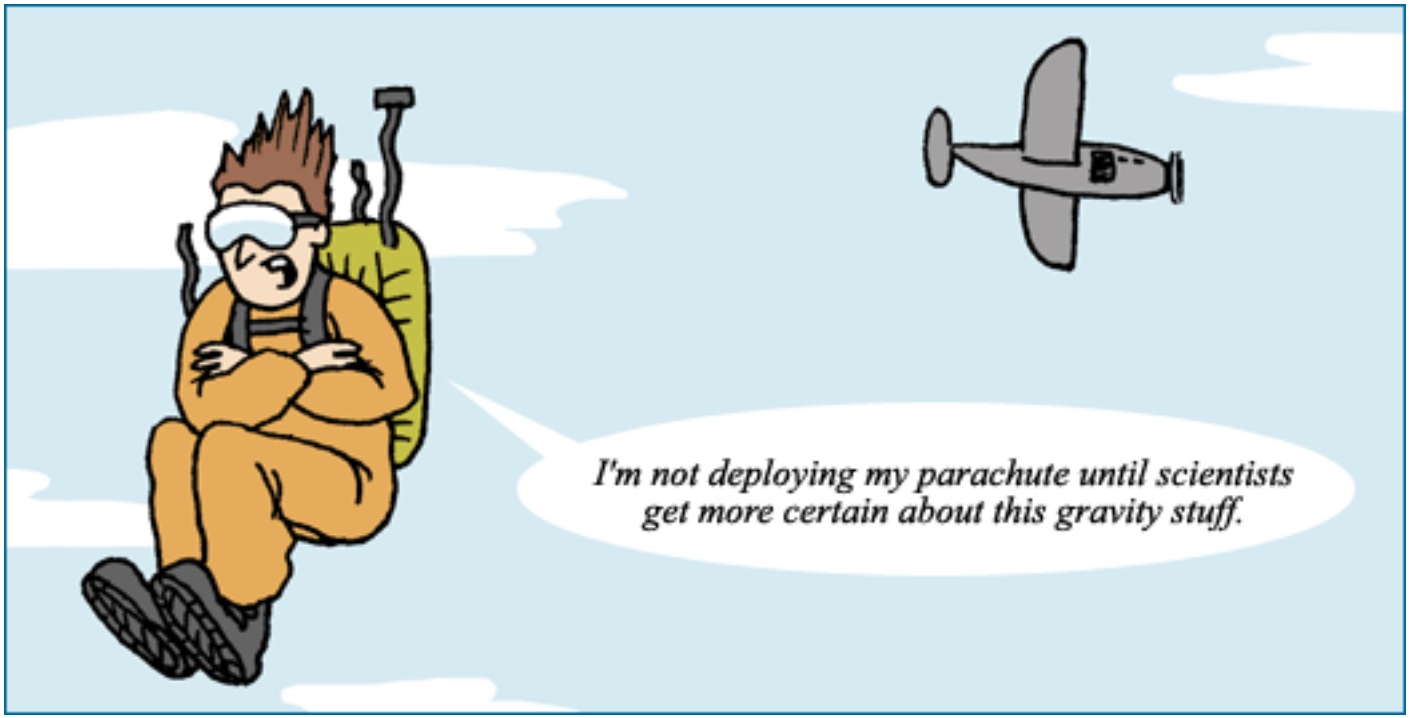
FACILITATE DEBATE ACTIVATE INNOVATE

Randomized Clinical Trials

- Large and expensive
- Comparison with ‘best therapy’
- Randomised, to provide Evidence
  - In the 1940s A. Bradford Hill designed and conducted the first randomized clinical trial (RCT) of streptomycin in tuberculosis. This has changed anecdote and case study medicine into legitimate science
  - May 20, 1747: The actual first randomized trial by dr. James Lind, comparing cider, vitriolic elixir (diluted sulfuric acid), vinegar, sea water, two oranges and a lemon, or a purgative mixture, in the treatment of scurvy, in 6 pairs of 2 sailors.



Sometimes, scientific evidence may be difficult to get



THE CHALLENGE OF RARE DISEASES
Soft Tissue Sarcomas (STS)

SOFT TISSUE TUMOURS

WHO Classification of Soft Tissue Tumours

1 Adipocytic tumours
Lipoma
Lipomatosis
Lipomatosis of nerve
Lipoblastoma / Lipoblastomatosis
Angiolipoma
Myolipoma of soft tissue
Chondroid lipoma
Spindle cell lipoma / Pleomorphic lipoma
Hibernoma
Atypical lipomatous tumour / Well differentiated liposarcoma
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma
Mixed-type liposarcoma

2 Fibroblastic / Myofibroblastic tumours
Nodular fasciitis
Proliferative fasciitis and proliferative myositis
Myositis ossificans and fibroosseous pseudotumour of digits
Ischaemic fasciitis
Elastofibroma
Fibrous hamartoma of infancy
Myofibroma / Myofibromatosis
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma
Cellular angiofibroma
Nuchal-type fibroma
Gardner fibroma
Calcifying fibrous tumour
Giant cell angiofibroma
Superficial fibromatoses
Desmoid-type fibromatoses
Lipofibromatosis
Extrapleural solitary fibrous tumour and haemangiopericytoma
Inflammatory myofibroblastic tumour
Low grade myofibroblastic sarcoma
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcoma
Adult fibrosarcoma
Myxofibrosarcoma
Low grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosarcoma

3 So-called fibrohistiocytic tumours
Giant cell tumour of tendon sheath
Diffuse-type giant cell tumour
Deep benign fibrous histiocytoma
Plexiform fibrohistiocytic tumour
Giant cell tumour of soft tissue
Pleomorphic malignant fibrous histiocytoma / Undifferentiated high grade pleomorphic sarcoma
Giant cell malignant fibrous histic Undifferentiated pleomorphic with giant cells
Inflammatory malignant fibrous histiocytoma / Undifferentiated pleomorphic sarcoma with prominent inflammation

4 Smooth muscle tumours
Angioleiomyoma
Leiomyoma of deep soft tissue
Leiomyosarcoma

5 Pericytic (perivascular) tumours
Glomus tumours
Myopericytoma

6 Skeletal muscle tumours
Rhabdomyoma
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma

7 Vascular tumours
Haemangiomas
Epithelioid haemangioma
Angiomatosis
Lymphangioma
Kaposiform haemangioendothelioma
Retiform haemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite haemangioendothelioma
Kaposi sarcoma
Other intermediate vascular neoplasms
Epithelioid haemangioendothelioma
Angiosarcoma of soft tissue

8 Chondro-osseous tumours
Soft tissue chondroma
Extraskeletal osteosarcoma

9 Tumours of uncertain differentiation
Intramuscular myxoma
Juxta-articular myxoma
Deep 'aggressive' angiomyxoma
Pleomorphic hyalinizing angiectatic tumour of soft parts
Ectopic hamartomatous thymoma
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumour
Mixed tumour / Myoepithelioma / Parachordoma
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
[illegible]oma of soft tissue
[illegible]myxoid chondrosarcoma
[illegible]senchymoma
[illegible] small round cell tumour
[illegible]bdoid tumour
Neoplasms with perivascular epithelioid cell differentiation (PEComas)
Intimal sarcoma

BONE TUMOURS

WHO Classification of Bone Tumours

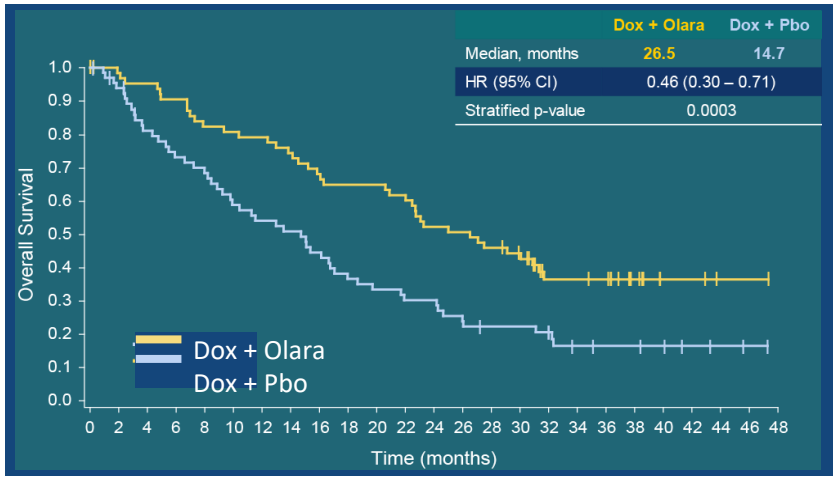
10 Cartilage tumours
Osteochondroma
Chondromas
Chondroblastoma
Chondromyxoid fibroma
Synovial chondromatosis
Chondrosarcoma
Dedifferentiated chondrosarcoma
Mesenchymal chondrosarcoma
Clear cell chondrosarcoma

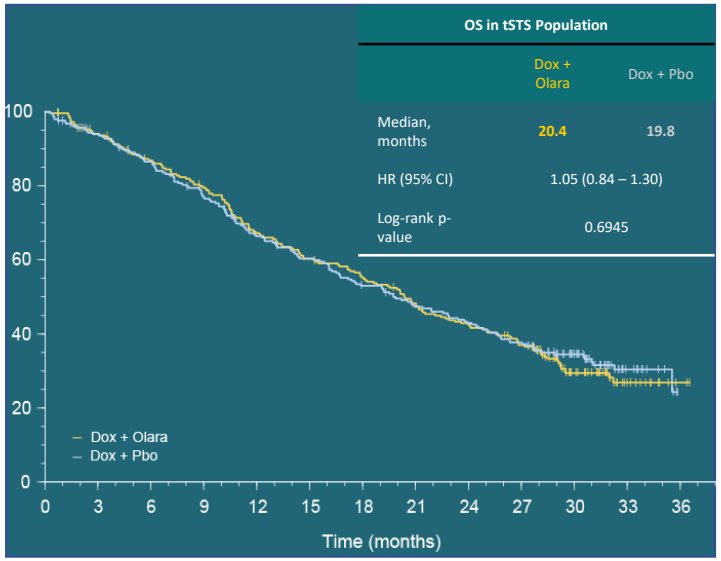
11 Osteogenic tumours
Osteoid osteoma
Osteoblastoma
Conventional osteosarcoma
Telangiectatic osteosarcoma
Small cell osteosarcoma
Low grade central osteosarcoma
Secondary osteosarcoma
Parosteal osteosarcoma
Periosteal osteosarcoma
High grade surface osteosarcoma

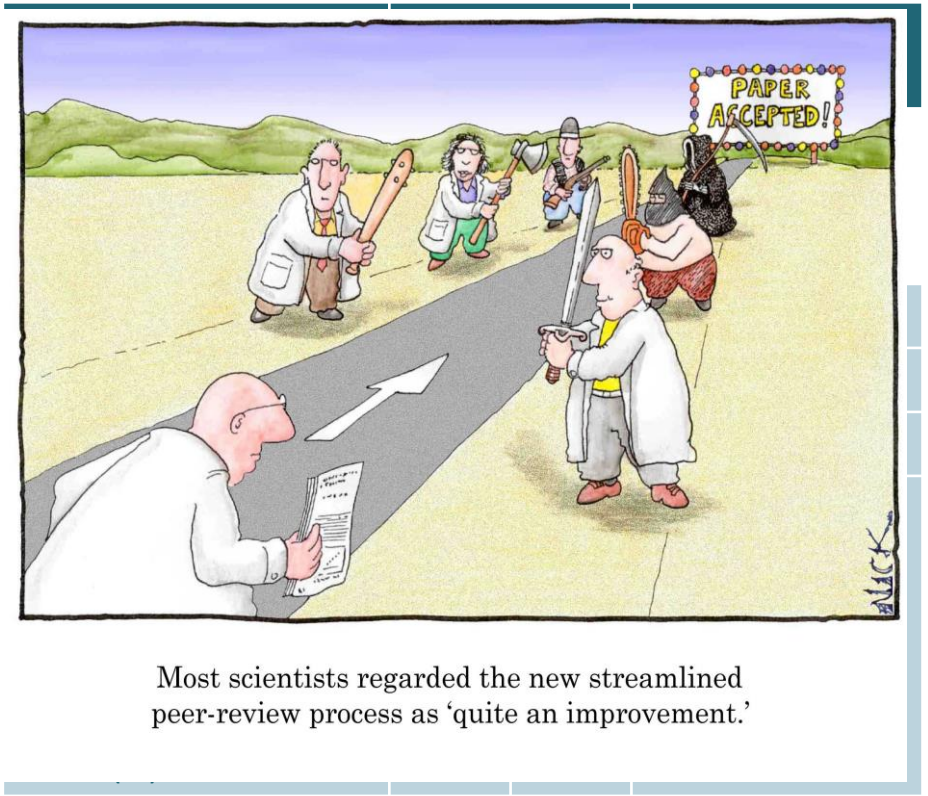
12 Fibrogenic tumours
Desmoplastic fibroma of bone
Fibrosarcoma of bone

- Rare (< 1% of all malignancies) and heterogeneous group of malignancies originating from mesenchymal precursors
- Current WHO classification of Soft Tissue Tumors identifies very large number of subtypes
- A double challenge for performing clinical trials

Doxorubicin +/- Olaratumab







Tap WD, et al. *Lancet* 2016;388:488-97 (updated 388:464)

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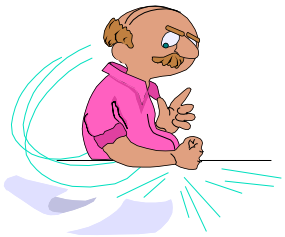


Levels of Scientific Evidence

Appropriateness for cause-effect relationship		Conclusion and [trustworthiness]
Very high	META-ANALYSIS OF RANDOMISED CONTROLLED STUDIES	It is shown that… [95%]
High	META-ANALYSIS OF NON-RANDOMIZED CONTROLLED AND/OR BEFORE-AFTER STUDIES RANDOMIZED CONTROLLED STUDY	It is shown that… [90%]
Moderate	META-ANALYSIS OF CONTROLLED AND/OR BEFORE-AFTER STUDIES NON-RANDOMIZED CONTROLLED BEFORE-AFTER STUDY INTERRUPTED TIME SERIES	It is likely that… [80%]
Limited	META-ANALYSIS OF CROSS-SECTIONAL STUDIES NON-RANDOMISED CONTROLLED OR BEFORE-AFTER STUDIES	It could be that… [70%]
Low	CROSS-SECTIONAL STUDY	There are signs that… [60%]
Not appropriate	OPINION PIECES	

SCIENCE FOR WORK

REGULATORY PERSPECTIVE

EMA (CHMP)

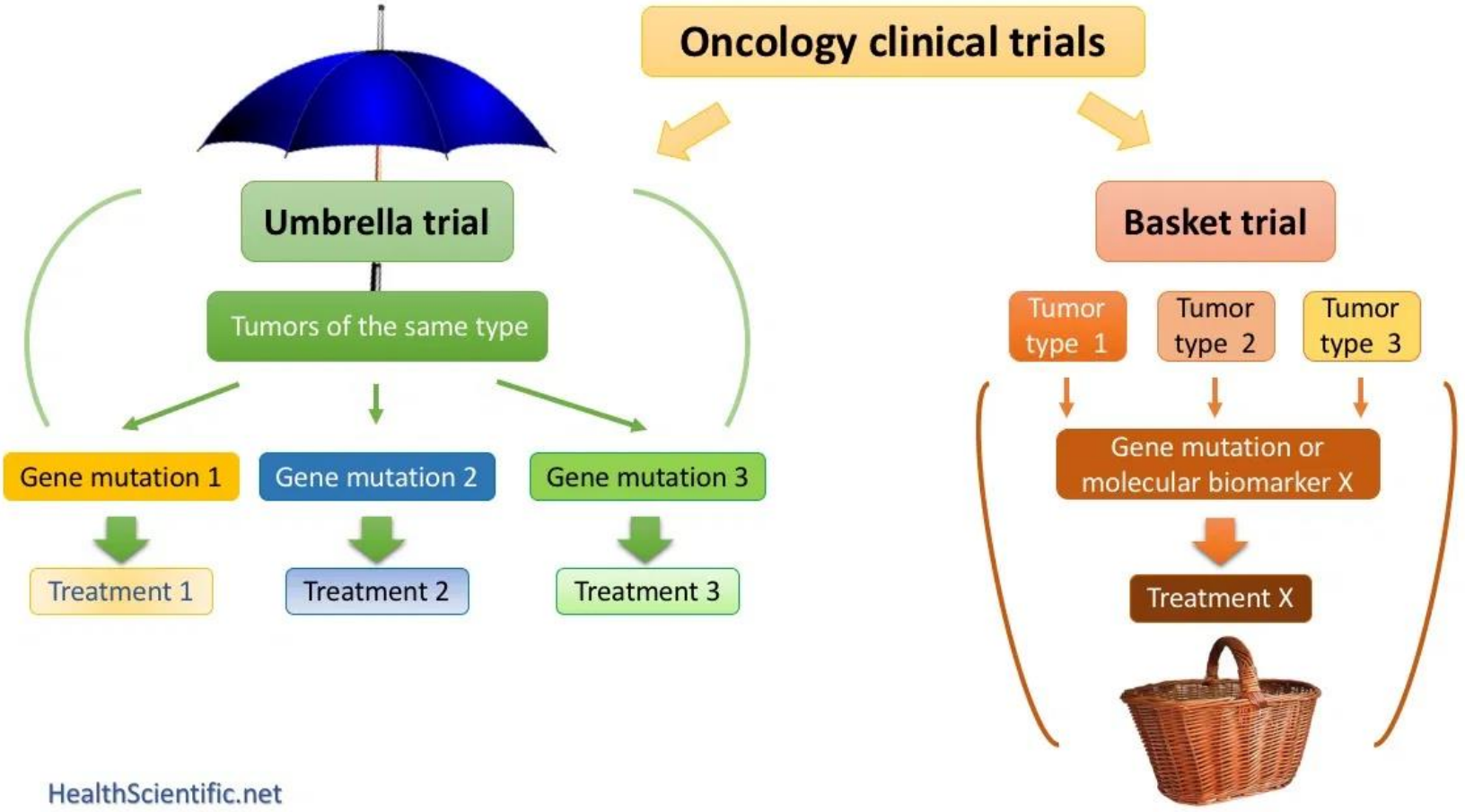
Standard authorization:

- Phase 3 Randomised Clinical Trial (RCT) of adequate size
- Statistically significant objective benefit

Conditional marketing authorization, if:

- The benefit-risk balance of the medicine is positive;
- Tt is likely that the applicant will be able to provide comprehensive data post-authorisation;
- The medicine fulfils an unmet medical need;
- The benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Umbrella and Basket studies



Tumor agnostic development

CONDITIONAL APPROVALS ("EVIDENCE") BASED ON SMALL NUMBERS

Tissue Agnostic Drug Approvals

Drug	Indication*	Efficacy ORR (95% CI)	Post Approval Studies?	Device?
2017: Pembrolizumab N=149	MSI-H; dMMR[1]	40% (32, 48)	Yes	No
2018: Larotrectinib N=55	NTRK-fusions	75% (61, 85)	Yes	No
2019: Entrectinib N=54	NTRK-fusions	57.4% (43, 77)	Yes	No
2020: Pembrolizumab N=102	TMB-H[1]	29% (21, 39)	Yes	Yes

*Approved for adult and pediatric patients
[1]Extrapolation from adults to pediatrics
ORR= Overall response rate by RECIST 1.1

Muddy waters

IN SUMMARY

- Obtaining objective scientific clinical evidence of effect in oncology, is challenging
- Increasing knowledge, fragments diseases into rare diseases
- Rare diseases create a challenge for large trials
- Scientific rigor may oppose patient needs

CONTINUOUS DISCUSSION AMONG STAKEHOLDERS IS CRUCIAL, TO JOINTLY FIND THE MOST BALANCED WAY TO SCIENTIFICALLY SERVE PATIENT AND SOCIETY NEEDS

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THANK YOU FOR YOUR ATTENTION

FACILITATE DEBATE ACTIVATE INNOVATE