RARE CANCERS EUROPE

Joining forces for action

Uncontrolled evidence in rare cancers

Paolo G. Casali
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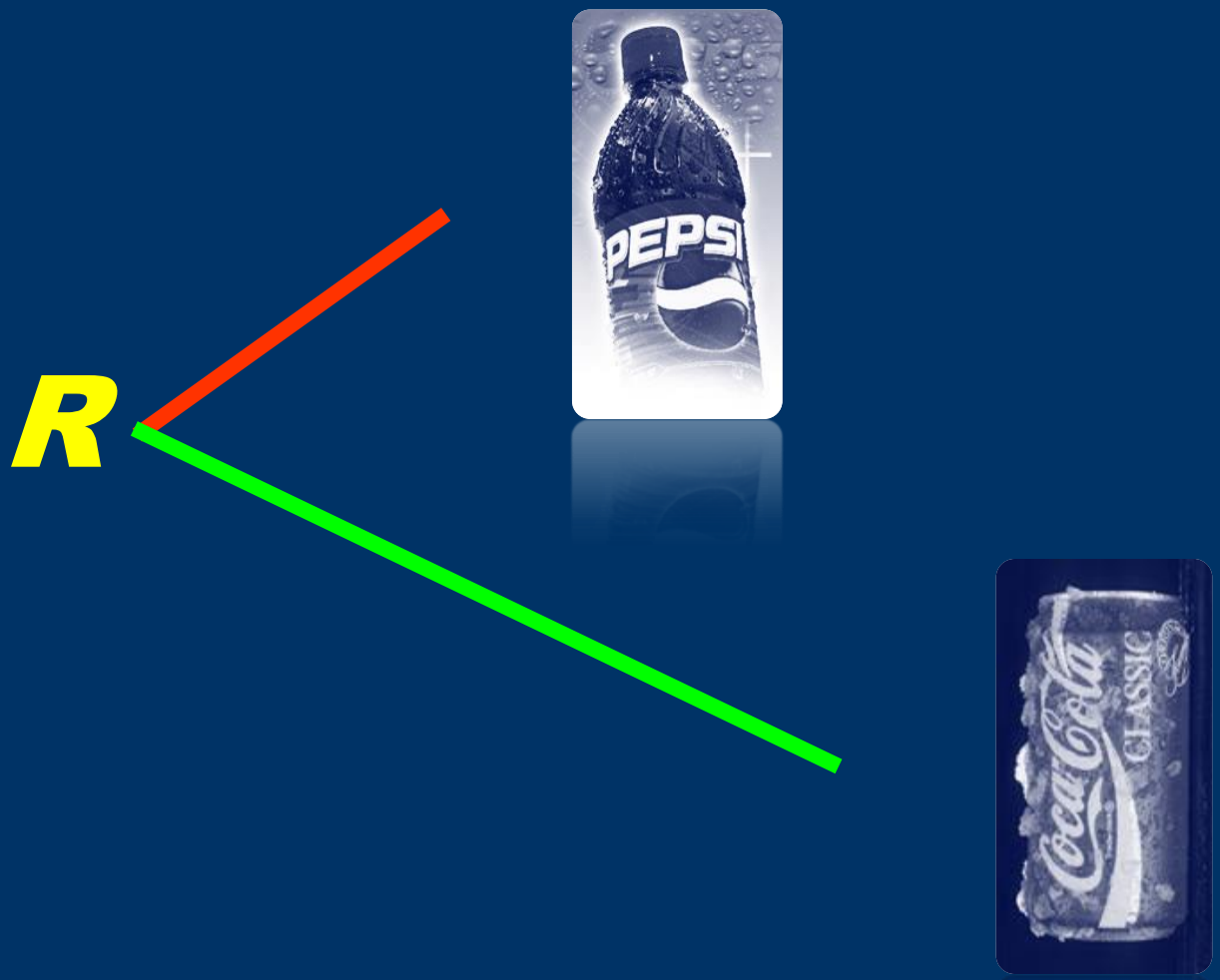
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Rare cancers are not so rare: The rare cancer burden in Europe

Gemma Gatta [a,*], *Jan Maarten van der Zwan* [b], *Paolo G. Casali* [c], *Sabine Siesling* [b], *Angelo Paolo Dei Tos* [d], *Ian Kunkler* [e], *Renée Otter* [b], *Lisa Licitra* [f], *Sandra Mallone* [g], *Andrea Tavilla* [g], *Annalisa Trama* [a], *Riccardo Capocaccia* [g], *The RARECARE working group*

Table 3 – Data quality indicators and other characteristics of malignant cancers diagnosed in European cancer registries 1995-2002 and included in the analyses.

Country	Registry	Number of malignant cancers	Data quality indicators					
			Death certificate only (%)	Autopsy (%)	Microscopic verification (%)	Cases 1995-1998 censored before 5 years (%)	Morphology code NOS[a] (%)	Topography code NOS[a] (%)
Austria	Austria	304,695	8.9	0.0	85.2	5.9	10.1	0.6
Belgium	Flanders	144,715	0.0	0.2	89.8	0.0	7.3	0.5
France	Bas Rhin	13,113	0.0	0.0	95.8	3.3	3.9	0.2
	Calvados	5895	0.0	0.0	98.1	6.1	2.5	0.3
	Calvados digestive	2801	0.0	0.0	87.0	4.4	10.5	0.3
	Côte d'Or digestive	4376	0.0	0.0	82.8	0.5	17.5	0.2
	Côte d'Or haematol.	1884	0.0	0.0	100.0	7.2	0.0	0.5
	Doubs	5762	0.0	0.0	95.8	2.1	3.2	0.3
	Haut Rhin	9073	0.0	0.0	96.4	5.8	2.9	0.1
	Hérault	10,505	0.0	0.0	0.0	6.4	1.5	0.1
	Isère	12,526	0.0	0.0	94.1	4.6	4.1	0.1
	Loire Atlantique	3766	0.0	0.0	100.0	6.8	0.0	0.0
	Manche	6367	0.0	0.0	96.5	2.7	3.4	0.3
	Marne and Ardennes	168	0.0	0.0	100.0	3.6	0.0	0.0
	Somme	6481	0.0	0.0	94.2	6.6	5.5	0.8
	Tarn	4935	0.0	0.0	93.8	2.0	5.9	1.3
Germany	Saarland	54,132	3.9	0.0	91.8	5.8	8.0	0.5
Iceland	Iceland	8854	0.1	1.4	96.6	0.0	3.5	0.0
Ireland	Ireland	156,529	2.0	0.3	86.7	0.0	11.0	0.7
Italy	Alto Adige	18,676	0.7	0.0	89.5	0.0	9.2	0.5
	Biella	11,770	1.3	0.4	87.0	0.0	12.5	0.3
	Ferrara	23,760	1.1	0.0	88.1	0.4	9.7	0.6
	Firenze	66,087	0.9	0.1	80.4	0.4	17.7	0.8
	Friuli VG	78,882	0.6	1.9	91.0	0.3	9.8	2.1
	Genova	44,307	1.8	0.0	81.4	0.0	16.6	0.9
	Macerata	10,386	1.3	0.0	87.4	0.2	13.1	0.6
	Modena	34,967	0.5	0.0	88.6	0.4	11.8	0.5
	Napoli	8165	3.9	0.0	73.0	1.9	17.6	1.4
	Palermo	581	2.2	0.0	92.6	0.0	7.2	0.0
	Parma	23,836	1.0	0.0	86.0	0.5	13.1	0.7
	Ragusa	10,687	1.9	0.8	80.9	0.1	26.6	0.6
	Reggio Emilia	22,152	0.2	0.0	88.1	0.0	13.8	0.5
	Romagna	60,667	2.4	0.0	87.9	0.1	12.3	0.5
	Salerno	26,917	2.5	0.0	77.5	4.0	23.7	1.1
	Sassari	18,084	2.9	0.2	84.4	0.0	16.4	0.7
	Trento	17,788	2.0	0.0	85.0	0.3	27.8	3.8
	Umbria	45,221	0.7	0.0	84.0	0.1	12.6	0.6
	Varese	24,758	1.1	0.0	89.0	11.5	10.8	0.4
	Veneto	84,528	1.5	0.2	87.5	0.8	13.7	1.7

Eur J Cancer 2011;47:2493

review

Annals of Oncology 00: 1–7, 2014
doi:10.1093/annonc/mdu459

Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali[1]*, P. Bruzzi[2], J. Bogaerts[3] & J.-Y. Blay[4] on behalf of the Rare Cancers Europe (RCE) Consensus Panel

[1]*Adult Mesenchymal Tumour Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan;* [2]*Clinical Epidemiology Unit, National Institute for Cancer Research, Genova, Italy;* [3]*European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium;* [4]*Department of Medical Oncology, Centre Léon Bérard, Centre de Recherche en Cancérologie, Université de Lyon, Lyon, France*

Received 29 July 2014; revised 18 September 2014; accepted 19 September 2014

While they account for one-fifth of new cancer cases, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical as well as for population-based decision making. Rules of rational decision making in conditions of uncertainty should be rigorously followed and would need widely informative clinical trials. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied. While clinical studies are the mainstay to test hypotheses, the potential of electronic patient records should be exploited to generate new hypotheses, to create external controls for future studies (when internal controls are unpractical), to study effectiveness of new treatments in real conditions. Framework study protocols in specific rare cancers to sequentially test sets of new agents, as from the early post-phase I development stage, should be encouraged. Also the compassionate and the off-label settings should be exploited to generate new evidence, and flexible regulatory innovations such as adaptive licensing could convey new agents early to rare cancer patients, while generating evidence. Though validation of surrogate end points is problematic in rare cancers, the use of an updated notion of tumor response may be of great value in the single patient to optimize the use of therapies, all the more the new ones. Disease-based communities, involving clinicians and patients, should be regularly consulted by regulatory bodies when setting their policies on drug approval and reimbursement in specific rare cancers.

Key words: rare cancers, clinical trials, research methodology

- **Clinical decision-making**
- **Methods to combine evidence**
- **New study designs**
- **Surrogate end points**
- **Organization of studies**

How can we help you ? SEARCH

REPORTS FROM PAST EVENTS / Rare Cancers Conference 2012

Rare Cancers Conference 2012

Exploring ways to improve clinical research on rare cancers

Date : 01 Mar 2012

Organised by the European Society for Medical Oncology (ESMO) and Rare Cancers Europe, the Rare Cancers Conference, held on 10 February 2012 in Brussels, provided a multi-stakeholder platform for rare cancer and rare disease experts from across Europe to exchange views and share insights into what can be done to improve the methodology of clinical research on rare cancers.

The first two conference sessions offered an overview of rare cancers and associated challenges for clinical research and drug development and also presented a variety of (potential) solutions as well as best practice examples. Where traditional frequent clinical research approaches are not possible, due to the small numbers of patients, it is particularly challenging to make sure that rare cancer patients are not being left without appropriate clinical research and therapeutic progress.

The third session of the conference therefore also highlighted the need for reaching a broad multi-stakeholder consensus on a set of recommendations on improving the methodology of clinical research on rare cancers. These recommendations will be the product of an ongoing multidisciplinary and multi-stakeholder online consensus discussion, promoted by Rare Cancers Europe. They will focus on best methods, including innovative ones, for clinical research on rare cancers, and rare subgroups of frequent cancers, with the goal of encouraging:

- clinical researchers to exploit innovative solutions for the design and analysis of clinical studies;
- clinicians to exploit innovative solutions for the combination of all available knowledge;
- regulators to accept evidence built through these solutions;
- clinicians' and patients' communities to exploit all forms of collaboration to put together as large series as possible for prospective and retrospective clinical and translational research;
- methodologists to advance research into new methodological solutions better fitting the needs of studies on small series

All interested stakeholder groups are encouraged to actively participate in this open discussion, the result of which will be a consensus paper to be publicly presented in autumn 2012. This paper could then be used for related advocacy efforts. All parties interested in joining this discussion are invited to contact Rare Cancers Europe.

review

Annals of Oncology 00: 1–7, 2014
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Key words: rare cancers, clinical trials, research methodology

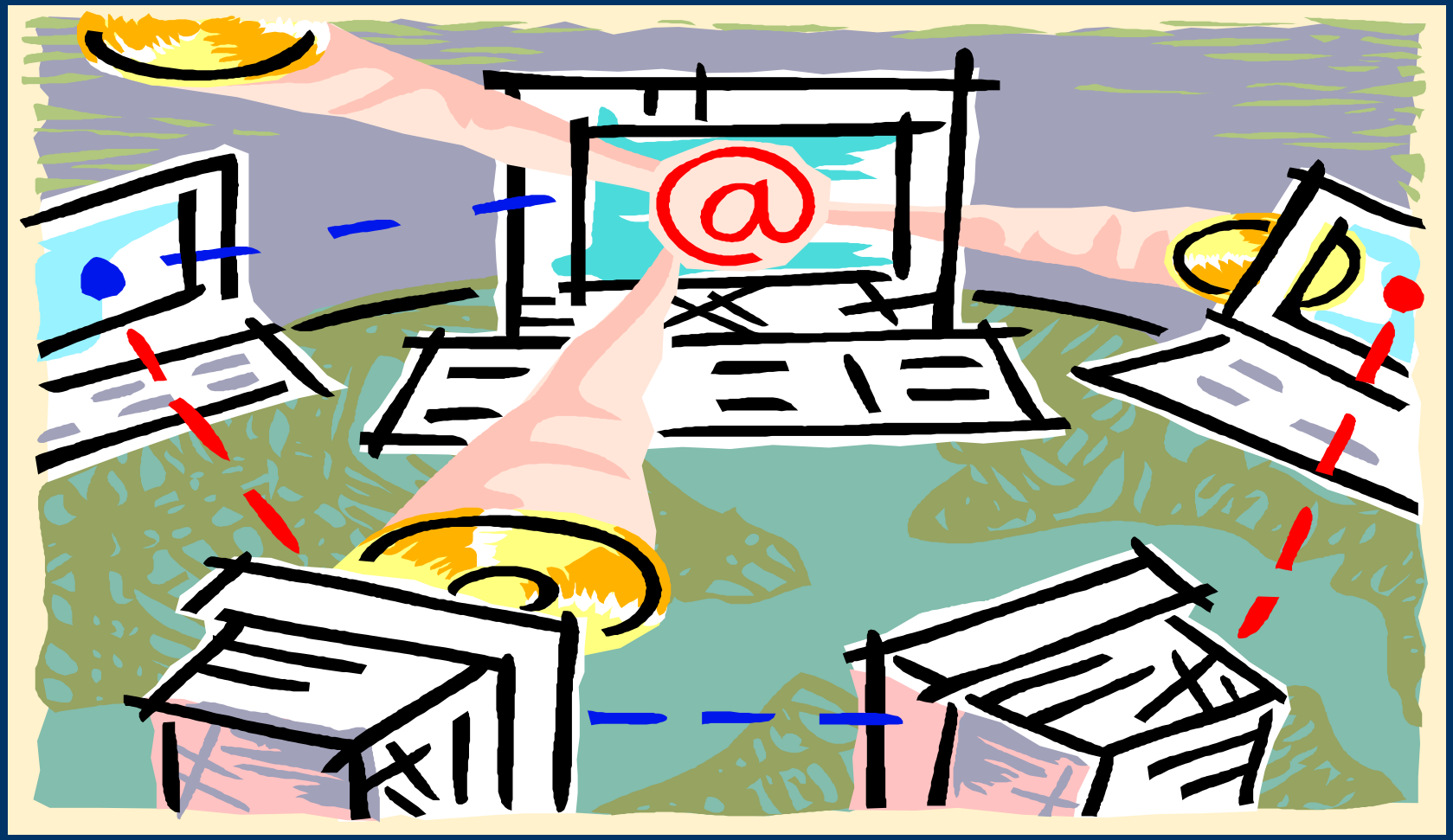
Josh Sommer

@sommerjo

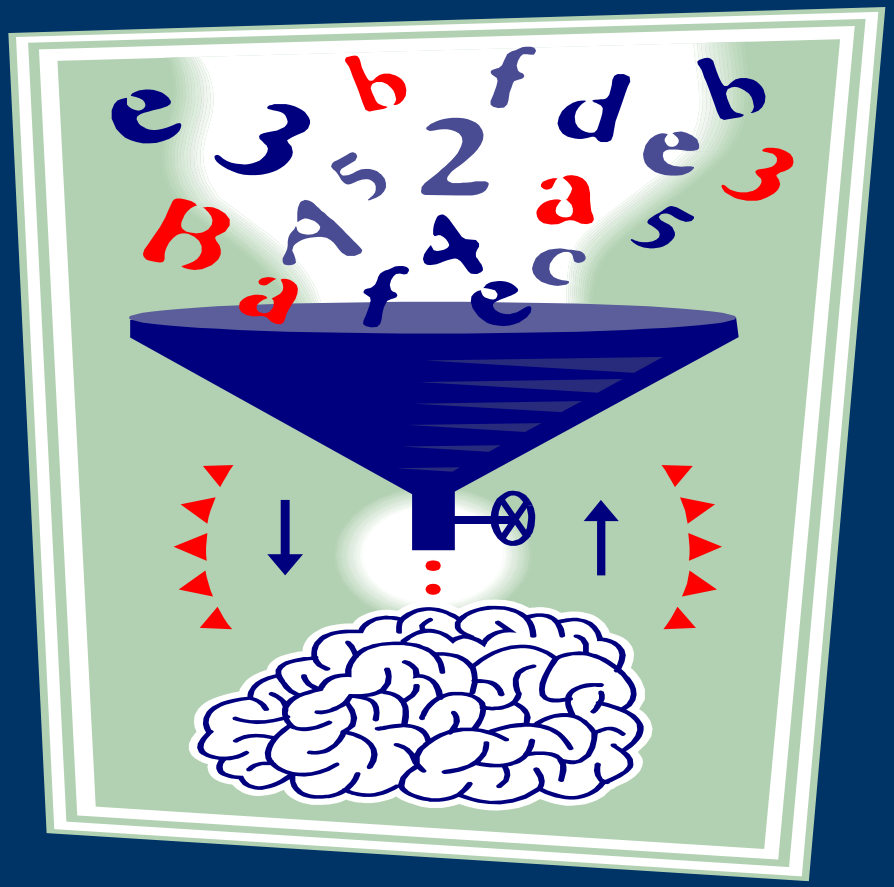
Today at EMA regulators, clinicians, @ChordomaFDN agreed to work together on guidance for chordoma trials. Progress!
pic.twitter.com/ShR3SA8KXZ

30/04/2015 19:47:22

Prospective clinical data bases

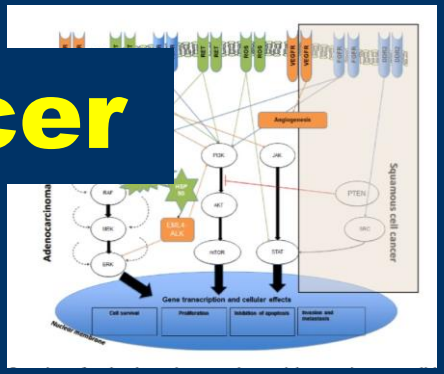


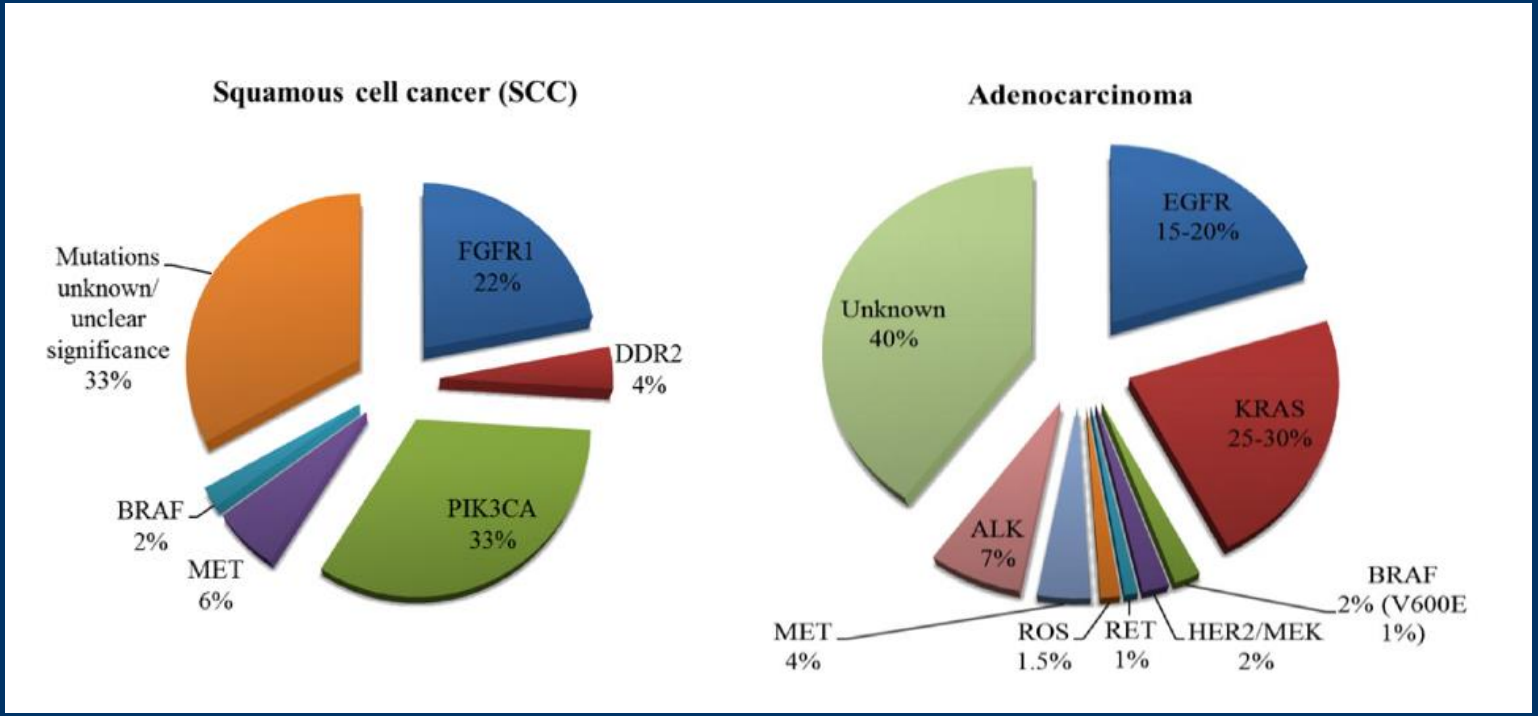
«Big clinical data»...




Phase I
dose!
✓ MTD
activity!
Phase II
Phase III
✓ OR
✓ OS
✓ QoL
efficacy!
standard

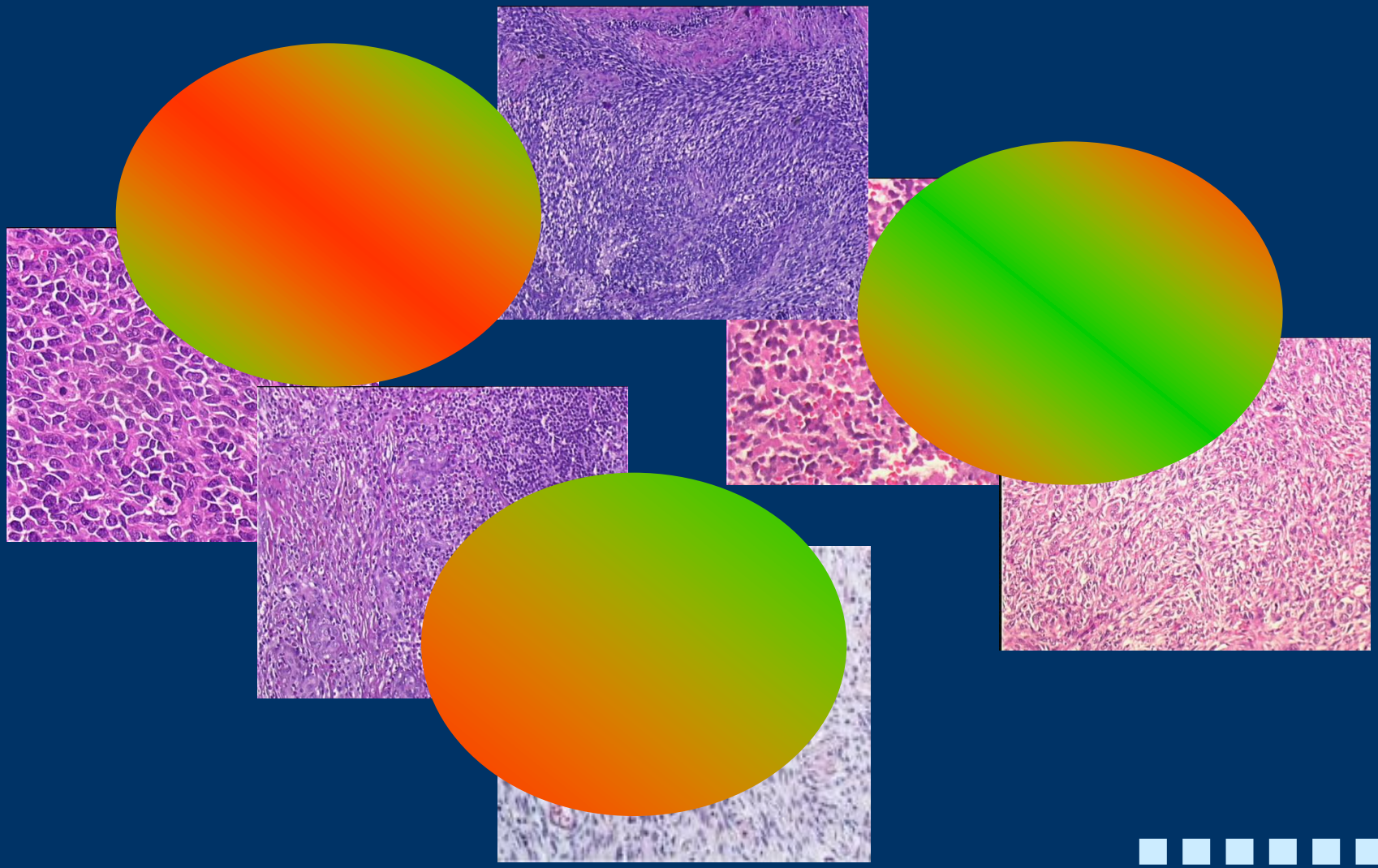
Lung cancer

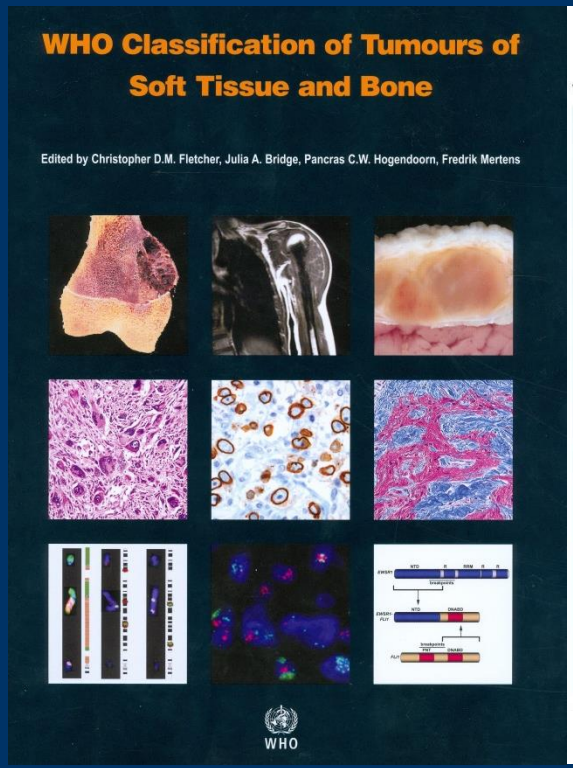




Boolell V et al. Cancers 2015;71815

Soft tissue sarcomas & GIST





WHO classification of tumours of soft tissue[a,b]

ADIPOCYTIC TUMOURS

Benign

Lipoma	8850/0
Lipomatosis	8850/0
Lipomatosis of nerve	8850/0
Lipoblastoma/lipoblastomatosis	8881/0
Angiolipoma	8861/0
Myolipoma	8890/0
Chondroid lipoma	8862/0
Extra-renal angiomyolipoma	8860/0
Extra-adrenal myelolipoma	8870/0
Spindle cell/pleomorphic lipoma	8857/0
Hibernoma	8880/0

Intermediate (locally aggressive)

Atypical lipomatous tumour/ well differentiated liposarcoma	8850/1 8850/3

Malignant

Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Pleomorphic liposarcoma	8854/3
Liposarcoma, not otherwise specified	8850/3

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign

Nodular fasciitis	8828/0*
Proliferative fasciitis	8828/0*
Proliferative myositis	8828/0*
Myositis ossificans	
Fibro-osseous pseudotumour of digits	
Ischaemic fasciitis	
Elastofibroma	8820/0
Fibrous hamartoma of infancy	
Fibromatosis colli	
Juvenile hyaline fibromatosis	
Inclusion body fibromatosis	
Fibroma of tendon sheath	8813/0
Desmoplastic fibroblastoma	8810/0
Mammary-type myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	8816/0*
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Nuchal-type fibroma	8810/0
Gardner fibroma	8810/0
Calcifying fibrous tumour	8817/0*

Intermediate (locally aggressive)

Palmar/plantar fibromatosis	8813/1*
Desmoid-type fibromatosis	8821/1
Lipofibromatosis	8851/1*
Giant cell fibroblastoma	8834/1

Intermediate (rarely metastasizing)

Dermatofibrosarcoma protuberans	8832/1*
Fibrosarcomatous dermatofibrosarcoma protuberans	8832/3*
Pigmented dermatofibrosarcoma protuberans	8833/1*
Solitary fibrous tumour	8815/1*
Solitary fibrous tumour, malignant	8815/3
Inflammatory myofibroblastic tumour	8825/1
Low-grade myofibroblastic sarcoma	8825/3*
Myxoinflammatory fibroblastic sarcoma/ Atypical myxoinflammatory fibroblastic tumour	8811/1*
Infantile fibrosarcoma	8814/3

Malignant

Adult fibrosarcoma	8810/3
Myxofibrosarcoma	8811/3
Low-grade fibromyxoid sarcoma	8840/3*
Sclerosing epithelioid fibrosarcoma	8840/3*

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Tenosynovial giant cell tumour localized type	9252/0
diffuse type	9252/1*
malignant	9252/3
Deep benign fibrous histiocytoma	8831/0

Intermediate (rarely metastasizing)

Plexiform fibrohistiocytic tumour	8835/1
Giant cell tumour of soft tissues	9251/1

SMOOTH MUSCLE TUMOURS

Benign

Deep leiomyoma	8890/0

Malignant

Leiomyosarcoma (excluding skin)	8890/3

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)	8711/0
Glomangiomatosis	8711/1*
Malignant glomus tumour	8711/3
Myopericytoma	8824/0
Myofibroma	8824/0
Myofibromatosis	8824/1
Angioleiomyoma	8894/0

SKELETAL MUSCLE TUMOURS

Benign

Rhabdomyoma	8900/0
Adult type	8904/0
Fetal type	8903/0
Genital type	8905/0

Malignant

Embryonal rhabdomyosarcoma (including botryoid, anaplastic)	8910/3
Alveolar rhabdomyosarcoma (including solid, anaplastic)	8920/3
Pleomorphic rhabdomyosarcoma	8901/3
Spindle cell/sclerosing rhabdomyosarcoma	8912/3

VASCULAR TUMOURS OF SOFT TISSUE

Benign

Haemangioma	9120/0
Synovial	
Venous	9122/0
Arteriovenous haemangioma/malformation	9123/0
Intramuscular	9133/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma	9130/1

Intermediate (rarely metastasizing)

Retiform haemangioendothelioma	9136/1*
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9136/1
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9136/1
Kaposi sarcoma	9140/3

Malignant

Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma	9220/0
Extraskeletal mesenchymal chondrosarcoma	9240/3
Extraskeletal osteosarcoma	9180/3

GASTROINTESTINAL STROMAL TUMOURS

Benign gastrointestinal stromal tumour	8936/0
Gastrointestinal stromal tumour, uncertain malignant potential	8936/1
Gastrointestinal stromal tumour, malignant	8936/3

NERVE SHEATH TUMOURS

Benign

Schwannoma (including variants)	9560/0
Melanotic schwannoma	9560/1*
Neurofibroma (incl. variants)	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9671/0
Malignant perineurioma	9671/3
Granular cell tumour	9580/0
Dermal nerve sheath myxoma	9562/0
Solitary circumscribed neuroma	9570/0
Ectopic meningioma	9530/0
Nasal glial heterotopia	
Benign Triton tumour	
Hybrid nerve sheath tumours	9563/0*

Malignant

Malignant peripheral nerve sheath tumour	9540/3
Epithelioid malignant peripheral nerve sheath tumour	9542/3*
Malignant Triton tumour	9561/3
Malignant granular cell tumour	9580/3
Ectomesenchymoma	8921/3

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Acral fibromyxoma	8811/0
Intramuscular myxoma (including cellular variant)	8840/0
Juxta-articular myxoma	8840/0
Deep ("aggressive") angiomyxoma	8841/0*
Pleomorphic hyalinizing angiectatic tumour	8822/1*
Ectopic hamartomatous thymoma	8587/0

Intermediate (locally aggressive)

Haemosiderotic fibrolipomatous tumour	8811/1*

Intermediate (rarely metastasizing)

Atypical fibroxanthoma	8830/1
Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	8842/0
Ossifying fibromyxoid tumour, malignant	8842/3*
Mixed tumour NOS	8940/0
Mixed tumour NOS, malignant	8940/3
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Phosphaturic mesenchymal tumour, benign	8990/0
Phosphaturic mesenchymal tumour, malignant	8990/3

Malignant

Synovial sarcoma NOS	9040/3
Synovial sarcoma, spindle cell	9041/3
Synovial sarcoma, biphasic	9043/3
Epithelioid sarcoma	8804/3
Alveolar soft-part sarcoma	9581/3
Clear cell sarcoma of soft tissue	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
Extraskeletal Ewing sarcoma	9364/3
Desmoplastic small round cell tumour	8806/3
Extra-renal rhabdoid tumour	8963/3
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	
PEComa NOS, benign	8714/0*
PEComa NOS, malignant	8714/3*
Intimal sarcoma	9137/3*

UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

Undifferentiated spindle cell sarcoma	8801/3
Undifferentiated pleomorphic sarcoma	8802/3
Undifferentiated round cell sarcoma	8803/3
Undifferentiated epithelioid sarcoma	8804/3
Undifferentiated sarcoma NOS	8805/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (916A). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumours. [b] The classification is modified from the previous WHO histological classification of tumours (870A) taking into account changes in understanding of these lesions. * These new codes were approved by the IARC/WHO Committee for ICD-O in 2012.

STS: advanced disease

$R <$

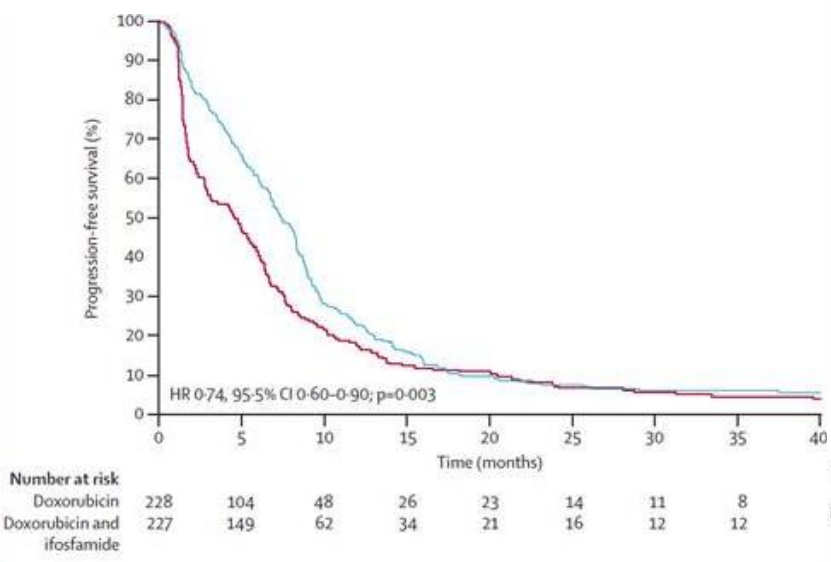
ADM 75 mg/sqm

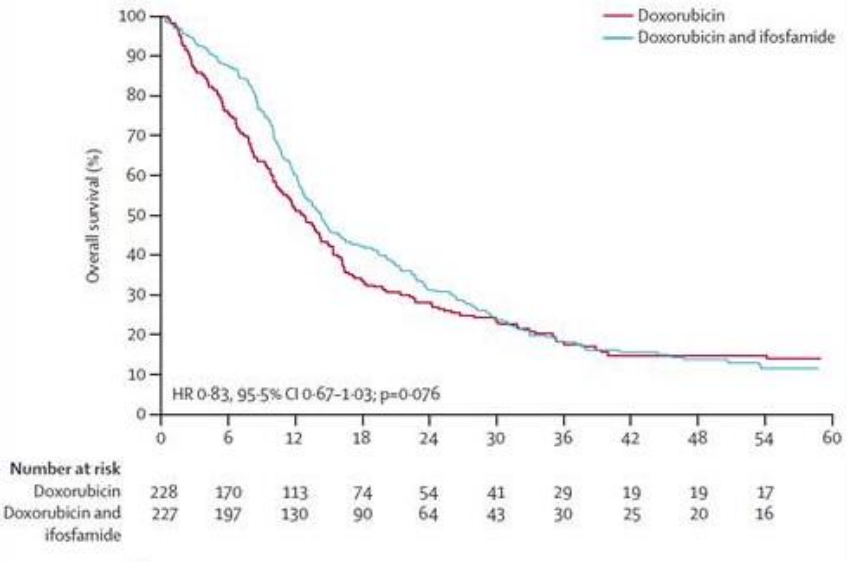
ADM 75 mg/sqm + IFX 7.5 g/sqm

EORTC
Soft Tissue & Bone Sarcoma Group

Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group**





Lancet Oncol 2014;15:415

The ESMO/European Sarcoma Network Working Group*

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- Paolo G. Casali, Italy (*Moderator*)
- Jean-Yves Blay, France (*Moderator*)
- Alexia Bertuzzi, Ireland
- Stefan Bielack, Germany
- Bodil Bjerkehagen, Norway
- Sylvie Bonvalot, France
- Ioannis Boukovinas, Greece
- Paolo Bruzzi, Italy
- Angelo Paolo Dei Tos, Italy
- Palma Dileo, UK
- Mikael Eriksson, Sweden
- Alexander Fedenko, Russian Federation
- Andrea Ferrari, Italy
- Stefano Ferrari, Italy
- Hans Gelderblom, Belgium
- Robert Grimer, UK
- Alessandro Gronchi, Italy
- Rick Haas, Netherlands
- Kirsten Sundby Hall, Norway
- Peter Hohenberger, Germany
- Rolf Issels, Germany
- Heikki Joensuu, Finland
- Ian Judson, UK
- Axel Le Cesne, France
- Saskia Litière, Belgium
- Javier Martin-Broto, Spain
- Ofer Merimsky, Israel
- Michael Montemurro, UK
- Carlo Morosi, Italy
- Piero Picci, Italy
- Isabelle Ray-Coquard, France
- Peter Reichardt, Germany
- Piotr Rutkowski, Poland
- Marcus Schlemmer, Germany
- Silvia Stacchiotti, Italy
- Valter Torri, Italy
- Annalisa Trama, Italy
- Frits Van Coevorden, Netherlands
- Winette Van der Graaf, Netherlands
- Daniel Vanel, Italy
- Eva Wardelmann, Germany

Standard chemotherapy is based on anthracyclines as the first-line treatment [I, A]. As of today, there is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival (OS). However, a higher response rate can be expected, in particular in a number of sensitive histological types, according to several, although not all, randomised clinical trials [18, 19]. Therefore, multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumour response is felt to be potentially advantageous and patient performance status is good.

In angiosarcoma, taxanes are an alternative option, given their high antitumour activity in this specific histological type [20] [III, B]. An alternative option is gemcitabine ± docetaxel [21] [V, B].

Doxorubicin plus dacarbazine is an option for multiagent first-line chemotherapy of leiomyosarcoma, where the activity of ifosfamide is far less convincing in available retrospective evidence, or solitary fibrous tumour [22] [V, B].

Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans who are not amenable to non-mutilating surgery or with metastases deserving medical therapy [23, 24] [III, A].

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy and Safety of Trabectedin in Patients With Advanced or Metastatic Liposarcoma or Leiomyosarcoma After Failure of Prior Anthracyclines and Ifosfamide: Results of a Randomized Phase II Study of Two Different Schedules

George D. Demetri, Sant P. Chawla, Margaret von Mehren, Paul Ritch, Laurence H. Baker, Jean Y. Blay, Kenneth R. Hande, Mary L. Keohan, Brian L. Samuels, Scott Schuetze, Claudia Lebedinsky, Yusri A. Elsayed, Miguel A. Izquierdo, Javier Gómez, Youn C. Park, and Axel Le Cesne

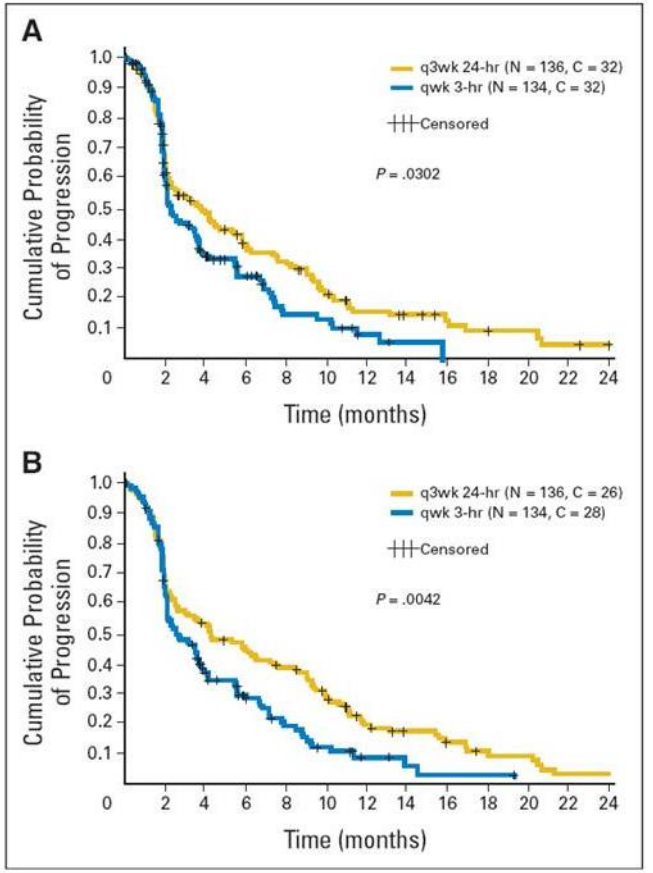
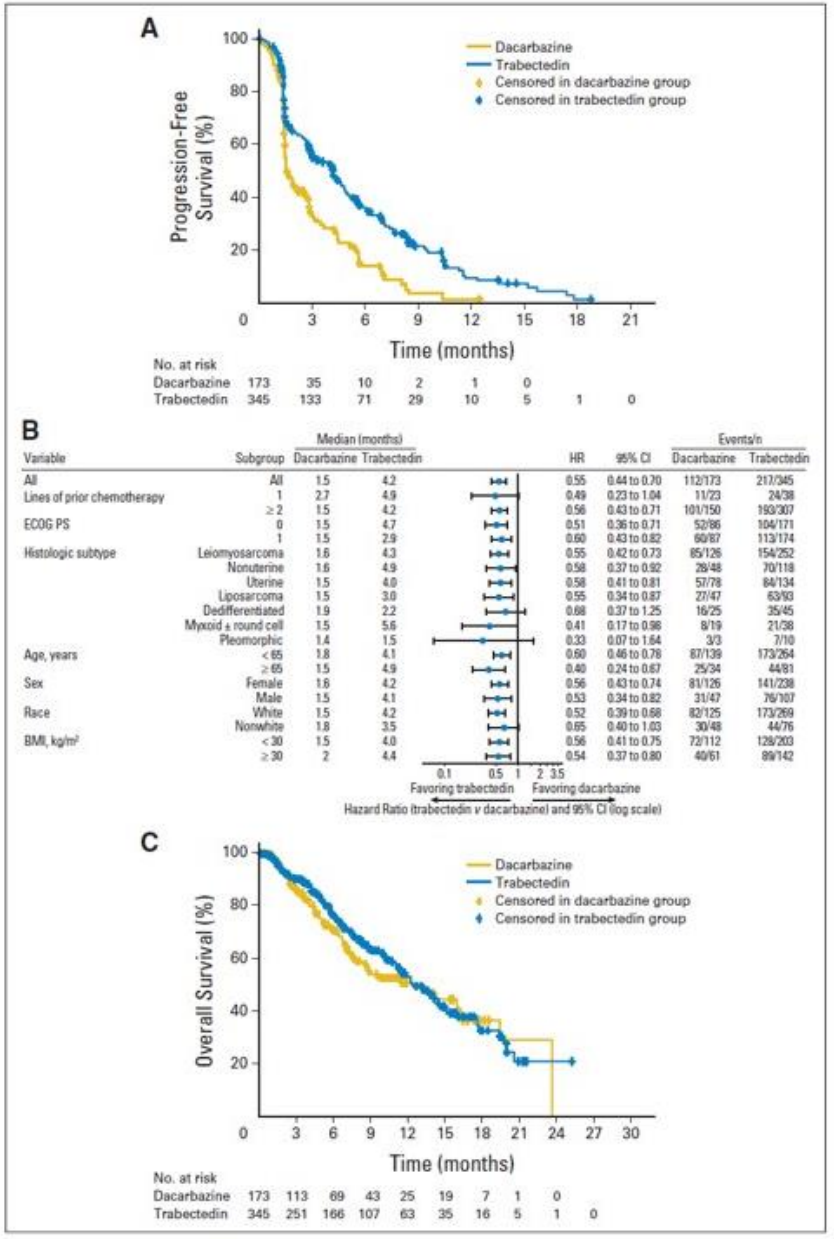


Fig 2. Kaplan-Meier plot of time to progression. (A) Independent review. (B) Investigator's assessment. qwk 3-hour, 3-hour IV infusion every week for 3 consecutive weeks of a 4-week cycle; q3wk 24-hour, 24-hour IV infusion once every 3 weeks; N, number of patients; C, censored patients.

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

George D. Demetri, Margaret von Mehren, Robin L. Jones, Martee L. Hensley, Scott M. Schuetze, Arthur Staddon, Mohammed Milhem, Anthony Elias, Kristen Ganjoo, Hussein Tawbi, Brian A. Van Tine, Alexander Spira, Andrew Dean, Nushmia Z. Khokhar, Youn Choi Park, Roland E. Knoblauch, Trilok V. Parekh, Robert G. Maki, and Shreyaskumar R. Patel

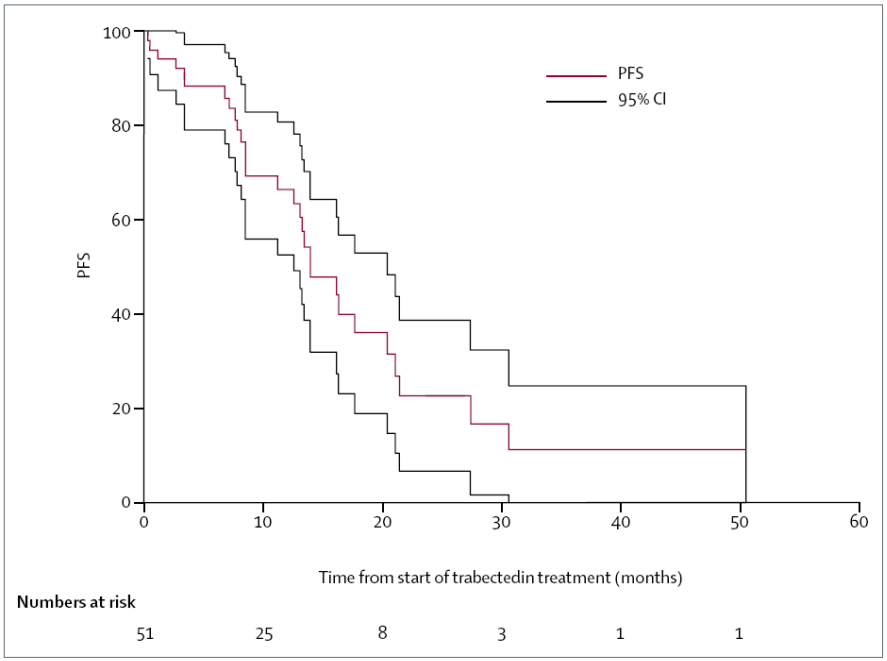


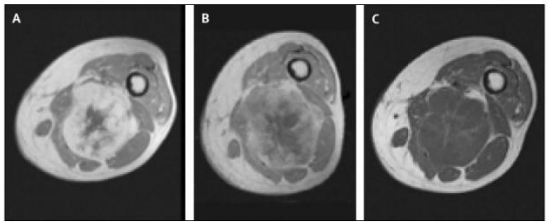
J Clin Oncol 2015;Epub

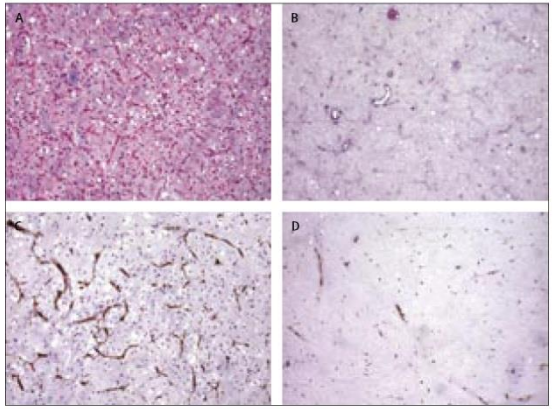
Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

Federica Grosso, Robin L Jones, George D Demetri, Ian R Judson, Jean-Yves Blay, Axel Le Cesne, Roberta Sanfilippo, Paola Casieri, Paola Collini, Palma Dileo, Carlo Spreafico, Silvia Stacchiotti, Elena Tamborini, Juan Carlos Tercero, Josè Jimeno, Maurizio D'Incalci, Alessandro Gronchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali

Lancet Oncol 2007; 8: 595–602



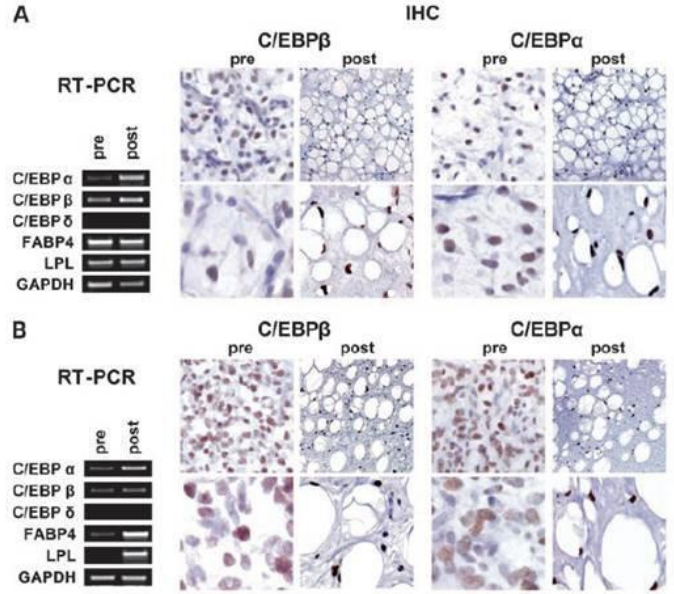


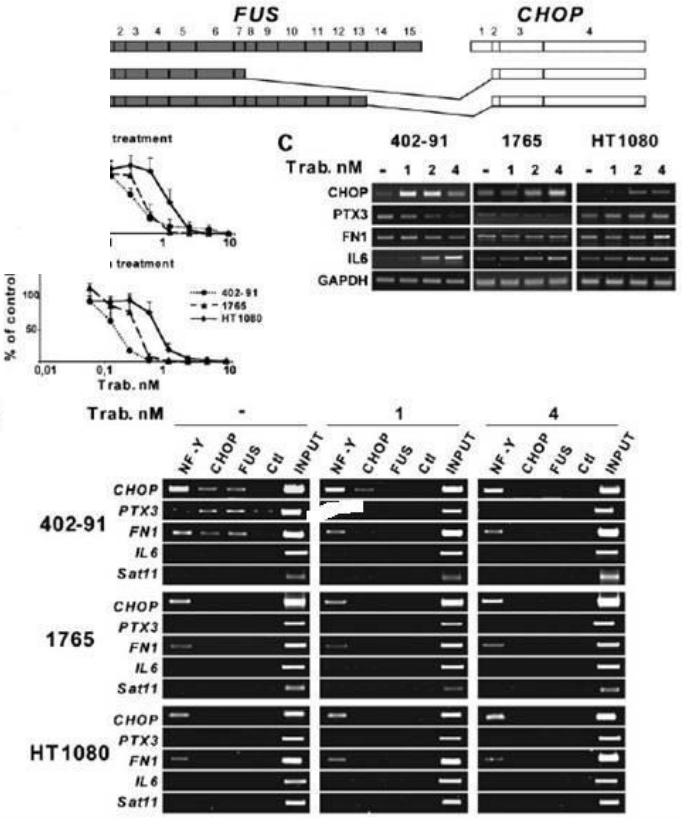


Trabectedin (ET-743) promotes differentiation in myxoid liposarcoma tumors

Claudia Forni,[1] Mario Minuzzo,[1] Emanuela Virdis,[2]
Elena Tamborini,[2] Matteo Simone,[3]
Michele Tavecchio,[3] Eugenio Erba,[3]
Federica Grosso,[2] Alessandro Gronchi,[2]
Pierre Aman,[4] Paolo Casali,[2] Maurizio D'Incalci,[3]
Silvana Pilotti,[2] and Roberto Mantovani[1]

[1]Dipartimento di Scienze Biomolecolari e Biotecnologie, Università degli Studi di Milano; [2]Fondazione IRCCS, Istituto Nazionale Tumori; [3]Dipartimento di Oncologia, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; and [4]Lundberg Laboratory for Cancer Research, Department of Pathology, Göteborg University, Gothenburg, Sweden

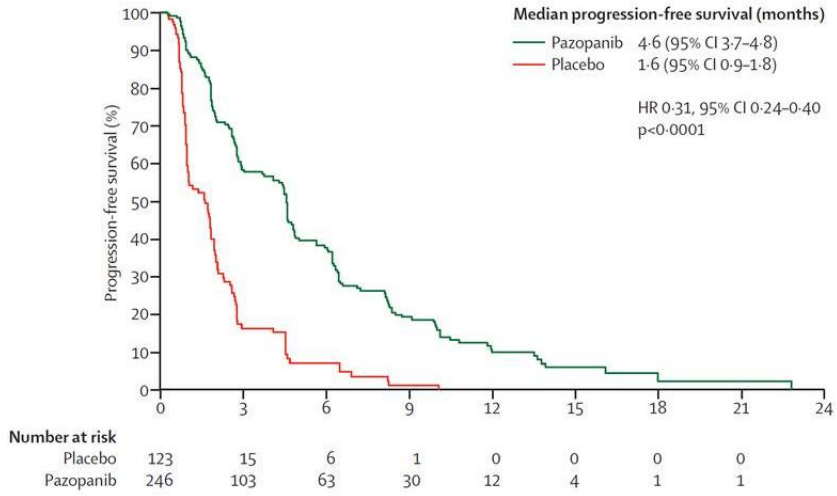


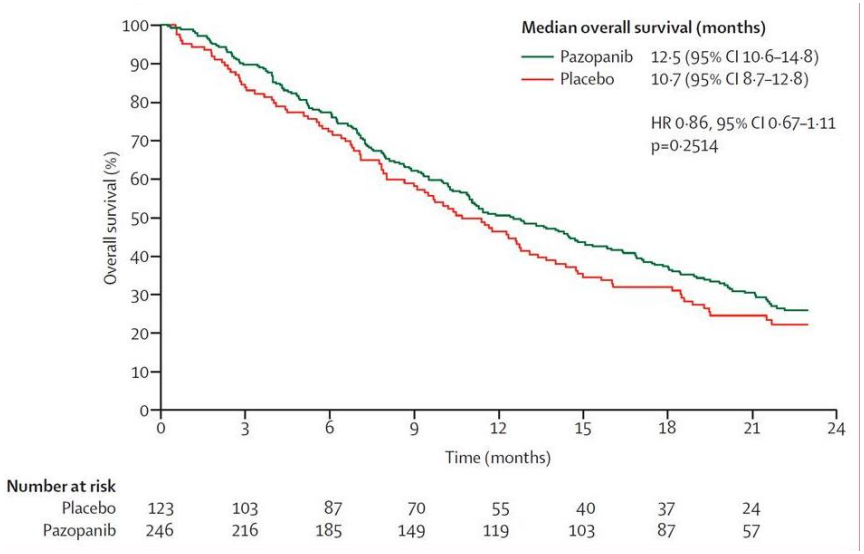


Mol Cancer Therap 2009;8:449

Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group





Van Der Graaf WTA et al, Lancet 2012;379:1879

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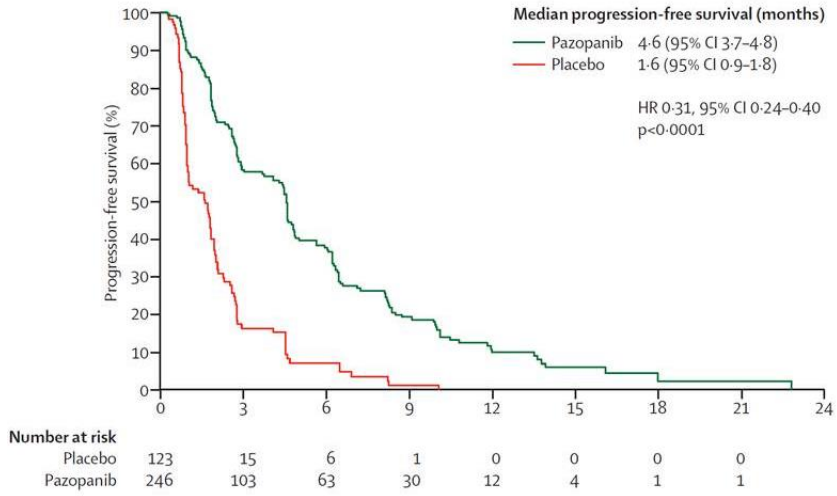

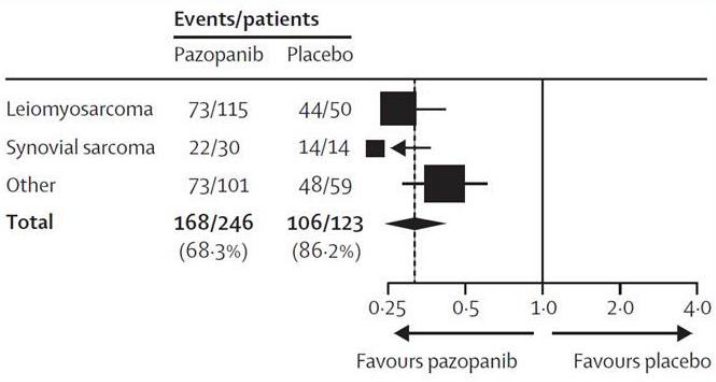

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European Journal of Cancer (2014) 50, 3021–3028

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Original Research

Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour

S. Stacchiotti [a,*,1], M. Tortoreto [b], G.G. Baldi [c], G. Grignani [d], A. Toss [e], G. Badalamenti [f], D. Cominetti [b], C. Morosi [g], A.P. Dei Tos [h], F. Festinese [i], E. Fumagalli [a], S. Provenzano [a], A. Gronchi [j], E. Pennacchioli [k], T. Negri [l], G.P. Dagrada [l], R.D. Spagnuolo [l], S. Pilotti [l,1], P.G. Casali [a,1], N. Zaffaroni [b]

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[d] Medical Oncology, IRCCS – Istituto di Candiolo, Candiolo, Italy
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[k] Melanoma and Sarcoma, Surgery Department, Istituto Europeo di Oncologia, Milan, Italy
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KEYWORDS
Sarcoma
Solitary fibrous tumour
Pazopanib
Sunitinib
Tyrosine kinase
Chemotherapy

Abstract ***Background:*** To explore the activity of pazopanib in solitary fibrous tumour (SFT). ***Patients and methods:*** In a preclinical study, we compared the activity of pazopanib, sorafenib, sunitinib, regorafenib, axitinib and bevacizumab in a dedifferentiated-SFT (DSFT) xenotransplantat into Severe Combined Immunodeficiency (SCID) mice. Antiangiogenics were administered at their reported optimal doses when mean tumour volume (TV) was 80 mm³. Drug activity was assessed as TV inhibition percentage (TVI%). From May 2012, six consecutive patients with advanced SFT received pazopanib, on a national name-based programme. In one case sunitinib was administered after pazopanib failure.

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E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Stacchiotti).
[1] These authors equally contributed to the paper.

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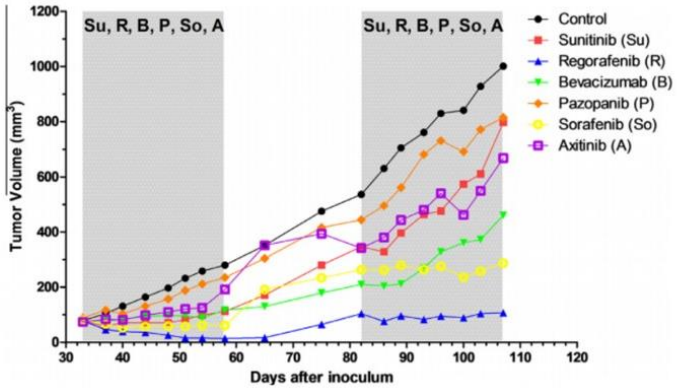

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Original Research

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[a] Adult Mesenchymal Tumor Medical Oncology Unit, Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
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[1] These authors equally contributed to the paper.

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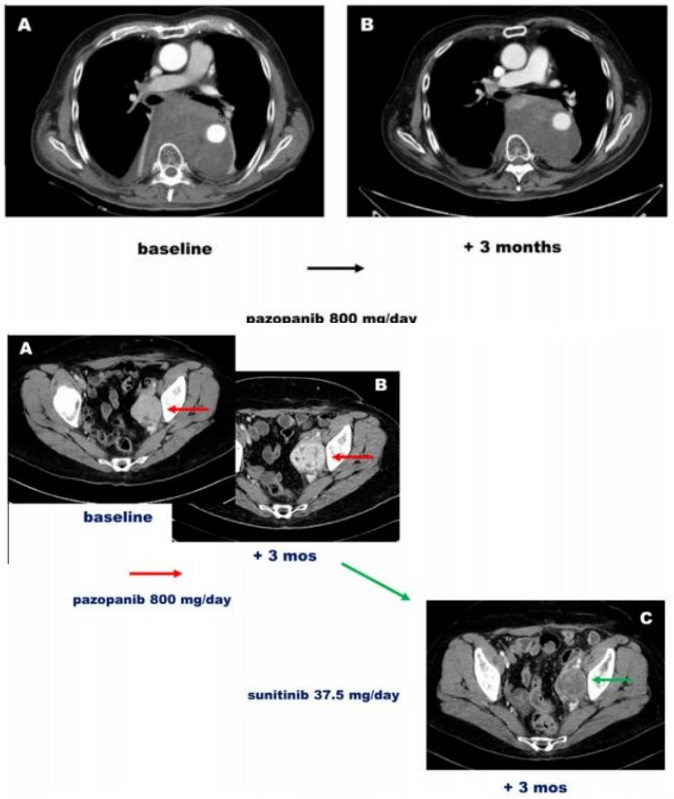
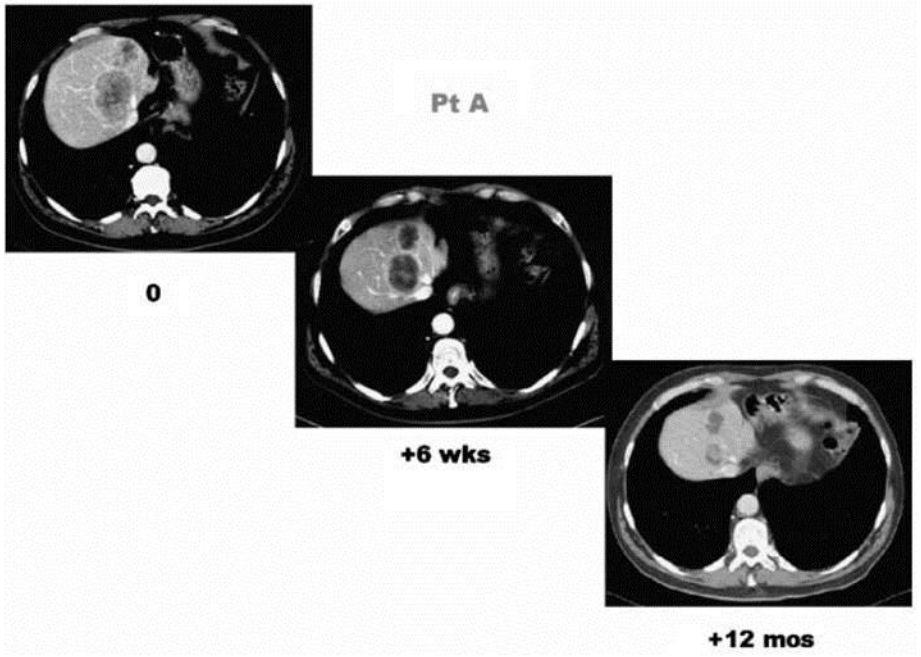
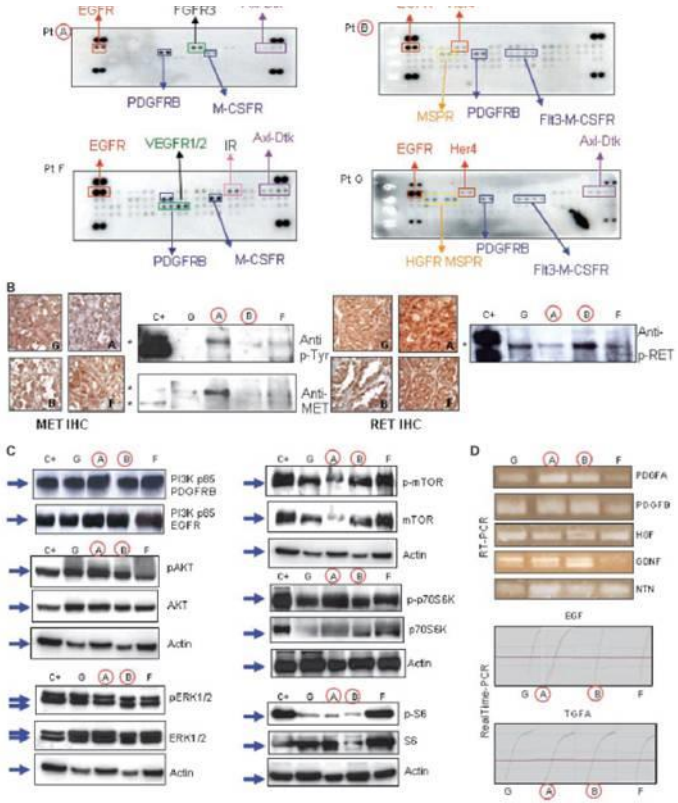


Cancer Therapy: Clinical

Response to Sunitinib Malate in Advanced Alveolar Soft Part Sarcoma

Silvia Stacchiotti,[1] Elena Tamborini,[2] Andrea Marrari,[1] Silvia Brich,[2] Sara Arisi Rota,[2] Marta Orsenigo,[2] Flavio Crippa,[3] Carlo Morosi,[4] Alessandro Gronchi,[5] Marco A. Pierotti,[2] Paolo G. Casali,[1] and Silvana Pilotti[2]





original article

Annals of Oncology
doi:10.1093/annonc/mdq644

Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect

S. Stacchiotti[1]*, T. Negri[2], N. Zaffaroni[3], E. Palassini[1], C. Morosi[4], S. Brich[2], E. Conca[2], F. Bozzi[2], G. Cassinelli[3], A. Gronchi[5], P. G. Casali[1] & S. Pilotti[2]

Departments of [1]Cancer Medicine; [2]Pathology, Laboratory of Experimental Molecular Pathology; [3]Experimental Oncology and Molecular Medicine; [4]Radiology; [5]Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

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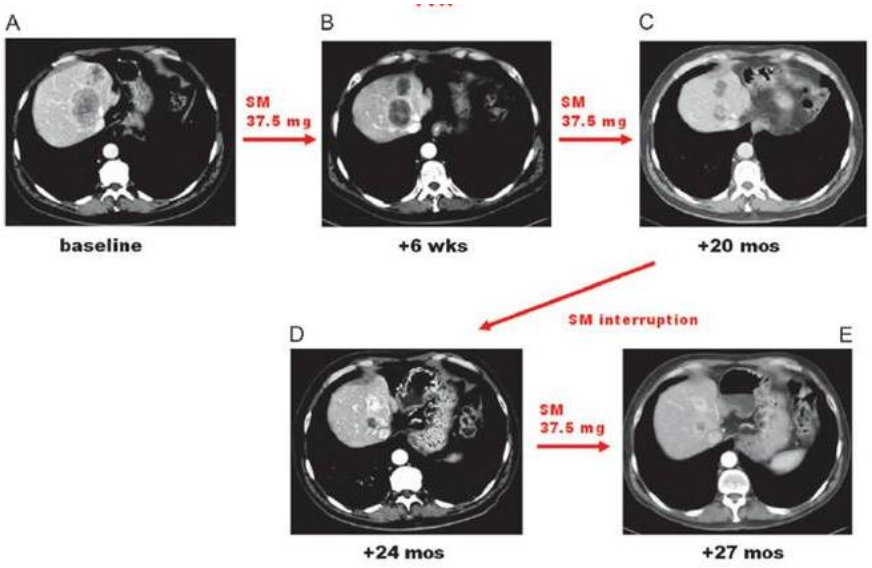

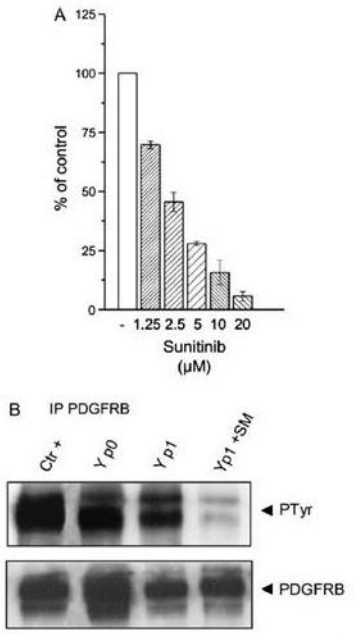

Annals of Oncology 18: 1923–1925, 2007
doi:10.1093/annonc/mdm517

The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO)

All drugs need to be given a marketing authorization by a relevant regulatory body in order for patients to receive them [1]. The marketing authorization is granted if the drug is judged to be safe and effective for a given indication following a given administration regimen. This is the drug 'label'. When the drug is used for other indications, it is used 'off label'.

This is different from when a drug is 'unlicensed'. In this case, the drug is not accessible on the market, and, in principle, its use can take place only within clinical studies, or a compassionate/expanded access setting, generally being provided for free by the pharmaceutical company.

The off-label use of drugs in oncology has been estimated to reach 50%, or even more [2–4]. In pediatrics, the off-label issue is particularly widespread, all the more in pediatric oncology [5]. Often, these uses of drugs, although off-label, are fully 'evidence based', and therefore fall within the state of the art. In spite of this, off-label uses of drugs might be viewed as illegal, in a sense. In practice, off-label uses are often 'tolerated' under restrictions, in spite of the size of the phenomenon, especially in some medical areas.

In principle, a drug can be off label under three conditions: (i) because steps to extend the approval have not been made, although evidence of efficacy is available; (ii) because it falls into the so-called 'gray zone' of evidence-based medicine, within which high-level evidence is difficult to reach even for treatments which are likely effective (this may be the case of rare diseases, which do not lend themselves to large clinical studies) and (iii) because the drug is ineffective or at least there is no reason to believe it is effective. Obviously, the off-label issue is of the greatest concern under the first condition, and constitutes a problem under the second, while ineffective treatments simply should not be done.

The off-label issue is more acute in oncology than in other medical areas for some reasons. The main one is the number of cancer types. In fact, each anticancer drug may be useful in several of them. In practice, many widespread anticancer drugs have not got the label for all the indications under which they can be effectively employed. When the drug patent is over, no pharmaceutical company will ever have any interest to pursue any label extension. Rare entities are all the more problematic. With regard to these, benefits are granted to pharmaceutical companies seeking the approval of new drugs for rare diseases, the so-called 'orphan drugs': in essence, economic incentives are guaranteed if the drug is approved [6]. Several anticancer agents are now obtaining the approval as orphan drugs. The mechanism, however, is not a guarantee at all, and in any case applies only to rare diseases. In general, the more specific the label is, the more likely some minor indications may remain uncovered, and this can well occur also if the disease is frequent.

In the end, there is a problem in principle that the approval of a new drug can be sought exclusively by the pharmaceutical company which produces it. If the pharmaceutical company does not have enough interest to pursue the approval on a specific indication, this will be left uncovered, and the use of the drug for such an indication will be off label. The wide diversity of clinical practice adds to this, creating the above-mentioned gray zone of evidence-based medicine [7]. The paradox is that clinical practice guidelines often recommend to use drugs off label, thus outside existing regulatory boundaries, 'against' the law, in a sense. In theory, the reverse should take place: regulatory boundaries should be wider, and clinical practice guidelines should be selective within them.

The off-label issue continuously creates problems to clinical practice, and at intervals may become more acute in one country or another. According to its Bylaws, European Society for Medical Oncology (ESMO) is dedicated 'to promote equal access to optimal cancer care of all cancer patients' [8]. As stated recently by American Society of Clinical Oncology (ASCO) and ESMO, 'health care plans should aspire to meet certain common goals to ensure access to, and the continuity of, quality cancer care' [9]. In regard to the off-label uses of drugs, ESMO believes:

- that the problem of off-label uses of drugs should be urgently addressed and solved positively, when such uses are supported by evidence and amount to standard practice;
- that regulatory bodies should take some responsibility on the off-label issue;
- that, pragmatically, lists of drugs with acceptable indications should be worked out in order to remove them from the off-label area, and in the European Union (EU) this might follow the principle underlying the centralized procedure for approval of new drugs, thus possibly involving the EU regulatory body, the European Medicines Agency (EMEA);
- that, in perspective, new regulatory mechanisms should be searched, by which uses of drugs could be expanded even beyond the initiative of pharmaceutical companies producing them.

The problem needs to be urgently addressed

The persisting need to use drugs off-label constitutes a serious concern. In fact, by prescribing a drug off-label, the physician is asked to take a special responsibility. Formally, he is prescribing something which the regulatory body has not stated is safe and effective. Therefore, he/she may be called to respond for any problem arising from the use of the drug as if he/she had done something outside the state of the art. Often this is not the case, but the burden of the proof rests on the physician. In any case, the responsibility can be administrative, and third payers may claim that the prescription was not allowed, so that the physician may even be called to reimburse personally or be threatened to do so. Indeed, this may be actually foreseen, although it is often left to the discretion of 'watchdogs' to decide how much to pursue controls. At the very least, physicians may be facing more red tape in order to prescribe off-label drugs. All this can discourage evidence-based prescriptions of off-label drugs. More simply, third payers, whether public (national health systems, and the like) or private, might just refuse to reimburse some off-label drugs, at their discretion. In other words, there is room for improper denials of effective therapies, in an age of mounting health costs constraints. Overall, this might add to existing inequalities in treatment [3, 4, 10].

Regulatory bodies should take responsibility

Regulatory bodies often argue that reimbursing off-label drugs or not is exclusively a matter of third payers. The argument is tenable to some extent, but nonetheless is weak if it implies that regulatory bodies are completely out of the story. The first reason is that, as said above, the implications of the off-label use of drugs are not only financial, but also affect physicians' professional responsibility. Another reason is that third payers, in principle, should 'buy' drugs only from among on-label ones. This is exactly why regulatory bodies do exist: to allow patients and their proxies to find safe and effective drugs on the market. As was said, a 'general off-label use of drugs is the death of the idea of regulation' [11]. Indeed, it is well accepted that regulatory bodies take some responsibility to ensure that effective drugs get to the market even when there are obstacles (thus, for instance, the provisions about orphan drugs). A different argument at the EU level is that these are internal matters of individual states. In the EU, however, anticancer drugs are now subjected to the centralized procedure for marketing authorization of medicinal products, by which the EU regulatory body, EMEA, is responsible for evaluating all the applications, which are centrally made by companies and whose outcomes are relevant for all the EU states [12]. Therefore, the principle of central responsibility for anticancer drugs by the regulatory body, EMEA, is well established in the EU.

Lists of acceptable drugs should be worked out

Pragmatically, tools which make it possible for some patients to receive off-label drugs are in place in some countries, in an effort to overcome a limitation which in the end is only bureaucratic. These tools may well include lists of drugs accepted for selected indications, outside those recognized in the labels, as a very practical way to let patients receive what they need for. In 2006, the ASCO stressed the need to update and fully implement the 'standard medical compendia' used by Medicare in the United States to cover selected, evidence-based, off-label uses of anticancer drugs [2]. As they stated, 'working closely with the cancer community, Congress has fashioned a strong system for identifying medically appropriate cancer therapies, including those that involve off-label uses of United States Food and Drug Administration approved drugs. The system has worked well, as reflected in improvement of cancer morbidity and mortality' [2]. In Europe, states have different policies in regard to the off-label issue, which are often unclear and liable to lead to improper denials. ESMO is carrying out a survey of such policies. There is an obvious need to improve and assimilate them. A powerful solution would be that the EU regulatory body might facilitate the production of compendia of anticancer drugs, enlisting those off-label uses judged to be legitimate.

The initiative of seeking label extensions, or the mechanisms to expand drugs uses, should not depend exclusively on pharmaceutical companies

Medicines for human use are common goods. A high level of social responsibility is implied. A pharmaceutical company may, however, not be willing to pursue label extensions for some of its drugs. Efforts such as those on orphan drugs are to be warmly appreciated, but they may not be enough, since in the end the decision is left to the company, and, furthermore, rare tumors are not the only problem. On the other hand, approving a label extension may not be as demanding as approving a drug for its first indication, first of all in regard to safety. Therefore, while obviously it is only up to the pharmaceutical company to decide whether to bring a new agent onto the market or not, extending an existing label might well follow different rules [11]. Why communities of researchers, the academy, advocacy groups and professional/scientific societies should not have any say in all this in cooperation with the regulatory bodies?

In conclusion, at a time when health expense constraints may easily lead to inequalities in patients' access to available appropriate care, ESMO advocates concrete political steps about the off-label uses of anticancer drugs. Likewise, ESMO wants to support medical oncologists who in this regard find themselves before health administrators or third payers in the need to assert some essential principles of good quality of care.

P. G. Casali
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Istituto Nazionale Tumori, Milano, Italy
(E-mail: paolo.casali@istitutotumori.mi.it)

acknowledgements

This editorial has been prepared with the substantial contribution of Pascale Blaes, Director of the ESMO Brussels Office, and Svetlana Jezdic, ESMO Head Office Medical Oncologist.

references

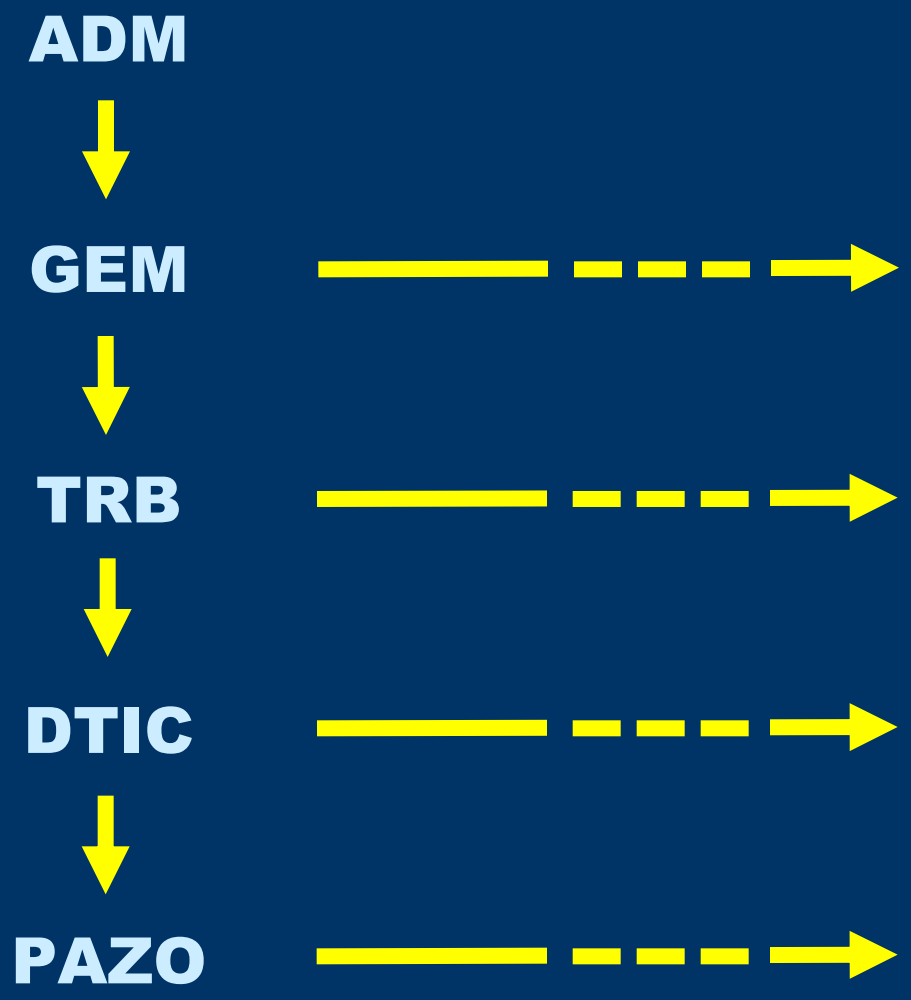
1. EudraLex. The rules governing medicinal products in the European Union. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm.

Multivariate Analysis of Overall Survival (patients treated with systemic treatment, n=1600)

	p-value	HR [IC95%]
Locoregional treatment of metastases	<.0001	0.413 [0.361; 0.472]
Grade: 3	<.0001	1.610 [1.409; 1.840]
Histotype	<.0001	
Leiomyosarcoma	0.0239	0.826 [0.700; 0.975]
Liposarcoma - dedifferentiated	0.2642	1.152 [0.898; 1.478]
Malignant peripheral nerve sheath tumour (MPNST)	0.5015	1.128 [0.794; 1.600]
Synovial sarcoma	0.0274	1.269 [1.027; 1.568]
Undifferentiated pleomorphic sarcoma	0.1024	1.218 [0.961; 1.543]
Polychemotherapy (1st line)	0.0005	0.786 [0.690; 0.896]
Use of off-labelled drugs	0.0012	0.847 [0.738; 0.972]
Sex: Female	0.0016	0.792 [0.695; 0.903]
Inclusion in a clinical trial	0.0076	0.797 [0.680; 0.934]
Number of metastatic sites: >1	0.0074	1.248 [1.061; 1.469]

Italiano A et al.
Patterns of care and outcome of patients (pts) with metastatic soft-tissue sarcoma (STS) according to histological subtype and treatment setting: The METASTAR study.
ASCO Ann. Meet. 2016, #11014

Leiomyosarcoma




T
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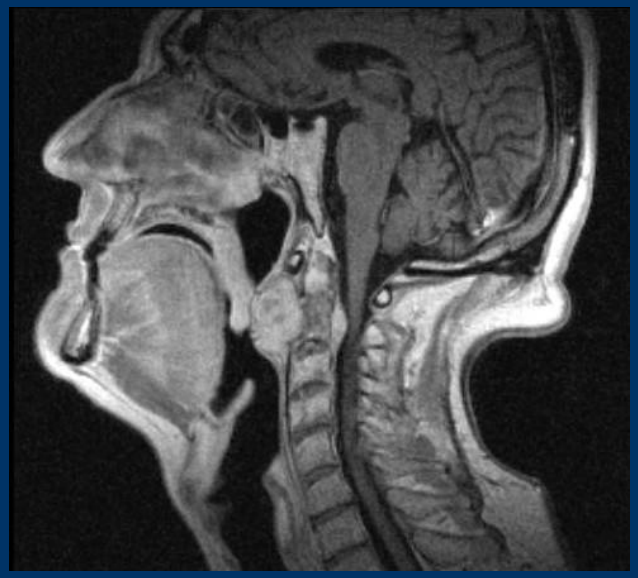
response
progression

Tumor response as a surrogate

Quality of life



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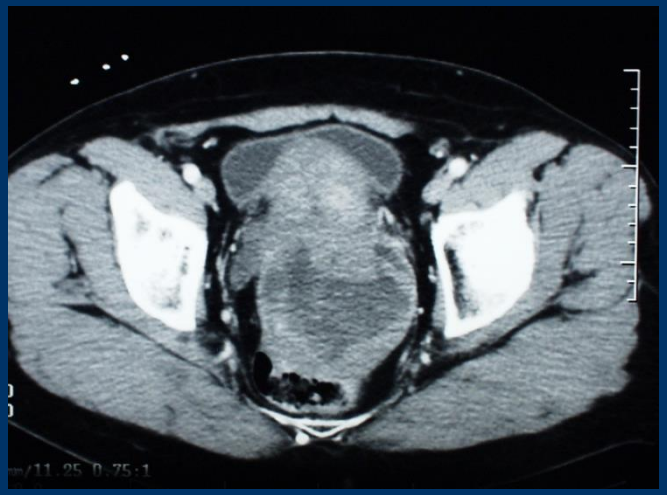
Quality of life



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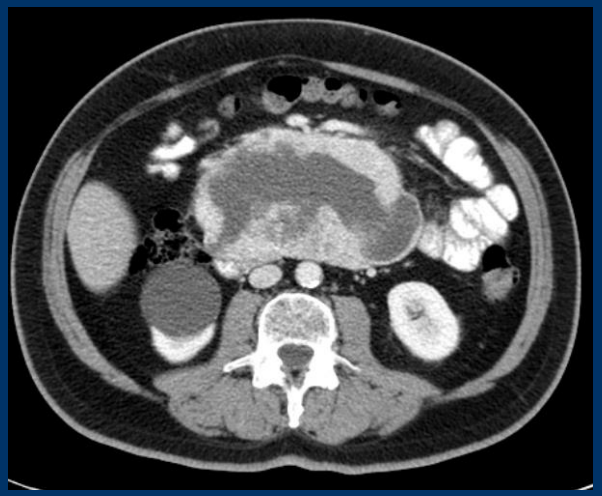
Survival…



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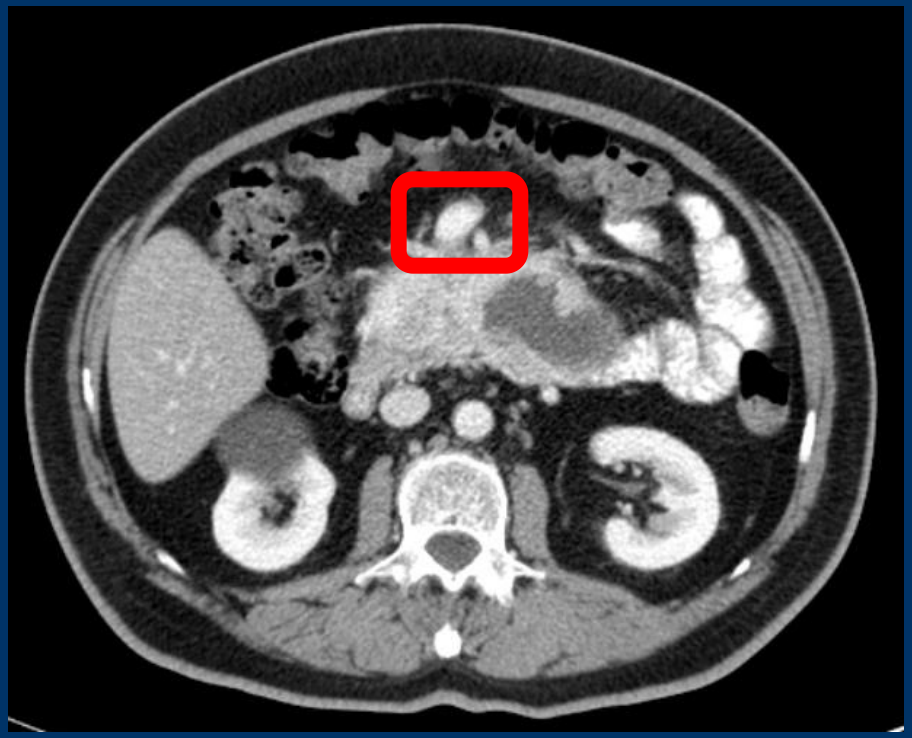
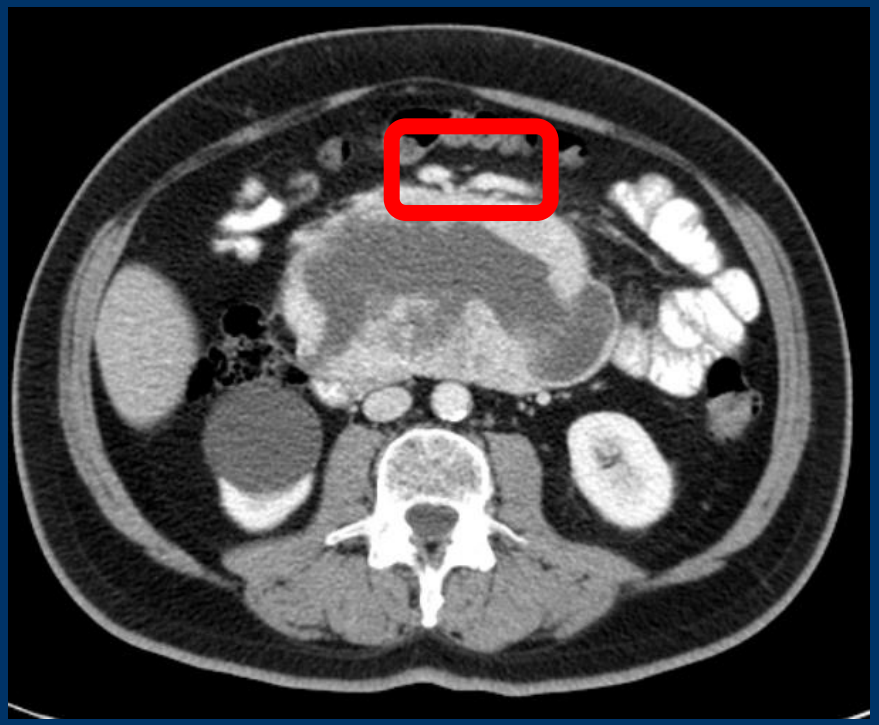
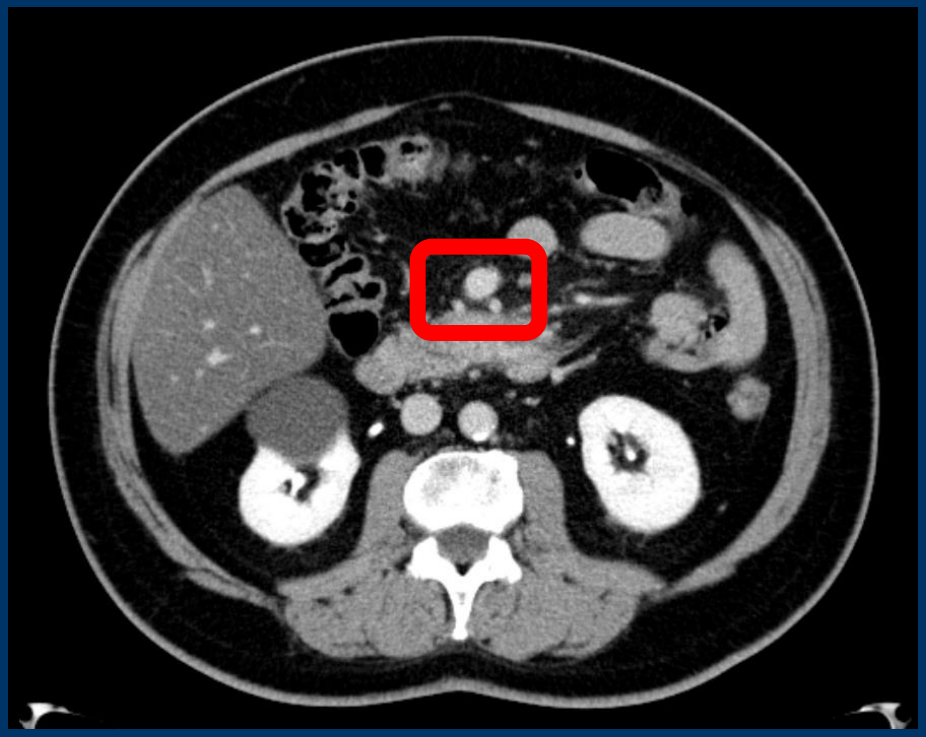
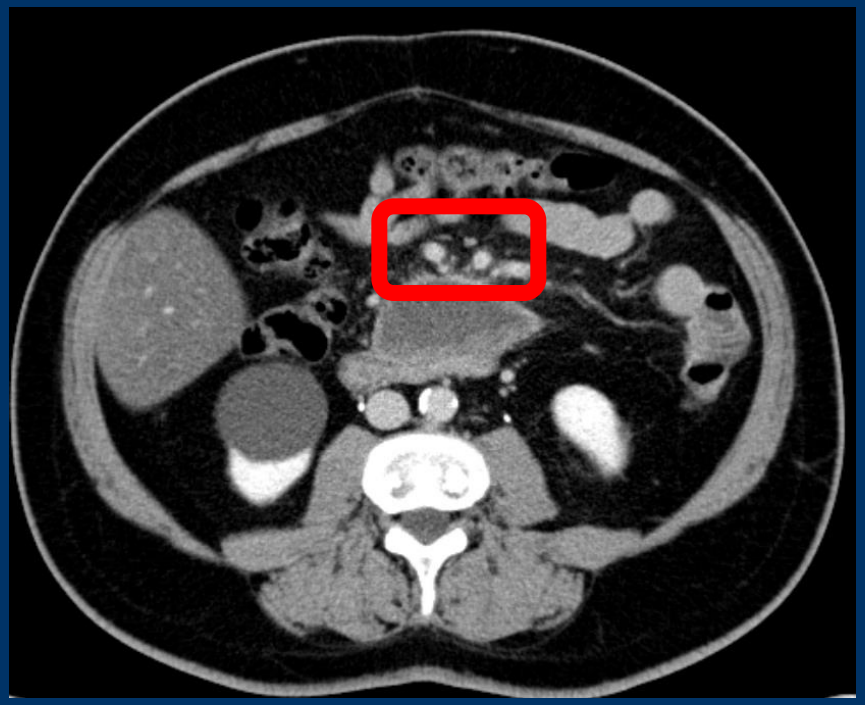








Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

HULTON/GETTY

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

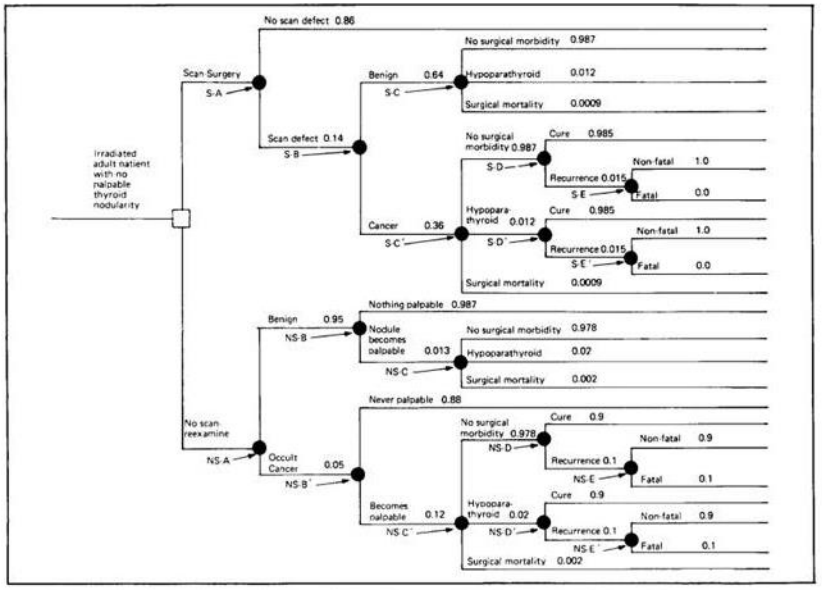
BMJ 2003;327:1459

MEDICAL PROGRESS

DECISION ANALYSIS

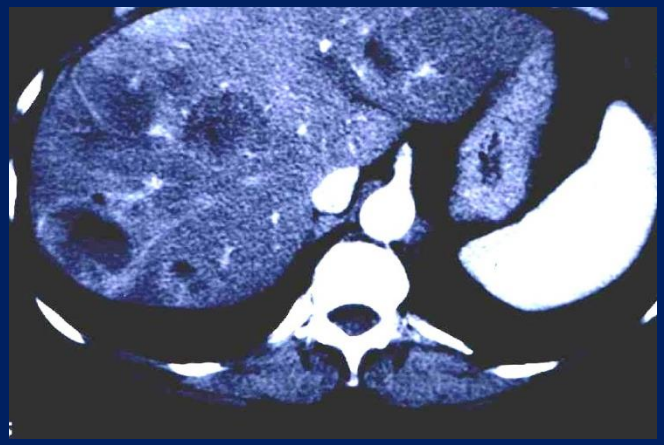
STEPHEN G. PAUKER, M.D., AND JEROME P. KASSIRER, M.D.

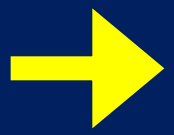
$$* \quad P_{dis|find} = \frac{P_{dis} \times P_{find|dis}}{\sum_{i=1}^{n} P_{dis\,i} \times P_{find|dis\,i}},$$

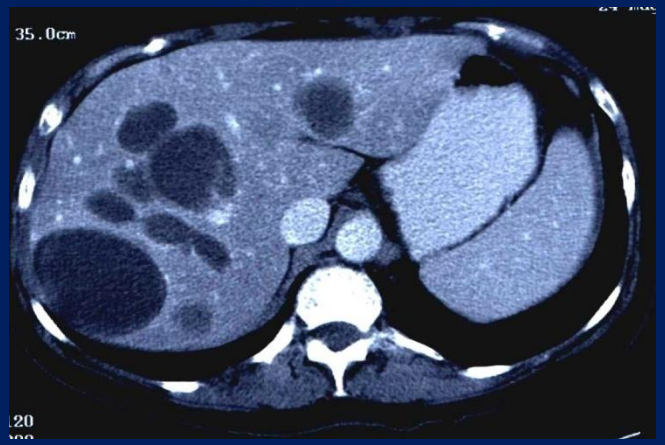


N Engl J Med 1987;316:250

GIST: tumor response

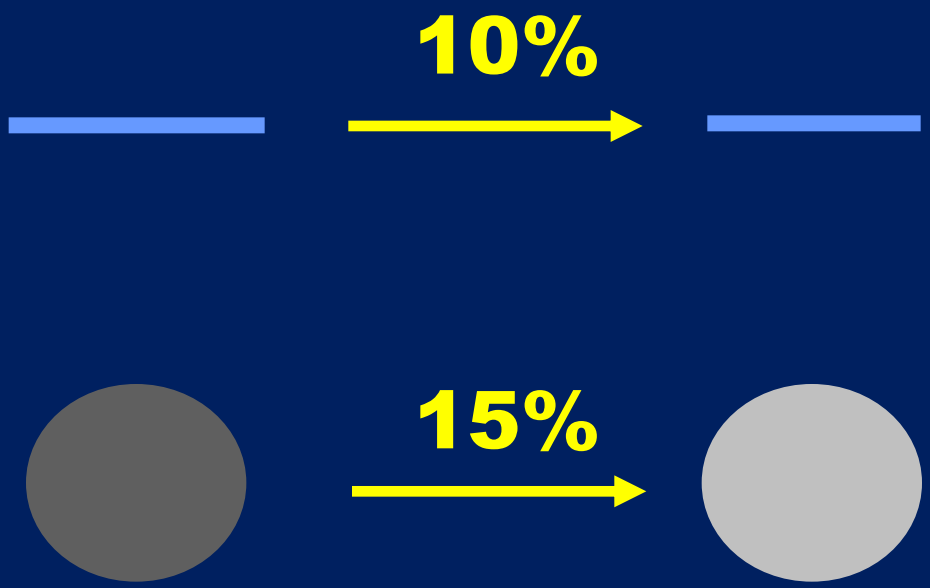






GIST: tumor response

Choi's



VOLUME 25 · NUMBER 13 · MAY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

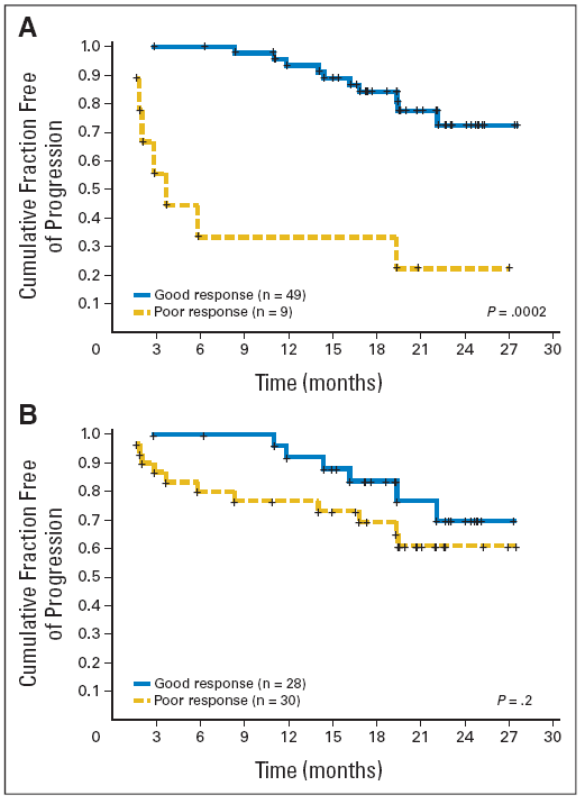
ORIGINAL REPORT

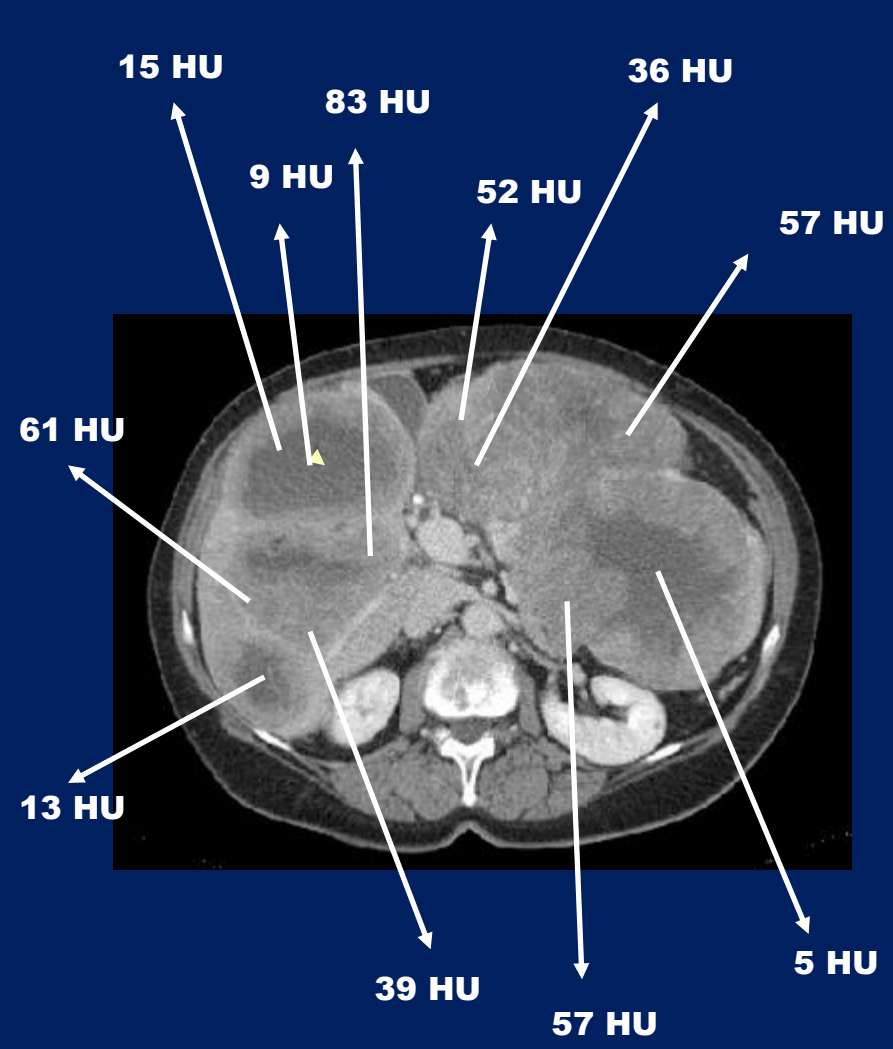
We Should Desist Using RECIST, at Least in GIST

Robert S. Benjamin, Haesun Choi, Homer A. Macapinlac, Michael A. Burgess, Shreyaskumar R. Patel, Lei L. Chen, Donald A. Podoloff, and Chuslip Charnsangavej

Choi's

RECIST

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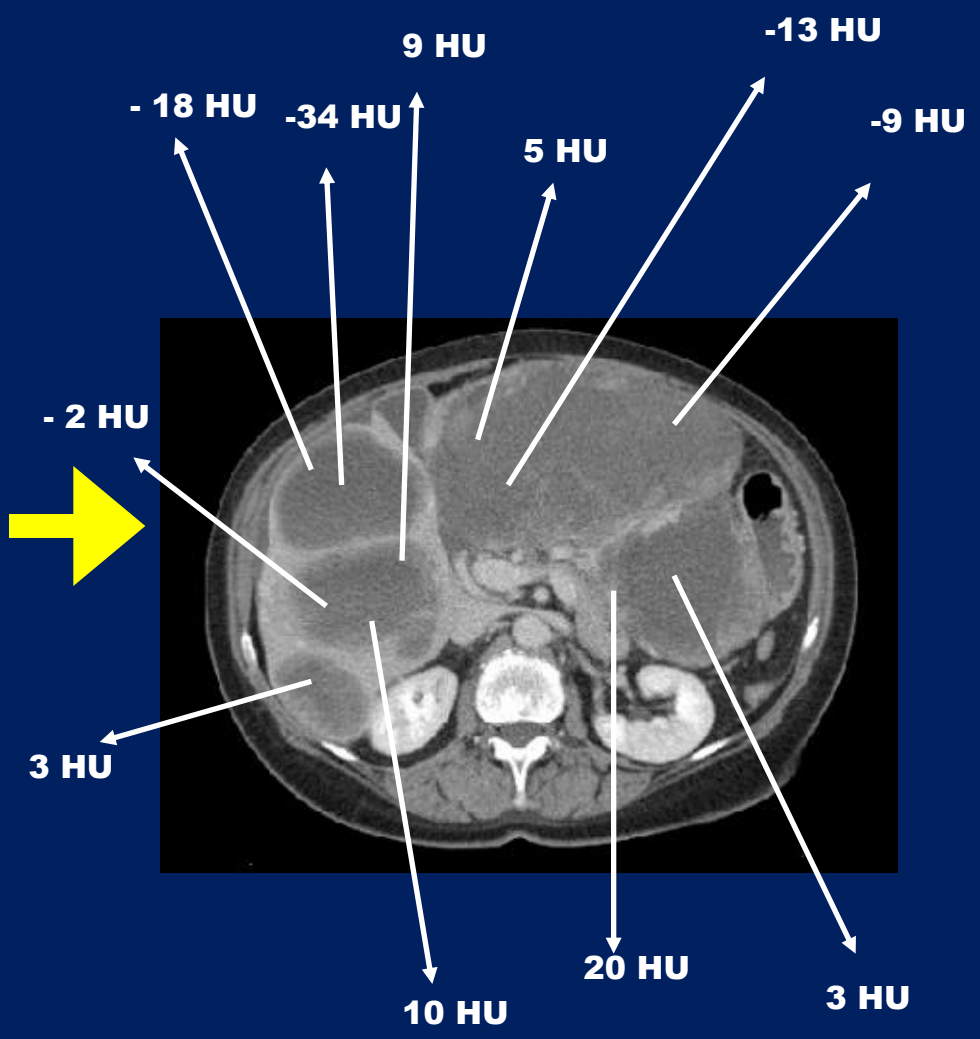
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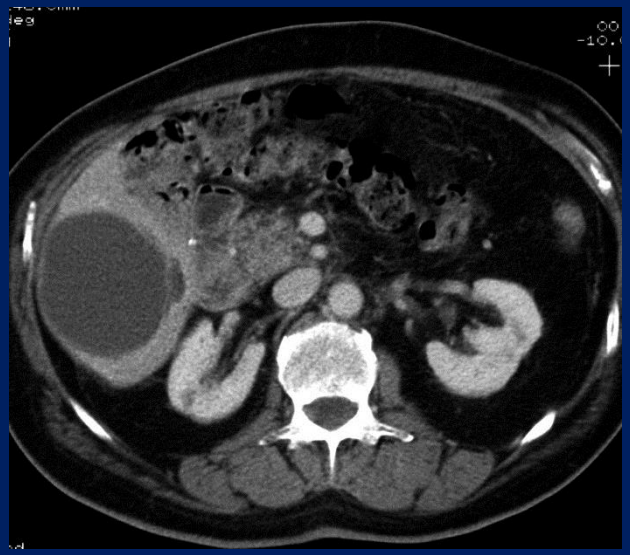
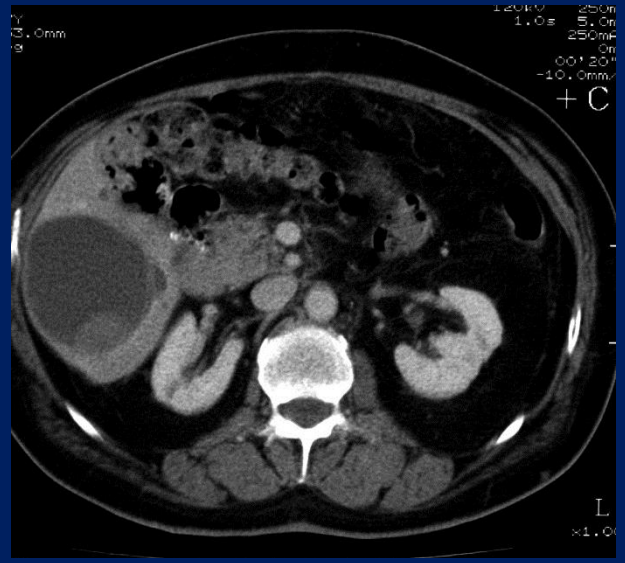




Immune therapies: tumor response

Table 2. Differences Between RECIST (version 1.1) and irRC

Factor	RECIST	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Complete response	Disappearance of all target and nontarget lesions; lymph nodes must regress to < 10-mm short axis; no new lesions; requires confirmation	Same as for RECIST
Partial response	≥ 30% decrease in tumor burden compared with baseline; requires confirmation	≥ 50% decrease in tumor burden compared with baseline; requires confirmation
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir; progression of nontarget lesions and/or appearance of new lesions (at any single time point)	≥ 25% increase in tumor burden compared with most recent prior evaluation; new lesions added to tumor burden; requires confirmation
Stable disease	Any response pattern that does not meet criteria for complete response, partial response, or progressive disease	Same as for RECIST

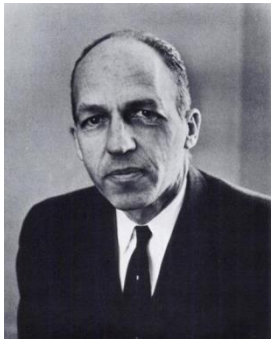
Abbreviation: irRC, immune-related response criteria.

Postow MA et al. J Clin Oncol 2015;33:1974

CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 2 *number* 6 November-December 1961

Editorial



Category I. Clinical benefit with favorable objective changes in all measurable criteria of disease.

I-A* Distinct subjective benefit with favorable objective changes in all measurable criteria for 1 month or more.

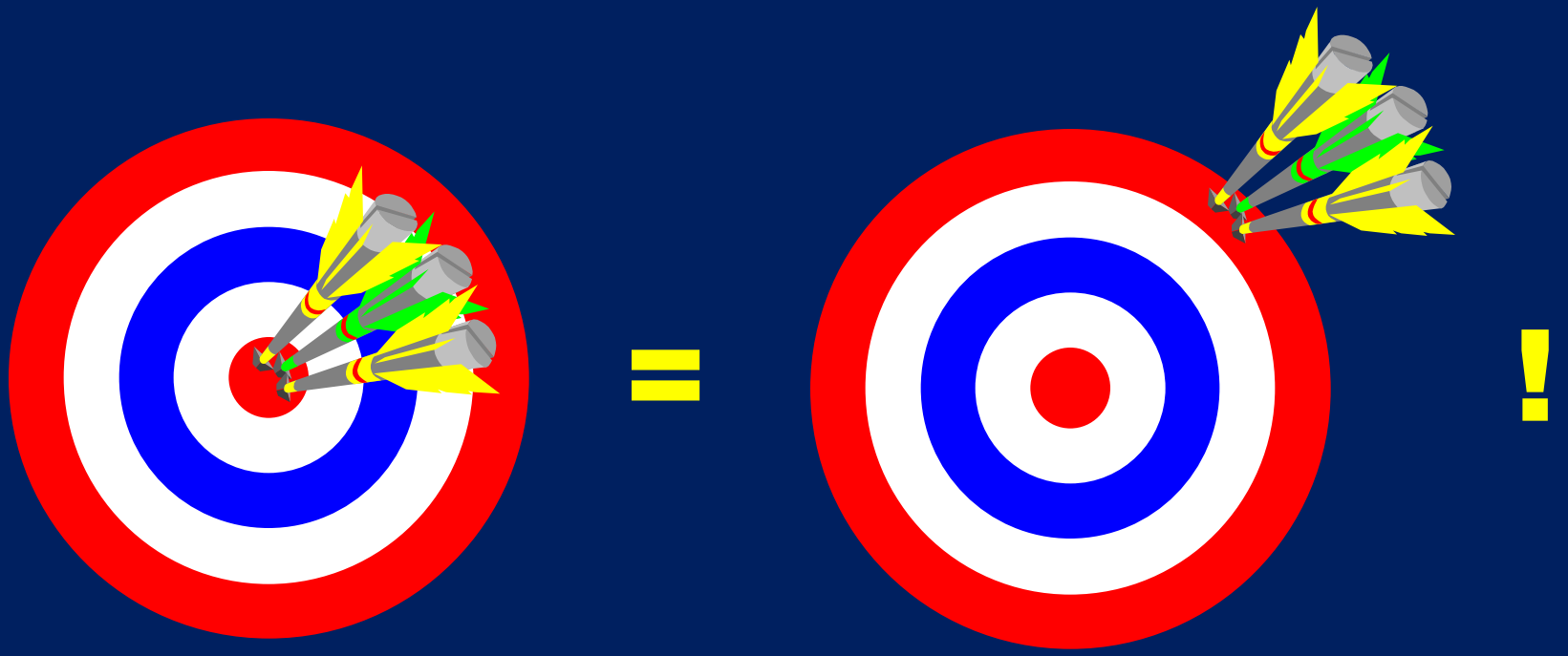
I-B* Objective regression of all palpable or measurable neoplastic disease for 1 month or more in a relatively asymptomatic patient who is able to carry on his usual activities without undue difficulty. The observed tumor regression should be unequivocal, and it is suggested that all lesions be reduced at least 50 per cent in bulk. This category applies as long as the regression persists and ends if any lesion, old or new, recurs.

I-C Complete relief of symptoms, if any, and regression of all manifestations resulting from the active disease for 1 year or more. The relation to the frequency of therapy is not relevant if the disease does not recur between courses of therapy.

Category II. Interruption or slowing in progression of disease without definite evidence of subjective or objective improvement. No criteria are presently available to classify this type of response. Statistical evidence of prolongation of survival time in specific patterns of cancer may some day be applicable.

Karnofsky DA, 1961;6:709

Reliability (reproducibility)



THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER

CHARLES G. MOERTEL, MD,* AND JAMES A. HANLEY, PHD†

In this study, 16 experienced oncologists each measured 12 simulated tumor masses employing their usual clinical methods. Unknown to the oncologists, two pairs of these tumors were identical in size. This permitted a total of 64 measurement comparisons of the same investigator measuring the same size mass and 1920 comparisons of different investigators measuring the same size mass. If a 50% reduction in the product of perpendicular diameters is accepted as a criterion, the objective response rate due to measuring error alone was 7.8% by the same investigator and 6.8% by different investigators. If a 25% reduction criterion is used, the respective "placebo" response rates were 19% and 25%. In the clinical setting it is recommended that the 50% reduction criterion be employed and that the investigator should anticipate an objective response rate of 5 to 10% due to human error in tumor measurement.

Cancer **38:388–394, 1976.**

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

The definition of a partial response, in particular, is an arbitrary convention—there is no inherent meaning for an individual patient of a 50% decrease in overall tumor load. It was not thought that increased precision of measurement of tumor volume was an important goal for its own sake. Rather, standardization and simplification of methodology were desirable. Nevertheless, the guidelines proposed in this document are not meant to discourage the development of new tools that may provide more reliable surrogate end points than objective tumor response for predicting a potential therapeutic benefit for cancer patients.

J Natl Cancer Inst 2000;92:205

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

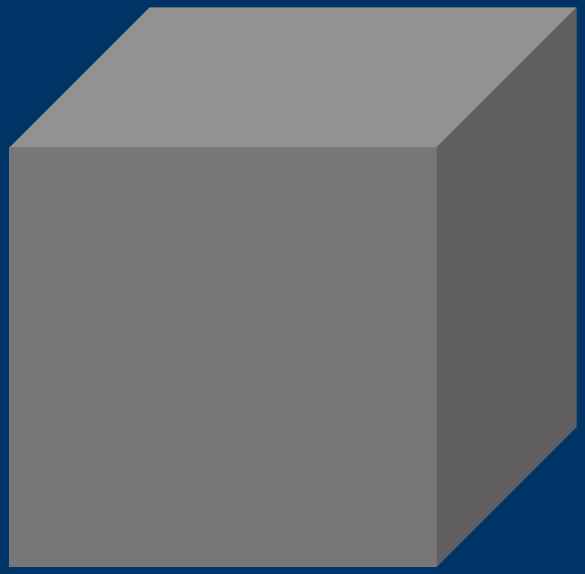
Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

1.1. Response Outcomes in Daily Clinical Practice of Oncology

The evaluation of tumor response in the daily clinical practice of oncology may not be performed according to predefined criteria. It may, rather, be based on a subjective medical judgment that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. The defined criteria developed further in this document are not necessarily applicable or complete in such a context. It might be appropriate to make a distinction between "clinical improvement" and "objective tumor response" in routine patient management outside the context of a clinical trial.

J Natl Cancer Inst 2000;92:205

1. Personalized tool



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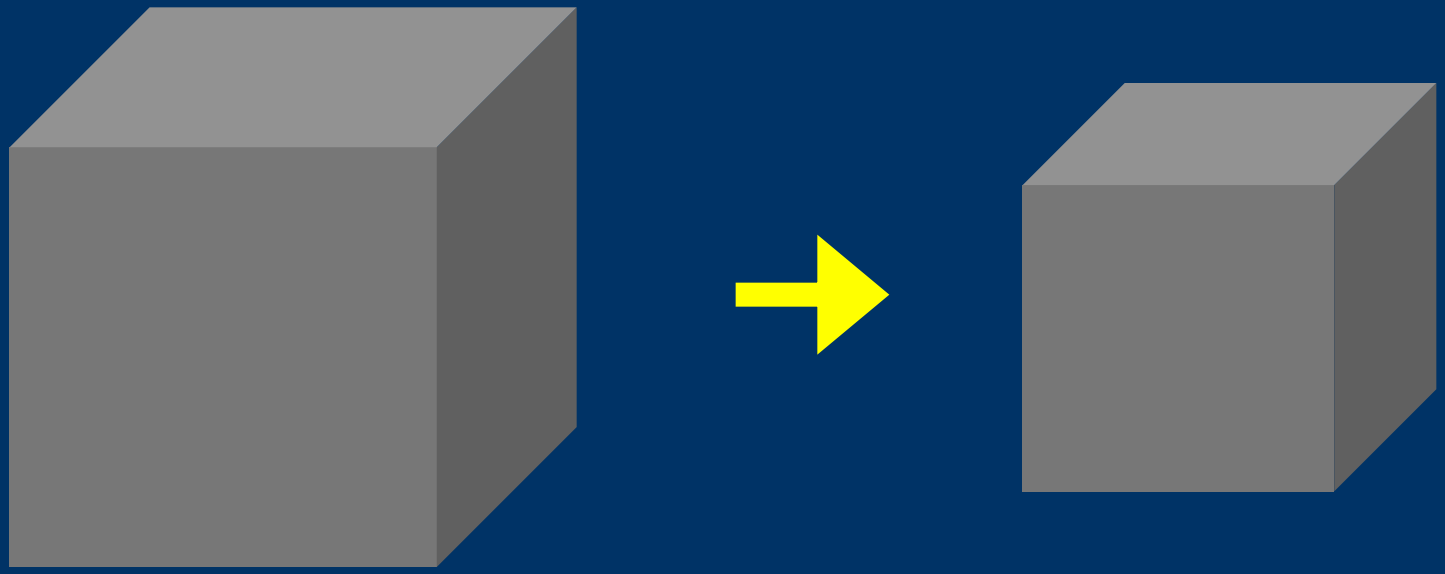
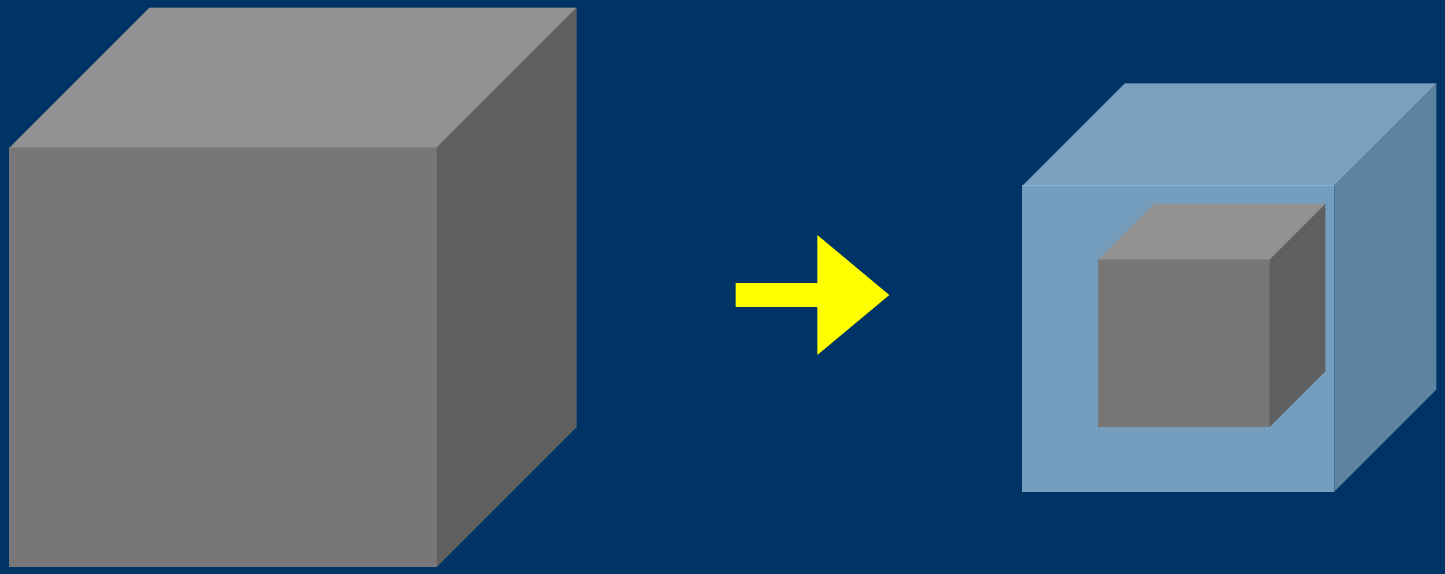
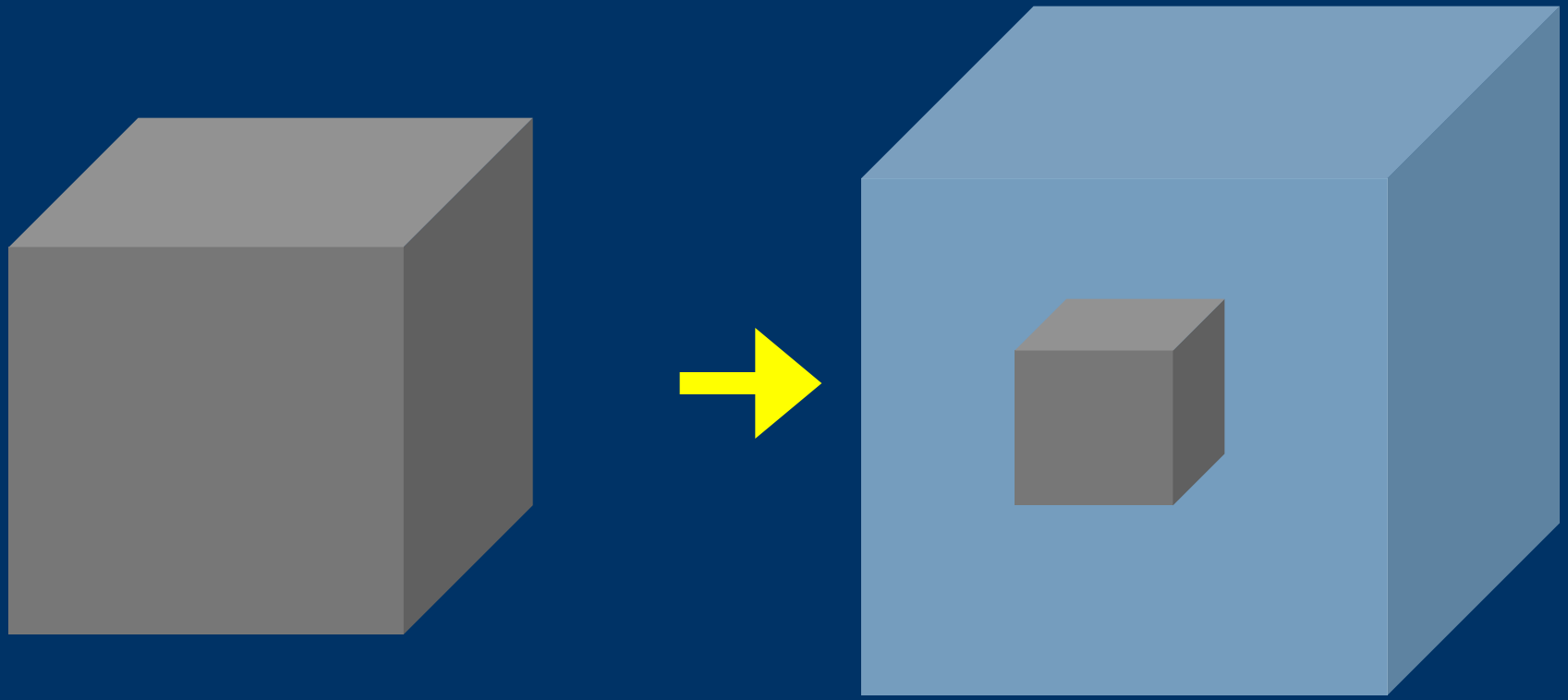
2. Volume

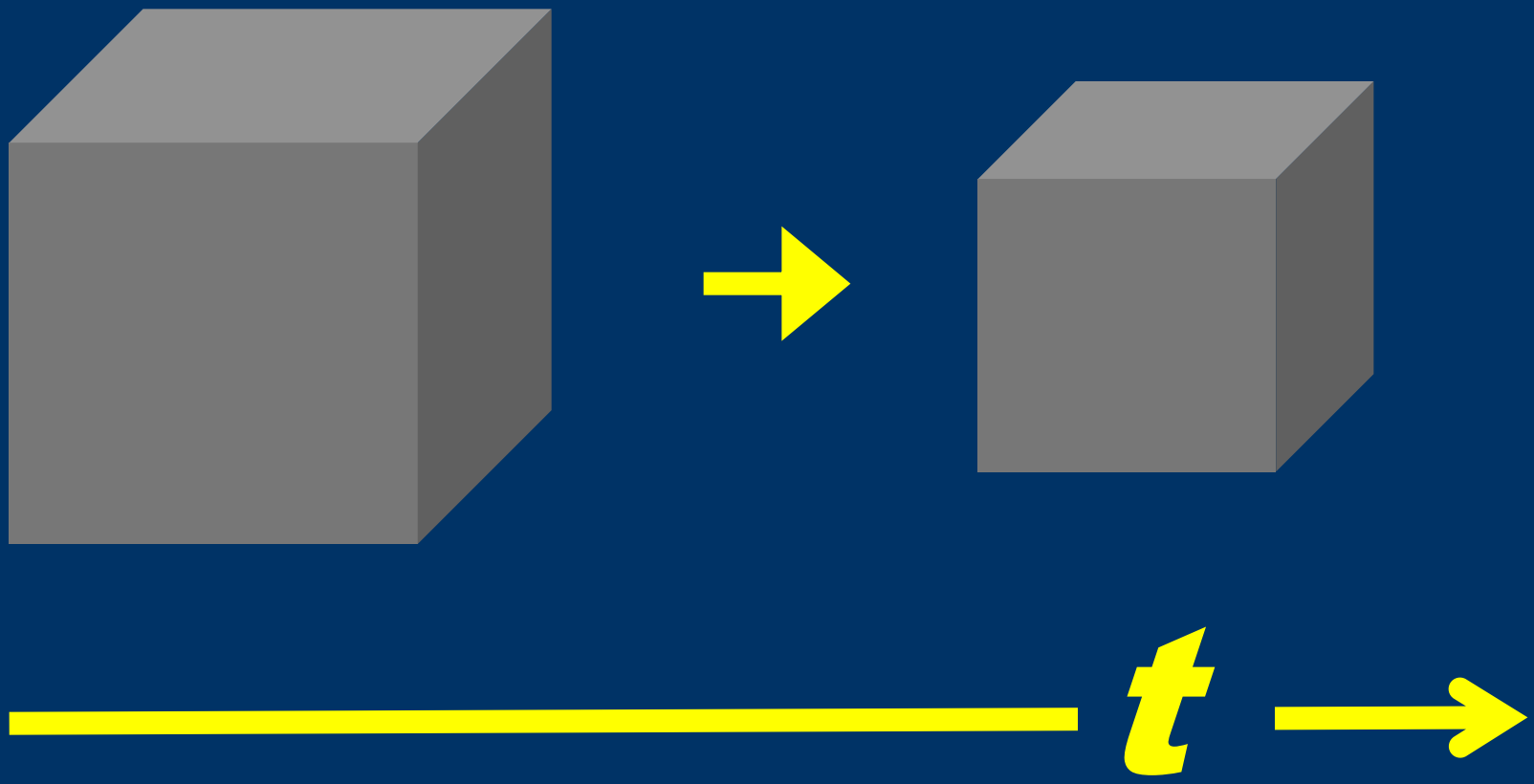


3. Non-dimensional changes

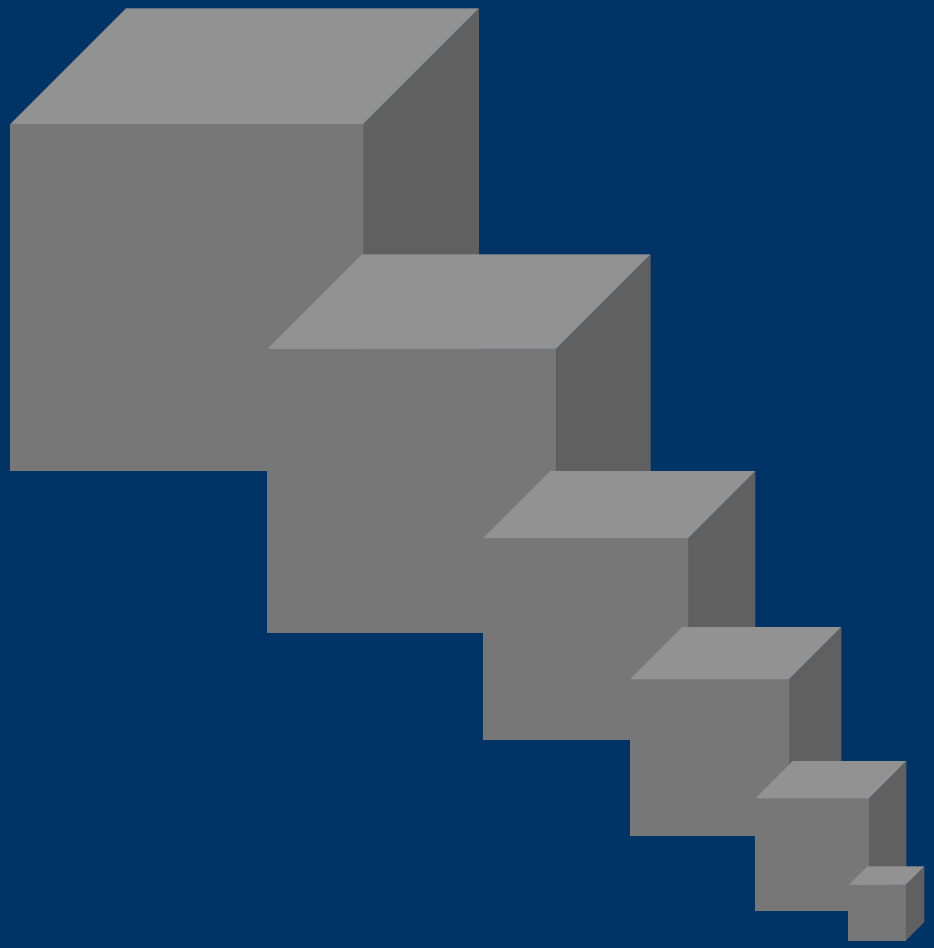




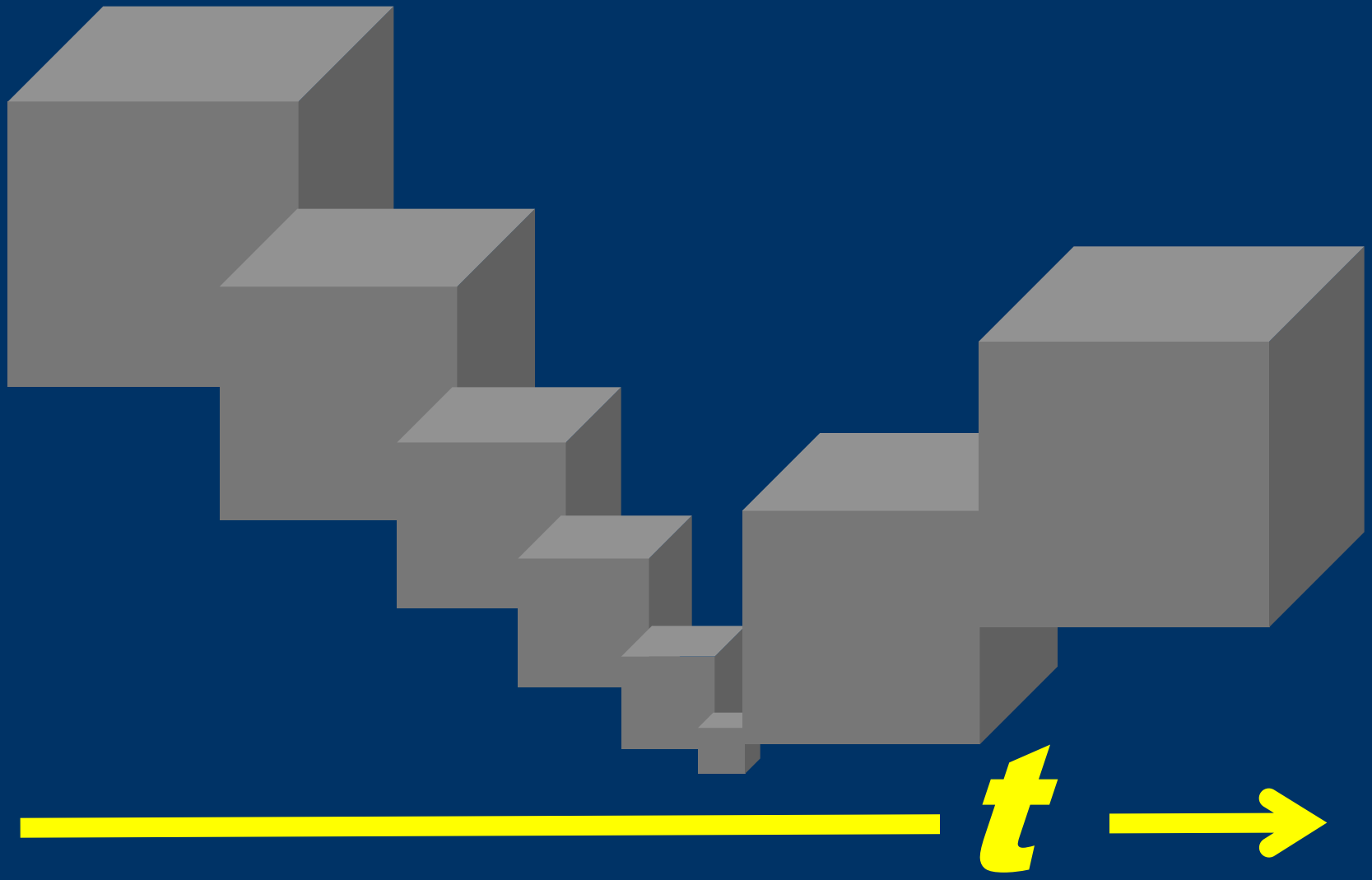
4. Temporal dimension

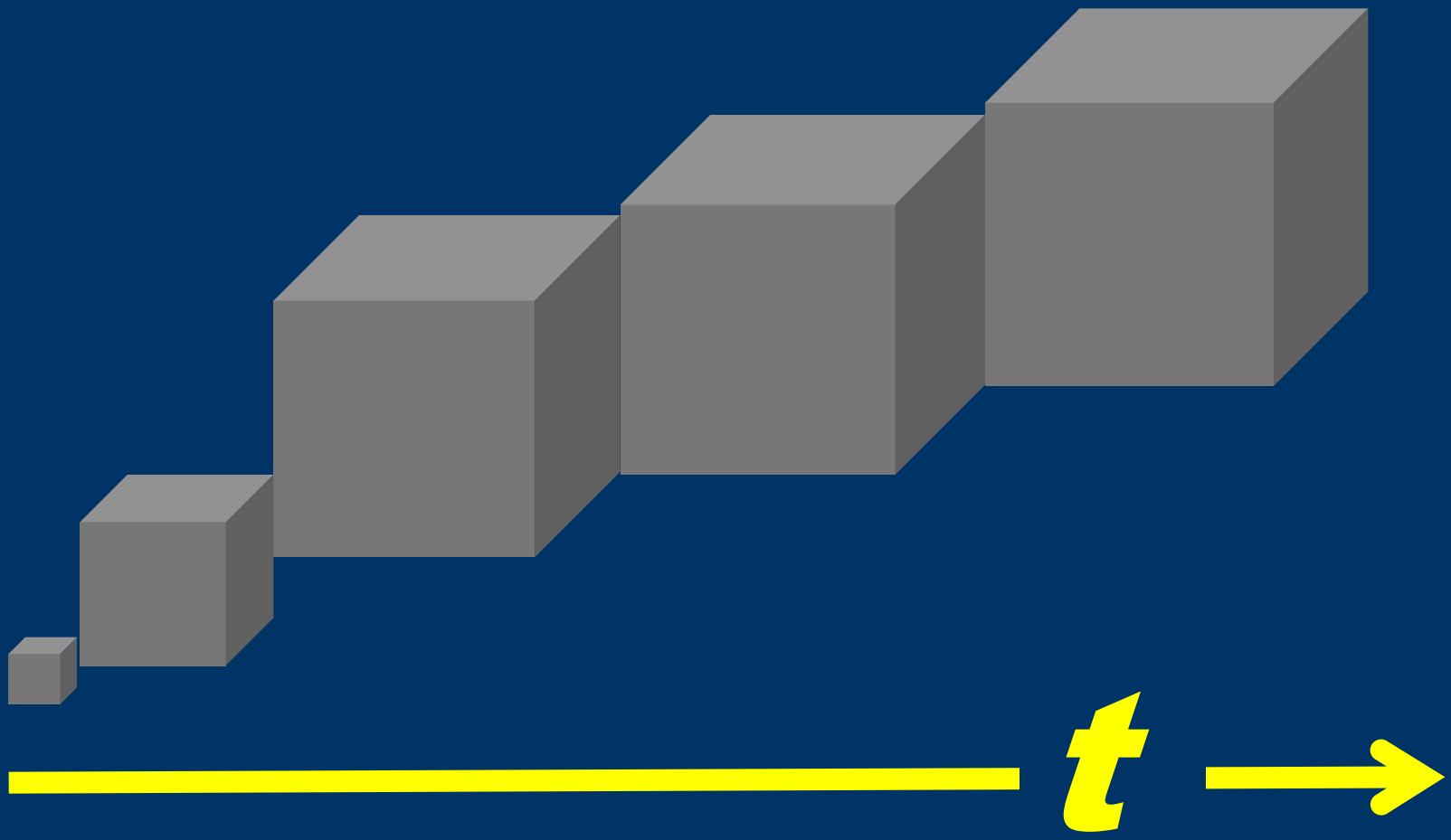


5. Continuous variable



6. Growth rate

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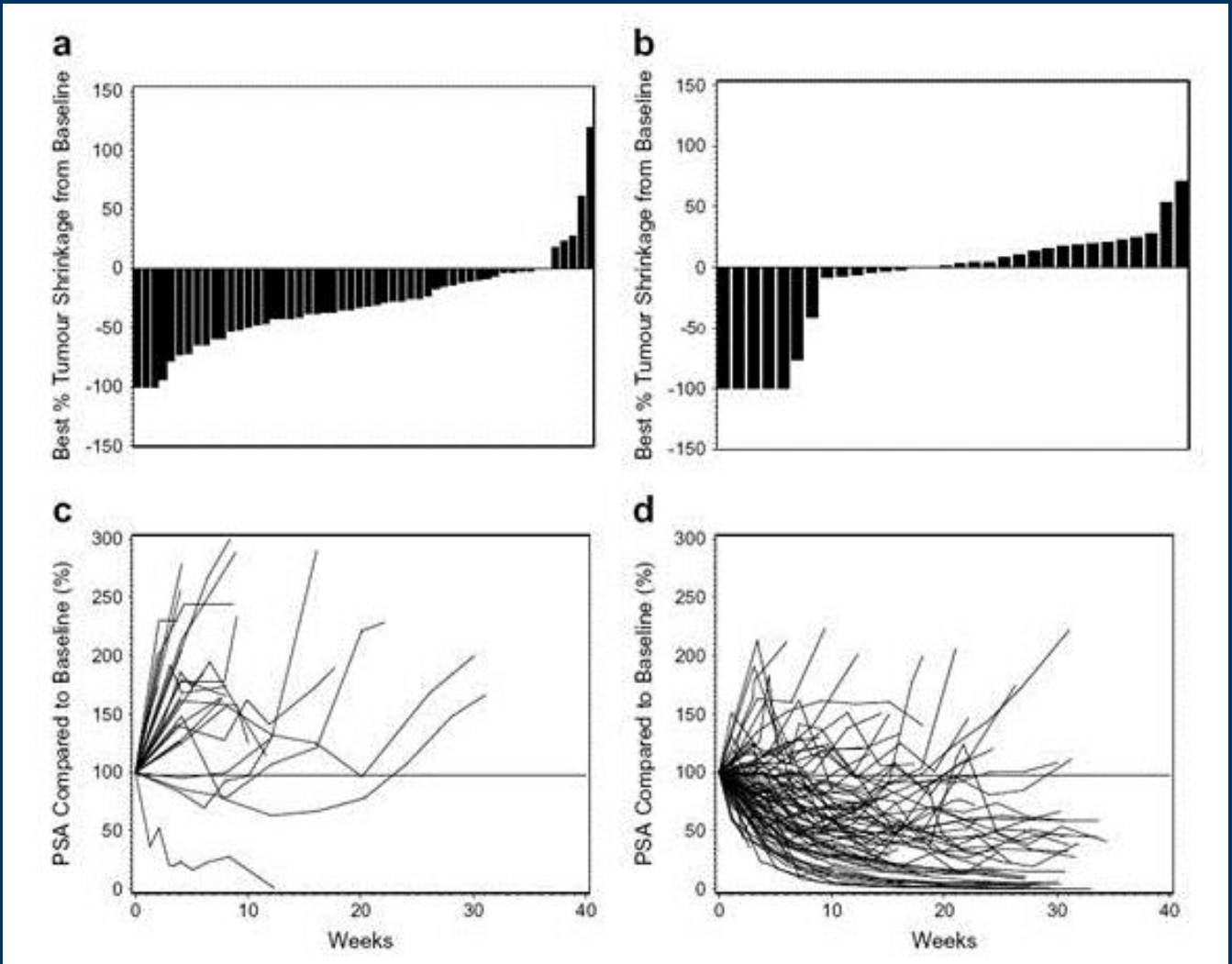


Booth CM et al. Eur J Cancer 2008;44:25

Phase II Clinical Trial Design for Noncytotoxic Anticancer Agents for Which Time to Disease Progression Is the Primary Endpoint

Rosemarie Mick, MS, John J. Crowley, PhD, and Raymond J. Carroll, PhD

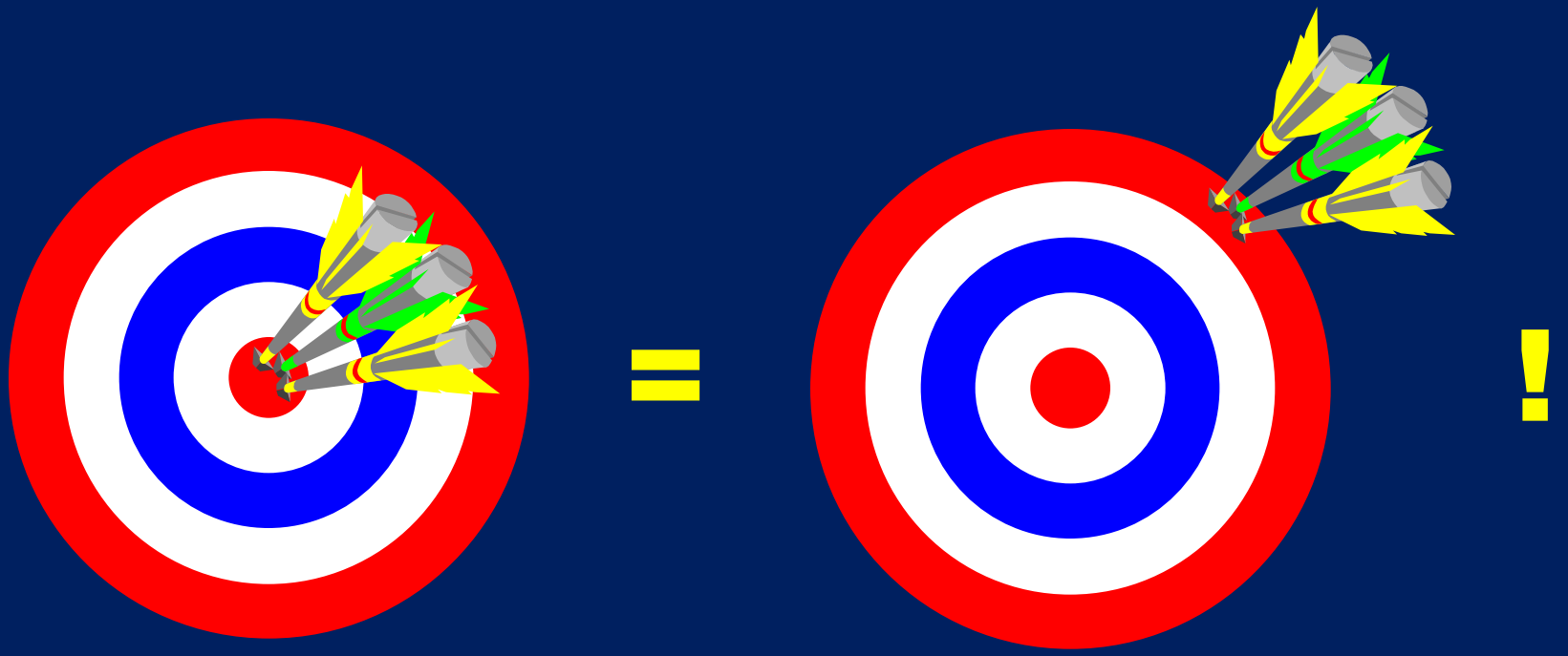
Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania (R.M.); Program in Biostatistics, Fred Hutchinson Cancer Research Center, Seattle, Washington (J.J.C.); Department of Statistics, Texas A&M University, College Station, Texas (R.J.C.)

We defined TTP_1 and TTP_2 to be:

$$TTP_1 = \frac{(X_0 + X_1)m}{\ln[2]} \text{ and } TTP_2 = \frac{(X_0 + X_2)m[\exp(\beta)]}{\ln[2]}.$$

Controll Clin Trials 2000;21:343

Reliability (reproducibility)



Annals of Oncology 26: 1547–1573, 2015
doi:10.1093/annonc/mdv249
Published online 30 May 2015

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

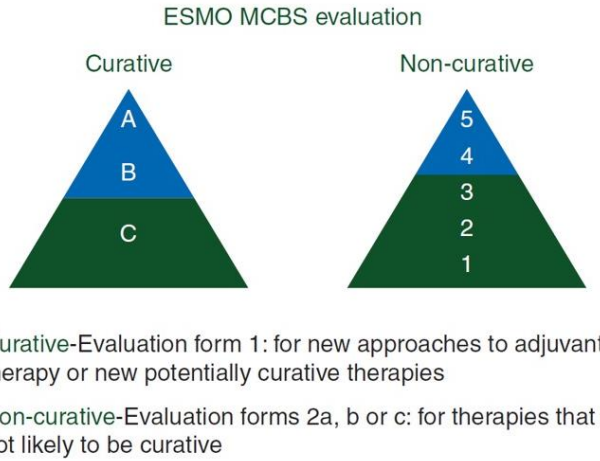


Figure 3. Visualisation of ESMO-MCB scores for curative and non-curative setting. A & B and 5 and 4 represent the grades with substantial improvement.

Grade A
>5% improvement of survival at ≥3 years follow-up
Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data
Grade B
≥3% but ≤5% improvement at ≥3 years follow-up
Improvement in DFS alone (primary endpoint) (HR 0.65–0.8) without mature survival data
Non inferior OS or DFS with reduced treatment toxicity or improved Quality of Life (with validated scales)
Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)
Grade C
<3% improvement of survival at ≥3 years follow-up
Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data

Annals of Oncology 26: 1547–1573, 2015
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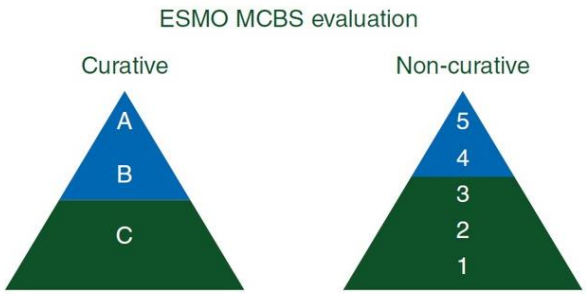


Curative-Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Non-curative-Evaluation forms 2a, b or c: for therapies that are not likely to be curative

Figure 3. Visualisation of ESMO-MCB scores for curative and non-curative setting. A & B and 5 and 4 represent the grades with substantial improvement.

IF median OS with the standard treatment is ≤1 year

Grade 4
HR ≤0.65 AND Gain ≥3 months
Increase in 2 year survival alone ≥10%
Grade 3
HR ≤0.65 AND Gain 2.5–2.9 months
Increase in 2 year survival alone 5 - <10%
Grade 2
HR >0.65–0.70 OR Gain 1.5–2.4 months
Increase in 2 year survival alone 3 - <5%
Grade 1
HR >0.70 OR Gain <1.5 months
Increase in 2 year survival alone <3%

Quality of Life assessment /grade 3–4 toxicities assessment*

Does secondary endpoint quality of life show improvement
Are there statistically significantly less grade 3–4 toxicities impacting on daily well-being*

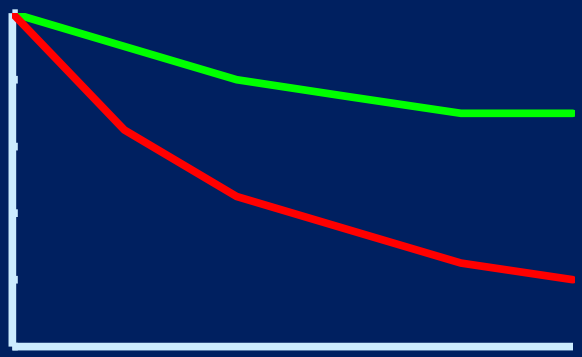
*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

European Action Against Rare Cancers

Recommendations Addressing Regulatory Barriers in Rare Cancer Care

We:

1. Acknowledge that while the process for establishing the efficacy of new medicines is in principle the same for all cancers, the strength of the evidence – intended as level and quality of evidence and statistical precision – that is achievable in common cancers is difficult to achieve in rare conditions and, therefore, a higher degree of uncertainty should be accepted for regulatory as well as clinically informed decision-making.



RARE CANCERS EUROPE

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GOOD SCIENCE
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European Society for Medical Oncology

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