

Corso di Metodologia sulla ricerca clinica

Milano, 15-16 novembre 2012

**Lo sviluppo clinico di un farmaco in
ambito oncologico
(percorso storico, sviluppi fino ad oggi)**

Francesco Perrone

Oncologo
Unità Sperimentazioni Cliniche
Istituto Nazionale Tumori di Napoli



Presentazioni

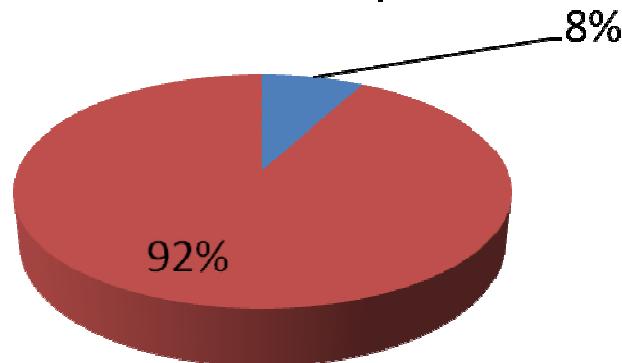
- Sono oncologo
- Dirigo l'Unità Sperimentazioni Cliniche (all'Istituto Tumori di Napoli, IRCCS pubblico) che agisce come promotore di sperimentazioni non-profit multicentriche
 - Aspetti scientifici
 - Aspetti procedurali e di conduzione
- ... e a breve attività clinica di fase 1

Alcuni numeri 2001-2011

- 53 studi
- 578 centri partecipanti
- 9.493 pazienti

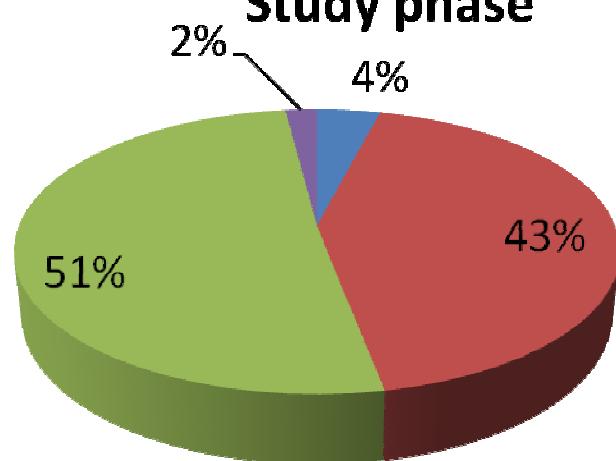
Type of study

■ Profit ■ Non profit



Study phase

■ 1-2 ■ 2 ■ 3 ■ 4

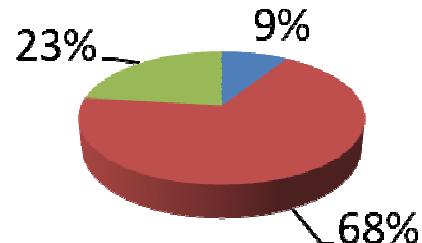


Study setting

■ Single centre

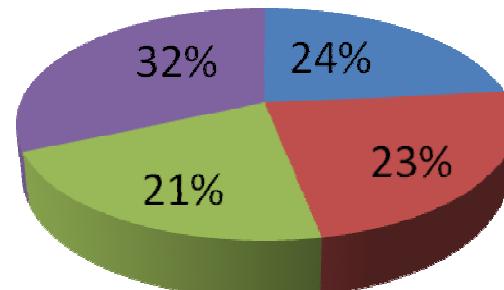
■ Multicentre (Italy)

■ Multicentre (International)



Primary tumor site

■ Lung ■ Gynecology ■ Breast ■ Other

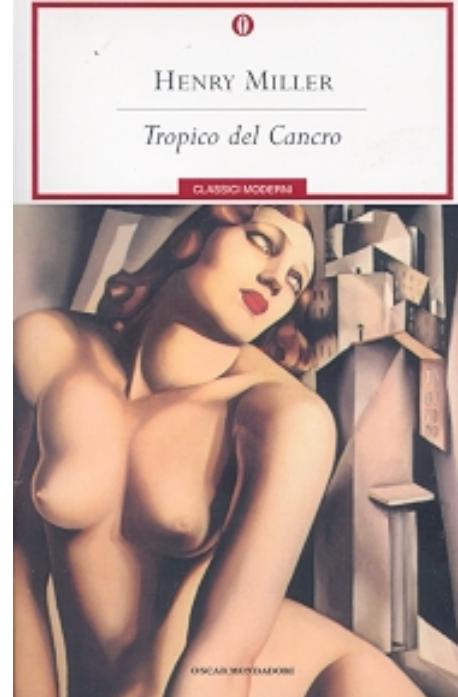


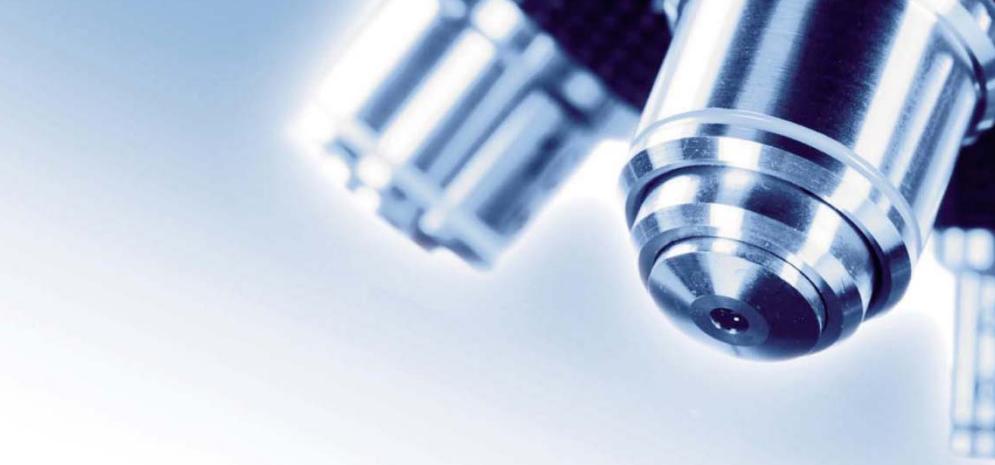
2001-2011

- 53 studi
- 578 centri partecipanti
- 9.493 pazienti
- 117 articoli peer-reviewed
- 974 punti di IF totale
- 8.3 punti di IF medio per articolo
- ...
- Tentando di onorare le richieste del nostro datore di lavoro, lo Stato

Il legame tra oncologia e sperimentazione clinica

E' molto forte...





LA Sperimentazione clinica dei medicinali in Italia

11° Rapporto nazionale
2012



Tabella 2

Spesa lorda a carico del Servizio Sanitario Nazionale per classificazione terapeutica – 2011

Classificazione terapeutica – ATC 1° livello	Spesa totale (milioni di euro)	Spesa pro-capite (euro)	%
C Sistema cardiovascolare	4.407	72,7	35,6
A Apparato gastrointestinale e metabolismo	1.905	31,4	15,4
N Sistema nervoso	1.448	23,9	11,7
R Sistema respiratorio	1.095	18,1	8,8
J Antimicrobici generali per uso sistemico	1.034	17,1	8,3
B Sangue e organi emopoietici	574	9,5	4,6
M Sistema muscolo-scheletrico	558	9,2	4,5
G Sistema genito-urinario e ormoni sessuali	404	6,7	3,3
L Antineoplastici e immunomodulatori	336	5,5	2,7
H Preparati ormonali sistematici, escl. ormoni sessuali	225	3,7	1,8
S Organi di senso	211	3,5	1,7
V Vari	120	2,0	1,0
D Dermatologici	59	1,0	0,5
P Antiparassitari, insetticidi e repellenti	12	0,2	0,1
Totale	12.388	204,3	100,0



Tabella 11

Sperimentazioni per classificazione terapeutica e fase

SC totali: 3.783 di cui 3.773 (99,7%) con ATC di almeno un farmaco in test specificato

Classificazione terapeutica ATC 1° livello	SC	% Fase I Fase II Fase III Fase IV Bioeq / Biod						Totale
		Fase I	Fase II	Fase III	Fase IV	Bioeq / Biod		
L Antineoplastici e immunomodulatori	1.487	10,1	51,5	34,2	4,2	0,0	100,0	
N Sistema nervoso	416	1,4	27,2	48,6	21,2	1,7	100,0	
J Antimicrobici generali per uso sistemico	351	4,8	31,9	44,2	18,2	0,9	100,0	
A App. gastrointestinale e metabolismo	310	1,6	29,0	53,2	15,5	0,6	100,0	
B Sangue e organi emopoietici	279	6,5	22,2	53,8	17,6	0,0	100,0	
C Sistema cardiovascolare	252	6,3	41,7	33,3	18,3	0,4	100,0	
V Vari	249	0,4	28,5	49,0	20,1	2,0	100,0	
H Prep. ormonali sistematici, escl. ormoni sessuali	149	4,7	37,6	33,6	19,5	0,7	100,0	
M Sistema muscolo-scheletrico	141	3,5	31,2	37,8	21,8	6,4	100,0	
R Sistema respiratorio	114	0,0	22,8	62,3	14,0	0,9	100,0	
G Sistema genito-urinario e ormoni sessuali	93	3,2	34,4	46,2	15,1	1,1	100,0	
S Organi di senso	90	0,0	30,0	47,8	22,2	0,0	100,0	
D Dermatologici	52	3,8	32,7	44,2	19,2	0,0	100,0	
P Antiparassitari, insetticidi e repellenti	11	9,1	36,4	36,4	18,2	0,0	100,0	

39%

La stessa sperimentazione può coinvolgere più farmaci in test e quindi essere conteggiata in diverse classificazioni ATC.



Mi sono chiesto di che cosa parlarvi...

- Il titolo assegnato è molto ampio...
- Quasi un assegno in bianco!
- **L'impatto della biologia molecolare**
- **L'importanza del punto di vista dei pazienti**
- Vertiginosamente lontani, in apparenza
- Ma l'oncologia è bella per questo...
- E la ricerca ancor di più!



La ricerca clinica in oncologia...

Il luogo nel quale il metodo della sperimentazione

- è maggiormente cresciuto nelle ultime decadi
- si lega sempre più ai problemi regolatori
- si lega sempre più a sostenibilità e accessibilità

- Farmaci citotossici
 - Dagli anni '50 in poi
- Terapie ormonali
 - OOX nel 19° secolo
 - Dagli anni '70 in poi
- Farmaci a bersaglio molecolare (*target-based, intelligenti, ecc...*)

La ricerca clinica in oncologia...

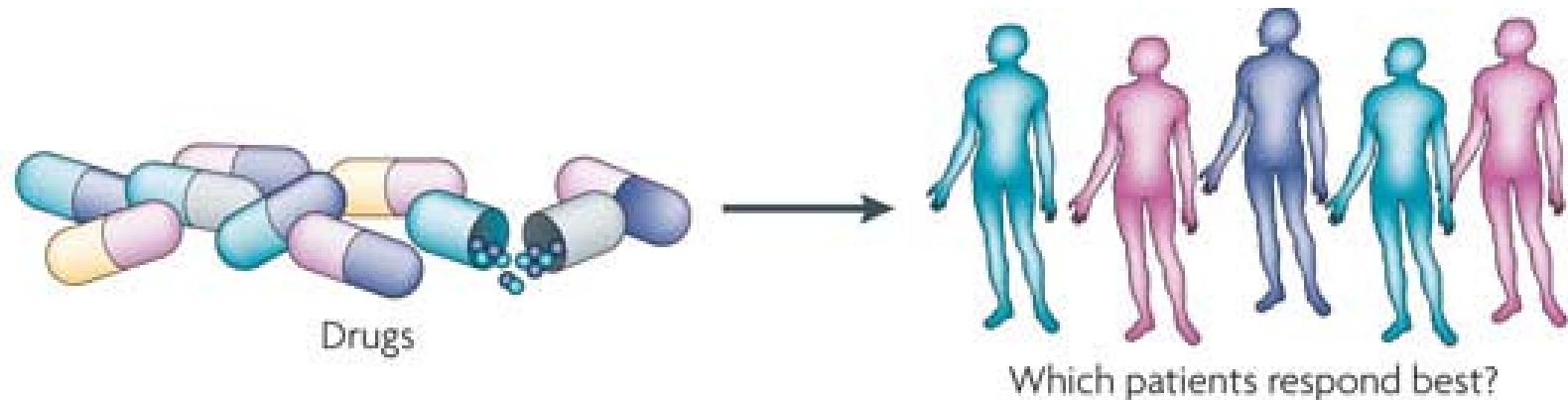
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Personalized medicine



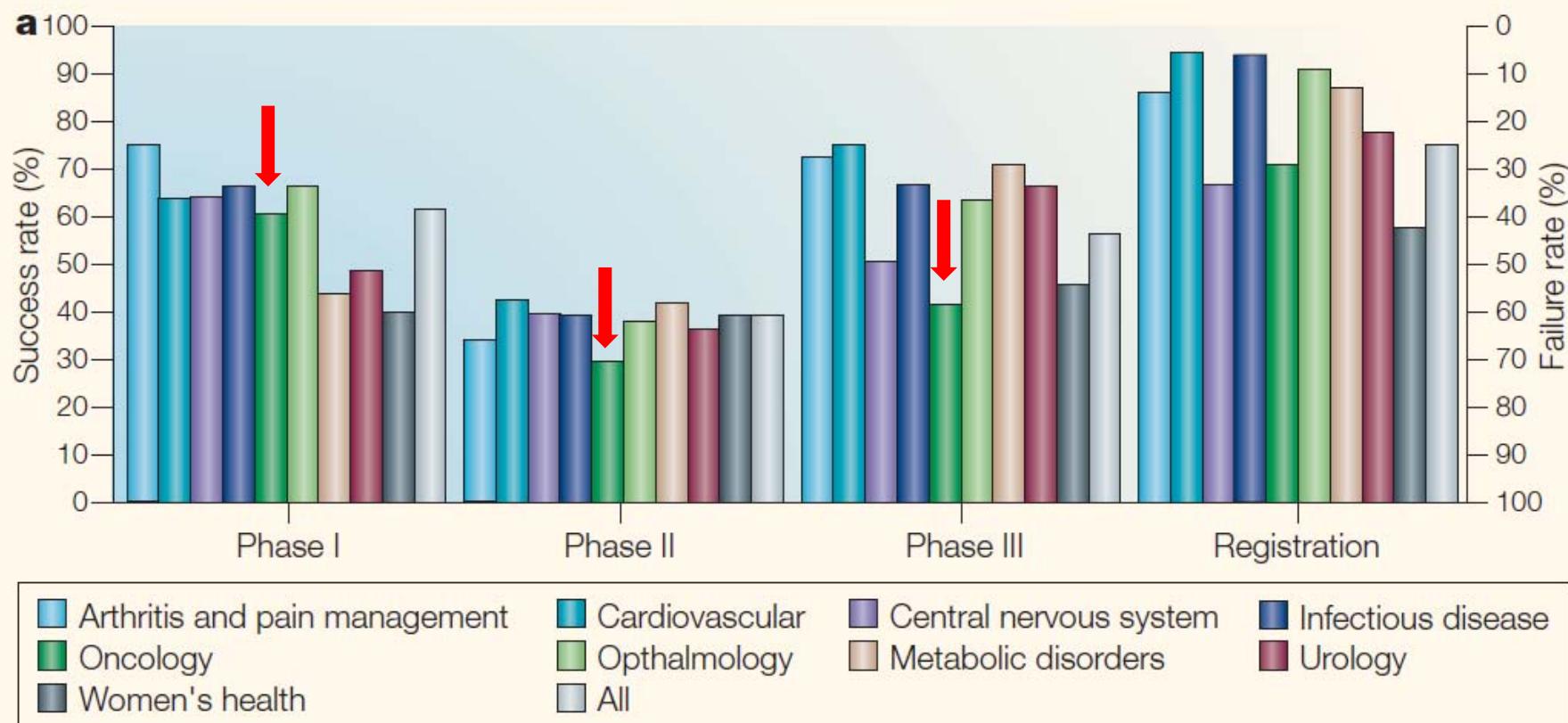
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Past



Can the pharmaceutical industry reduce attrition rates?

Ismail Kola and John Landis

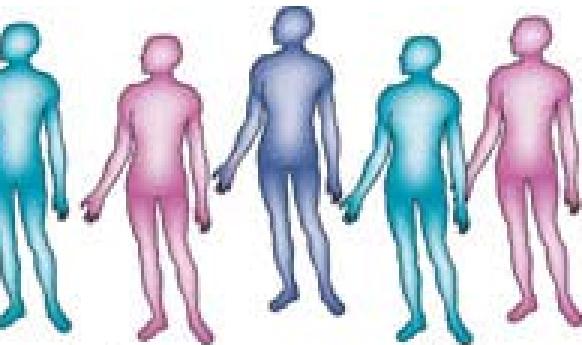


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Past



Drugs



Which patients respond best?

Current
and future



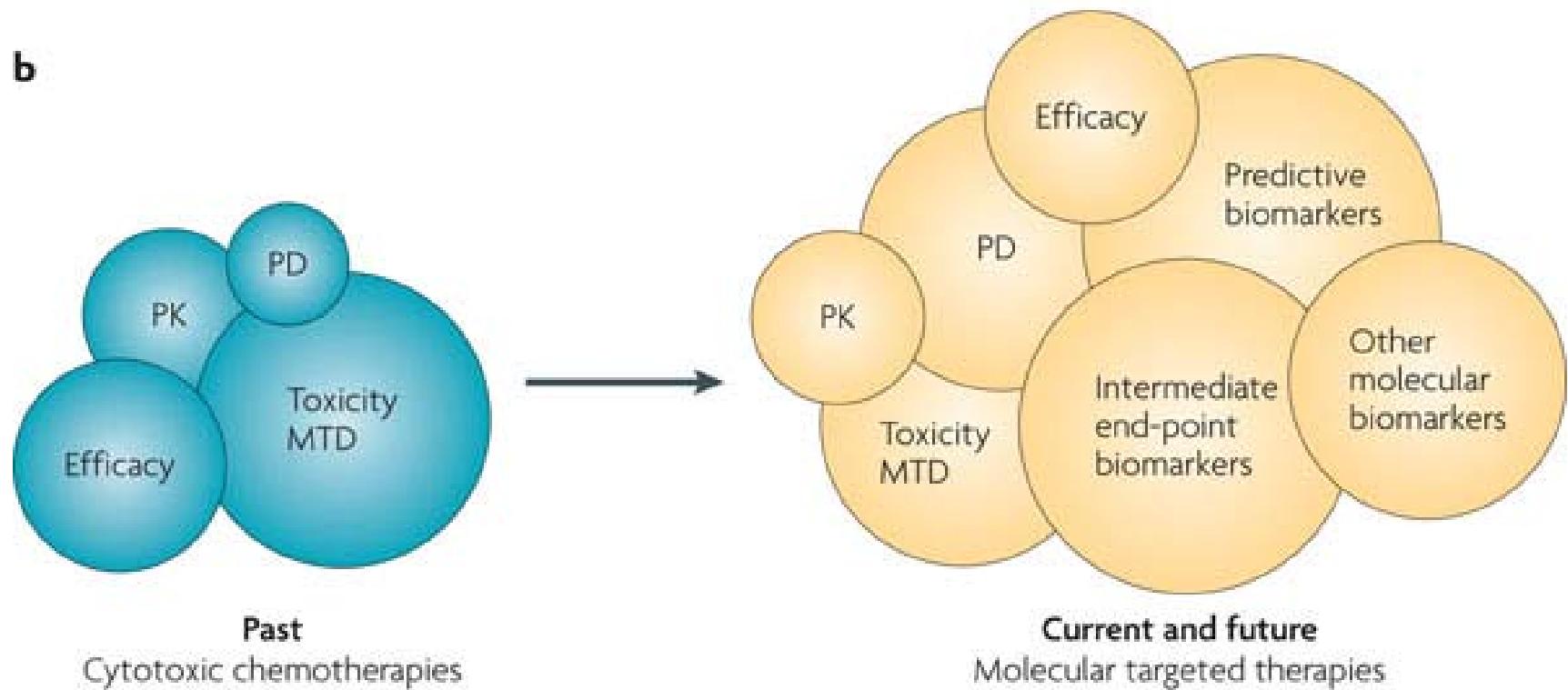
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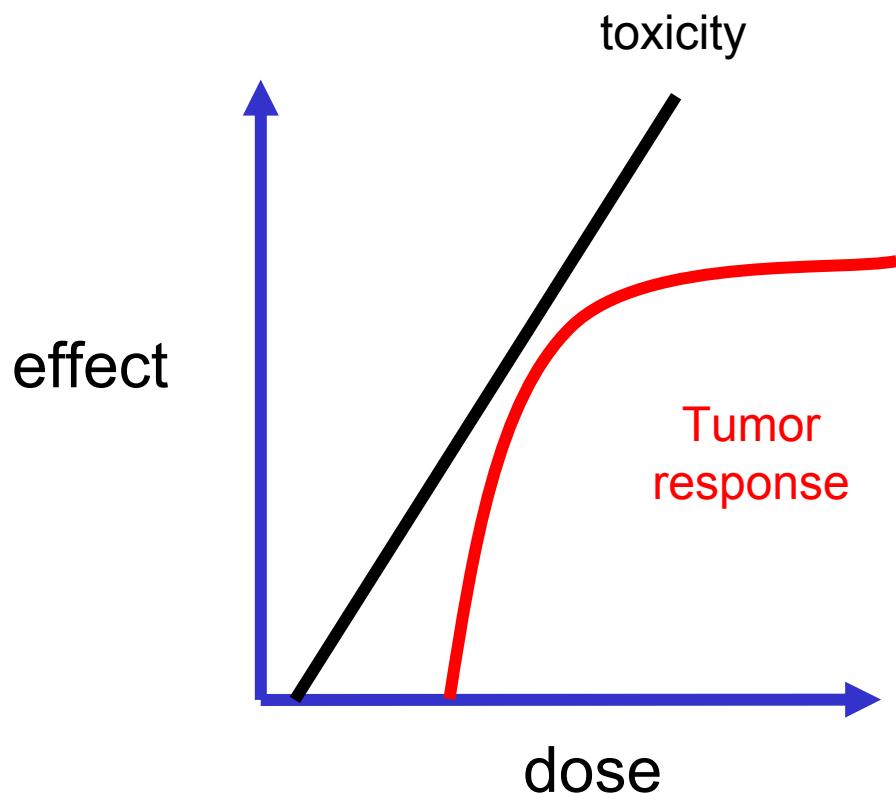
Determine molecular profile
of the patient's tumour

Determine which drugs
are most appropriate

b

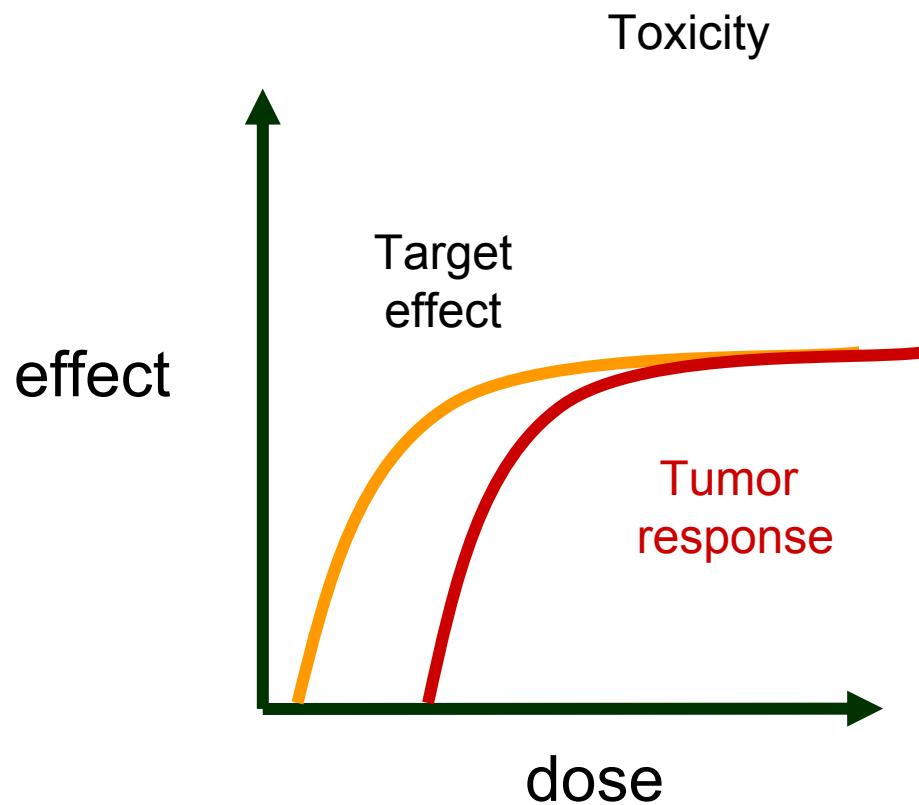


Old-style cytotoxics...

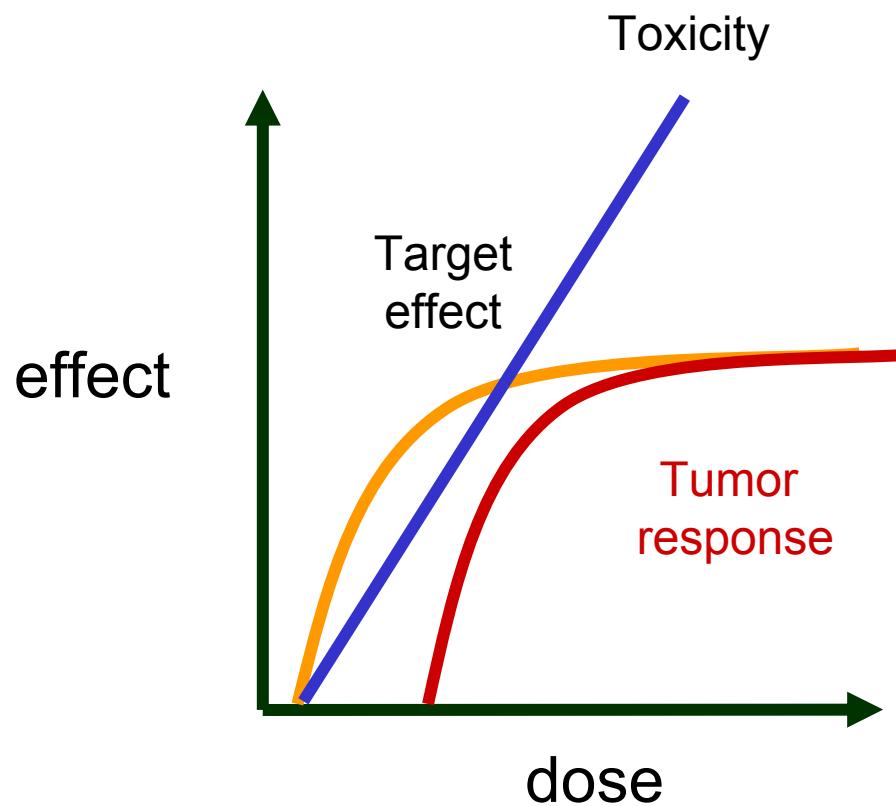


- Usually have a direct correlation between dose and toxicity
- Over a threshold, toxicity limits activity
- Phase I aims to find out maximum tolerated dose (MTD) as conducive to the highest efficacy

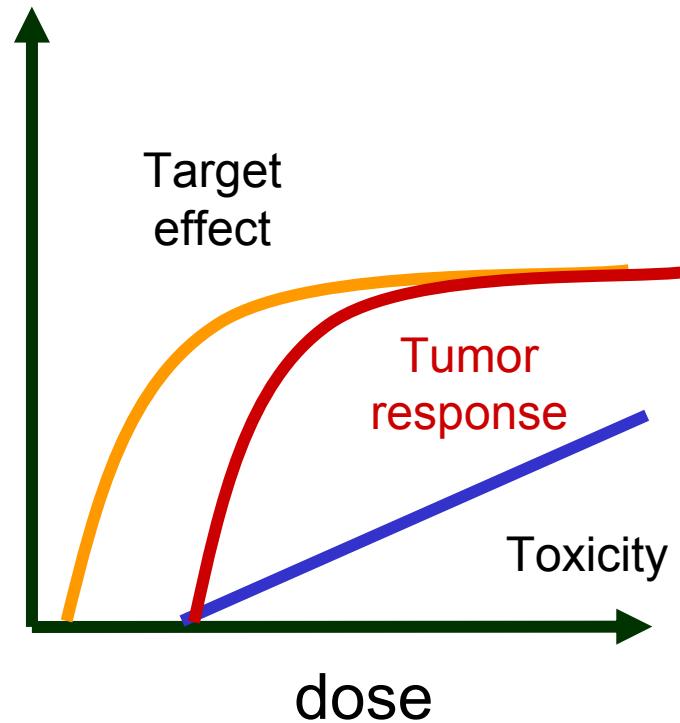
... modern target-based



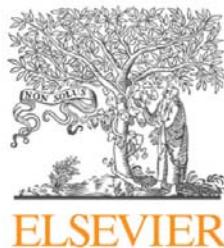
... modern target-based



Specificity: low



Specificity: high



available at www.sciencedirect.com



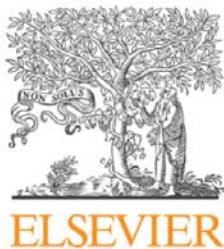
journal homepage: www.ejconline.com



Position Paper

Endpoints and other considerations in phase I studies of targeted anticancer therapy: Recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT)

*Christopher M. Booth^{a,e}, A. Hilary Calvert^b, Giuseppe Giaccone^c, Marinus W. Lobbezoo^d,
Lesley K. Seymour^a, Elizabeth A. Eisenhauer^{a,*}, On behalf of the Task Force on Methodology
for the Development of Innovative Cancer Therapies*



available at www.sciencedirect.com



journal homepage: www.ejconline.com



Position Paper

Endpoints and other considerations in phase I studies of targeted anticancer therapy: Recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT)

- (i) should the **primary endpoint** for phase I trials of
targeted agents be **toxicity**?

Table 2 – Using toxicity as primary phase I endpoint: pros and cons

Pros	Cons
1. Toxic effects of new drugs must be measured, so a required component of trials in any case	1. Toxic dose: <ul style="list-style-type: none"> – may not be necessary – may not be optimal
2. Dose escalation will not proceed if toxic effects do not permit it	2. Toxic dose is not a sophisticated endpoint
3. Highest tolerable dose less likely to be too low	3. Toxicities may not be dose-related
4. Toxicity itself may be mediated by target effect	4. If toxicity is not target mechanism-based then may not guide dose selection (i.e. ‘correct’ dose may be different than maximally tolerated)

ARTICLES

Phase I Trial Design for Solid Tumor Studies of Targeted, Non-Cytotoxic Agents: Theory and Practice

Wendy R. Parulekar, Elizabeth A. Eisenhauer

Table 1. Classification of trials, by class of agent

Class of agent	No. of agents reviewed	No. of trials
Antisense oligodeoxynucleotide	4	9
Antibody	6	6
Small molecule	20	42
Other	1	3
Total	31	60

ARTICLES

Phase I Trial Design for Solid Tumor Studies of Targeted, Non-Cytotoxic Agents: Theory and Practice

Wendy R. Parulekar, Elizabeth A. Eisenhauer

Table 3. Reasons for halting dose escalation, by trial and agent

Reason	No. of trials	No. of agents*	References
Toxicity	36	20	
Pharmacokinetic data (+/- other)	8	5	(10,27,28,33,36, 44,52,57)
Other			
Design, maximum planned dose	5	4	(25,26,39,40,46)
Limited drug supply	4	2	(20,21,24,64)
Other phase I results	2	2	(34,37)
Drug activity observed	1	1	(18)
Not stated	4	4	(45,56,61,63)
Total	60		



available at www.sciencedirect.com



journal homepage: www.ejconline.com



Position Paper

Endpoints and other considerations in phase I studies of targeted anticancer therapy: Recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT)

- (i) should the primary endpoint for phase I trials of targeted agents be toxicity?
- (ii) should phase II dose recommendation be the highest tolerable dose based **only on toxicity**?

ARTICLES

Phase I Trial Design for Solid Tumor Studies of Targeted, Non-Cytotoxic Agents: Theory and Practice

Wendy R. Parulekar, Elizabeth A. Eisenhauer

Table 4. Recommended phase II dose and primary reason for dose recommendation

Recommended phase II dose	Primary basis for recommendation	No. of trials	No. of agents
Not stated		6	6
Not recommended		2	1
Recommended			
	Toxicity	35	19
	Pharmacokinetic data	11	7
	Other trial results (toxicity)	2	2
	Clinical activity*	1	1
	PBMC findings†	1	1
	Effect in tumor (target or response)	1	1
	Convenient dosing schedule	1	1
Total		60	

ARTICLES

Phase I Trial Design for Solid Tumor Studies of Targeted, Non-Cytotoxic Agents: Theory and Practice

Wendy R. Parulekar, Elizabeth A. Eisenhauer

Table 8. Use of laboratory and imaging studies for dose selection

Type of study	No. of trials	Primary dose determinant	Secondary dose supportive
Tumor	5	1	4
Surrogate tissue			
PBMC*	12	1	6
Skin	2	0	2
Buccal mucosa	2	0	2
Imaging	6	0	1
Total	27	2	15

ARTICLES

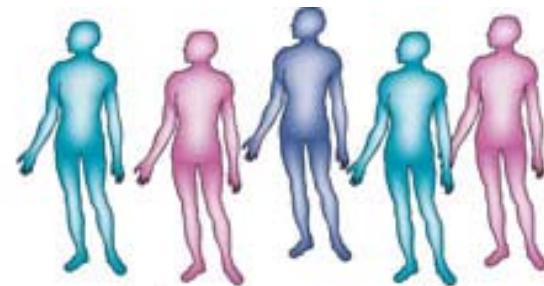
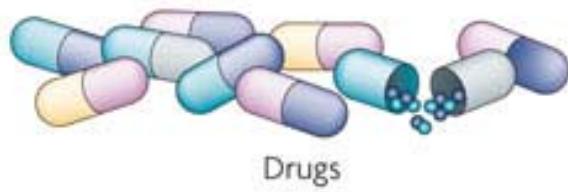
Phase I Trial Design for Solid Tumor Studies of Targeted, Non-Cytotoxic Agents: Theory and Practice

Wendy R. Parulekar, Elizabeth A. Eisenhauer

Conclusions: To date, phase I studies of targeted anticancer agents have generally used traditional endpoints for selection of the recommended phase II dose. More research is needed to define suitable molecular measures of drug effect and the means to incorporate them in the early drug development process. [J Natl Cancer Inst 2004;96:990–7]

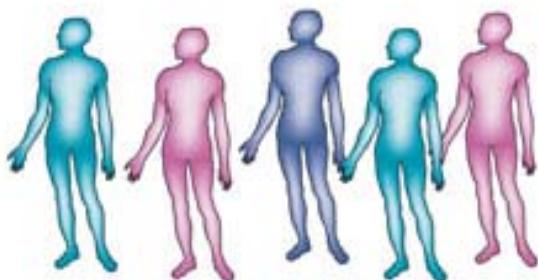
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Past



Which patients respond best?

Current
and future

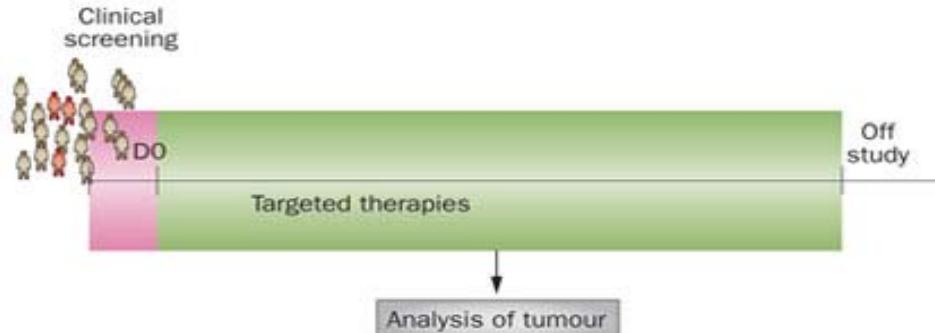


Determine molecular profile
of the patient's tumour

Determine which drugs
are most appropriate

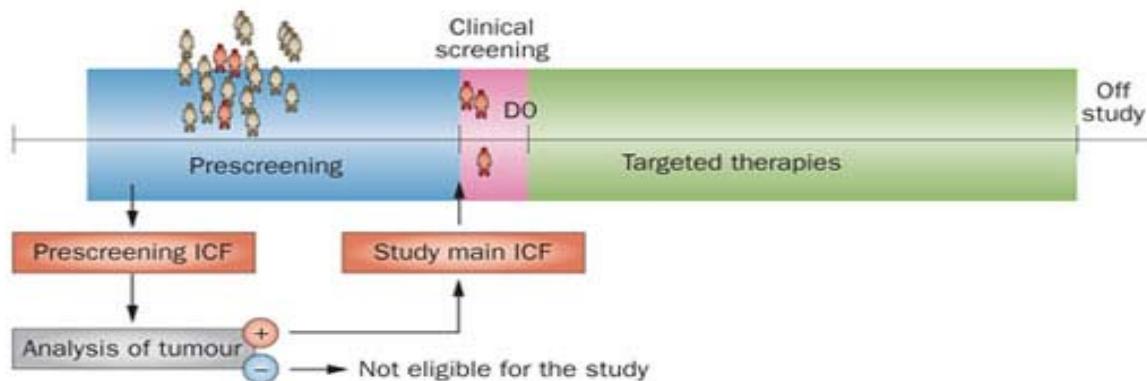


Strategy one: no preselection

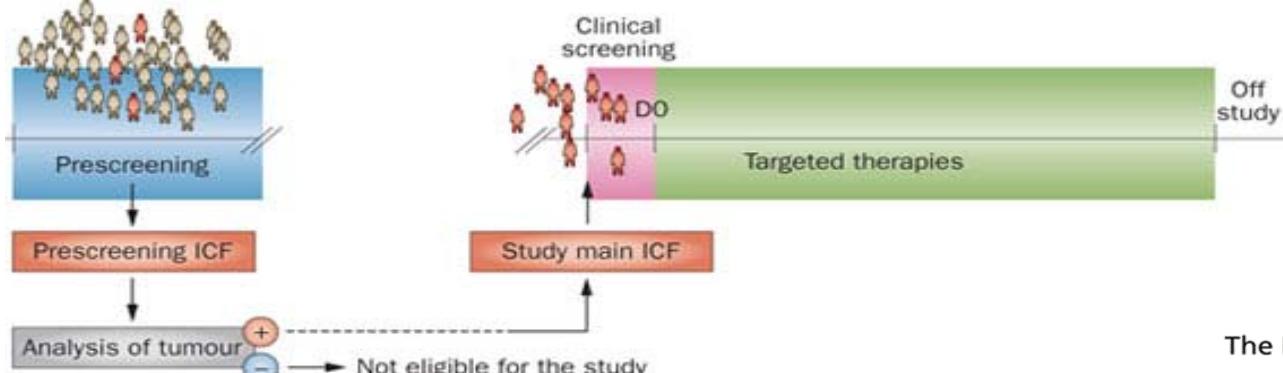


CANCER CENTER

Strategy two: prescreening before phase I trial



Strategy three: prescreening population with metastatic disease

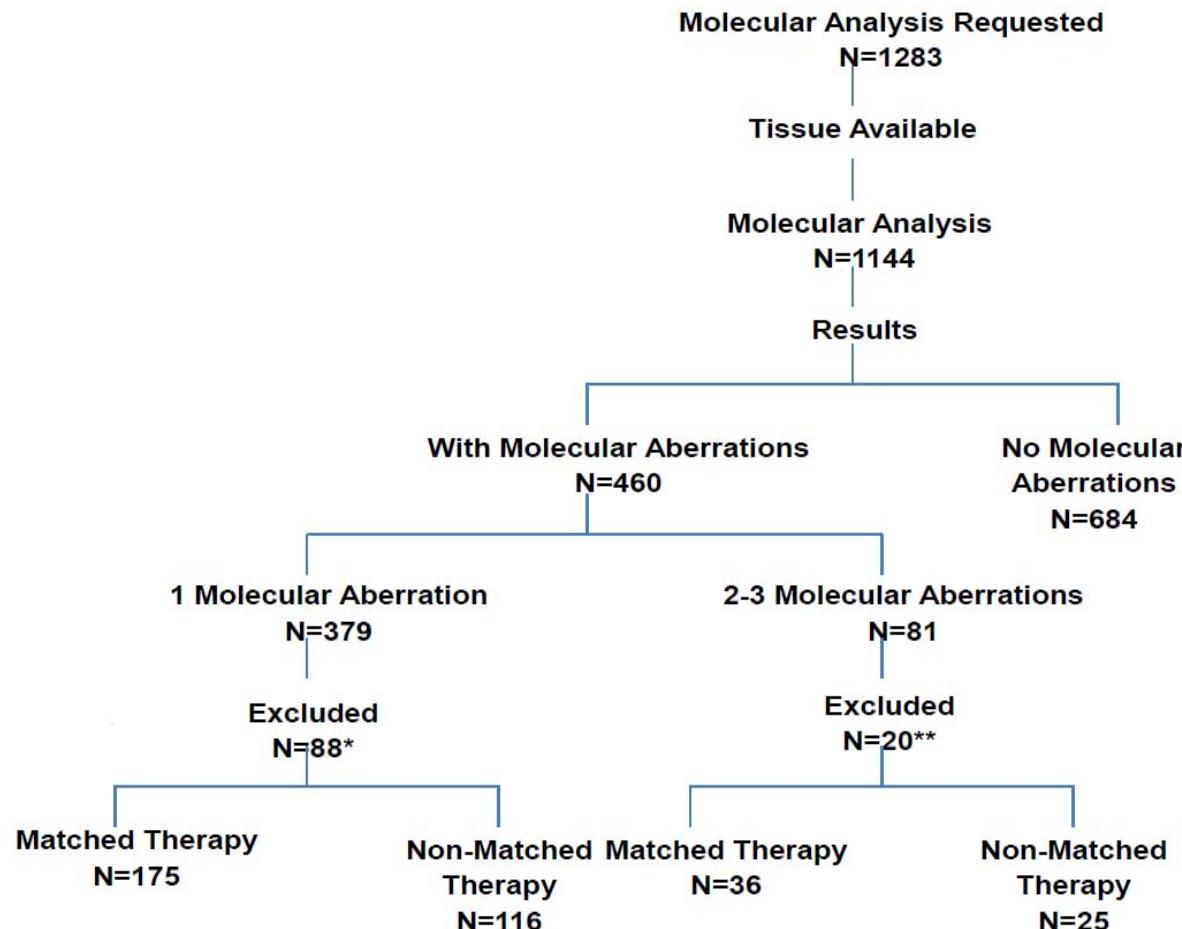


Personalized Medicine in a Phase I Clinical Trials Program: The MD Anderson Cancer Center Initiative

Apostolia M. Tsimberidou, Nancy G. Iskander, David S. Hong, et al.

Clin Cancer Res Published OnlineFirst September 10, 2012.

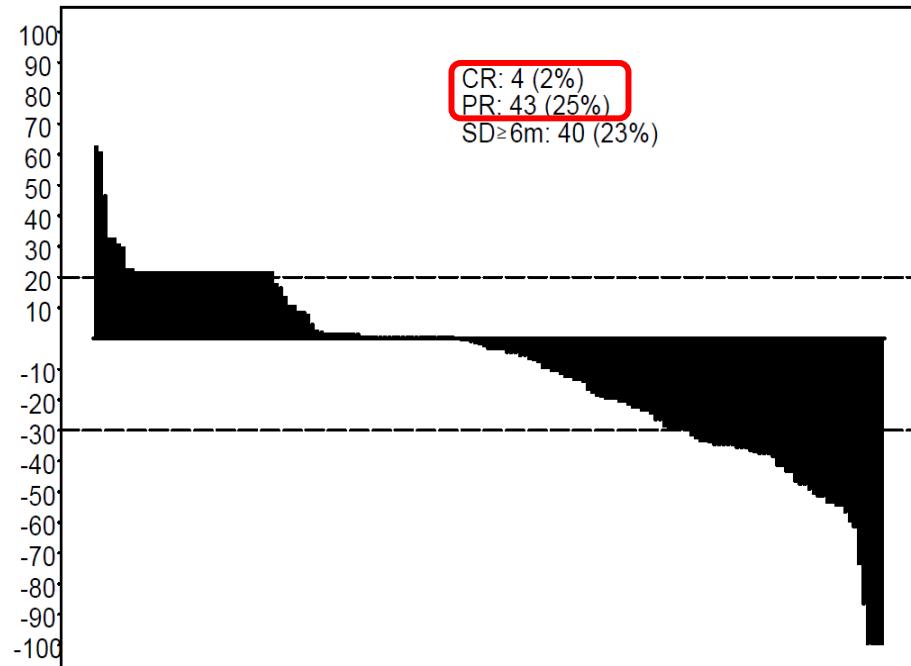
Figure 1. Consort diagram



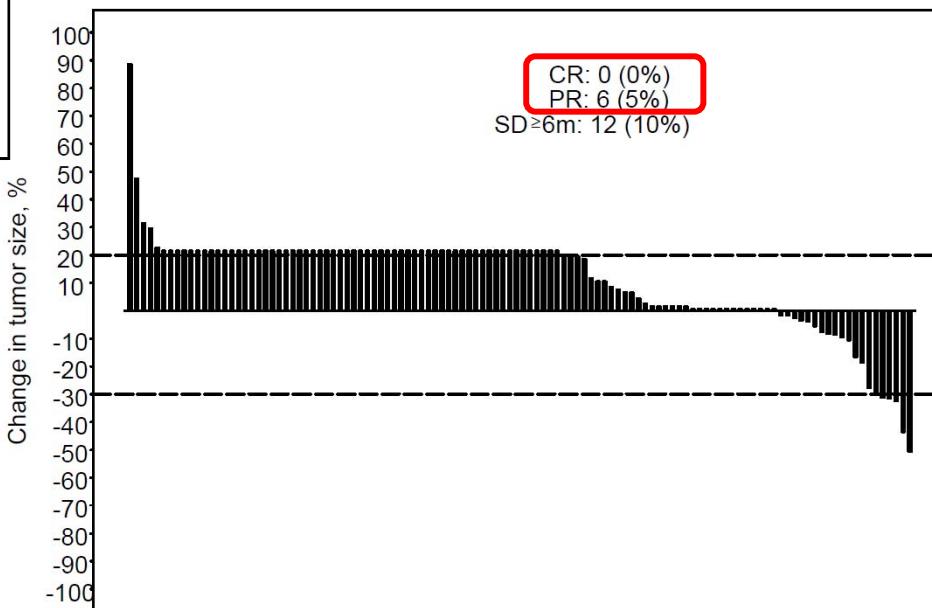
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← matched



unmatched →

ASCO 2005

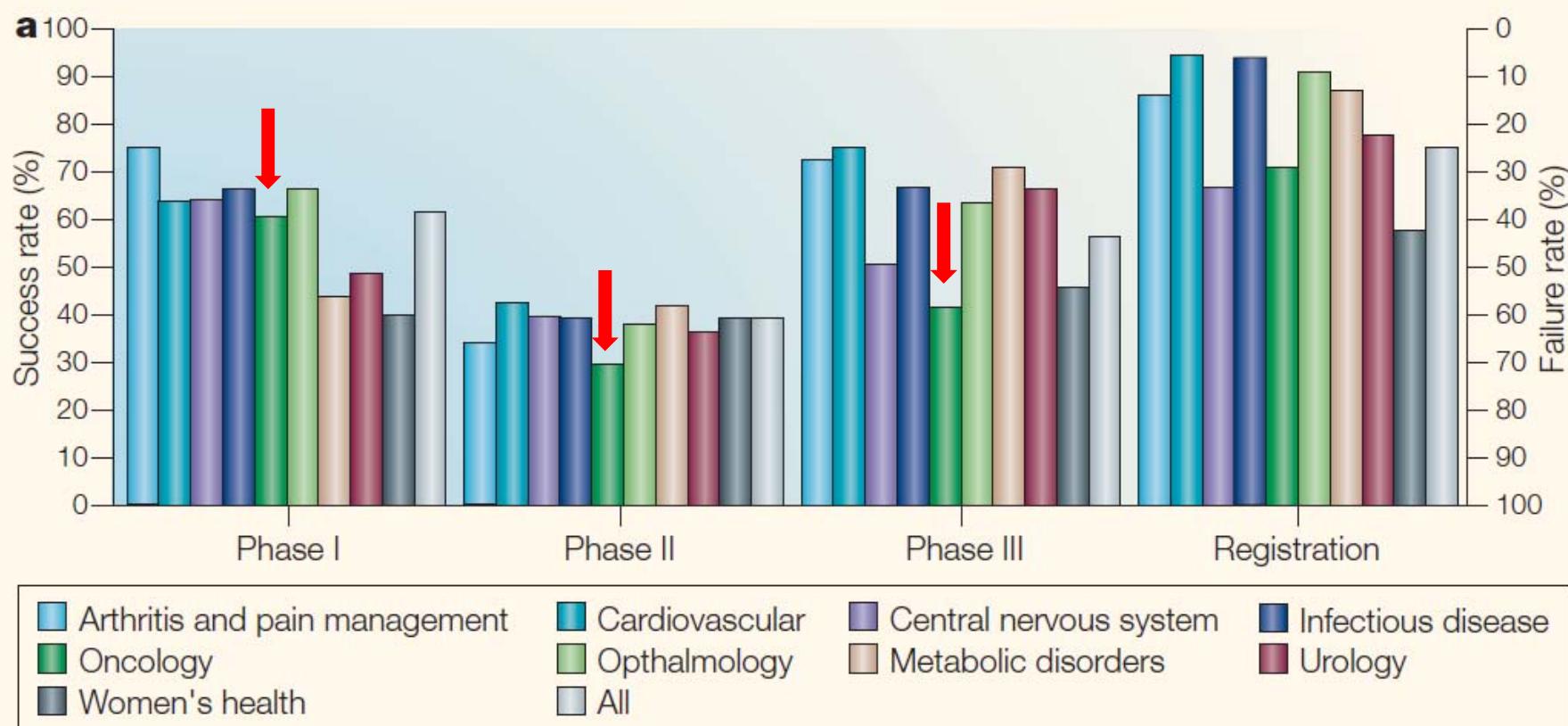
Breaking with Convention: Novel Clinical Trial Designs for Phase II Studies

Anthony W. Tolcher
Institute for Drug Development



Can the pharmaceutical industry reduce attrition rates?

Ismail Kola and John Landis



Review of Phase II Trial Designs Used in Studies of Molecular Targeted Agents: Outcomes and Predictors of Success in Phase III

Robert H. El-Maraghi and Elizabeth A. Eisenhauer

Conclusion

In practice, phase II design for targeted agents is similar to that for cytotoxics. Objective response seems to be a useful end point for screening new targeted agents because, in our review, its

Methods

We retrieved reports of single-agent phase II trials in six solid tumors for 19 targeted drugs.

Results

Eighty-nine trials were identified. Objective response was the primary or coprimary end point in the majority of trials (61 of 89 trials).

Higher overall response rates were predictive of regulatory approval in the tumor types reviewed ($P = .005$).



Review of Phase II Trial Designs Used in Studies of Molecular Targeted Agents: Outcomes and Predictors of Success in Phase III

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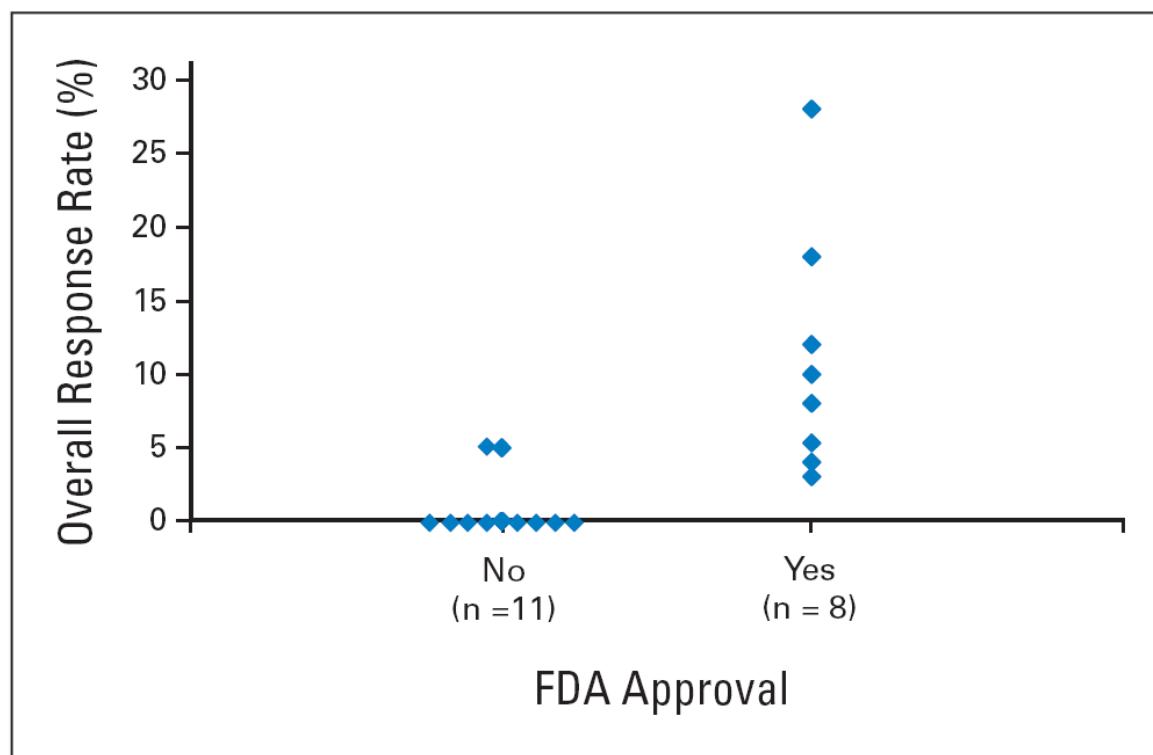


Fig 1. Overall single-agent phase II response rate for each agent versus US Food and Drug Administration (FDA) approval (as of June 2007) in at least one of the reviewed tumor types.

Review of Phase II Trial Designs Used in Studies of Molecular Targeted Agents: Outcomes and Predictors of Success in Phase III

Robert H. El-Maraghi and Elizabeth A. Eisenhauer

Table 2. Trial Design and End Points

Design and End Point	No. of Reports (N = 65)	Trials (N = 89)	
		No.	%
Nonrandomized	51	62	70
Randomized	14	27	30
Comparator arms:			
Placebo/standard		3	
Other investigational drug		4	
Other dose of same agent		20	
Primary end point			
Objective response		51	57
Multinomial (response and progressive disease)		10	11
Proportion progression free		8	9
Progression-free survival		8	9
Other		12	13



Setting the Bar in Phase II Trials: The Use of Historical Data for Determining “Go/No Go” Decision for Definitive Phase III Testing

Andrew J. Vickers,^{1,2} Vennus Ballen,¹ and Howard I. Scher¹

Clin Cancer Res 2007;13(3) February 1, 2007

Table 2. Null and alternative response rates specified in the 134 evaluable studies

Null response rate (%)	Number of trials (% of total)	Alternative response rate* (%)	Number of trials
<5	8 (6%)	10	2
		15	5
		20	1
5-10	64 (48%)	15	3
		20	32
		25	13
		30	16
11-20	25 (19%)	30	9
		35	4
		40	11
		45	1
21-30	15 (11%)	35	1
		40	1
		45	3
		50	10
31-40	7 (5%)	50	1
		55	1
		60	5
41-50	10 (7%)	70	7
		75	2
		80	1
51-60	3 (2%)	80	3
61-70	2 (1%)	80	1
		85	1
Total	134 (100%)		134



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Dovrebbe derivare dalla
letteratura precedente

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		35	4
		40	11
		45	1
21-30	15 (11%)	35	1
		40	1
		45	3
		50	10
31-40	7 (5%)	50	1
		55	1
		60	5
41-50	10 (7%)	70	7
		75	2
		80	1
51-60	3 (2%)	80	3
61-70	2 (1%)	80	1
		85	1
Total	134 (100%)		134



Setting the Bar in Phase II Trials: The Use of Historical Data for Determining “Go/No Go” Decision for Definitive Phase III Testing

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Clin Cancer Res 2007;13(3) February 1, 2007

Table 3. Association between study results and citation of prior data

Citation of historical data	Number	Conclusions		Results	
		Unclear	Clear	Reject alternative (agent not worthy of further study)	Reject null (agent worthy of further study)
No historical data cited	32	3	29	6 (21%)	23 (79%)
Historical data cited					
Did not meet criteria	29	2	27	4 (15%)	23 (85%)
Met criteria	9	0	9	6 (67%)	3 (33%)



Setting the Bar in Phase II Trials: The Use of Historical Data for Determining “Go/No Go” Decision for Definitive Phase III Testing

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Editorial

Testing the Wrong Hypothesis in Phase II Oncology Trials: There Is a Better Alternative

□□ *Commentary on Vickers et al., p. 972*

Mark J. Ratain and Theodore G. Garrison



Briefly

- Uncontrolled single-arm phase 2 trials
 - Are effective tools to show that a drug is not active (high negative predictive value - NPV)
 - Are NOT efficient to select the best *challengers* for phase 3 (low positive predictive value - PPV)
- Controlled randomized comparative phase 2 trials
 - The best way to improve PPV
 - Of course
 - Have to be conducted with relaxed statical criteria (eg one-sided alfa = 0.20)
 - Have to be followed by typical phase 3 trials, if positive



SPECIAL ARTICLE

Clinical Trial Designs for Cytostatic Agents: Are New Approaches Needed?

By Edward L. Korn, Susan G. Arbuck, James M. Pluda, Richard Simon, Richard S. Kaplan, and Michael C. Christian

Journal of Clinical Oncology, Vol 19, No 1 (January 1), 2001: pp 265-272

A trial using $\alpha = 0.20$ may be an attractive option, provided that the investigators understand the implications of using such a large alpha. At the conclusion of the trial, a $P \leq .20$ should be considered sufficient evidence of activity to perform the follow-up trial. However, an inactive agent will lead one in five times to a $P \leq .20$.



Effects on end-point choice

- The best end-point for phase 2 is the one that would be used in phase 3 (not perfect for accelerated approval)
- A time-event should be preferred
 - *Overall survival* (controlling subsequent treatment)
 - *Progression-free survival* or similar (biases!)
- Objective response...
 - In principle, means going back, not reasonable





ASCO 2005

Breaking Novel Clinic Phas

Anth
Institute f

ASCO, Educational Session, May 15, 2005

BREAKING FROM TRADITION IN THE DESIGN OF PHASE III CLINICAL TRIALS

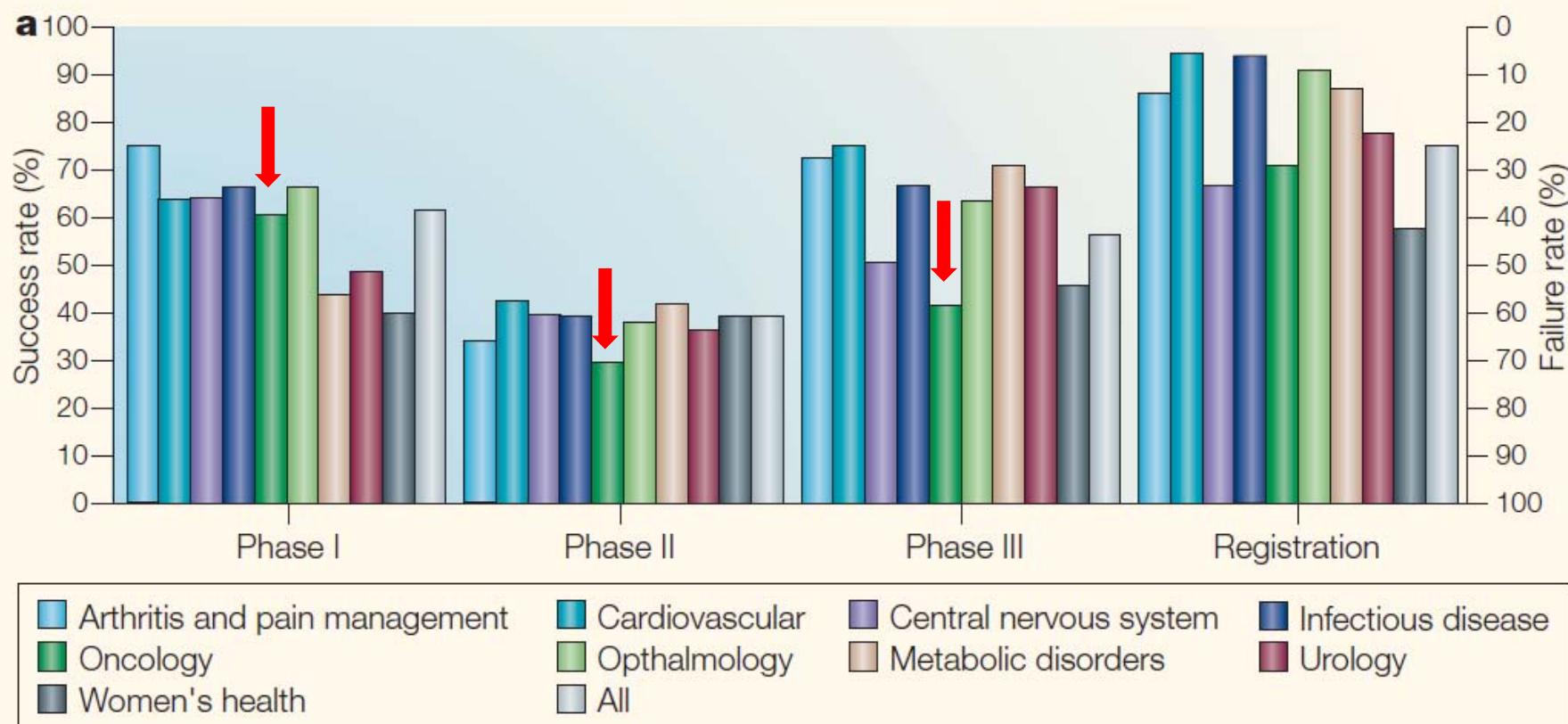
Martine J. Piccart-Gebhart, MD, PhD
Jules Bordet Institute, Brussels, Belgium

Marc Buyse, ScD
International Drug Development Institute (IDDI)
Brussels, Belgium



Can the pharmaceutical industry reduce attrition rates?

Ismail Kola and John Landis



Influence of Unrecognized Molecular Heterogeneity on Randomized Clinical Trials

By Rebecca A. Betensky, David N. Louis, and J. Gregory Cairncross

Purpose: In solid tumor oncology, decisions regarding treatment and eligibility for trials are governed by histologic diagnosis. Despite this reliance on histology and the assumption that histology defines the disease, underlying molecular heterogeneity likely differentiates among patients' outcomes.

Patients and Methods: To illustrate how unrecognized molecular heterogeneity might obscure a truly effective new therapy for cancer, we analyzed the planning assumptions and results of a hypothetical randomized controlled trial of chemoradiotherapy for a cancer found to be drug sensitive in preliminary phase II studies.

Results: Randomized controlled trials of effective cancer therapies can be falsely negative if therapeutic

benefit is overestimated during study design because of enrichment of phase II trials for treatment-sensitive subtypes, a beneficial effect in responding patients is diluted by large numbers of nonresponding patients, or a beneficial effect in responders is reversed by a negative effect in nonresponders.

Conclusion: Molecular heterogeneity, if it confers different risks to patients and is unaccounted for in the design of a randomized study, can result in a clinical trial that is underpowered and fails to detect a truly effective new therapy for cancer.

J Clin Oncol 20:2495-2499. © 2002 by American Society of Clinical Oncology.



Table 2. Sample Sizes Required for 80% Power Based on Pilot Data With 50% Genetic Subtype 1*

True Proportion of Genetic Subtype 1	Scenario I	Scenario II	Scenario III
0.0	234	NAT	424
0.1	270	31,209	946
0.2	304	8,802	2,485
0.3	335	4,259	10,950
0.4	363	2,542	21,105,915
0.5	386	1,693	14,159
0.6	403	1,203	3,629
0.7	415	891	1,654
0.8	421	679	944
0.9	420	526	604
1.0	412	412	412

*For comparison, the sample size based on the correct model is 286.

†In scenario II, the treatment effect is only among patients with tumors of genetic subtype 1.



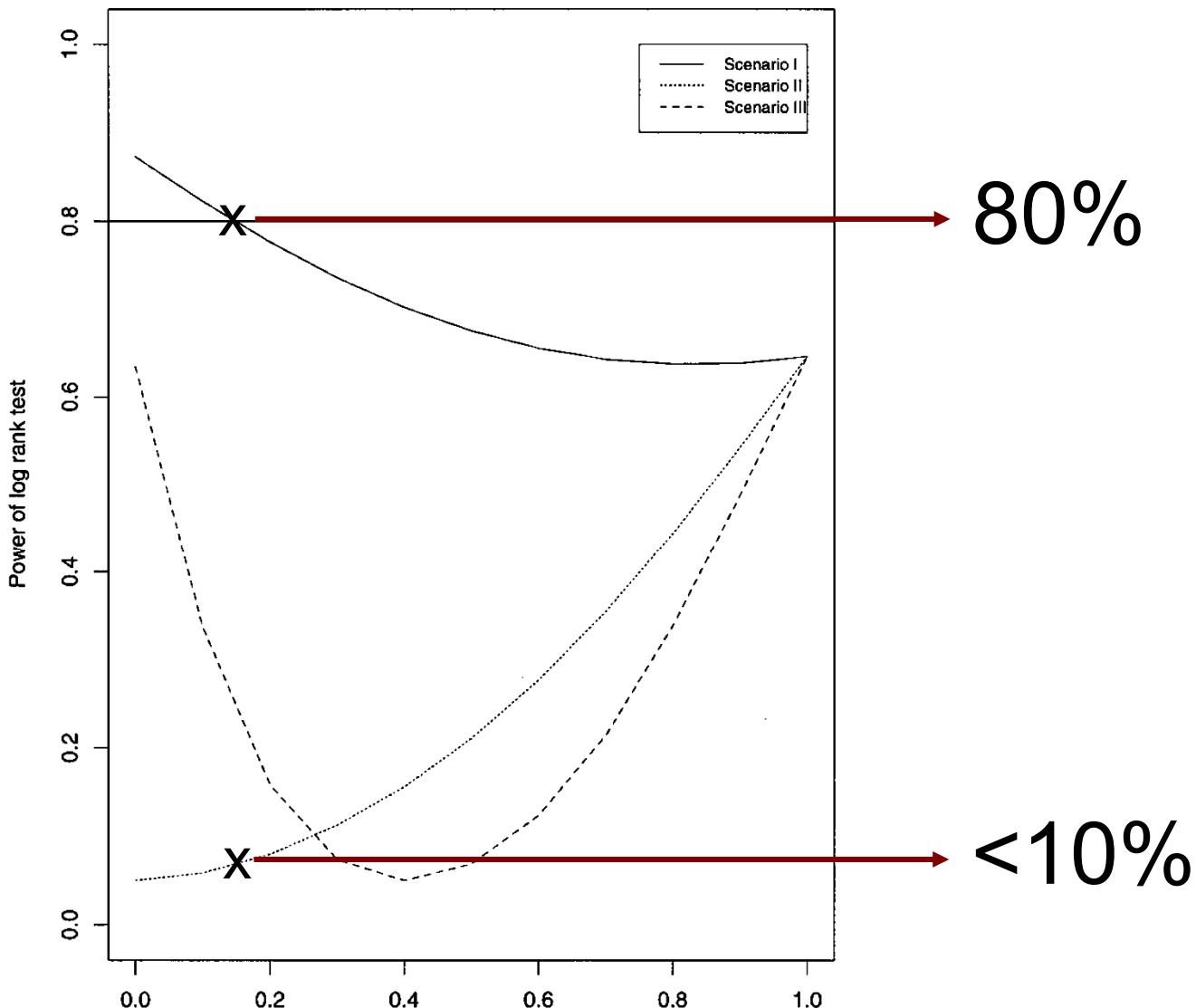


Fig 1. Power of the log-rank test under the three scenarios as a function of true proportion of genetic subtype 1 in the study population.

TRIAL OF CHEMOTHERAPY ± HERCEPTIN FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

	ACTUAL TARGETED TRIAL	HYPOTHETICAL NON-TARGETED TRIAL
N = 469	HER-2 ++ or +++	All patients
Response rate	50% vs 32% P < 0.001	37% vs 32% P = 0.27
One-year mortality	22% vs 33% P=0.008	30% vs 33% P = 0.45

Slamon et al.,
New Engl. J Med., 2001



Drug killed !

Sembra facile

- Ma non è detto che il target, pur se evidente, sia quello buono...

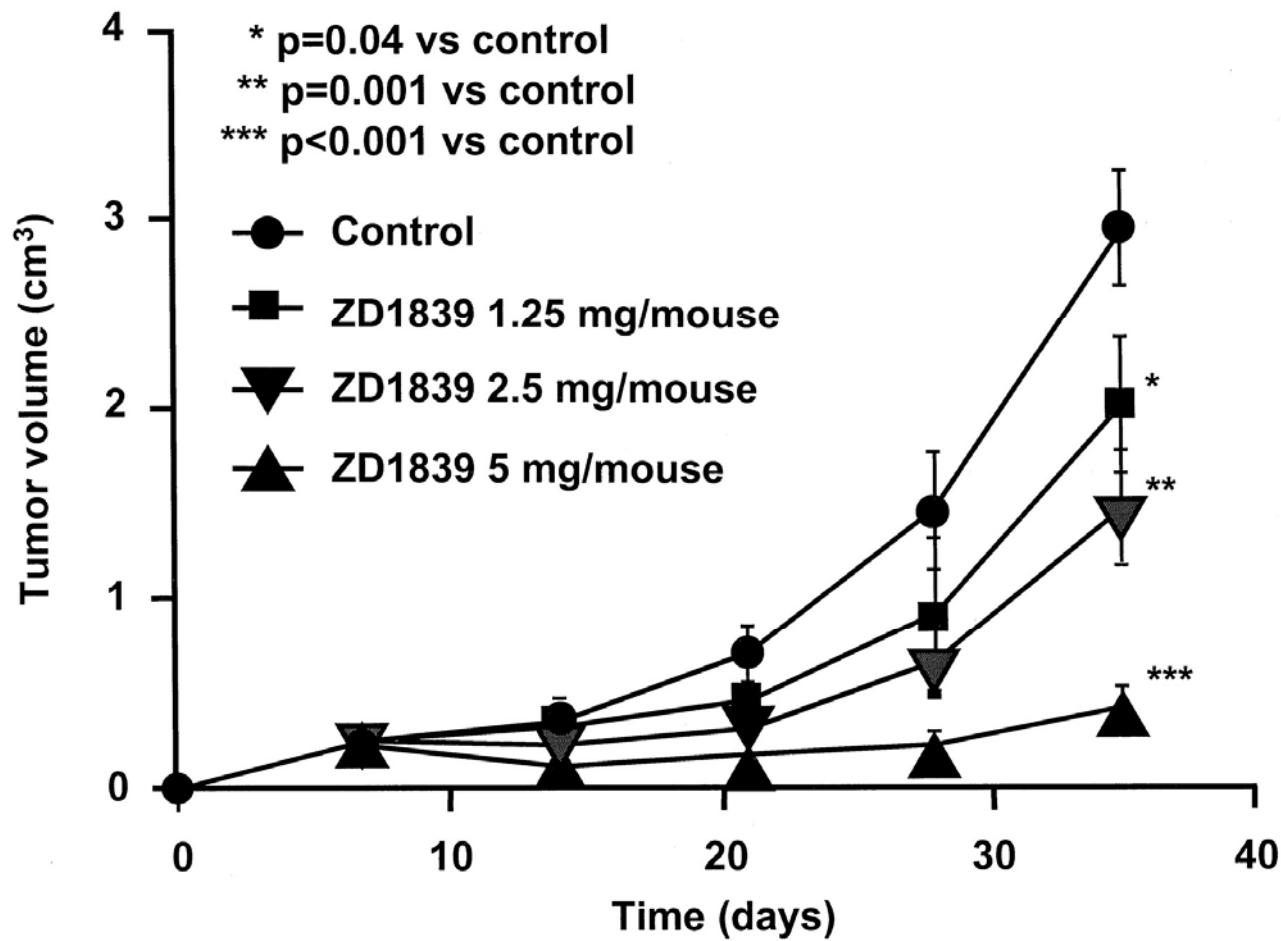
Un target fortunato: EGFR

Type of cancer	EGFR
lung	40-80%
breast	14-91%
stomach	33-74%
colon	25-77%
oesophagus	43-89%
liver	47-68%
pancreas	30-50%
prostate	40-80%
kidney	50-90%
bladder	35-86%
ovary	35-70%
head and neck	36-100%

Overexpression of EGFR is related to:

- Aggressive phenotype
- Worse prognosis
- Chemo-resistance
- Radio-resistance

EGFR inhibitors: attività preclinica

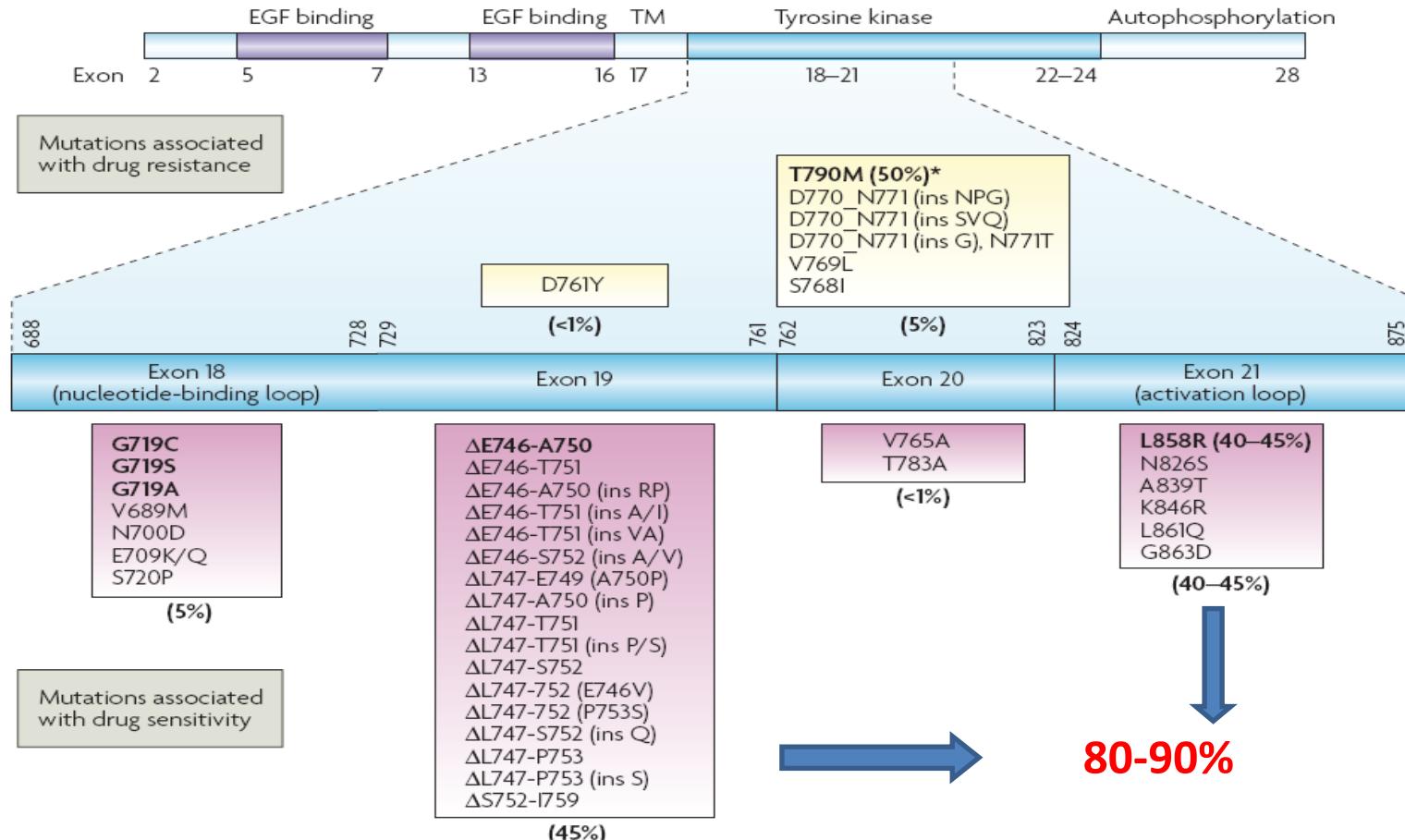


Study	n	ORR (%)	mPFS (mos)	mOS (mos)
IDEAL1 : Gefitinib 250 vs 500mg/day	103 vs 106	18.4 vs 19	2.7 vs 2.8	7.6 vs 8
IDEAL 2: Gefitinib 250 vs 500mg/day	102 vs 114	12 vs 9	NR	7 vs 6
INTACT 1: CG +Gef 250 vs CG+Gef 500 vs CG +placebo	365 vs 365 vs 363	51.3 vs 50.3 vs 47.2	9.9 vs 9.9 vs 10.9	5.8 vs 5.5vs 6
INTACT 2: CP +Gefi250 vs CP+Gef 500 vs CP +placebo	345 vs 347 vs 345	30.4 vs 30 vs 28.7	5.3 vs 4.6 vs 5.3	9.8 vs 8.7 vs 9.9
ISEL: Geftinib 250 vs placebo	1129 vs 563	8 vs 1.3	3 vs 2.6	5.6 vs 5.1
INTEREST: Gefitinib vs Docetaxel	733 vs 733	9.1 vs 7.6	2.2 vs 2.7	7.6 vs 8
INVITE: Gefitinib 250 vs Vinorelbine	97 vs 99	3.1 vs 5.1	2.7 vs 2.9	5.9 vs 8
TORCH: Erlotinib->CG vs CG->Erlotinib	380 vs 380	9 vs 28* *E vs CG	2.2 vs 5.7*	8.5 vs 12

Risultati deludenti

- Scarsa efficacia se usati come agenti singoli
- Poco o nullo sinergismo se aggiunti alla chemioterapia
- Addirittura danno se sostituiti alla chemioterapia o anticipati alla prima linea
- ...
- Approccio unidirezionale dalla preclinica alla clinica
- Con poca attenzione agli aspetti biologici

Le mutazioni...



doi:10.1038/nrc2088

Lynch, T. et al. N Engl J Med 2004;350:2129-2139

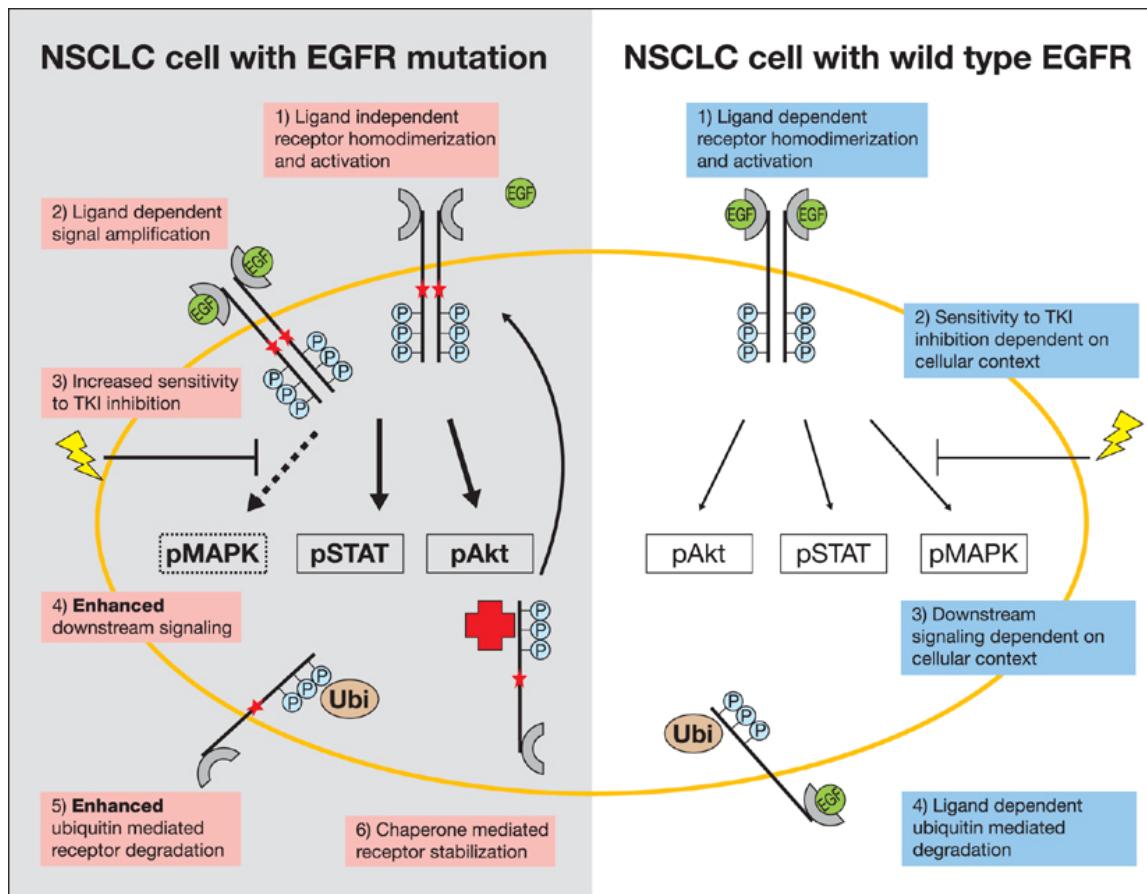


Le mutazioni...

Oncogene 26, 5693-5701 (23 August 2007) | doi:10.1038/sj.onc.1210383

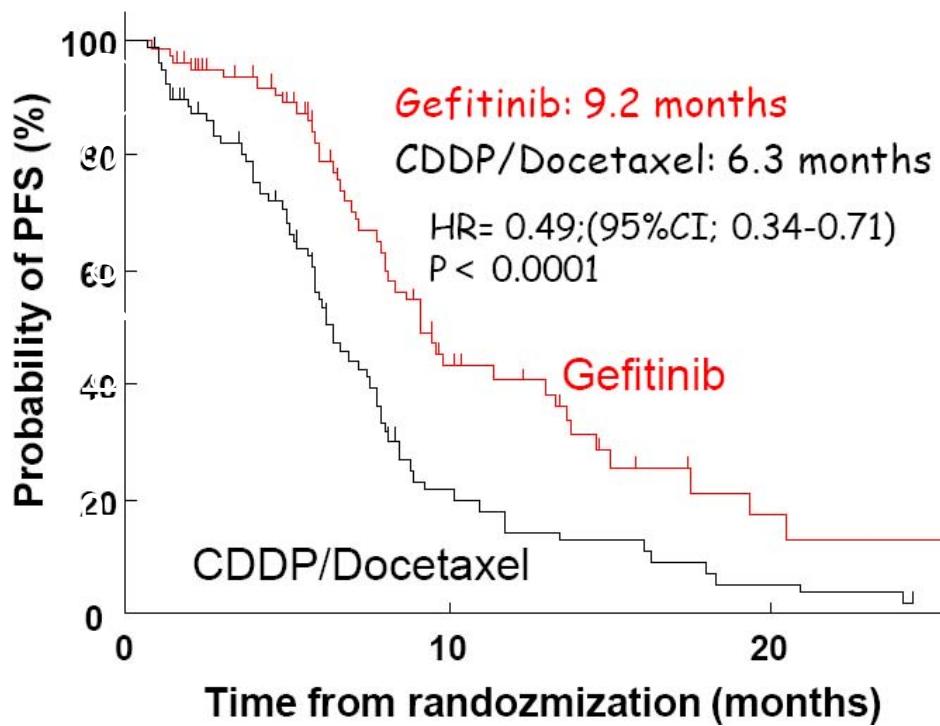
EGFR kinase domain mutations – functional impact and relevance for lung cancer therapy EGFR kinase domain mutations

D Irmer, J O Funk and A Blaukat

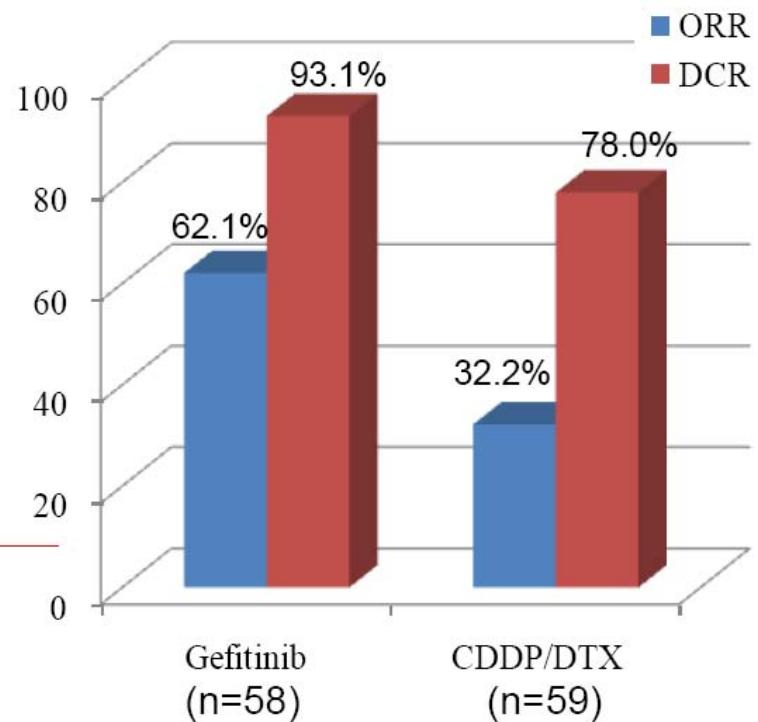


Pazienti con mutazione EGFR

Progression-free survival

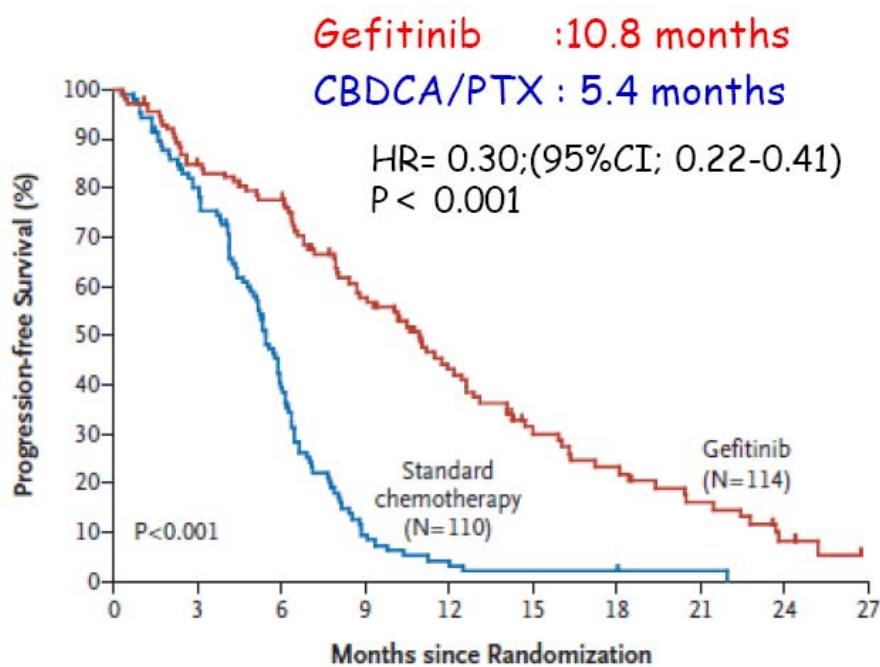


Response rate

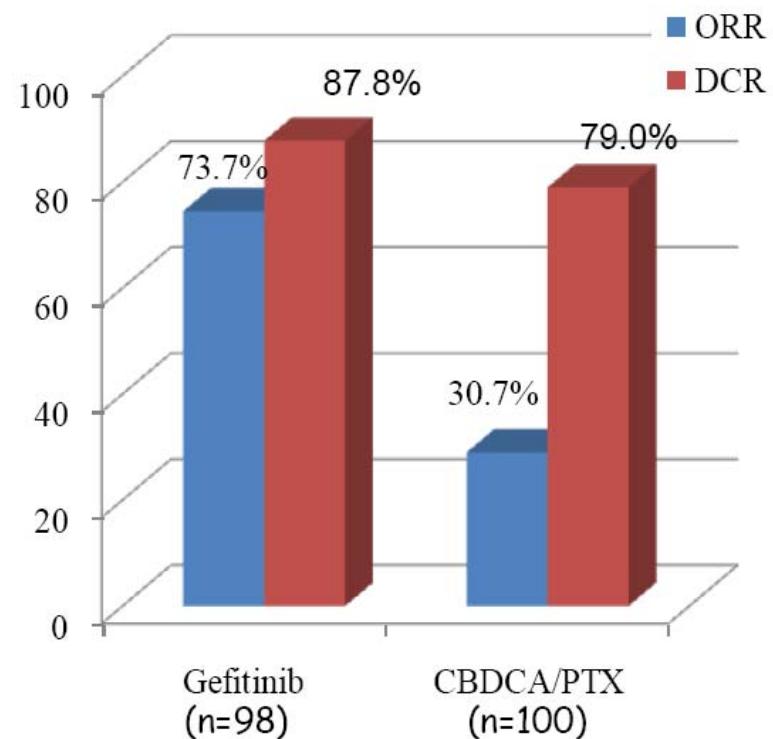


Pazienti con mutazione EGFR

Progression-free survival

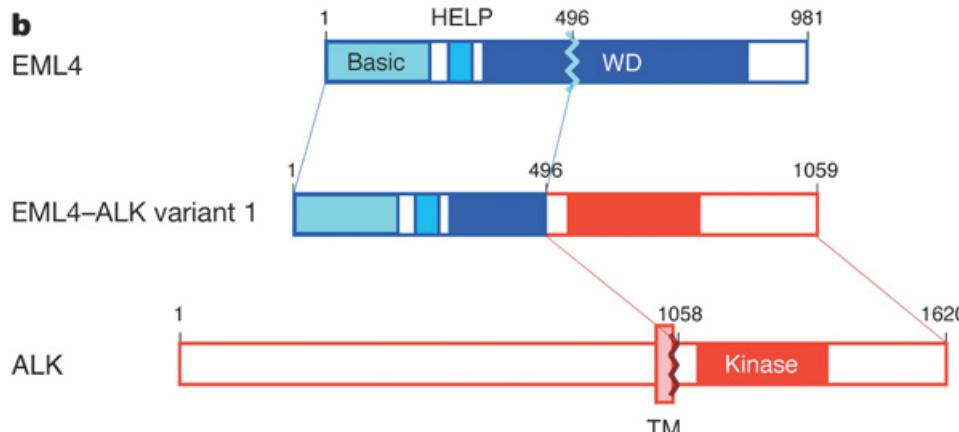
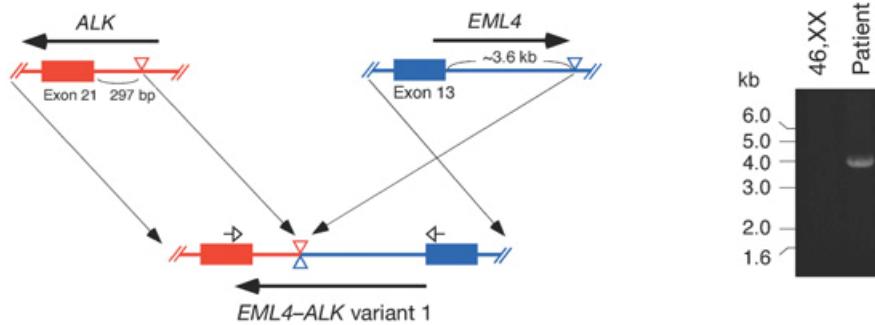


Response rate



Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer

Manabu Soda^{1,2}, Young Lim Choi¹, Munehiro Enomoto^{1,2}, Shuji Takada¹, Yoshihiro Yamashita¹, Shunpei Ishikawa⁵, Shin-ichiro Fujiwara¹, Hideki Watanabe¹, Kentaro Kurashina¹, Hisashi Hatanaka¹, Masashi Bando², Shoji Ohno², Yuichi Ishikawa⁶, Hiroyuki Aburatani^{5,7}, Toshiro Niki³, Yasunori Sohara⁴, Yukihiko Sugiyama² & Hiroyuki Mano^{1,7}

b**c**

- Screened cDNA library derived from tumor
- Fusion results from a small inversion within chromosome 2p
- N-terminal half of EML4 is fused to intracellular kinase domain of ALK
- Found in **2-5%** of NSCLC patients
- Mutually exclusive with EGFR mutations

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 28, 2010

VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell
Lung Cancer

- Crizotinib: oral selective inhibitor of ALK and MET tyrosine kinases
- Study Design: Open-label, multicenter, two-part phase 1 trial
- Maximum tolerated dose of 250mg po BID, one cycle was 28 days



The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 28, 2010

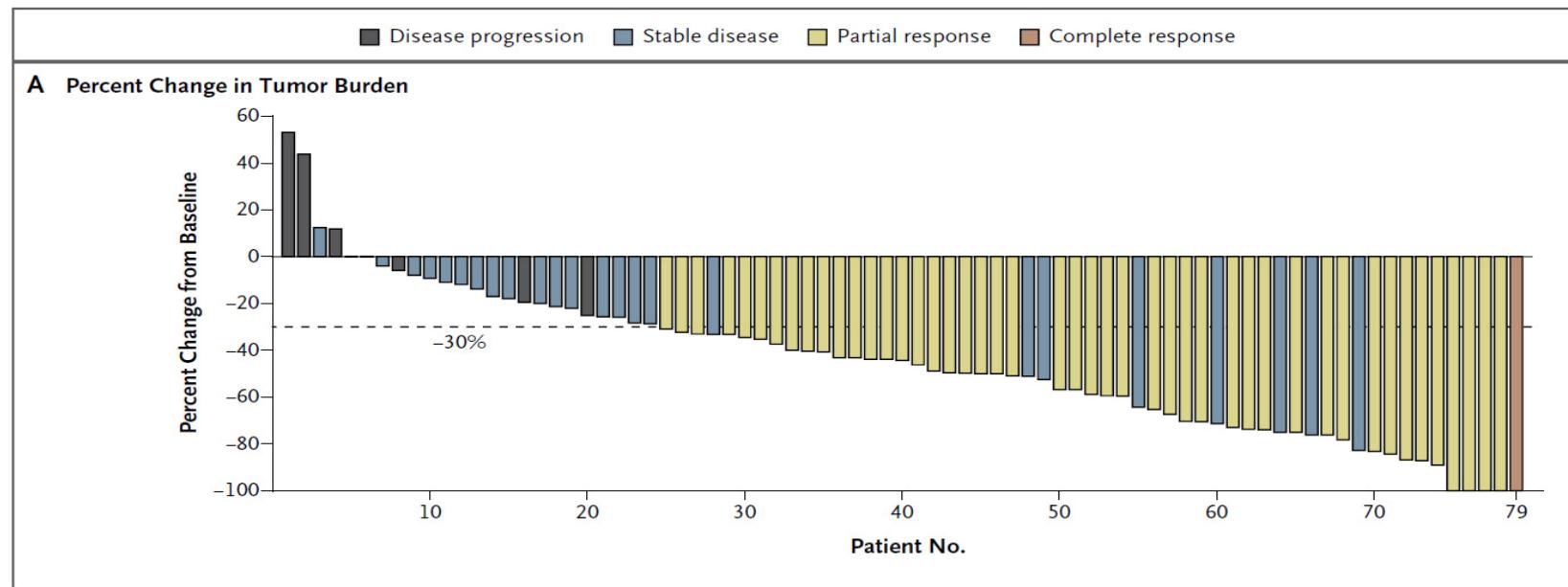
VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer

- Dramatic response during dose-escalation in 2 NSCLC patients with FISH positive for ALK rearrangement
- Large-scale prospective screening for ALK rearrangement in NSCLC
- 1500 patients screened from 2008-2010
- 82 (5%) patients found positive

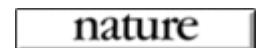


Risposte obiettive: 47/82, 57% [95% CI 46-68]



ALK-Positive Timeline

EML4-ALK chromosomal rearrangements reported in NSCLC^[1]



2007

EML4-ALK defines a molecular subset of NSCLC with distinct clinical characteristics^[4]

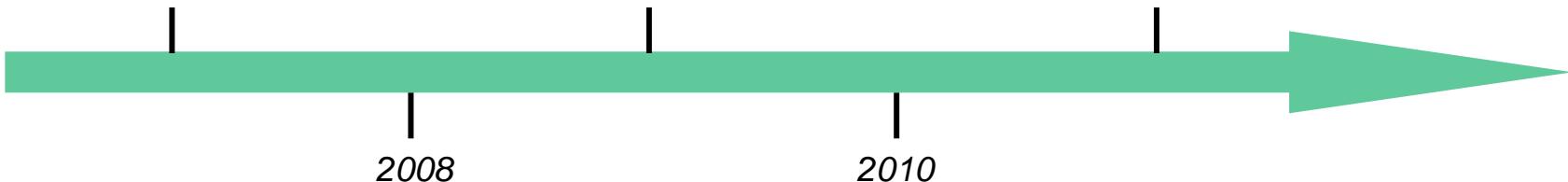


2009

FDA approves crizotinib for treatment of *ALK*⁺ NSCLC^[6]



2011



Preclinical studies document antitumor activity of ALK inhibitors in lung cancer cell lines and xenografts^[2,3]

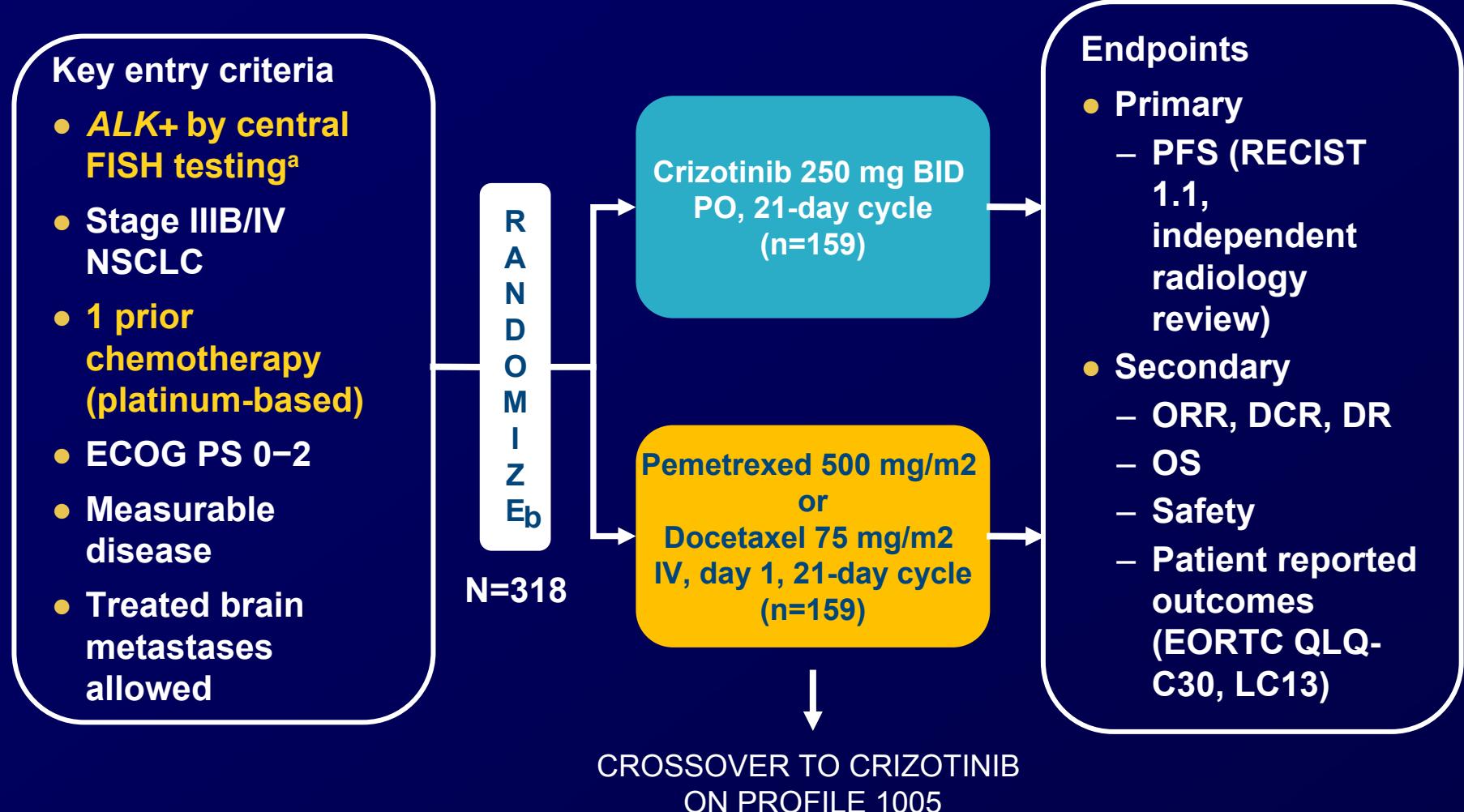
Crizotinib produces a response in 47/82 *ALK*⁺ patients and a 6-month PFS of 72%^[5]



1. Soda M, et al. Nature 2007; 448: 561-566.
2. McDermott U, et al. Cancer Res 2008; 68: 3389-3395.
3. Koivunen JP, et al. Clin Cancer Res 2008; 14: 4275-4283.
4. Shaw AT, et al. JCO 2009; 27: 4247-4253.
5. Kwak EL, et al. N Engl J Med. 2010; 363: 1693-1703.
6. US Food and Drug Administration.



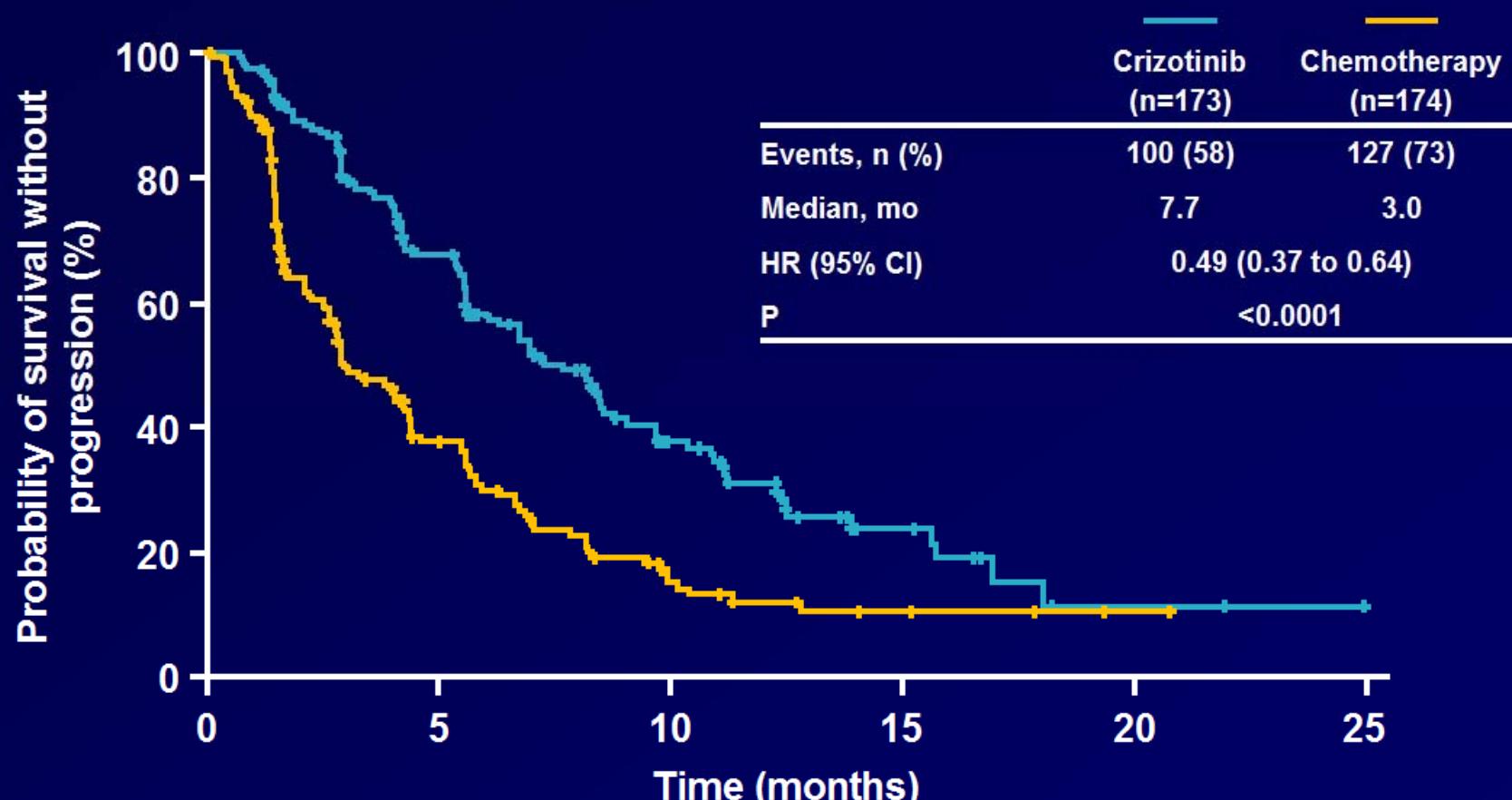
PROFILE 1007: Study Design



^aALK status determined using standard ALK break-apart FISH assay

^bStratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

Primary Endpoint: PFS by Independent Radiologic Review (ITT Population)



No. at risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Tre esempi vincenti

- HER2 – trastuzumab (e poi lapatinib, pertuzumab, TDM1...)
- Mutazione di EGFR (gefitinib, erlotinib, afatinib...)
- Traslocazione di ALK (crizotinib...)

**Ma abbiamo trovato la chiave per risolvere
tutti i problemi dello sviluppo di nuovi
farmaci?**

Assolutamente no

- I biomarker sono costosi (in molti sensi...)
- Richiedono prelievi/biopsie seriati per lo sviluppo (morbilità, difficoltà logistica)
- Richiedono standardizzazione e controlli di qualità dei metodi (AIOM-SIAPEC)
- ...
- Non ci sono biomarkers specifici per alcuni farmaci/pathways (i.e. antiangiogenetici)
- Non tutti i pazienti con un tumore esprimono biomarkers...



ORIGINAL ARTICLE

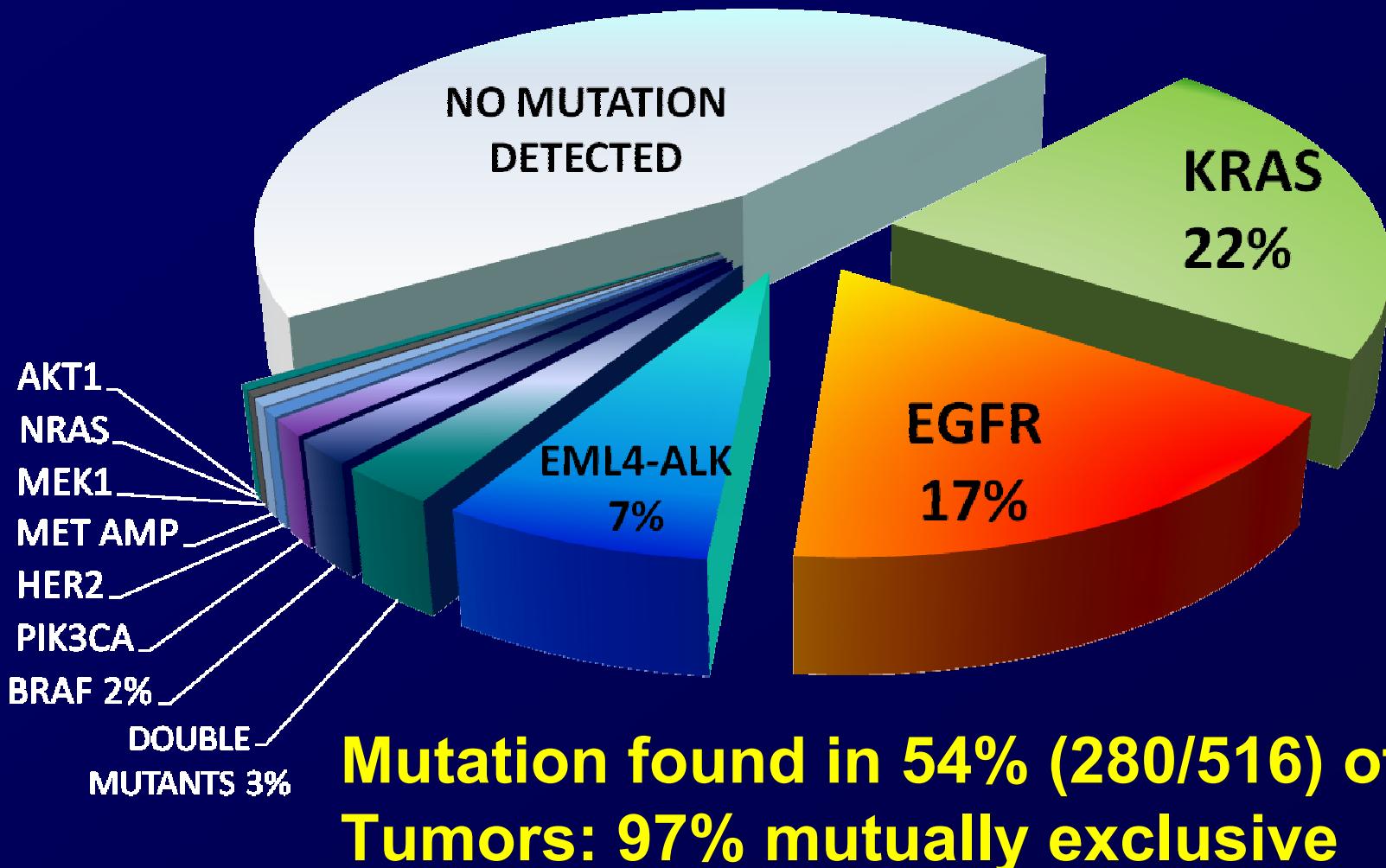
Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer

Variable	All Patients (N=2105)	Patients with EGFR Mutations (N=350)	Frequency of Mutations	
			number of patients	percent (95% CI)
Sex				
Female	814	244	30.0 (26.9–33.2)	69.7 (64.7–74.3)
Male	1287	106	8.2 (6.8–9.9)	30.3 (25.7–35.3)
Missing data	4	0		
Age				
<56.7 yr	638	89	13.9 (11.5–16.9)	27.1 (24.9–29.2)
56.7–69.1 yr	638	99	15.5 (12.9–18.6)	30.1 (27.8–32.4)
>69.1 yr	632	141	22.1 (19.1–25.6)	42.8 (40.2–45.5)
Missing data	197	21		
Smoking history				
Former smoker	958	91	9.5 (7.8–11.6)	26.2 (24.2–28.2)
Current smoker	424	25	5.8 (4.0–8.6)	7.2 (6.5–7.9)
Never smoked	612	231	37.7 (34.0–41.7)	66.6 (64.2–68.9)
Missing data	111	3		
Tumor type				
Adenocarcinoma	1634	283	17.3 (15.5–19.3)	80.9 (76.4–84.7)
Bronchioloalveolar adenocarcinoma	147	34	23.1 (17.0–30.7)	9.7 (7.0–13.3)
Large-cell carcinoma	287	33	11.5 (8.3–15.8)	9.4 (6.8–13.0)
Missing data	37	0		

16.6%

CI denotes confidence interval.





Farmaci con sviluppo non marker-driven nel NSCLC

Target	Drug	Clinical Development Phase
cMET	ARQ197	Phase II/III
VEGFRs; PDGFRs; bFGFRs; B-Raf	Sorafenib	Phase III (ESCAPE, NExUS failed; others ongoing)
VEGFRs; c-Kit; PDGFRs	Cediranib (AZD2171)	Phase II/III (with some concerns about dose)
VEGFRs; c-Kit; PDGFRs	Motesanib (AMG706)	Phase III (MONET-1 biologically selected population)
IGFR-1	Figitumumab	Phase III (failed to demonstrate a benefit)
TRAIL-Rs (DR4 e 5)	Mapatumumab Conatumumab Lexatumumab Apomab	Phase II (failed) Phase II
HDAC	Vorinostat	Phase I/II
PARP	BSI-201	Phase III (Eclipse started in March 2010)

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MARCH 8, 2012

VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

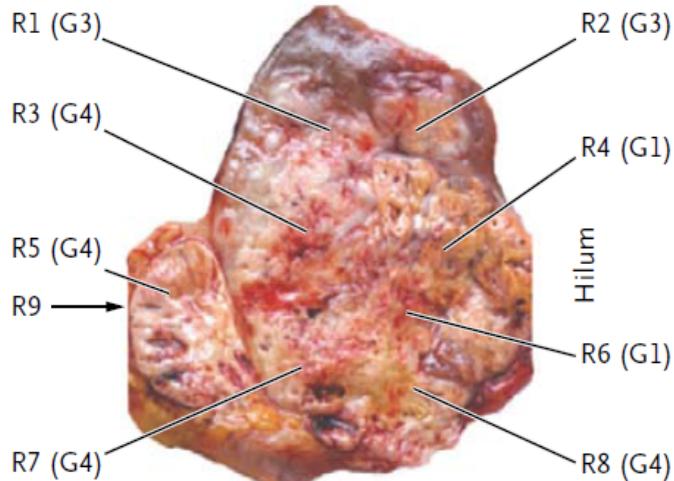
Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D.,
David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,
Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc.,
Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc.,
Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D.,
Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D.,
Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.



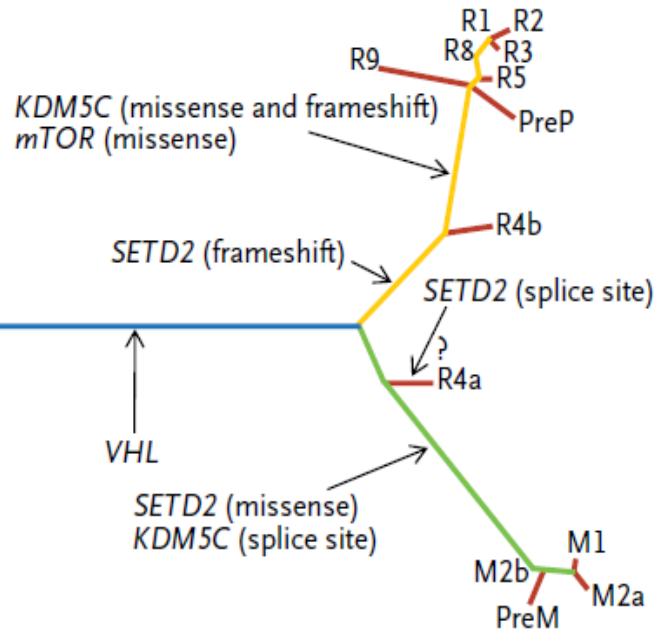
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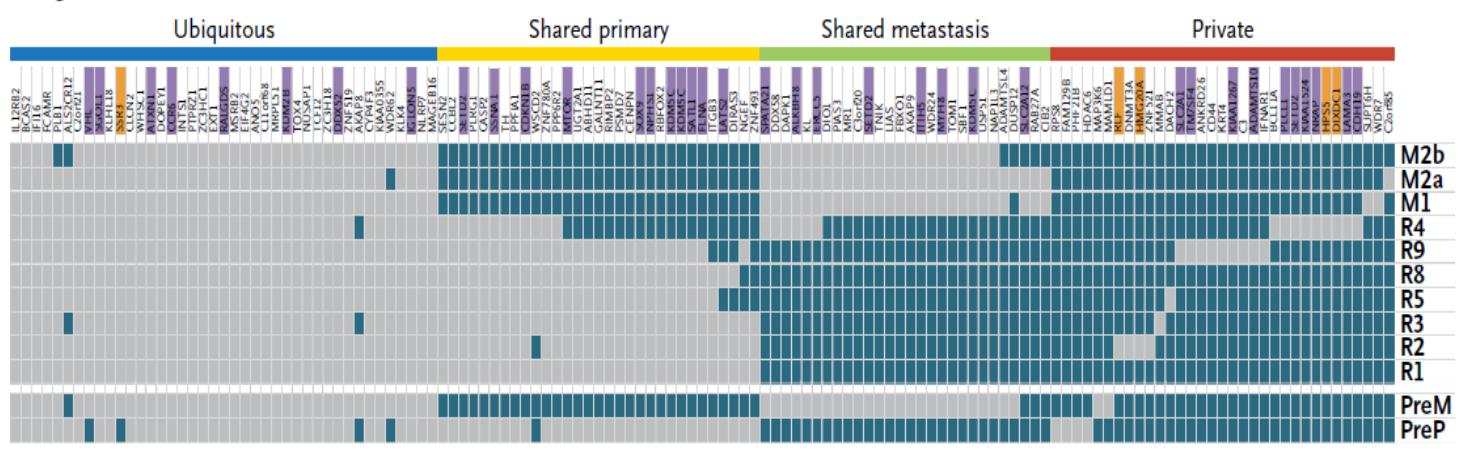
MARCH 8, 2012



- Ubiquitous
- Shared primary
- Shared metastasis
- Private



B Regional Distribution of Mutations



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 8, 2012

VOL. 366 NO. 10

- Solo il 55% delle mutazioni somatiche presenti in tutto il tumore è catturato in una singola biopsia
- Solo il 34% delle mutazioni presenti in tutto il tumore è presente in ogni singola regione (“ubiquitous”)
- Delle 71 mutazioni presenti nella biopsia pretrattamento, 67 presenti nel tumore post trattamento
- I campioni del primitivo e della metastasi pre-trattamento condividono solo il 40% delle mutazioni



**Entusiasmo dunque sì, ma con
ragionevolezza e prudenza...**



Mi sono chiesto di che cosa parlarvi...

- Il titolo assegnato è molto ampio...
- Quasi un assegno in bianco!
- **L'impatto della biologia molecolare**
- **L'importanza del punto di vista dei pazienti**
- Vertiginosamente lontani, in apparenza
- Ma l'oncologia è bella per questo...
- E la ricerca ancor di più!



In questi giorni

- Ho scritto un editoriale dal titolo:

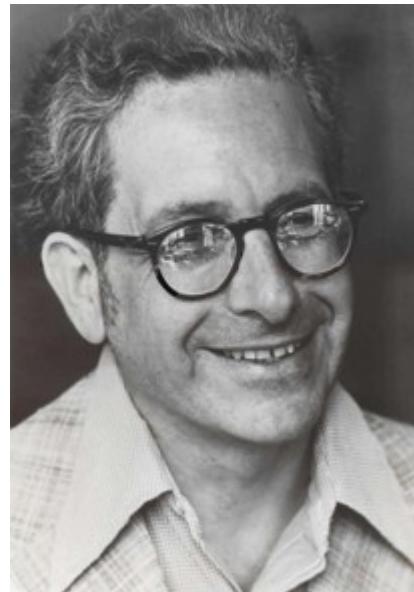
**The world outside the
Kaplan-Meier curve**

Edward L Kaplan



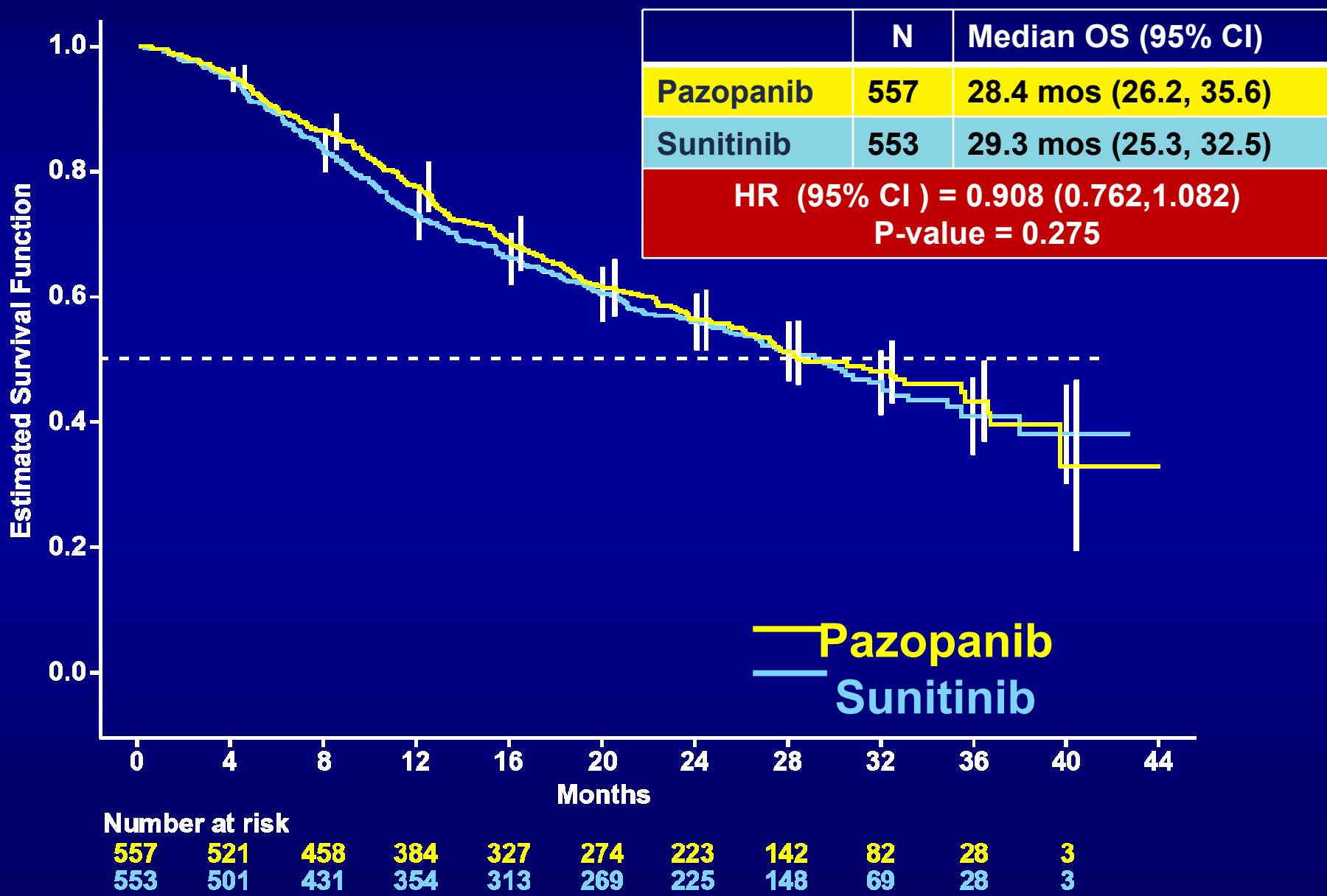
Died 2006

Paul Meier



Died 2011

Interim Analysis of Overall Survival



Nel mio editoriale...

- The burning question is...

**Crediamo veramente che
tutto quello che conta sia
nelle curve di Kaplan-Meier?**

Endpoints in oncology

**Activity against
the disease**

**Effect favouring
the patient**

- ❖ Objective tumor response
- ❖ Response duration
- ❖ TTP/PFS

- ❖ Overall survival
- ❖ Quality of life
- ❖ Toxicity

**Carboplatin Plus Paclitaxel Versus Carboplatin Plus
Pegylated Liposomal Doxorubicin As First-Line Treatment
for Patients With Ovarian Cancer: The MITO-2
Randomized Phase III Trial**

Sandro Pignata, Giovanni Scambia, Gabriella Ferrandina, Antonella Savarese, Roberto Sorio, Enrico Breda, Vittorio Gebbia, Pietro Musso, Luigi Frigerio, Pietro Del Medico, Alessandra Vernaglia Lombardi, Antonio Febbraro, Paolo Scollo, Antonella Ferro, Stefano Tamberi, Alba Brandes, Alberto Ravaioli, Maria Rosaria Valerio, Enrico Aitini, Donato Natale, Laura Scaltriti, Stefano Greggi, Carmela Pisano, Domenica Lorusso, Vanda Salutari, Francesco Legge, Massimo Di Maio, Alessandro Morabito, Ciro Gallo, and Francesco Perrone

Conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Sandro Pignata, MD, PhD, Istituto Nazionale Tumori, via Mariano Semmola, 80131 Napoli, Italy; e-mail: sandro.pignata@gmail.com.

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0732-183X/11/2927-3628/\$20.00
DOI: 10.1200/JCO.2010.33.8566

and six cycles.

Conclusion

Carboplatin/PLD was not superior to carboplatin/paclitaxel, which remains the standard first-line chemotherapy for advanced ovarian cancer. However, given the observed CIs and the different toxicity, carboplatin/PLD could be considered an alternative to standard therapy.

J Clin Oncol 29:3628-3635. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Ovarian cancer is the fourth leading cause of cancer-related death in women.¹ Intensive surgical staging and cytoreduction, followed by chemotherapy with carboplatin/paclitaxel, represent the standard treatment approach.²⁻⁶ However, even after optimal debulking surgery and response to systemic therapy,

the risk of recurrence is high, and long-term survival remains poor. Furthermore, standard medical treatment of ovarian cancer negatively impacts on quality of life (QoL) as a result of frequent toxicity, such as alopecia, neurotoxicity, and fatigue.

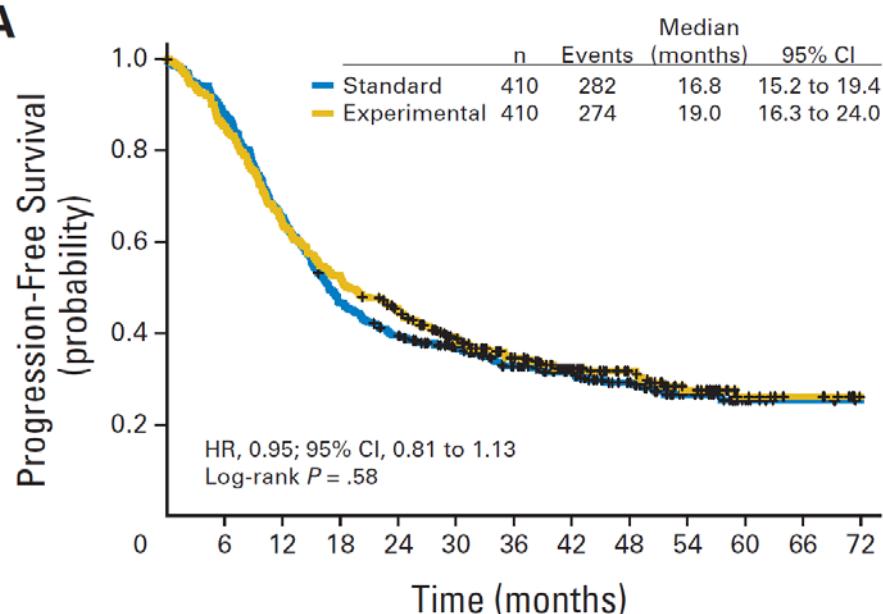
Anthracyclines were used in the first-line treatment of advanced ovarian cancer before the introduction of taxanes, with data from meta-analyses



Carboplatin Plus Paclitaxel Versus Carboplatin Plus Pegylated Liposomal Doxorubicin As First-Line Treatment for Patients With Ovarian Cancer: The MITO-2 Randomized Phase III Trial

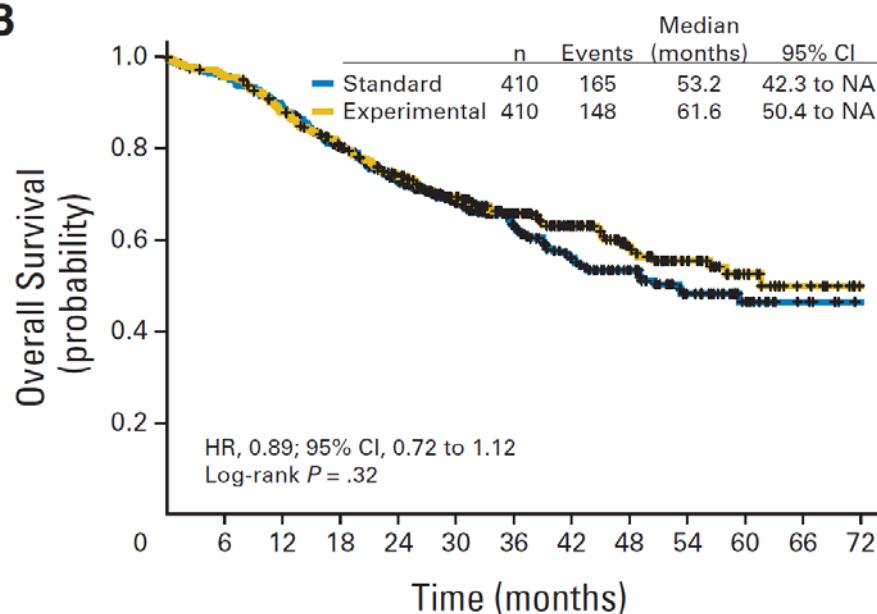
Sandro Pignata, Giovanni Scambia, Gabriella Ferrandina, Antonella Savarese, Roberto Sorio, Enrico Breda, Vittorio Gebbia, Pietro Musso, Luigi Frigerio, Pietro Del Medico, Alessandra Vernaglia Lombardi, Antonio Febbraro, Paolo Scollo, Antonella Ferro, Stefano Tamberi, Alba Brandes, Alberto Ravaioli, Maria Rosaria Valerio, Enrico Aitini, Donato Natale, Laura Scaltriti, Stefano Greggi, Carmela Pisano, Domenica Lorusso, Vanda Salutari, Francesco Legge, Massimo Di Maio, Alessandro Morabito, Ciro Gallo, and Francesco Perrone

**Journal of
Clinical Oncology,
29: 3628-3635, 2011**

A

No. at risk

Standard	410	361	269	191	159	125	89	72	52	30	14	7	4
Experimental	410	349	262	215	177	135	98	70	52	32	18	12	5

B

No. at risk

Standard	410	393	363	315	270	210	154	109	77	44	26	13	6
Experimental	410	391	354	315	268	213	158	119	78	48	27	14	5

GRAZIE AL VOSTRO AIUTO, RENDIAMO IL CANCRO SEMPRE PIÙ CURABILE.

Nel 2011, sono stati destinati alla ricerca 99,4 milioni di euro: migliaia di ricercatori hanno potuto lavorare nei centri d'eccellenza del Paese grazie alla generosità di soci, sostenitori e volontari. Tra i tanti risultati già ottenuti, ne abbiamo selezionati alcuni tra quelli pubblicati sulle più importanti riviste scientifiche internazionali. Una testimonianza concreta di come, insieme, stiamo mettendo il cancro all'angolo.

TUTTO SULLA LEUCEMIA A CELLULE CAPELLUTE

Rivista: New England Journal of Medicine
Autore: Brunangelo Falini e altri

Università degli studi, Perugia
Un gruppo di ricercatori di Perugia ha tracciato l'identikit molecolare di questa particolare forma di leucemia, migliorando le possibilità di diagnosi e aprendo la strada a terapie mirate.

IL RUOLO CRUCIALE DELLA PROTEINA YAP

Rivista: Nature
Autore: Stefano Piccolo e altri
Università degli studi, Padova

Come fa la nostra struttura corporea a rimanere inalterata se le cellule continuano a cambiare? Un gruppo di ricercatori di Padova ha trovato la risposta, aprendo nuovi orizzonti per lo studio delle malattie genetiche e del cancro: è l'ambiente, l'architettura del tessuto nel suo insieme, a governare i destini delle cellule, anche nei tessuti malati.

LE DOTI NASCOSTE DEI VECCHI FARMACI

Rivista: Nature
Autore: Marco Foiani, Saverio Minucci e altri
Istituto FIRC di oncologia molecolare, Milano
Genetica e farmacologia unite per valorizzare le potenzialità terapeutiche di farmaci già conosciuti e utilizzati.

TUMORI AL SENO: CAPIRE I PIÙ AGGRESSIVI

Rivista: Cancer Cell
Autore: Giannino Del Sal e altri
Consorzio interuniversitario biotecnologie, Trieste

Uno studio condotto a Trieste identifica alcuni elementi fondamentali dell'aggressività dei tumori alla mammella. La scoperta permette di caratterizzare meglio la malattia e predirne l'esito e offre la possibilità di fare previsioni sulla risposta delle pazienti ai trattamenti.

LA PROTEINA VIGILE DEI SEGNALI CELLULARI

Rivista: Nature Cell Biology
Autore: Antonio Feliciello e altri
Università degli studi Federico II, Napoli

I ricercatori dell'Università Federico II di Napoli hanno identificato una proteina responsabile del corretto funzionamento della trasmissione di alcuni messaggi cellulari.

TUMORI DELL'OVATO, TERAPIE MENO TOSSICHE

Rivista: Journal of Clinical Oncology
Autore: Francesco Perrone e altri
Istituto nazionale tumori Fondazione Pascale, Napoli

Uno studio coordinato dall'Istituto tumori di Napoli dimostra che con uno schema di chemioterapia innovativo si possono ridurre la caduta dei capelli e la tossicità neurologica, senza diminuire l'efficacia del trattamento.

LE DUE FACCE DI UNA MOLECOLA

Rivista: Journal of Experimental Medicine
Autore: Giovanni Monteleone e altri
Università Tor Vergata, Roma

Ricercatori romani hanno individuato uno dei meccanismi responsabili dello sviluppo di tumori in chi soffre di malattie infiammatorie croniche.



IL SEGNALE DI STOP PER LA CRESCITA DEGLI ORGANI

Rivista: Hepatology
Autore: Amedeo Columbano e altri

Individuato nei laboratori dell'Università di Cagliari un collegamento tra i meccanismi che regolano la dimensione degli organi e l'insorgenza di tumori.

BLOCCARE IL CANALE CHE RENDE RESISTENTE LA LEUCEMIA

Rivista: Blood
Autore: Annarosa Arcangeli e altri

Scoperto a Firenze il tallone di Achille delle leucemie linfatiche acute pediatriche che non rispondono alle cure tradizionali.

IDENTIFICATI I GENI RESPONSABILI DEL LINFOMA MARGINALE SPLENICO

Rivista: Blood
Autore: Gianluca Gaidano e altri

Università degli studi del Piemonte orientale Amedeo Avogadro, Novara
I ricercatori dell'Università Amedeo Avogadro di Novara hanno identificato alcuni geni responsabili dello sviluppo di un tipo di linfoma che cresce nella milza. Terapie mirate contro il linfoma

potranno essere sviluppate grazie a questa scoperta.

LEUCEMIA: TRAPIANTI PIÙ EFFICACI

Rivista: Blood
Autore: Alessandro Moretta, Lorenzo Moretta e altri Università degli studi, Genova

Uno studio condotto a Genova ha trovato che alcune delle cosiddette cellule Natural Killer (NK) sono non soltanto in grado di uccidere le cellule leucemiche, ma possono anche prevenire il rigetto del trapianto di midollo e la cosiddetta malattia "Graft versus host", in cui le cellule trapiantate attaccano l'ospite. La scoperta permetterà di selezionare in maniera più accurata il donatore per il trapianto, nei casi di leucemia, riducendo le complicazioni.

NUOVA STRATEGIA CONTRO IL TUMORE DELL'OVATO

Rivista: Proceedings of the National Academy of Sciences of the United States of America

Autore: Maria Paola Costi e altri
Università degli studi, Modena e Reggio Emilia

Un gruppo di ricerca dell'Università di Modena ha identificato il meccanismo d'azione di un peptide in grado di ridurre la crescita delle cellule del tumore all'ovario. Questa scoperta apre la strada a nuove possibilità di cura.

Per conoscere nel dettaglio questi progetti e per consultare il nostro Bilancio sociale:
www.bilanciosociale.airc.it



FIRC

GRAZIE AL VOSTRO AIUTO.



METTIAMO
IL CANCRO
GOLO.

**REI
SEM**

Nel 2011, sono
di ricercatori i
grazie alla ger
già ottenuti, r
più importanti
concreta di c

**TUTTO SULLA LEU
CAPELLUTE**
Rivista: New Englan
Autore: Brunangelo
Università degli stu
Un gruppo di ricerc
l'identikit molecol
forma di leucemia,
di diagnosi e apr
mirate.

IL RUOLO CRUCIALE
Rivista: Nature
Autore: Stefano Pic
Università degli stu
Come fa la nostra si
inalterata se le cell
Un gruppo di ricerc
risposta, aprendo n
delle malattie gene
biente, l'architettura
a governare i dest
tessuti malati.

LE DOTI NASCOSTE
Rivista: Nature
Autore: Marco Foa
Istituto FIRC di onc
Genetica e farmaci
le potenzialità ter
conosciuti e utilizza

TUMORI AL SENO:
Rivista: Cancer Cell
Autore: Giannino Del Sal e altri
Consorzio interuniversitario biotecnologie, Trieste

tumori in chi soffre di malattie infiammatorie
croniche.

potranno essere sviluppate grazie a questa
scoperta.

Università degli studi, Modena
e Reggio Emilia



TUMORI DELL'OVARIO, TERAPIE MENO TOSSICHE

Rivista: Journal of Clinical Oncology

Autore: Francesco Perrone e altri

Istituto nazionale tumori Fondazione Pascale,
Napoli

Uno studio coordinato dall'Istituto tumori di Napoli dimostra che con uno schema di chemioterapia innovativo si possono ridurre la caduta dei capelli e la tossicità neurologica, senza diminuire l'efficacia del trattamento.

getti
ale:

AIRC |  **FIRC**

DEVELOPMENT OF THE PATIENT-REPORTED OUTCOMES (PRO) VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE)

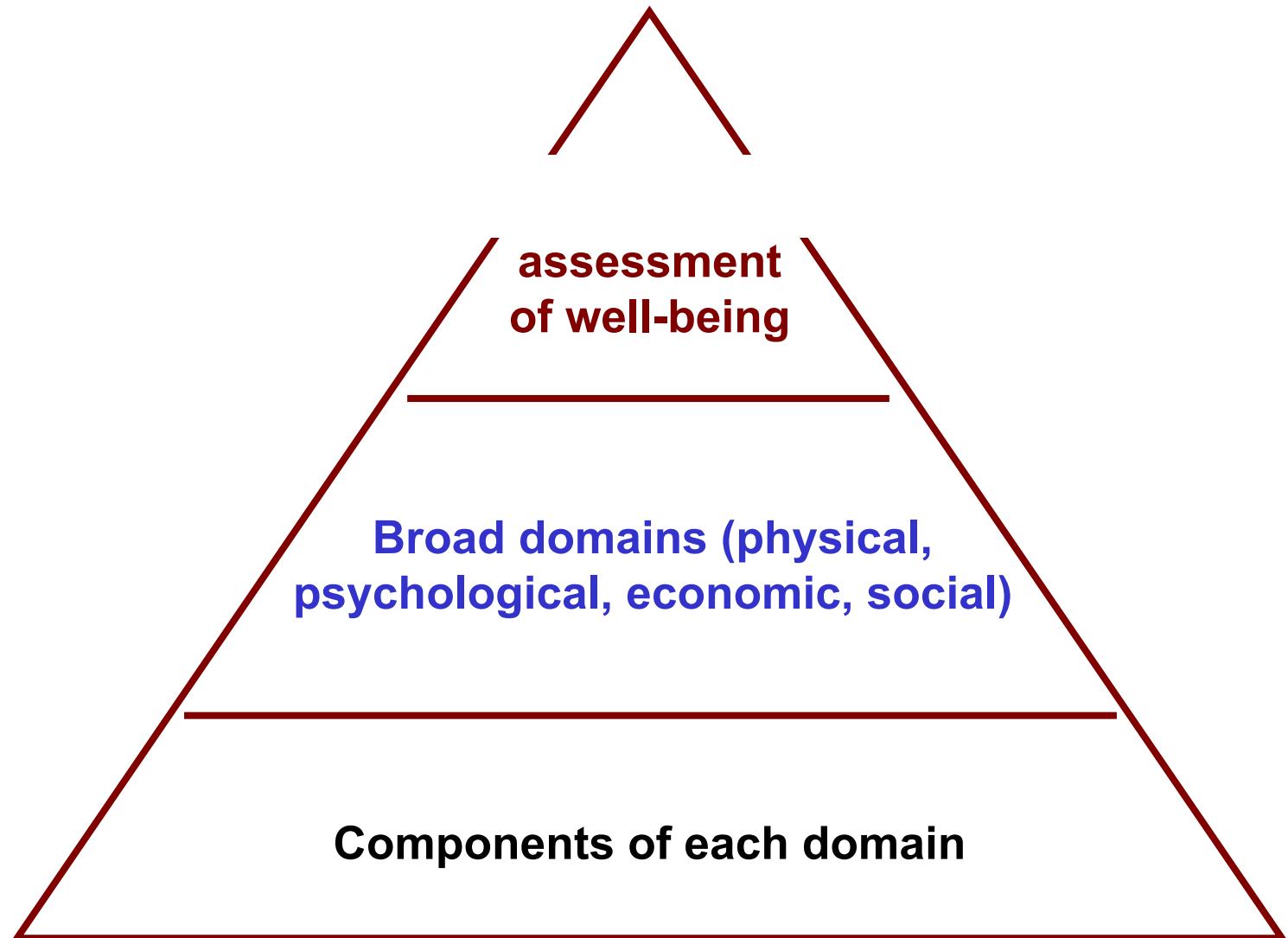
[HTTP://OUTCOMES.CANCER.GOV/TOOLS/PRO-CTCAE.HTML](http://OUTCOMES.CANCER.GOV/TOOLS/PRO-CTCAE.HTML)

- △ Develop a PRO version of the CTCAE to capture a comprehensive range of symptoms and functioning that enhances monitoring of adverse events in cancer clinical trials.
- △ Approximately 78 CTCAE items may benefit from PRO conversion, e.g.
 - Pain
 - Fatigue
 - Nausea/Vomiting
 - Elimination
 - Sexual Function
 - Swallowing
 - Dyspnea
- △ Web-based platform that can also be completed via paper and pencil.

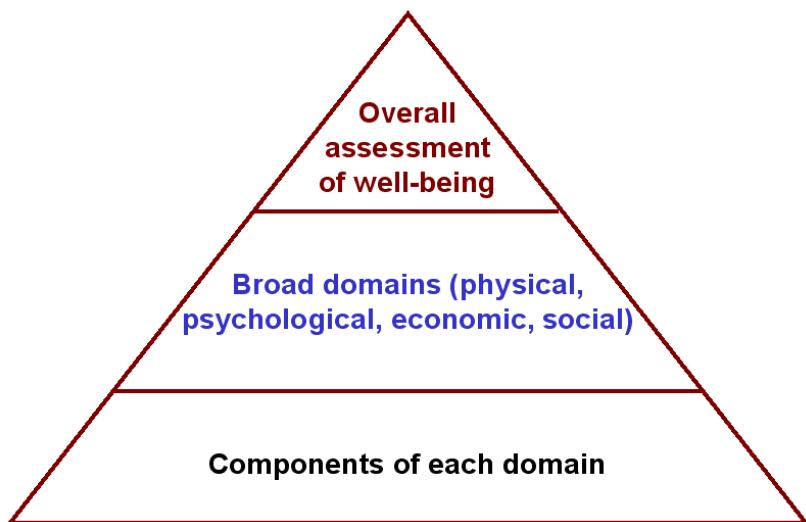
L'importanza della qualità di vita



è meglio ridere in compagnia che intristirsi da soli...



Strumenti non facili da impiegare



Complessità dei metodi
multifattorialità
eterogeneità

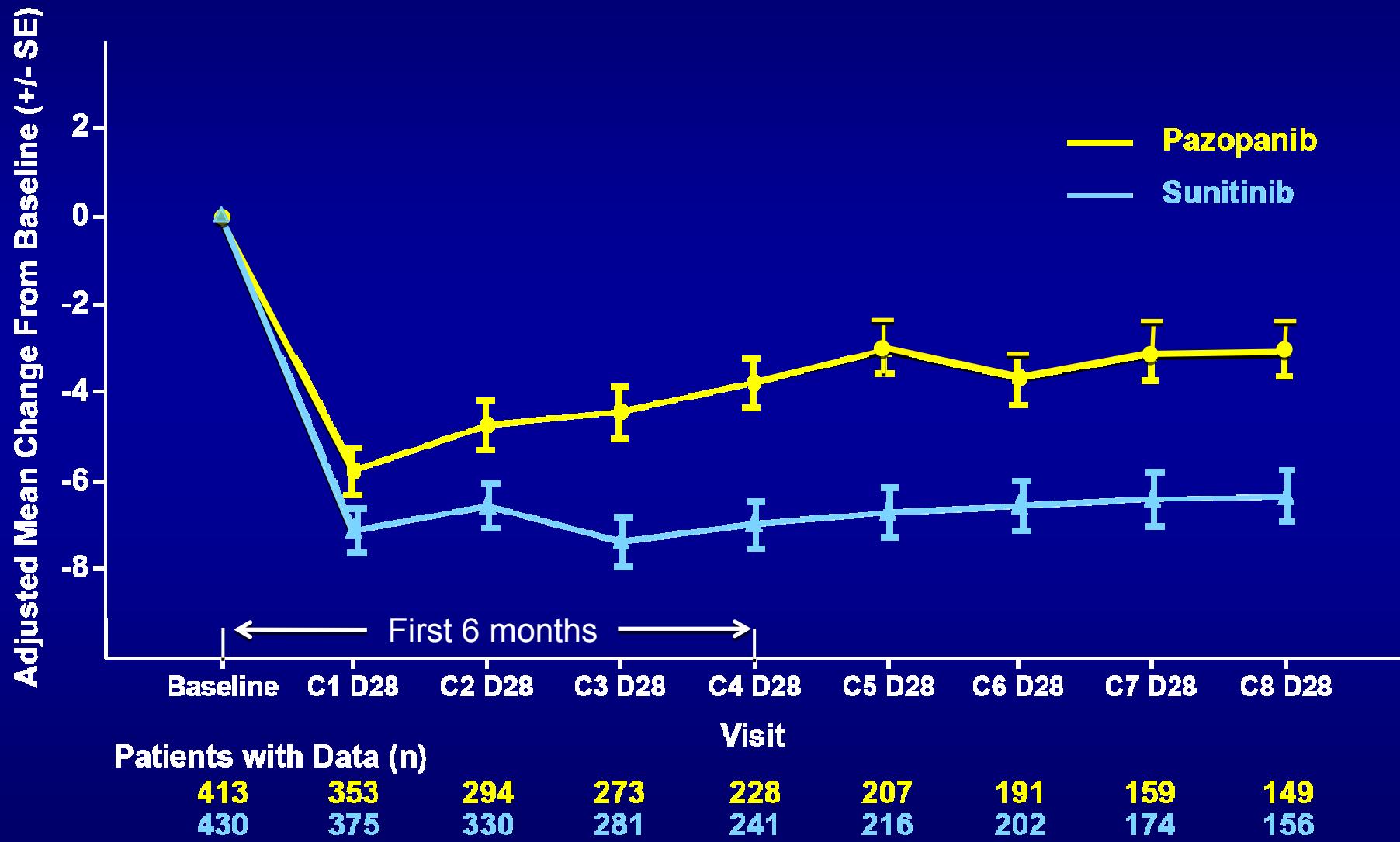
Quality of Life Results (first 6 months¹)

Instrument	Domain Description	Treatment difference : mean change from baseline ²	P -value
FACIT-F	Fatigue/Total score	2.32	<0.001
FKSI-19	Kidney Symptom Index/Total score	1.41	0.018
	Physical	0.78	0.027
	Emotional	0.05	0.409
	Treatment Side Effects	0.31	0.033
	Functional Well Being	0.31	0.098
Cancer Treatment Satisfaction Questionnaire (CTSQ)	Expectations of Therapy	1.41	0.284
	Feelings about Side Effects	8.50	<0.001
	Satisfaction with Therapy	3.21	<0.001
Supplementary Quality of Life Questionnaire (SQLQ)	Worst mouth/throat soreness	0.505	<0.0001
	Worst foot soreness	0.204	0.0016
	Worst hand soreness	0.267	0.0008
	Limitations due to mouth/throat soreness	0.94	<0.001
	Limitations due to foot soreness	0.65	0.014

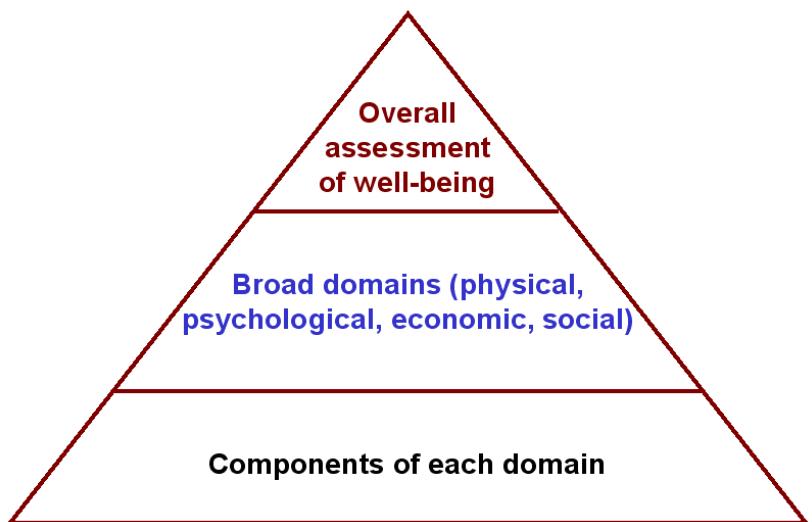
¹Pre-specified analysis. HRQoL changes in mean scores over time were analyzed with a repeated measures analysis of covariance (ANCOVA).

²**Yellow Font**: favors pazopanib. Blue Font: favors sunitinib. P-value <0.05 is statistically significant

Quality of Life Result: FACIT-Fatigue



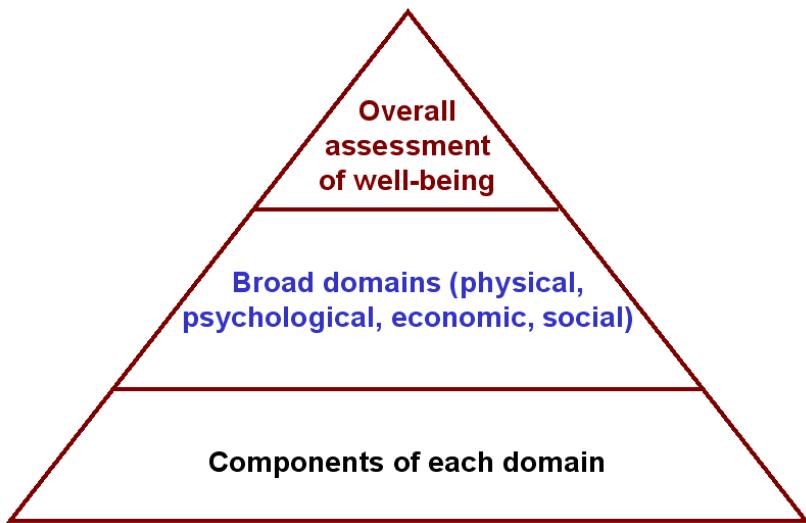
Strumenti non facili da impiegare



Complessità dei metodi
multifattorialità
eterogeneità

Ipersemplificazione
necessaria
inadeguata

Strumenti non facili da impiegare



Complessità dei metodi
multifattorialità
eterogeneità

Ipersemplificazione
necessaria
inadeguata

Atipia dei risultati
comprendere
integrazione
trasferimento

Dovremmo evitare di fare come...

Robert McNamara, the United States Secretary of Defense from 1961 to 1968, who said that US were winning the Vietnam War based on the enemy body count, ignoring other variables.



McNamara fallacy

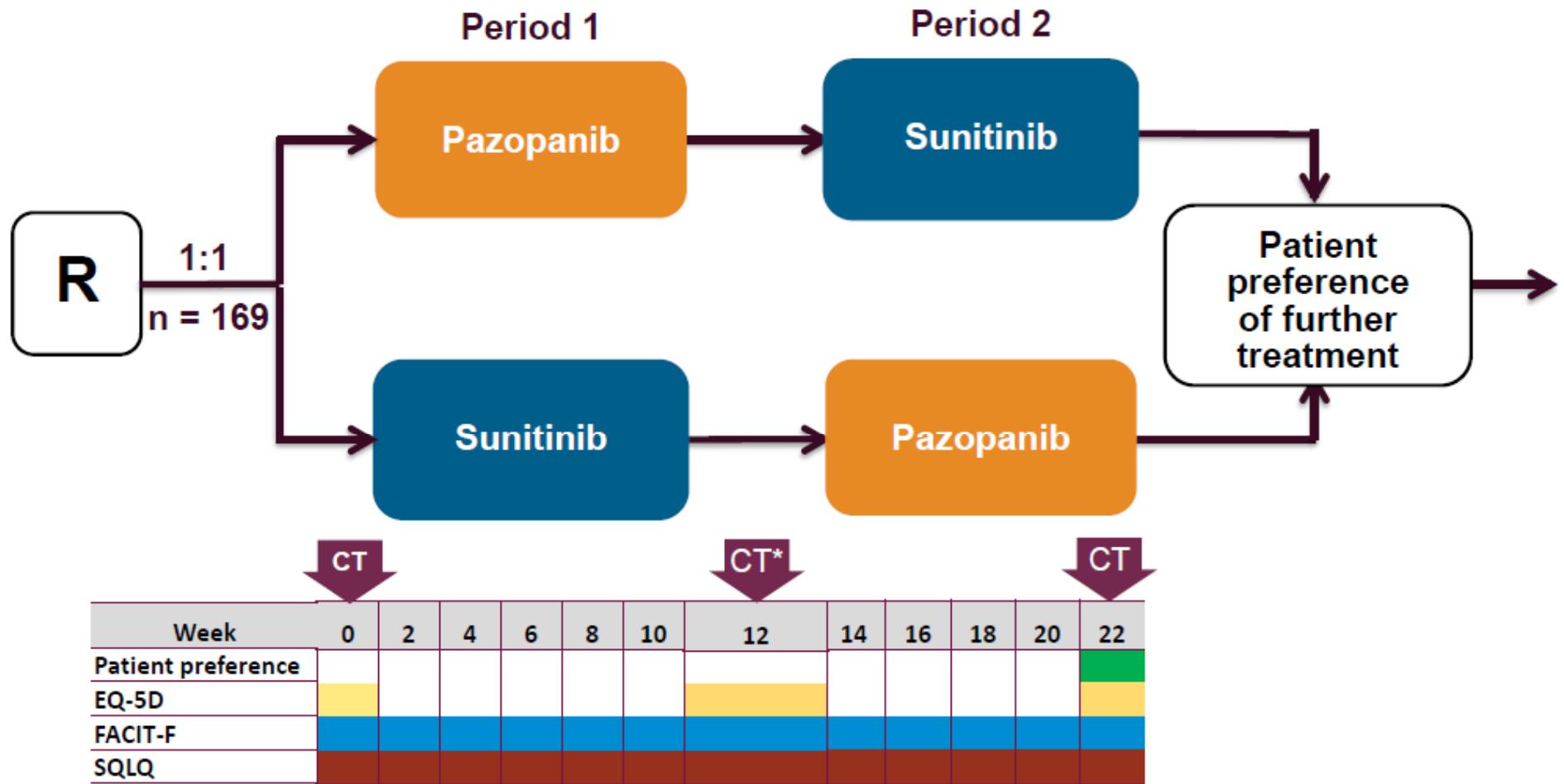
- First, measure whatever can be easily measured.
- Second, disregard that which can't be easily measured or give it an arbitrary quantitative value.
- Third, presume that what can't be measured easily really isn't important.
- Fourth, say that what can't be easily measured really doesn't exist.

Integrazioni difficili

Survival	QoL		
	Better	Equal	Worse
Longer	<i>QoL not of interest (?)</i>		
No change	<i>Crucial</i>		
Shorter	<i>QoL not of interest</i>		



Study Design



*Could occur earlier if the patient crossed over early due to AE

Health-Related Quality of Life

Cross over analysis

- Difference between each patients scores while on pazopanib and sunitinib tested for significance

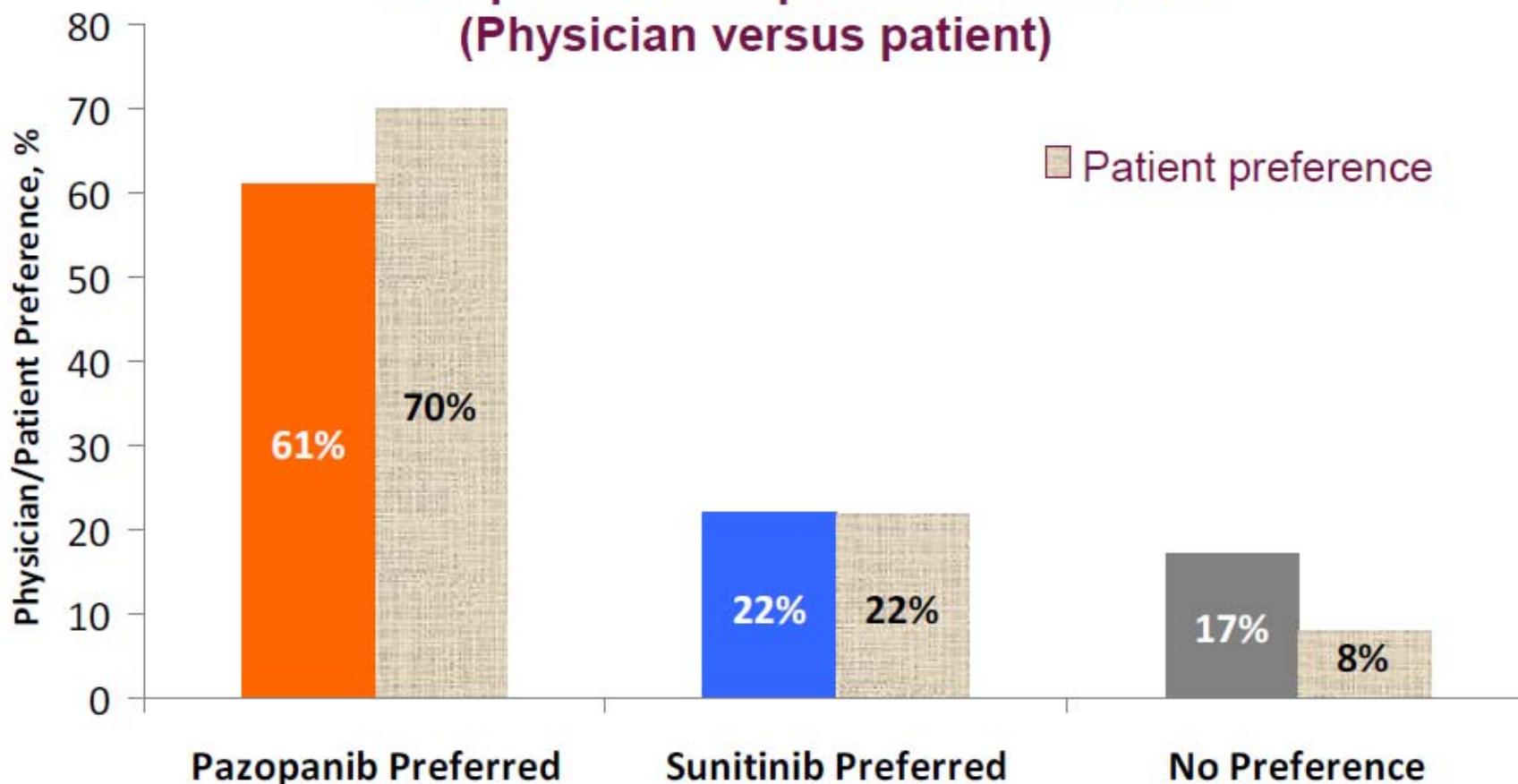
Instrument	Timing	Description	Scale	Favoured	P value
FACIT- F	q2w	13 items on fatigue	0 – 52	Pazopanib	.002
		Mouth / Throat soreness (MTS)	0 – 3	Pazopanib	< .001
		Hand (H)		Pazopanib	.026
Supplementary Questionnaire*	q2w	Foot (F) soreness		Pazopanib	.005
		Limitations due to MTS		Pazopanib	< .001
		Limitations due to F soreness	0 – 15	Pazopanib	.003

*Validation analyses ongoing

Physician Preference

Primary Analysis Population

- Completed while patient still blinded
(Physician versus patient)



Integrazioni difficili

Survival	QoL		
	Better	Equal	Worse
Longer	<i>QoL not of interest (?)</i>		
No change	OK!	<i>Doesn't help</i>	<i>Try another game</i>
Shorter	<i>QoL not of interest</i>		



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**U.S. Food and Drug Administration
Approval: Ruxolitinib for the Treatment
of Patients with Intermediate and High-
Risk Myelofibrosis**

Clin Cancer Res June 15, 2012; 18:3212-
3217; Published OnlineFirst April 27,
2012;



Modified TSS

- Abdominal related symptoms
 - Abdominal discomfort score
 - Feeling fullness score
 - Pain under ribs
- Other symptoms
 - Night sweats
 - Itching
 - Bone or Muscle Pain

Trials

- # 1 – RCT comparing ruxolitinib to placebo
 - Primary endpoint – response rate ($\geq 35\%$ reduction in spleen volume) at 24 weeks – **42% vs. 1% significant**
 - Key secondary – response ($\geq 50\%$ improvement from baseline in modified TSS symptom score) at 24 weeks – **46% vs. 5% significant**
- # 2 – RCT comparing ruxolitinib to best available therapy
 - Primary endpoint - response rate ($\geq 35\%$ reduction in spleen volume) at 48 weeks – **29% vs. 0% significant**

American Society of Clinical Oncology Provisional Clinical Opinion: The Integration of Palliative Care Into Standard Oncology Care

Thomas J. Smith, Sarah Temin, Erin R. Alesi, Amy P. Abernethy, Tracy A. Balboni, Ethan M. Basch, Betty R. Ferrell, Matt Loscalzo, Diane E. Meier, Judith A. Paice, Jeffrey M. Peppercorn, Mark Somerfield, Ellen Stovall, and Jamie H. Von Roenn

Recent Data

Seven published RCTs form the basis of this PCO.

Tabella 1											
	Sample size					Finding (measure, P value)					
Ref., yr	SC	PC	Population	Rate of cancer pts	PC interventions (actors)	Symptoms	QoL	Mood	Satisfaction	Resource Utilization	OS
Bakitas, 2009	161	161	Advanced cancer, rural	100	Psychoeducational: 4 weekly session, monthly follow-up (APN, MD).	Improved (p=0.06)	Improved (p=0.02)	Improved (p=0.02)	Not measured	No difference	No difference
Brumley, 2007	152	145	Homebound, life exp<1 yr, ≥1 ER/hospital admission in 1 yr	47	Home-based care program hospice-model (MD, RN, SW)	Not measured	Not measured	Not measured	Improved (p<0.05)	Lower cost (p=0.03) Shorter hospital stay (p<0.001) Less ED visits (p=0.02)	No difference
Gade, 2008	237	275	Hospitalized, life-limiting illness	27	Consultant service (MD, nurse, SW, chaplain)	No difference	No difference	No difference	Improved (p=0.04)	Lower cost (p<0.001) Longer hospice stay (p=0.04)	No difference
Meyers, 2011	128	348	Clinical trial pts and their caregiver	100	Educational intervention with pts and caregivers, COPE problem-solving model	Not measured	No difference for pts Better for caregivers	No difference	Not measured	Not measured	Not measured
Pantilat, 2010	53	54	Hospitalized elderly pts	22	Daily MD visits and recommendation done to primary attending MD	No difference	Not measured	No difference (anxiety)	Not measured	Not measured	Not measured
Rabow, 2004	40	50	Outpatient, advanced CHF, COPD or cancer	33	Intervention on 7 components: assessment, social work, caregiver training, medication review, spiritual/psychologic support, home visits, phone calls (SW, nurse, chaplain, pharmacist, psychologist, art therapist, 3 MDs)	Less dyspnoea (p=0.01)	No difference	Less anxiety (p=0.05)	No difference	No difference	No difference
Temel, 2010	74	77	Outpatient, advanced NSCLC	100	Met with outpatient PC team within 3 weeks then at least monthly (6 MDs, APN)	Improved (p=0.04)	Improved (p=0.03)	Less depression (p=0.01)	Not measured	Less aggressive care (p=0.05)	Prolonged 11.6 vs 8.9 months (p=0.02)

Ref. =reference, yr=year, SC=standard care, PC=palliative care, pts=patients, QoL=quality of life, OS=overall survival, APN=advanced practice nurse, MD=medical doctor, RN=registered nurse, SW=social worker, ED=Emergency Department

Provisional Clinical Opinion

Therefore, it is the Panel's expert consensus that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.

Mi sono chiesto di che cosa parlarvi...

- Il titolo assegnato è molto ampio...
- Quasi un assegno in bianco!
- **L'impatto della biologia molecolare**
- **L'importanza del punto di vista dei pazienti**
- Vertiginosamente lontani, in apparenza
- Ma l'oncologia è bella per questo...
- E la ricerca ancor di più!

Grazie per l'attenzione