Uso, abuso e mancato uso dei PROs nella sperimentazione clinica

Francesco Perrone

Istituto Nazionale Tumori

Napoli

Quel che è peggio…

- Ricordo che il titolo l'ho suggerito io, avendo in mente qualcosa che mi sembrava interessante… che poi ho assolutamente dimenticato

- L'età…

Fondazione Smith Kline

Personalità giuridica riconosciuta (D.P.R. 917 del 9. 9. 1982)

Aiom

Associazione Italiana Oncologia Medica

PROs in Oncologia
DISPENSA BIBLIOGRAFICA

Palazzo delle Stelline, Milano **10 Ottobre 2013**

Perchè io?

- Forse perché in vita mia ho coordinato 4 studi no-profit in cui un PRO era l'*endpoint* primario e uno studio in cui era un *coprimary endpoint*
  - (e nessuno di questi riguarda terapie di supporto)

Il mio background 4+1

- ELVIS: vinorelbina nel NSCLC elderly (JNCI 1999)
- GEMVIN3: platinum-based vs GemVin nel NSCLC adulti (JCO 2003)
- DISTAL1: docetaxel w vs 3w NSCLC 2° line (BJC 2004)
- Breast10: EpiTxtx w vs 3w (BMCcancer 2011)

- MITO7: CarboTaxol w vs 3w (plenaria AIOM 2013)

Perchè io?

- Forse perché in vita mia ho coordinato 4 studi no-profit in cui un PRO era l'*endpoint* primario e uno studio in cui era un *coprimary endpoint*
  - (e nessuno di questi riguarda terapie di supporto)

- Forse perché un anno fa ho fatto una relazione che a quanto mi risulta è stata molto apprezzata
  - (questo "sospetto" non modifica la mia indipendenza ma concorda con una riflessione che farò alla fine)

Francesco Perrone

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Scaletta

- Quello che ho imparato facendo gli studi sulla qualità di vita
- Quello che ho imparato studiando la selezione bibliografica
- Quello che ho pensato, alla luce di quello che ho imparato

Effects of Vinorelbine on Quality of Life and Survival of Elderly Patients With Advanced Non-Small-Cell Lung Cancer

The Elderly Lung Cancer Vinorelbine Italian Study Group

J Natl Cancer Inst 1999;91: 66–72

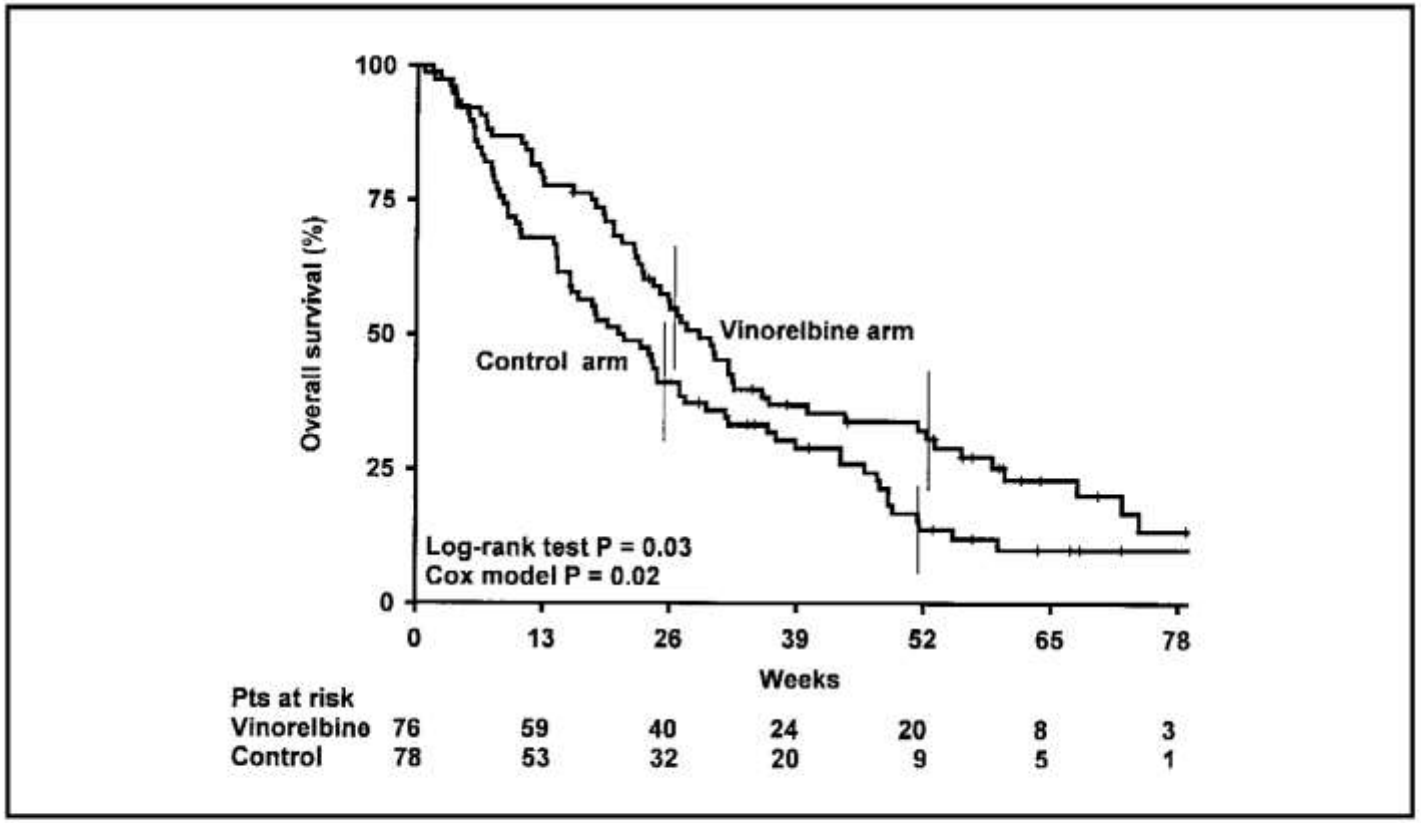

Fig. 3. Estimated survival according to treatment arm as calculated by the Kaplan–Meier method. Number of patients at risk by treatment arm is shown at the bottom. Pts = patients. Vertical bars = representative 95% confidence intervals.

Effects of Vinorelbine on Quality of Life and Survival of Elderly Patients With Advanced Non-Small-Cell Lung Cancer

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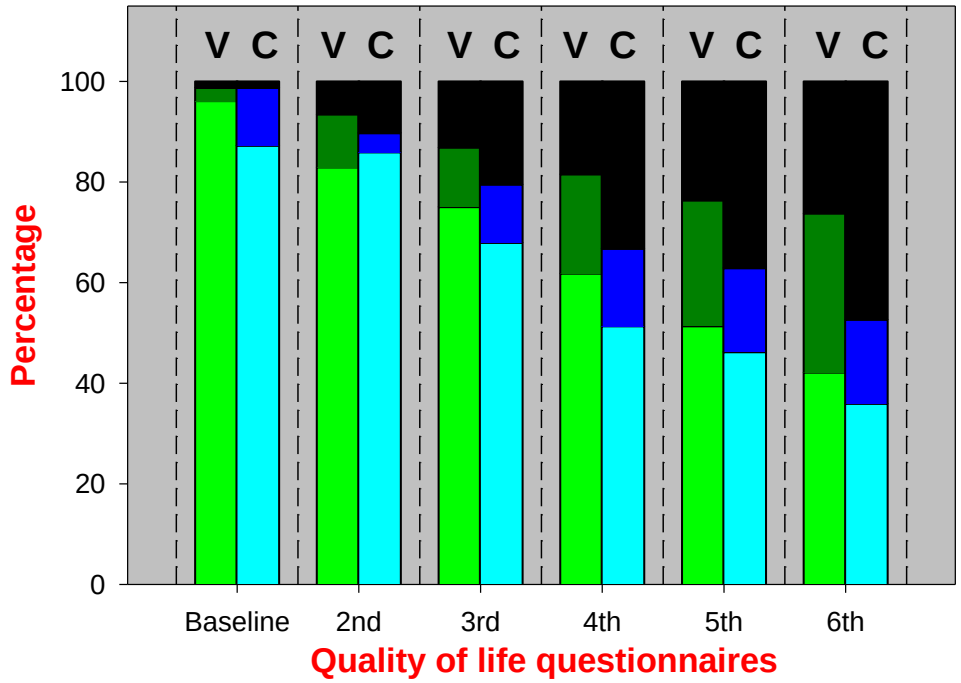

V = vinorelbine
C = controls

Effects of Vinorelbine on Quality of Life and Survival of Elderly Patients With Advanced Non-Small-Cell Lung Cancer

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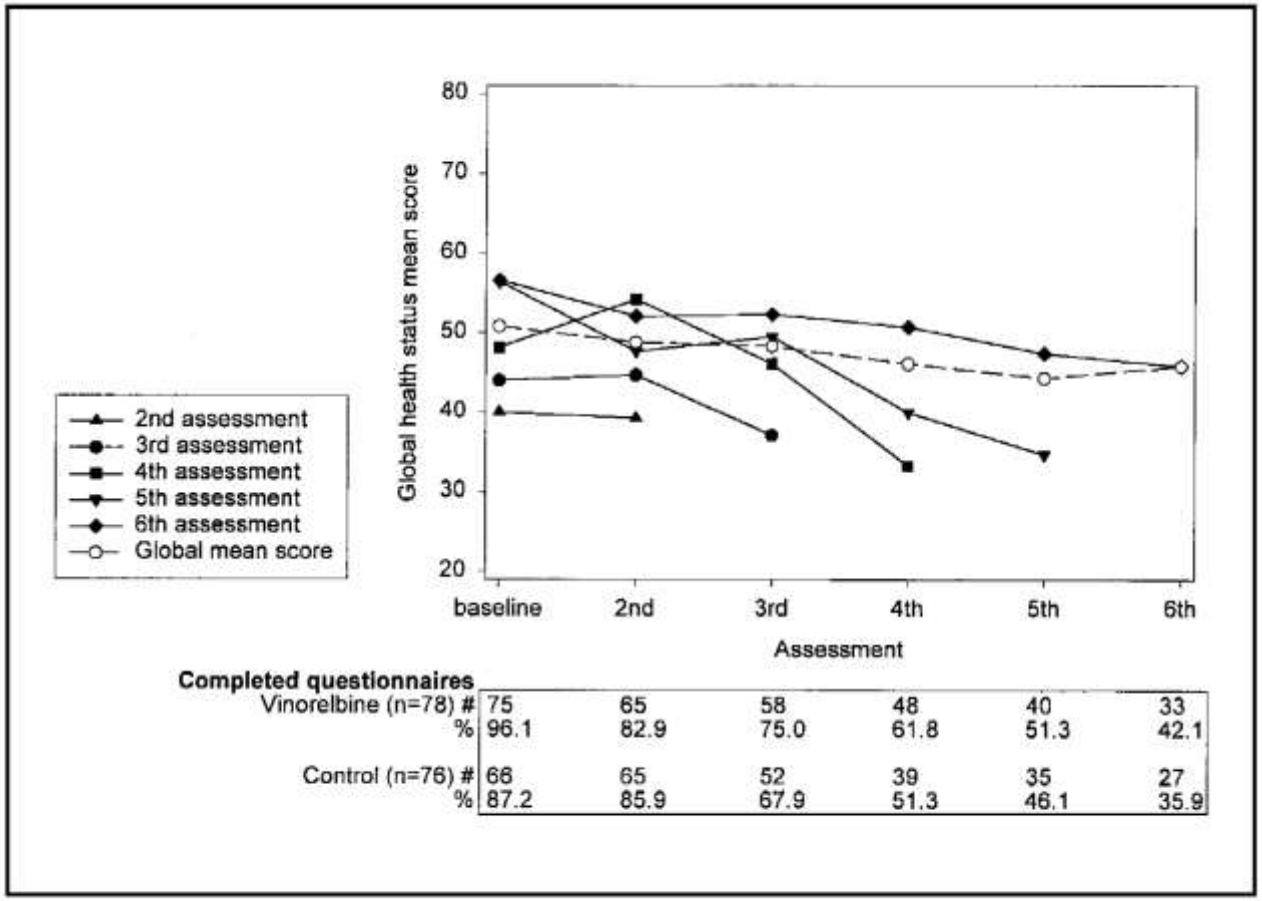
J Natl Cancer Inst 1999;91: 66–72



Completed questionnaires						
Vinorelbine (n=78) #	75	65	58	48	40	33
%	96.1	82.9	75.0	61.8	51.3	42.1
Control (n=76) #	66	65	52	39	35	27
%	87.2	85.9	67.9	51.3	46.1	35.9

Fig. 2. Global health status mean score (global and by time of dropout). Patient compliance (%) to quality-of-life assessment by treatment arm is shown at the bottom.

Gemcitabine Plus Vinorelbine Compared With Cisplatin Plus Vinorelbine or Cisplatin Plus Gemcitabine for Advanced Non–Small-Cell Lung Cancer: A Phase III Trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group

By Cesare Gridelli, Ciro Gallo, Frances A. Shepherd, Alfonso Illiano, Francovito Piantedosi, Sergio Federico Robbiati, Luigi Manzione, Santi Barbera, Luciano Frontini, Enzo Veltri, Brian Findlay, Silvio Cigolari, Robert Myers, Giovanni P. Ianniello, Vittorio Gebbia, Giampietro Gasparini, Sergio Fava, Vera Hirsh, Andrea Bezjak, Lesley Seymour, and Francesco Perrone

J Clin Oncol 21:3025-3034. © *2003*

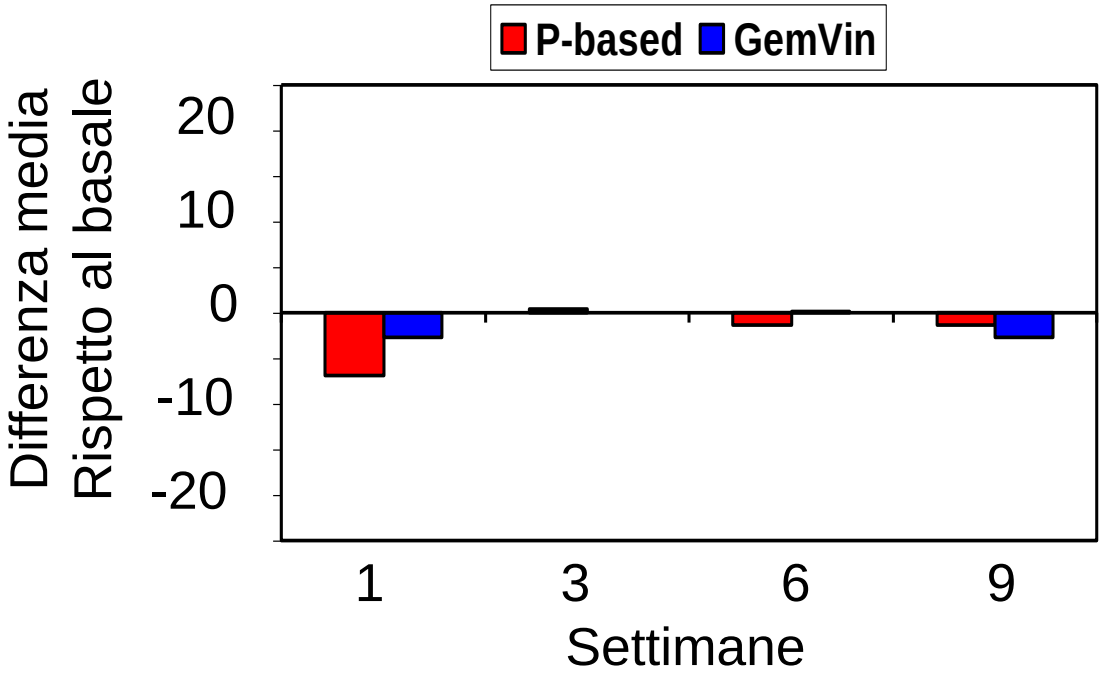
Gemcitabine Plus Vinorelbine Compared With Cisplatin Plus Vinorelbine or Cisplatin Plus Gemcitabine for Advanced Non–Small-Cell Lung Cancer: A Phase III Trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group

Table 4. Toxicity Observed in the Two Compared Arms (worst degree for each patient) According to WHO Criteria (grades 1 to 4) and Presented as Percent

Type of Toxicity	Cisplatin Based (N = 241)				Gemcitabine + Vinorelbine (N = 246)				P*	P†
	1	2	3	4	1	2	3	4		
Anemia	25	22	6	1	21	14	4	1	.0008	.44
Leukopenia	13	20	15	8	15	16	7	4	.0006	.001
Neutropenia	11	12	15	17	13	14	7	7	< .0001	< .0001
Infection	3	4	3	< 1	3	4	1	< 1	.22	.09
Thrombocytopenia	9	12	2	2	9	4	3	1	.006	.83
Bleeding	2	1	—	< 1	2	1	< 1	—	.91	.99
Vomiting	25	33	12	1	34	11	1	—	< .0001	< .0001
Diarrhea	8	2	< 1	< 1	7	2	—	—	.48	.24
Renal	8	3	< 1	< 1	2	—	—	—	< .0001	.24
Pulmonary	4	2	1	1	4	2	1	—	.40	.28
Hepatic	6	1	2	< 1	14	6	< 1	1	.0002	.50
Fever	9	5	1	—	11	7	3	—	.05	.18
Allergy	1	—	< 1	—	2	< 1	—	—	.72	.49
Cutaneous	4	1	< 1	—	5	1	< 1	—	.54	.99
Mucositis	11	5	< 1	< 1	8	2	1	—	.07	.99
Hair loss	16	11	6	—	11	3	1	—	< .0001	.006
CNS	5	1	—	1	2	—	—	< 1	.01	.62
PNS	10	1	1	—	9	2	—	—	.34	.12
Constipation	17	13	1	< 1	19	8	3	—	.55	.38
Hearing	2	3	2	—	2	—	—	—	.0004	.03
Cardiac	1	1	< 1	2	1	1	1	2	.87	.79
Fatigue	20	28	8	1	24	19	5	—	.004	.12

J Clin Oncol 21:3025-3034. © *2003*

Gemcitabine Plus Vinorelbine Compared With Cisplatin Plus Vinorelbine or Cisplatin Plus Gemcitabine for Advanced Non–Small-Cell Lung Cancer: A Phase III Trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group



Global QoL - EORTC C30 items 29 & 30

Come valuterebbe in generale la sua salute / qualità di vita nel corso dell'ultima settimana?

J Clin Oncol 21:3025-3034. © *2003*

Gemcitabine Plus Vinorelbine Compared With Cisplatin Plus Vinorelbine or Cisplatin Plus Gemcitabine for Advanced Non–Small-Cell Lung Cancer: A Phase III Trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group

Table 2. Quality-of-Life Analysis

	Cisplatin Based								Gemcitabine + Vinorelbine									
	Baseline		Improved		Stable		Worse		Baseline		Improved		Stable		Worse			
Domain and Item	Mean	SD	N	%	N	%	N	%	Mean	SD	N	%	N	%	N	%	P*	P†
Global QoL	54	23	73	38	48	25	71	37	54	21	70	39	42	23	68	38	.97	.96
Physical	77	18	45	23	60	31	87	45	75	22	50	27	59	32	77	41	.38	.56
Role	69	29	52	27	47	25	92	48	66	31	61	33	52	28	73	39	.09	.17
Emotional	68	22	85	44	45	23	62	32	63	22	89	49	50	27	44	24	.17	.28
Cognitive	86	20	49	26	66	34	77	40	86	18	53	28	65	35	68	37	.43	.66
Social	78	25	60	32	51	27	78	41	78	25	58	32	61	33	65	35	.49	.35
Pain	32	28	96	50	41	21	55	29	34	28	95	51	39	21	52	28	.85	.87
Appetite	22	26	51	27	43	22	98	51	22	27	51	28	69	37	65	35	.03	.01
Constipation	16	27	39	20	66	35	86	45	14	23	34	18	76	41	76	41	.70	.42
Financial	13	24	32	17	116	62	39	21	13	23	29	16	112	61	43	23	.54	.73
Fatigue	35	24	72	38	26	14	93	49	36	24	76	41	35	19	74	40	.19	.16
Vomiting	8	15	30	16	37	19	124	65	8	17	30	16	88	48	67	36	< .0001	< .0001
Sleeping	29	30	55	29	69	36	66	35	30	32	53	29	78	42	54	29	.50	.41
Diarrhea	4	14	16	8	137	72	37	19	5	14	19	10	142	76	25	13	.13	.24
Dyspnoea	29	20	71	37	69	36	52	27	26	22	50	27	66	36	68	37	.02	.16
Cough	40	24	85	45	73	38	33	17	37	25	68	38	61	34	52	29	.03	.13
Hemoptysis	6	16	22	11	157	82	13	7	9	18	32	18	134	74	16	9	.36	.68
Sore mouth	4	14	11	6	116	60	65	34	5	15	16	9	114	63	51	28	.15	.29
Swallowing	6	16	18	9	120	62	54	28	9	19	26	14	110	60	46	25	.24	.63
Neuropathy	7	17	25	13	103	54	64	33	8	18	27	15	107	58	49	27	.20	.30
Hair loss	2	8	5	3	95	50	91	48	2	13	4	2	117	64	63	34	.01	.01
Pain, chest	18	24	52	27	94	49	46	24	21	26	62	34	67	37	53	29	.78	.52
Pain, shoulder	26	30	61	32	85	45	44	23	26	28	66	36	68	37	49	27	.92	.69
Pain, elsewhere	24	30	61	33	72	39	54	29	22	29	52	29	78	43	50	28	.74	.76
Analgesic	61	49	50	26	112	59	29	15	55	50	29	16	128	71	24	13	.16	.75

J Clin Oncol 21:3025-3034. © *2003*

British Journal of Cancer (2004) 91, 1996 – 2004
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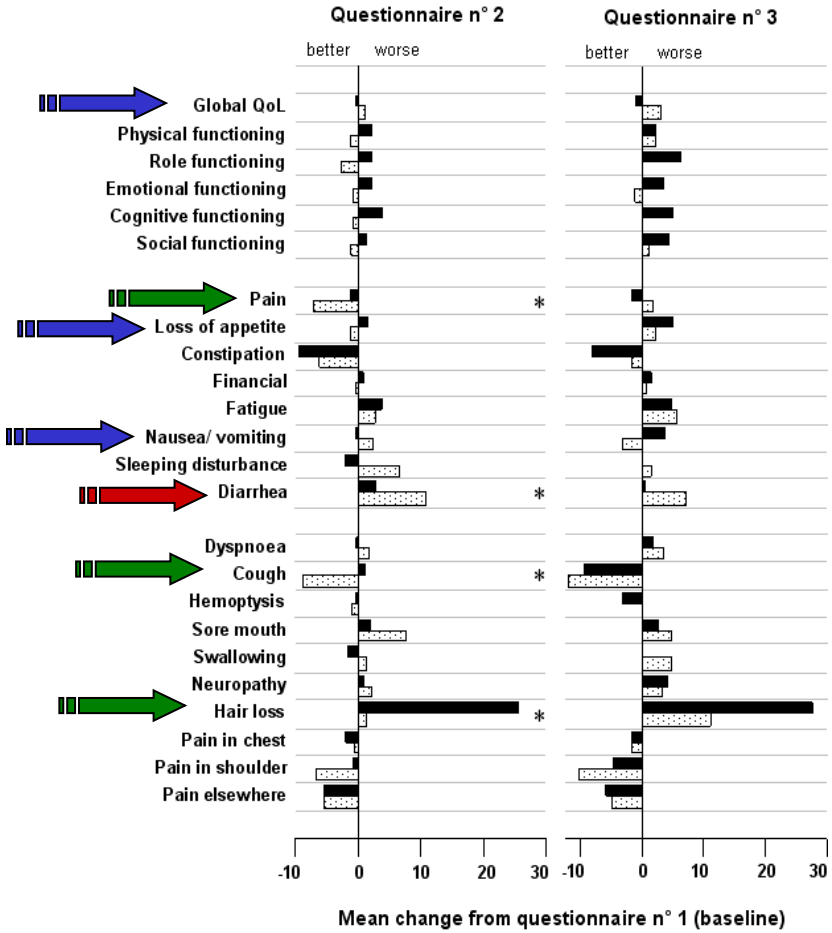
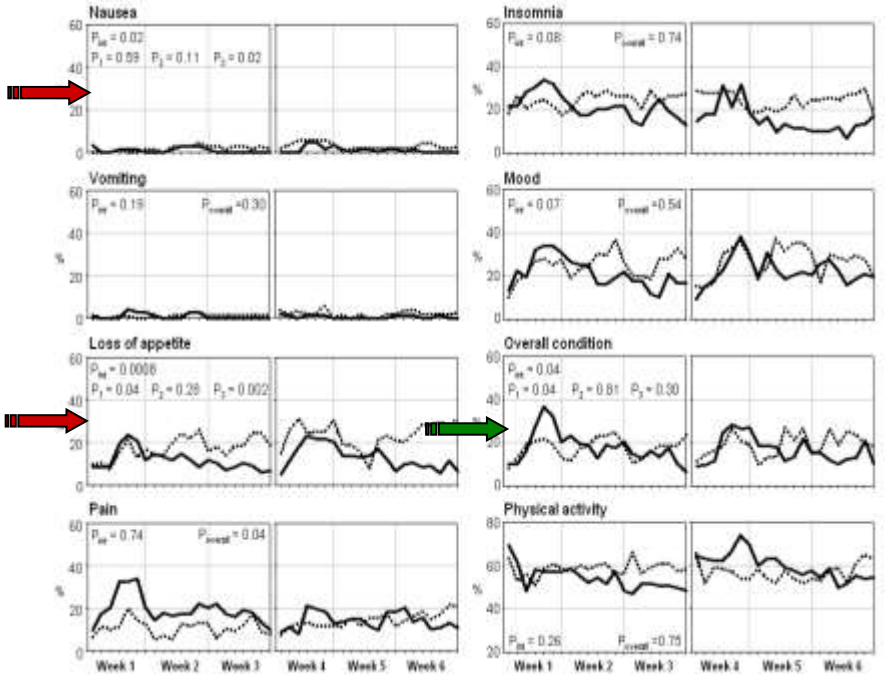
www.bjcancer.com

C Gridelli[6,*], C Gallo[2], M Di Maio[3], E Barletta[4], A Illiano[5], P Maione[1], S Salvagni[6], FV Piantedosi[7], G Palazzolo[8], O Caffo[9], A Ceribelli[10], A Falcone[11], P Mazzanti[12], L Brancaccio[5], MA Capuano[13], L Isa[14], S Barbera[15] and F Perrone[3] on behalf of the DISTAL (Docetaxel In Second-line Treatment of Advanced Lung cancer) Investigators

A randomised clinical trial of two docetaxel regimens (weekly *vs* 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study





Nuzzo et al. BMC Cancer 2011, 11:75
http://www.biomedcentral.com/1471-2407/11/75

BMC Cancer

RESEARCH ARTICLE Open Access

Effects on quality of life of weekly docetaxel-based chemotherapy in patients with locally advanced or metastatic breast cancer: results of a single-centre randomized phase 3 trial

Francesco Nuzzo[†1], Alessandro Morabito[†1], Adriano Gravina[1], Francesca Di Rella[1], Gabriella Landi[1], Carmen Pacilio[1], Vincenzo Labonia[1], Emanuela Rossi[1,3], Ermelinda De Maio[1,4], Maria Carmela Piccirillo[1], Giuseppe D'Aiuto[1], Renato Thomas[1], Massimo Rinaldo[1], Gerardo Botti[1], Maurizio Di Bonito[1], Massimo Di Maio[1], Ciro Gallo[2], Francesco Perrone[1*], Andrea de Matteis[1]

Table 3 EORTC quality of life scores by treatment arm

	Mean baseline score (SD)		Mean 6 weeks score (SD)		Mean difference (SD)		
	3-weekly N = 48	Weekly N = 41	3-weekly N = 48	Weekly N = 41	3-weekly	Weekly	P value*
Global QoL	62.8 (22.8)	64.0 (21.2)	67.9 (16.0)	60.0 (19.0)	5.0 (26.0)	-3.5 (20.5)	**0.03**
Functional scales							
Physical functioning	86.3 (16.6)	81.9 (19.6)	82.3 (16.8)	78.0 (18.0)	-4.0 (11.8)	-3.9 (14.3)	0.64
Role functioning	84.7 (22.2)	79.3 (26.0)	84.0 (21.2)	72.0 (23.4)	-0.7 (22.3)	-7.3 (24.7)	**0.02**
			.5 (19.1)	64.8 (24.4)	12.3 (21.6)	4.5 (18.5)	0.055
			13 (14.9)	83.7 (23.7)	1.4 (19.1)	-6.1 (18.5)	0.055
			12 (26.6)	69.5 (28.6)	-1.4 (32.8)	-11.0 (29.7)	0.07
			13 (19.1)	22.4 (19.9)	-8.3 (23.8)	-3.7 (19.9)	0.08
			13 (21.7)	14.6 (21.1)	2.1 (29.5)	0.8 (24.1)	0.86
			17 (23.9)	20.0 (28.0)	4.3 (26.6)	5.8 (31.9)	0.71
			13 (23.8)	35.0 (33.3)	-3.5 (22.0)	15.4 (37.3)	**0.0007**
			16 (19.0)	36.9 (20.6)	12.2 (16.0)	12.7 (26.1)	0.39
			14 (25.0)	19.5 (22.6)	12.2 (24.0)	12.2 (21.4)	0.87
			19 (26.8)	29.2 (32.2)	-5.7 (28.1)	-10.8 (28.6)	0.90
			0 (17.9)	12.2 (20.8)	3.5 (19.7)	9.4 (20.2)	0.31
			0 (16.5)	19.2 (21.2)	3.5 (15.7)	4.2 (25.2)	0.10

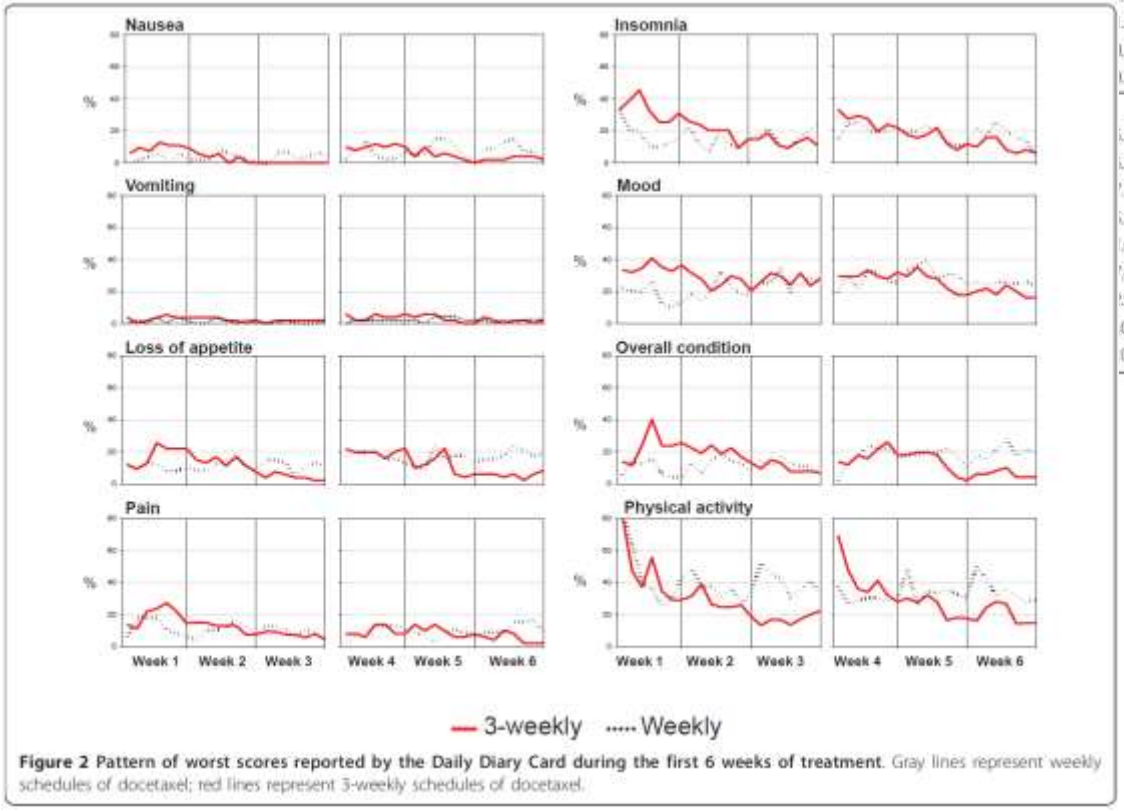
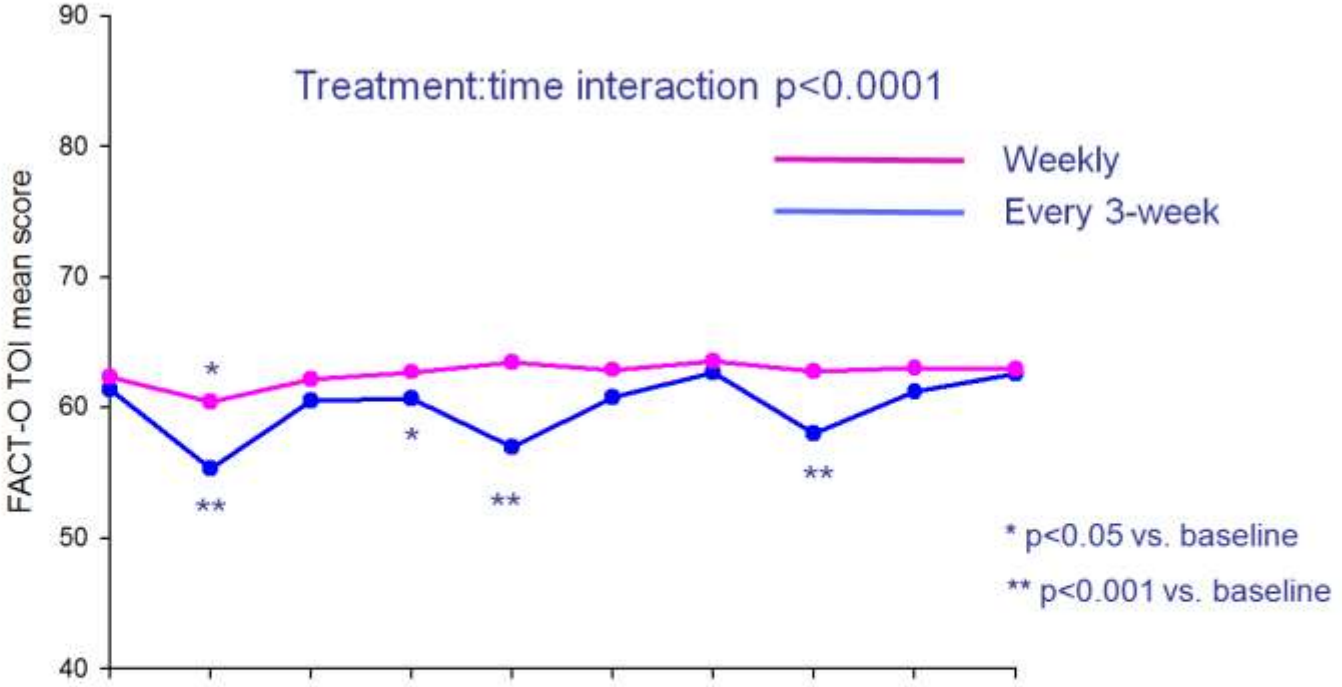


Figure 2 Pattern of worst scores reported by the Daily Diary Card during the first 6 weeks of treatment. Gray lines represent weekly schedules of docetaxel; red lines represent 3-weekly schedules of docetaxel.

QoL: FACT-O TOI, first 9 weeks



Week	0	1	2	3	4	5	6	7	8	9
Pts (weekly)	308	266	254	237	239	238	218	212	223	177
Pts (q3w)	301	229	208	250	209	195	221	193	177	169

In all scales, higher values represent better outcome.
All tests are adjusted by performance status, stage, residual disease after surgery, age category, and size of the institution

Quello che ho imparato dai “miei” studi

- Da ELVIS
  - I dati *missing* esistono (!), sono informativi e rappresentano un enorme problema metodologico in oncologia
- Da GEMVIN3
  - La relazione inversa tossicità/QdV non è scontata e comunque può non essere colta dagli indicatori complessivi ma solo dai singoli *items*
- Da DISTAL1 e BREAST10
  - La molteplicità (necessaria) di *items* e strumenti pone notevoli problemi di incosistenza e interpretazione
- Da MITO7
  - Alcuni effetti, pur importanti, possono essere transitori

Nel complesso…

- In un sistema del tutto “tranquillo” e non polemico…
  - Ricerca no profit, tutti farmaci già registrati, nessun interesse economico…

ho imparato che…

- Si può (e forse si deve) utilizzare la QdV come obiettivo degli studi clinici ma…
- …quanto più lo si fa più se ne comprende la difficoltà e le trappole

Scaletta

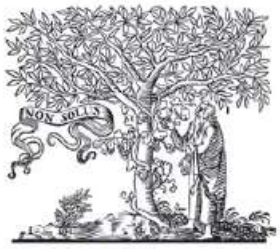
- Quello che ho imparato facendo gli studi sulla qualità di vita

- Quello che ho imparato studiando la selezione bibliografica

  (sulla quale mi sono “adagiato” e me ne scuso)

- Quello che ho pensato, alla luce di quello che ho imparato

VALUE IN HEALTH 15 (2012) 437–442



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Patient-Reported Outcomes

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010

Ari Gnanasakthy, MSc[1,], Margaret Mordin, MS[2], Marci Clark, PharmD[2], Carla DeMuro, MS[2], Sheri Fehnel, PhD[2], Catherine Copley-Merriman, MS[2]*

[1]*Novartis Pharmaceuticals Corporation, East Hannover, NJ, USA;* [2]*RTI Health Solutions, Durham, NC, USA*

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[1]Novartis

Table 1 – Number of products approved and number of PRO claims granted by reviewing divisions.

Reviewing division	Products reviewed	Number of products approved	Number of products that include a PRO claim
Anesthesia, Analgesia and Rheumatology Products	Chantix,* Arcalyst,* Nucynta,* Lusedra, Savella,* Uloric, Simponi,* Ilaris, Actemra,* Xiaflex	10	6
Antimicrobial Products	Durezol*	1	1
Anti-infective and Ophthalmology Products	Lucentis, Altabax, Doribax, Besivance, Vibativ, Bepreve,* Lastacaft,* Teflaro	8	2
Antiviral Products	Prezista, Tyzeka, Selzentry, Isentress, Intelence, PegIntron/Rebetol Combo Pack, acyclovir, hydrocortisone, Zidovudine	8	0
Biologic Oncology Products	Vectibix, Arzerra	2	0
Cardiovascular and Renal Products	Tekturna, Letairis,* Bystolic, Cleviprex, Samsca, Tyvaso, Effient, Multaq, Asclera,* Pradaxa	10	2
Dermatology and Dental Products	Veregen, Ulesfia, Stelara	3	0
Drug Oncology Products	Dacogen, Sprycel, Zolinza, Tykerb, Torisel, Ixempra Kit, Tasigna, Treanda, Firmagon, Mozobil, Afinitor, Folotyn, Votrient, Istodax, Jevtana, Halaven	16	0
Gastroenterology Products	Myozyme, Elaprase, Cimzia,* Relistor, Entereg, Vpriv, Carbaglu, Lumizyme	8	1
Medical Imaging and Hematology Products	Soliris,* Ammonia N 13, Mircera, Lexiscan, Eovist, Nplate, AdreView, Promacta, Ablavar	9	1
Metabolism and Endocrinology Products	Januvia, Somatuline Depot, Kuvan, Onglyza, Livalo, Victoza, Egrifta*	7	1
Neurology Products	Azilect,* Neupro, Xenazine, Vimpat,* Banzel,* Dysport,* Extavia, Sabril 500-mg tablet,* Ampyra,* Xeomin,* Gilenya	11	7
Nonprescription Clinical Evaluation Products	Anthelios SX, Cetirizine Hydrochloride Allergy,* Cetirizine Hydrochloride Hives Relief*	3	2
Psychiatry Products	Invega , Vyvanse,* Pristiq, Fanapt, Invega Sustenna, Saphris, Latuda	7	1
Pulmonary and Allergy Products	Omnaris,* Kalbitor,* Krystexxa	3	2
Reproductive and Urologic Products	Toviaz,* Rapaflo,* Natazia, Ella, Prolia	5	2
Special Pathogen and Transplant Products	Eraxis, Noxafil, Pylera, Coartem, Zortress	5	0
Total		116	28

PRO, patient-reported outcome.
* Products with PRO claims in the label.

Oncology **16** **0**

ASCO guide-lines

Treatment activity **against** the disease	Tretment benefit **for** the patient
❖ Tumor response ❖ Response duration ❖ Time to progression	❖ Overall survival ❖ **Quality of life** ❖ Toxicity

ASCO guide-lines J Clin Oncol 1996; 14: 671-679

VALUE IN HEALTH 15 (2012) 437–442

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Patient-Reported Outcomes

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010

Ari Gnanasakthy, MSc[1,], Margaret Mordin, MS[2], Marci Clark, PharmD[2], Carla DeMuro, MS[2], Sheri Fehnel, PhD[2], Catherine Copley-Merriman, MS[2]*

[1]*Novartis Pharmaceuticals Corporation, East Hannover, NJ, USA;* [2]*RTI Health Solutions, Durham, NC, USA*

Acknowledgments

We gratefully acknowledge the research assistance of Emily Evans in the development of this article. We also gratefully acknowledge Lynda Doward for her review of the article.

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In realtà…

- Salvo miei errori, 6 su 10 degli articoli selezionati hanno come autore/coautore un dipendente di azienda farmaceutica
- Oltre a GSK*, Novartis, AZ, Genentech, Pfizer… non esattamente piccole *biotech*

  – *Arpinelli&Bamfi, un commento alla guidance FDA, eccellente e assolutamente onesto e trasparente, anzi lo userò alla fine…

EXPERT REVIEWS

A point of minimal important difference (MID): a critique of terminology and methods

Expert Rev. Pharmacoeconomics Outcomes Res. 11(2), 171–184 (2011)

Madeleine T King

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Journal of Clinical Epidemiology 61 (2008) 102–109

Journal of Clinical Epidemiology

REVIEW ARTICLES

Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes

Dennis Revicki[a,*], Ron D. Hays[b], David Cella[c], Jeff Sloan[d]

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[b]*Division of General Internal Medicine and Health Services Research, University of California Los Angeles and RAND Corporation, Health Sciences Program, Los Angeles, CA, USA*
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Accepted 31 March 2007

What is new?

- Recommend that the minimal important difference (MID) be based primarily on appropriate patient-based and clinical anchors that are correlated at ≥ 0.30 with the patient-reported outcome (PRO), with clinical trial experience used to further inform understanding of MID.
- MID may vary by population and context, and thus a single MID may be insufficient for all study applications involving a PRO instrument.
- Estimation of MID for a specific PRO measure should be based on multiple approaches and triangulation of methods.
- Various methods for estimating MIDs often converge, and generalizability of MID estimates for similar applications is supported.
- Recommend basing the final selection of MID values on systematic review and evaluation process such as a modified Delphi method.

DRAFT

Defining Clinically Meaningful Outcomes: ASCO Recommendations to Raise the Bar for Clinical Trials

Lee M. Ellis, David Bernstein, Emile Voest, Jordan Berlin, Daniel Sargent, Patricia Cortazar, Elizabeth Garrett-Mayer, Roy Herbst, Rogerio Lillenbaum, Camelia Sima, Alan Venook, Mithat Gonen, Lowell Schnipper

and the ASCO Clinically Meaningful Outcomes Working Groups

Table 1: Summary of recommended targets for meaningful clinical trial goals.

Cancer Type	Patient Population	Current Baseline Median OS	Improvement Over Current OS That Would be Clinically Meaningful	Target Hazard Ratios	1 Yr Survival Rate (Current/ Target)
Pancreatic Cancer	FOLFIRONOX Eligible Patients	10 – 11 months	4-5 months	0.67 – 0.69	48% / 56%
Pancreatic Cancer	Gemcitabine Eligible Patients	6 - 8 months	3-4 months	0.6 – 0.679	21% / 24%
Lung Cancer	Non-squamous cell carcinoma	13 months	3.25-4 months	0.76-0.8	53% / 61%
Lung Cancer	Squamous cell carcinoma	10 months	2.5-3 months	0.77-0.8	44% / 53%
Breast Cancer	Metastatic triple negative, previously untreated for metastatic disease	18 months	4.5-6 months	0.75-0.8	63% / 69%
Colon Cancer	disease progression on all prior therapies (or not a candidate for standard 2nd or 3rd line options)	4-6 months	3-5 months	0.44 – 0.67*	N/A

*Hazard ratios represent a 5 month improvement on a baseline of 4 month median OS and a 3 month improvement on a baseline of 6 month median OS

DRAFT

Quello che ho imparato dalla rassegna della letteratura

- Il ruolo dei PROs in oncologia è ancora complementare
  - Nessun PROs “approvato” FDA
- L’interesse delle aziende farmaceutiche è crescente e va in parallelo con l’attenzione delle agenzie regolatorie
  - Parallelo… forse qualcuno tira e l’altro insegue… ma chi?
- La *querelle* metodologica si gioca a livelli molto alti
  - Ma è prevalentemente concentrata sul valore dell’*outcome* (intenso dibattito su “*minimally important differences*”) piuttosto che sulla sua attendibilità e opportunità

Poi mi sono ricordato di vari lavori recenti…

Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study

*Karim Fizazi, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, Fred Saad, Paul Mainwaring, Stephen Harland, Oscar B Goodman Jr, Cora N Sternberg, Jin Hui Li, Thian Kheoh, Christopher M Haqq, Johann S de Bono, for the COU-AA-301 Investigators**

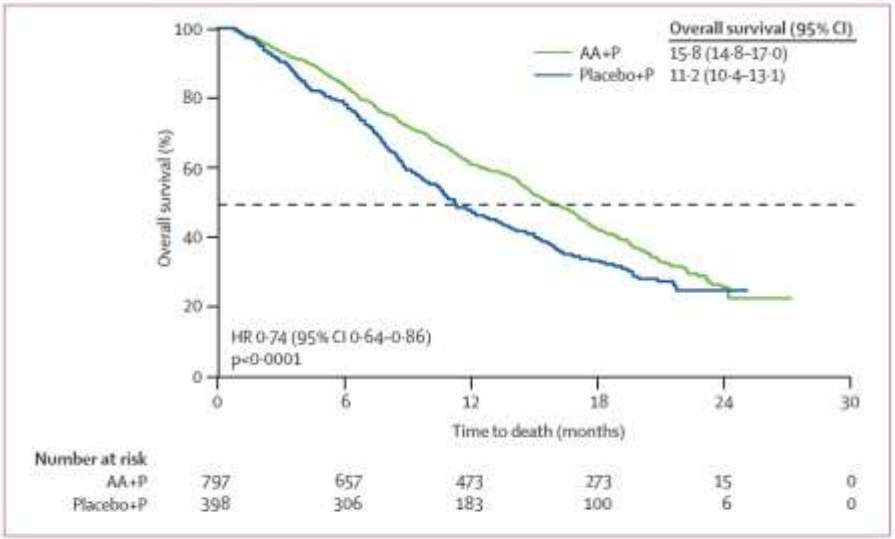

Figure 2: **Overall survival**
HR=hazard ratio. AA=abiraterone acetate. P=prednisone.

Lancet Oncol 2012; 13: 983–92

Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial

Ethan Bi … thkopf, Matthev …

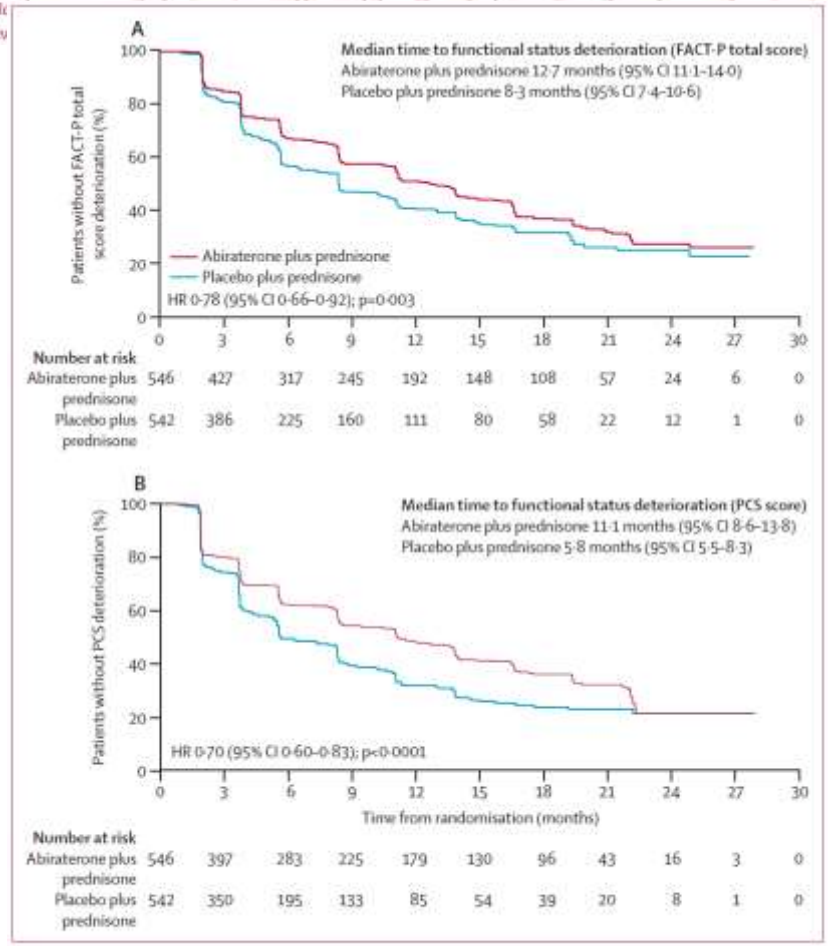

Figure 2: **Kaplan-Meier curve for time to deterioration of (A) FACT-P total score and (B) score on prostate-cancer-specific subscale**
FACT-P=Functional Assessment of Cancer Therapy—Prostate. HR=hazard ratio.

Published Online
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Disegno degli studi clinici
Quali endpoint?

Francesco Perrone

Il Pensiero Scientifico Editore

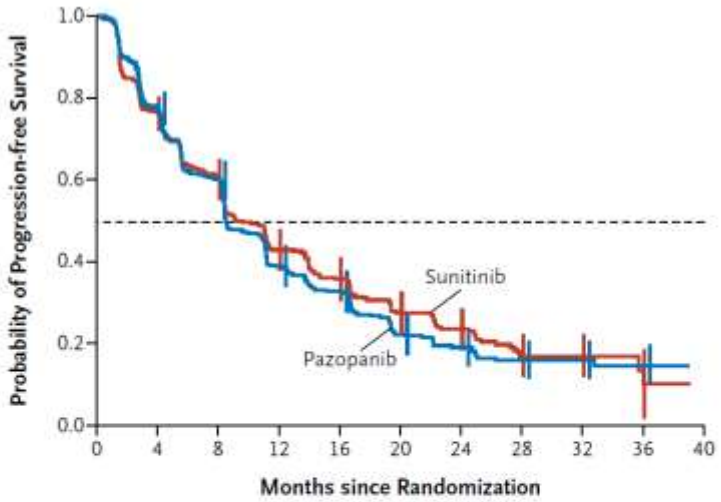
Agli occhi dei pazienti, nelle parole dei medici
L'importanza della qualità di vita, un'ovvietà?

Inoltre, è chiaro che l'effetto sulla qualità della vita dovrebbe o potrebbe risultare cruciale nel caso (molto frequente) di farmaci che non producano modificazioni sostanziali della sopravvivenza.[8] Al contrario, è molto (troppo) raro che le pubblicazioni scientifiche e i foglietti illustrativi contengano informazioni sugli effetti che i nuovi farmaci producono sulla qualità di vita dei pazienti.[9]

Il valore degli effetti sulla qualità della vita di un nuovo farmaco alla luce del suo effetto sulla sopravvivenza.

Sopravvivenza	Qualità della vita		
	Migliore	Simile	Peggiore
Più lunga	Irrilevante		Rilevante
Non modificata	**Cruciale**		
Più breve	Irrilevante		

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma



No. at Risk

Pazopanib	557	361	245	136	105	61	46	19	13	1
Sunitinib	553	351	249	147	111	69	48	18	10	3

Figure 1. Kaplan–Meier Estimates of Progression-free Survival According to Independent Review.

The median progression-free survival was 8.4 months with pazopanib (95% CI, 8.3 to 10.9) and 9.5 months with sunitinib (95% CI, 8.3 to 11.1). The dotted line represents the median (0.5), and vertical lines represent 95% confidence intervals.

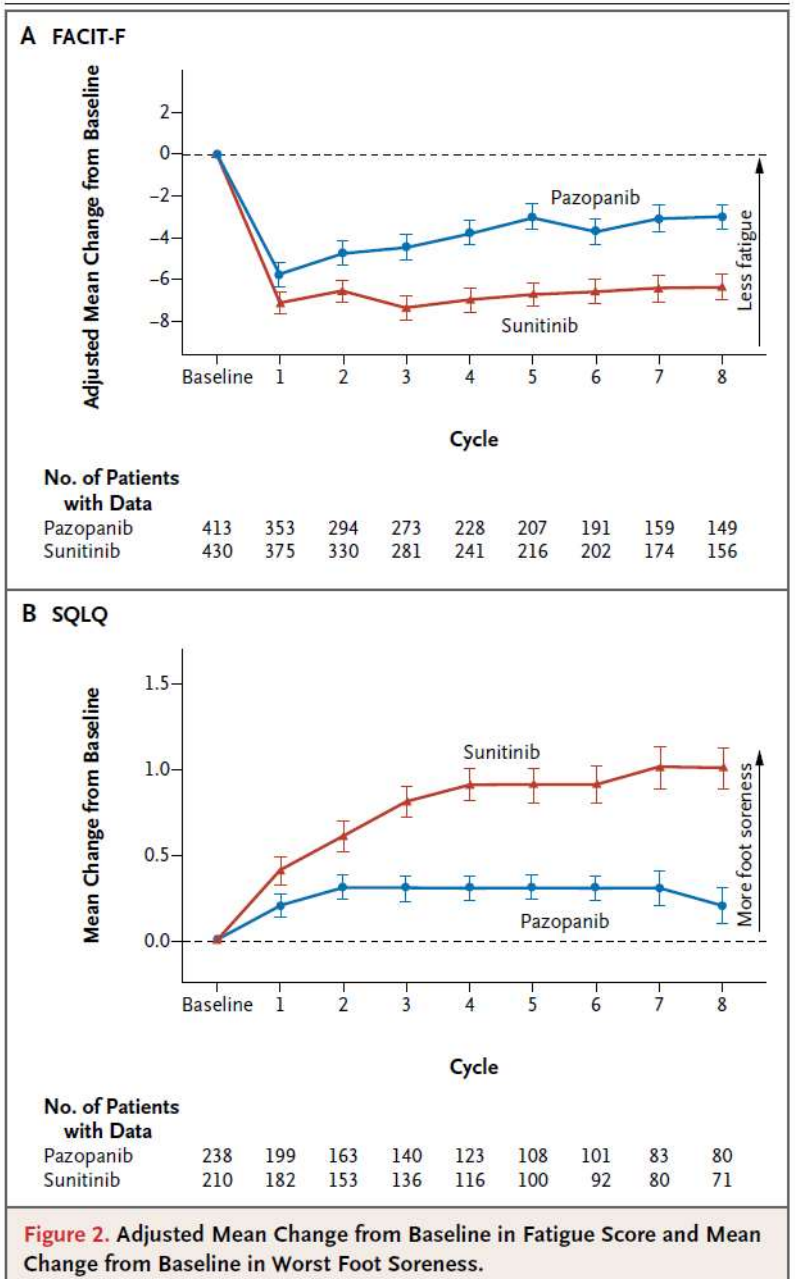


Figure 2. Adjusted Mean Change from Baseline in Fatigue Score and Mean Change from Baseline in Worst Foot Soreness.

N Engl J Med 2013;369:722-31.

Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial

Gustavo Ismael, Roberto Hegg, Susanne Muehlbauer, Dominik Heinzmann, Bert Lum, Sung-Bae Kim, Tadeusz Pienkowski, Mikhail Lichinitser, Vladimir Semiglazov, Bohuslav Melichar, Christian Jackisch

Funding F Hoffmann-La Roche.

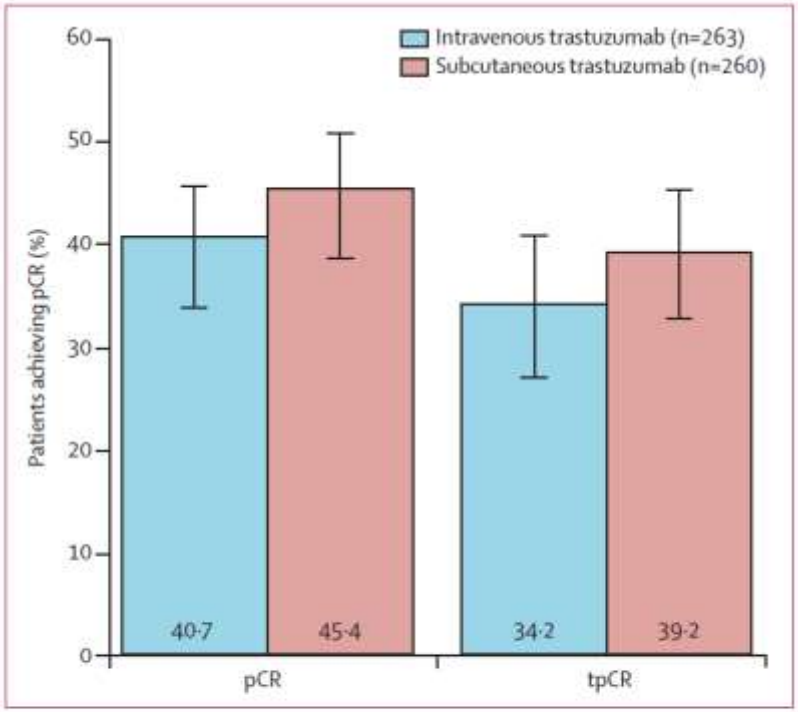


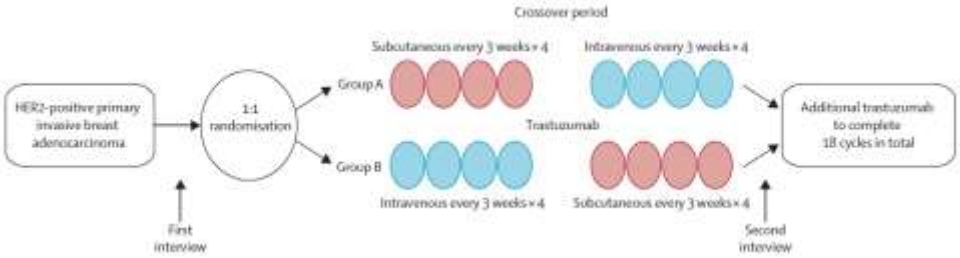
Figure 3: **Proportion of patients who achieved a pathological complete response**
Responses assessed in the efficacy per-protocol population. pCR=pathological complete response (defined as the absence of invasive neoplastic cells in the breast). tpCR=total pathological complete response (defined as the absence of invasive neoplastic cells in the breast and lymph nodes).

Lancet Oncol 2012; 13: 869–78

Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study

Xavier Pivot, Joseph Gligorov, Volkmar Müller, Peter Barrett-Lee, Sunil Verma, Ann Knoop, Giuseppe Curigliano, Vladimir Semiglazov, Guillermo López-Vivanco, Valerie Jenkins, Nana Scotto, Stuart Osborne, Lesley Fallowfield, for the PrefHer Study Group

Funding F Hoffmann-La Roche.



	n*
Subcutaneous preferred, n=216	
Time saving	195
Less pain/discomfort	88
Convenience to patient	35
Ease of administration	33
Problems with intravenous	25
Less stress/anxiety	15
Other	6
Intravenous preferred, n=16	
Fewer reactions (less pain, bruising, irritation, etc)	11
Other	5
Environment/staff	2
Perceived efficacy	1
Ecological considerations	1

Lancet Oncol 2013; 14: 962–70

Scaletta

- Quello che ho imparato facendo gli studi sulla qualità di vita
- Quello che ho imparato studiando la selezione bibliografica

  (sulla quale mi sono “adagiato” e me ne scuso)
- Quello che ho pensato, alla luce di quello che ho imparato


DALLA
ALLA
DALLA PADELLA ALLA BRACE

La padella

- Attenzione complessivamente ancora troppo scarsa a QdV e PROs in oncologia
- Prevalentemente in contesti non regolatori
- Notevoli difficoltà intrinseche alla materia e agli strumenti di studio
- Risultati non facili da interpretare
- Un enorme *grano salis* necessario per trasformare opportunamente i risultati in una migliore pratica clinica e una più onesta e completa informazione dei pazienti

La brace

- PROs come nuovo campo di battaglia dove si affrontano
  - Le aziende farmaceutiche tra di loro
  - Le aziende farmaceutiche contro gli enti pagatori
- Con la complicità delle agenzie regolatorie
- La chimera della precisione e della affidabilità in una materia che per definizione non lo è
- Un enorme rischio di strumentalizzazione
- Un possibile tradimento di premesse umane ed etiche assolutamente rilevanti

Health and Quality of Life Outcomes

BioMed Central

Commentary

Open Access

The FDA guidance for industry on PROs: the point of view of a pharmaceutical company

Fabio Arpinelli* and Francesco Bamfi

In our paper we aim to report some considerations on this Guidance. Our comments focus especially on the characteristics of instruments to use, the Minimal Important Difference, and the methods to calculate it. Furthermore, we present the advantages and opportunities of using the Patient-Reported Outcomes in drug development, as seen by a pharmaceutical company. The Patient-Reported Outcomes can provide additional data to make a drug more competitive than others of the same pharmacological class, and a well demonstrated positive impact on the patient' health status and daily life might allow a higher price and/or the inclusion in a reimbursement list. Applying extensively the FDA Guidance in the next trials could lead to a wider culture of subjective measurement, and to a greater consideration for the patient's opinions on his/her care. Moreover, prescribing doctors and payers could benefit from subjective information to better define the value of drugs.

Mi fermo qui

Con la speranza di aver fornito spunti e provocazioni che siano utili per la discussione