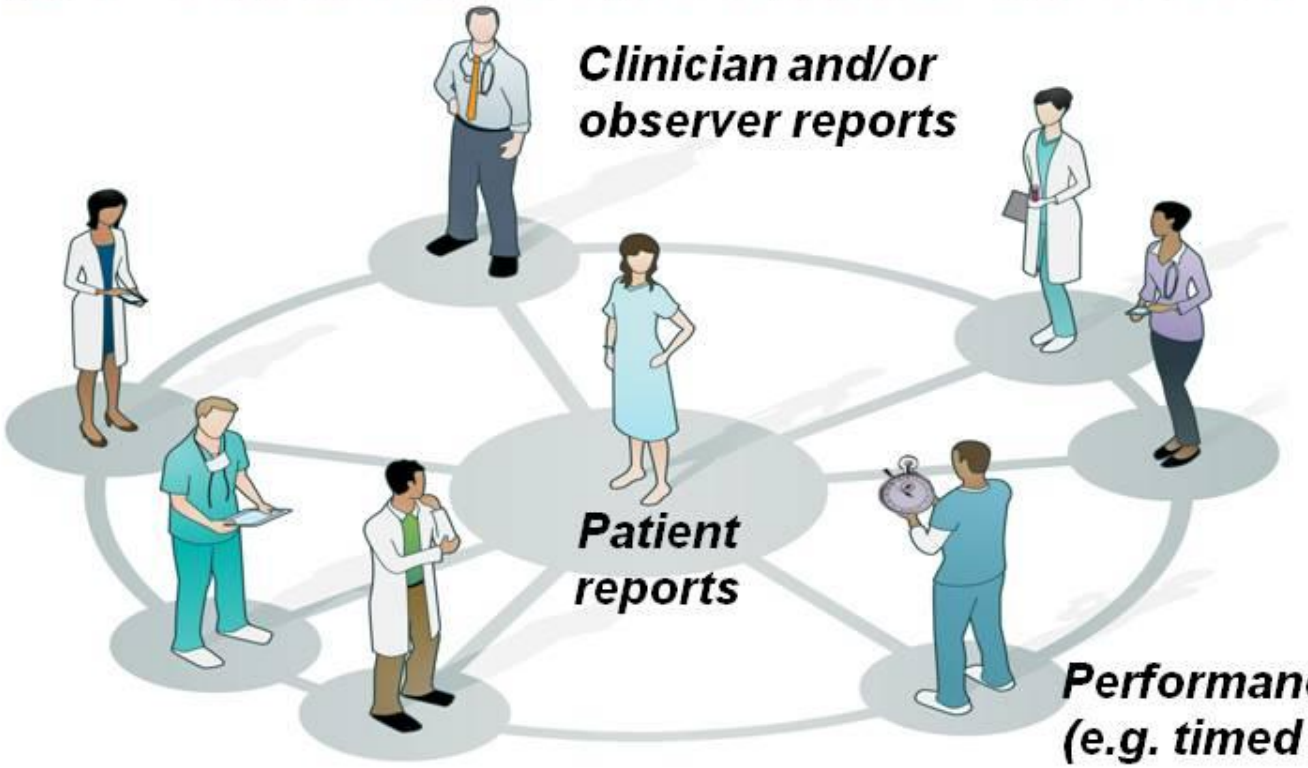
Il ruolo attivo del paziente nella valutazione delle tossicità:

I PRO (patient reported outcomes)

Alessia Levaggi

Verona, 18 settembre 2015

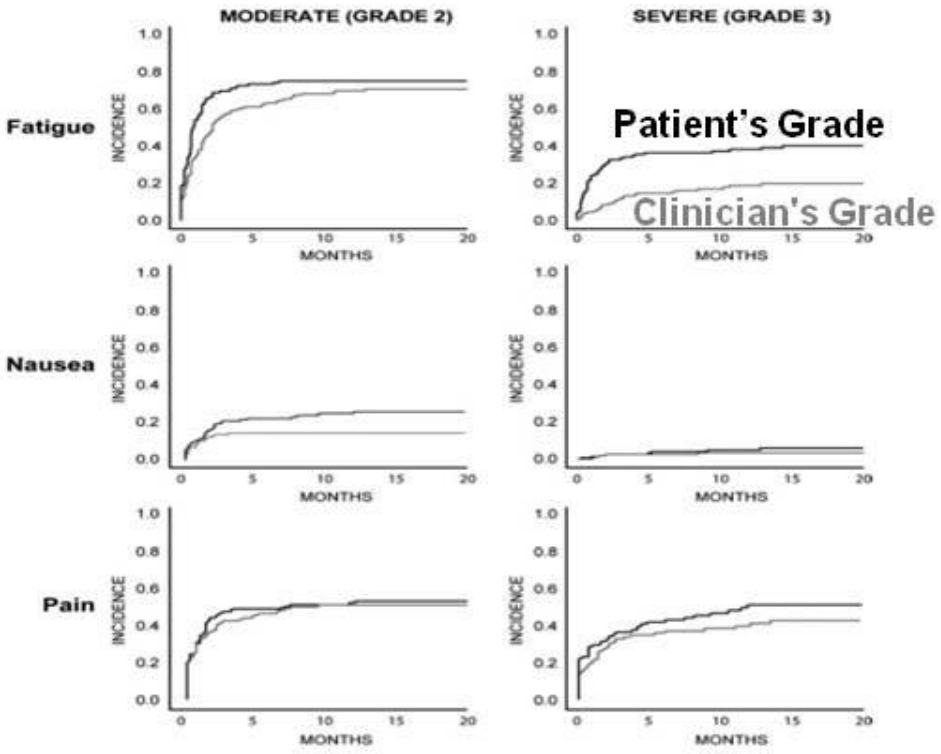
How are clinical outcomes assessed?



Presented by: @scientre

Patient vs. Clinician Reporting of Symptoms

Patient reporting of CTCAE symptoms was more strongly associated with measures of daily health status than clinicians

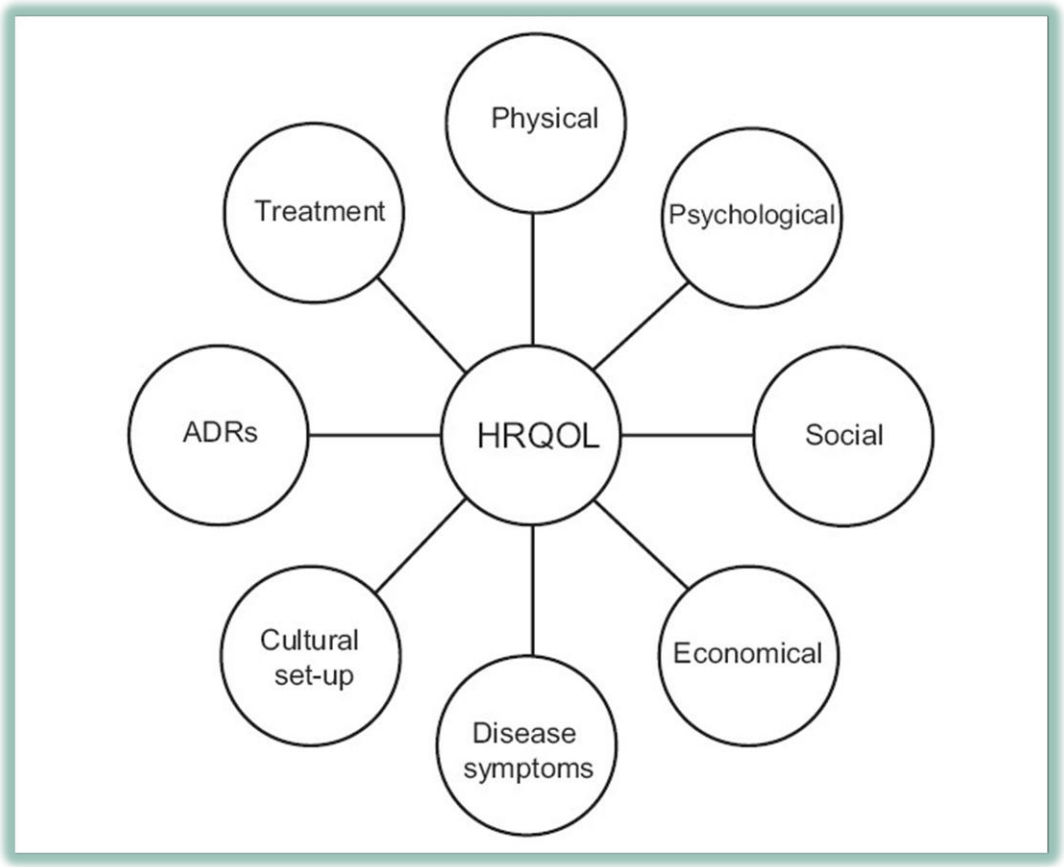


JNCI, 2009, 101, 1624-1632

Patient-reported Outcomes

- A PRO includes any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s). Patient reported outcome is an umbrella term covering both single dimension and multidimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, etc.

HRQL-
Health-related quality of life



- specific type of PRO and is a broad concept which can be defined as the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well being. The notion of multidimensionality is a key component of the definition of HRQL.

PROs vs CTC(AE)

Table 1. Complementary Use of Common Terminology Criteria for Adverse Events (CTC[AE]) and Patient-Reported Outcomes (PROs) in Clinical Trials

	CTC(AE)	PROs
Primary use	Toxic effects reporting	Health status reporting
Most useful for	Objective assessment (e.g., diagnostic test, imaging, overt sign, such as bleeding)	Subjective assessment (e.g., cannot be seen, felt, heard, observed, or clinically tested by physician)
Best captures	Severity, need for physician intervention	Severity, function, effect on quality of life and treatment adherence
Valid	Not tested	Yes[a]
Reliable	No	Yes[a]
Data capture method	Through layers of interpretation	Directly from the patient
Time of data capture	As it occurs/as physician picks it up	At designated time points

[a] Legacy instruments psychometrically tested to varying degrees; for current U.S. Food and Drug Administration use, must conform to stringent guidelines

Bruner et al. ASCO 2012

PRO Instruments

Table 1 Examples of Frequently Used PRO Instruments in Oncology

Type of tool	PRO instrument
Health-related quality of life	
Generic	• EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) • FACT-G (Functional Assessment of Cancer Therapy-General) • SF-36 (Short Form 36-Item) • PROMIS (Patient-Reported Outcomes Measurement Information System)
Cancer-specific	• FLIC (Functional Living Index-Cancer) • EORTC QLQ-BN20 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 and Brain) • EORTC QLQ-BR23 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast) • EORTC QLQ-LC13 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung) • FACT-L (Functional Assessment of Cancer Therapy-Lung) • FACT-B (Functional Assessment of Cancer Therapy-Breast)
Symptoms and symptom burden	
Generic	• Visual analog scale • Symptom Distress Scale • Memorial Pain Assessment Card • Rotterdam Symptom Checklist
Cancer-specific	• LCSS (Lung Cancer Symptom Scale) • MDASI (Monroe Dunaway Anderson Symptom Assessment Inventory)

PRO indicates patient-reported outcome.

How can PROs be used?

- Improved patient care
- Receiving FDA approval of drugs

How are oncologists using PROs in clinical practice?

Table 4. Summary of impact of PROMs on patient and clinical practice outcomes

PROMs	Patient outcomes				Clinical practice outcomes			
	Patient satisfaction	Perceived quality of care	Patient health outcomes	Acceptability	Patient–clinician communication	Clinical decision making	Symptom monitoring	Length of clinical encounter
FLIC	=[48]		=[48]					
PSQ-III	=[48]		=[48]					
Brief POMS -17	=[48]		=[48]					
SCNS-SHORT		+[39]	=[39]	+[39]				
HADS		+[39]	=[39]	+[39]	+[46]			
EORTC QLQ-C30			=[40, 51]	+[40]	+[46, 47, 51]	+[51]	+[50]	
ESAS		+[59]		+[59]		+[43]		
PROMIS-Short Forms		+[22]				+[22]	+[22]	
EPIC		+[22]				+[22]	+[22]	
EORTC QLQ-BR23		+[22]				+[22]	+[22]	
PRO-CTCAE		±[21]				+[21]	+[21]	
EQ-5D		±[21]				+[21]	+[21, 58]	
ECS-CP						+[59]	+[59]	
PedsQL	=[55]				+[55, 60]		+[55]	
TAPQOL	=[55]				+[55, 60]		+[55]	
MSQ					+[65]		+[65]	
UW-QOL							+[57]	
EORTC QLQ-BN20							+[50]	
FACT-G			+/[20, 48]				+[20]	
EORTC QLQ-LC13			+[51]		+[51]	+[51]		
ESRA-C						+[54]		
DT						+[61]		
SDI						+[52]		

+, signifies a positive finding; =, signifies no statistically significant findings; ±, signifies mixed results.

Howell D, Ann Oncol 2015

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REVIEW ARTICLE

The Prognostic Significance of Patient-Reported Outcomes in Cancer Clinical Trials

Carolyn C. Gotay, Crissy T. Kawamoto, Andrew Bottomley, and Fabio Efficace

From the Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI; Quality of Life Unit, European Organization for Research and Treatment of Cancer, Brussels, Belgium; and Health Outcome Research Unit, Italian Group for Adult Hematologic Diseases (GIMEMA) Data Center, Rome, Italy.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose

Patient-reported outcomes (PROs), routinely collected as a part of cancer clinical trials, have been linked with survival in numerous clinical studies, but a comprehensive critical review has not been reported. This study systematically assessed the impact of PROs on patient survival after a cancer diagnosis within the context of clinical trials.

Design

Cancer clinical trials that assessed baseline PROs and mortality were identified through MEDLINE (through December 2006) supplemented by the Cochrane database, American Society of Clinical Oncology/European Society for Medical Oncology abstracts and hand searches. Inclusion criteria were publication in English language and use of multivariate analyses of PROs that controlled for one or more clinical factors. Two raters reviewed each study, abstracted data, and assessed study quality; two additional raters verified abstractions.

Results

In 36 of 39 studies (N = 13,874), at least one PRO was significantly associated with survival ($P < .05$) in multivariate analysis, with varying effect sizes. Studies of lung (n = 12) and breast cancer (n = 8) were most prevalent. The most commonly assessed PRO was quality of life, measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 in 56% of studies. Clinical variables adjusted for included performance status (PS), treatment arm, stage, weight loss, and serum markers. Results indicated that PROs provide distinct

Reasons to include PROs in clinical trial

- Understand how a novel treatment impacts on patient functioning
- Add information on the positive and negative effects of a therapy by complementing efficacy and safety data e.g. help assess the relationship between efficacy/ clinical endpoints (OS, PFS, disease stabilization) and HRQL
- Identify treatment related symptoms that need additional management and supportive care
- Attempt to differentiate two treatments with similar efficacy (late palliative line, maintenance therapy)

Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials

Jürg Bernhard, Weixiu Luo, Karin Ribi, Marco Colleoni, Harold J Burstein, Carlo Tondini, Graziella Pinotti, Simon Spazzapan, Thomas Ruhstaller, Fabio Puglisi, Lorenzo Pavesi, Vani Parmar, Meredith M Regan, Olivia Pagani, Gini F Fleming, Prudence A Francis, Karen N Price, Alan S Coates, Richard D Gelber, Aron Goldhirsch, Barbara A Walley

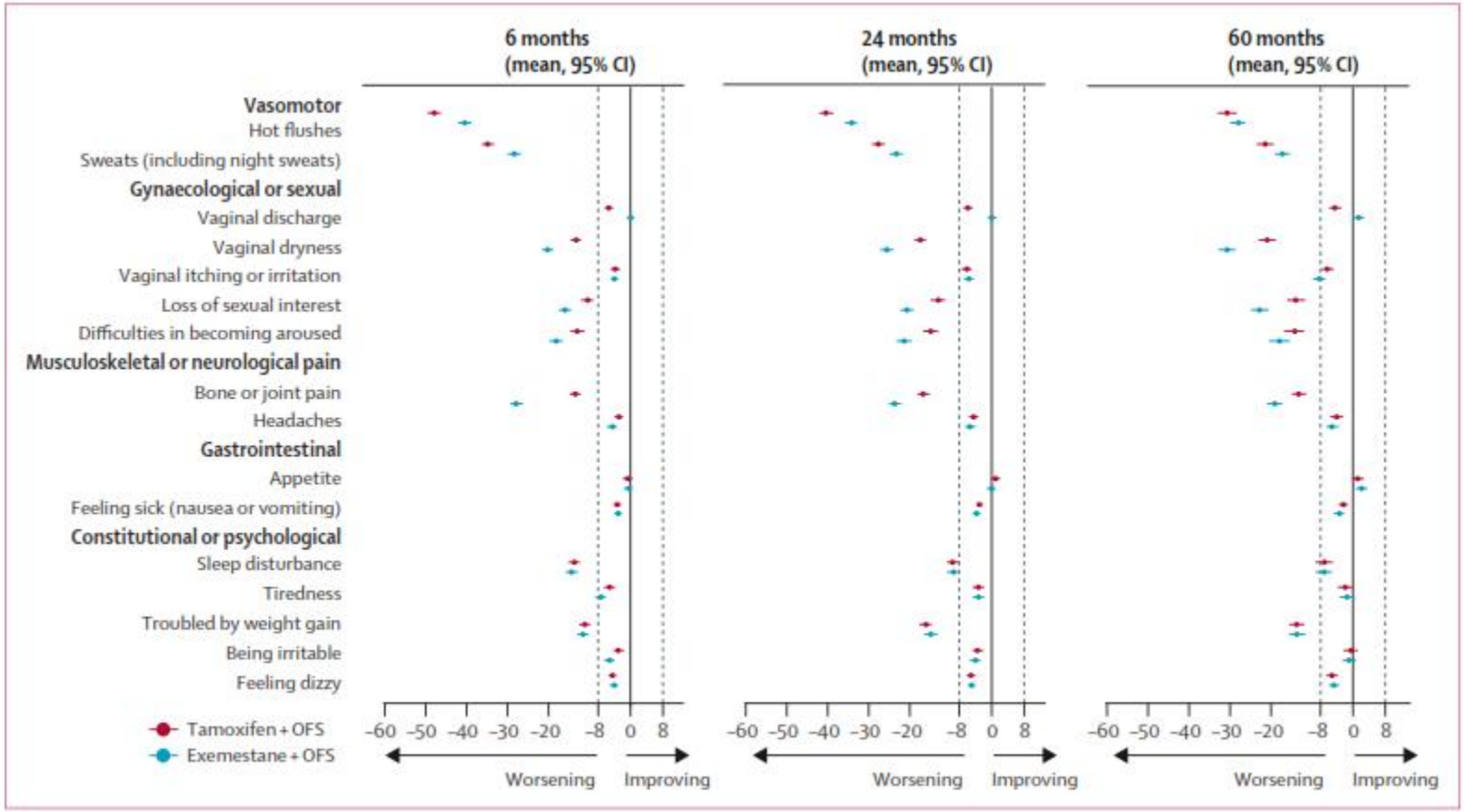


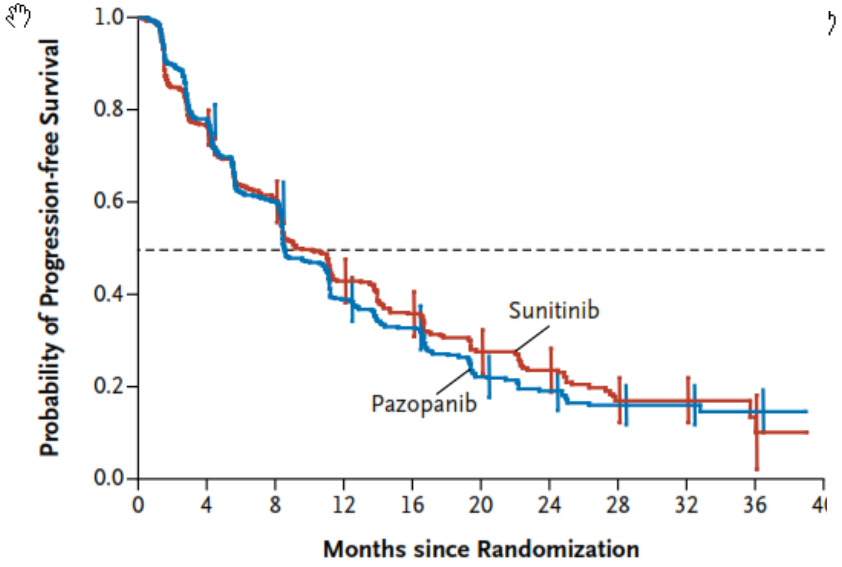
Figure 3: **Change in QoL symptom indicator scores from baseline to 6 months, 24 months, and 60 months for overall TEXT and SOFT population according to treatment assignment**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

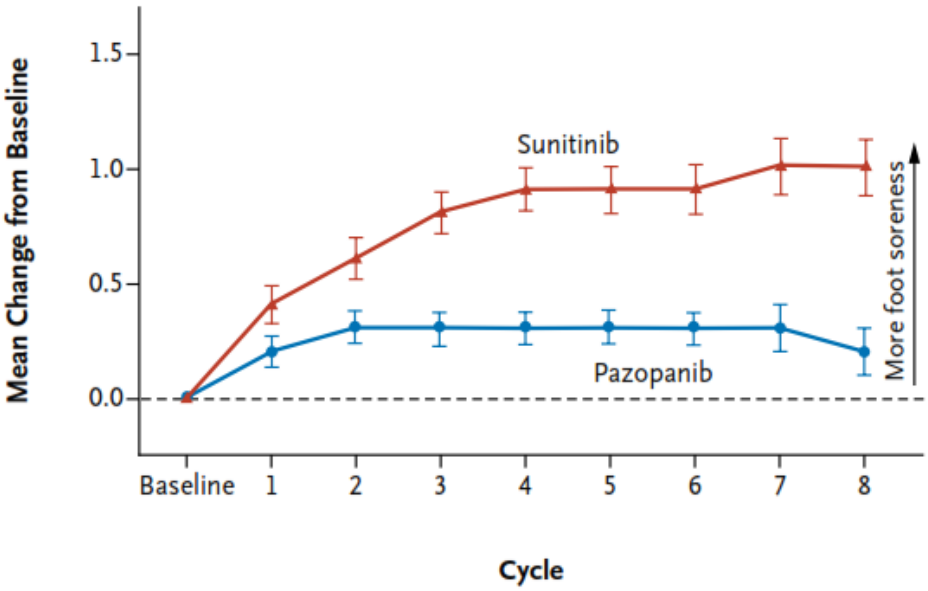
Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D.,



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

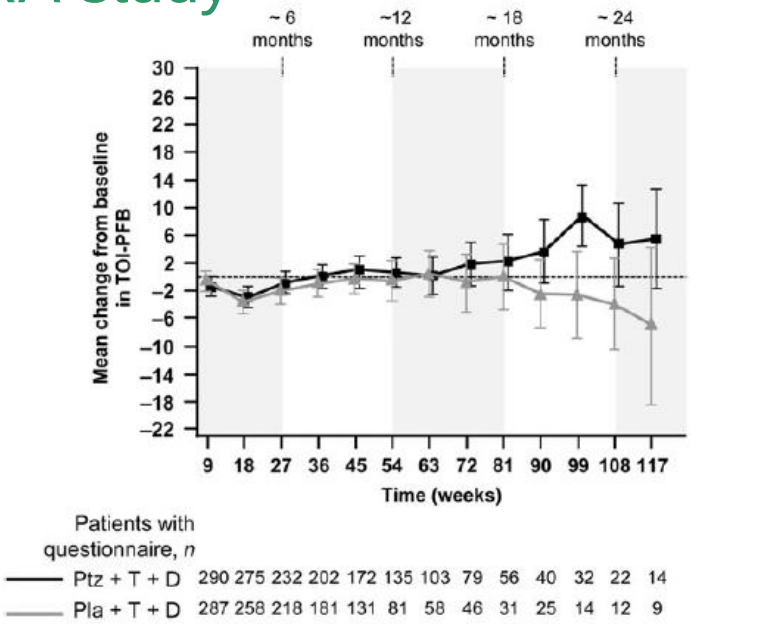


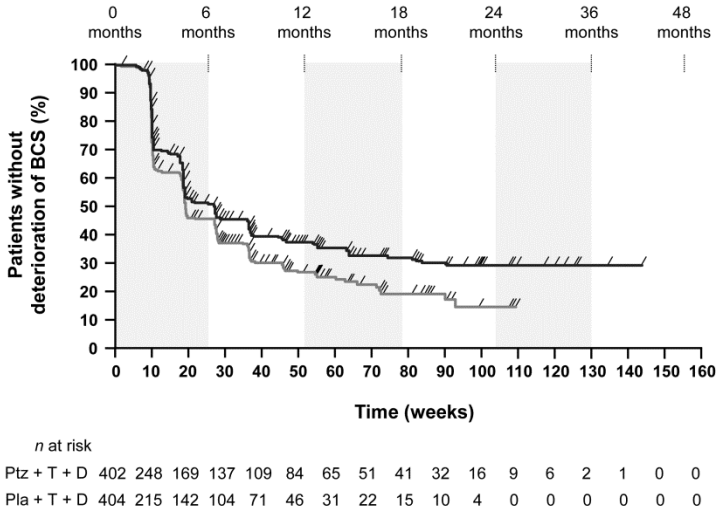
HER2+ MBC. QoL in «dual HER2 targeted therapy». CLEOPATRA study

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Placebo plus Trastuzumab plus Docetaxel (N=397)	Pertuzumab plus Trastuzumab plus Docetaxel (N=407)
	number (percent)	
Most common events, all grades†		
Diarrhea	184 (46.3)	272 (66.8)
Alopecia	240 (60.5)	248 (60.9)
Neutropenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	96 (24.2)	137 (33.7)
Decreased appetite	105 (26.4)	119 (29.2)
Mucosal inflammation	79 (19.9)	113 (27.8)
Asthenia	120 (30.2)	106 (26.0)
Peripheral edema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropenia	30 (7.6)	56 (13.8)
Dry skin	17 (4.3)	43 (10.6)

N Engl J Med 2012;366:109-19.





Annals of Oncology 24: 2630–2635, 2013

Can PROs be used in oncology drug development?

Case study: Hormone refractory prostate cancer (HRPC)

- 1996: Supplemental approval of mitoxantrone for pain relief
- 2006: Draft FDA guidance on PROs to support labels
- 2007: FDA guidance on oncology trial endpoints includes PROs
- 2009: Final FDA guidance on PROs to support label
- 2010-2013: FDA approves abiraterone, cabizataxel, enzalutamide, radium Ra 223 dichloride, and sipuleucel-T
  - Registration trials all included PROs
  - Only enzalutamide and abiraterone granted pain symptom claims

Health Qual Life Outcomes. 2014;12:104.

FDA rationales for using PRO measures in medical product development:

- (1) some treatment effects (eg, pain intensity and pain relief) are known only to the patient;
- (2) patients provide a unique perspective on treatment effectiveness (since “improvements in clinical measures of a condition may not necessarily correspond to improvements in how the patient feels or functions”);
- (3) formal assessment by patients may be more reliable than informal interviews with providers or other sources of information about the patient’s condition

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]*

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

Prostate cancer: PRO label claims

Table 1 PRO label claims achieved in the US compared to the EU

Product (brand name/generic name)	US approval year	US product label claim(s)	EU approval year	EU SmPC claim(s)
Xtandi/enzalutamide	2012	Yes	2013	Yes
Zytiga/abiraterone	2011	Yes	2011	Yes
Jevtana/cabazitaxel	2010	No	2011	Yes
Xofigo/radium Ra 223 dichloride	2013	No	2013	Yes
Provenge/sipuleucel-T	2010	No	2013	No

EU = European Union; SmPC = Summary of Product Characteristics; US = United States.

Clark et al. Health and Quality of Life Outcomes 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 June 2014
EMA/CHMP/292464/2014
Oncology Working Party

Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies

Draft

What we stand to lose without the routine incorporation of PROs in clinical trials

- Missing prognostic information
- Lack of Understanding of Patient Adherence
- Lack of Information for Comparative Effectiveness
- Lack of Information for Patient and Clinical Decision Making
- Lack of Information for Labeling Claims

Conclusions

- PROs provide a unique perspective in oncology
- PROs can be used in clinical practice
- FDA and EMA approved drugs can include PROs in their label claims
- The futureof PROs will include technology to assist patients with data capture