Organ Toxicities from Targeted Therapies

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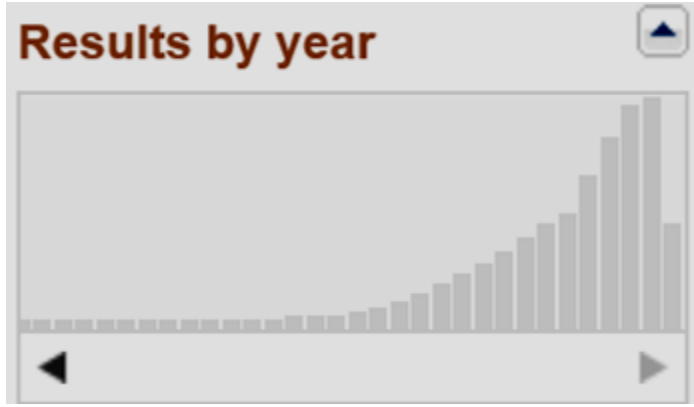
Faculty Disclosure

I have no conflict of interest to declare.

TARGETED THERAPIES

A growing field in oncology

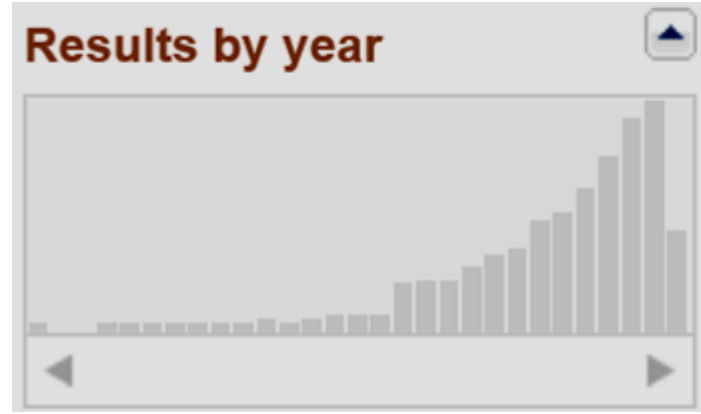
CANCER TARGETED TX



2009 → 2014
+ 100%
published
papers

PUBMED

CANCER TARGETED TX and TOXICITIES



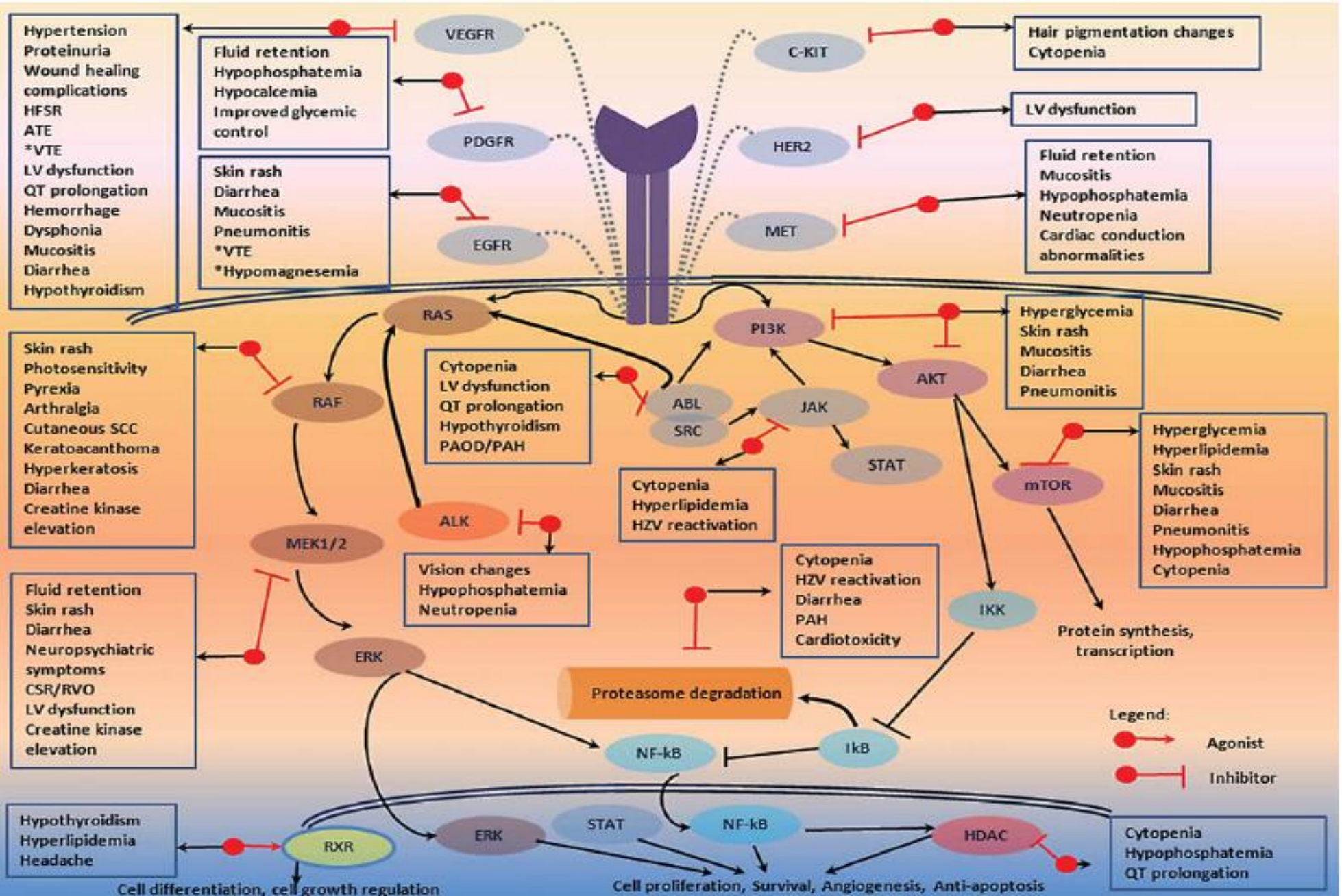
Only 2.5% of all the papers specifically regarding TOXICITIES

TARGETED THERAPIES

The mirage of the target?

"*They are able to act only on cancer cells, so producing fewer adverse events than traditional chemotherapy drugs*"

AN OVERVIEW OF THE MOLECULAR



Grace K DY,
CA: A Cancer Journal for Clinicians 2013

AN OVERVIEW OF THE TOXICITIES

Pulmonary Tox

Gastroenteric Tox

Neurotoxicity

Dermatological tox

Endocrine Tox

Systemic Tox

Cardiac and cardiovascular Tox

Muscoloskeletal Tox

Hematologic Tox

TARGETED THERAPIES

Class effect toxicities

- Toxicities typical of the target (e.g. skin rash or hypertension)

Off target toxicities

- Inhibition of other unintended targets (e.g. hepatotoxicity or some types of diarrhea)

TARGETED THERAPY TOXICITIES

MEASUREMENT:
who measures? – which grade of toxicity?
third axis - cost/effectiveness

DURATION:
late toxicities – cumulative effects

IMPACT:
underreported? – frail patients
compliance – dose reduction

METHODS: ANALYSIS OF 5 TRIALS LEADING TO FDA APPROVAL OF NEW TT

Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial

Brian I Rini, Bernard Escudier, Piotr Tomczak, Andrey Kaprin, Cezary Szczylik, Thomas E Hutson, M Dror Michaelson, Vera A Gorbunova, Martin E Gore, Igor G Rusakov, Sylvie Negrier, Yen-Chuan Ou, Daniel Castellano, Ho Yeong Lim, Hirotsugu Uemura, Jamal Tarazi, David Cella, Connie Chen, Brad Rosbrook, Sinil Kim, Robert J Motzer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer

David Cunningham, M.D., Yves Humblet, M.D., Ph.D., Salvatore Siena, M.D., David Khayat, M.D., Ph.D., Harry Bleiberg, M.D., Ph.D., Armando Santoro, M.D., Danny Bets, M.Sc., Matthias Mueser, M.D., Andreas Harstrick, M.D., Chris Verslype, M.D., Ph.D., Ian Chau, M.B., B.S., and Eric Van Cutsem, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

METHODS:
ANALYSIS OF 5 TRIALS LEADING TO FDA APPROVAL OF NEW TT

FIRST AUTHOR/YEAR	CANCER DISEASE	TREATMENT
Cunningham D, 2004	Colon cancer	CETUXIMAB
Rini B, 2011	Renal cancer	AXITINIB
Chapman P, 2011	Melanoma	VEMURAFENIB
Gianni L, 2012	Breast cancer	PERTUZUMAB
Shaw A, 2013	NSCLC cancer	CRIZOTINIB

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

MEASUREMENT

- Different methods of collecting data regarding AEs lead to large differences in the reported rates in clinical trials

- Detailed Patient Reported questionnaires are able to discover more AEs compared with unstructured reporting

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

MEASUREMENT

- Scientific evidence demonstrates that health professionals underestimate the burden and severity of symptoms in comparison to pts

- Increased regulatory focus on PROs as subjective domains for clinical research

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

MEASUREMENT

Annals of Internal Medicine | ARTICLE

Brief Communication: Better Ways To Question Patients about Adverse Medical Events

A Randomized, Controlled Trial

Stephen Bent, MD; Amy Padula, MS; and Andrew L. Avins, MD, MPH

JOURNAL OF CLINICAL ONCOLOGY | EDITORIAL

Using Patient-Reported Outcomes in Clinical Practice: A Promising Approach?

Claire F. Snyder, *Johns Hopkins School of Medicine; Johns Hopkins Bloomberg School of Public Health; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

EDITORIAL | Annals of Internal Medicine

Adverse Events: The More You Search, the More You Find

VOLUME 22 · NUMBER 17 · SEPTEMBER 1 2004
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

How Accurate Is Clinician Reporting of Chemotherapy Adverse Effects? A Comparison With Patient-Reported Symptoms From the Quality-of-Life Questionnaire C30

Erik K. Fromme, Kristine M. Eilers, Motomi Mori, Yi-Ching Hsieh, and Tomasz M. Beer

VOLUME 25 · NUMBER 32 · NOVEMBER 10 2007
JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Patient-Reported Outcomes and the Evolution of Adverse Event Reporting in Oncology

Andy Trotti, A. Dimitrios Colevas, Ann Setser, and Ethan Basch

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

MEASUREMENT

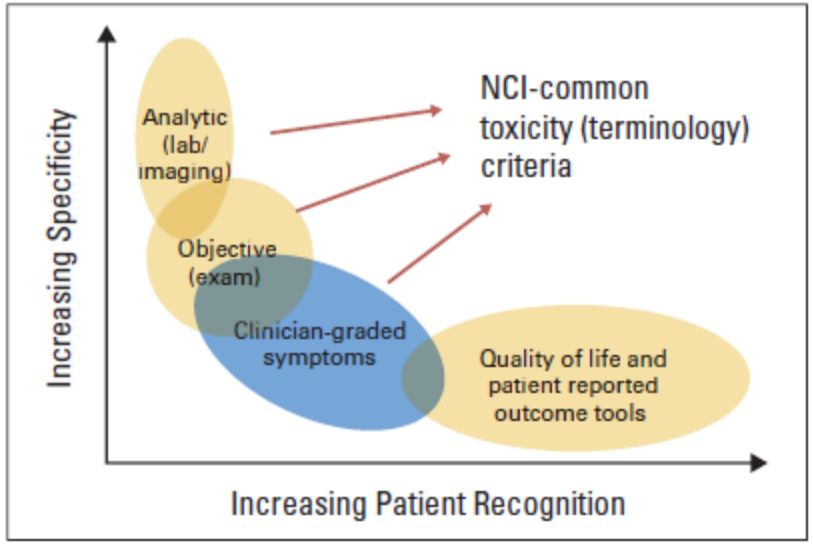


Fig 1. Adverse effects domains. NCI, National Cancer Institute. Adapted with permission.[8]

Patient self-reporting improves the accuracy of recording subjective AEs

MEASUREMENT

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

PROs offer opportunity for labeling claims and are tools for comparative effectiveness

Towards the development of a PRO version of the CTCAE

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

MEASUREMENT

What about assessment of toxicities due to targeted agents with PROs?

PHYSICIAN ASSESSED OR PATIENT REPORTED OUTCOME?

FIRST AUTHOR/DRUG	CTCAE	PRO
Cunningham D, CETUXIMAB	YES	NO
Rini B AXITINIB	YES	NO
Chapman P VEMURAFENIB	YES	NO
Gianni L PERTUZUMAB	YES	NO
Shaw A CRIZOTINIB	YES	YES

PATIENT REPORTED OUTCOME and PHYSICIAN ASSESSED TOXICITIES

The case of palifermin and the value of PRO:

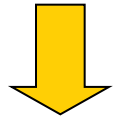
hematopoietic stem-cell transplantation

VOLUME 24 · NUMBER 33 · NOVEMBER 20 2006
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Palifermin Reduces Patient-Reported Mouth and Throat Soreness and Improves Patient Functioning in the Hematopoietic Stem-Cell Transplantation Setting

Patrick J. Stiff, Christos Emmanouilides, William I. Bensinger, Teresa Gentile, Bruce Blazar, Thomas C. Shea, John Lu, John Isitt, Alessandra Cesano, and Ricardo Spielberger

head and neck cancer



VOLUME 29 · NUMBER 20 · JULY 10 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Palifermin Reduces Severe Mucositis in Definitive Chemoradiotherapy of Locally Advanced Head and Neck Cancer: A Randomized, Placebo-Controlled Study

VOLUME 29 · NUMBER 20 · JULY 10 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Palifermin Decreases Severe Oral Mucositis of Patients Undergoing Postoperative Radiochemotherapy for Head and Neck Cancer: A Randomized, Placebo-Controlled Trial

Michael Henke, Marc Alfonsi, Paolo Foa, Jordi Giralt, Etienne Bardet, Laura Cerezo, Michaela Salzwimmer, Richard Lizambri, Lara Emmerson, Mon-Gy Chen, and Dietmar Berger

MEASUREMENT

Both trials were positive according to physician-assessed mucositis

hematopoietic stem-cell transplantation

head and neck cancer

Palifermin significantly reduced the intensity and duration of WHO grade 3 and 4 mucositis in respect to placebo

MEASUREMENT

A different result was obtained when employing PRO (OMDQ or OMWQ)

hematopoietic stem-cell transplantation

head and neck cancer

The OMDQ was able to detect a statistically significant improvement of patient self-reported MTS

The benefit of palifermin in physician-assessed mucositis was not paralleled by a better patient-reported outcome

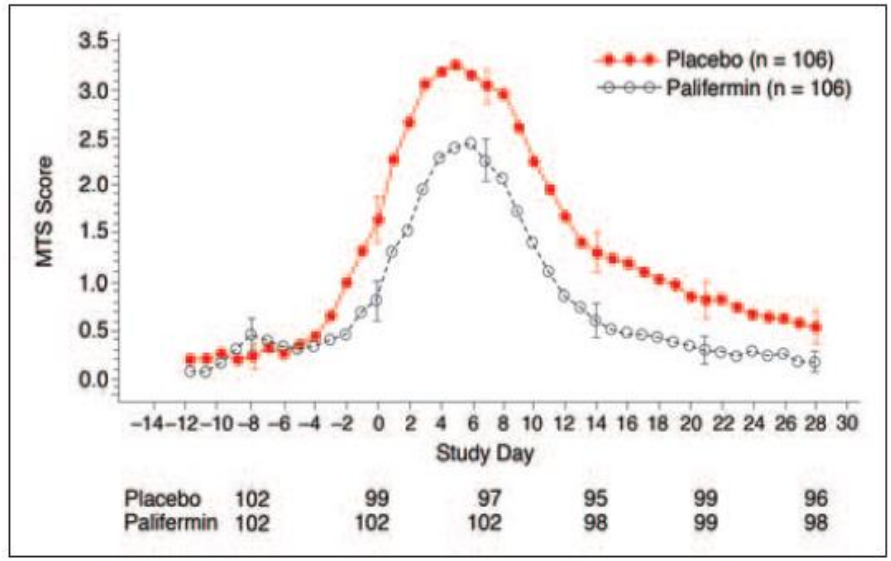
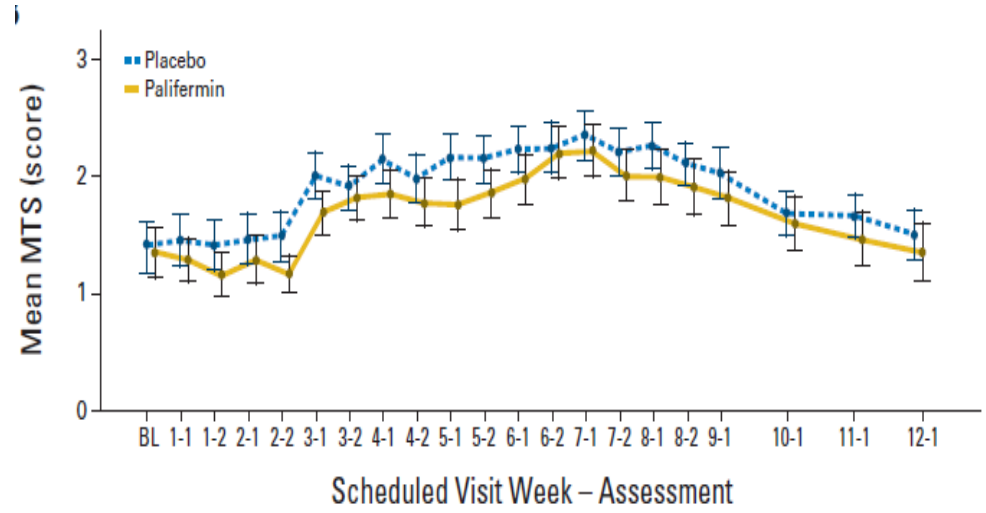


Fig 4. Mouth and throat soreness (MTS) scores (placebo *v* palifermin). Vertical lines represent 95% CIs.



MEASUREMENT

QUALITY OF INFORMATION

- Reporting toxicities is highly dependent on the **methods employed** and the **rigor adopted** to elicit information (Ioannidis 2006)

Table. **Improving the Identification and Understanding of Information about Medication-Related Harms**

Variable	Strategy
Generalizability	Study appropriate clinical settings and patients.
Validity	Use unambiguous definitions, validated assessment instruments, appropriate comparison groups, and masked assessments when possible.
Reporting	Follow CONSORT (Consolidated Standards of Reporting Trials) guidance.*
Interpretation	Appreciate limitations of small sample sizes and different sources of evidence and measurement methods; distinguish between clinical harms and their surrogates.
Standardization	Promote common definitions and assessment methods for similar conditions and treatments.
Sources	Support the collection of high-quality trial and observational data.
Integration	Produce large-scale evidence by combining data from multiple trials.

MEASUREMENT

QUALITY OF INFORMATION

"We must no longer accept confusing lists of noncomparable percentages of adverse events for clinical or for scientific purposes.

(…)

We must insist on better understanding about how numbers about harms were collected, where they came from, and what they mean."

MEASUREMENT

WHAT THEY MEAN…

- The case of vismodegib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma

ADVERSE EVENTS

As of the data-cutoff point, approximately half the patients had discontinued the study treatment, and the median duration of drug exposure was approximately 10 months in both cohorts (Table 2). The most common reasons for discontinuation of vismodegib were disease progression in the group of patients with metastatic basal-cell carcinoma (18%) and the patient's decision in the group of patients with locally advanced basal-cell carcinoma (25%) (Table 3 in the Supplementary Appendix); the reasons for this decision were not documented.

All patients had at least one adverse event during the study; more than half the treated patients (57%) had only grade 1 or 2 adverse events. Adverse events of any grade occurring in 20% or more of patients are summarized in Table 3; these findings are consistent with the pattern of adverse events in the phase 1 study. Adverse events of grade 3 or 4 included muscle spasms, weight loss, fatigue, and loss of appetite. Of the 104 patients in the study, 13 (12%) had an adverse event leading to the discontinuation of the study drug; the most common was muscle spasms, reported in 2 patients.

Table 3. Commonly Reported Adverse Events, According to Grade.*

Event	Any Grade	Grade 1	Grade 2	Grade 3 or 4
		percentage of patients		
Muscle spasms	68	48	16	4
Alopecia	63	49	14	0
Dysgeusia	51	28	23	0
Decrease in weight	46	27	14	5
Fatigue	36	27	5	4
Nausea	29	21	7	1
Decrease in appetite	23	14	6	3
Diarrhea	22	16	5	1

* These adverse events occurred in at least 20% of all patients and were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.1. The highest grade of event is reported here for each patient.

MEASUREMENT

RECORDING ALL GRADE TOX?

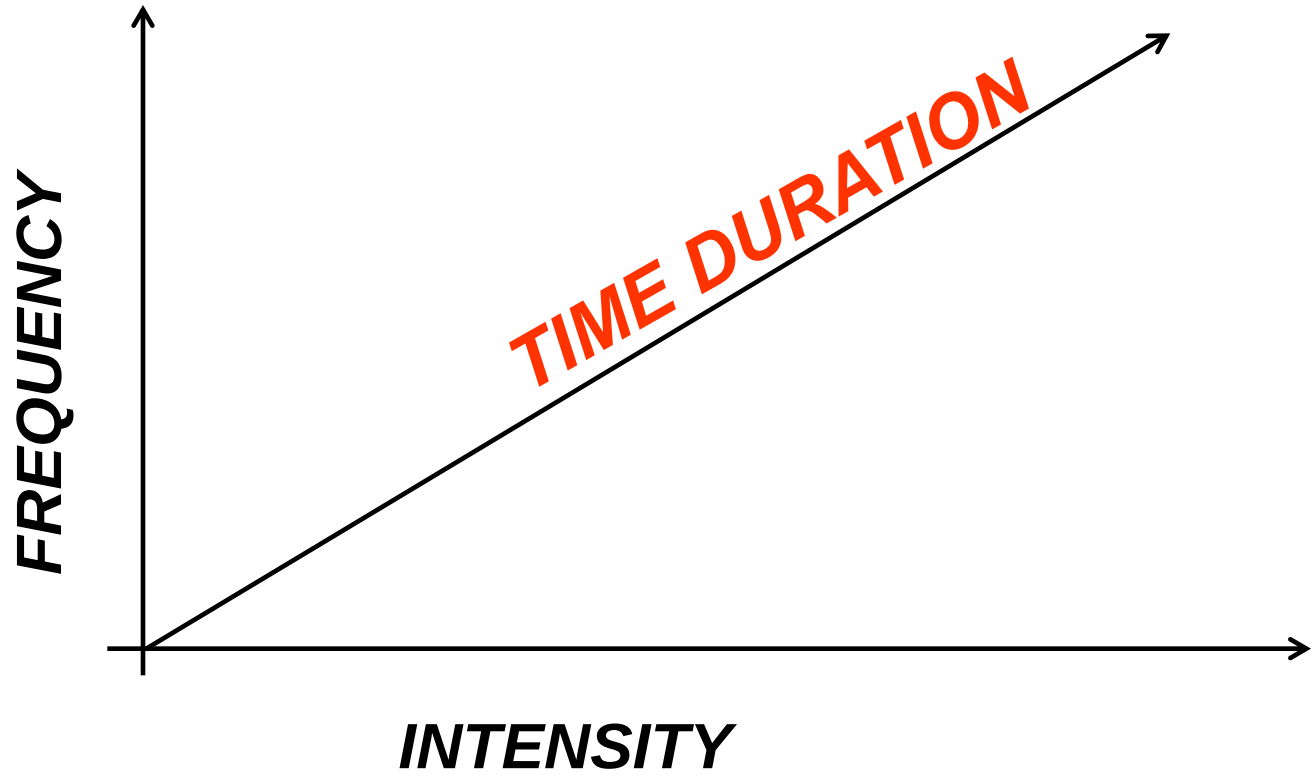
- Grade 3-4 toxicities are usually more reliably scored and reported (protocol-specific guidance; dose reduction; clinical alert)

- If we record only maximum grade of toxicity or only grade $\geq$ 3 we may neglect a considerable burden of lower grade adverse effects

ALL-GRADE TOXICITIES OR ONLY THE HIGHEST?

FIRST AUTHOR/DRUG	GRADE 1-2?	GRADE 3-4?
Cunningham D, CETUXIMAB	NO	YES
Rini B AXITINIB	YES	YES
Chapman P VEMURAFENIB	YES	YES
Gianni L PERTUZUMAB	YES	YES
Shaw A CRIZOTINIB	YES	YES

THE THIRD AXIS: TIME



MEASUREMENT

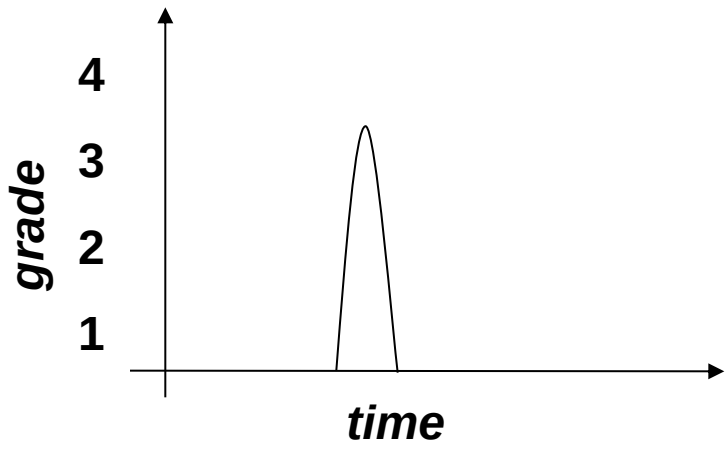
THE THIRD AXIS: TIME

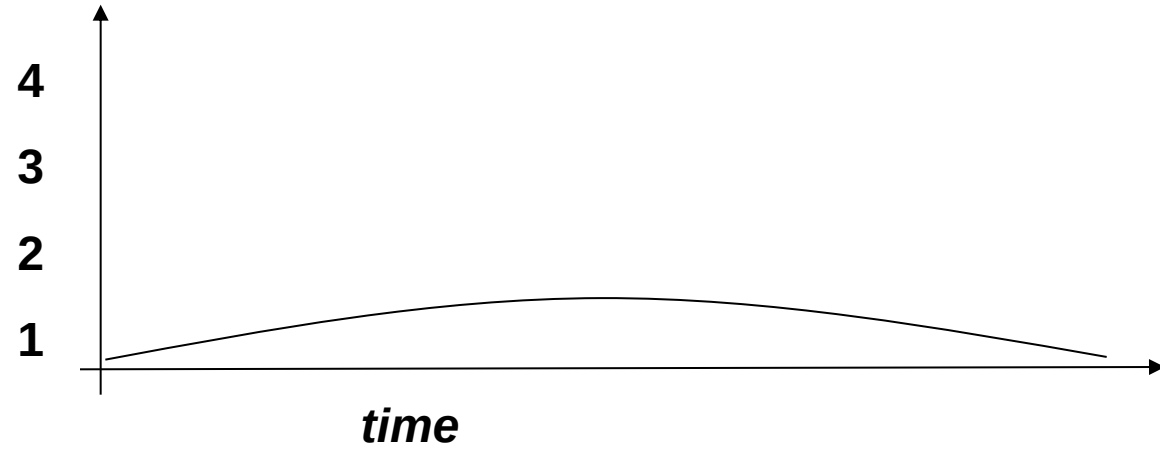
- Evaluating the impact of adverse event duration on patients' well being

- Greater impact inasmuch as the duration of TT treatment is increasing

MEASUREMENT

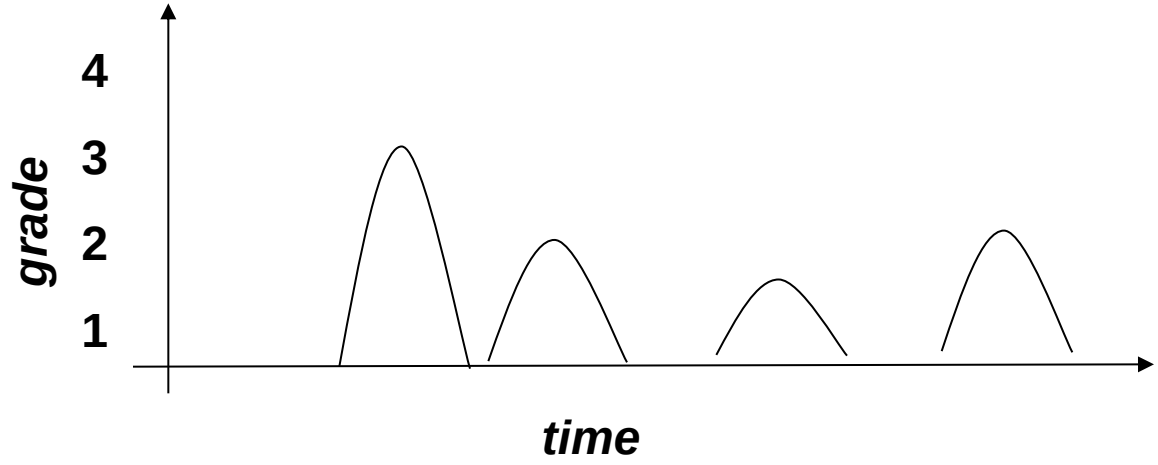
- Which toxicity worsens QoL the most?





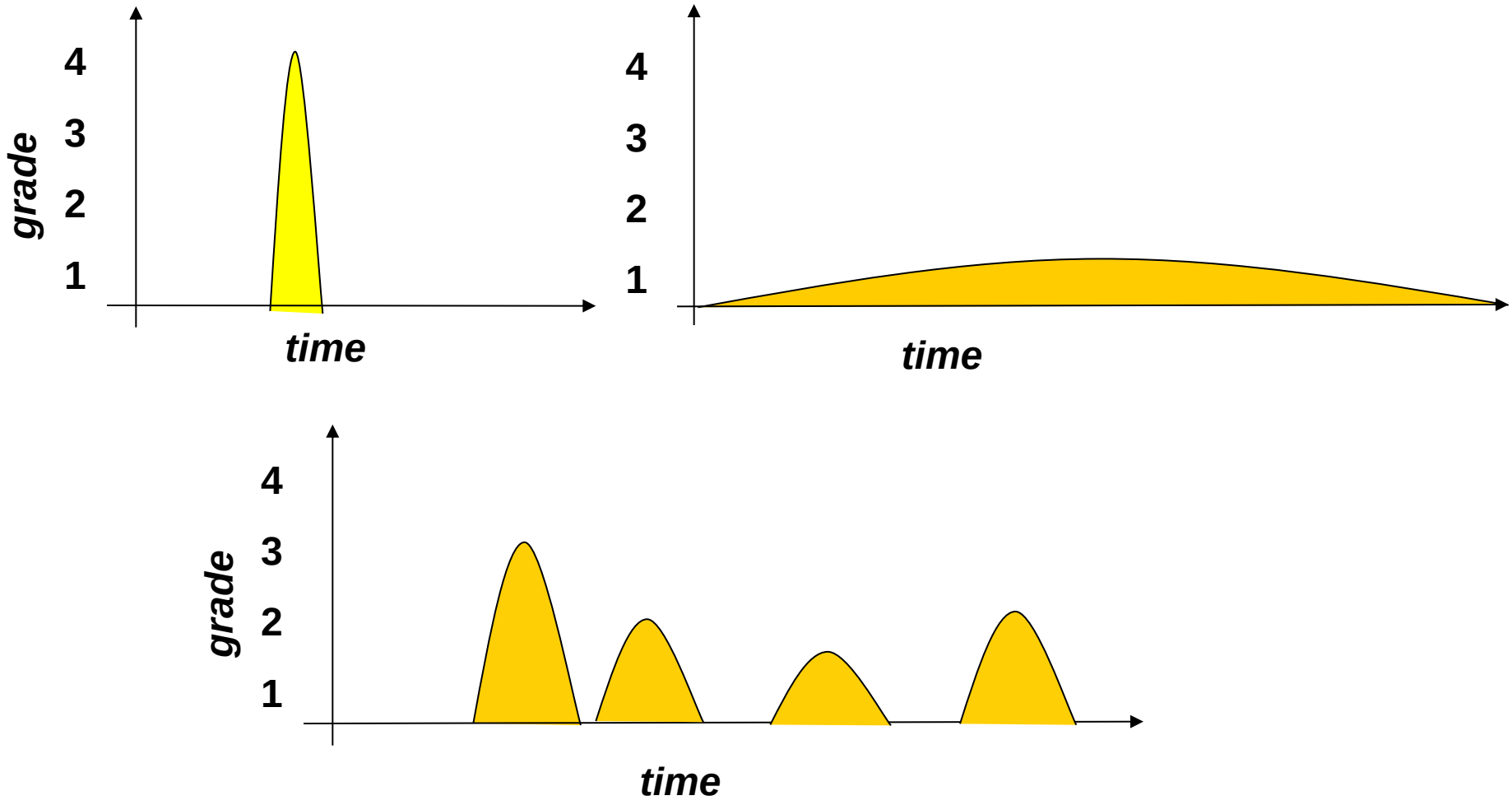
What is worse? A grade 3 diarrhea induced by polychemotherapy lasting for 3 days or a grade 1 diarrhea due to multikinase angiogenesis inhibitors for several months?

- How to measure recurring adverse events?



MEASUREMENT

ARE WE READY FOR AUC ?



MEASURING DURATION OF AE?

FIRST AUTHOR/DRUG	DURATION OF AE	RECURRING TOXICITY
Cunningham D, CETUXIMAB	NO	NO
Rini B AXITINIB	NO	NO
Chapman P VEMURAFENIB	NO	NO
Gianni L PERTUZUMAB	NO	NO
Shaw A CRIZOTINIB	NO	NO

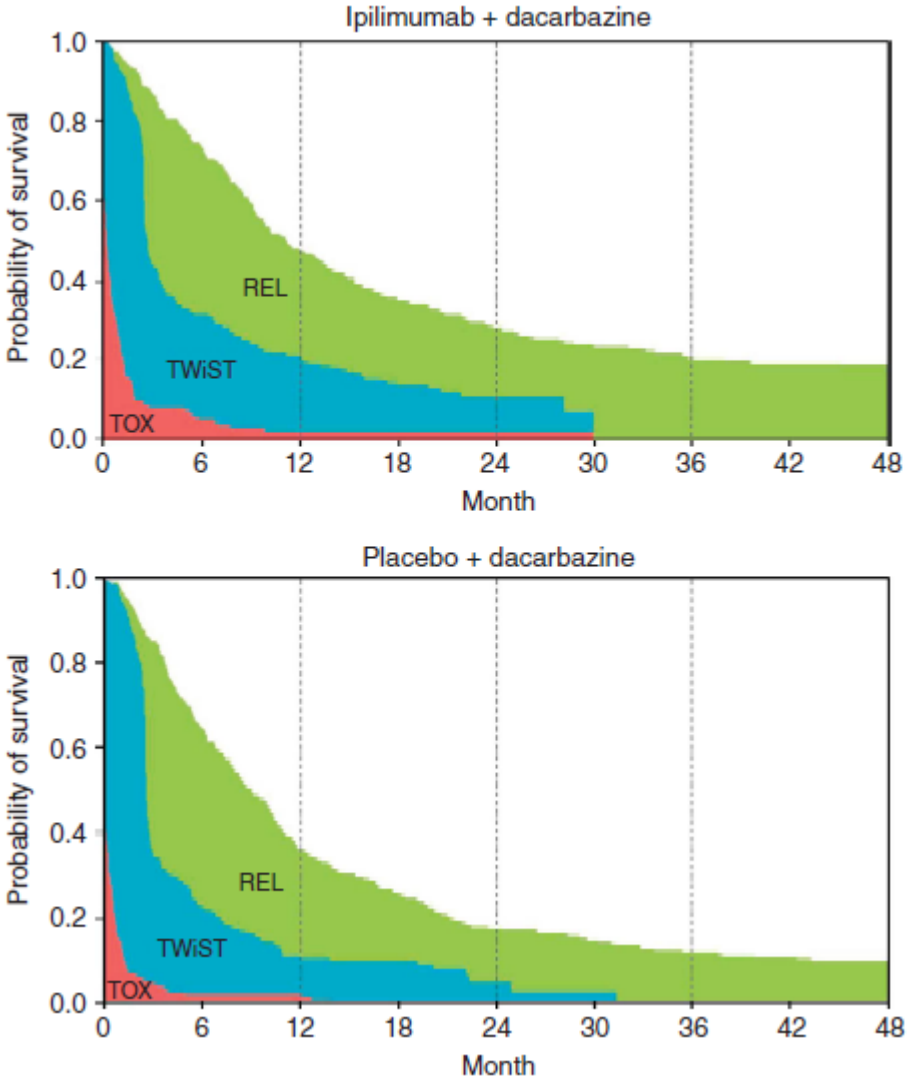
MEASUREMENT

READY TO RELY ON Q-TWiST?

Q-TWiST is an analytical approach comparing
time with toxicities + **clinical outcomes**
to evaluate the trade-off between
AEs and **benefits** of treatment
during the entire survival period.

MEASUREMENT

READY TO RELY ON Q-TWiST?



Q-TWiST analysis comparing ipilimumab/dacarbazine *vs* placebo/dacarbazine for patients with stage III/IV melanoma

B Sherrill*[,1], J Wang[1], S Kotapati[2] and K Chin[2]

BJC British Journal of Cancer (2013)

MEASUREMENT

READY TO RELY ON Q-TWiST?

In terms of cost-effectiveness, it is important to give a **utility weight** to each period, considering each grade of toxicities.

In terms of shared decision, the patients **have their own ways of valuing their time**, so it's important to customize the utility weights.

LATE EFFECTS

Early effects → *poor compliance to tx*

Late effects → *affect long term quality of life of survivors and may compromise the survival benefit from Tx (regardless disease status)*

DURATION

DURATION

LATE EFFECTS

Most trials fail to detect late toxicities

- too limited follow up?

- accustomed to evaluating late effects of TT?

- lack of standards for reporting?

- setting of population where TT employed?

LATE EFFECTS MEASURED?

FIRST AUTHOR/DRUG	LATE EFFECTS BY PHYSICIAN	LATE EFFECTS BY PATIENT REPORTED OUTCOME
Cunningham D, CETUXIMAB	NO	NO
Rini B AXITINIB	NO	NO
Chapman P VEMURAFENIB	NO	NO
Gianni L PERTUZUMAB	NO	NO
Shaw A CRIZOTINIB	NO	NO

DURATION

LATE EFFECTS

The problem of fast approval:

FDA Safety and Innovation Act of 2012 compelled the FDA to create a new status, known as a “breakthrough” designation, for treatments of life-threatening diseases where “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies.

DURATION

LATE EFFECTS

The balance between the need to get new drugs to patients fast and the competing desire to make sure they are safe and effective first.

This is particularly true for late toxicities… should we wait for long-term toxicity data to approve a new drug?

TT TOXICITIES ARE UNDER-REPORTED?

New drugs are tested in clinical trials with selected population: the rates of AEs may underestimate the frequency or severity of toxicities seen in practice.

→ Trials are conducted under controlled dosing and monitoring conditions

→ Patients with few comorbidities and are not using many concomitant medications.

TT TOXICITIES ARE UNDER-REPORTED?

The case of cetuximab plus RT in H&N cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D.,

IMPACT

Table 4. Adverse Events.*

Adverse Event	Radiotherapy Alone (N=212)		Radiotherapy plus Cetuximab (N=208)		P Value†	
	All Grades	Grades 3–5	All Grades	Grades 3–5	All Grades	Grades 3–5
	percent of patients					
Mucositis	94	52	93	56	0.84	0.44
Acneiform rash	10	1	87	17	<0.001	<0.001
Radiation dermatitis	90	18	86	23	0.24	0.27
Weight loss	72	7	84	11	0.005	0.12
Xerostomia	71	3	72	5	0.83	0.32
Dysphagia	63	30	65	26	0.68	0.45
Asthenia	49	5	56	4	0.17	0.64
Nausea	37	2	49	2	0.02	1.00
Constipation	30	5	35	5	0.35	1.00
Taste perversion	28	0	29	0	0.83	—
Vomiting	23	4	29	2	0.18	0.42
Pain	28	7	28	6	1.00	0.84
Anorexia	23	2	27	2	0.26	1.00
Fever	13	1	26	1	0.001	1.00
Pharyngitis	19	4	26	3	0.10	0.80
Dehydration	19	8	25	6	0.16	0.57
Oral candidiasis	22	0	20	0	0.63	—
Coughing	19	0	20	<1	1.00	0.50
Voice alteration	22	0	19	2	0.47	0.06
Diarrhea	13	1	19	2	0.11	0.50
Headache	8	<1	19	<1	0.001	1.00

TT TOXICITIES ARE UNDER-REPORTED?

The case of cetuximab plus RT in H&N cancer

Radiotherapy and Oncology 98 (2011) 38–41

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Head and neck radiotherapy

Toxicity of cetuximab versus cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell cancer (LAHNSCC)

Lorraine Walsh, Charles Gillham *, Mary Dunne, Ian Fraser, Donal Hollywood, John Armstrong, Pierre Thirion

Table 2
Compliance and toxicity data.

	RT-CDDP ($n = 33$) A	RT/CTX ($n = 34$) B	Comparing A with B
RTX skin dermatitis			
Grade ⩾3	6 (18%)	21 (62%)	$p = 0.0004$
Oral mucositis			
Grade ⩾3	14 (42%)	25 (74%)	$p = 0.014$
Acneiform rash			
Grade ⩾3	NA	3 (11%)	NA
Compliance with treatment			
Yes	16 (48%)	25 (74%)	$p = 0.05$
No	17 (52%)	9 (26%)	
Delay >5 days			
Yes	12 (36%)	5 (15%)	$p = 0.05$
No	21 (64%)	29 (85%)	
Received <5 infusions			
Yes	12 (36%)	5 (15%)	$p = 0.05$
No	21 (64%)	29 (85%)	
Hospital admission			
Elective	17 (52%)	19 (56%)	$p = 0.60$
Unplanned	8 (24%)	10 (29%)	
Not admitted	8 (24%)	5 (15%)	
% Weight loss			
⩾10%	5 (15%)	14 (41%)	$p = 0.03$
Enteral feeding			
No	17 (52%)	9 (26.5%)	$p = 0.097$
Elective	9 (27%)	16 (47%)	
Symptomatic	7 (21%)	9 (26.5%)	

Key: NA – not applicable.

IMPACT

TT TOXICITIES ARE UNDER-REPORTED?

CLINICAL INVESTIGATION **Head and Neck**

GRADE 3/4 DERMATITIS IN HEAD AND NECK CANCER PATIENTS TREATED WITH CONCURRENT CETUXIMAB AND IMRT

GABRIELA STUDER, M.D.,* MICHELLE BROWN, M.D.,* EVELINE BARATA SALGUEIRO,* HILDEGARD SCHMÜCKLE,* NATALIE ROMANCUK,* GISELA WINKLER,* SOON JAE LEE,* ARIANE STRÄULI,* BEATRIX KISSLING,* REINHARD DUMMER, M.D.,† AND CHRISTOPH GLANZMANN, M.D.*

Radiotherapy and Oncology 90 (2009) 166–171

Contents lists available at ScienceDirect

Radiotherapy and Oncology

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EGFr inhibitor toxicity

High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: Results of a survey in EORTC institutes

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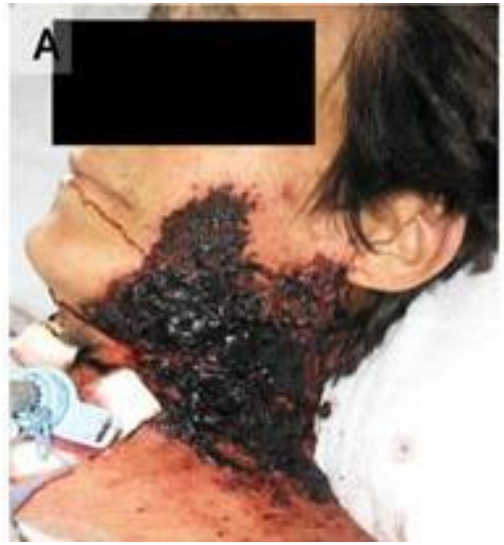
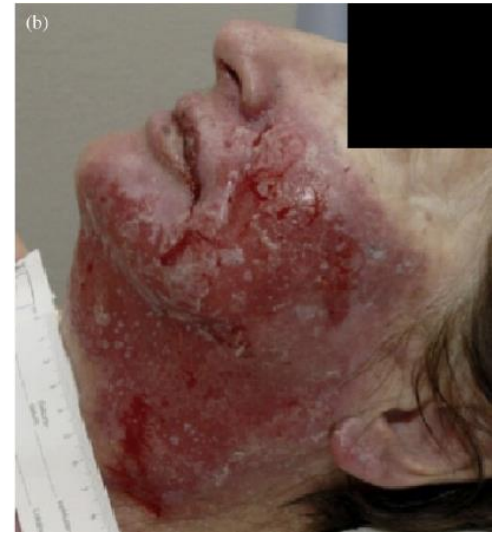
Concomitant cetuximab resulted in a 10-fold increase in the rate of severe transient dermatitis

IMPACT

TT TOXICITIES ARE UNDER-REPORTED?





The NEW ENGLAND JOURNAL of MEDICINE

Severe Cutaneous Reaction during Radiation Therapy with Concurrent Cetuximab

IMPACT

IMPACT OF TOXICITIES DUE TO TARGETED THERAPIES

Specific population of frail patients

→elderly

→ with comorbidities

→ low PS

Lack of information about the impact of TT in these patients regarding toxicities

IMPACT

Conclusions: take home messages

1) **Measurement (importance of screening toxicity in routine care):**

- **The importance of PRO in parallel with physician assessed toxicities**
- **Evaluate also lower grades**
- **Third axis: time**
- **New instruments for AE evaluation: PRO-CTCAE, Area Under the Curve, Q-TWiST**

Conclusions: take home messages

2) Duration:

- **late effects (assess to complete safety profile)**
- **Recurring adverse events**

3) Impact

- **Compliance to the treatment**
- **Lack of data on frail population**

Next steps

- **Need to build protocol-specific safety plan for each study**

- **Endpoint: fully inform the patients about foreseen toxicities and share with them the impact of the treatment**

Thanks for your attention!

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