Second Annual Workshop on Clinical Outcome Assessments in Cancer clinical trials

April 25, 2017 ■ Bethesda, MD

Co-sponsored by

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Session 2
Assessment of Safety and Tolerability – Emerging Patient-Focused Methods

SECOND ANNUAL WORKSHOP ON

CLINICAL OUTCOME ASSESSMENTS IN CANCER CLINICAL TRIALS

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Disclaimer

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Session Objectives

- Explore and discuss methods to collect and describe safety information
- Explore practical considerations regarding the use and implementation of PRO-CTCAE
- Explore differences between longitudinal adverse assessments versus static per-patient incidence rates of adverse events

Session Participants

Chair

- *Steven Lemery, MD, MHS* – Lead Medical Officer (Team Leader), Office of Hematology and Oncology Products, FDA

Presenters

- *Lori Minasian, MD, FACP* – Deputy Director, Division of Cancer Prevention, NCI, NIH
- *Sheetal Patel, PhD* – Outcomes Research Scientist – Oncology, Genentech, a member of the Roche Group; Co-Chair, PRO-CTCAE Industry WG
- *Anna Rydén, PhD* – Director, Patient Science, AstraZeneca
- *Gita Thanarajasingam, MD* – Senior Associate Consultant, Division of Hematology, Mayo Clinic; Assistant Professor of Medicine, Mayo Clinic College of Medicine

Panelists

- *Christopher R. Blackburn* – Cancer Patient and Senior Corporate Development Manager, GZA GeoEnvironmental
- *Daniel O'Connor, MB, ChB, PhD, MFPM* – Expert Medical Assessor, MHRA
- *Rajeshwari (Raji) Sridhara, PhD* – Division Director, Division of Biometrics V, Office of Biostatistics, OTS, CDER, FDA

Adverse Event Reporting: CTCAE PRO-CTCAE

Lori Minasian, M.D., FACP
Deputy Director
NCI Division of Cancer Prevention

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CTCAE

- Library of >800 adverse event items
  - Grading criteria for medical safety
- Not every item is used in one trial
  - Every item is available to report an unexpected event
- Selected relevant AE items are chosen
  - For prospective assessment
  - To specify dose modifications based upon severity
- Designed to report an event that occurred
  - Clinician must assign attribution (separate from CTCAE)

PRO-CTCAE™

- Item Library of 78 AE items
  - Derived from CTCAE
  - Patients asked to score attributes (presence, severity, frequency, and interference) independently
  - (https://healthcaredelivery.cancer.gov/pro-ctcae)

- Not every item is intended for use in one trial
- Designed to systematically capture symptomatic AEs from patients and complement clinician rated CTCAE

- Selected relevant PRO-CTCAE items are chosen
  - For prospective assessment
  - ***Not currently for protocol specific action***

MEDRA Compliance

- All CTCAE items are MEDRA compliant items
- MEDRA does not include a systematic grading criteria

- PRO-CTCAE items derived from CTCAE items
  - Plain language used to create PRO-CTCAE term from a CTCAE item and items validated
  - These plain language items are consistent with the lowest level MEDRA terms

PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE™) ITEM LIBRARY (Version 1.0)

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	P
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Gynecologic/Urinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	P
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	PI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Dimensions	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence /Amount

CTCAE vs. PRO-CTCAE Item Structures

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

PRO-CTCAE Score vs. CTCAE Grade

- PRO-CTCAE responses are scored from 0 to 4
  - Up to three questions per AE Item
    - Frequency, Severity, Interference
    - Some items have Presence/Absence only

- Clinician CTCAE Grade
  - Bundles the constructs of severity, frequency and interference
  - Grading dependent upon clinician judgement of medical significance

- Clinician Grade ≠ PRO-CTCAE Score
  - One **grade** by clinician
  - Up to three patient reported **scores** per Item
  - CTCAE Grade 4 does not exist for most of the PRO-CTCAE items

Item Selection for PRO-CTCAE

- Anticipated AEs with corresponding PRO-CTCAE
  - Use corresponding PRO-CTCAE item with associated attributes
  - Focus on items for ongoing monitoring
  - Items collected to complement clinician reporting

- Study Design
  - Identify symptomatic AEs
  - Determine trajectory of symptomatic AEs
  - Explore dosing regimens for tolerability over time

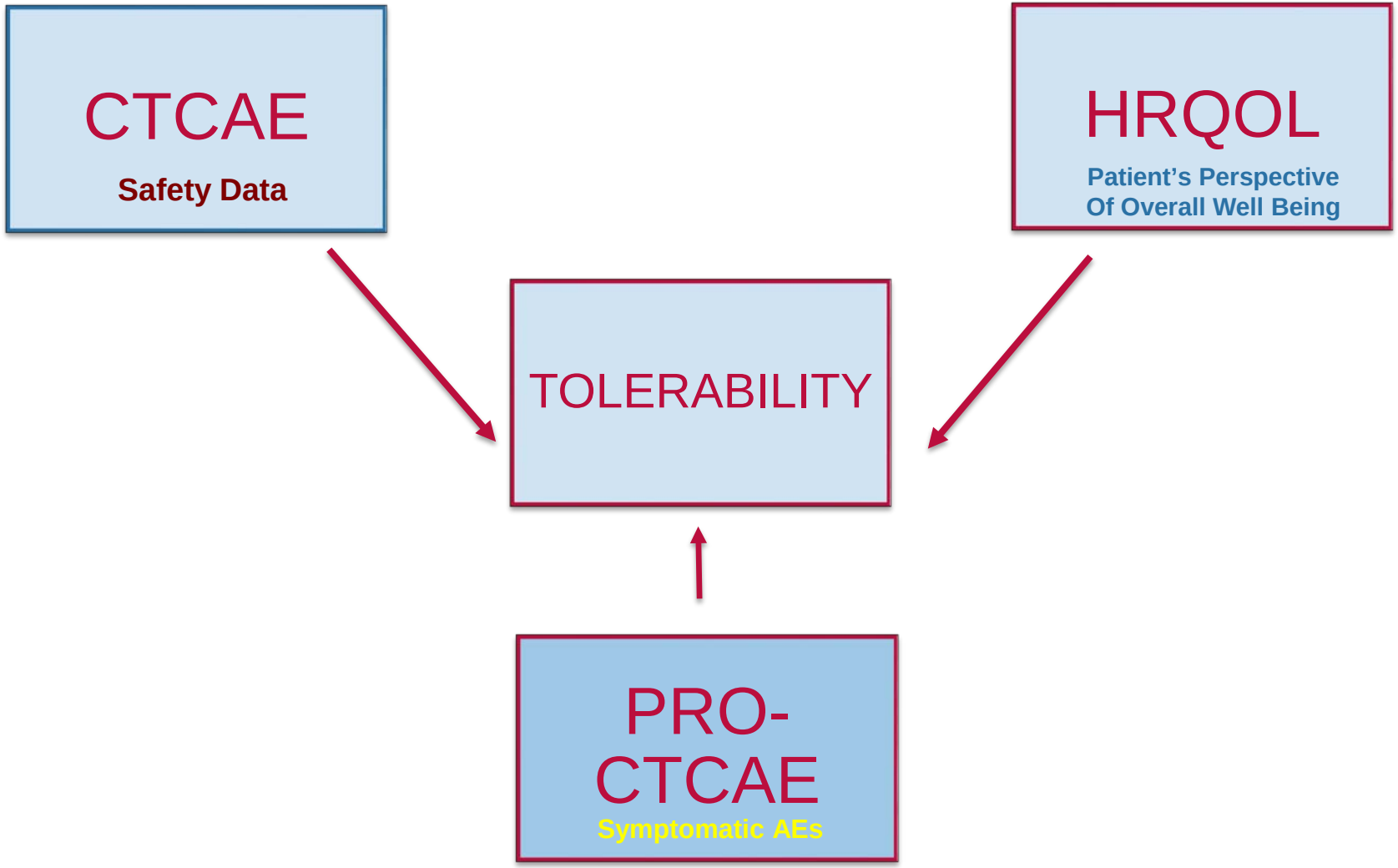
Traditional Use of CTCAE Item Grades

- Use of AE item CTCAE Grades depends on trial designs.
  - Early phase trials
  - Typically AE assessment in cycle #1
    - Safety Assessment
      - Table of most severe events experienced by any patient
    - Maximum Tolerated Dose
    - Identify Recommended Phase 2 Dose
      - (consider beyond cycle #1)
  - Late Phase
    - Evaluate Efficacy
    - Evaluate Risk/Benefit in comparison to standard regimen

Anticipated Use for PRO-CTCAE items

- No summary score
  - Score for each attribute is independent
  - Descriptive reporting for each symptomatic AE
    - May describe combinations of different symptomatic AEs for specific clinical scenarios
- Analytic evaluation still under development
  - Longitudinal assessment may be useful for identifying tolerability
- PRO-CTCAE data probably will look differently than existing tables of CTCAE items by worst severity

Using PRO Measures to Evaluate Tolerability



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www.cancer.gov www.cancer.gov/espanol

Overview of the PRO-CTCAE Industry Working Group: Objectives, Goals, Activities

Sheetal Patel, PhD, on behalf of the PRO-CTCAE Industry WG

Outcomes Research Scientist – Oncology, Genentech, a member of the Roche Group

Co-chair, PRO-CTCAE Industry WG

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Outline

- Objective of PRO-CTCAE Working Group
- Tactical barriers to industry adoption of PRO-CTCAE
- Strategies for implementation of PRO-CTCAE

} Outcomes of 2015 Friends-Brookings Conference

- Road Map of WG activities for 2016 + progress
  - Task 1: Translation and linguistic validation
  - Task 2: Item selection approaches
- 2017 Work plan and Next steps

Working Group Members

- Alicyn Campbell, Genentech
- Sheetal Patel, Genentech
- Jeff Allen, FoCR
- Mark Stewart, FoCR
- Denise Globe, Novartis
- Jamae Liu, Novartis
- Josephine Norquist, Merck
- Ashley Slagle, Ind. Consulting
- Kelly McQuarrie, JNJ
- Ethan Basch, UNC
- Steven Blum, GSK
- Paivi Miskala, Pfizer
- Katarina Halling, AZ
- Anna Rydén, AZ
- Astra Liepa, Lilly
- James Shaw, BMS
- Ronaldo Fujii, EMD Serono

Working Group Objective

Solution-focused group to address tactical barriers to implementation of PRO-CTCAE in oncology trials

- Identify tactical barriers to implementation
- Develop solutions for prioritized issues to obtain descriptive symptomatic adverse event data for inclusion in USPI
- Provide proposals for FDA and NCI to review
- Gain consensus and buy-in from broader community
- Support NCI's overall program for implementation of PRO-CTCAE in oncology trials

Outcome of 2015 Friends-Brookings Conference

Tactical Barriers to Industry Adoption of PRO-CTCAE

- **Simplified license process**
  - Current Material Transfer Agreement process is too lengthy for inclusion in global trials
- **Availability of global translations**
  - Current need for global translations
- **Item selection**
  - Need for strategy and evidence to identify key PRO-CTCAE items
- **Data collection standards**
  - NCI platform vs. sponsor developed platforms
  - Enabling, coding + analyzing patient write-in responses
- **Data analysis and presentation standards**
  - Need for consensus on data scoring/analysis
  - Need for mechanism for sharing results with clinicians and patients

Strategies for Operationalizing PRO-CTCAE in Drug Development

Issues	Potential Solutions
Licensing process	**Open access w/ online registration system to enable documentation and tracking of users**
Availability of global translations	**A process and plan for cooperative investment in translation + linguistic validation**
Item selection	**Develop consensus on item selection approaches for particular contexts of use** **Engagement w/ regulators + payers to reduce duplicity while ensuring PRO strategy meets evidentiary needs**
Data collection standards	**Develop consensus on approaches to enabling, coding + analyzing patient write-in responses**
Data analysis + presentation standards	**Develop consensus on data scoring/analysis + how to present data in submissions, publications and drug labels**

PRO-CTCAE Working Group: 2016 Activities + Progress

Road Map of WG Activities - 2016

Kick-off meeting: February 9th 2016

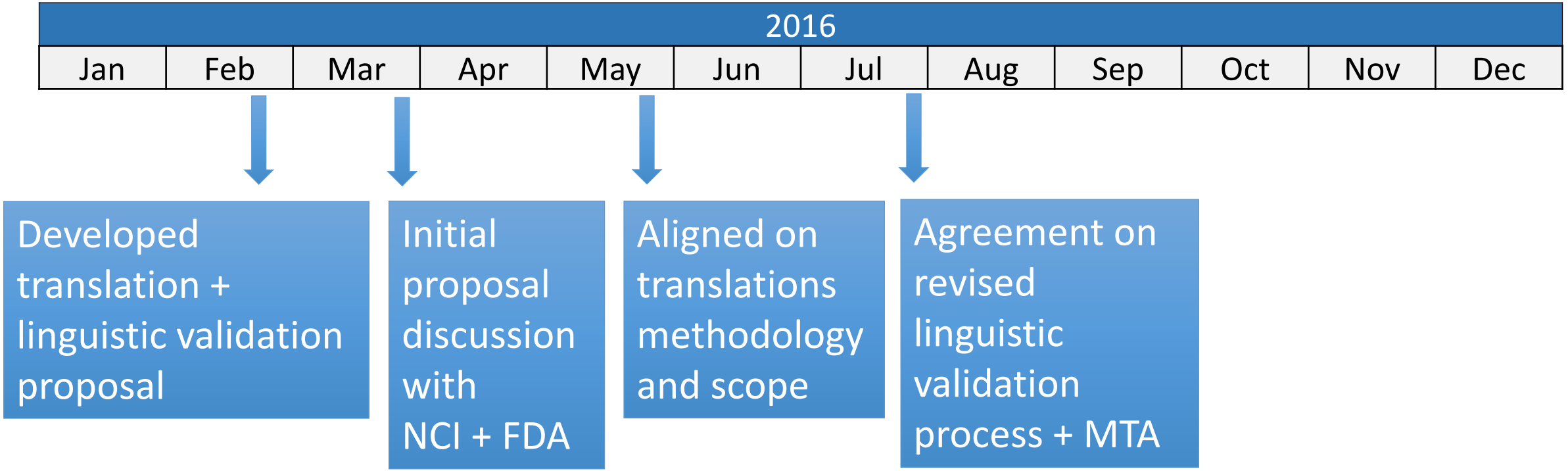
Issues	WG Task	Time Frame
Licensing process	Assess NCI's on-line registration platform to evaluate whether it addresses current access barriers	Short-term **Completed – on-line registration platform launched April 2016** ✓
Linguistic and quantitative validation	**Task 1**: Develop proposal for translation and linguistic validation of PRO-CTCAE into 30 languages	Short-term **Project initiated, on-going** ✓
Item selection	**Task 2**: Develop consensus recommendations on item selection approaches for particular contexts of use • Process for early and late stage studies reviewed by WG	Short-term **Publication - ISOQOL abstract on approach for early phase trials** ✓

Road Map of WG Activities - 2016

Initiated long-term activities

Issues	WG Task	Time Frame
Data collection standards	**Task 3**: Develop consensus recommendations on approaches to enabling, coding, + analyzing patient write-in responses	Long-term **Initiated/shared learnings and discussed options w/ WG in Sept**
Data analysis + presentation standards	**Task 4**: Develop consensus recommendations on data scoring/analysis, and data presentation formats	Long-term **Initiated work in August**

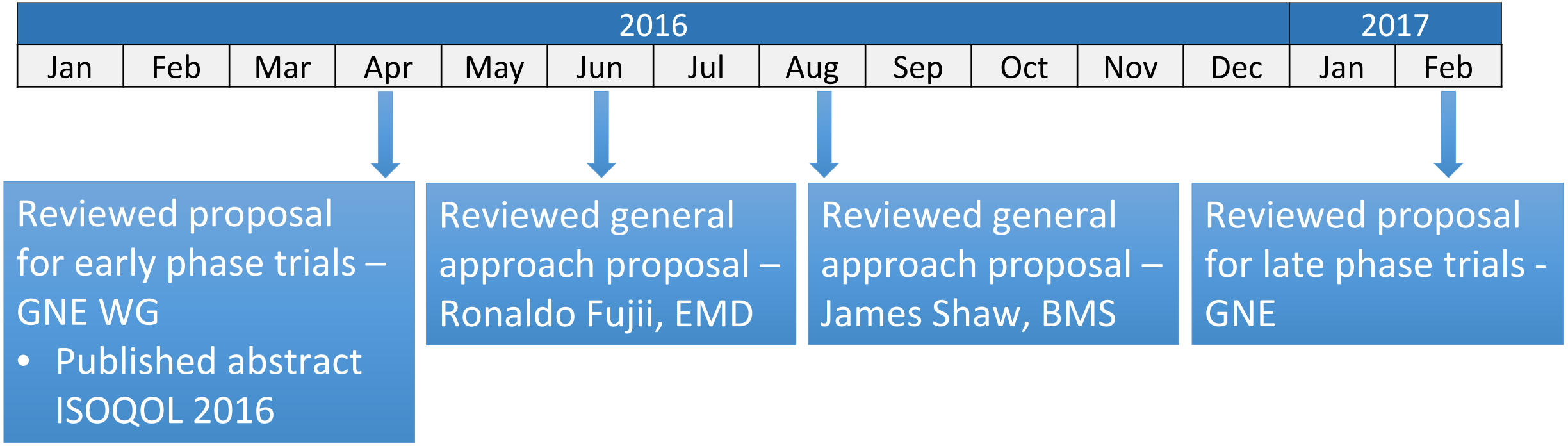
Task 1 Progress Overview: Translation and Linguistic Validation



Pharma-led translations project underway in collaboration with NCI and Cti

- Completion of 13 translations for use across 17 countries expected **end of 2017**

Task 2 Progress Overview: Item Selection



- Preparing manuscript on approaches for early + late phase studies
- Discuss item selection approaches with NCI + FDA at Q2 WG meeting
- Engagement w/ international regulators + payers to reduce multiplicity while still meeting evidentiary needs

PRO-CTCAE Working Group: 2017 Work Plan + Next Steps

Remaining Challenges: Work Plan 2017

Issues	WG Task	Time Frame
Data collection standards	**Task 3:** Develop consensus recommendations for: - approaches to enabling + handling patient write-in responses - safety monitoring of PRO-CTACE data - consistency of platforms for electronic administration	Short-term
Data analysis standards	**Task 4**: Develop consensus recommendations for data scoring/analysis	Short/Long-term
Data presentation standards	**Task 5:** Develop consensus recommendations for presenting data in submissions, manuscripts, drug label	Short/Long-term

+ On-going publication plans

Summary of Next Steps

- Committed to working with NCI, FDA, + other key stakeholders to further operationalize the PRO-CTCAE
  - Quarterly meetings scheduled for WG, FDA + NCI
    - **Q1:** Discussed progress + 2017 work plan; addressed questions on safety monitoring/reconciliation of PRO-CTCAE data
    - **Q2:** Item selection approaches; expanding item library
    - **Q3:** Analysis and interpretation approaches
    - **Q4:** Presentation of PRO-CTCAE data in the PI
- We are cognizant that we will not be able to address all issues at once
  - Organized sub-teams to tackle prioritized issues
  - **Happy to have others join the WG and support the effort** *(contact: patels65@gene.com)*
  - Stay tuned!

Experience of Implementing PRO-CTCAE in Clinical Trials

Anna Rydén, PhD, Patient Science Director, AstraZeneca

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Position on PRO-CTCAE?

Augmenting understanding scale

More traditional approach

Patient-centric approach

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Augmenting understanding scale

More traditional approach

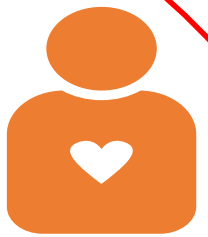
Patient-centric approach

Output/representation of data may overlap with what is already shown in other safety sections (e.g., CTCAE, safety sheet, other PRO tools etc)

Allows novel representation of information that is meaningful to patients - how treatment will affect daily life and overall experience

AZ position (so far) on PRO-CTCAE

Augmenting understanding scale



More traditional approach

Patient-centric approach

Output/representation of data may overlap with what is already shown in other safety sections (e.g., CTCAE, safety sheet, other PRO tools etc)

Allows novel representation of information that is meaningful to patients - how treatment will affect daily life and overall experience

AZ position (so far) on PRO-CTCAE

- Not used for safety monitoring:
  - *possible* treatment-related symptoms (concomitant medication, co-morbidities, disease progression, etc)
  - not evaluated by physician
  - missing data
  - few language versions available
  - more PRO-CTCAE data needed
  - 7 day recall too long?

AZ position (so far) on PRO-CTCAE

- Regarded as any other PRO data, i.e. treated as confidential to:
  - minimize bias (what's desired?)
  - optimize honest answers (not underreport of fear being taken of drug)
  - select items to avoid overlap with what's captured by other PRO measures
    - except if additional information (e.g., impact)

Implementation

- Electronic
- Timing of PRO measures aligned
- Reported at home
- Weekly at first, then every 3 weeks
- Site and monitor training
- Alarm to minimize missing

Implementation

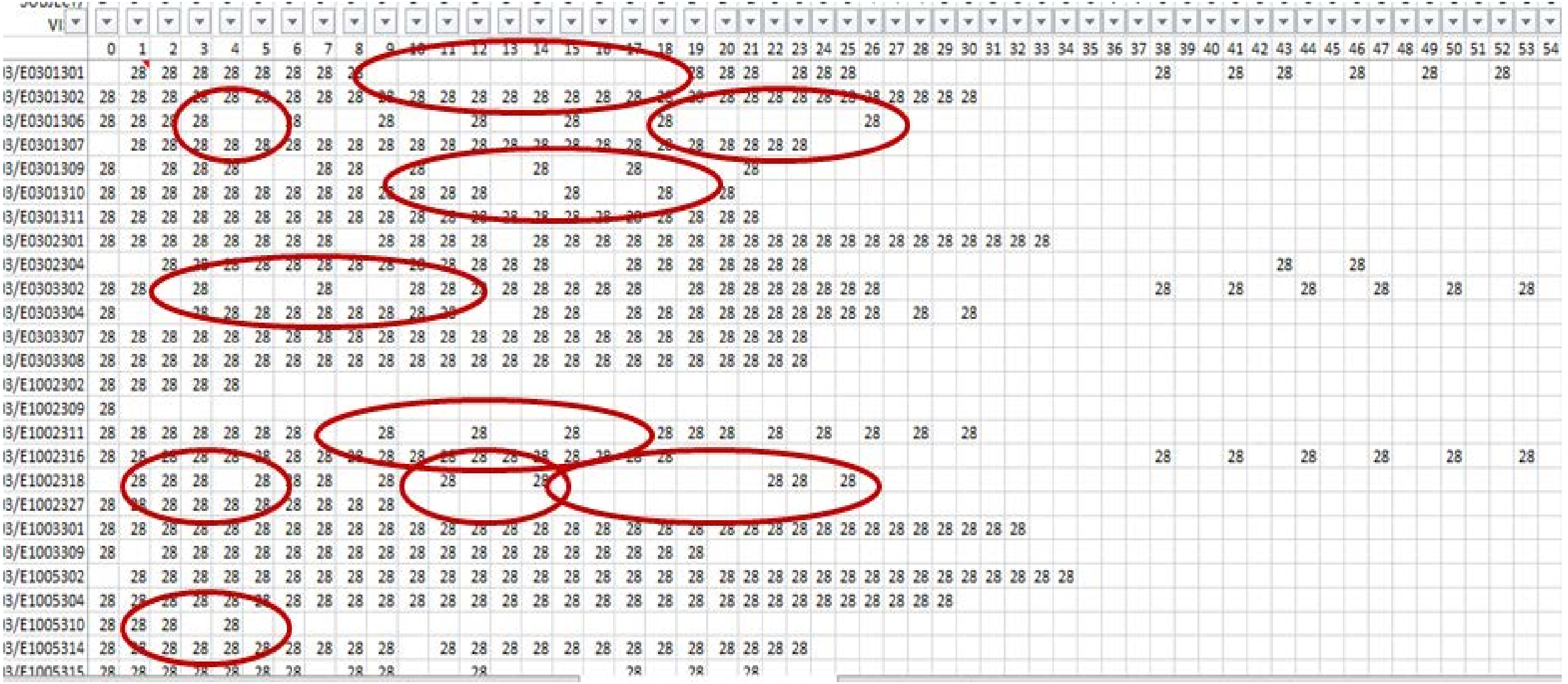
- (e)PRO still meet resistance
  - Internally perceived as higher cost
  - Externally (sites)
    - devices too complicated to set up
    - takes too much time
    - too difficult for patients to use
    - burden to sick patients
    - no/little value
    - monitoring...

Implementation

- Missing data during study – why:
  - Sites did not assign device at randomization
  - Devices correctly programmed but alerts not acted upon by monitors and/or sites

- Missing at discontinuation:
  - Patients forgot to bring device so discontinuation could not be reported in real time

Implementation



Implementation

- Baseline needed to capture ‘true’ change
- Need to determine how incomplete records are handled
  - commonly used imputation rules not applicable

Investigator interviews - comments

"This is extremely important and a very good way to report side effects. This is extremely useful..."

"Efficacy will carry the drug to MDs practice easily but having other qualitative parameters such as PRO will further enhance the information about the drug and make it even more useful for physicians to know what this drug can do for their patients"

"It would be really interesting to see... the side effects that have a huge discrepancy between physician and patient ratings... e.g. physician can rate a diarrhoea grade 1 but realistically how much does that clinician know about how much diarrhoea the patient has? It is not something visible, is something the patient tells the clinician. It can be the worst diarrhoea the patient ever had but still rated as grade 1"

Investigator interviews – key take-aways

- Patients often consider ‘lab-based’ symptoms that could result in treatment discontinuation to be less bothersome
- Better understanding of this relationship through PRO data will support the physician in providing more meaningful and insightful information to the patient
- Patient education is important – improving communication of patient experience with the treatment will support improved understanding for both patient and physician
- PRO-CTCAE data must be effectively communicated to physicians and patient information sources

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Investigator interviews – key take-aways

- Patients often consider ‘lab-based’ symptoms that could result in treatment discontinuation to be less bothersome
- Better understanding of this relationship through PRO data will support the physician in providing more meaningful and insightful information to the patient
- Patient education is important – improving communication of patient experience with the treatment will support improved understanding for both patient and physician
- PRO-CTCAE results must be effectively communicated to physicians and patients at the end of the trial

Conclusions

- We need to:
  - better inform HCP of the importance and value of PRO data
  - find optimal ways of communicating PRO-CTCAE data to both patients and HCP
  - more patient input on patient burden
  - increase quality of monitoring

Toxicity over Time (ToxT): Longitudinal Adverse Event Analysis in Cancer Clinical Trials

Gita Thanarajasingam, MD

Assistant Professor of Medicine

Rochester, Minnesota, USA

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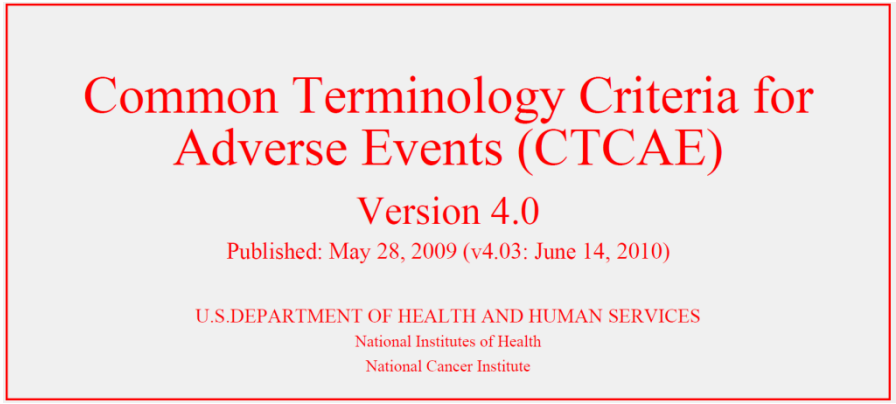
Conventional AE Evaluation is Incomplete

- Does not account for the time profile of AEs
  - When do they arise?
  - How long will they last?
  - When will they be worst?



- Does not capture the impact of chronic, low grade toxicity on the ability to continue treatment
- Does not incorporate patient reported outcomes (PRO)
- Not sufficiently patient-oriented

Basch E. N Engl J Med 2013; 369;5:397-400
Trotti A. J Clin Oncol 2007;25:5121-5127
Thanarajasingam G et al. J Natl Cancer Inst 2015. 107(10)
Carrabou M. Ann Oncol 2016; 27(8)1633-8.

Current Approach: CTCAE Max Grade Only

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Table 3. Toxicity Grade ≥ 3 and Second-Line Treatment

Toxicity Grade ≥3	Oxaliplatin and Irinotecan (n = 256)	Oxaliplatin and Fluorouracil Plus Leucovorin (n = 258)	P‡
Nausea	19	6	.001
Vomiting	22	3	.001
Diarrhea	24	12	.001
Febrile neutropenia	11	4	.002
Dehydration	6	4	.41
Paresthesias	7	18	.001
Neutropenia	36	50	.002

Table 4. Adverse Events Deemed Related to Panobinostat (≥ 10% any grade) As of June 11, 2010

	Any Grade		Grade 3 to 4	
Adverse Event	No.	%	No.	%
Thrombocytopenia	110	85	102	79
Diarrhea	85	66	4	3
Nausea	77	60	1	1
Anemia	49	38	27	21
Fatigue	49	38	12	9
Vomiting	42	33	4	3
Neutropenia	34	26	27	21
Decreased appetite	32	25	4	3
Dysgeusia	19	15	1	1
Constipation	15	12	—	
Asthenia	14	11	3	2
Leukopenia	13	10	7	5
Hypothyroidism	13	10	—	

Chronic low grade diarrhea?

National Cancer Institute. CTCAE v.4.0. Bethesda, MD: Us. Department of Health and Human Services; 2009

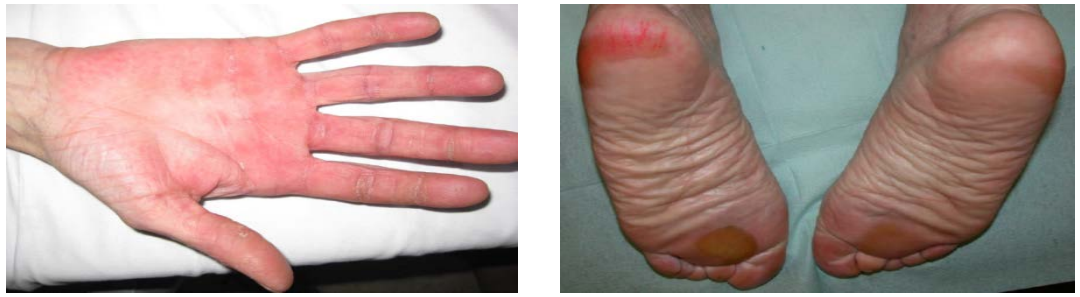
Goldberg et al. J Clin Oncol 2004;22:23-30.

Younes et al. J Clin Oncol 2012;30:2197-203.

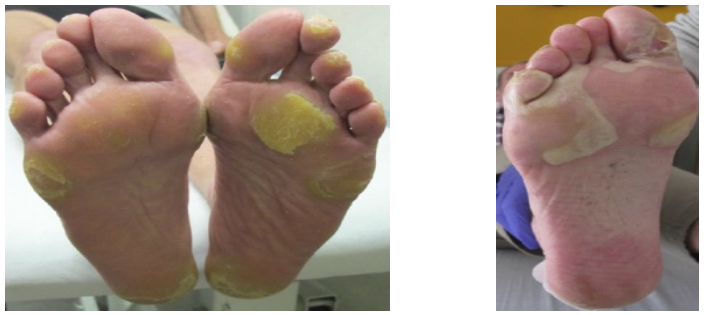
Relevance of AE time profile

Two targeted agents that produce a similar AE

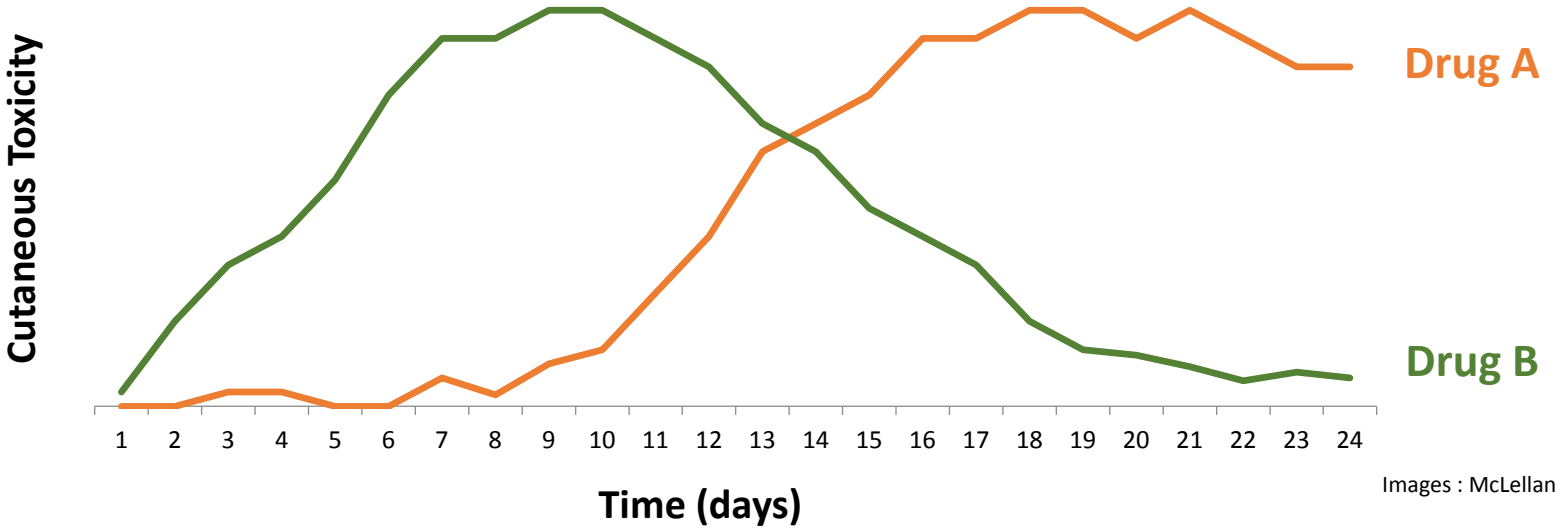
Hand-foot syndrome (**Drug A**)



Hand-foot skin reaction (**Drug B**)



Clinicians' observations on time of presentation: ramifications on AE intervention?



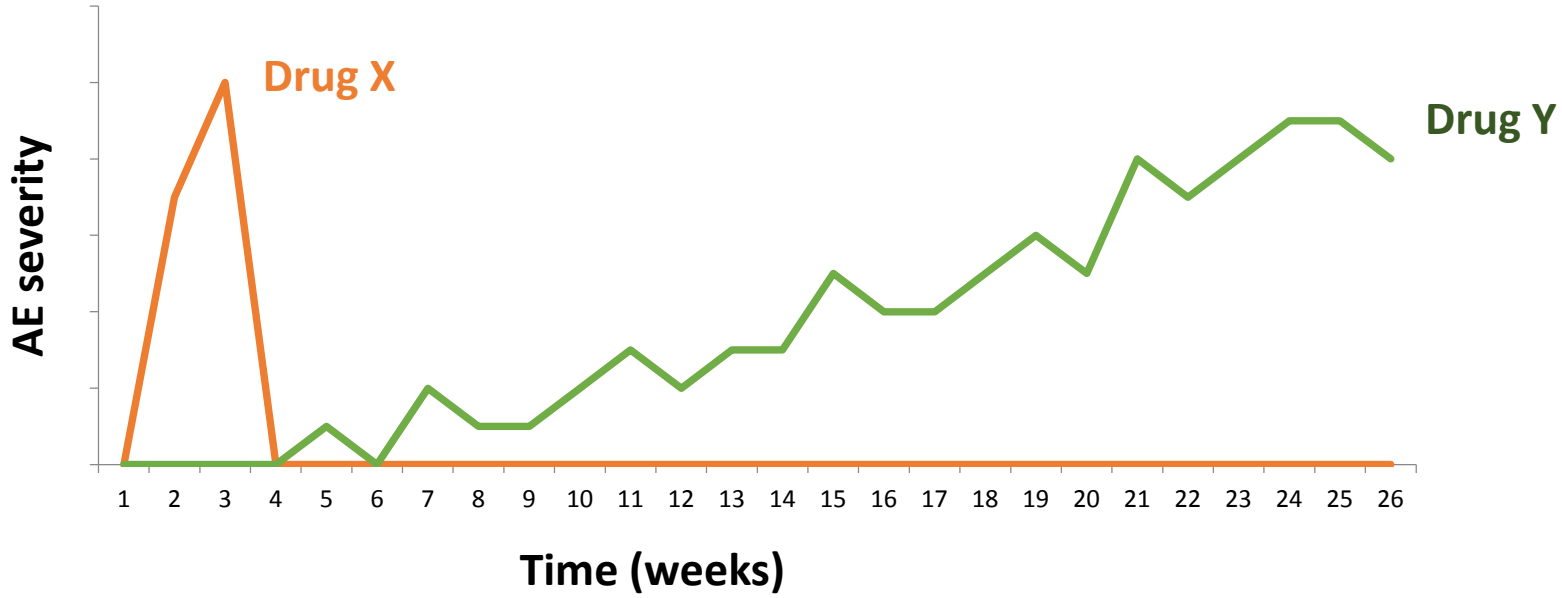
Images : McLellan et al. Ann Oncol (2015) 26 (10): 2017-2026.

Relevance of AE time profile

Two grade 3+ AEs with similar incidence (conventional maximum grade reporting)

Grade 3 or higher	Drug X + standard regimen (n=463)	Drug Y + standard regimen (n=456)
Dyspnea	25 (**5%**)	10 (2%)
Peripheral neuropathy	6 (1%)	24 (**5%**)

Hypothetical patient experience of AE: which is more burdensome?



Toxicity over Time (ToxT) Analytic Approach

- Standardized package of statistical tools that are more comprehensive than conventional methods for AE analysis
- Produces graphical and tabular outputs of AE data
- Uncovers time-dependent aspects of toxicity that are clinically relevant to cancer patients and are missed in traditional maximum grade analyses
- Demonstrated in a phase III GI trial and phase II symptom control trial (Alliance/NCCTG N9741 and 979254), recently in phase II hematologic malignancy trials
- Ongoing application to a variety of studies across different tumor types

Thanarajasingam G et al. Lancet Oncol. 2016; 17:663-70

AE Incidence/Grade by Cycle

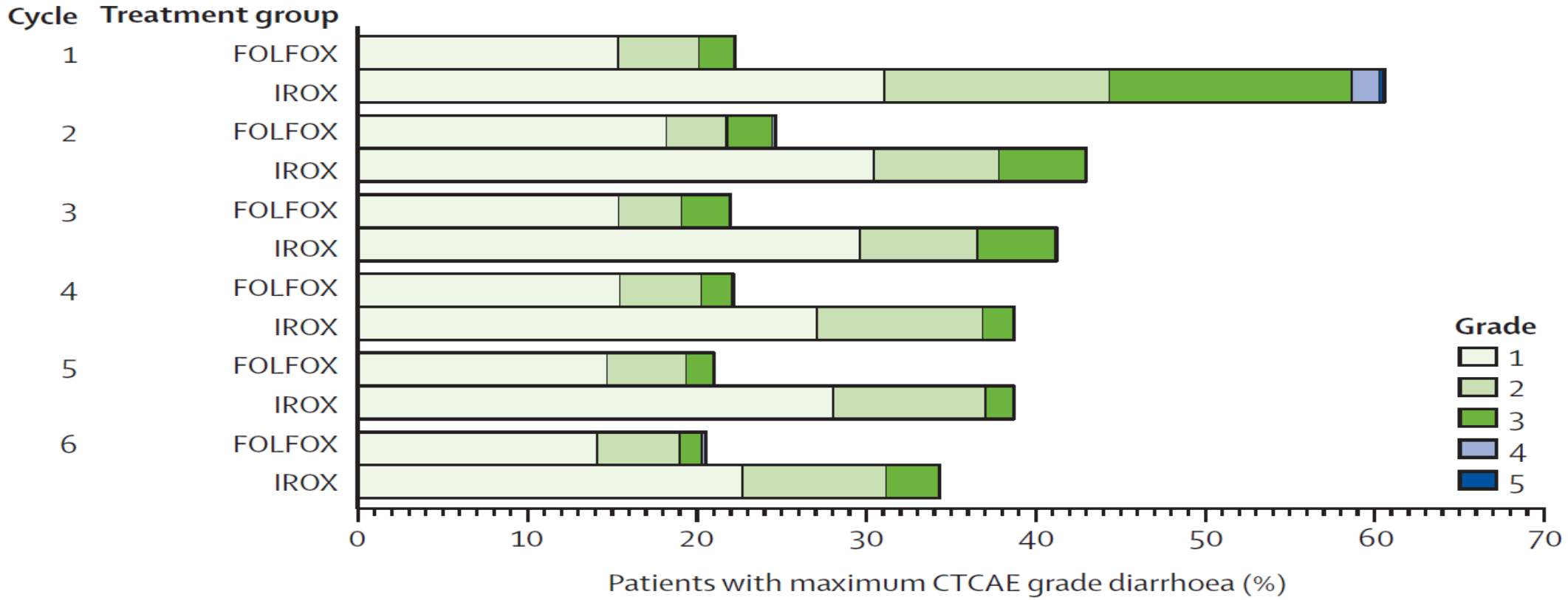
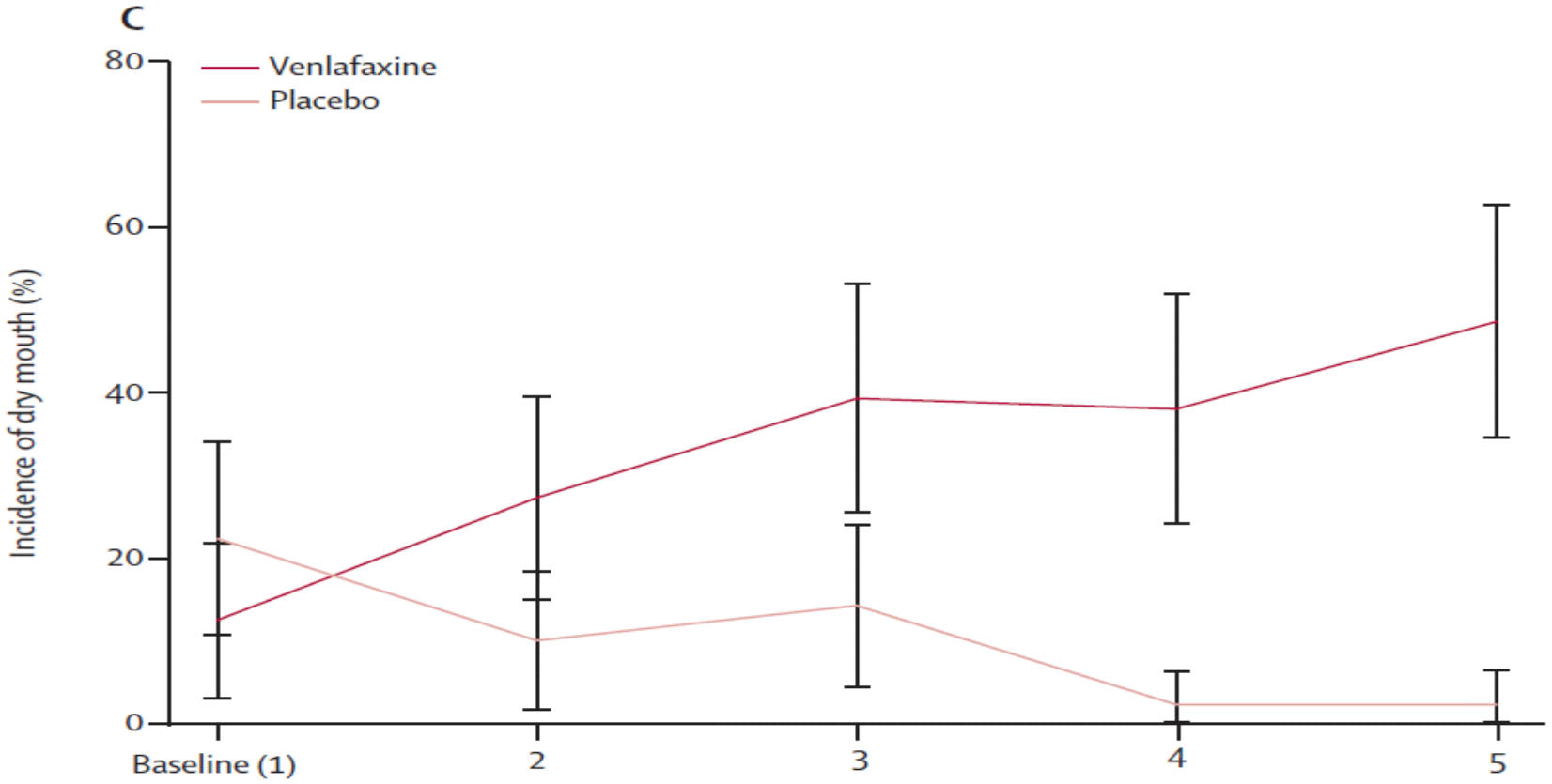


Figure 1: **Incidence of diarrhoea in patients given FOLFOX and IROX in NCCTG N9741 by drug cycle and adverse event grade**

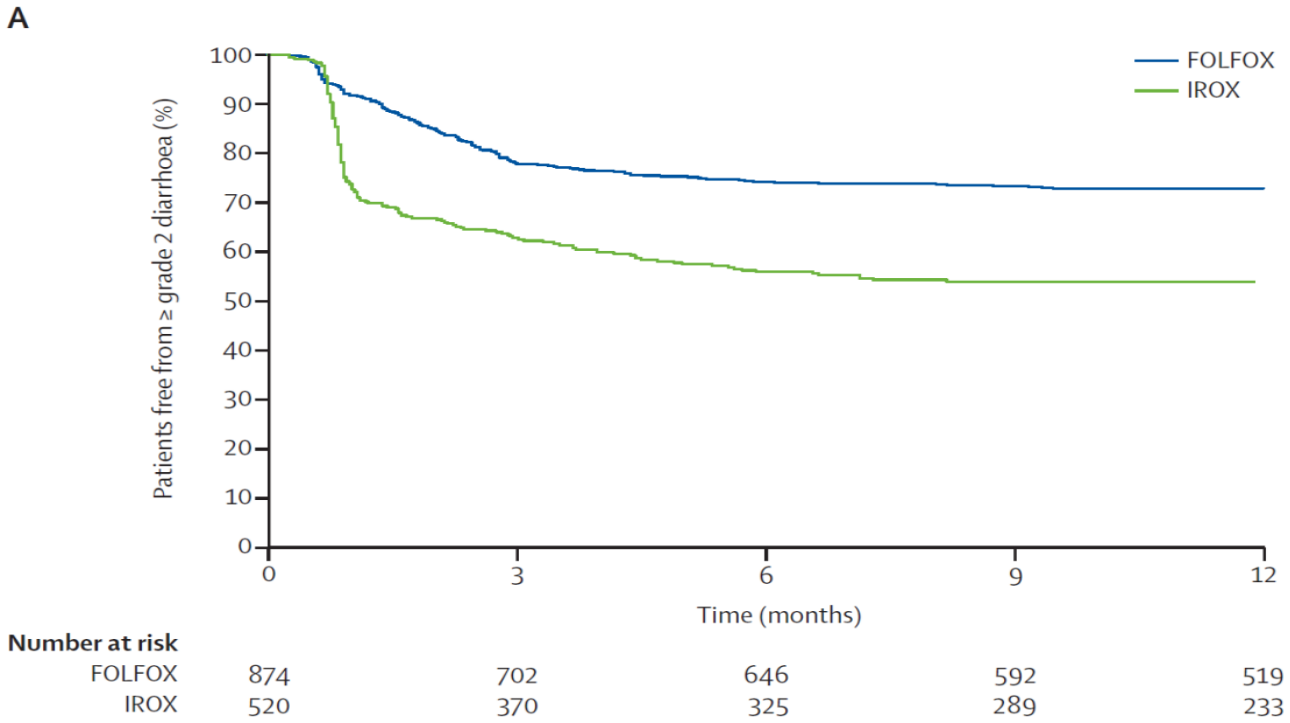
FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. CTCAE=Common Terminology Criteria for Adverse Events.

Stream Plot: AE by Cycles (two study arms)



Number of patients					
150 mg venlafaxine	48	51	48	47	49
Placebo	49	50	49	47	46

Time-to-Toxicity Analyses



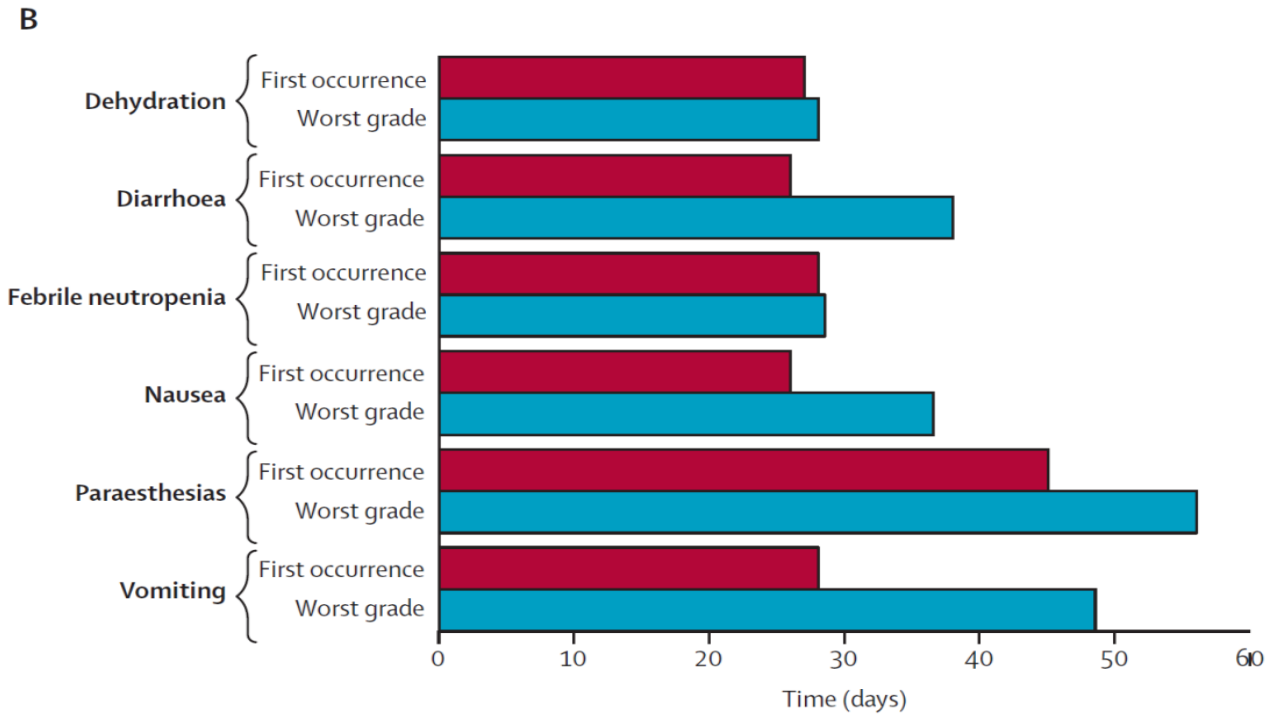


Figure 4: **Time-to-event analyses for onset of adverse events**
FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. (A) Time to grade 2 or worse diarrhoea in patients given FOLFOX and IROX in NCCTG N9741. (B) Median time to first occurrence and worst grade toxic effect in patients given IROX in NCCTG N9741.

Event Charts

Individual patient data per cycle

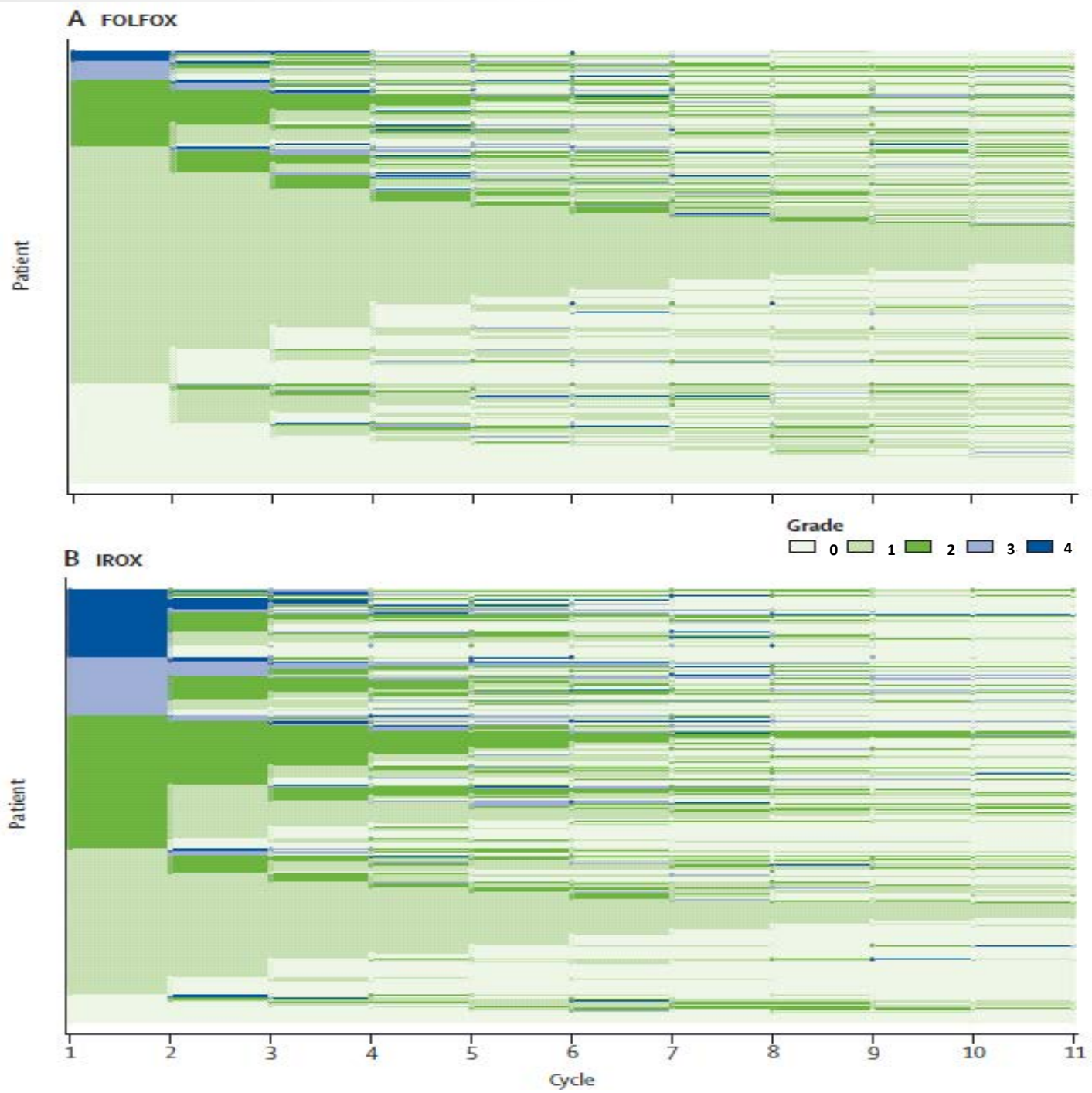


Figure 5: **Event charts for severity and timing of diarrhoea on an individual patient level in NCCTG N9741**

FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. Each horizontal line represents one patient. (A) Event chart of diarrhoea in patients given FOLFOX. (B) Event chart of diarrhoea in patients given IROX.

Area Under Curve (AUC)

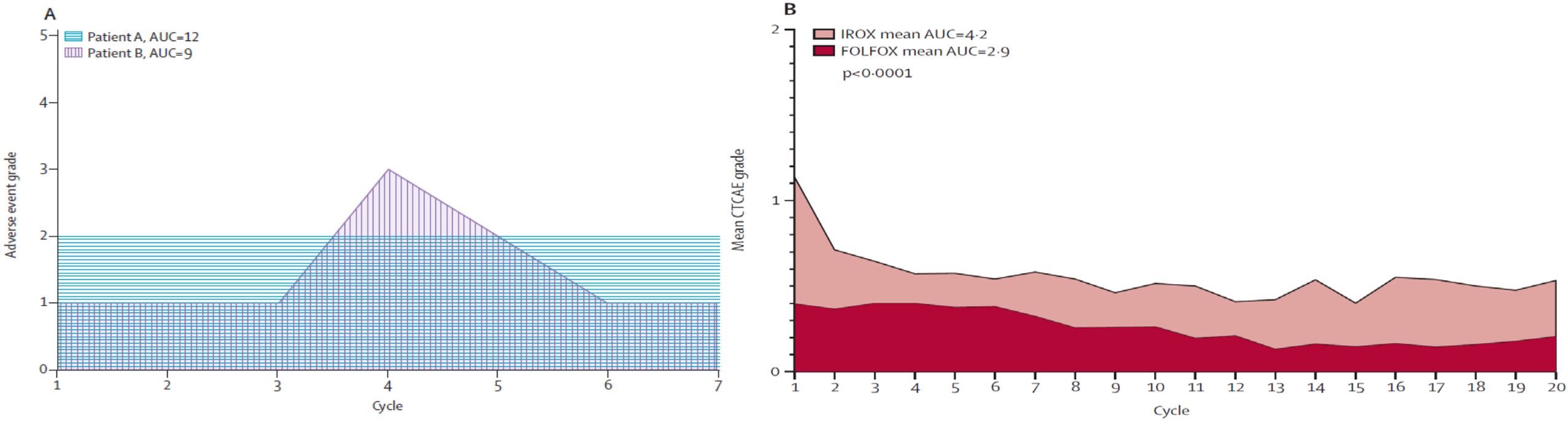


Figure 6: **AUC analysis to compare adverse events over time**
AUC=area under the curve. FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. (A) Conceptual example of AUC analysis. (B) Application of AUC analysis, mean diarrhoea grade over time in patients given FOLFOX and IROX in NCCTG N9741.

Beyond maximum grade in AE analysis

	Conventional maximum grade CTCAE analysis	Longitudinal toxicity analysis of CTCAE data	Longitudinal toxicity analysis of PRO-CTCAE data
Describes non-symptomatic AEs	✓	✓	✗
Documents UNEXPECTED AEs	✓	✓	✗/✓*
Incidence / severity (high grades)	✓	✓	✓
Duration / trajectory / resolution	✗	✓	✓
Burden of chronic low grade AEs	✗	✓	✓
Direct patient perspective	✗	✗	✓
Systematic assessment that includes baseline	✗	✗	✓

* "Write-in" option available to capture unanticipated symptomatic adverse events not selected in the initial assessment

Significance of longitudinal toxicity analysis

- Addresses an unmet need in oncology clinical trials that is crucial to the assessment of tolerability
- Has the potential to guide rational dosing approaches
- May define toxicity-related secondary endpoints in cancer trials
- Applicable to trial data collected with CTCAE, PRO-CTCAE and other tools that collect AE information over defined time points
- Can facilitate real-time and PRO-based toxicity analysis in cancer trials
- Highly relevant for patients

Bottomley et al, Lancet Oncol 2016; 17:e510-14
Kluetz et al, Clin Cancer Res 2016; 22(7); 1553-8

Summary

- Current methods of AE assessment are incomplete, particularly in the era of novel, chronically administered, cancer therapies
- The ToxT approach can readily analyze CTCAE and PRO-CTCAE data and produce more comprehensive evaluation of toxicity relevant to patients
- Patient-focused longitudinal analyses are necessary to capture time-dependent toxicity and chronic low grade AEs that are relevant to tolerability

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Panel Discussion and Q & A

Chair

- *Steven Lemery, MD, MHS* – Lead Medical Officer (Team Leader), Office of Hematology and Oncology Products, FDA

Presenters

- *Lori Minasian, MD, FACP* – Deputy Director, Division of Cancer Prevention, NCI, NIH
- *Sheetal Patel, PhD* – Outcomes Research Scientist – Oncology, Genentech, a member of the Roche Group; Co-Chair, PRO-CTCAE Industry WG
- *Anna Rydén, PhD* – Director, Patient Science, AstraZeneca
- *Gita Thanarajasingam, MD* – Senior Associate Consultant, Division of Hematology, Mayo Clinic; Assistant Professor of Medicine, Mayo Clinic College of Medicine

Panelists

- *Christopher R. Blackburn* – Cancer Patient and Senior Corporate Development Manager, GZA GeoEnvironmental
- *Daniel O'Connor, MB, ChB, PhD, MFPM* – Expert Medical Assessor, MHRA
- *Rajeshwari (Raji) Sridhara, PhD* – Division Director, Division of Biometrics V, Office of Biostatistics, OTS, CDER, FDA