FDA Oncology Center of Excellence Patient-Reported Outcomes Initiatives

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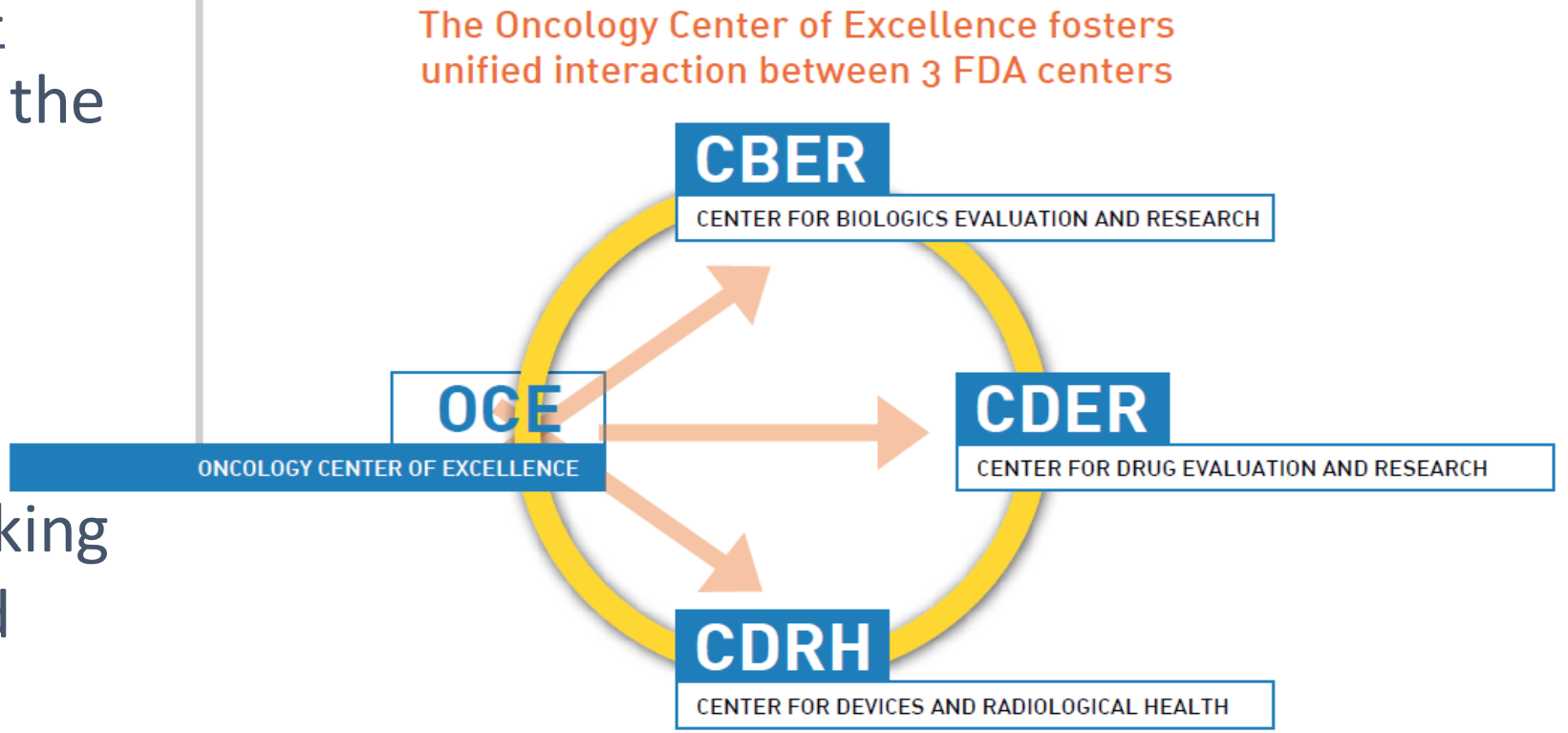
November 10, 2021

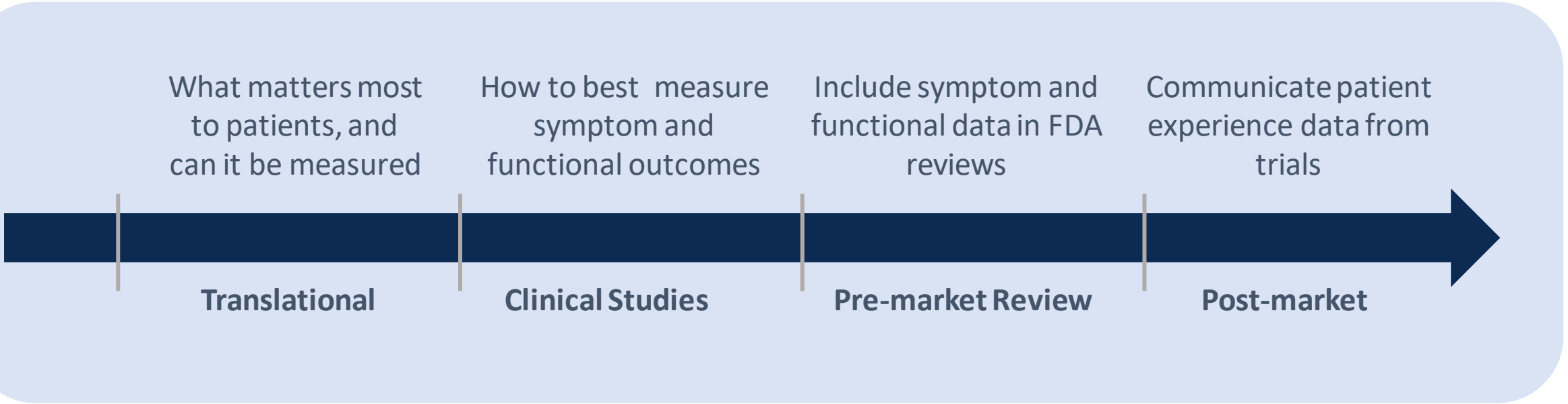
Oncology Center of Excellence

- The agency's first inter-center institute (Under the Cures Act)
- **Mission:** to achieve **patient-centered** regulatory decision making through innovation and collaboration



Patient Focused Drug Development

Applying Patient Focused Drug Development to Advance Rigorous Use of Patient-reported Outcome (PRO) data



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PRO Challenges

- 21st Century Cures Act encourages FDA to review and communicate patient experience data submitted in product reviews
- PRO data are frequently submitted; heterogeneity exists in analysis and presentation of data
- Product label (USPI) offers limited space to communicate patient experience data adequately

FOCR Tolerability White Paper

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

BROADENING THE DEFINITION OF TOLERABILITY IN CANCER CLINICAL TRIALS TO BETTER MEASURE THE PATIENT EXPERIENCE

OBJECTIVE

Robust safety and tolerability data are essential in cancer therapeutic studies, and some trials are specifically designed with a key objective of demonstrating improved safety and tolerability. The development of a clinical trial framework and data elements to demonstrate comparative safety and tolerability requires a suite of endpoints and approaches to enable meaningful interpretation of results for regulatory and clinical decision-making. Identification of data elements suitable for a comparative tolerability trial design would be useful across cancer clinical trial settings where a comprehensive characterization of safety and tolerability is a critical component in the evaluation of individual and collective patient benefit.

A multi-stakeholder working group was convened, including drug sponsors, regulators from the US and Europe, researchers, and patients, to develop a contemporary definition of tolerability that better encompasses the patient experience receiving a given treatment; to identify a broader array of data elements and methodologies that more fully characterize tolerability; and to consider a trial design framework that includes patient-reported outcome (PRO) endpoints and other clinical outcomes to support patient treatment choice, regulatory and clinician decision-making, and direct patient communication in U.S. Food and Drug Administration (FDA) labeling. The concepts outlined in this whitepaper were conceived to foster patient focused drug development.

CONTRIBUTORS

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Example of PRO in Labeling - Tolerability

XALKORI (crizotinib) Section 6.1

"Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with XALKORI in Studies 1 and 2 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally was within the first week of drug administration. The majority of patients on the XALKORI arms in Studies 1 and 2 (>50%) reported visual disturbances which occurred at a frequency of 4–7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in the VSAQ-ALK questionnaire."

Individual Toxicity versus Overall Side Effect Measure

- Drugs cause many symptomatic side effects (e.g., rash, diarrhea, neuropathy)
- How an individual “weighs” one over the other can differ
- Could an overall side effect measure be a useful summary metric?

Possible Options from Commonly Used Item Libraries Include:

- FACIT GP5 Question: “I am bothered by the side effects of treatment”
- EORTC Q168: “To what extent have you been troubled with side-effects from your treatment”

Core Outcomes

Overall Survival
Progression Free Survival
Overall Response Rate
Serum Biomarkers

CTCAE Safety Data
Dose Modifications

Hospitalizations
ED Visits
Morbid Procedures
Supportive Care Use

Clinician Reported and Biomarker Data

Disease Symptoms

Symptomatic Adverse Events

Overall Side Effect Impact

Physical Function:

Ability to Carry Out Activities that Require Physical Effort

Role Function:

Ability to Work and Perform Leisure Activities

Patient Generated Data

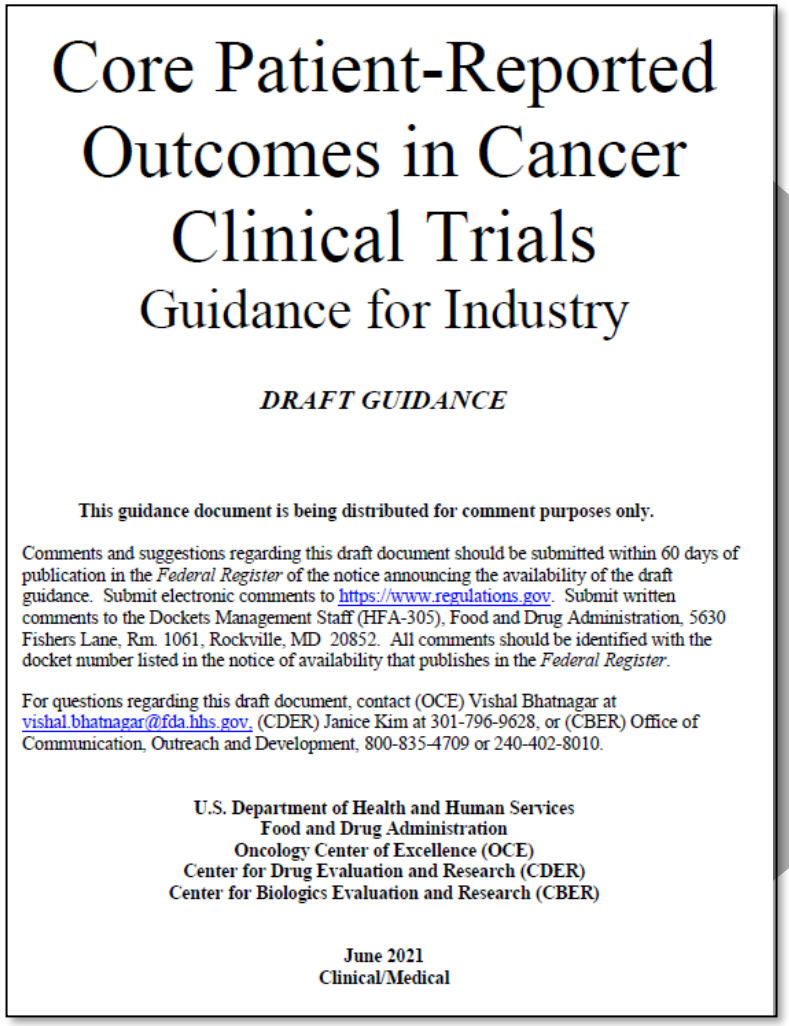
Example Assessment Frequency

	Six-month treatment period												Follow-up	
	BL	w2	w3	w4	w5	w6	w7	w8	M3	M4	M5	M6	M9	M12*
Symptomatic AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single Item Side Effect Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Function	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Role Function	X		X		X		X		X	X	X	X	X	X
Disease Symptoms	X				X				X			X		X
Other HRQOL	X								X			X		X

*Assessments at further timepoints would be context dependent

Additional relevant items outside of the Core Outcomes may be necessary depending on the context (e.g., swallowing function in a head and neck cancer trial)

OCE Core Outcomes Guidance



Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE) Vishal Bhatnagar at vishal.bhatnagar@fda.hhs.gov, (CDER) Janice Kim at 301-796-9628, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2021
Clinical/Medical

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials

What Is the Source of Symptomatic Toxicity Data?

- Tolerability is impacted by symptomatic side effects such as diarrhea, rash, neuropathy and nausea…

- What is the source of this data?

Clinicians – Common Terminology Criteria for Adverse Events (CTCAE)

Patients – Validated patient-reported outcome (PRO) measures

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) Item Library (Version 1.0)

FDA

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	A
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

Genitourinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	A
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	FI
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

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

NIH National Cancer Institute

*Complete library of items available at: https://healthcaredelivery.cancer.gov/pro-ctcae

Version date: 3/11/2020

PRO-CTCAE ⊗ (is not) CTCAE

CTCAE

Grade 1 Diarrhea	Grade 2 Diarrhea	Grade 3 Diarrhea	Grade 4 Diarrhea	Grade 5 Diarrhea
Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24hrs	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization	Life-threatening consequences (e.g., hemodynamic collapse)	Death

PRO-CTCAE

In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (diarrhea)?

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

PRO in Cancer Trials and Potential Implications

- PRO-CTCAE are generated by patients without interpretation by clinicians or other health care providers.
- **Differences between patient-reported and clinician-reported symptomatic AEs *are expected*.**
- There is no expectation that PRO data be reported to the FDA directly as safety data in cancer trials.
- PRO is not used to inform errors in clinician reporting, such as during clinical investigator site inspection.
- There is no expectation that PRO will be monitored real-time, however this should be clear in study materials (protocol, informed consent, etc.) and to patients.

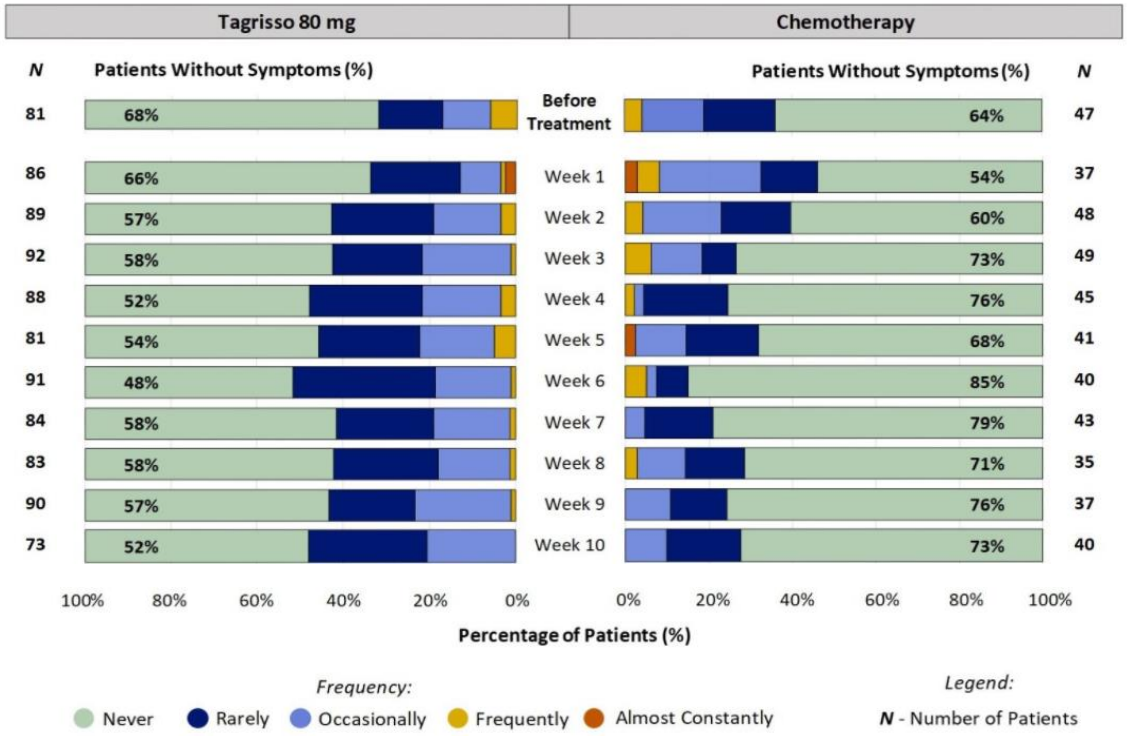
Kim et al. CCR 2018 https://pubmed.ncbi.nlm.nih.gov/29237718/

Communication is Key!

Patient-Reported Diarrhea During the First 24 Weeks on Treatment for Patients Who Completed a Questionnaire:

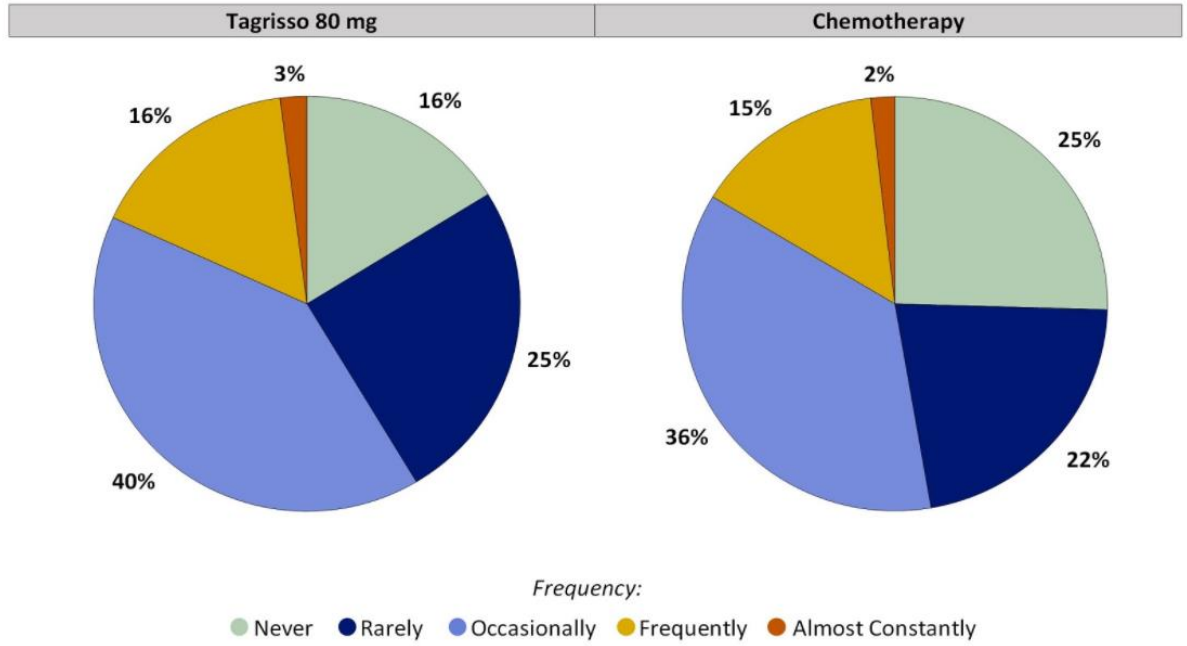
Figure 1 shows the percentage of patients reporting how often they had Diarrhea at each time point. For example, at week 2, 43% of patients taking Tagrisso reported Diarrhea (ranging from Rarely to Frequently). The range of patients who had any Diarrhea during the first 24 weeks of treatment with Tagrisso was between 34% - 53%. Click here for more information on how to read the graphs below.

Figure 1. Patient-Reported Diarrhea During the First 24 Weeks on Treatment



Worst Response Option for Diarrhea That Patients Reported During the First 24 Weeks on Treatment

Figure 2. Worst Patient-Reported Diarrhea During the First 24 Weeks on Treatment



https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice

Project Patient Voice

Project Patient Voice is an online platform for patients and caregivers along with their healthcare providers to look at patient-reported symptom data collected from cancer clinical trials.

What is the purpose of Project Patient Voice?

The aim is to show patient-reported symptom data consistently from select cancer clinical trials of approved products. This data is usually not in the US Prescribing Information (drug label) but can give healthcare providers extra information to discuss with patients and caregivers. If you are a patient or caregiver, and have questions about what you see here, ask your healthcare professional for more information.

Why is this needed?

What is the source of this patient-reported symptom information?

What is the difference between patient-reported symptom information and the safety information in the drug label?

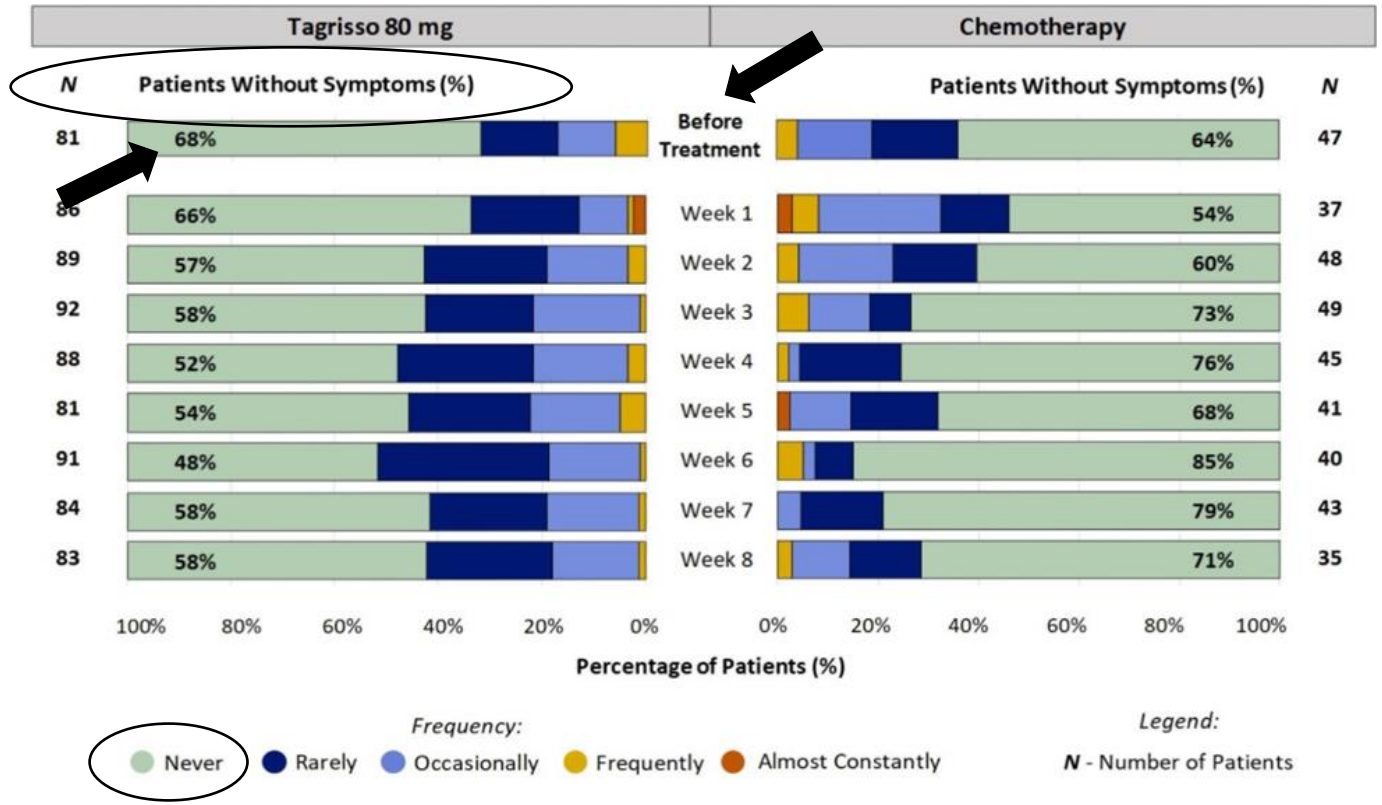
What is the Pilot Phase of Project Patient Voice?

How to use Project Patient Voice

Content current as of:
06/23/2020

"Patients Like Me"
What is Unique about PRO Symptomatic Side Effect Data?

Figure 1. Patient-Reported Diarrhea During the First 24 Weeks on Treatment

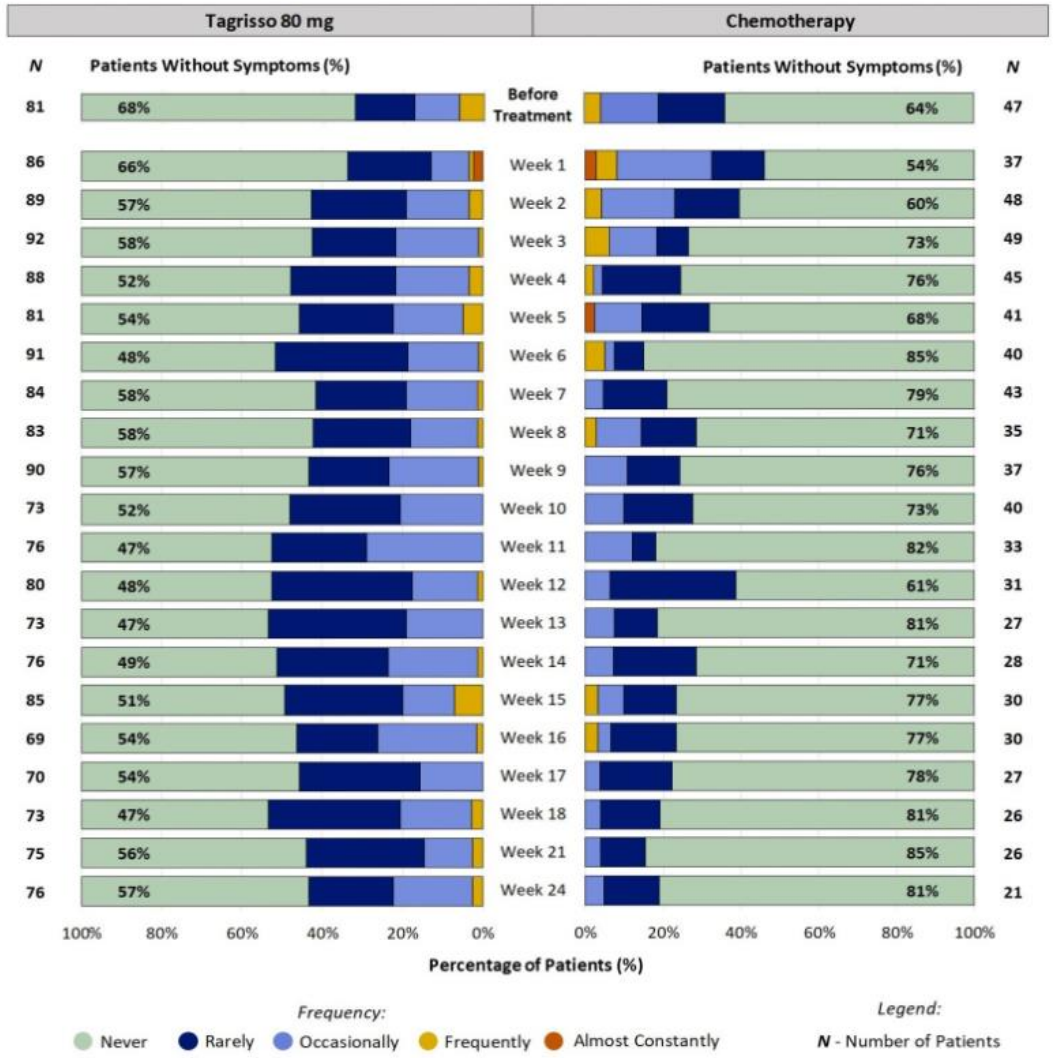


Baseline (before treatment) Information!

"I don't have any diarrhea... How might this drug affect patients like me?"

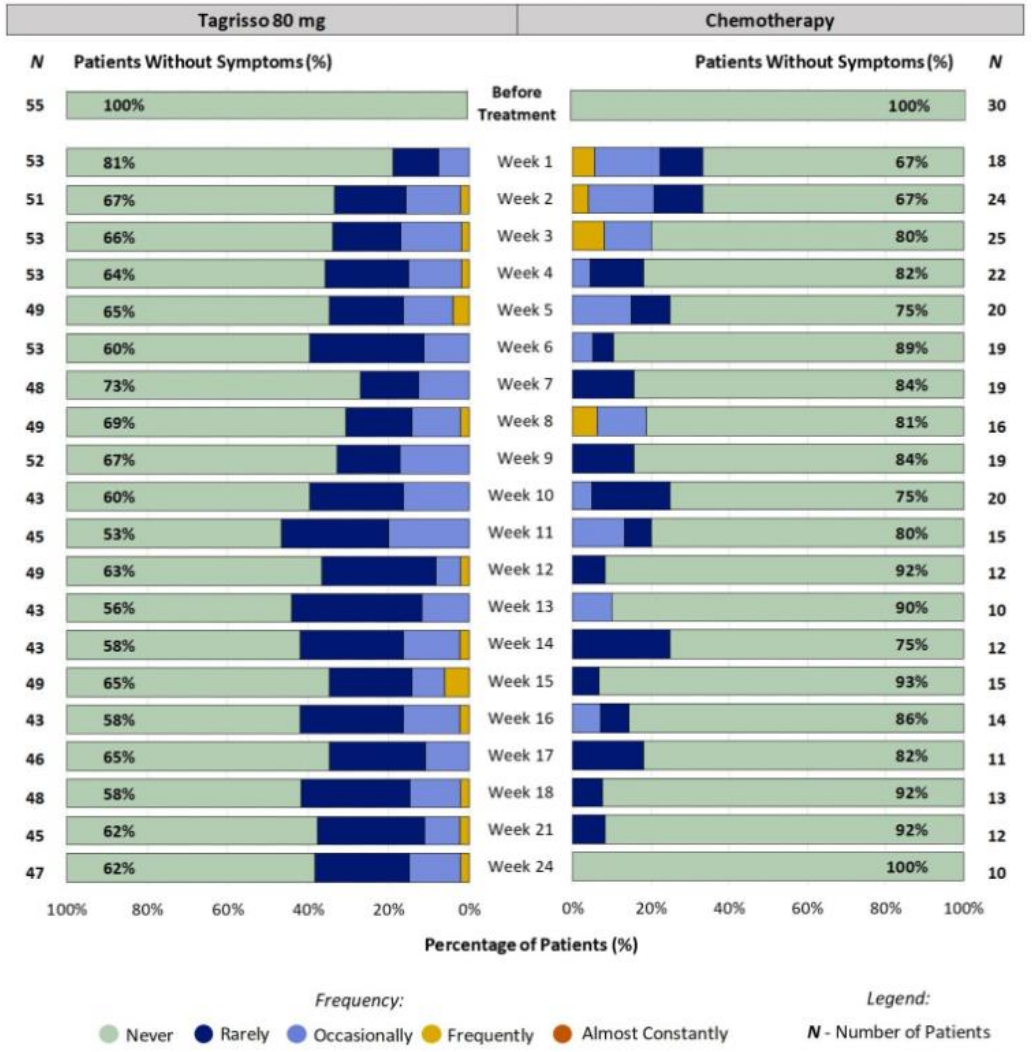
All Patients Treated

Figure 1. Patient-Reported Diarrhea During the First 24 Weeks on Treatment



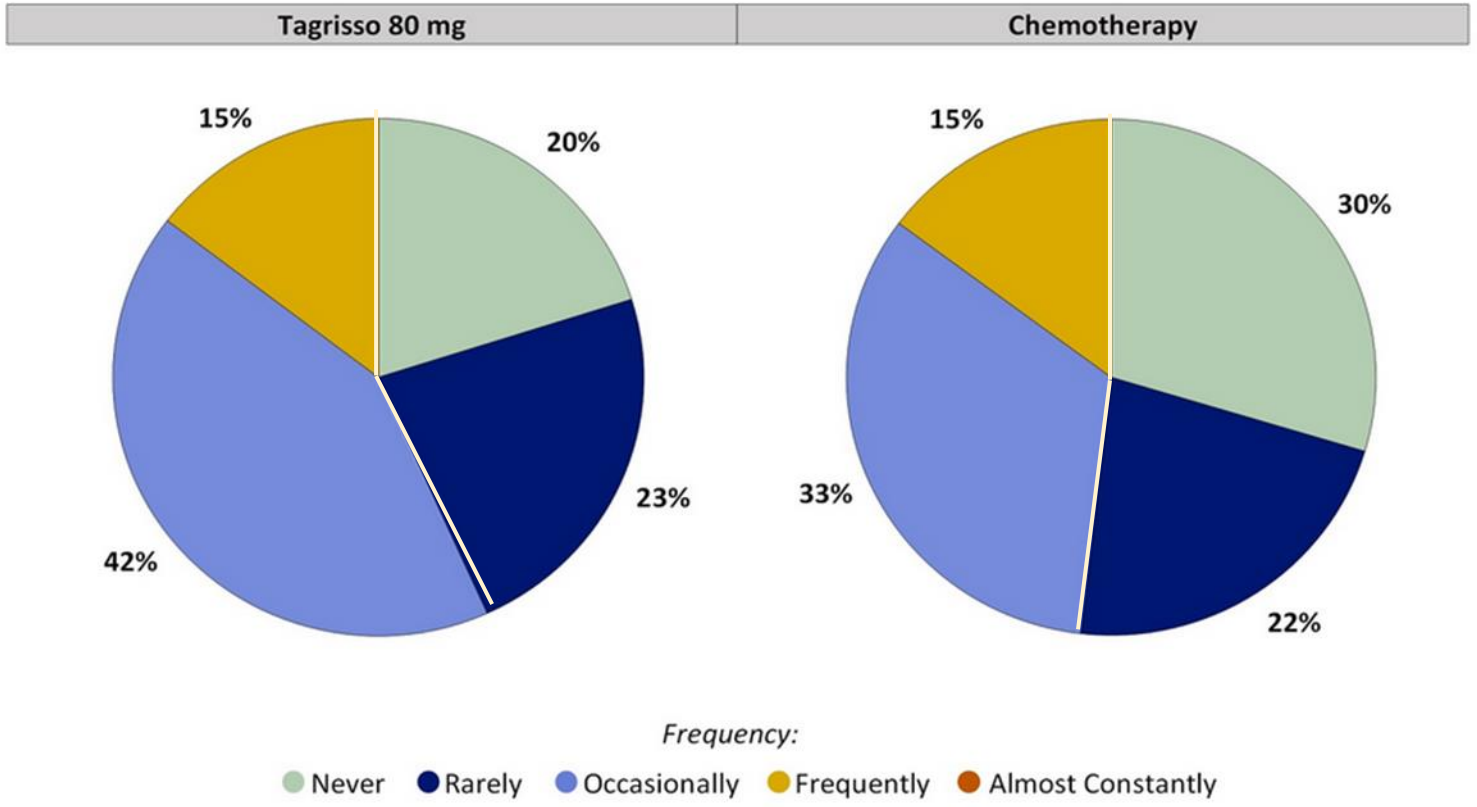
No Diarrhea at Baseline

Figure 3. Patient-Reported Diarrhea During the First 24 Weeks on Treatment: Patients Without Diarrhea Before Treatment



Worst Response Option for Diarrhea That Patients Reported During the First 24 Weeks on Treatment, for Patients Who Did Not Have Diarrhea Before Treatment:

Figure 4. Worst Patient-Reported Diarrhea During the First 24 Weeks on Treatment: Patients Without Diarrhea Before Treatment



Patients who had no Diarrhea before treatment and at least one on-treatment Diarrhea score were included in the analysis. Tagrisso (N=55), Chemotherapy (N=27).

Note challenge with sample size when evaluating subgroups…

From Aspirational to Practical
The Future of Patient Generated Data

- PRO can provide systematic and accurate data on patient symptoms
- Data quality for PRO has improved significantly since FDA Oncology initiated its patient-focused drug development program
- Digital Health Technology is improving symptom and function assessment (ePRO, wearables)
- ePRO and wearables can facilitate decentralized trial conduct
- Ongoing work to assess and describe physical function and overall side effect bother to assist in comparative tolerability assessment
- FDA increasing communication options from manuscripts to FDA label to Project Patient Voice

Acknowledgements

FDA Collaborators and Support

Rick Pazdur

Erica Horodniceanu

Mallorie Fiero

Jeff Chen

Laura Lee Johnson

External Collaborators

Lori Minasian

Sandra Mitchell

Amylou Dueck

Bellinda King-Kallimanis

Gita Thanarajasingam