Fifth Annual Clinical Outcomes Assessments In Cancer Clinical Trials (COA-CCT) Workshop

Session 4: Project Patient Voice – Methodological Perspectives

Fifth Annual

COA-CCT Workshop

FDA U.S. FOOD & DRUG ADMINISTRATION
ONCOLOGY CENTER OF EXCELLENCE

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SESSION 4

Project Patient Voice – Methodological Perspectives

MODERATOR
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#OCEOutcomes20

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Project Patient Voice Introduction

Project Goal

Adhere to the spirit of the 21st Century Cures mandate by creating a web-based public source of patient experience data that is accessible to patients, caregivers, and providers

Issue- Communicating PRO Data

- 21st Century Cures Act encourages FDA to review and communicate patient experience data submitted in product reviews
- Patient-reported outcome (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

Solution- Project Patient Voice

- Project Patient Voice is a pilot, web-based, public source of PRO data describing patient-reported side effects
- Develop consistent analytic presentations
- Partner with sponsors who volunteer to submit their existing trial data for consideration

Drug Trials Snapshots Serves as a Precedent for Project Patient Voice*

Drug	Active Ingredient	Date of FDA Approval	What is it Approved For	Package Insert
ADDYI	flibanserin	August 18, 2015	Treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women	Addyi
ADLYXIN	lixisenatide	July 27, 2016	Improvement of blood sugar control in adults with diabetes mellitus (DM) type 2 when used in addition to diet and exercise	Adlyxin
AEMCOLO	rifamycin	November 16, 2018	Treatment of traveler's diarrhea in adults	Aemcolo
AIMOVIG	erenumab-aooe	May 17, 2018	Preventive treatment of migraine in adults	Aimovig
AJOVY	fremanezumab-vfrm	September 14, 2018	Preventive treatment of migraine in adults	Ajovy
AKYNZEO	fosnetupitant and palonosetron	April 20, 2018	Prevention of the nausea and vomiting that happens right away or later in adults receiving certain anticancer medicines (chemotherapy)	Akynzeo

Drug Trials Snapshots provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. Information provided in these Snapshots highlights any differences in the benefits and side effects among sex, race and age groups. It is part of an overall FDA effort to make demographic data more available and transparent.

Current State

– FDA OCE Patient Focused Drug Development team:

Key Technical and Data Challenges

- Website design, deployment with multiple sponsor submissions and maintenance
- 508 compliance (access for people with disabilities) for complex graphs
- Agreement with commercial sponsor on tables and figures
- Providing adequate warning to users on limitations of the analyses (e.g. key side effects may not be captured by PRO surveys and this is not a replacement for clinician reported safety as described in the label)

Making Project Patient Voice Fully Accessible: Compliance with Section 508

- Commitment to accessible data to everyone
- The Rehabilitation Act requires programs and activities funded by federal agencies are accessible to individuals with disabilities
- Section 508 of that act covers information and communication technology
- Impacted colors chosen, font size, labels etc.

Future State

- Obtain feedback through a public workshop and other means…
- **Welcome to the 2020 COA-CCT Workshop!**

Project Patient Voice Live Demo

"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."

Vishal Bhatnagar, MD

Bellinda King-Kallimanis, PhD

Vishal and Bellinda will demonstrate how Project Patient Voice can be used by a clinician and patient

AURA3

Project Patient Voice is intended to be used with a healthcare professional when discussing the potential symptoms related to a cancer and cancer treatment. Do not rely on Project Patient Voice alone to make decisions about medical care. Do not use Project Patient Voice to substitute for advice from your health care professional. Conclusions about patient experiences with symptoms may be limited because not all symptoms may have been captured by the patient-reported questionnaire.

How Was the AURA3 Study Conducted?

AURA3 is a Phase III, open label, randomized study comparing TAGRISSO™ with platinum-based doublet chemotherapy. To be included in AURA3, patients had an abnormal epidermal growth factor receptor (EGFRm+/T790M+) lung cancer that had spread to other parts of the lungs or body (locally advanced or metastatic non-small cell lung cancer - NSCLC) and had previously been treated with an approved EGFR-TKI medicine that had stopped working or did not work. Patients were allocated by a ratio of 2:1 Tagrisso: chemotherapy. For more information on how this study was conducted, refer to the product label.

Which Questionnaire Was Used to Collect Patient-Reported Symptoms?

Patients reported their symptom experiences via the Patient Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire. PRO-CTCAE was developed by the National Cancer Institute (NCI) to evaluate symptomatic toxicity in patients in oncology clinical trials. The PRO-CTCAE questionnaire was designed to provide additional information that is complementary to existing safety and tolerability assessments reported by clinicians.

Table 1. Summary of Symptom Frequency

Column A	Column B		Column C		Column D		Column E	
Symptom (Attribute)	**No. of Patients[1]**		**Any symptom before treatment (%)[2]**		**Any Worsening on treatment (%)[3]**		**Worsening to Score 3 or 4 (%)[4]**	
	Tagrisso	**Chemo**	**Tagrisso**	**Chemo**	**Tagrisso**	**Chemo**	**Tagrisso**	**Chemo**
Nausea (F)	80	44	25%	32%	41%	77%	6%	39%
Blurry Vision (S)	80	44	29%	32%	39%	52%	3%	9%
Decreased Appetite (S)	80	44	54%	52%	39%	68%	10%	30%
Constipation (S)	80	44	43%	45%	38%	64%	10%	32%
Ridges or Bumps on your Fingernails or Toenails (O)	80	44	30%	34%	38%	30%	N/A	N/A
Problems Tasting Food or Drink (S)	80	44	24%	30%	36%	73%	6%	27%
Change in Color of your Fingernails or Toenails (O)	80	44	6%	7%	36%	32%	N/A	N/A
Skin Cracking at Corners of your Mouth (S)	80	44	14%	2%	34%	48%	5%	5%

Attributes: A = Amount; F = Frequency; O = Occurrence; S = Severity/Intensity
Chemo = Chemotherapy; N/A = Not Applicable (For symptoms with Occurrence attribute, worsening to score 3 or 4 is not applicable, as responses are either Yes or No)

[1] No. of Patients: The number of patients who provided a score before treatment and at least one on-treatment score (between weeks 1-24).
[2] Any Symptom Before Treatment (%): The percentage of patients whose symptom score before treatment was 1-4.
[3] Any Worsening (%): The percentage of patients whose symptom score increased during treatment, with respect to their score before treatment.
[4] Worsening to Score 3 or 4 (%): The percentage of patients whose symptom score increased to 3 or 4 during treatment, with respect to their score before treatment.

AURA3: Nausea

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← Back to summary table

Download symptom data (XLSX, 24KB)

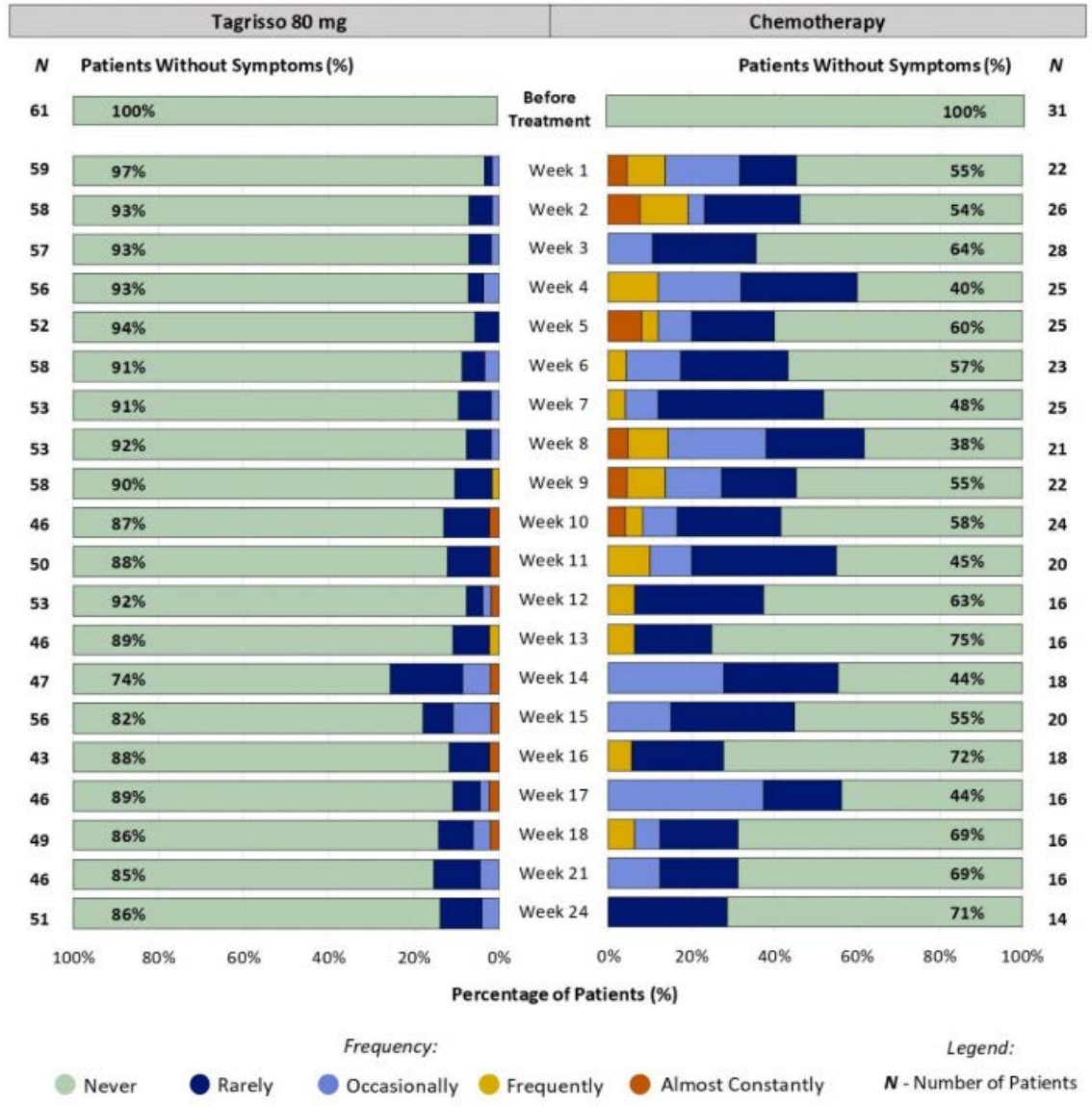
In AURA3 Study, Patients Were Asked: "In the last 7 days, how OFTEN did you have NAUSEA?"

Patients scored the frequency of their Nausea on a 5-point scale (Never, Rarely, Occasionally, Frequently, Almost Constantly)

Patient-Reported Nausea 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 Nausea at each time point. For example, at week 2, 20% of patients taking Tagrisso reported Nausea (ranging from Rarely to Frequently). The range of patients who had any Nausea during the first 24 weeks of treatment with Tagrisso was between 12% - 29%. Click here for more information on how to read the graphs below.

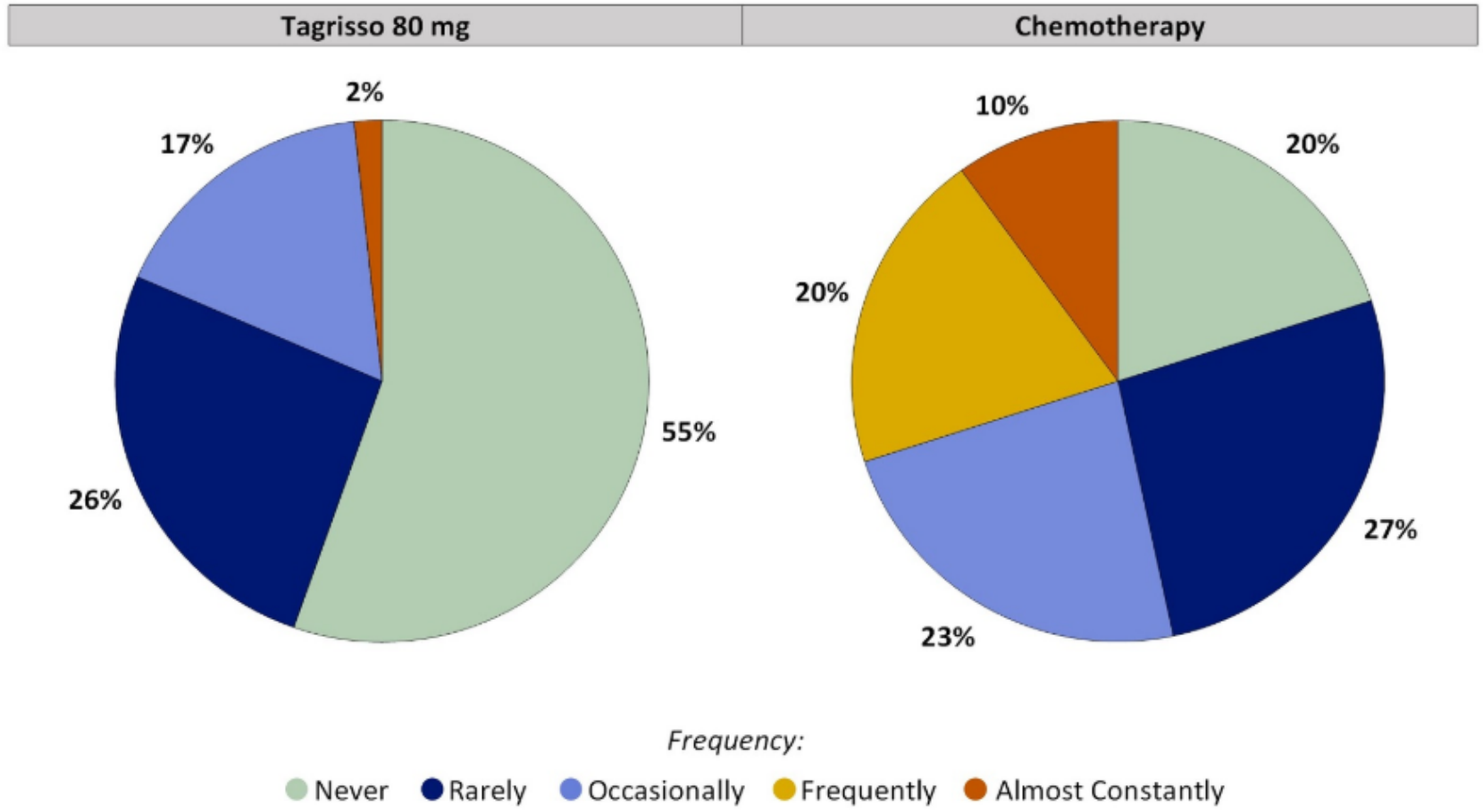
Figure 3. Patient-Reported Nausea During the First 24 Weeks on Treatment: Patients Without Nausea Before Treatment



All responses from patients who did not report Nausea before treatment were included in the analysis. Some patients did not report their symptoms every week, therefore the number of patients may vary between weeks. Furthermore, not all patients remained on the treatment for 24 weeks (e.g., some stop treatment for worsening disease) which is a reason for the change in the number of patients over the course of treatment.

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

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

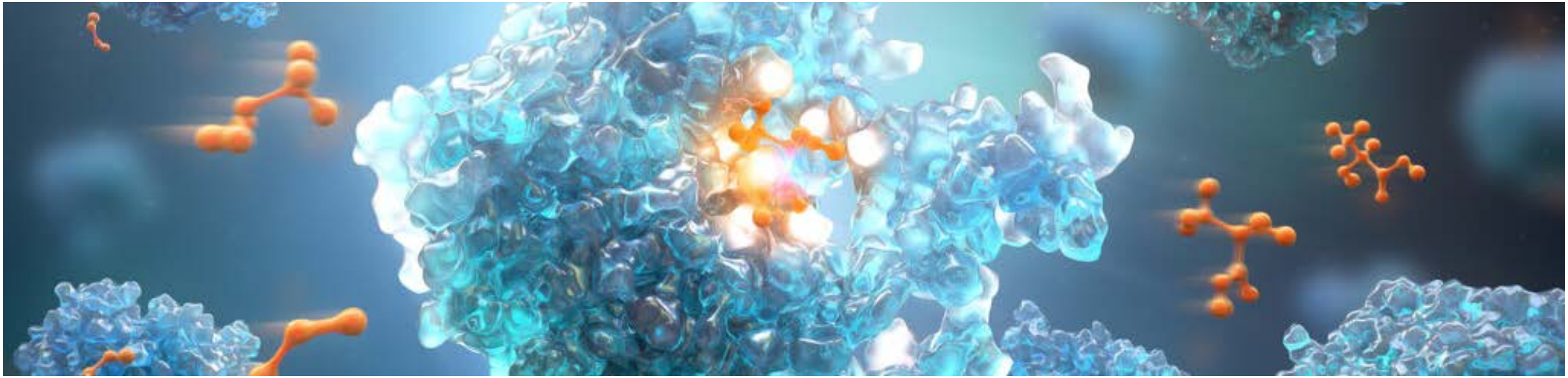


Patients who had no Nausea before treatment and at least one on-treatment Nausea score were included in the analysis. Tagrisso (N=60), Chemotherapy (N=30).

Katarina Halling

Visualization of Patient experience

Katarina Halling, BSc, Head Patient Centered Science, AstraZeneca



Case study: Tagrisso

PRO strategy starting in Phase1 aiming at ensuring patient experience is fully captured

Trials included patient reported symptoms, tolerability and HRQL
PRO instruments:
EORTC QLQ-C30, EORTC QLQ-LC13 and PRO-CTCAE

PRO-CTCAE item selection

- 28 symptoms
- Selected based on documented EGFR TKI class data, chemotherapy clinical data, emerging Phase I Tagrisso ® clinical data, targeted literature review, expert input, and patient interviews

Communication of PRO data to Stakeholders

- Regulatory: EMA approval of PRO label claims
- Payers: PRO data part of submissions
- Project Patient Voice gives opportunity to share the PRO data with patients and HCPs

Patients want to have information on patient reported side effect symptoms before starting cancer treatment

"Somebody new to cancer really doesn't know what to expect, and this can give you an overall picture of what to expect"

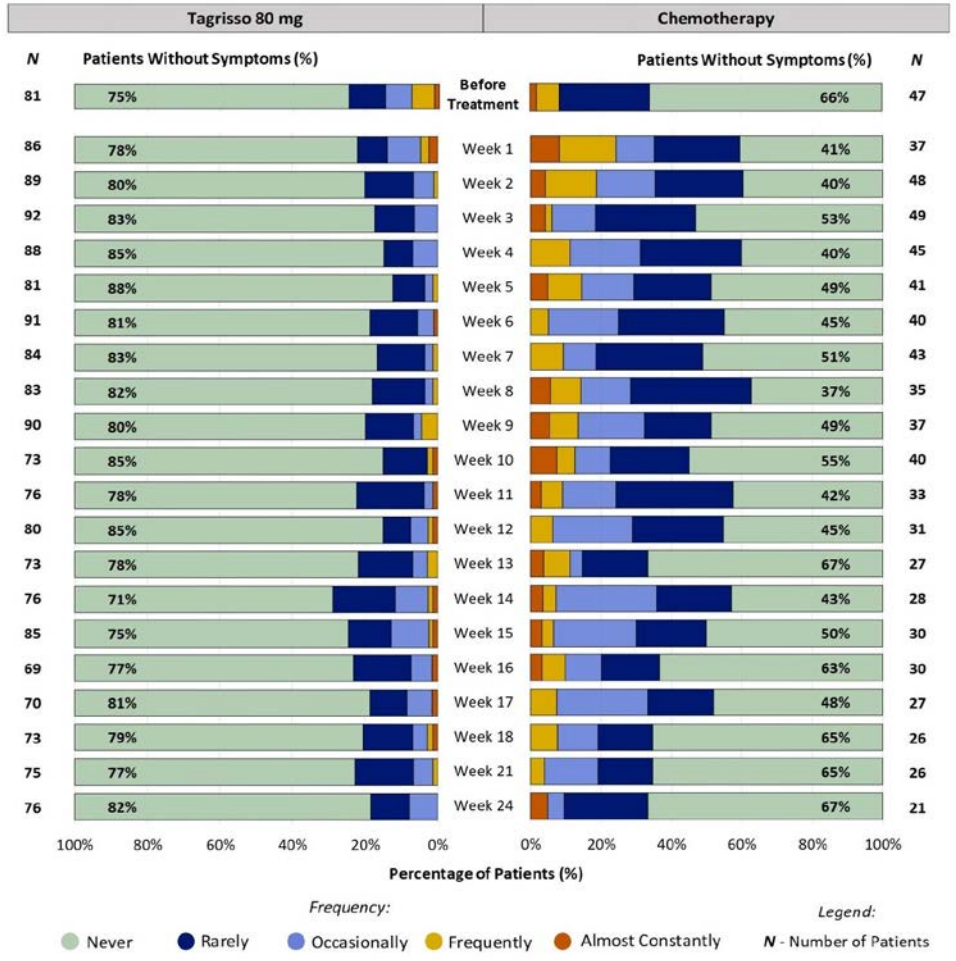
"I have never seen this [kind of information] before. This would have made a huge difference"

- Patients placed a high value on knowing other patients' experience before starting treatment
- Visualisations provided a good idea of what to expect whilst on treatment
- Would like to know this information before treatment

"This shows me how I may react to it [the drug]. Would like to see this at the point I have symptoms and doctor can tell me what will help"

"Helpful to see this information when [the] oncologist is talking to me about the plan – when trying to decide whether you want the treatment"

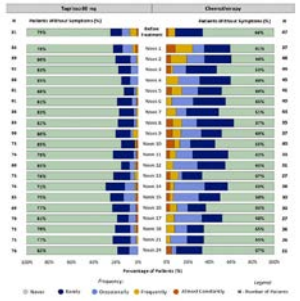
Visualization of patient experience



Key considerations:

- Display of comparator arm
- Including baseline assessment
- Visualizing frequency of experienced symptom
- Enabling overview of both treatments
- Number of patients at each assessment
- PRO-CTCAE assessment frequency clear

Learnings



- 28 PRO-CTCAE symptoms is too many in one study
- PRO-CTCAE data should be treated as other PRO data
- Has to be part of the patient experience strategy from early planning

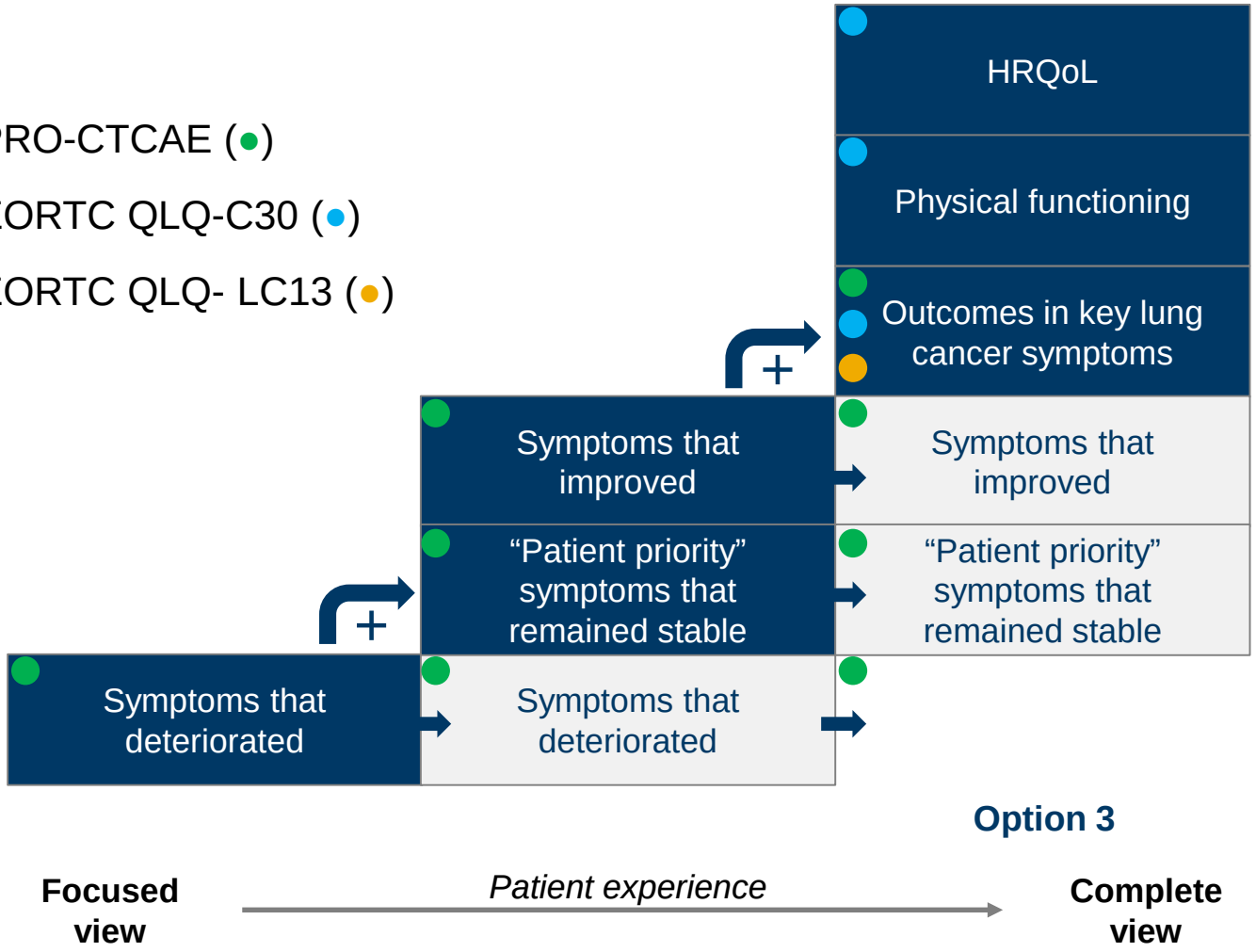
- The work took years and included multiple analytical and visual approaches
- The balance between comprehensive and simple is complex
- A standardized approach will allow for comparisons

Collaboration is critical

- Cross-functional in pharma
- With patients
- With FDA

Consideration for future 2: Visualisation of broader patient experience in addition to patient reported side effects

Approaches for summarizing PRO results



Presenting data collected from other PRO instruments alongside PRO-CTCAE can provide a more holistic view of the patient experience

Summary

- Project Patient Voice is a big milestone in Patient focused drug development
- Important step in sharing PRO data with patients and HCPs
- Opportunities to further improve visualizations of patient experience in cancer trials
- Thank you

Confidentiality Notice

Janice Kim

Discussion of Polling Question 1 & 2

Polling Question 1: What percentage of trial participants in the chemotherapy arm of this trial reported *fatigue, tiredness of lack of energy* before treatment?

77% answered correctly, 13% missing

Polling Question 2: Of the symptoms below, which had the largest proportion of worsening to a **score of 3 or 4** in the Tagrisso arm?

A. Loose or watery stools

B. Pain in the abdomen

C. Fatigue, tiredness or lack of energy

D. Hand-foot syndrome

94% answered correctly, 3% missing

Column A	Column B		Column C		Column D		Column E	
Symptom (Attribute)	No. of Patients[1]		Any symptom before treatment (%)[2]		Any Worsening on treatment (%)[3]		Worsening to Score 3 or 4 (%)[4]	
	Tagrisso	Chemo	Tagrisso	Chemo	Tagrisso	Chemo	Tagrisso	Chemo
Loose or Watery Stools (F)	*80*	*44*	31%	39%	70%	61%	19%	16%
Numbness or Tingling in Hands or Feet (S)	*80*	*44*	24%	30%	59%	50%	3%	7%
Pain in the Abdomen (F)	*80*	*44*	19%	43%	59%	61%	9%	14%
Fatigue, Tiredness or Lack of Energy (S)	*80*	*44*	64%	70%	58%	73%	24%	45%
Hand-Foot Syndrome (S)	*80*	*44*	31%	30%	54%	43%	5%	5%
Acne or Pimples on the Face or Chest (S)	*80*	*44*	36%	30%	53%	32%	0%	0%

Paul Kluetz

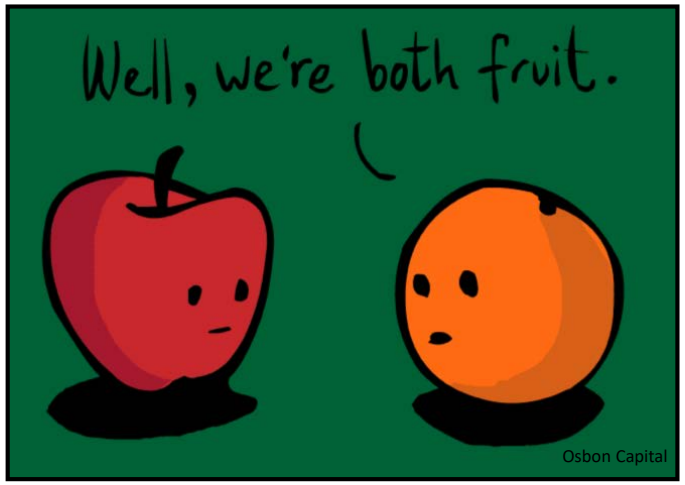
Lori Minasian

Mallorie Fiero

Direct comparisons between treatment arms may be misleading

- Not all randomized patients were evaluated
- Different reasons for patient dropout between the two arms
  - Example: More patients on one treatment arm dropped out due to drug toxicity or death
  - Missing data interferes with ability to compare effects (FDA PRO Guidance 2009)

Treatment arms are no longer comparable



Janice Kim

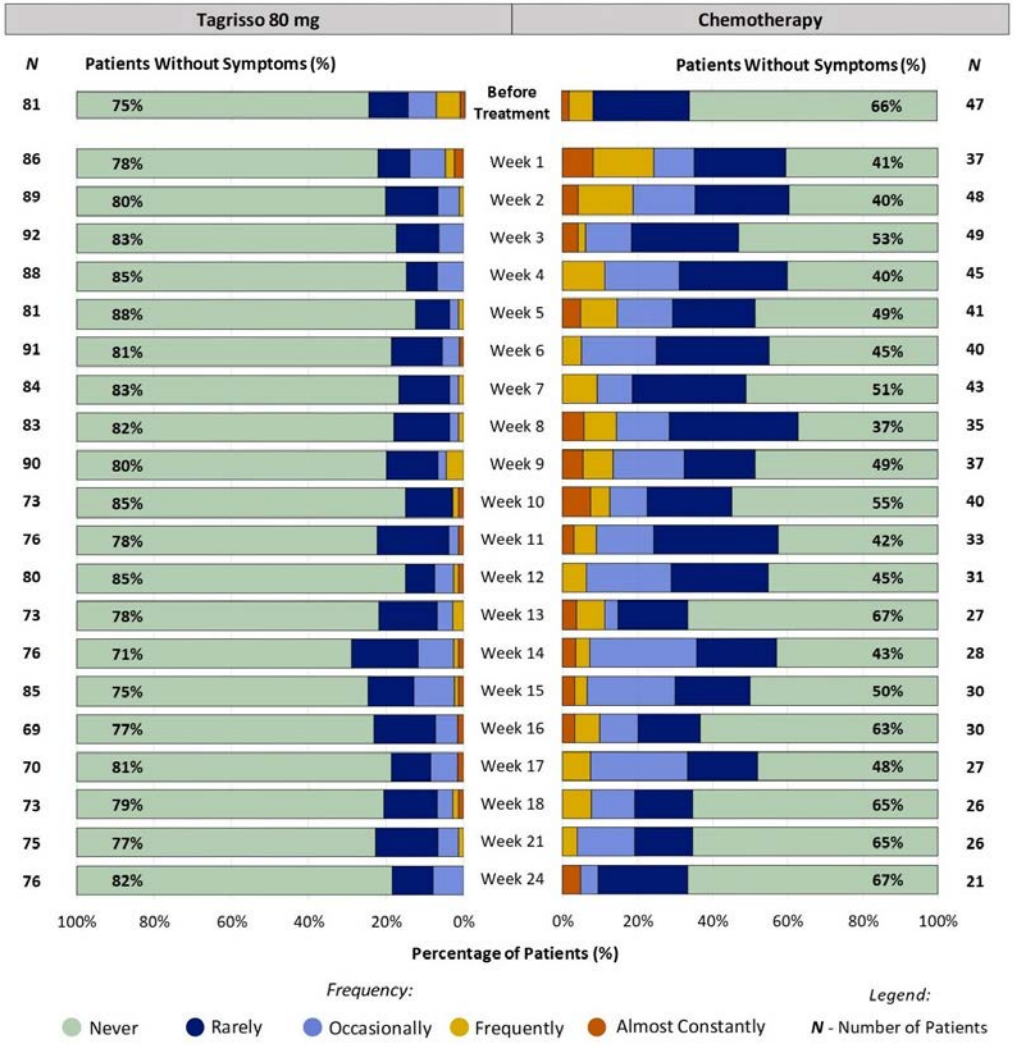
Discussion of Polling Question 3

Polling Question 3: From the weeks listed below, which week had the least participants reporting *never* for the Tagrisso arm?

A. Week 1
B. Week 11
C. Week 14
D. Week 16

83% answered correctly, 4% missing

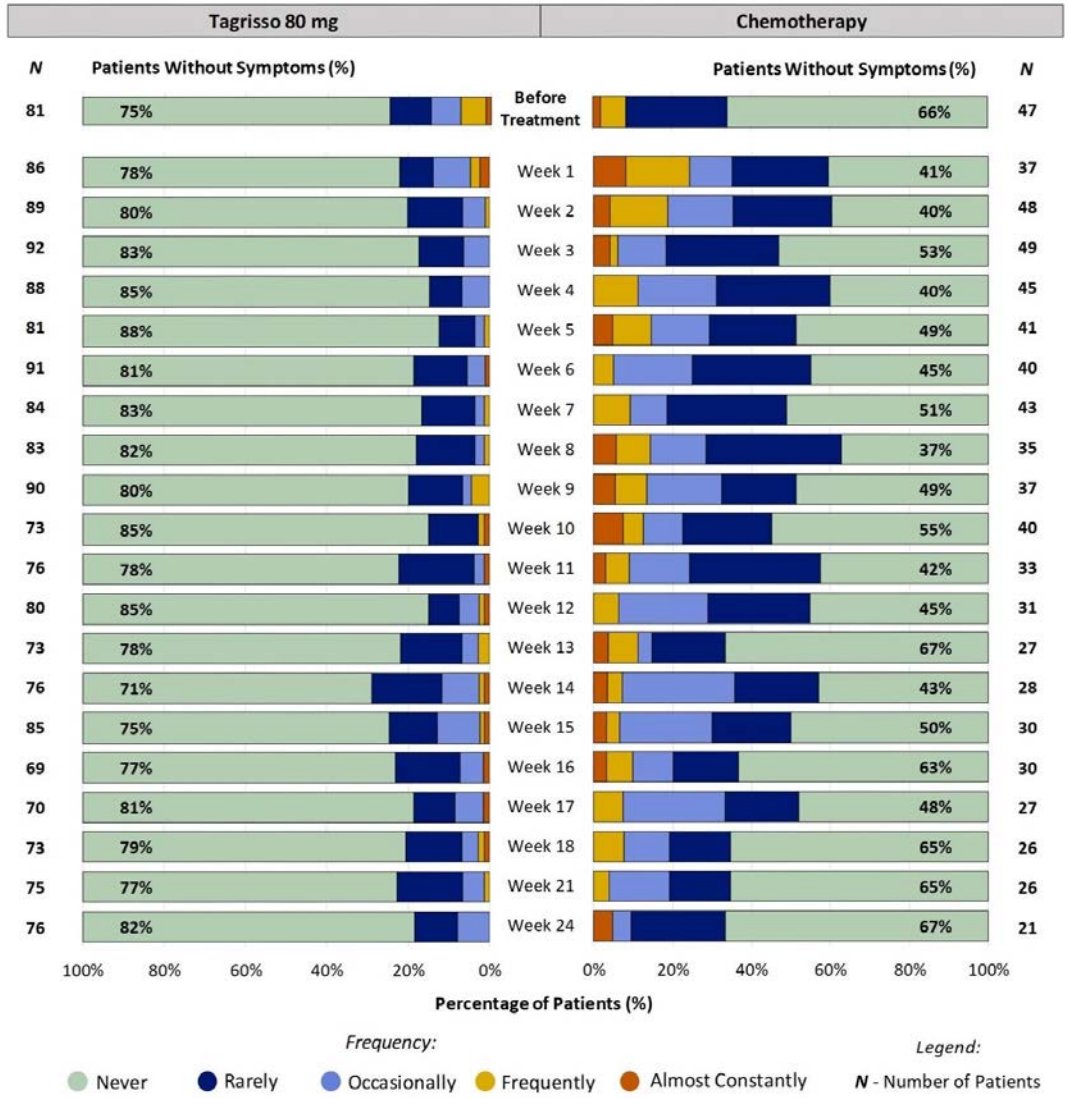
Figure 1. Patient-Reported Nausea During the First 24 Weeks on Treatment



Patient-Reported Nausea During the First 24 Weeks on Treatment for Patients Who Completed the Questionnaire

Paul Kluetz

Claire Snyder

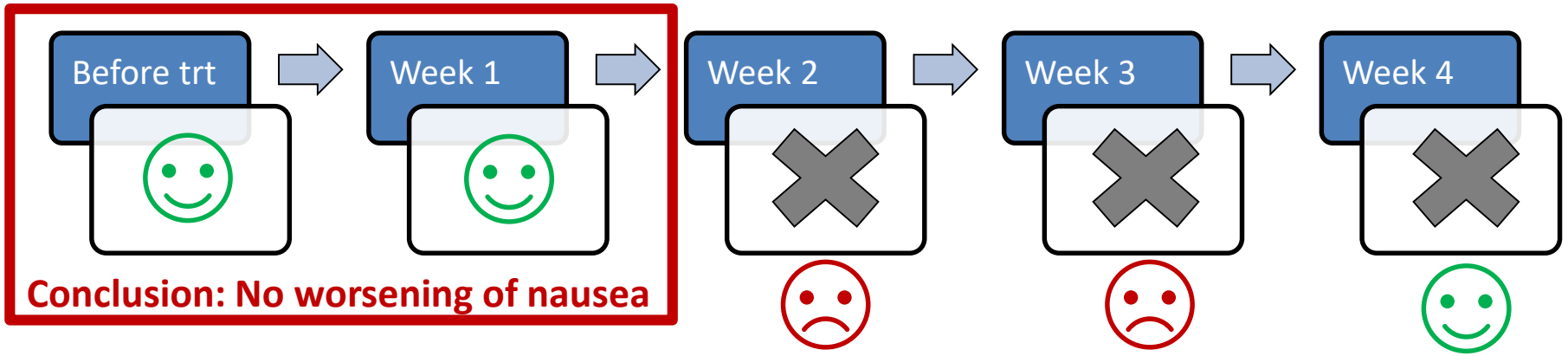


Mallorie Fiero

1. Missing assessments can impact interpretation of PROs

- Example: Overall PRO summary scores
  - Any worsening on treatment
  - Worsening to score 3 or 4
  - Worst patient-reported symptom

- However, is it possible for patients to feel so sick (e.g., nauseated) that they cannot fill out a PRO questionnaire?



Mallorie Fiero

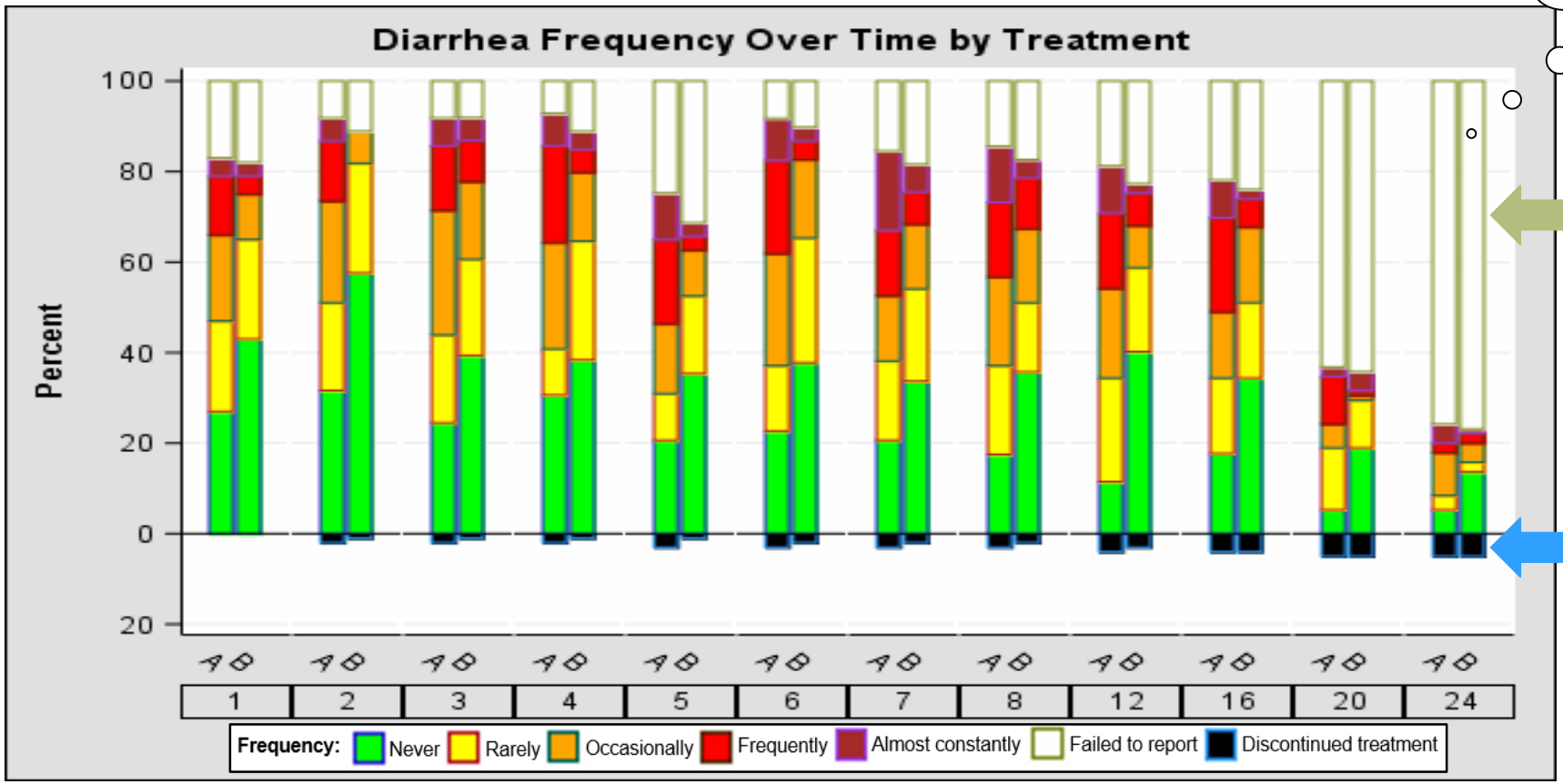
2. Excluding missing PRO assessments can lead to misinterpretation

- Patients who dropout are likely worse because of progression or death
  - Concern of misinterpreting patient experience when these events are not portrayed
- To get a full picture of patient experience, it is useful to display patients who are dropping out or failing to complete the questionnaire
  - Example: Some patients cannot tolerate the drug because of GI side effects and had to discontinue treatment
- It is important to collect reasons for missing PRO assessments

Mallorie Fiero

3. Informative description of missing data is useful

- We want to avoid misinterpretation of patient experience
- What is the best way to describe missing PROs over time in a way that is interpretable and useful? This is not an easy task.



Patients on treatment, but did not report

Patients who discontinued treatment

Source: Coens, COA-CCT 2017

Some Patients Did Not Report Nausea Before Treatment Before Treatment

Paul Kluetz

Lori Minasian

Discussion of Polling Question 4 & 5

Polling Question 4: What percentage of patients in the Tagrisso arm reported their worst diarrhea as occurring *Frequently?*

90% answered correctly, 5% missing

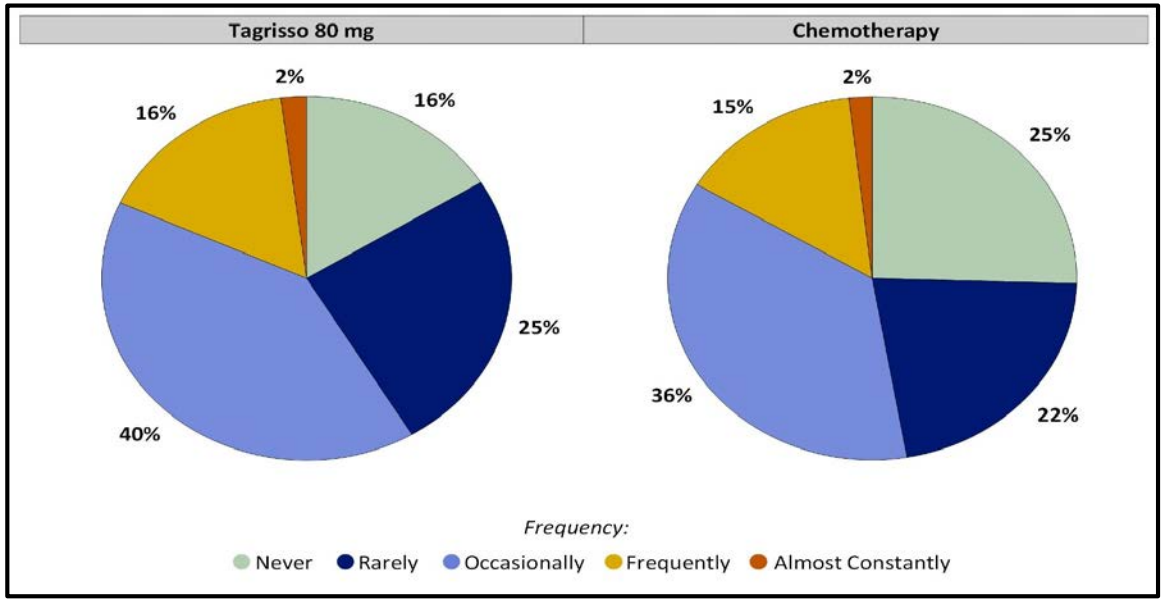
Polling Question 5: What would be best way to interpret 'Worst patient-reported diarrhea during the first 24 weeks on treatment' if you don't agree with one of the definitions shown?

a. The worst score a participants reported at any time during the first 24 weeks of their treatment
b. The average worst score reported by patients during the first 24 weeks of their treatment
c. Other

67% answered correctly, 4% missing

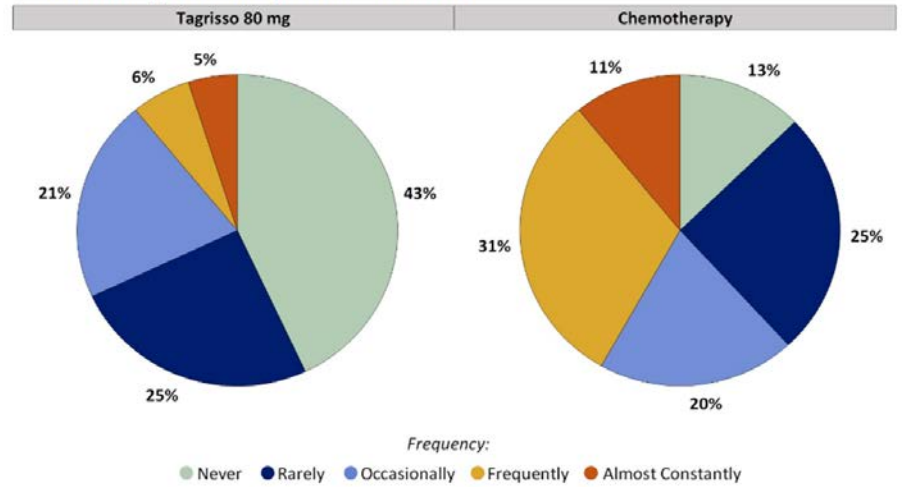
Janice Kim

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



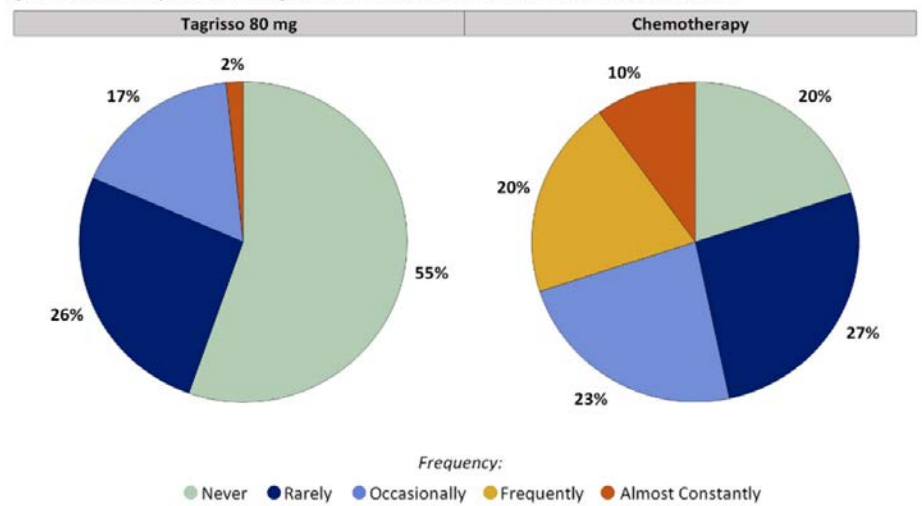
Worst Response Option for Nausea That Patients Reported During the First 24 Weeks on Treatment

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



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

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



SESSION 4 CONCLUDING REMARKS

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#OCEOutcomes