Beyond Maximum Grade:

NCI-Related Activities in Tolerability of Cancer Treatment

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Two Aspects in Adverse Event Reporting

Reporting of the individual events

- Clinical identification and grading that is clinician reported

- Real-time review of event and actionable

- Ongoing activities: integrate patient reporting of symptomatic adverse events (PRO-CTCAE)

Analyzing aggregate events across the trial

- Current, long-standing approach is the table of maximum grade experienced by a patient during the trial

- Ongoing activities: explore and develop analytic methods for chronic and cumulative events to describe tolerability

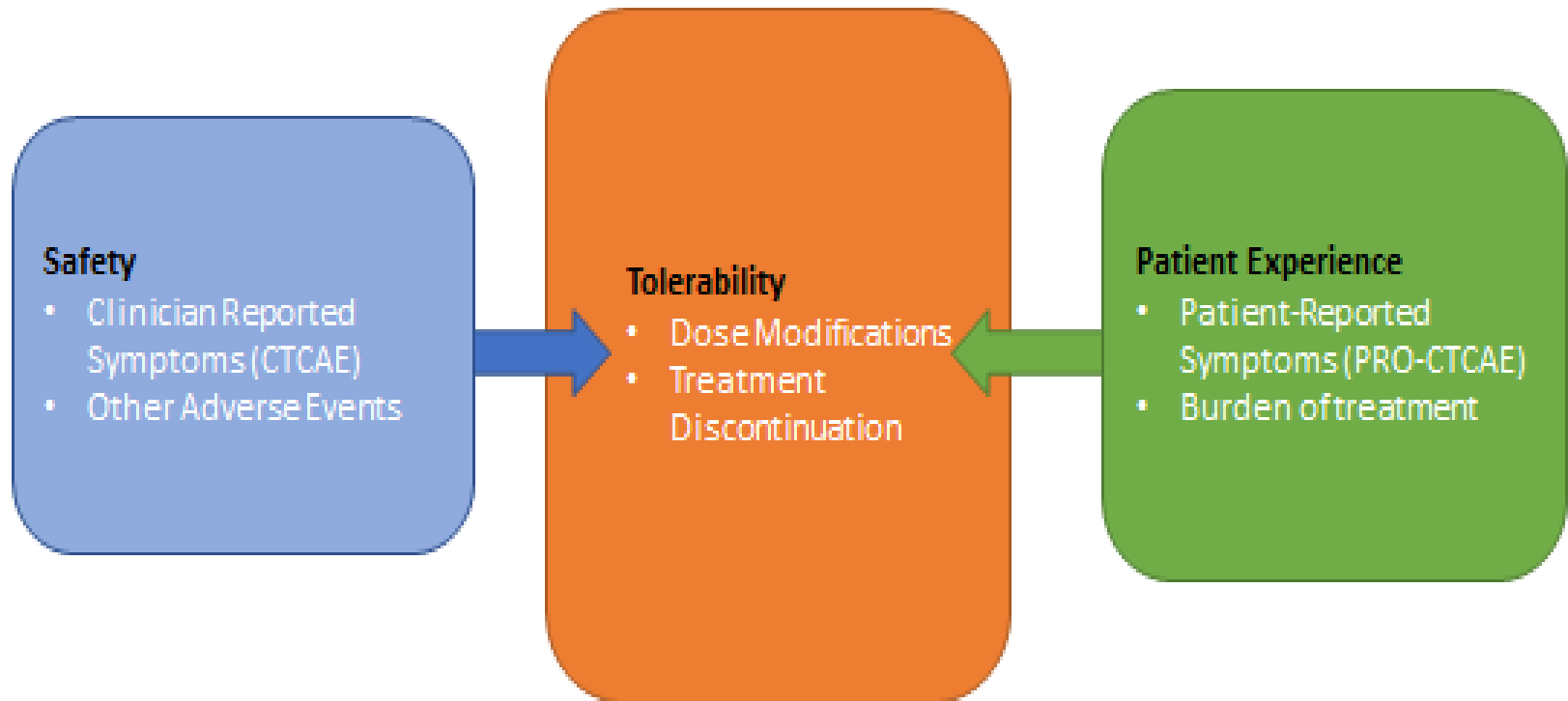# Inclusion of Patient Input for Tolerability

Clinicians and Patients Provide Complementary Information

- <u>Clinicians</u> focus on safety or toxicities requiring action

- <u>Patients</u> focus on day-to-day effects of therapies (tolerability)

NCI PRO-CTCAE specifically designed to capture patient reported symptomatic AEs to complement CTCAE reporting

- Grading schema for CTCAE involves frequency, severity and interference with activities of daily living

- For a PRO-CTCAE item, there are 1-3 questions that a patient answers to capture those attributes

  ➢ Opportunity to consider severity and interference separately for tolerability over time

Safety, Tolerability, and Patient Experience

Safety
- Clinician Reported Symptoms (CTCAE)
- Other Adverse Events

Tolerability
- Dose Modifications
- Treatment Discontinuation

Patient Experience
- Patient-Reported Symptoms (PRO-CTCAE)
- Burden of treatment

Pilot Project for Electronic Collection: ePRO

- A mobile app that collects patient responses to questionnaires/diaries and transfers data to the Medidata Clinical Cloud

  ➢ Integrated into remote data capture

- Allows use of multiple different PRO tools

  ➢ Patient diaries, questionnaires

- Facilitates patient compliance

  ➢ Allows conditional branching

- Reduces data entry burden by staff

- Available for Android and iOS mobile devices

- In use for NCTN, NCORP and ETCTN trials
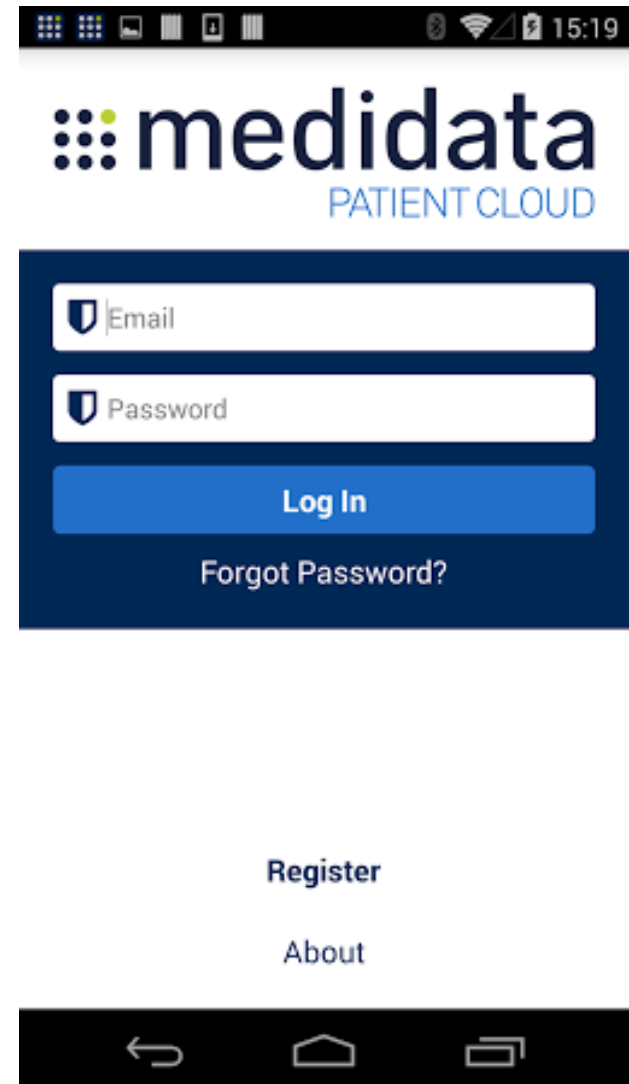
# Pilot for PRO-CTCAE in ETCTN Clinical Trials

- To capture patients' perception of symptomatic adverse events in a manner complementary to clinician-graded adverse events

  - ➤ Currently, 3 ETCTN trials with selected PRO-CTCAE items to be collected through electronic collection (ePRO)

  - ➤ PRO-CTCAE items complement the CTCAE items identified for monitoring

- Supplemental funding announcement sent to ETCTN investigators to help sites train staff and patients in use of ePRO

  - ➤ Three sites (Mayo Clinic, Duke, and Princess Margaret) have just received supplemental funding for training and utilization

- NCI Investigational Drug Branch and NCI ePRO team working to streamline and facilitate inclusion of PRO-CTCAE items in early phase trials

Current Method for Tolerability

Based upon Cytotoxic Chemotherapy:

- Standard Approach
  - Phase 1 dose escalation
    - Increasing doses levels based upon most severe adverse events reported in cycle #1
  - Safety assessment is based upon an agent having a narrow therapeutic window (dose for serious toxicity very close to dose for efficacy)
  - Assumes that tolerability is defined by the first cycle
  - Does not provide information regarding onset, resolution and trajectory of the adverse events over time

- Exploratory analysis for treatment emergent adverse events (TEAEs) already under consideration, but no standard approach

Characterization and Analysis of Treatment Emergent Adverse Events (TEAEs).
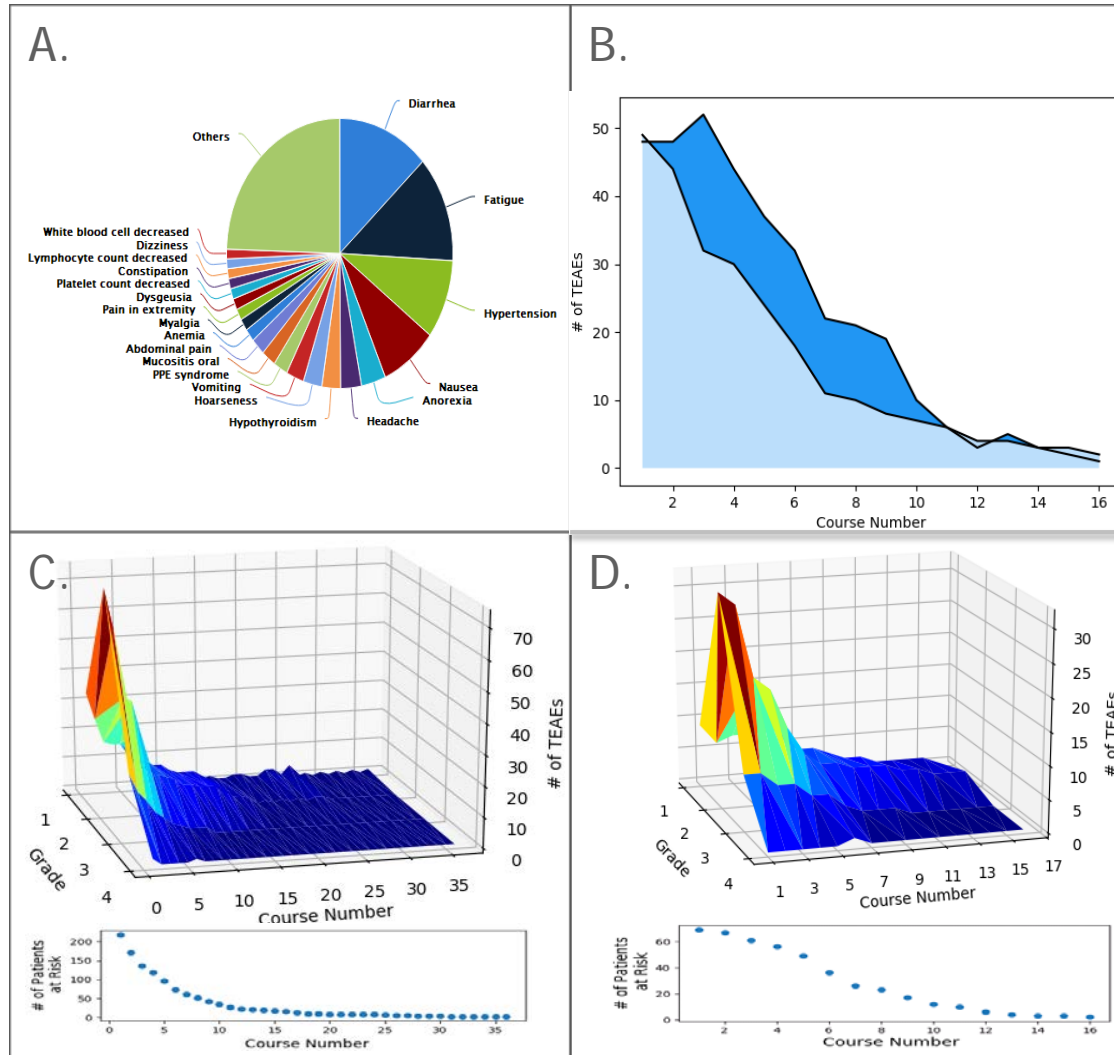
(A) Pie graph of all TEAEs by LLG MedDRA Term in patients on a Vascular Endothelial Growth Factor Receptor inhibitor (VEGFR2i) and a DNA Repair inhibitor (DNARi). (B) Risk-based monitoring of Diarrhea TEAEs seen in dark blue and Hypertension TEAEs seen in light blue in patients in a clinical trial of a VEGFR2i and a DNARi evaluating AE density by course using an area under the curve approach in a single clinical trial of this combination therapy. (C) Hypertension TEAEs in patients across 5 clinical trials with VEGFR2i evaluated by grade, course number and number of TEAEs using a contour map. Below is graph that depicts the number of patients at risk by course. (D) Hypertension TEAEs in patients given a VEGFR2i in a clinical trial evaluated by grade, course number and number of TEAEs using a contour map. Below is a graph that depicts the number of patients at risk by course

Moonshot RFA-CA-17-052

- Analyzing and Interpreting Clinician and Patient Adverse Event Data to Better Understand Tolerability

  - ➢ Using PRO-CTCAE with CTCAE data together with other clinically relevant data to determine tolerability

  - ➢ Evaluating clinician graded AEs along with patient scored symptomatic AE data and other relevant trial data

  - ➢ Evaluating associations of baseline symptoms (with pharmacologic or other laboratory data) with emerging symptomatic AEs over time

  - ➢ Using different approaches to address missing PRO-CTCAE data,

- Create a consortium to share analytic approaches

- Anticipate funded consortium by September 2018

Complementary FDA Activities

- Section of Lancet Commission dedicated to regulatory issues

- FDA-ASCO Workshop (6/2018) on inclusion and analysis of symptomatic AEs in cancer clinical trials

- FDA-Critical Path Workshop (4/2017) use of PROs to inform tolerability   (Kluetz, Value Health 2017)

- FDA, NCI, OHRP meeting (4/2017) handling of patient reported "severe" findings (Kim, Clin Cancer Res 2017)

  - ➢ Resolution: Patient-reported symptomatic AEs are not safety data, results analyzed in aggregate

- Digital Framework for submission of safety data

- Development of computational models for understanding safety events in real-world data

  - ➢ Long-term goal of digital pharmacovigilance

Questions?