

ET12

Interactive Visualization of Pooled Clinical Trial Safety Data

Sara Bodach

Ling Zhang

About the Authors

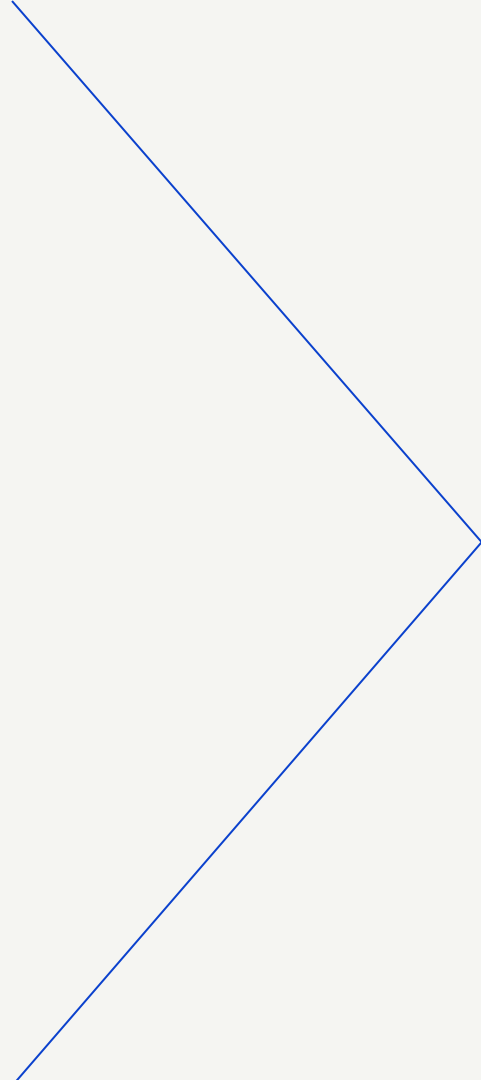
Sara Bodach

- Title: Principal Data Scientist
- Genentech, A Member of the Roche Group
- Sara supports late-stage oncology clinical trials in programming and analysis roles. She previously worked as a data analyst in the field of HIV/AIDS. She holds an MPH from Yale School of Public Health.

Ling Zhang

- Title: Senior Principal Data Scientist
- Hoffmann-La Roche Limited
- Ling is a Senior Principal Data Scientist at Roche, specializing in the Oncology portfolio. Before joining Roche, she worked as a statistical programmer consultant in the pharmaceutical industry. Ling holds an M.Sc. in Biostatistics from the University of Western Ontario, Canada.

Agenda

- 
- A large blue arrow pointing from the left towards the agenda items, formed by two diagonal lines meeting at a point on a vertical line.
- Introduction
 - Overview of ICSD Visualization Platform
 - Key Visualizations
 - Live Demo
 - Discussion
 - Key Takeaways

Introduction

- Pooling safety data is critical for regulatory submissions and safety assessments in drug development
 - By integrating datasets across diverse studies, stakeholders gain comprehensive insights into patient safety, treatment risks, and adverse events (AEs)
- Conventional data review methods rely on static tables or figures
- Interactive data visualization tools, such as those built on an open-source, web-based framework, offer transformative potential for analyzing pooled safety data

Overview of ICSD Visualization Platform

Data Pooling Approach

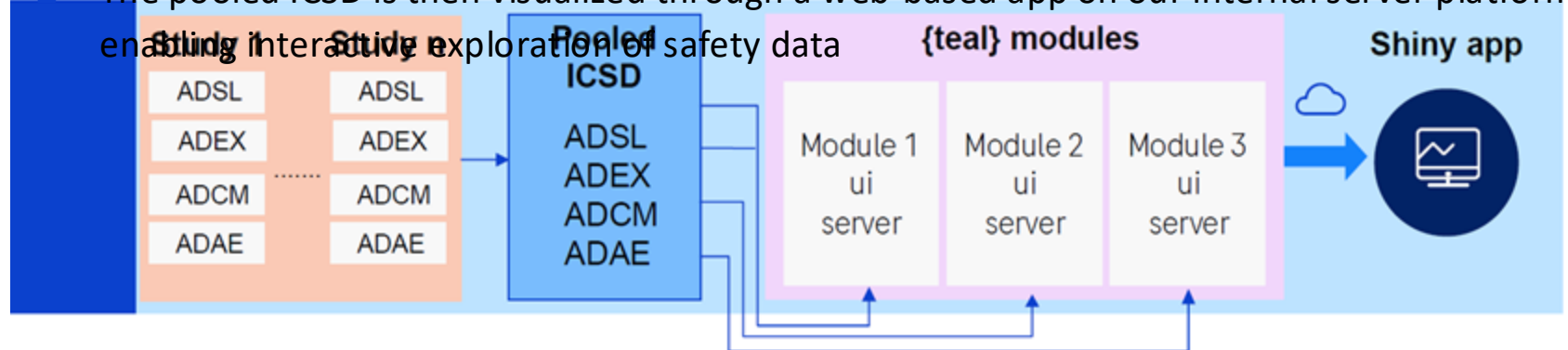
- Safety ADaMs from multiple clinical trials investigating an immunotherapy molecule are pooled into the *Integrated Clinical Safety Database* (ICSD)
- Integration includes demographics, treatment exposure, AEs, molecule-specific AEs of Special Interest (AESIs), trial indication, and cross-study comparisons for broader insights

Visualization Framework

- Developed using the {teal} framework, which is an open-source tool designed for interactive and reproducible data exploration
- Incorporates several key features to enhance usability and customization
 - Filtering options for studies and patients offers molecule-specific adjustments
 - Modular design to enable scale-up over time

Overview of ICSD Visualization Platform: Data Flow

- Individual study-level ADaM datasets (ADSL, ADEX, ADCM, and ADAE) are consolidated into the Integrated Clinical Safety Database
 - AE terms are upversioned to the latest dictionary, with key analysis variables harmonized
- The {teal} modules, each incorporating a user interface (UI) and server components, process these integrated data
- The pooled ICSD is then visualized through a web-based app on our internal server platform, enabling interactive exploration of safety data



Key Visualizations: General Information

- The general introduction tab provides an overview of the pooled studies, encompassing data from over 30 clinical trials for a late-stage immunotherapy molecule
- Molecule-specific populations that are included in regulatory labels are defined – e.g.,
 - Monotherapy vs. Combination Therapy population

List of studies and associated clinical cut-off dates of the studies included in the ICSD pool

Info Demographics Death Adverse Events Adverse Event by Medical Concept AEs by Basket Exposure Report previewer				
	ITRFL	SAFFL	Mono Treated	Combo Treated
GO29504 (BFAST), data cut-off: 2023-05-21				
BP40657 (MSCIN001), data cut-off: 2023-01-16				
CO35062 (Mhpire150), data cut-off: 2019-10-11				
CO39722 (Mhpire170), data cut-off: 2019-04-15				
GO27831 (PCD4989G), data cut-off: 2016-03-31				
GO28625 (FIR), data cut-off: 2015-01-07				
GO28753 (POPLAR), data cut-off: 2015-12-01				
GO28754 (BRCH), data cut-off: 2015-12-01				
GO28915 (OAK), data cut-off: 2016-07-07				
GO29293 (MVGOR210), data cut-off: 2016-07-04				
GO29294 (MVGOR211), data cut-off: 2017-03-13				
GO29431 (Mpower110), data cut-off: 2020-02-04				
GO29436 (MPOWER150), data cut-off: 2018-01-22				
GO29437 (MPOWER131), data cut-off: 2018-04-20				
GO29438 (MPOWER132), data cut-off: 2018-05-22				
GO29527 (MPOWER210), data cut-off: 2021-01-21				
GO29537 (Mpower130), data cut-off: 2018-03-15				

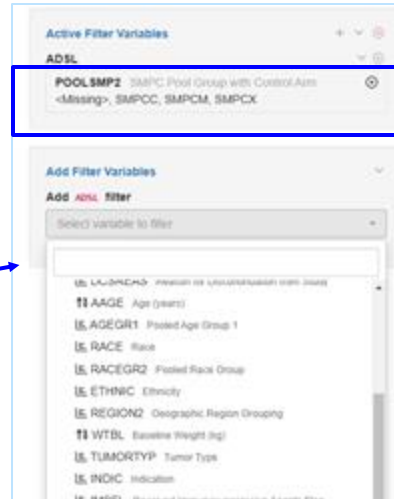
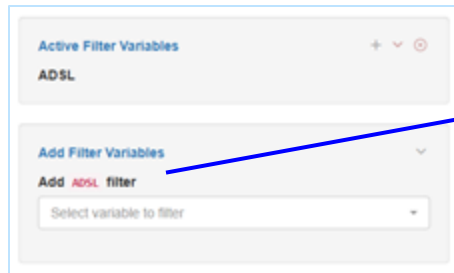
Overview of ICSD Visualization Platform: Filtering

- The Filtering panel restricts to the label-based populations or other characteristics of interest in the pooled subject-level data in ADSL
- User's existing knowledge of label-specific populations is helpful for targeted analyses

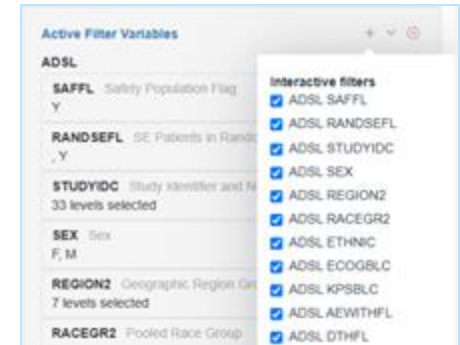


Among the Summary of Product Characteristics (SmPC) Population

Among a smaller group of studies or among some other characteristic

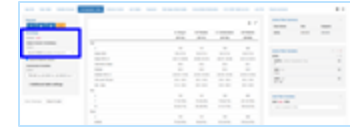


Additional flag variables specific for visualization needs can be added to support more intuitive filtering by end users



Overview of ICSD Visualization Platform: Column Variables

- For pooled analyses, the Encodings panel in which the end user selects the column variable drives the comparison



Presentation by Core Data Sheet (CDS) combination therapy and monotherapy populations

Presentation groupings used in the EU Risk Management Plan

Reporter

+ [Download Icon] [Close Icon]

Encodings

Datasets: ADSL, ADEX

Select Column Variable(s)

Dataset: ADSL

Select

STUDYIDC Study Identifier and Name

Dataset: ADEX

Select

TNDOSE Total number of doses admin

Study 1 vs. Study 2 vs. Study N

Select Column Variable(s)

Dataset: ADSL

Select

POOLCDS2 CDS Pool Group with Co

Dataset: ADEX

Select

TNDOSE Total number of doses admin

CDS combo pool vs. CDS mono pool

Select Column Variable(s)

Select

INDICGRP Integrated Indication Group

**Multi-level:
By Indication and by
Immunogenicity status**

INDICGRP Integrated Indication Gro

POOLTYPE Actual Treatment Combi

ADASTAT ADA Status

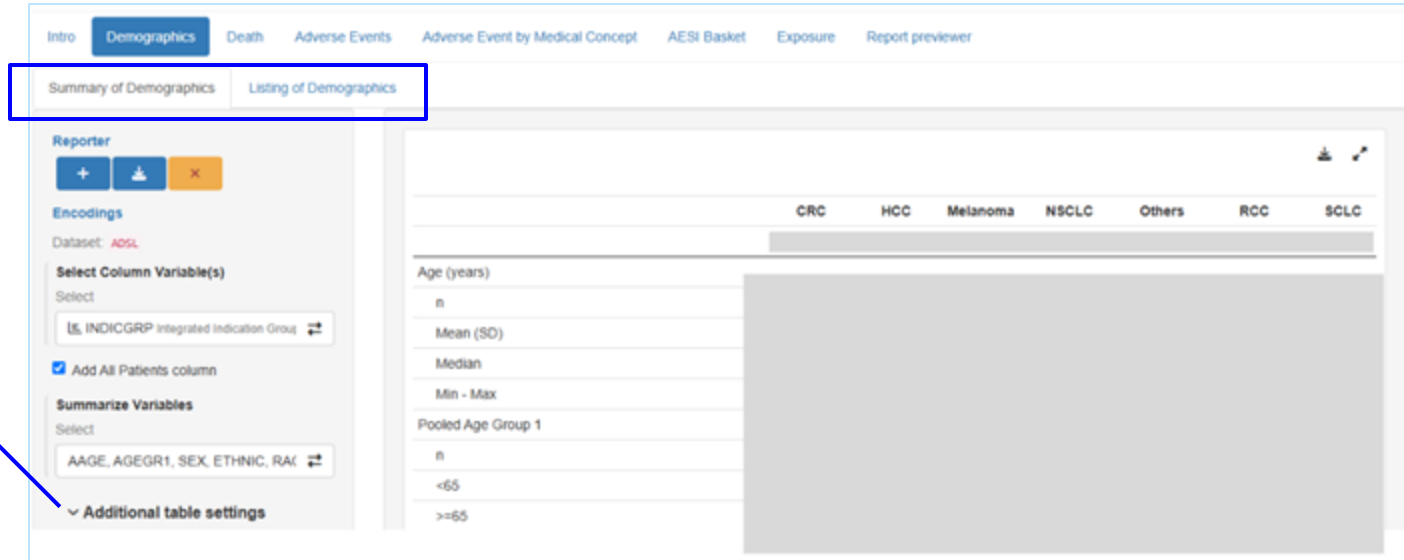
Key Visualizations: Baseline Characteristics

- Summary of Demographics: provides cross-study characteristics of the patient population and disease characteristics
- Additional exploration of patient characteristics via the listing and filtering features

Default settings exclude statistics not normally in formal outputs

Choose the statistics to display for numeric variables

- ☒ n
- ☒ Mean (SD)
- ☐ Mean 95% CI
- ☐ Geometric Mean
- ☒ Median
- ☐ Median 95% CI
- ☐ 25% and 75%-ile
- ☒ Min - Max



Intro **Demographics** Death Adverse Events Adverse Event by Medical Concept AESI Basket Exposure Report previewer

Summary of Demographics Listing of Demographics

Reporter

Encodings

Dataset: ADGL

Select Column Variable(s)

Select

US, INDICGRP Integrated Indication Group

☒ Add All Patients column

Summarize Variables

Select

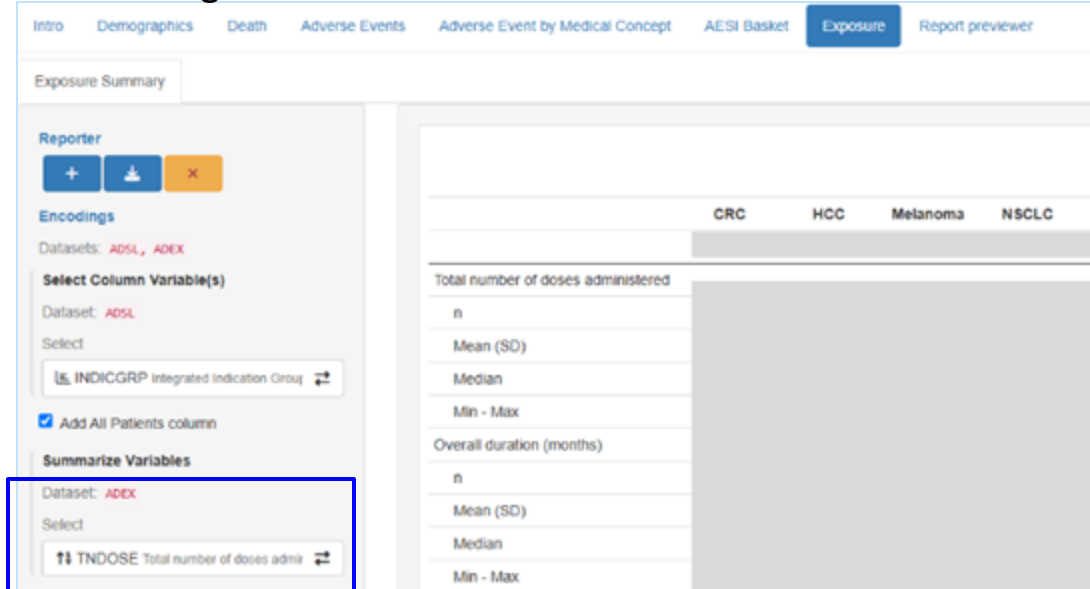
AAGE, AGEGR1, SEX, ETHNIC, RAC

Additional table settings

	CRC	HCC	Melanoma	NSCLC	Others	RCC	SCLC
Age (years)							
n							
Mean (SD)							
Median							
Min - Max							
Pooled Age Group 1							
n							
<65							
>=65							

Key Visualizations: Treatment Exposure

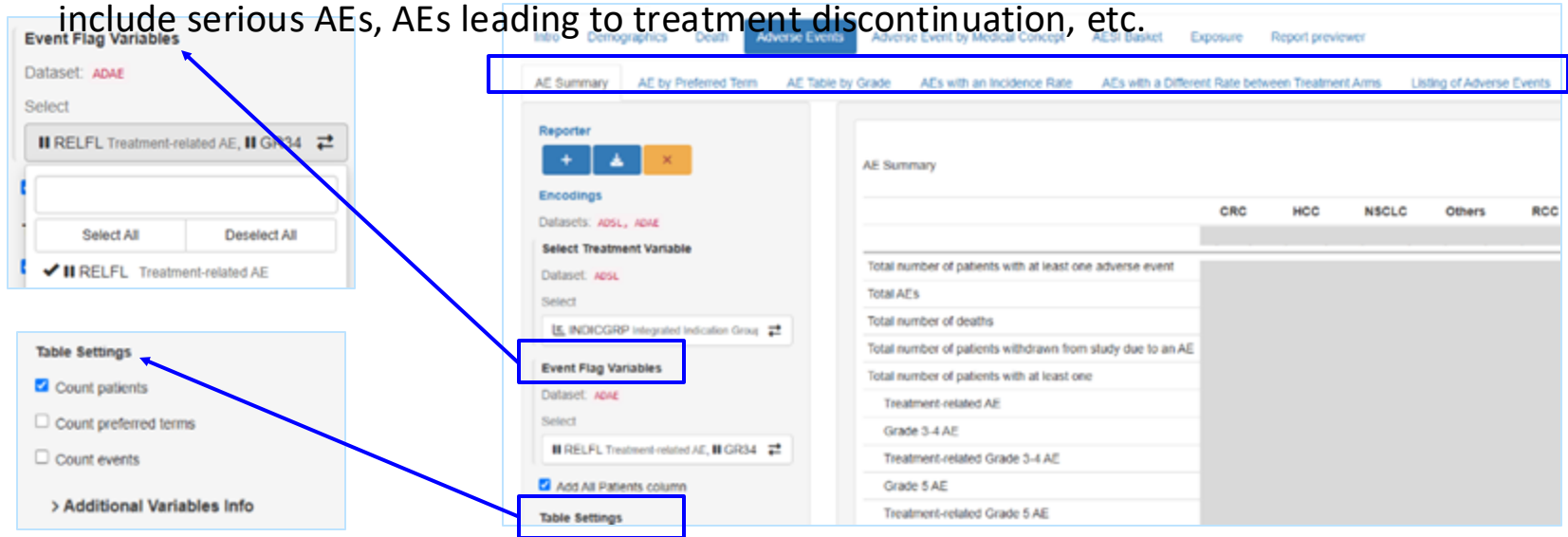
- Treatment Exposure tab offers the total number of doses administered and the overall treatment duration
- Dose intensity is available in the integrated ADaM ADEX and can be added as additional summary variables

Selections from additional parameters in ADEX, in ADaM Basic Data Structure

Key Visualizations: Adverse Events

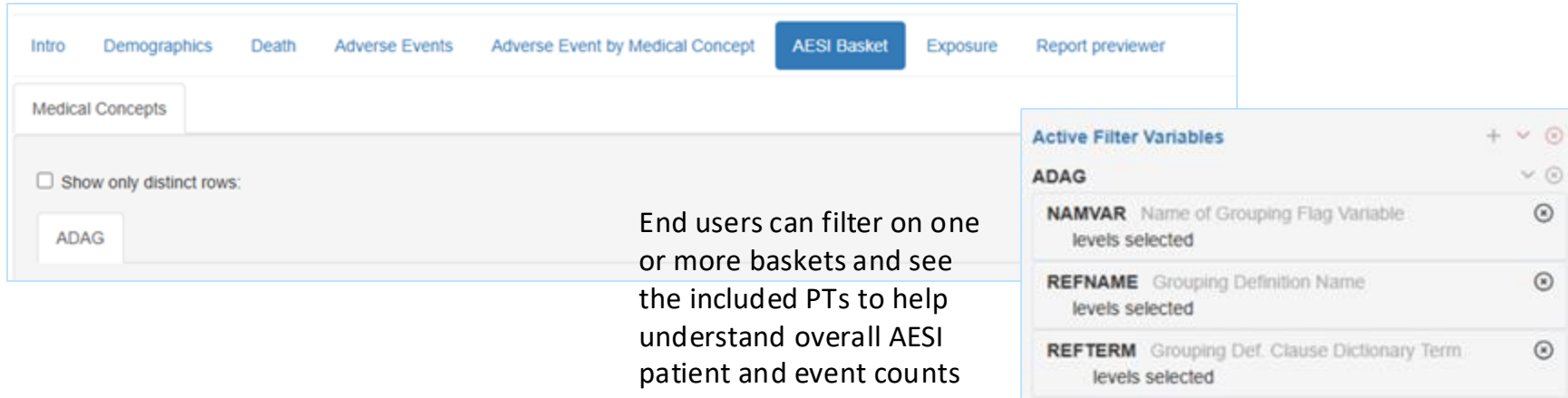
- Visualization shows an overview of AEs incidence for user-specified populations
- The visualizations are also presented by highest NCI CTCAE grade, incidence rates, and MedDRA preferred terms
- With flexibility to include more Event Flag Variables, the tabulations can be expanded to include serious AEs, AEs leading to treatment discontinuation, etc.



The screenshot displays the 'Adverse Events' section of a clinical trial analysis tool. The interface includes a top navigation bar with tabs for 'Intro', 'Demographics', 'Death', 'Adverse Events', 'Adverse Event by Medical Concept', 'AEs basket', 'Exposure', and 'Report previewer'. Below this is a sub-navigation bar with tabs for 'AE Summary', 'AE by Preferred Term', 'AE Table by Grade', 'AEs with an Incidence Rate', 'AEs with a Different Rate between Treatment Arms', and 'Listing of Adverse Events'. The main content area is divided into three panels: 'Reporter' (with '+', '↑', and '×' buttons), 'Encodings' (with 'Datasets: ADSL, ADAE' and a 'Select Treatment Variable' dropdown), and 'Event Flag Variables' (with 'Dataset: ADAE' and a 'Select' dropdown). The 'Table Settings' panel on the left shows options for 'Count patients' (checked), 'Count preferred terms' (unchecked), and 'Count events' (unchecked), along with an 'Add All Patients column' checkbox and a link to 'Additional Variables Info'. The 'AE Summary' table on the right shows a breakdown of adverse events by cancer type (CRC, HCC, NSCLC, Others, RCC) and grade (Total number of patients with at least one adverse event, Total AEs, Total number of deaths, Total number of patients withdrawn from study due to an AE, Total number of patients with at least one Treatment-related AE, Grade 3-4 AE, Treatment-related Grade 3-4 AE, Grade 5 AE, Treatment-related Grade 5 AE).

Key Visualizations: AESI Baskets

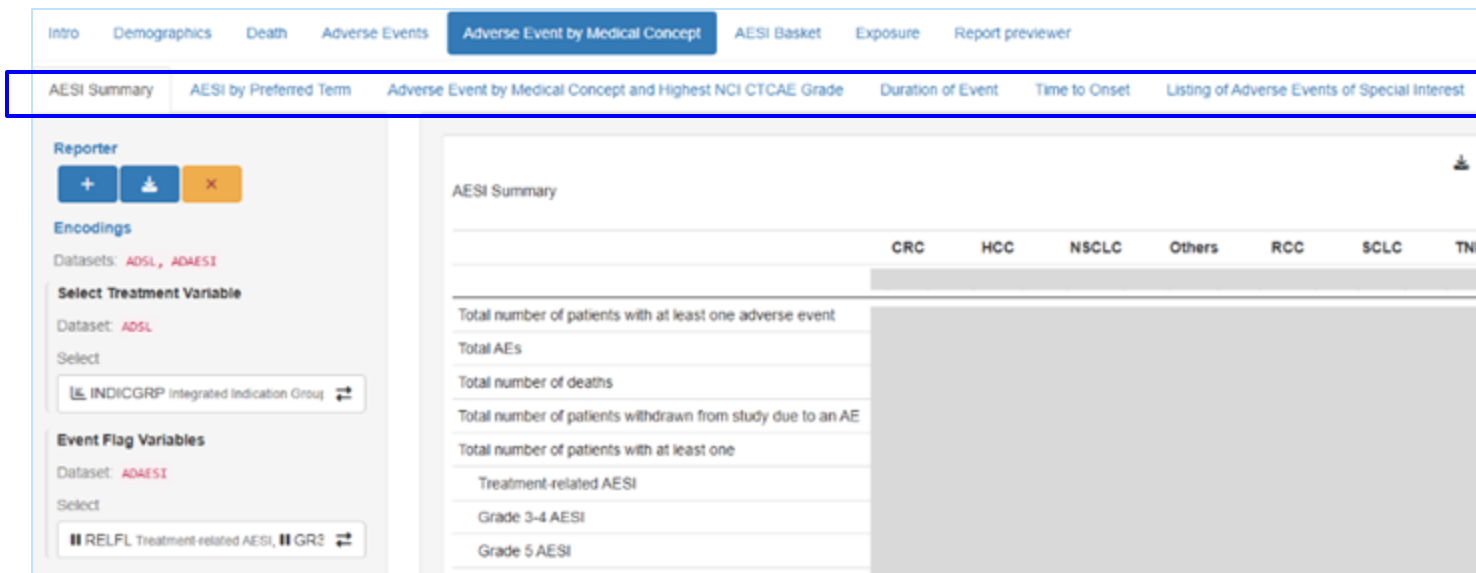
- Molecule-specific AEs of Specific Interest (AESIs) are a key component of the safety profile
 - Clinical Safety experts define the algorithms for each AESI basket
 - The semiannual upversion of MedDRA preferred terms (PTs) applies the latest SMQ and CQ groupings within pooled ADAE data
 - AE PTs defining each medical concept grouping can be explored



The screenshot displays the 'AESI Basket' interface. At the top, a navigation bar includes tabs for 'Intro', 'Demographics', 'Death', 'Adverse Events', 'Adverse Event by Medical Concept', 'AESI Basket' (which is highlighted), 'Exposure', and 'Report previewer'. Below the navigation bar, there is a 'Medical Concepts' section with a checkbox labeled 'Show only distinct rows:' and a button labeled 'ADAG'. To the right of this section, a text box states: 'End users can filter on one or more baskets and see the included PTs to help understand overall AESI patient and event counts'. On the far right, a panel titled 'Active Filter Variables' shows a list of variables under the heading 'ADAG': 'NAMVAR' (Name of Grouping Flag Variable), 'REFNAME' (Grouping Definition Name), and 'REFTERM' (Grouping Def. Clause Dictionary Term). Each variable has a 'levels selected' indicator and a circular icon with an 'x' for removal.

Key Visualizations: AESIs

- AESIs are also presented by highest NCI CTCAE grade, duration of event, and time to first AESI onset



The screenshot displays the 'Adverse Event by Medical Concept' report interface. The top navigation bar includes tabs for 'Intro', 'Demographics', 'Death', 'Adverse Events', 'Adverse Event by Medical Concept' (selected), 'AESI Basket', 'Exposure', and 'Report previewer'. Below this, a sub-navigation bar highlights 'AESI Summary', 'AESI by Preferred Term', 'Adverse Event by Medical Concept and Highest NCI CTCAE Grade', 'Duration of Event', 'Time to Onset', and 'Listing of Adverse Events of Special Interest'.

The left sidebar contains configuration options:

- Reporter:** Includes buttons for '+', 'Download', and 'Close'.
- Encodings:** Datasets: ADSL, ADAESI.
- Select Treatment Variable:** Dataset: ADSL. Selection: LE INDICGRP Integrated Indication Group.
- Event Flag Variables:** Dataset: ADAESI. Selection: RELFL Treatment-related AEsI, GR3.

The main content area shows the 'AESI Summary' table. The table has columns for CRC, HCC, NSCLC, Others, RCC, SCLC, and TN. The rows include summary statistics:

	CRC	HCC	NSCLC	Others	RCC	SCLC	TN
Total number of patients with at least one adverse event							
Total AEs							
Total number of deaths							
Total number of patients withdrawn from study due to an AE							
Total number of patients with at least one Treatment-related AEsI							
Grade 3-4 AEsI							
Grade 5 AEsI							

Key Visualizations: Death Summary

- The Death tab shows a key safety table in oncology, total number of deaths and primary cause of death
- A detailed listing of deaths allows for drilling down to individual patient-level information and the associated study, and for insights into the specific AE associated with cause of death

Intro Demographics Death Adverse Events Adverse Event by Medical Concept AESI Basket Exposure					
Deaths by Cause of Death		Listing of Death and the Cause of Death			
	CRC	HCC	NSCLC	Others	RCC
Total number of deaths					
Primary cause of death					
n					
ADVERSE EVENT					
DISEASE RECURRENCE/PROGRESSIVE DISEASE					
OTHER					

LIVE DEMO

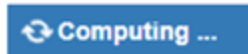
Discussion

Implementation of visualization for pooled molecule data

- The ICSD visualization has been successfully implemented for our immunotherapy molecule, improving data accessibility and analytical efficiency for pooled groups that are aligned with regulatory label populations
- Strengthened collaboration between data science and clinical safety teams, fostering more effective decision-making and streamlined workflows

Future Enhancements

- Optimizing performance for large, pooled datasets
- Expanding to lab analyses to gain deeper safety insights
- Customizing modules that can be used for common safety reports
- Using a validated server to host the interactive visualization



Key Takeaways

- Interactive visualization significantly **enhances clinical safety data review efficiency**
- Supports data-driven decision-making by **enabling exploration of large datasets**
- **Reproducibility, real-time adaptability, and user-centered design** ensure continued evolution in safety data analytics

Questions?

Contact Info

- Sara Bodach: bodachs@gene.com
- Ling Zhang: ling.zhang.lz2@roche.com

References

- Chendi Liao and Dony Unardi, TEAL: Enabling Comprehensive Interactive Data Analysis and Exploration in R with an Open Sourced Scalable Shiny Framework, PHUSE US Connect 2023. [Link](#)
- Teal: Interactive Exploratory Data Analysis with Shiny Web-Applications <https://insightsengineering.github.io/teal/latest-tag/>