The Role of Statistical Graphics in Oncology Drug Development:

Moving Beyond Scatter Plots and Survival Curves

Michael Durante
Oncology Early Development, GSK

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Presentation Outline

1. Background
    1. Foundations
    2. Tools
2. Graphics commonly utilized today
    1. Trial Design
    2. Safety
        1. Patient Level
        2. Subgroup or Study Level
    3. Efficacy
3. Moving beyond…
4. Conclusion, Acknowledgements

Background

Foundations

- Results of a 2004 internal GSK graphics user survey:
  - Too few graphs in general
  - Take too long to create
  - Poor quality
- Limited use of platforms commonly associated with object oriented programming and generally higher quality graphics
- Isolated pockets of those users who had experience in creation of graphics

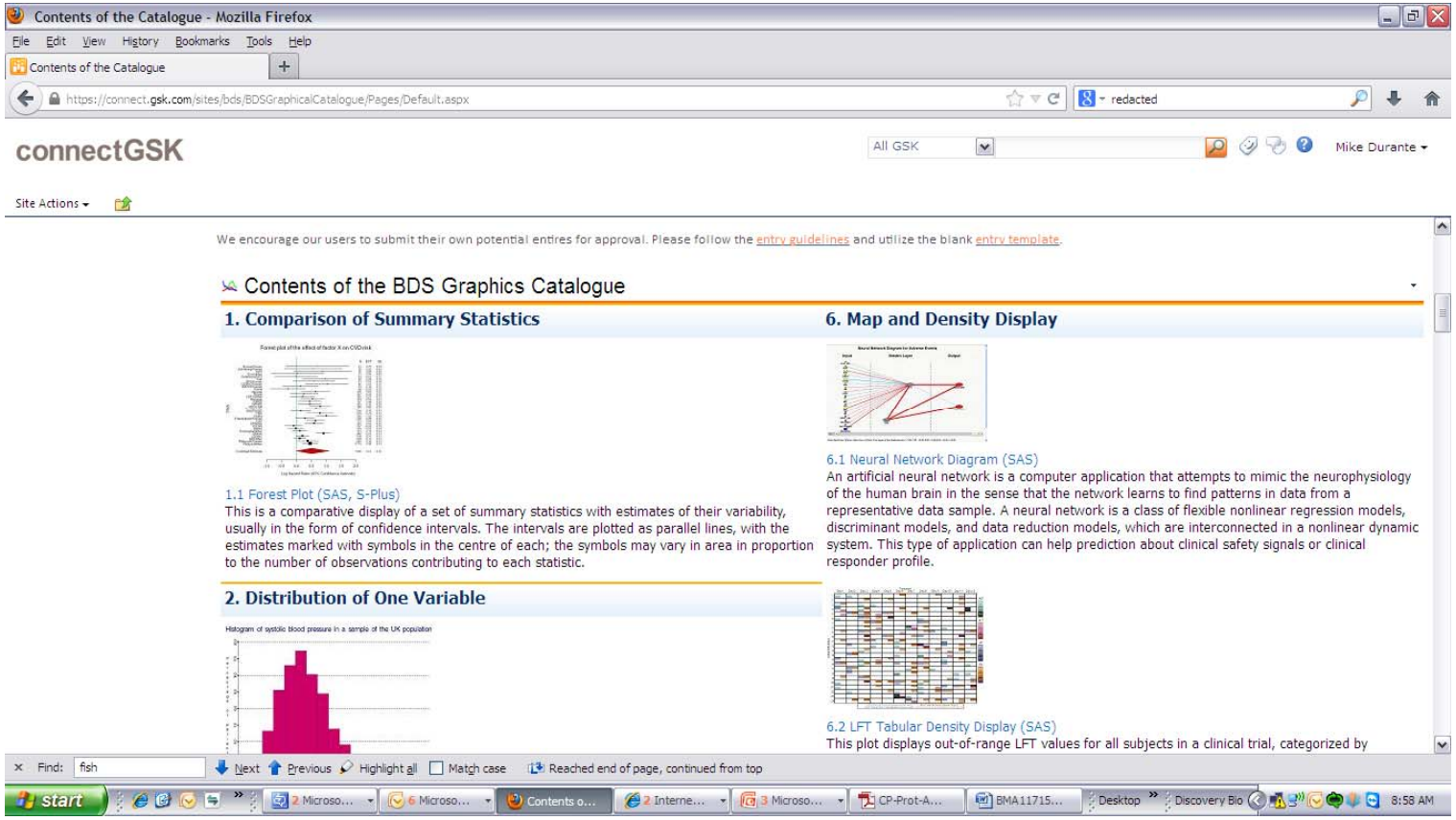
Foundations

- Graphics Team/Graphical Community Steering Team
  - Community of practice to serve as a grassroots action team
  - Work closely in development of tools and processes for creation of graphics
- Quality Graphic Tools
  - Graphics Catalog
  - GUI based tools
- Sponsorship, Supporting cast, Iterative development process
  - Senior management, Line management
  - GSK IT staff
  - Experienced, industry leading software vendor
  - Iterative development process

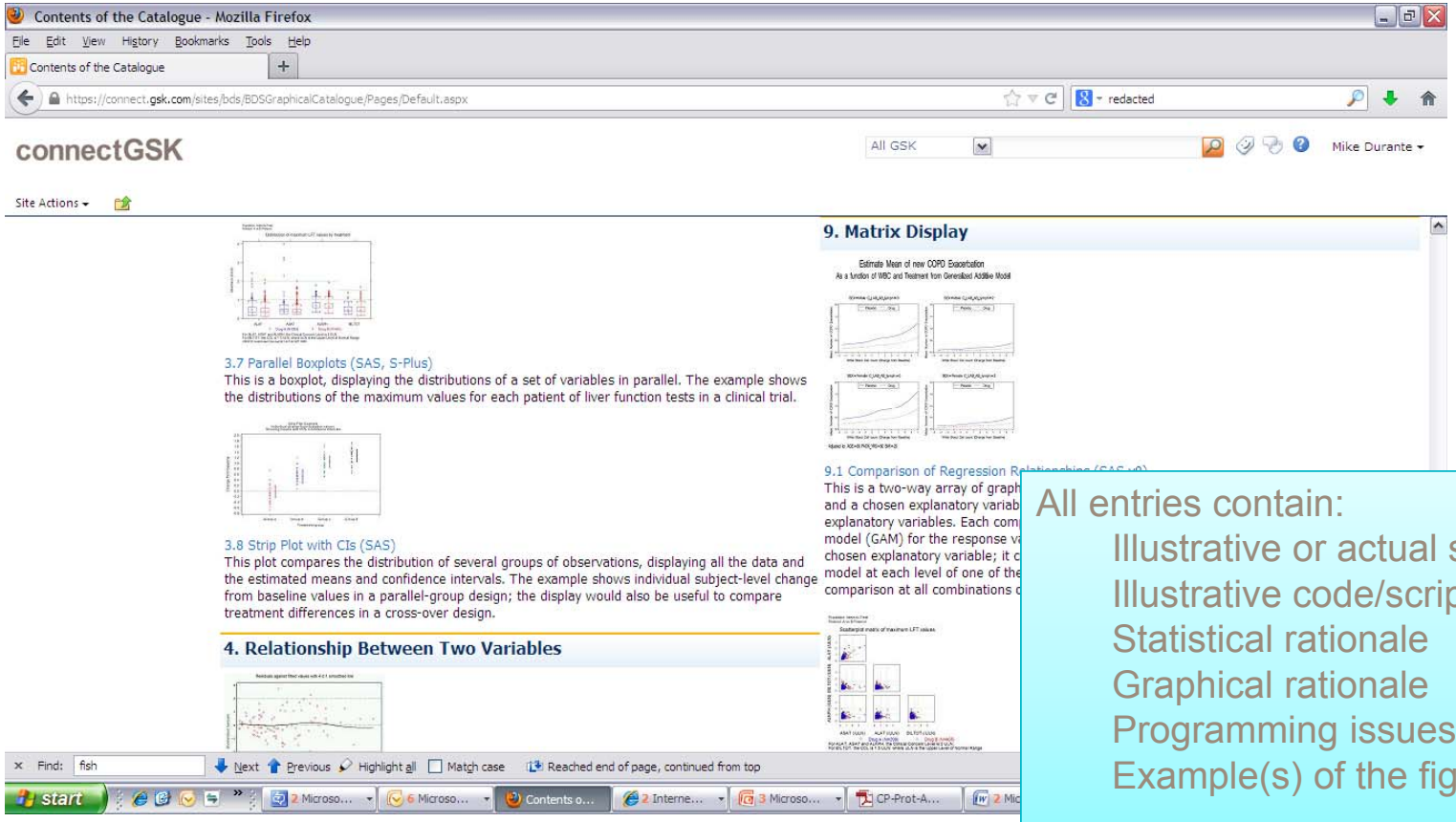
Tools
The Graphics Catalog

- Provides reliable and practical information to help produce effective displays
  - Formats, devices, fonts
  - Importing into MS documents
- Promotes good graphical principles and helpful tips
  - Graphical Principals (‘rules to live by…’)
  - “Choosing the Right Graph” guide
  - Index of graphical terms
- Dozens of catalog entries organized into groups by type of display, such as:
  - Relationship between two variables
  - Three dimensional displays
  - Comparison of distributions
- Learn from work done by others
  - avoid having to re-invent, re-develop code

Tools
The Graphics Catalog



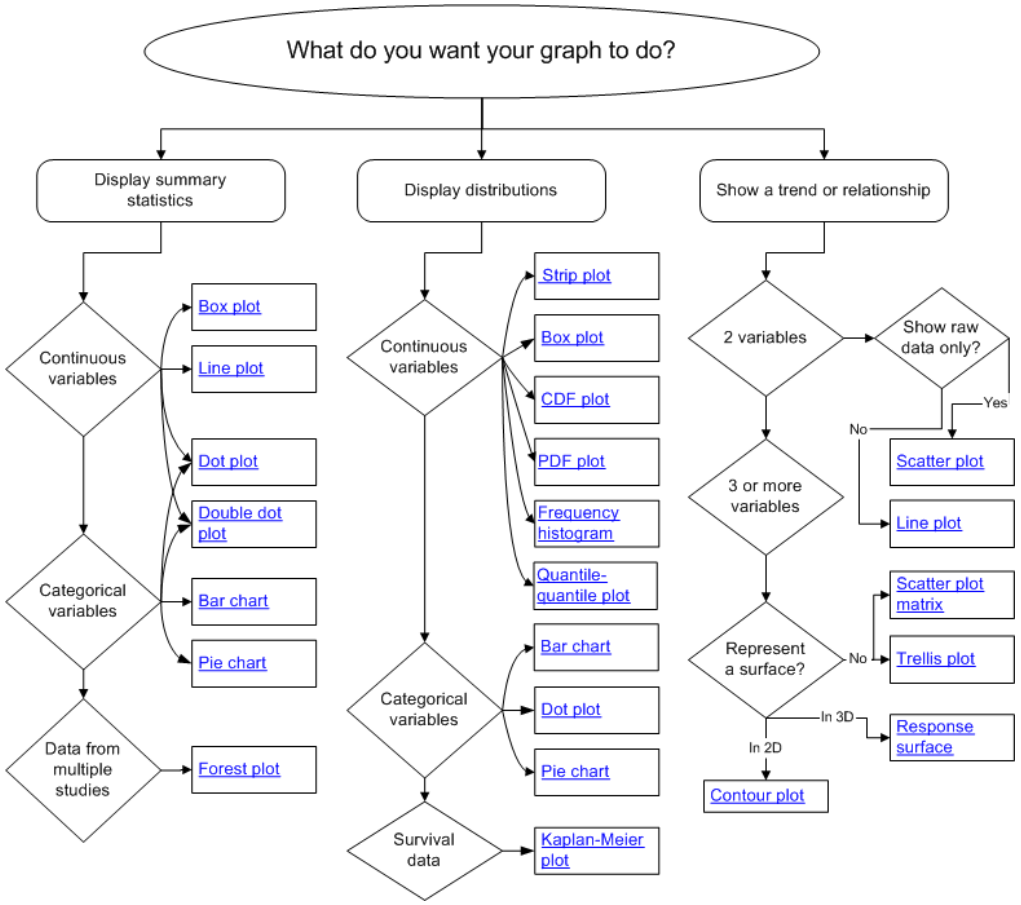
Tools
The Graphics Catalog



All entries contain:

- Illustrative or actual sample data
- Illustrative code/script (S+, SAS)
- Statistical rationale
- Graphical rationale
- Programming issues
- Example(s) of the figure

Tools
Choosing the Right Graph



Tools

We needed an easier way…

- There was determined to be a need for a graphics software that:
  - Was easy to use, less ‘barriers’ (less coding)
  - Provided good quality rendering
  - Was flexible
  - Kept end-to-end process in mind

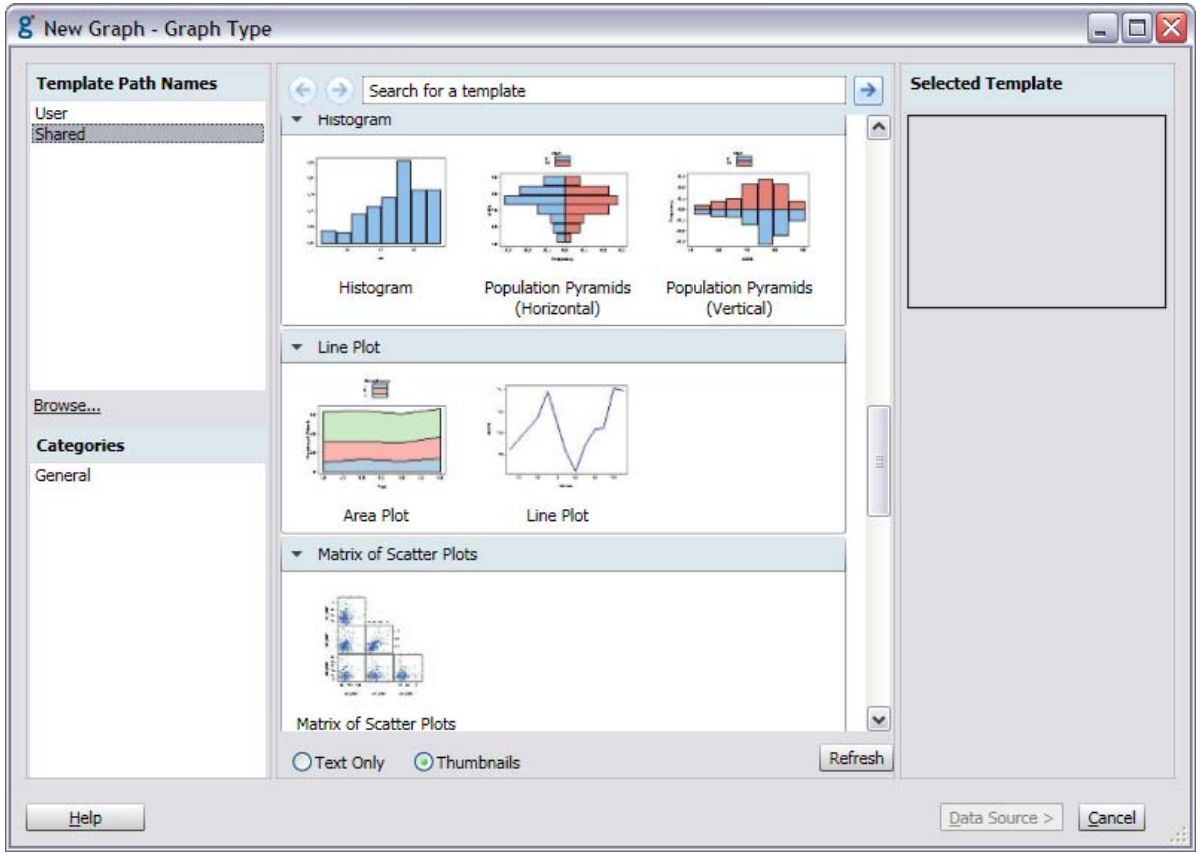
Tools

GUI Tools

- Teamed with Insightful® to create the **Graphical Workbench Environment** or GWE
  - Powerful, easy to use, GUI system for creating a number of figure styles
  - Provided the ability for anyone to create high quality graphs quickly with limited S-Plus training
  - Added functionality to work in combination with GSK's UNIX environment for submission activities
- GWE eventually replaced with a more polished version, **Tibco Spotfire Clinical Graphics** or TSCG
  - e-learning requirement
  - Standard graphic templates available
  - Many more customizations available to users
  - More complex graph types possible

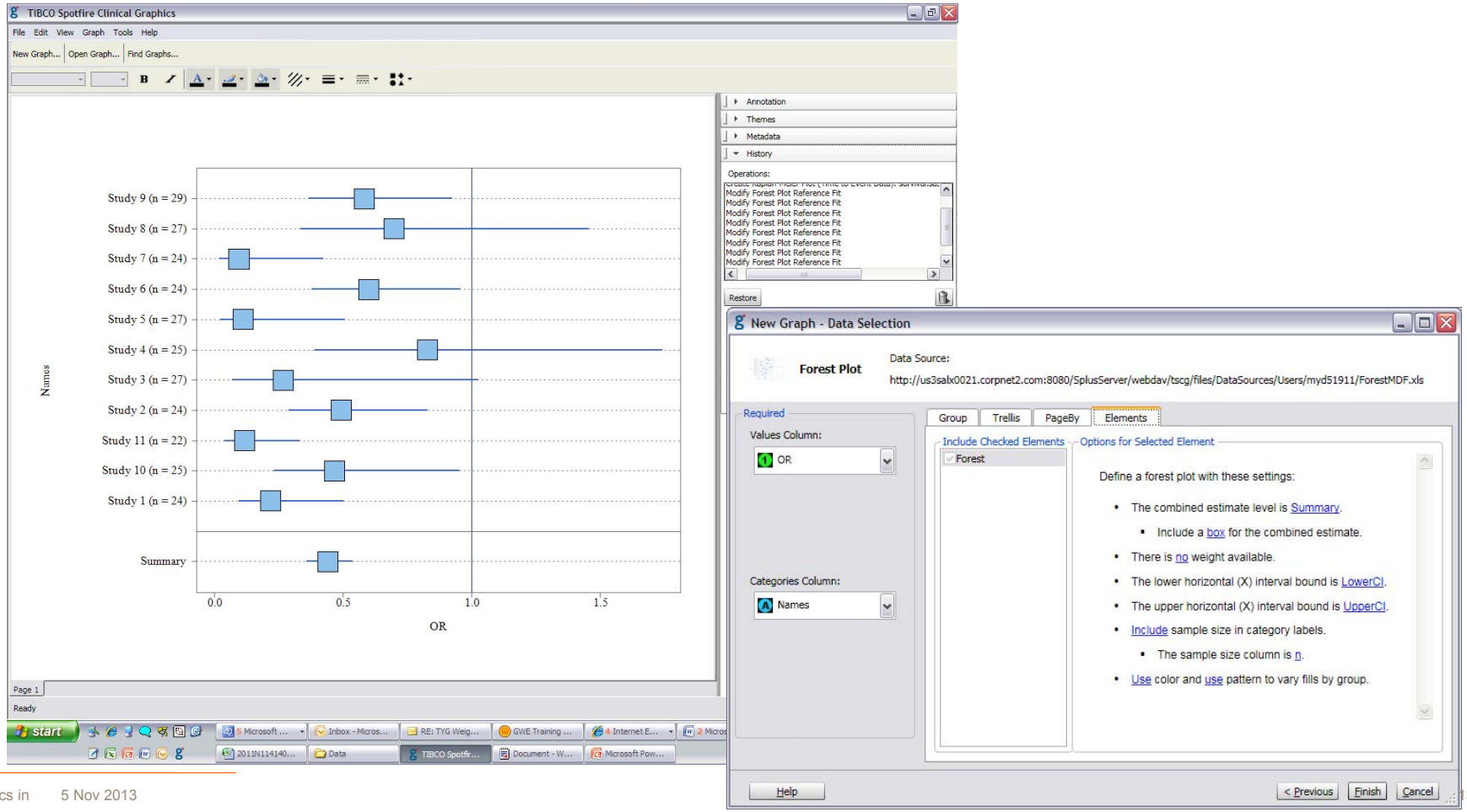
Tools

Graphics Workbench Environment (GWE)



Tools

Graphics Workbench Environment (GWE)



Graphics commonly utilized today

…Aiding in trial design

Dose Escalation

Trial Design

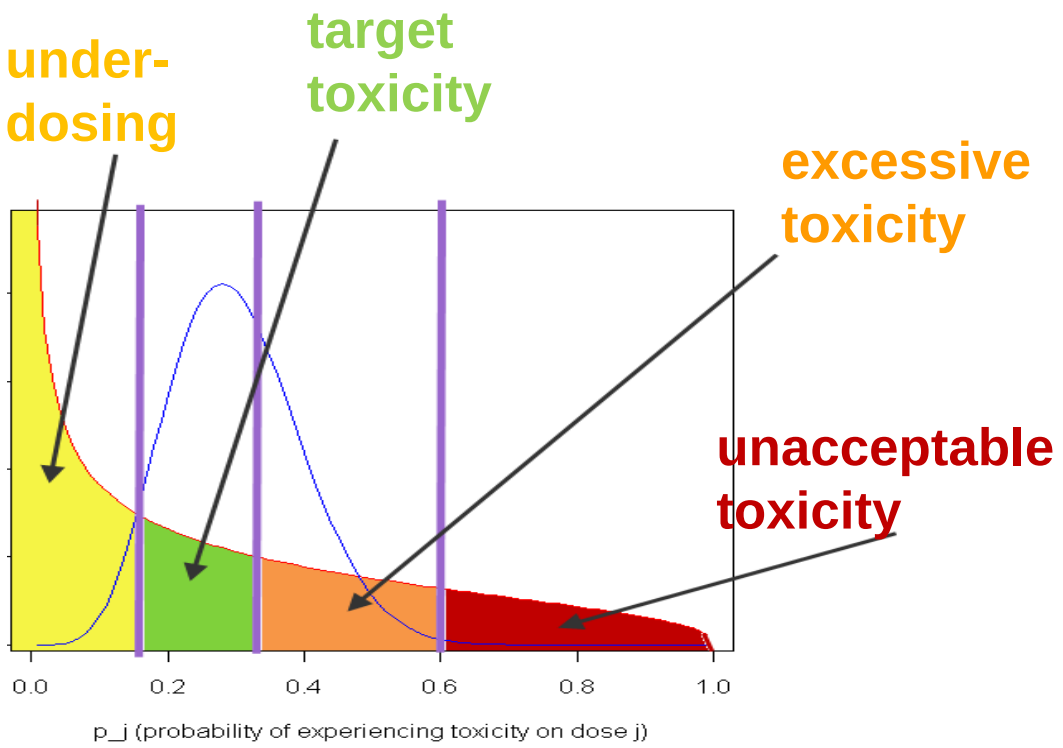
- Dose Escalation portions of many Phase I/II trials
  - Find an efficacious, well tolerated dose
  - Variety of designs
    - Rule based
      - 3+3
      - Accelerated Titration
    - Model Based
      - Escalation with Overdose Control (EWOC)
      - Continual Reassessment Model, N-CRM

- Graphics helpful in sharing simulation results during trial design discussions
  - Fixed and Adaptive Clinical Trial Simulator (FACTS™) software from Tessella and Berry Consultants

N-CRM: Posterior expectation of toxicity

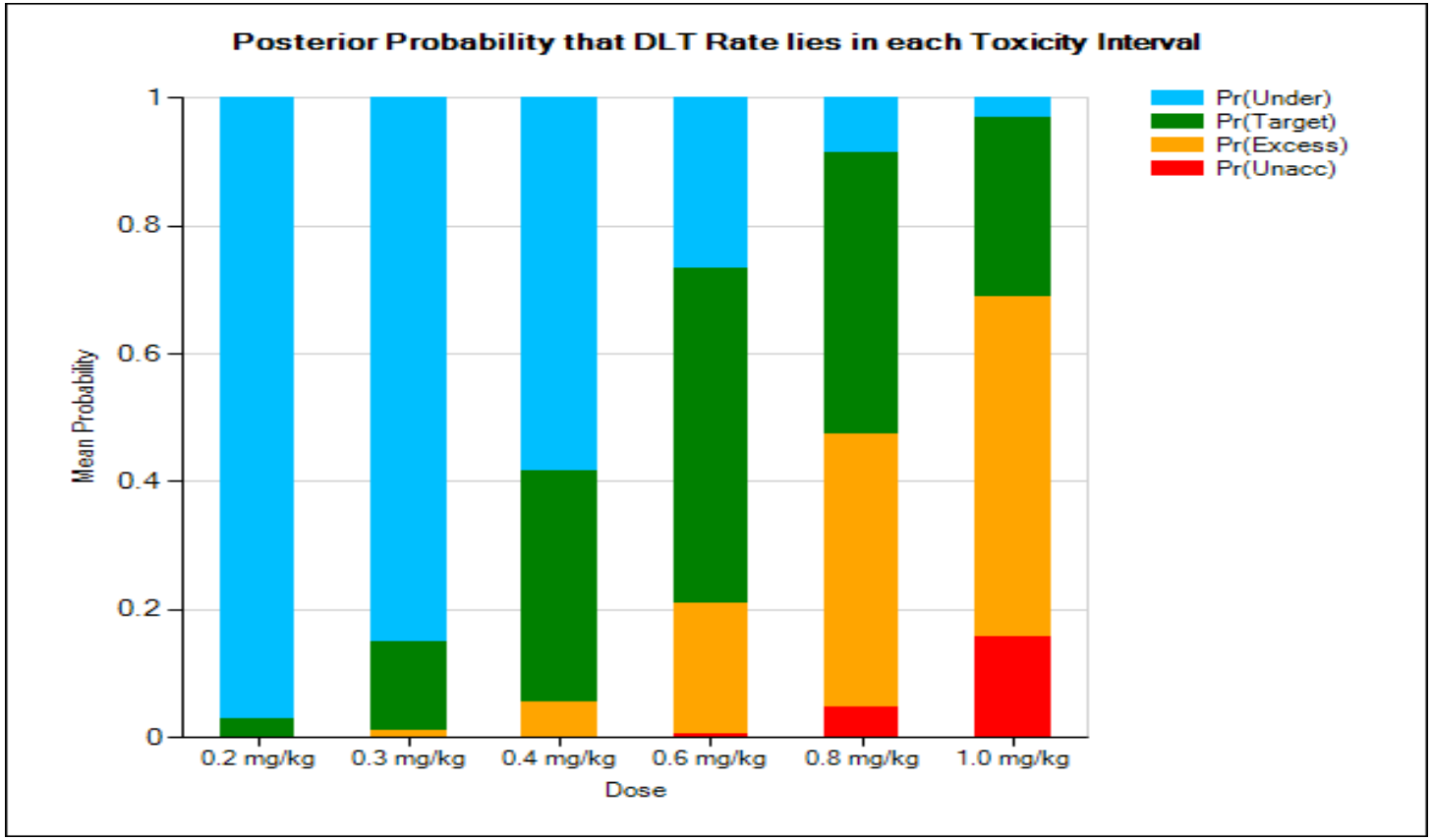
Trial Design

For each dose, we evaluate the posterior probability that the true toxicity of a dose rate lies in one of 4 toxicity intervals ….



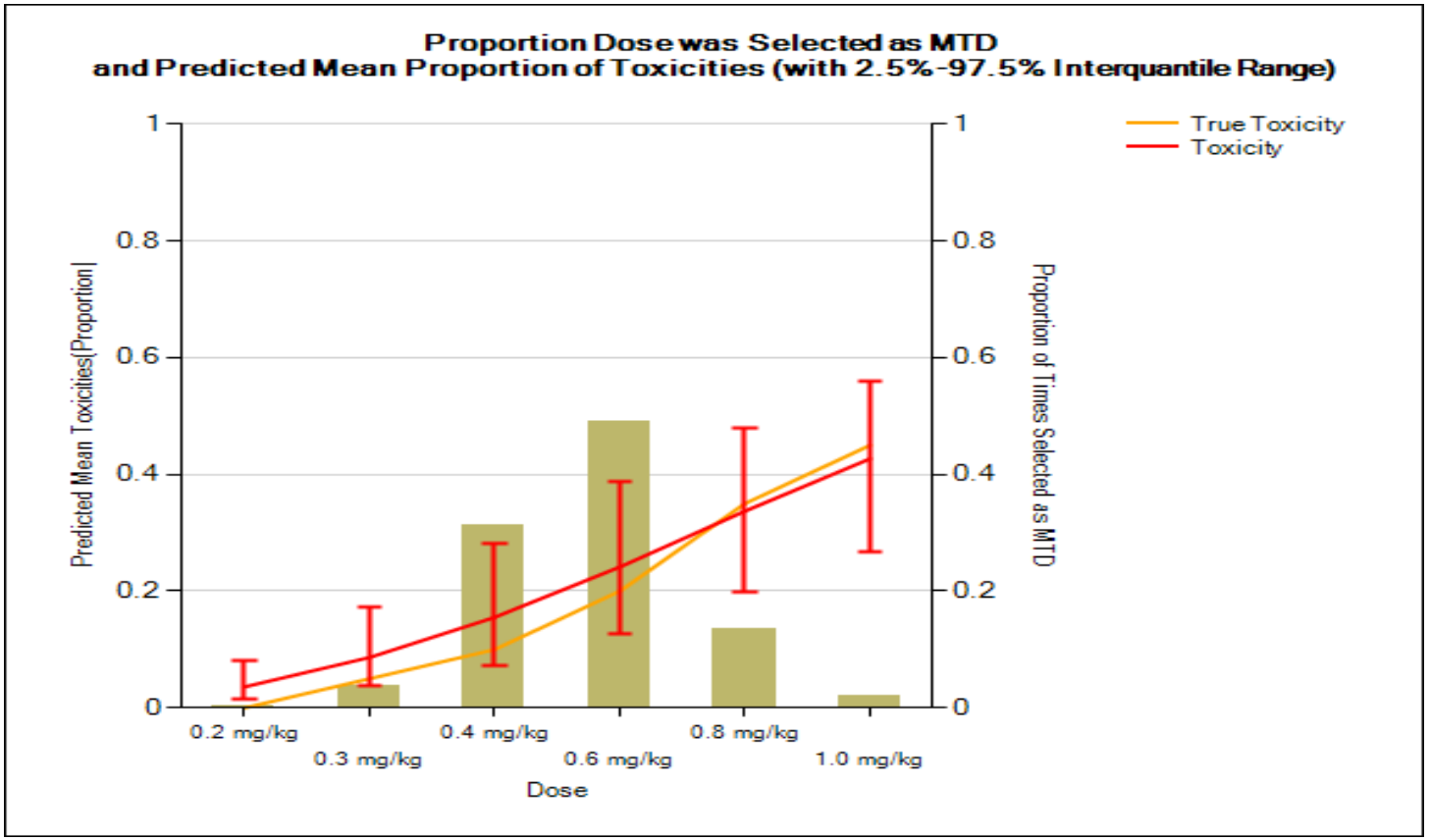
Posterior Probabilities

Trial Design



Dose Selection Overview

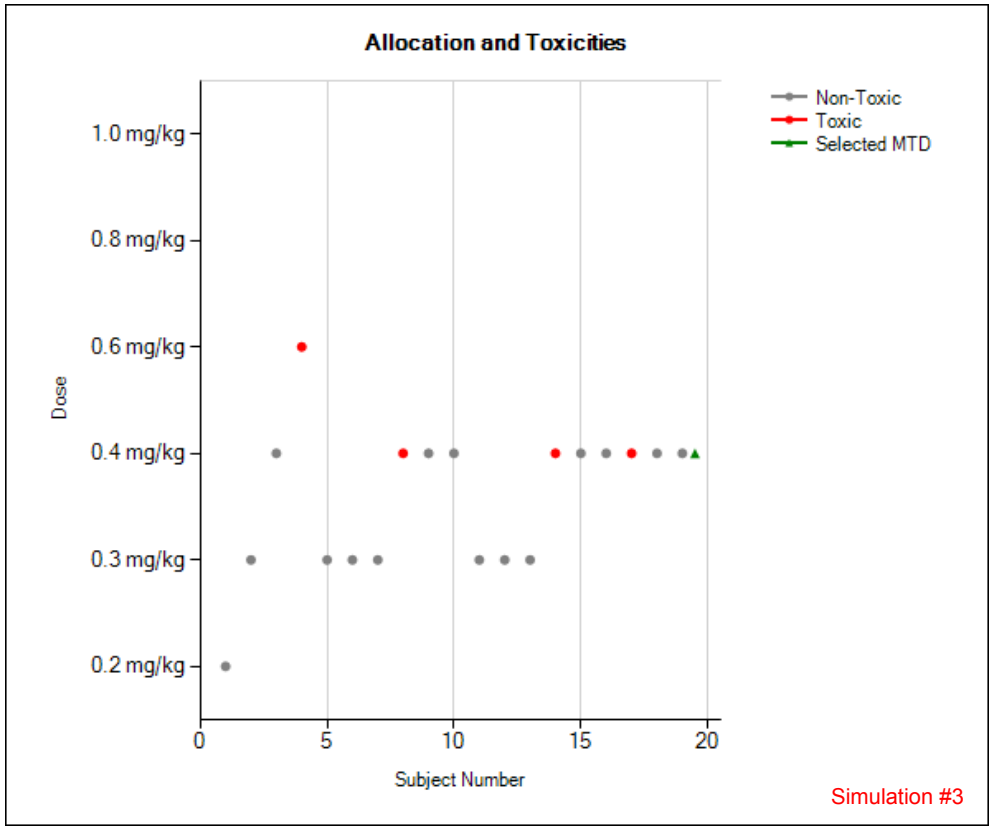
Trial Design



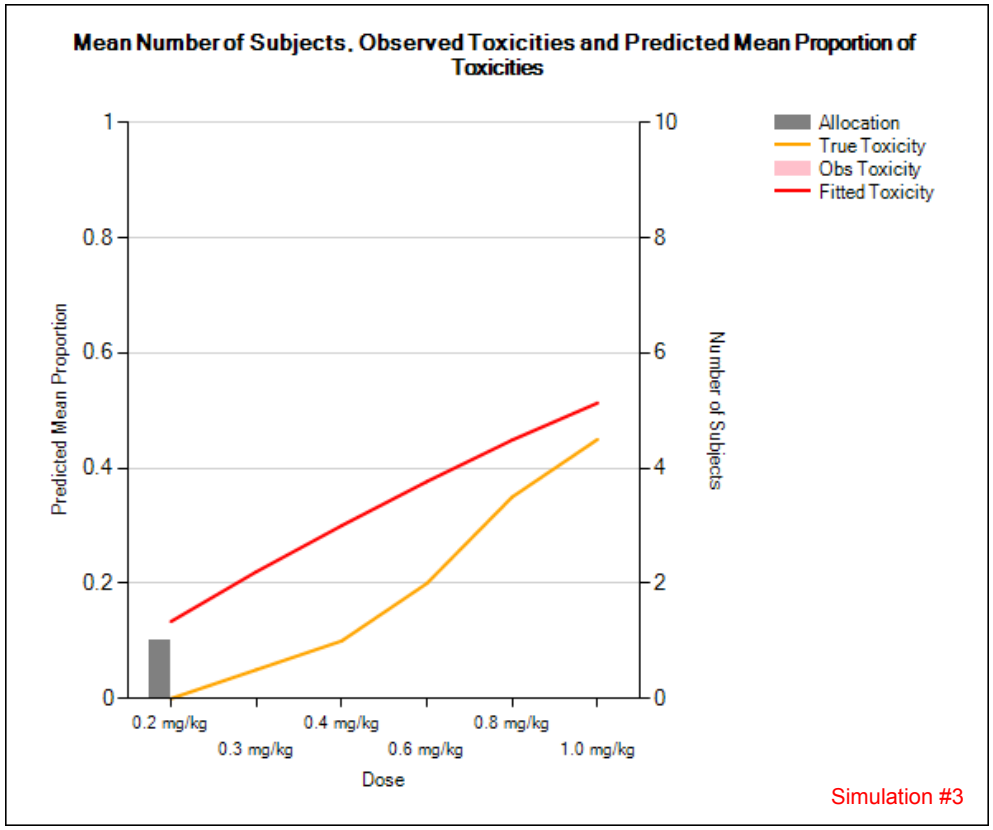
MTD: Maximum Tolerated Dose
1000 Simulations

Posterior Probabilities

Trial Design



Simulation Results: Dose Escalation Progression



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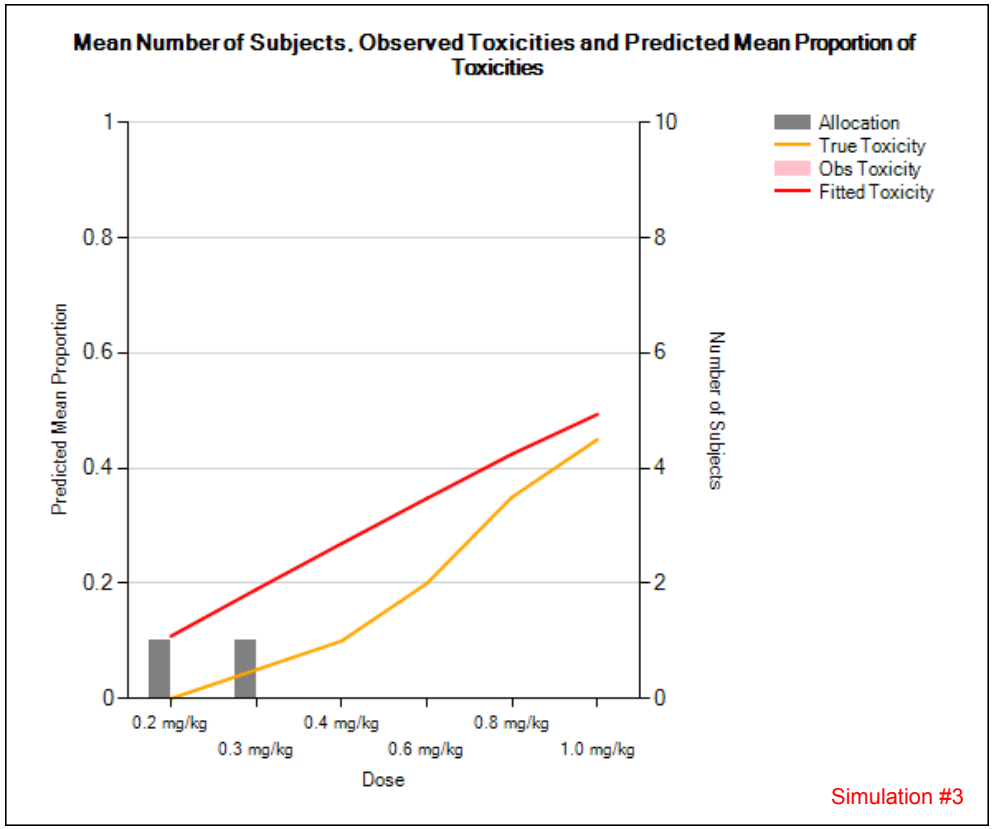

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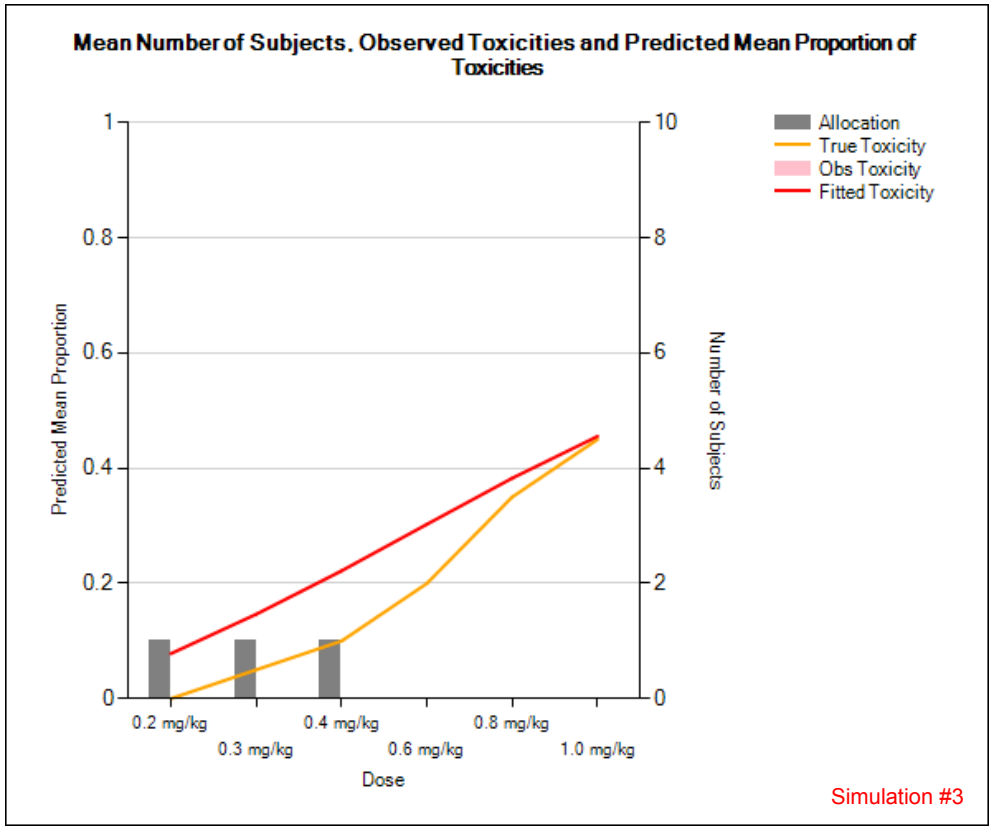

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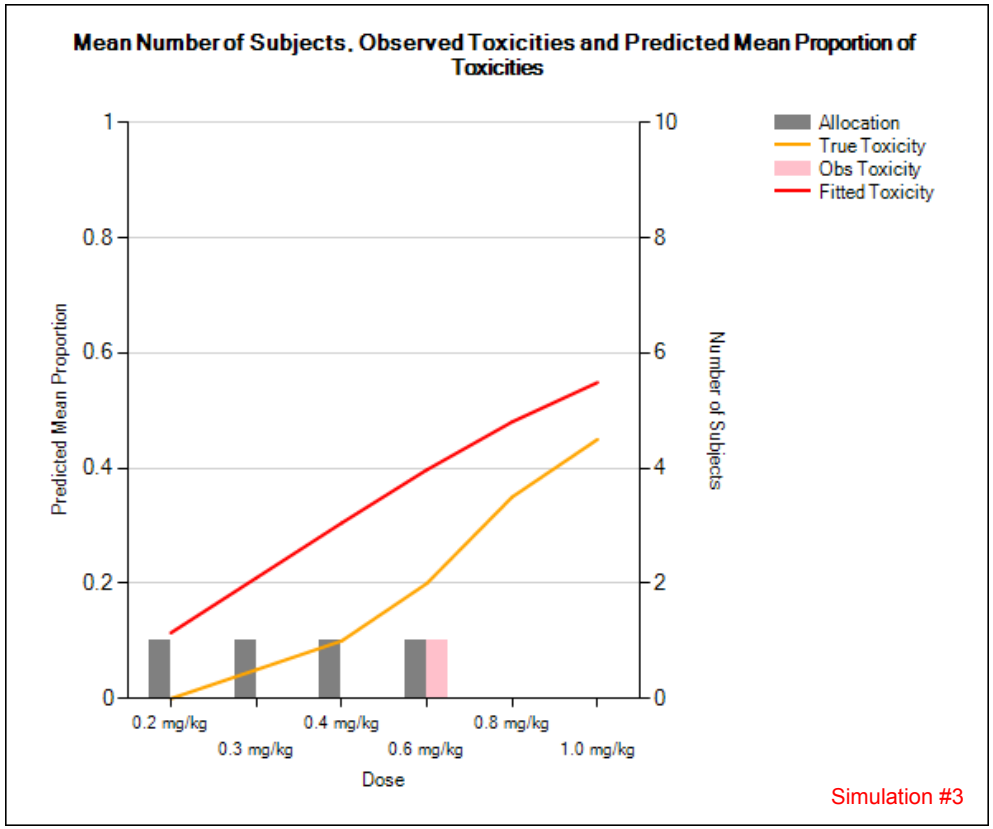

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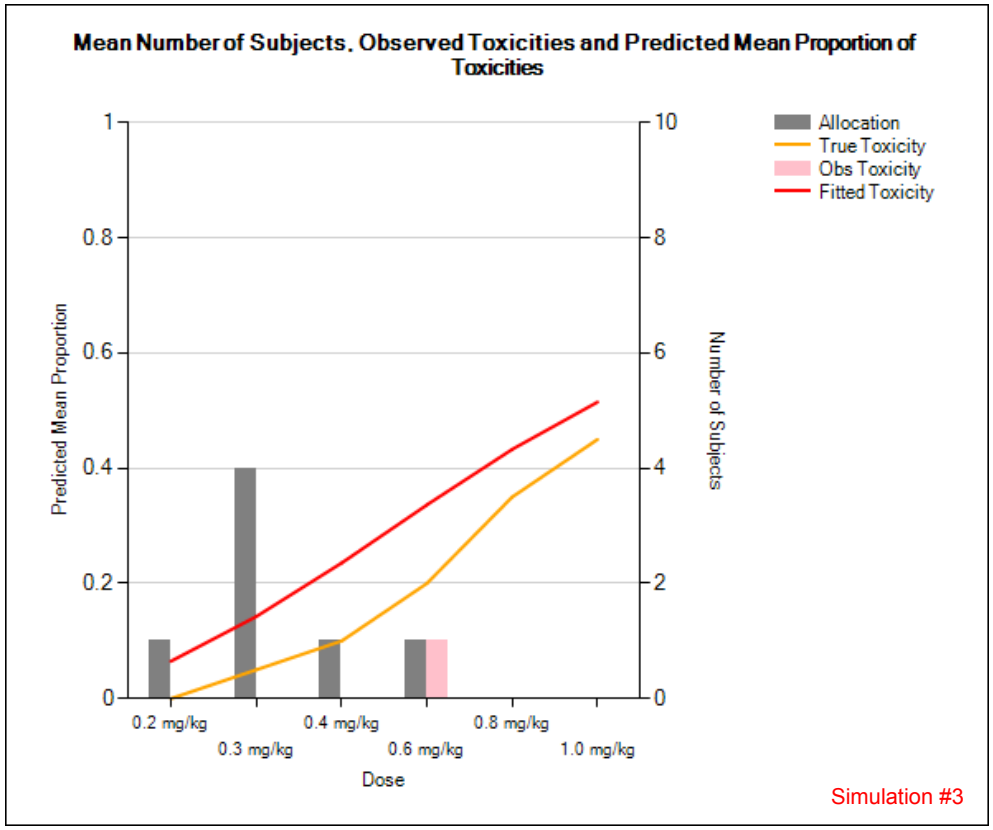

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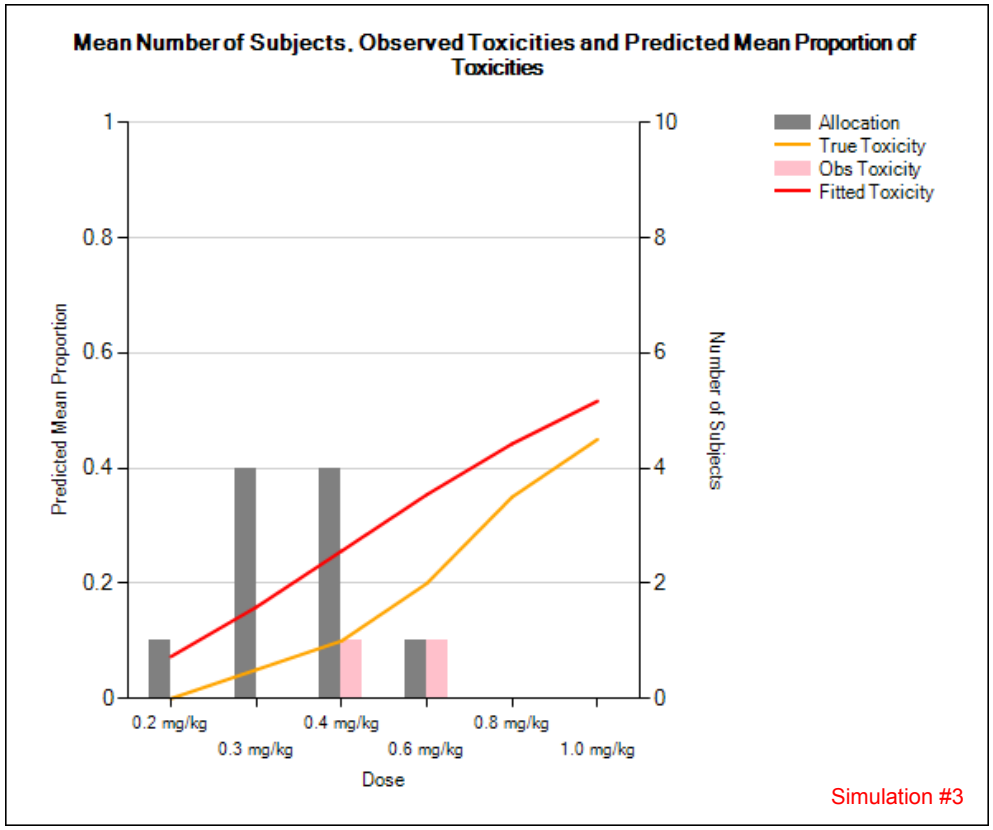

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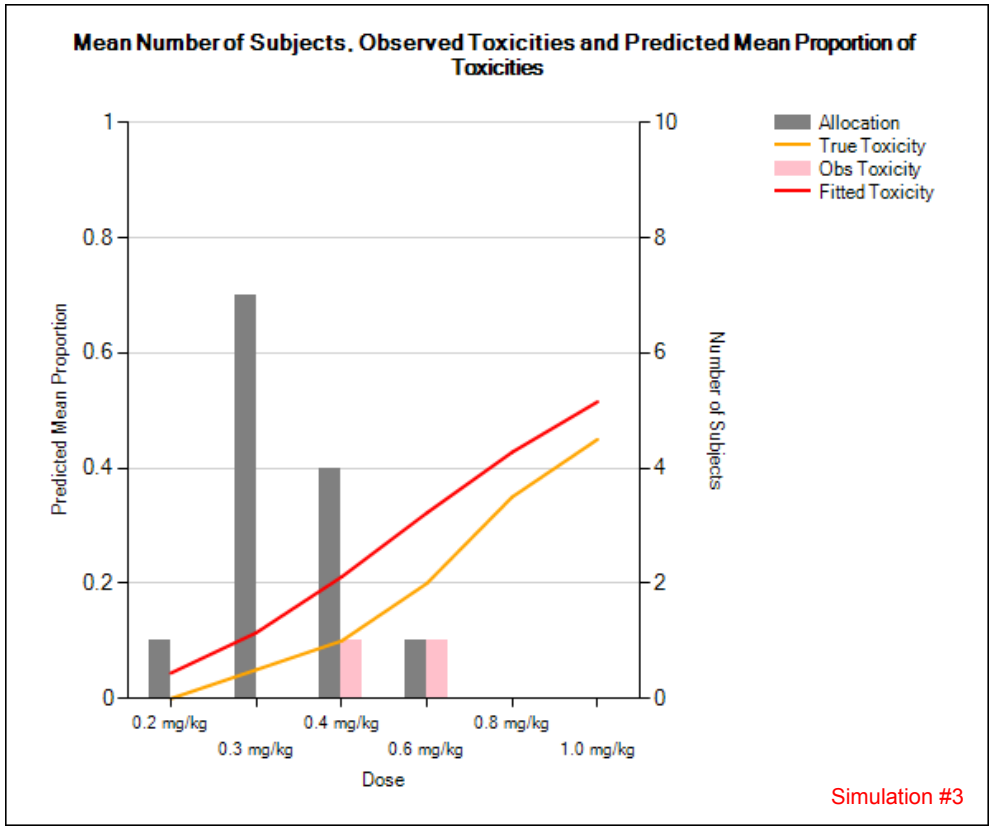

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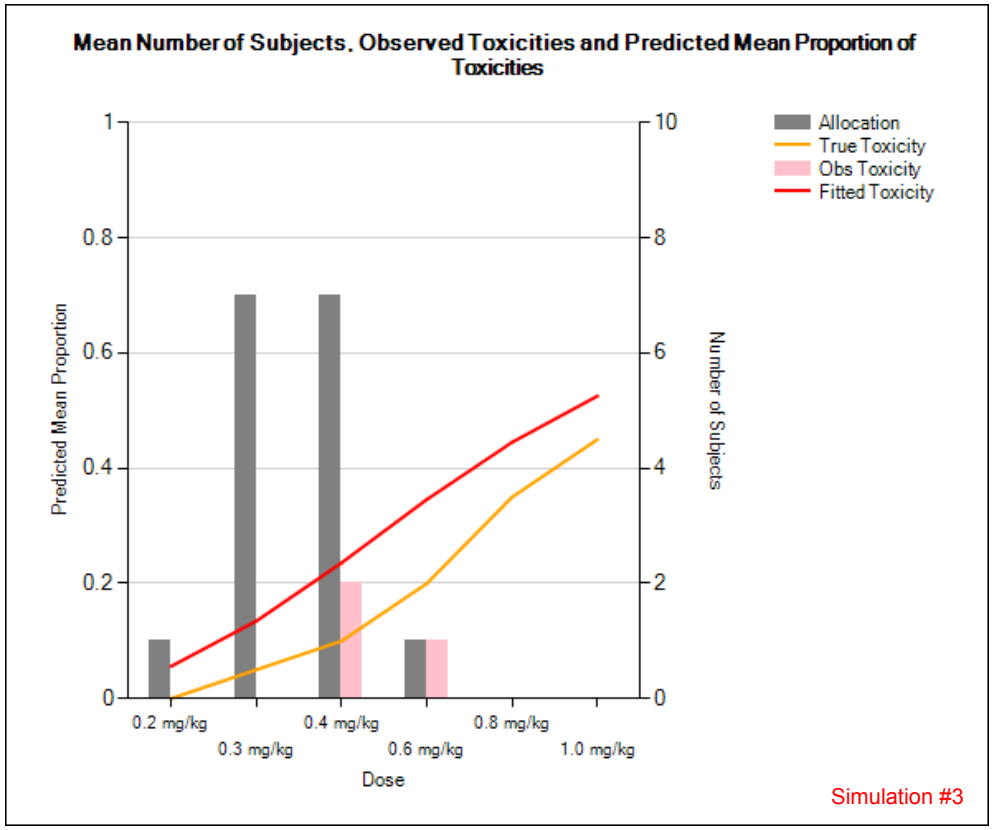

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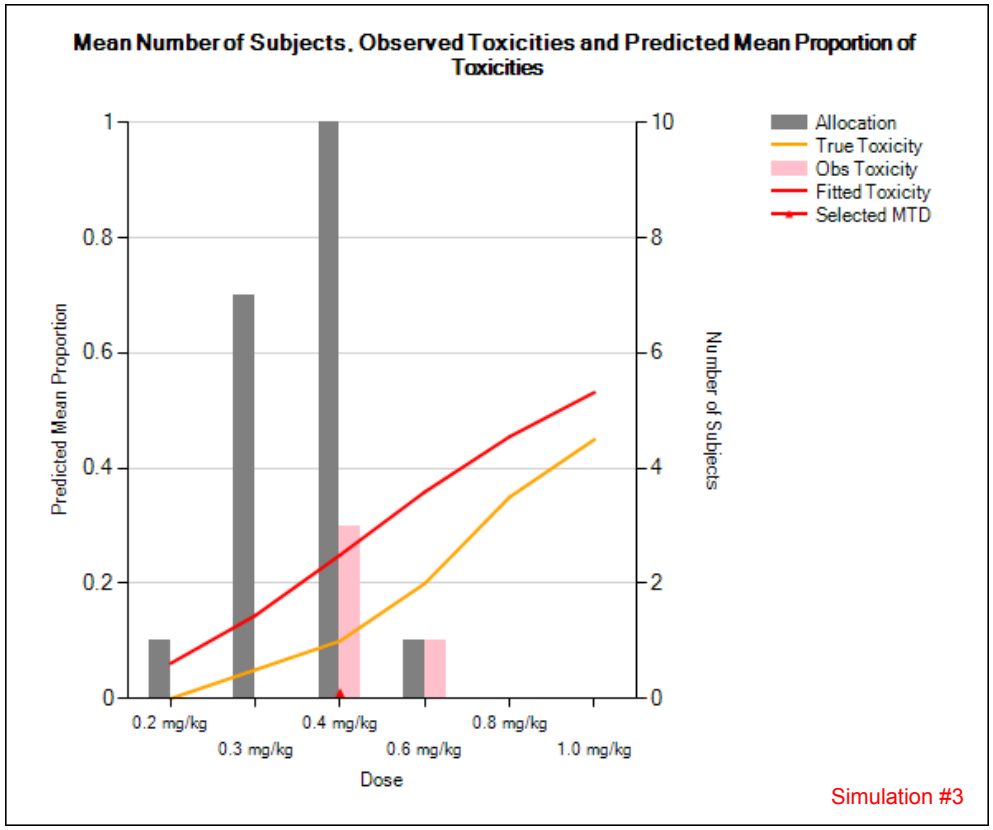


Graphics commonly utilized today

…For assessment of safety data

Background: Liver Function Tests (LFTs)

Safety

- Safety and tolerability of interest in all trials
  - Patient Level
  - Subgroup or Study Level
  - Emergent, in-stream data
  - Final, Submission, Publications, Product Labels
- Four primary liver function tests (LFTs):
  - ALT : *alanine aminotransferase*
  - AST: *aspartate aminotransferase*
  - Tot. Bili: *total bilirubin*
  - Alk. Phos: *alkaline phosphatase*
- Time to LFT elevation

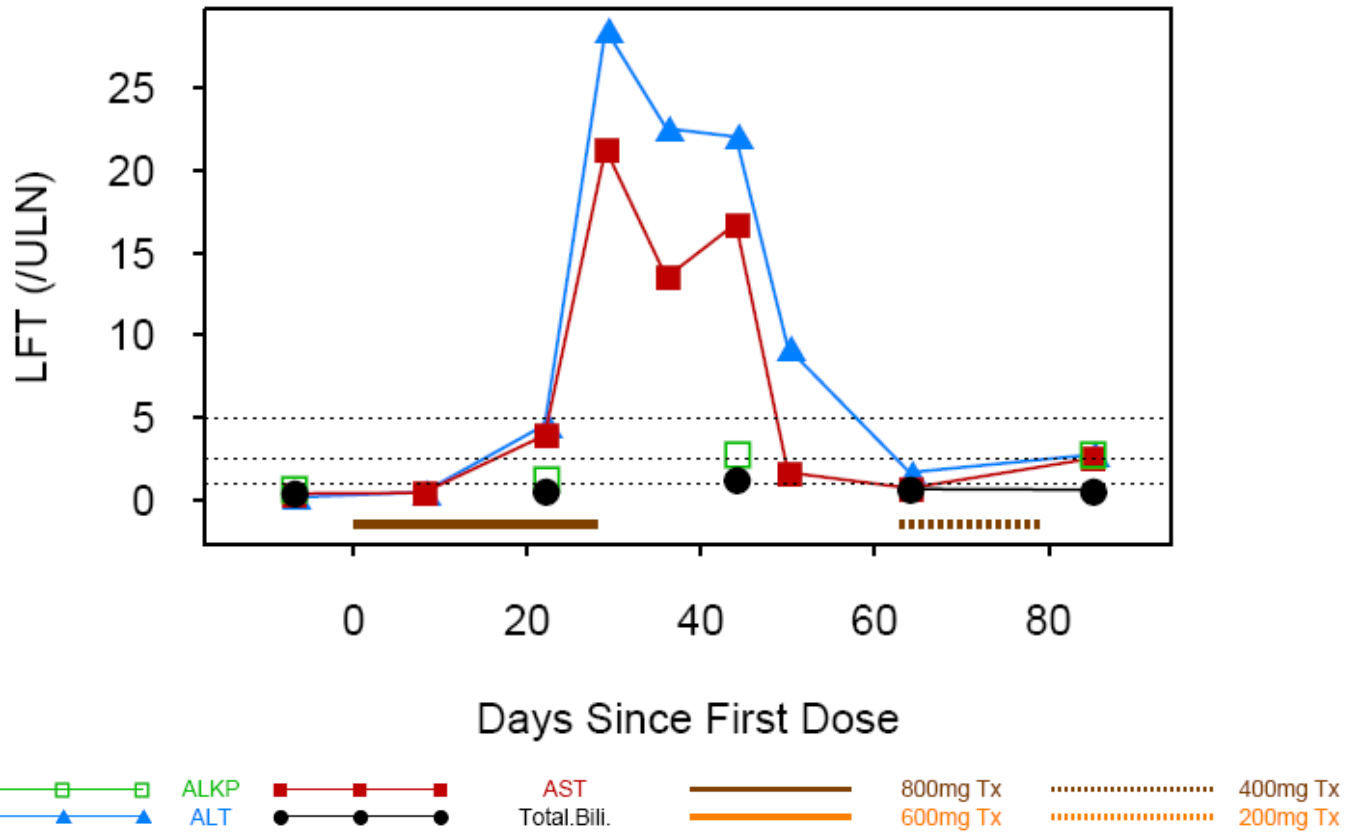
Typical Subject Level Safety Plots

Safety

- Patient Profile Plots
  - Displays patient level information typically in a trellis format
  - Can be restricted to patients of a certain subgroup
  - Allows observer to see the temporal relationships of multiple labs/events/treatments
  - May include additional information such as adverse events or concomitant medications
  - LFTs scaled by ‘upper limit of normal’ (ULN)

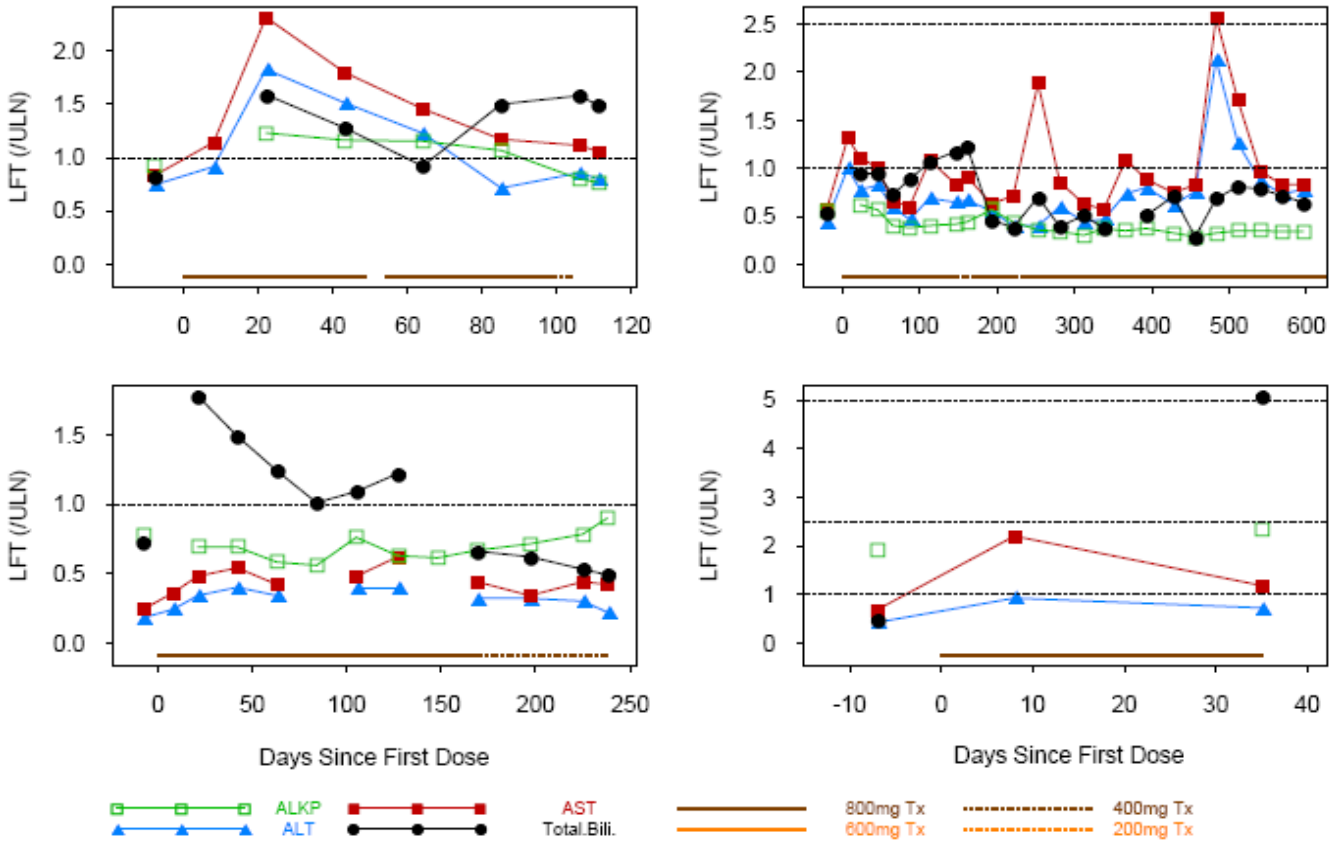
Liver Function Patient Profile plots

Safety



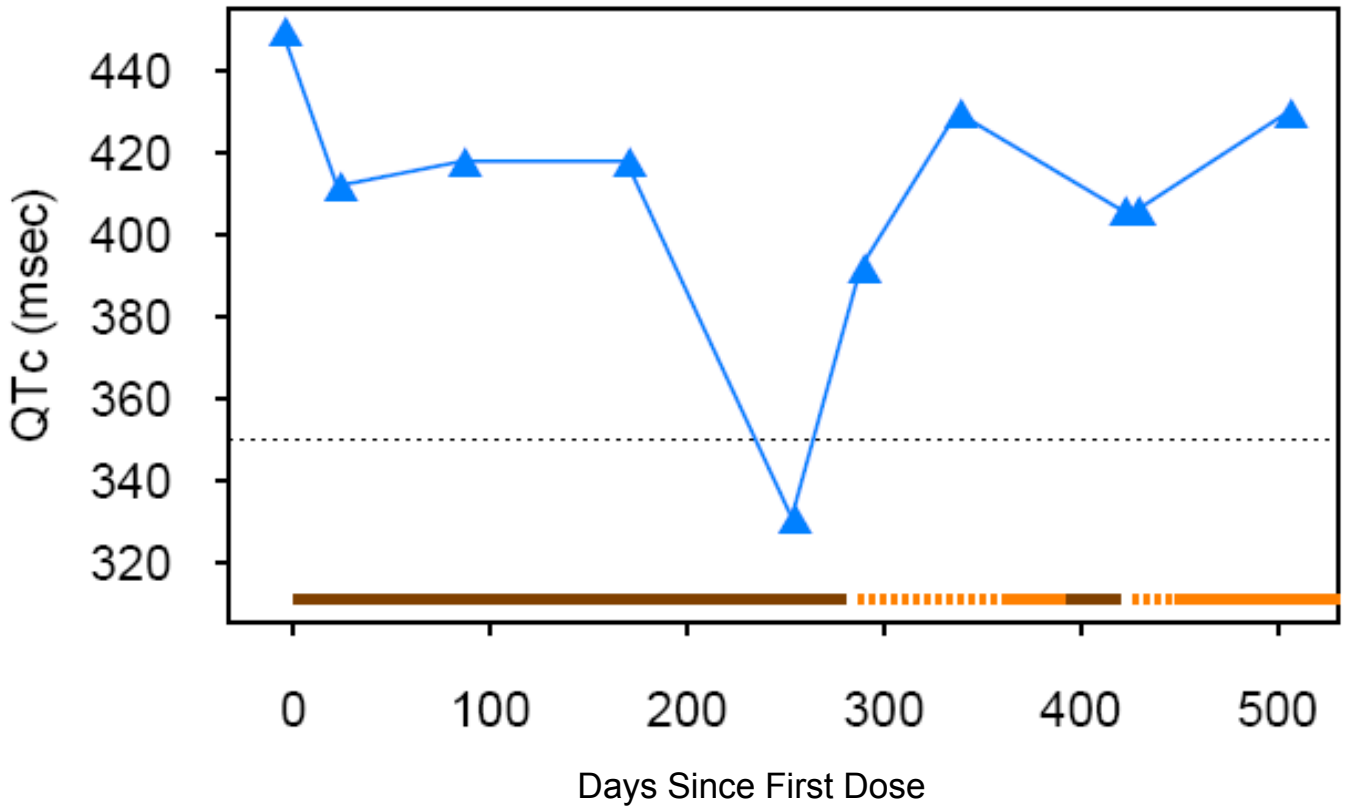
Liver Function Patient Profile plots

Safety



QTc Patient Profile Plot

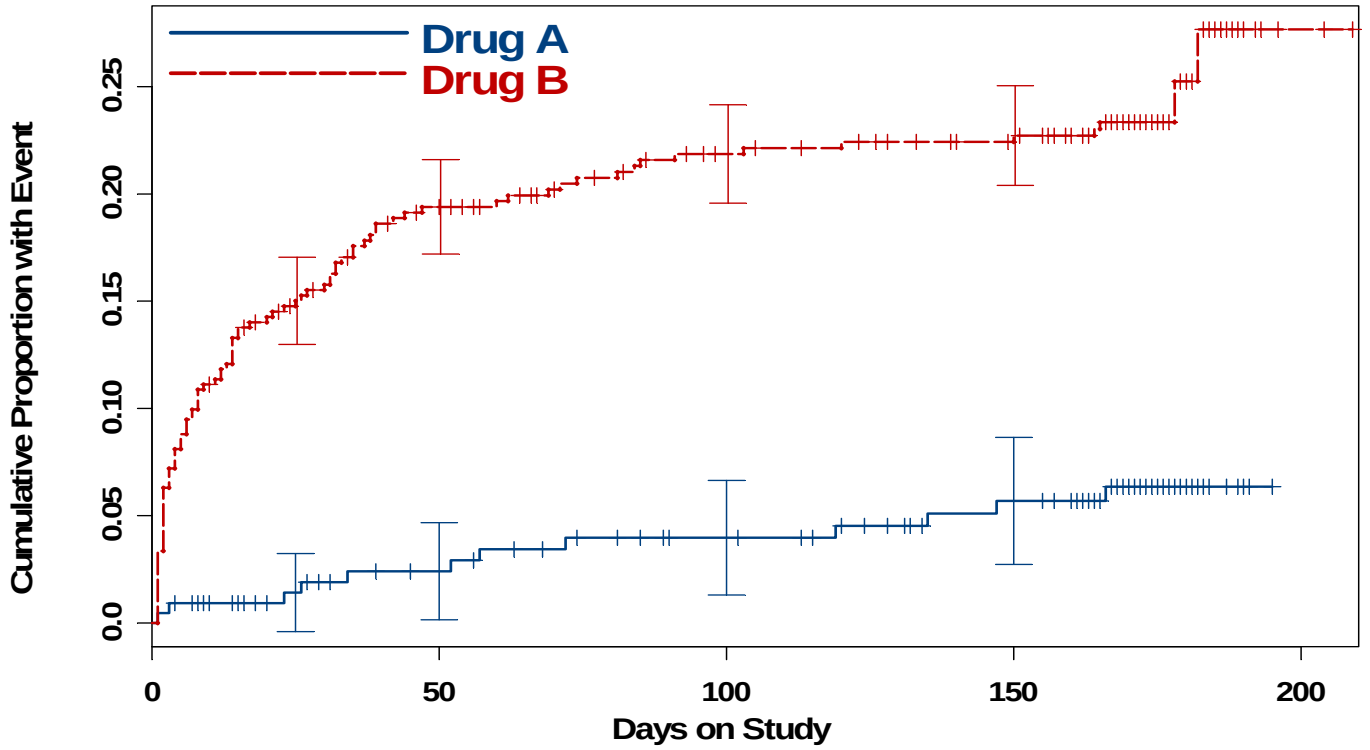
Safety



Typical Study Level Safety Plots

- Cumulative Incidence Plots
  - Provides a clear picture of the risk over time while making the appropriate modifications to the risk set as patients are censored
  - Competing risks
  - May include standard error bars, confidence bands, numbers at risk, etc.
  - Event can be defined in a variety of ways

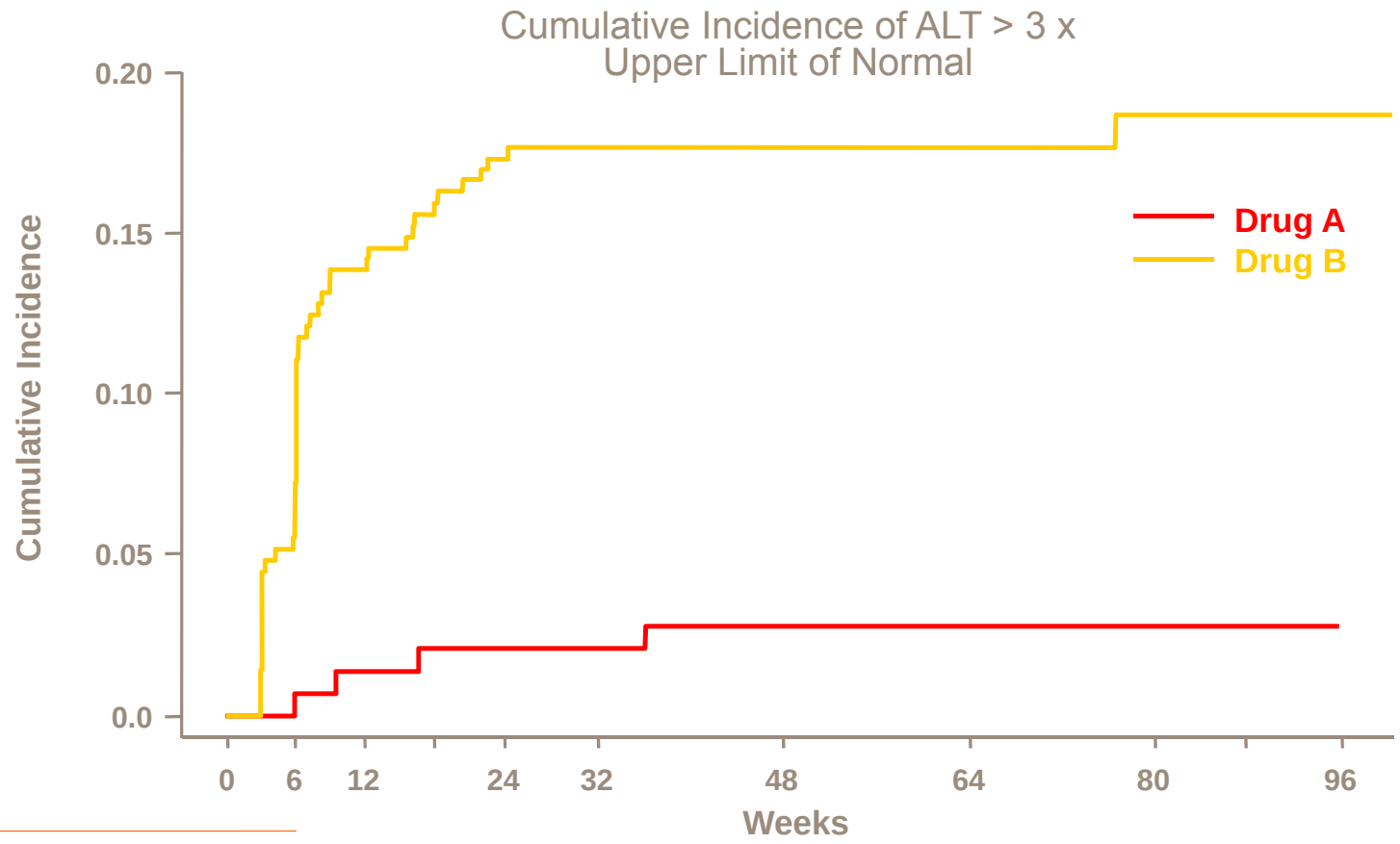
Generic Cumulative Incidence



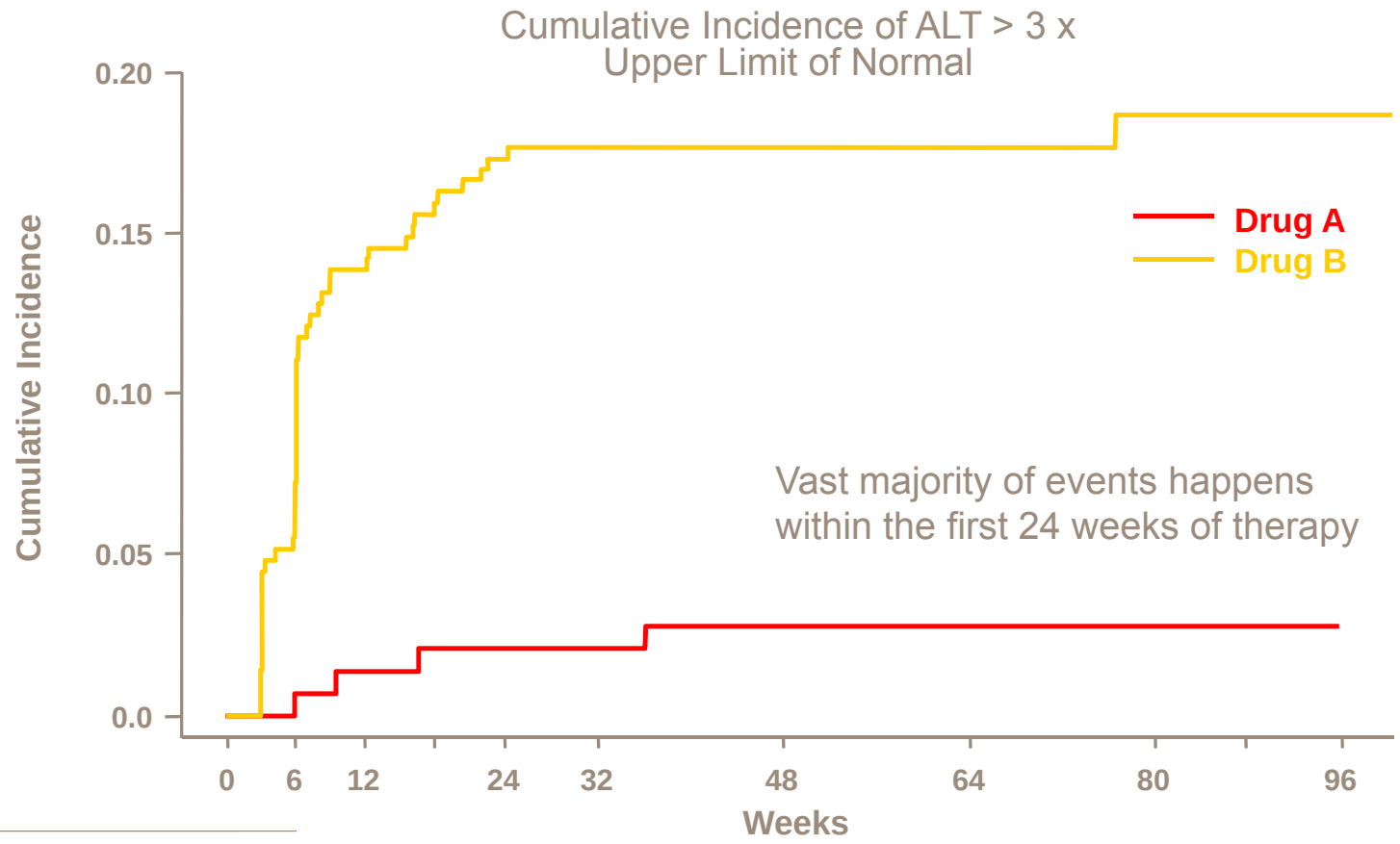
Subjects at Risk

Drug A	218	201	190	176	162	0
Drug B	447	339	305	278	264	2

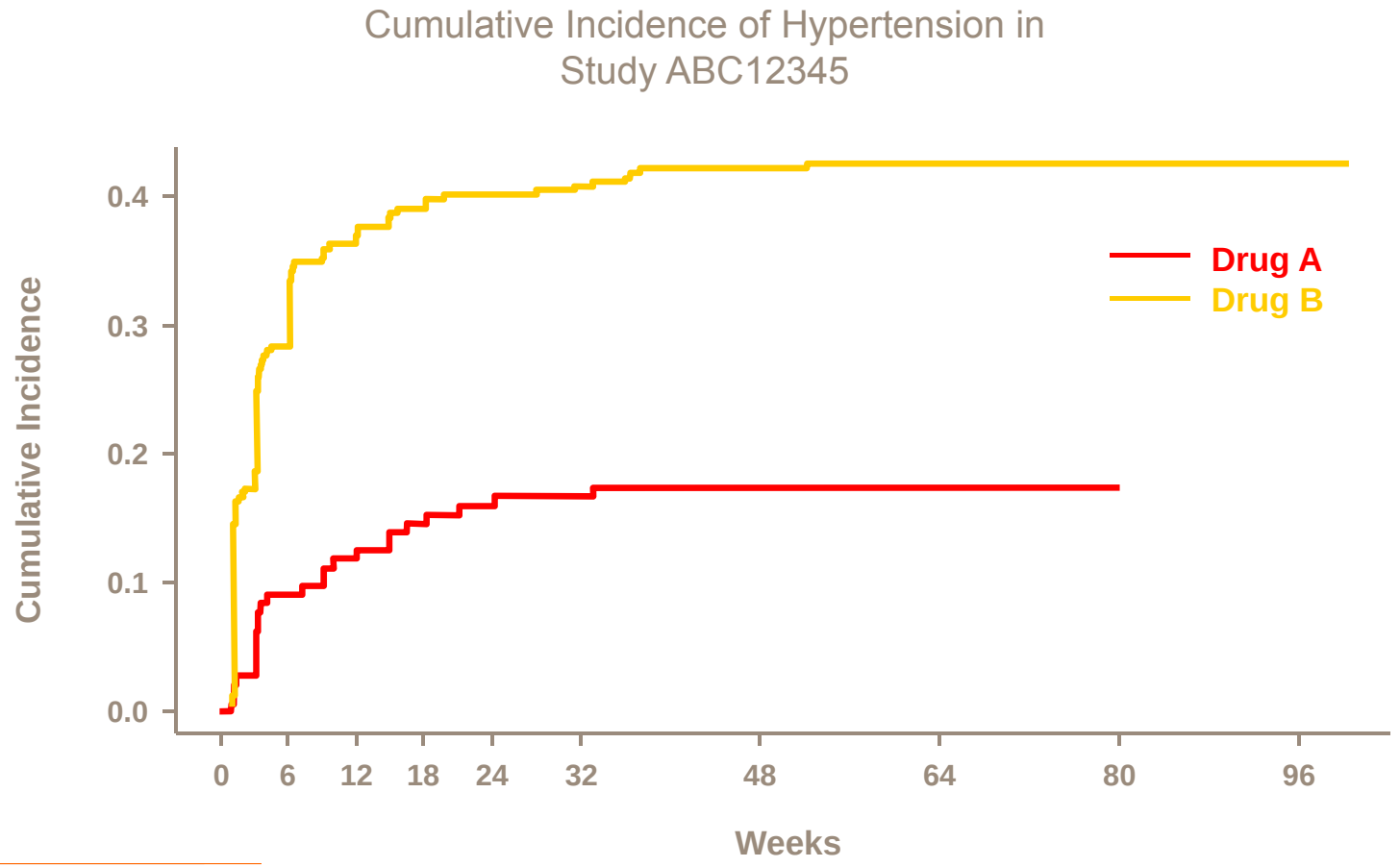
Cumulative Incidence for LFT Elevations



Cumulative Incidence for LFT Elevations



Cumulative Incidence for AEs of interest



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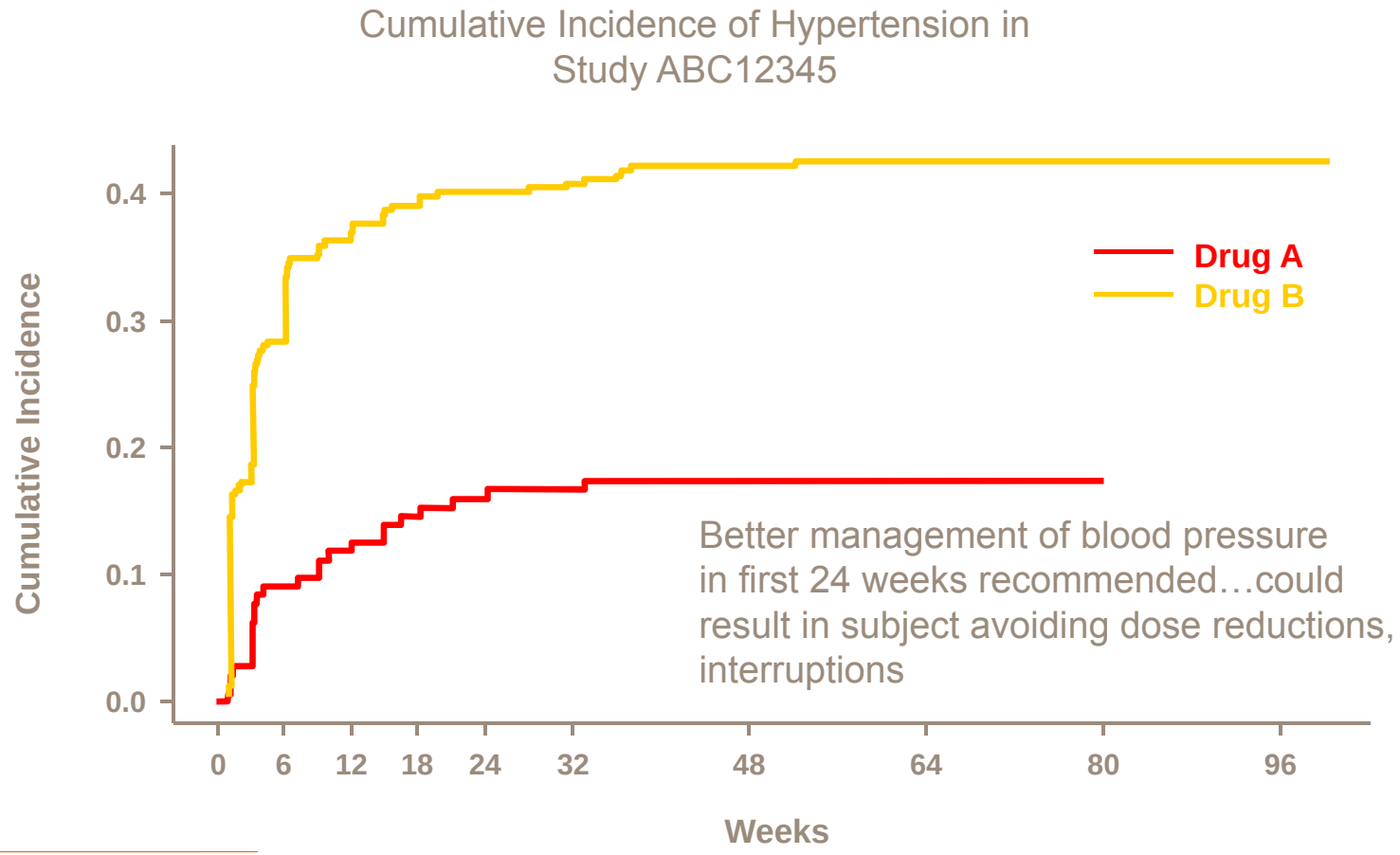
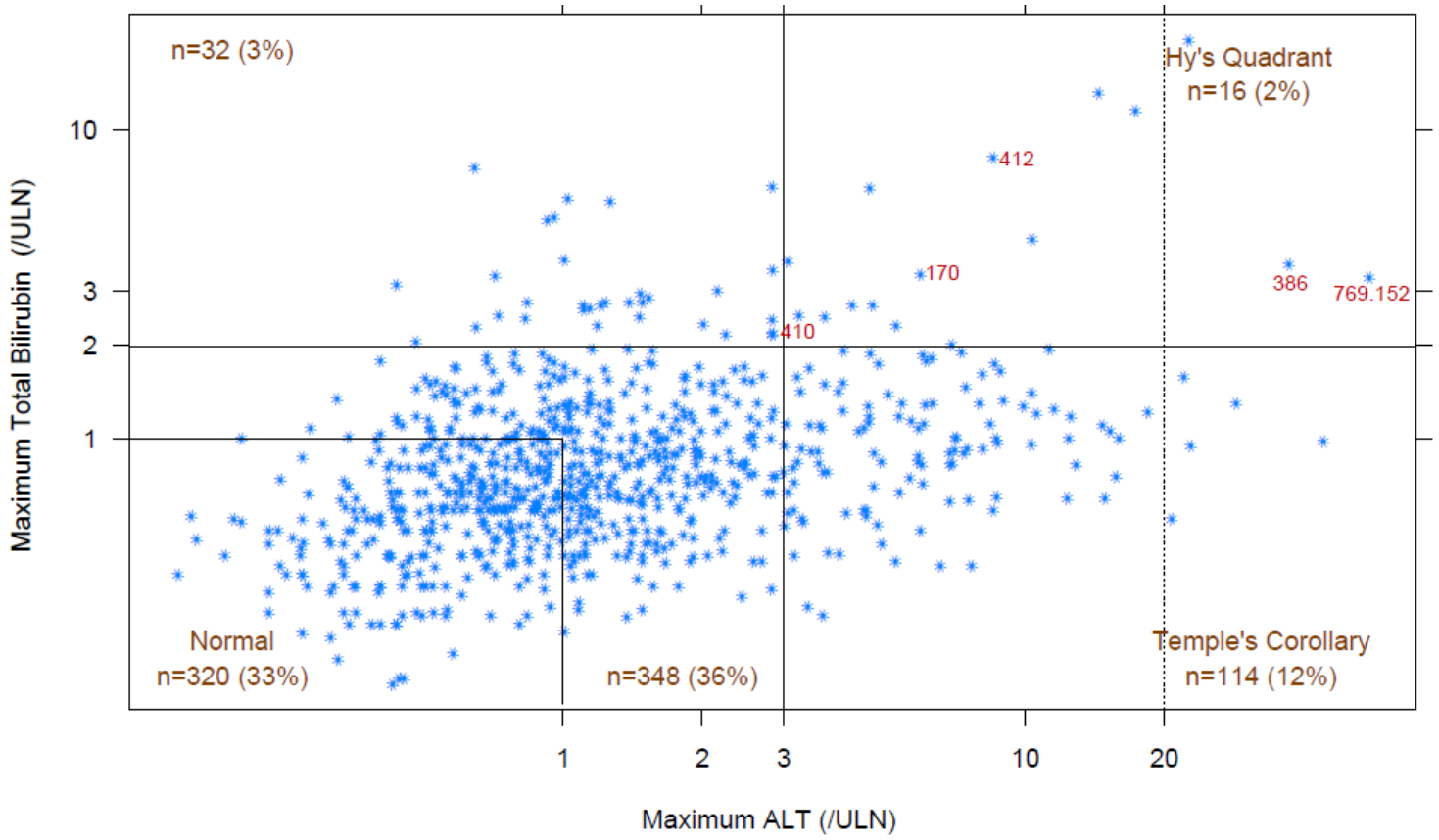


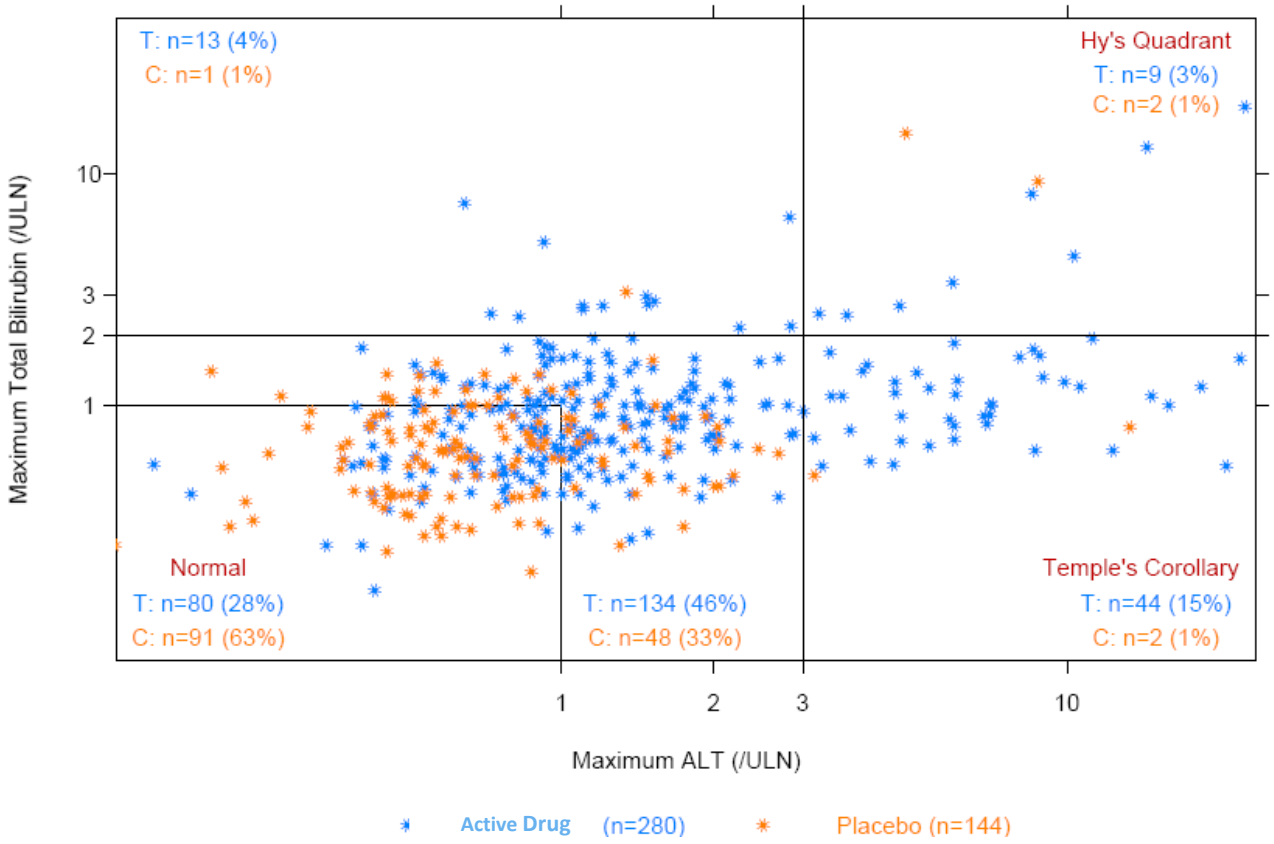
Typical Study Level Safety Plots

- Drug Induced Liver Injury Plots ('DILI')
  - Combining clinically meaningful LFT elevations of interest
  - Allows observer to easily identify the set of patients who's safety data warrant further investigation
  - Quick evaluation of potentially serious safety signals
  - Hy's Law Quadrant
    - Marker for potential to cause severe drug induced liver injury
    - Criteria (per FDA guidance, CTCAE toxicity grading):
      - ALT ≥ 3 x ULN (Upper Limit of Normal)
      - Tot. Bili ≥ 2 x ULN
      - No substantial Alk. Phos elevation
      - Rule out other more likely cause
  - Single or multi-arm trials

DILI Plots for Single Arm Studies



DILI Plots for Multi Arm Studies



Typical Study Level Safety Plots

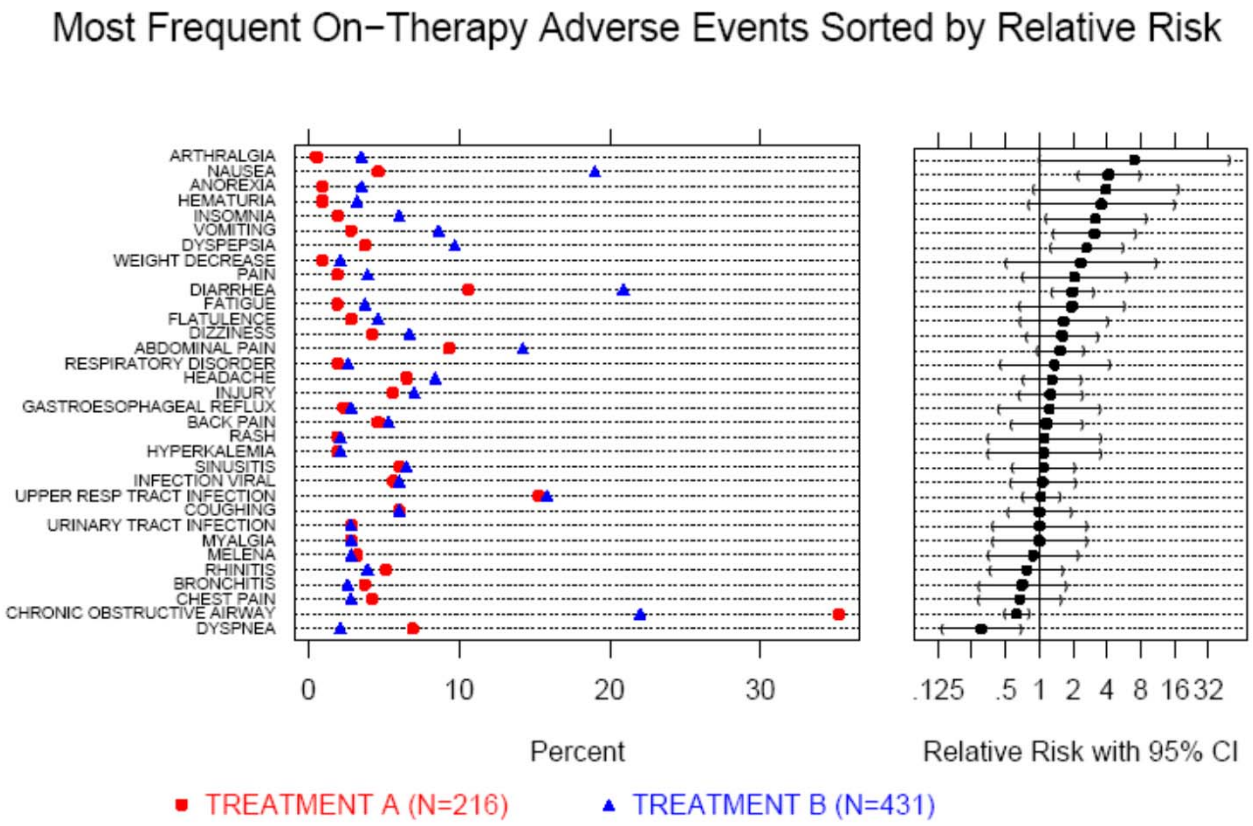
- Adverse Event Double Dot
  - saves reviewers time (internal and external)
  - Patterns easier to tease out

Tabular Adverse Event Results

Event	Drug A (%)	Drug B (%)	RelRisk	Low95%	Up95%
ARTHRALGIA	3.5	0.5	7.0	1.6	31.5
NAUSEA	19.0	4.6	4.1	2.5	6.9
ANOREXIA	3.5	0.9	3.9	1.2	13.1
HEMATURIA	3.2	0.9	3.6	1.0	12.2
INSOMNIA	6.0	1.9	3.2	1.3	7.5
VOMITING	8.6	2.8	3.1	1.5	6.2
DYSPEPSIA	9.7	3.7	2.6	1.4	4.9
WEIGHT DECREASE	2.1	0.9	2.3	0.6	9.0
PAIN	3.9	1.9	2.1	0.8	5.3
DIARRHEA	20.9	10.6	2.0	1.4	2.9
FATIGUE	3.7	1.9	1.9	0.7	5.1
FLATULENCE	4.6	2.8	1.6	0.7	3.7
DIZZINESS	6.7	4.2	1.6	0.8	3.1
ABDOMINAL PAIN	14.2	9.3	1.5	1.0	2.4
RESPIRATORY DISORDER	2.6	1.9	1.4	0.5	4.0
HEADACHE	8.4	6.5	1.3	0.7	2.3
INJURY	7.0	5.6	1.2	0.7	2.3
GASTROESOPHAGEAL REFLUX	2.8	2.3	1.2	0.4	3.3
BACK PAIN	5.3	4.6	1.2	0.6	2.3
HYPERKALEMIA	2.1	1.9	1.1	0.4	3.4
RASH	2.1	1.9	1.1	0.4	3.4
SINUSITIS	6.5	6.0	1.1	0.6	2.0
INFECTION VIRAL	6.0	5.6	1.1	0.6	2.1
UPPER RESP TRACT INFECTION	15.8	15.3	1.0	0.7	1.5
MYALGIA	2.8	2.8	1.0	0.4	2.6
URINARY TRACT INFECTION	2.8	2.8	1.0	0.4	2.6
COUGHING	6.0	6.0	1.0	0.5	1.9
MELENA	2.8	3.2	0.9	0.3	2.2
RHINITIS	3.9	5.1	0.8	0.4	1.7
BRONCHITIS	2.6	3.7	0.7	0.3	1.8
CHEST PAIN	2.8	4.2	0.7	0.3	1.6
CHRONIC OBSTRUCTIVE AIRWAY	22.0	35.2	0.6	0.5	0.8
DYSPNEA	2.1	6.9	0.3	0.1	0.8

Adverse Event Double Dot Plot

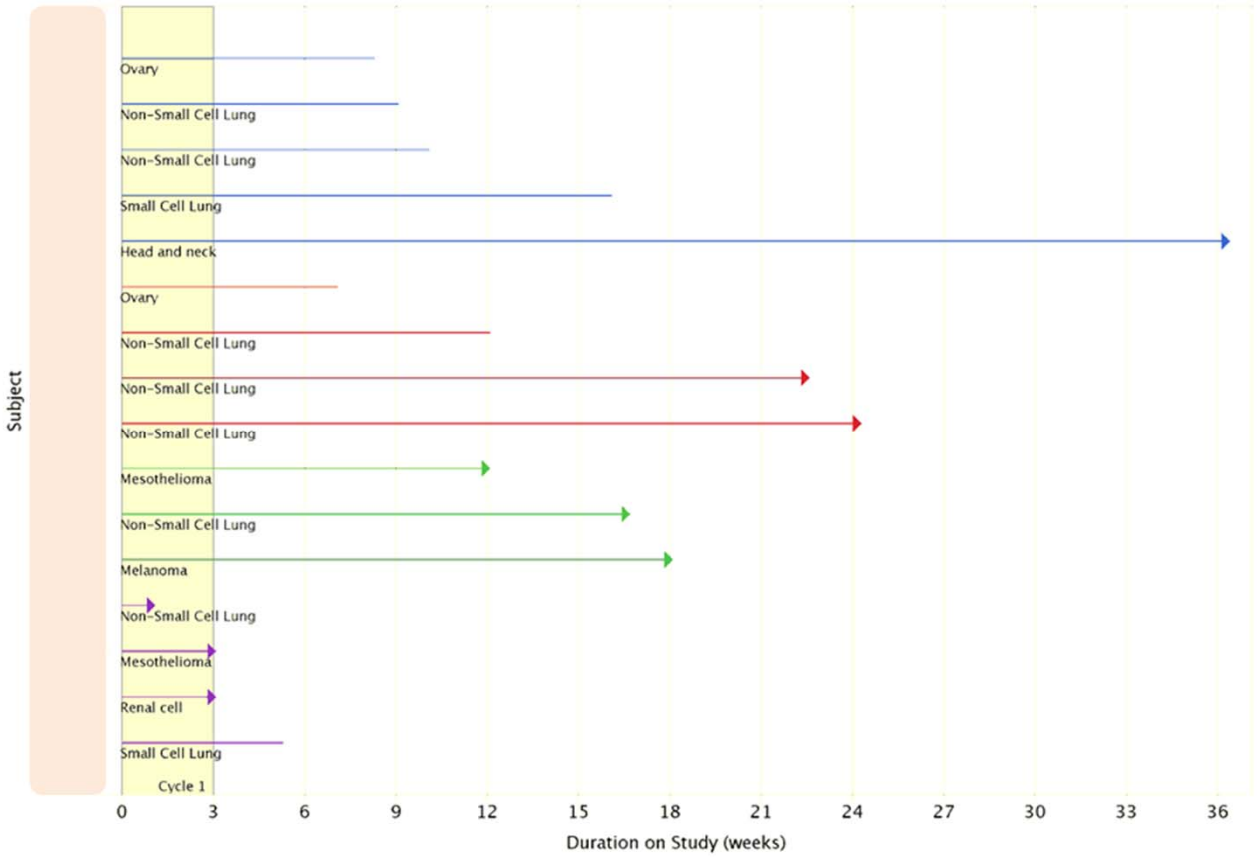
Same data, re-visualized



Typical Study Level Safety Plots

- Duration plots
  - Can contain many types of info
    - Exposure
    - Adverse Event
    - Clinical Response
    - Concomitant Med
    - Disease type, Demographics

Duration Plot



Graphics commonly utilized today

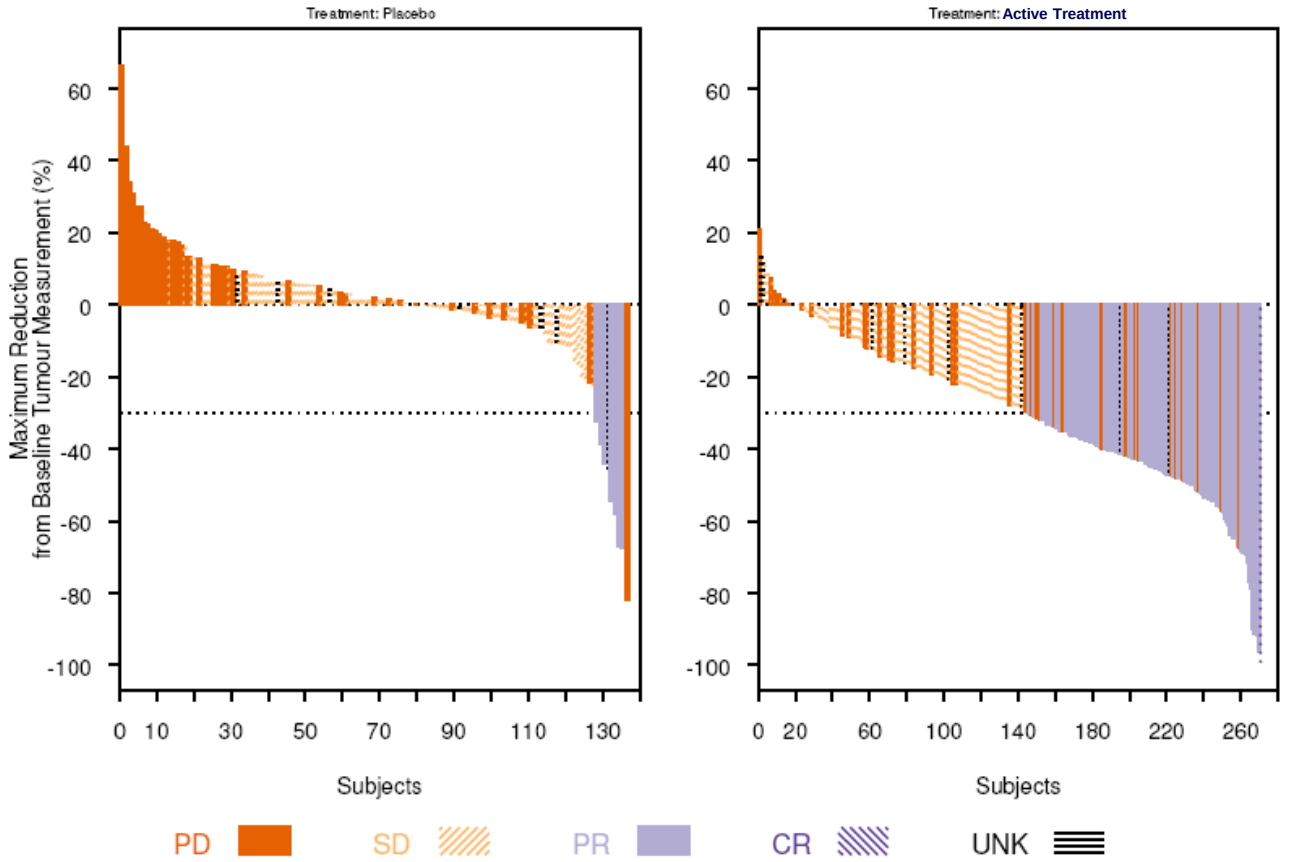
…For assessment of efficacy data

Typical Efficacy Plots

- Tumor diameter or volumetric shrinkage/growth
  - 'Waterfall' Plots
  - Method of displaying patients' maximum tumor shrinkage in Oncology studies
  - Clinical response at the corresponding time point
  - Qualitative visual evaluation of activity
  - Treatment comparisons via trellising
- Time to Event
  - Overall Survival (OS)
  - Progression Free Survival (PFS)
  - Duration of Response
- Hazard ratio summaries

Comparative ‘Waterfall Plot’

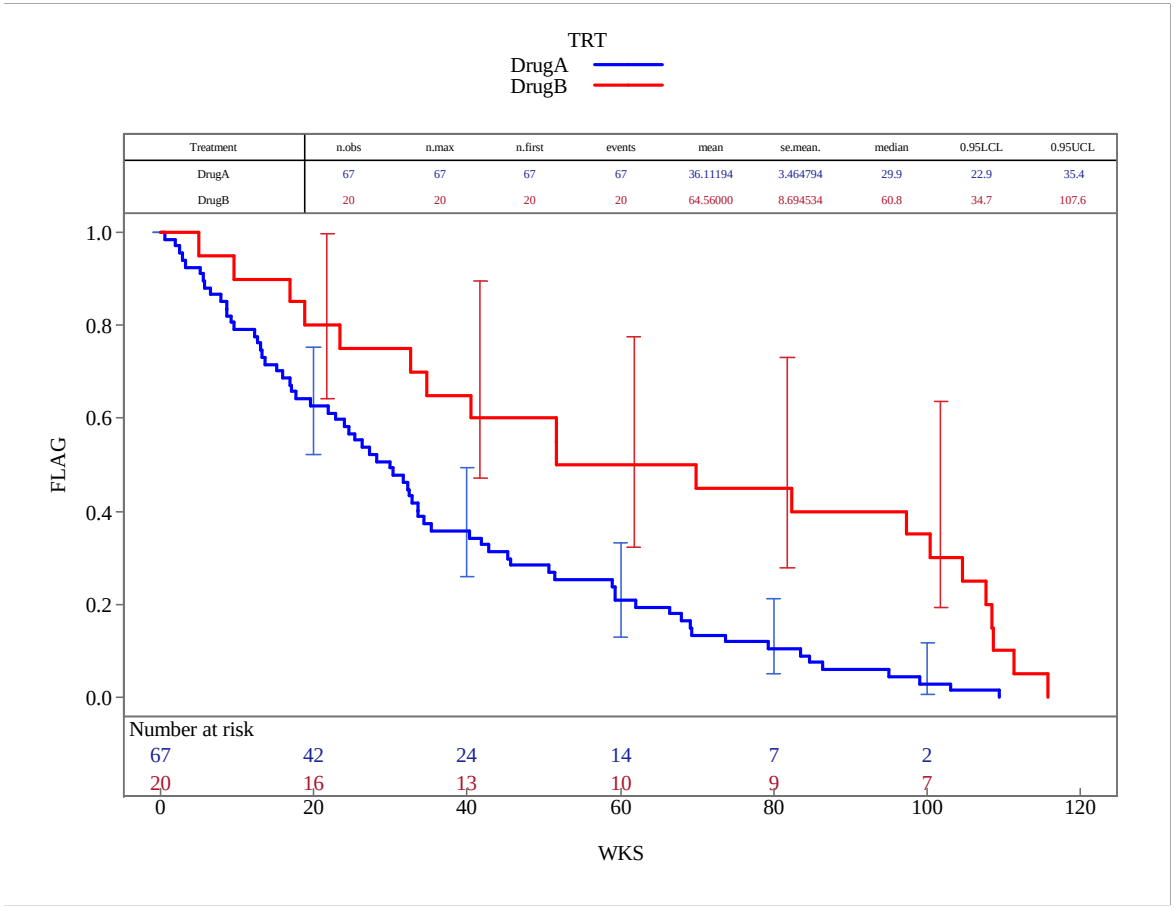
For lesion diameter changes from baseline



Typical Efficacy Plots

- Time to Event
  - Overall Survival (OS)
  - Progression Free Survival (PFS)
  - Duration of Response

Survival Curves

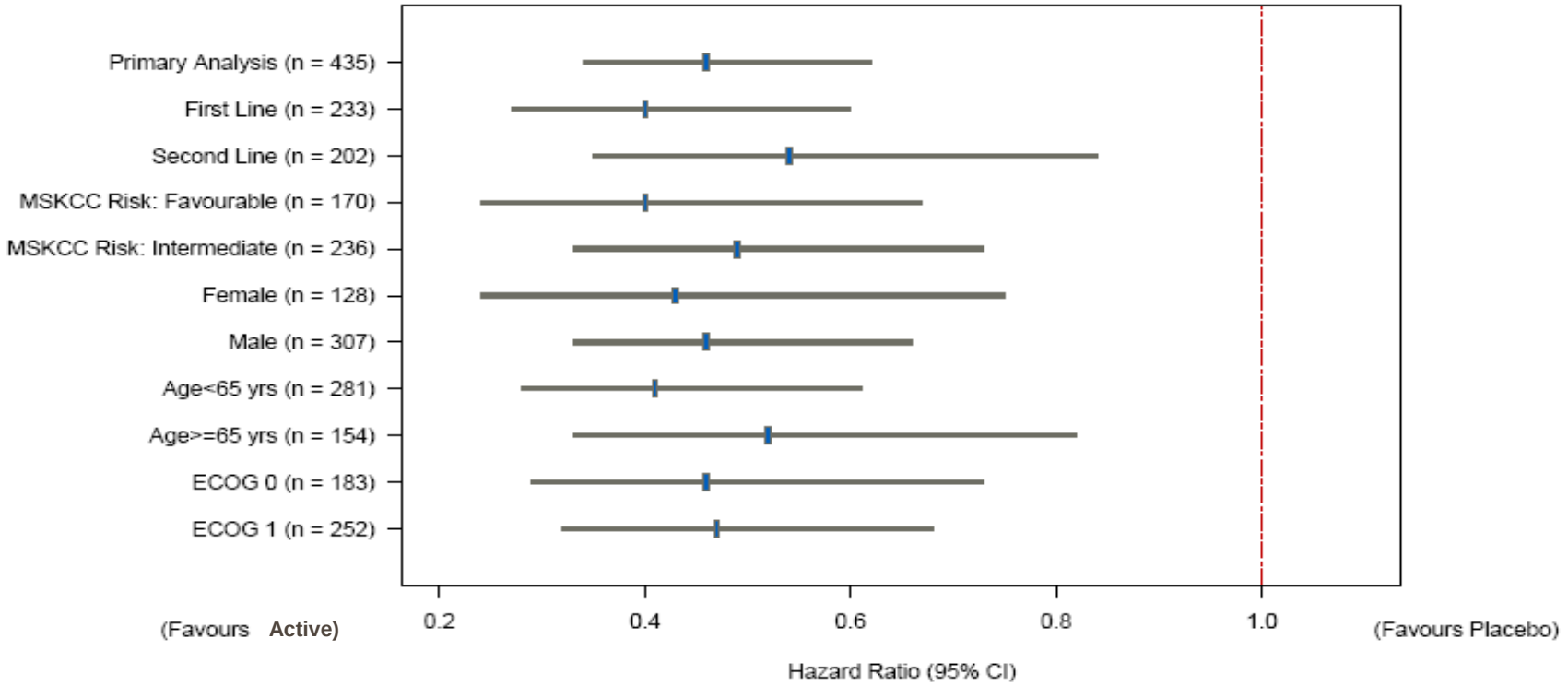


More Survival

Typical Efficacy Plots

- Forest Plots
  - Simply summarizes the relative treatment effects of many separate analysis in one display
  - Allows for key indirect comparisons to be made
  - Subgroup analyses

Forest Plot of Hazard Ratios (PFS)



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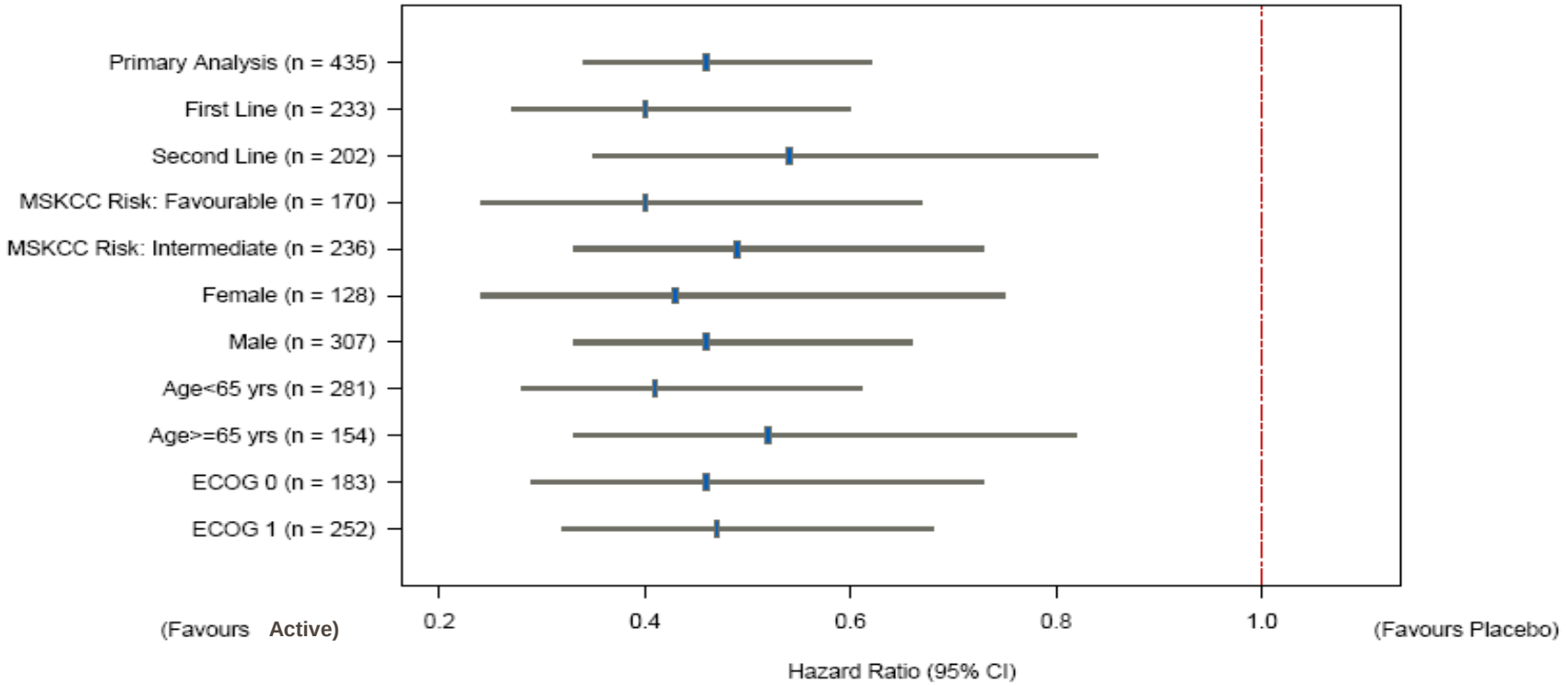
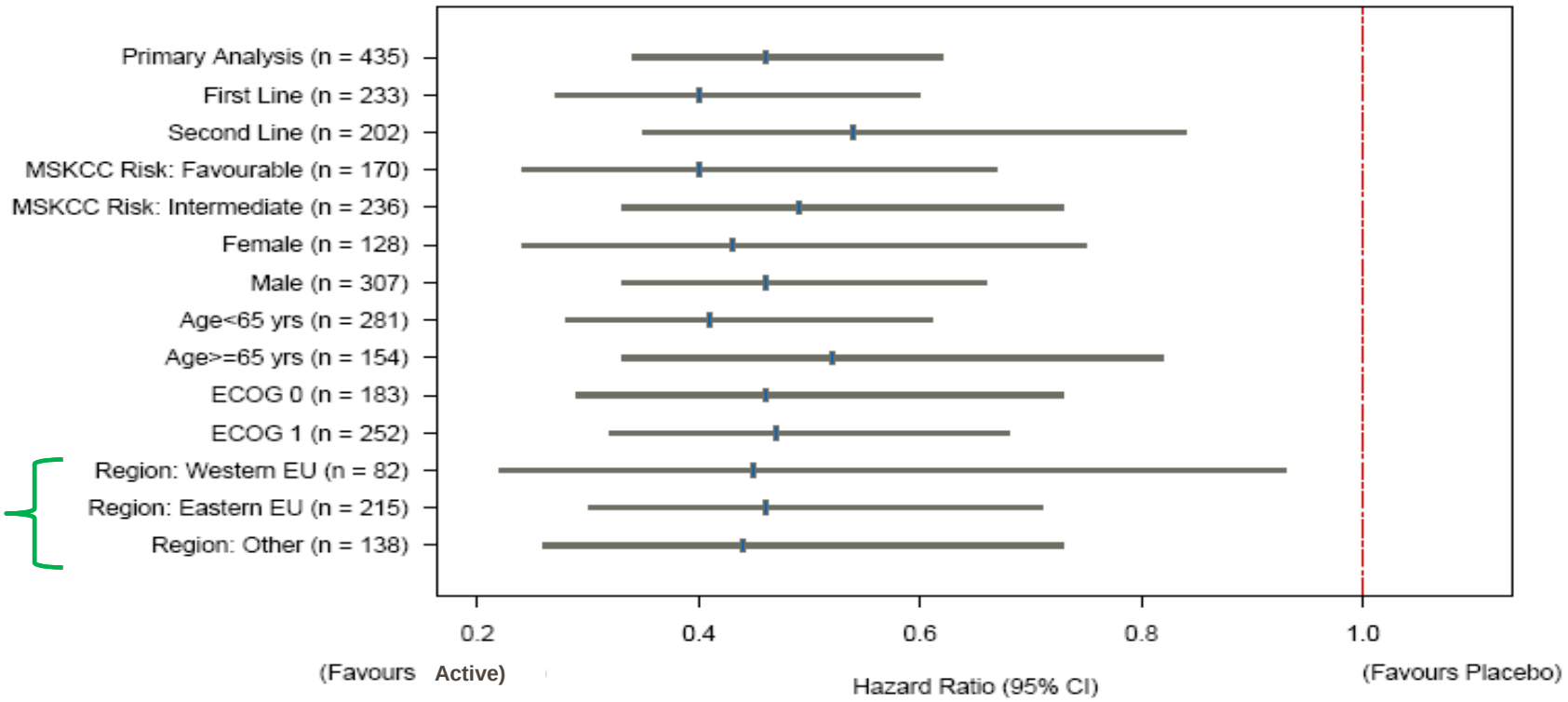


Regulatory question: Since this study had no US patients, how can we assume that the efficacy will be similar?

Forest Plot of Hazard Ratios (PFS)



Regulatory question: Since this study had no US patients, how can we assume that the efficacy will be similar?

GSK response: Regional analysis shows that there is no significant difference between regions analyzed. Phase II regional analysis that contains US patients supports this finding as well.

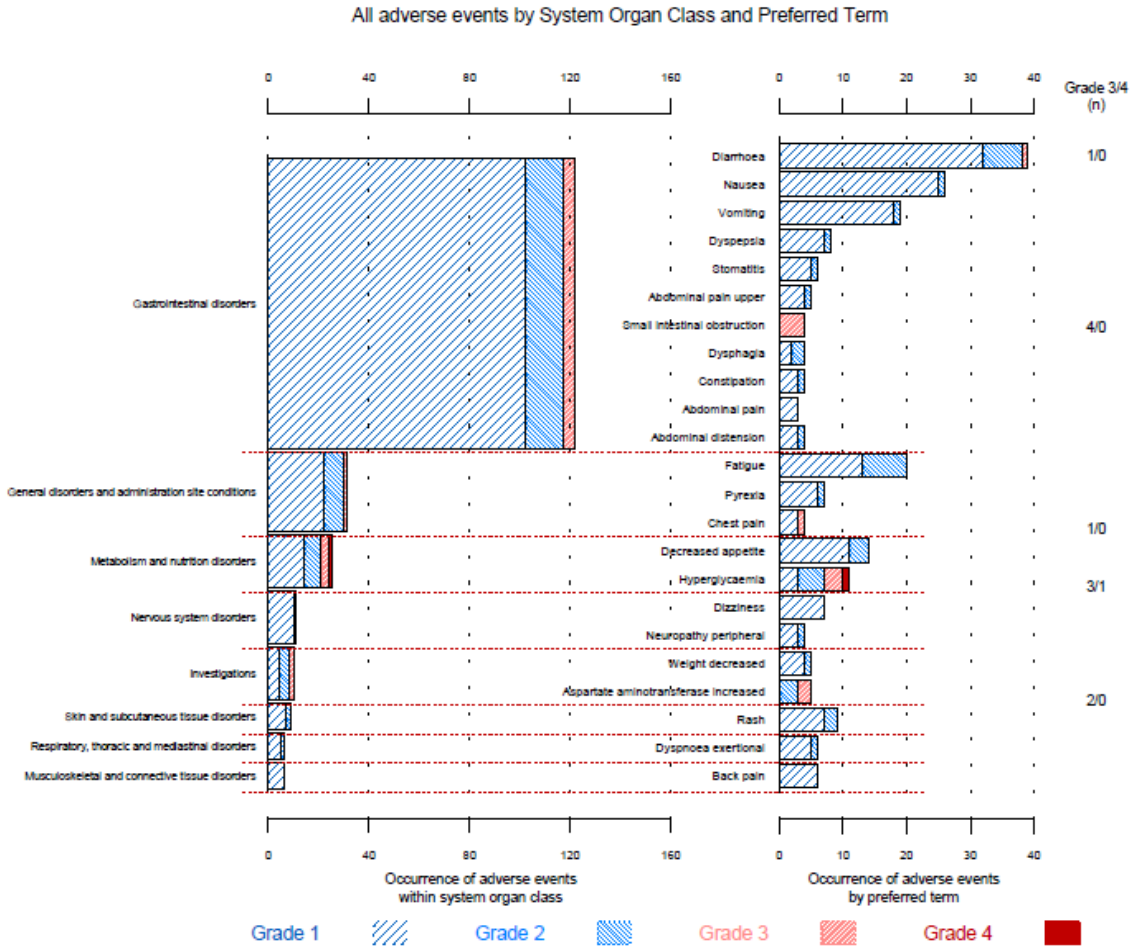
Moving Beyond…

Moving beyond…

- Sometimes the standard displays just don't cut it
  - specialized
  - Non-standard display
  - 80-20
- Highly customized, sometimes difficult to re-purpose
- Often improved iteratively with feedback from the end user
- Often need to be coded in R, S-Plus (sometimes SAS)
  - Some can be handled by GUI software

Adverse Event Stacked Bar Chart

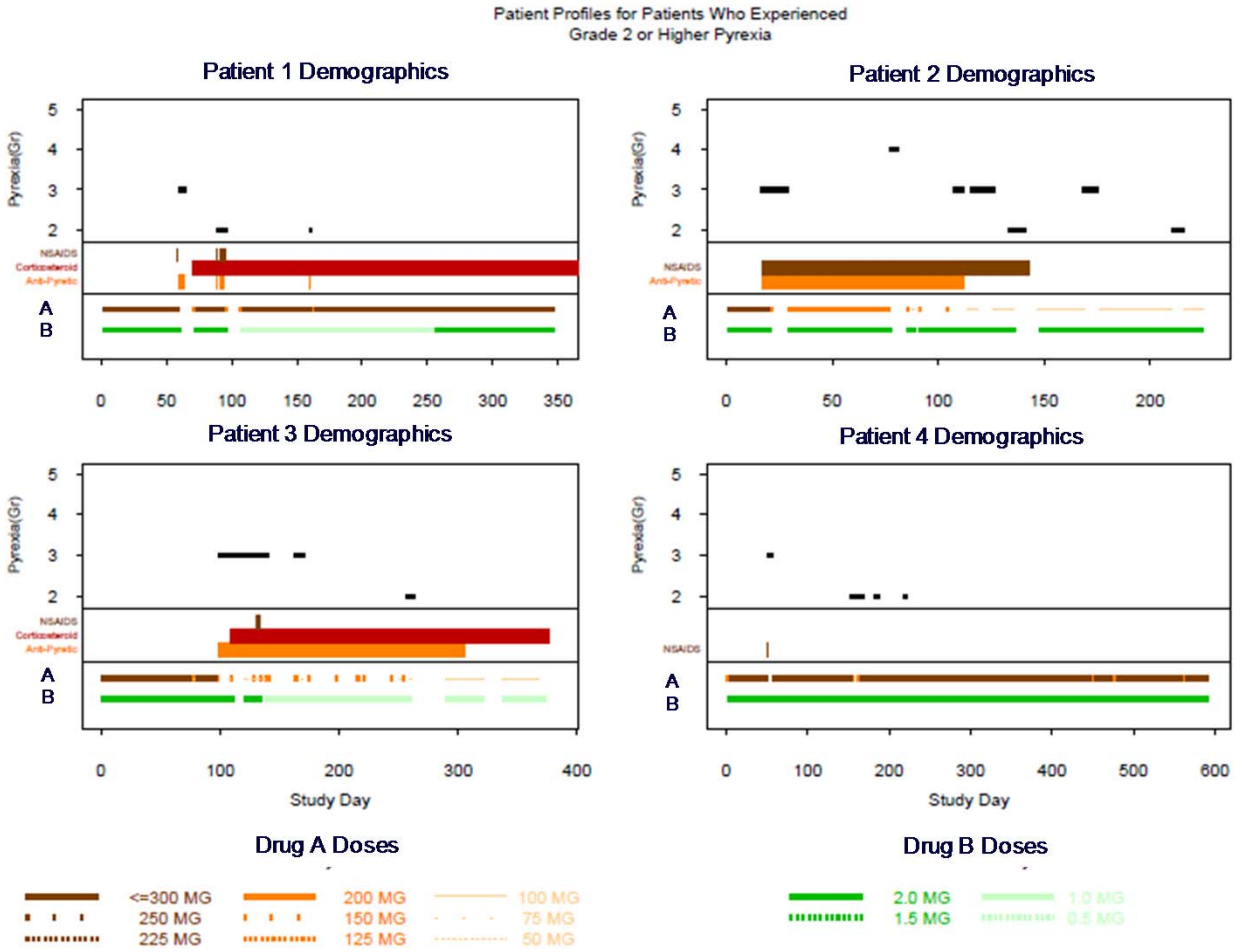
- Key Features:
  - Panels for System Organ Class (SOC) and Preferred Term
  - AE Severity
  - Counts for grades 3 and 4



Adverse Event Patient Profile

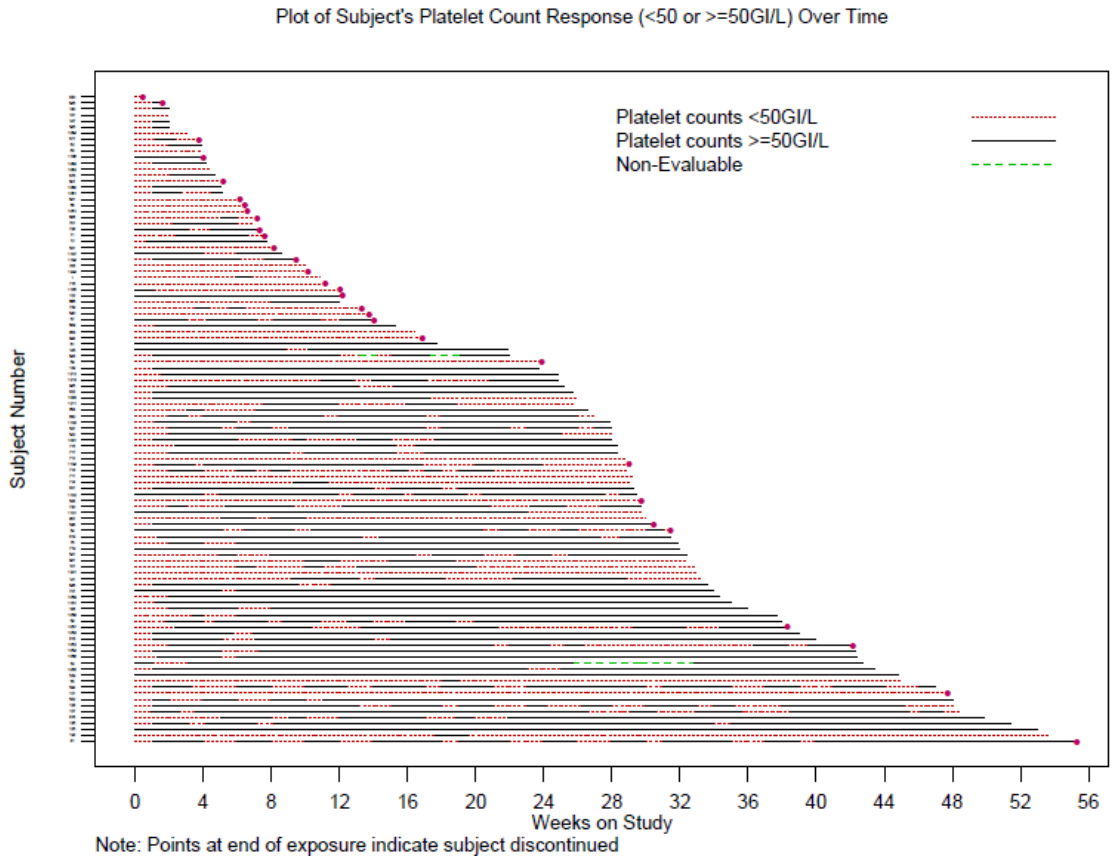
w/ Exposure and Concomitant Medication Info

- Key Features:
  - AE severity and duration
  - Corresponding concomitant med use
  - Corresponding exposure
    - Dose level
    - Delays/Interruptions
    - Escalations
  - Demographics
  - Subgroups



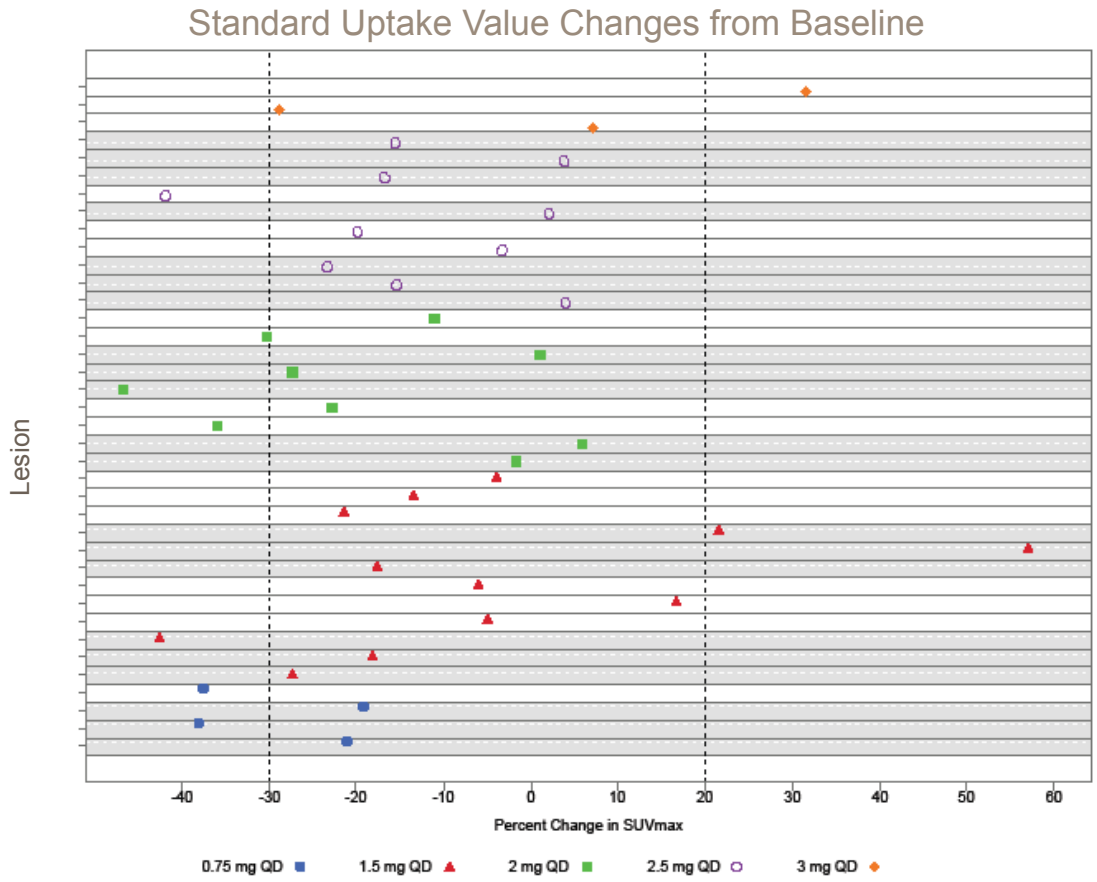
Efficacy Duration Plot

- Key Features:
  - Duration of efficacy signals
  - Intensity of signals
  - Patient and Study level
    - Individual subject numbers
  - Disposition information
    - Patient ongoing?

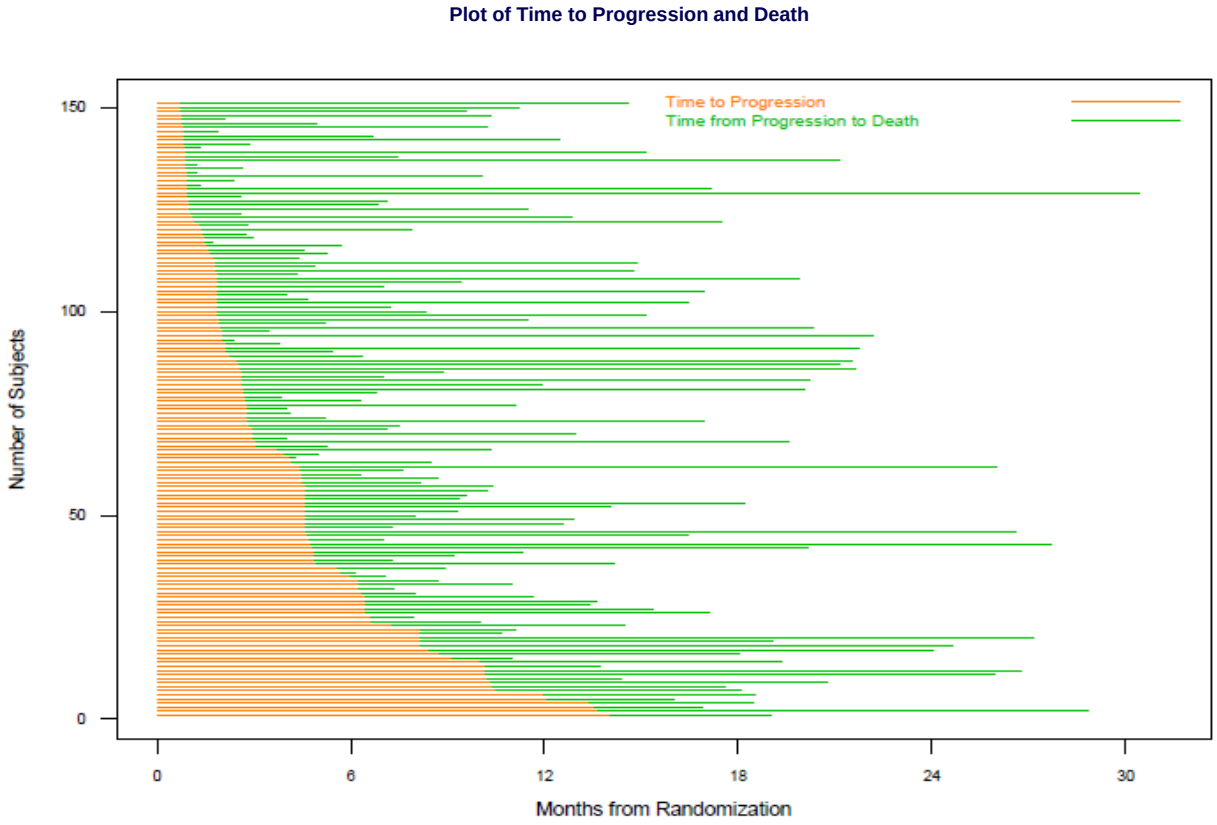


Dot Plot of Change from Baseline in SUVs

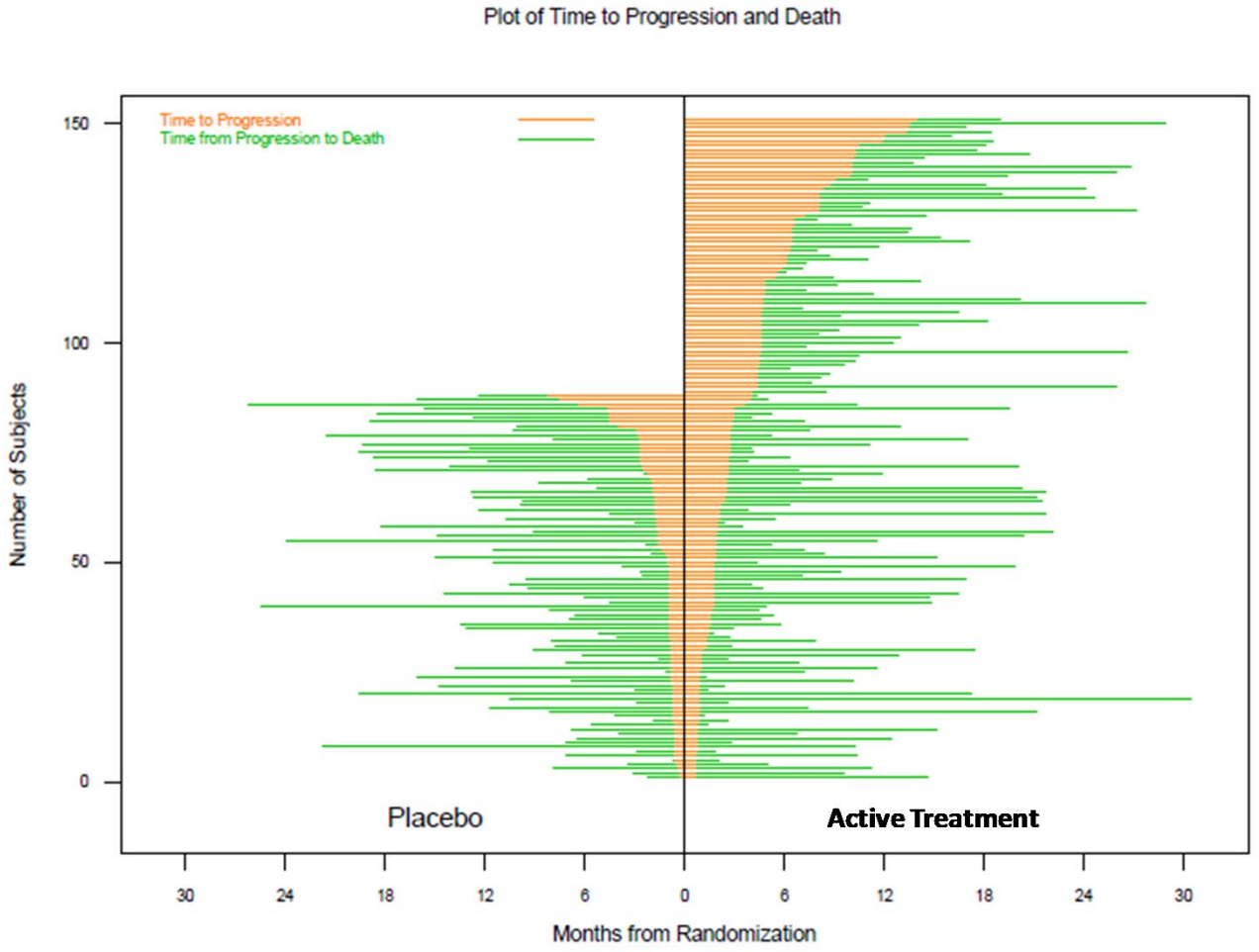
- Key Features:
  - Shows values for every monitored lesion
  - Gray/white bands are individual patients
  - Dose level
  - Clinical concern lines



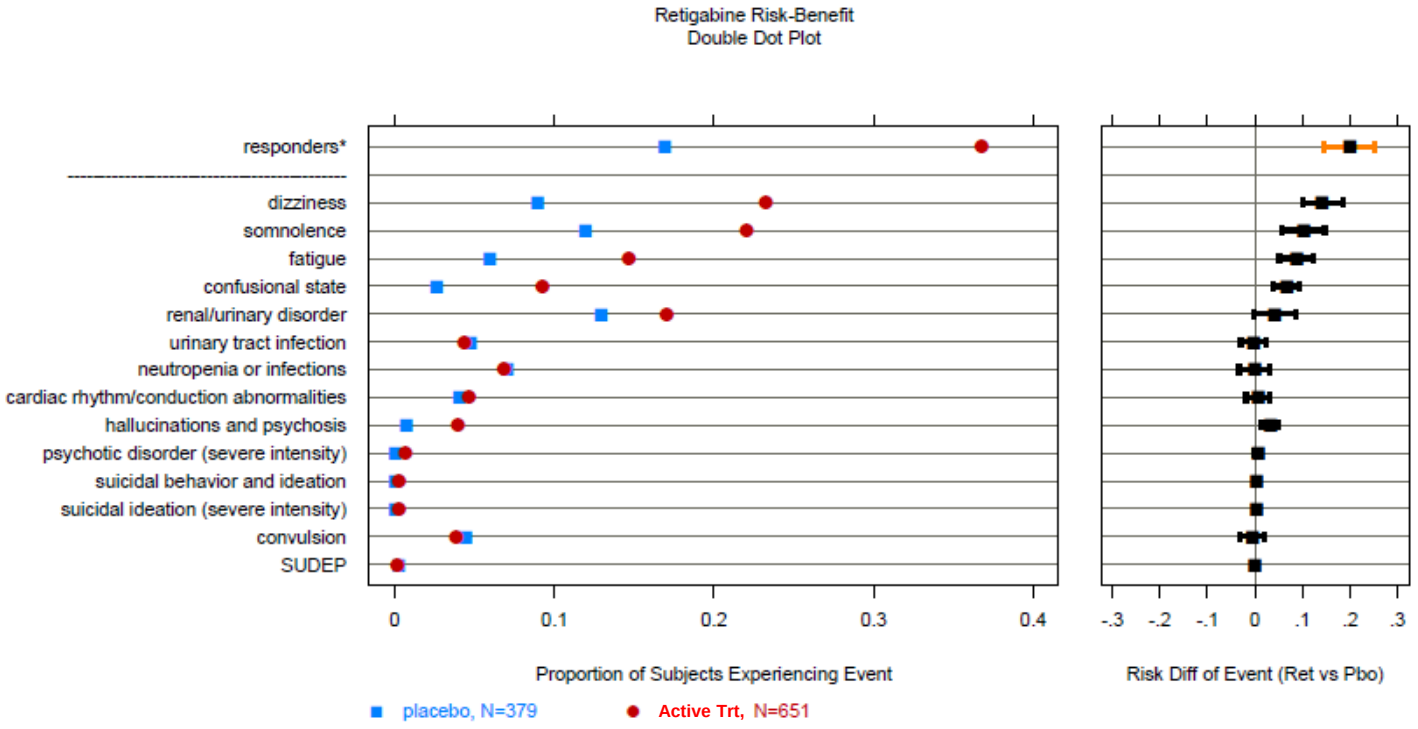
Time to Progression and Death Plot



- Key Features:
  - Can be comparative
    - Single vs multi arm
  - Helps highlight patterns in efficacy data
    - Does shorter time to progression lead to quicker death?

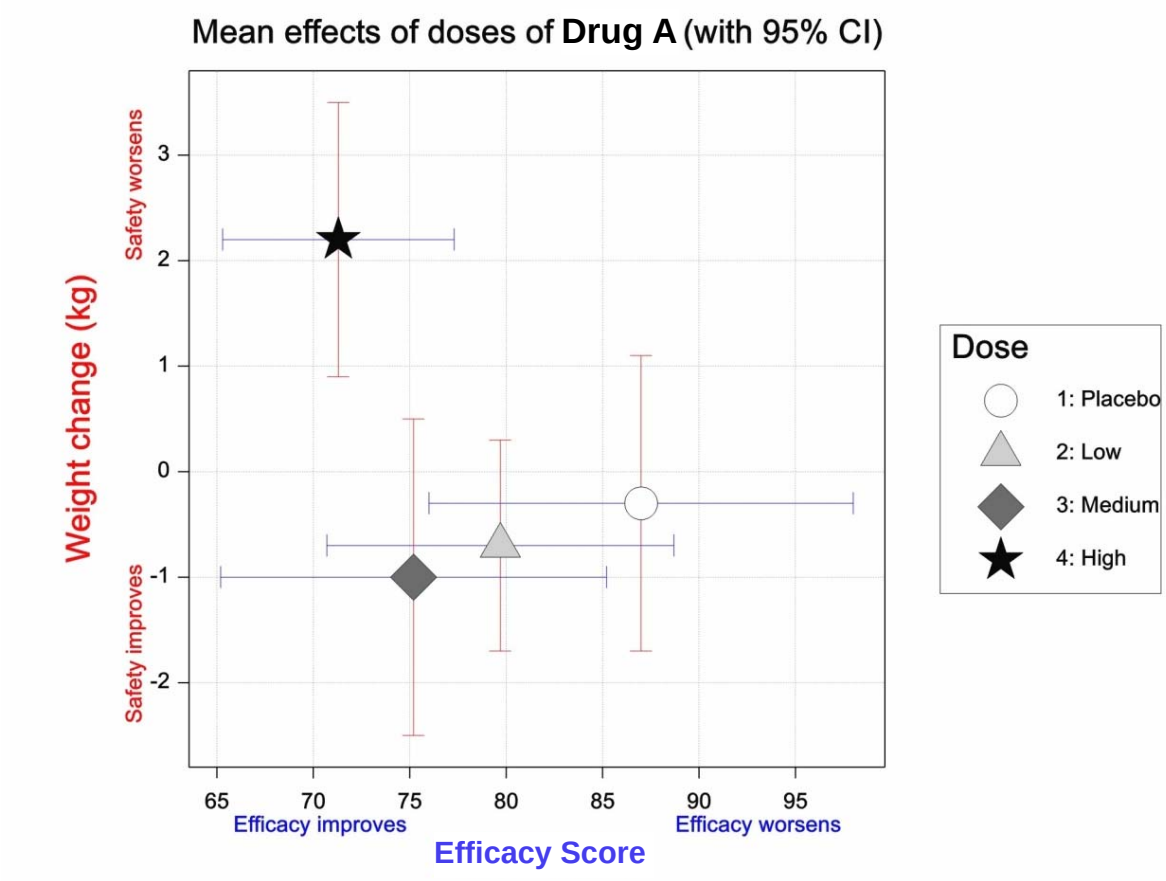


- Key Features:
  - Safety and Efficacy together
  - Relative ‘stregnth ‘of signals



Benefit Risk Scatter Plot

- Key Features:
  - Decisions can be quickly made
  - Easy to interpret
  - Confidence intervals



Conclusion and Acknowledgements

Conclusions

- Tools were put in place to aid the expansion and quality of well designed graphics
- Culture change
- Graphics can play a key role in many aspects of drug development
  - Influence decision making
  - Support medical monitoring
  - Aid in signal detection (and save time!)
- Subject level graphics can help provide a clear temporal overview of key safety (and efficacy) data
- Graphical presentations of the distribution are an important tool across a broad range of clinical trials data
- New, innovative and interesting graphics continue to developed and utilized

Acknowledgements

- Members of the GSK Graphics Team and Graphics Community Steering Team
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- Tibco Spotfire
- GSK Oncology Colleagues


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Questions?


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Thank you!