

Understanding Clinical Trial Data Through Use of Statistical Graphics

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A picture tells a thousand words

Lake Blanche

A picture tells a thousand words



Outline

- Introduction
- Patient Safety
 - Exposure
 - Laboratory data
 - Hy's law
 - AE relative risk
- Efficacy data
 - Waterfall plots
 - Skyline plots
 - Forest plots

Review of safety data

- Safety data from clinical trials is usually evaluated through simple summary tables and review of individual patient data
 - Formal analysis much less developed than for efficacy
 - Scan tables and patient listings and highlight “important” results in textual summaries
- The safety of a molecule is best understood by understanding data at the individual patient level
- Ideal opportunity to use graphical methods
 - Present concise summaries
 - Communicate main messages
 - Increase efficiency of review

Exposure

- Before looking at safety we need to answer a key question:

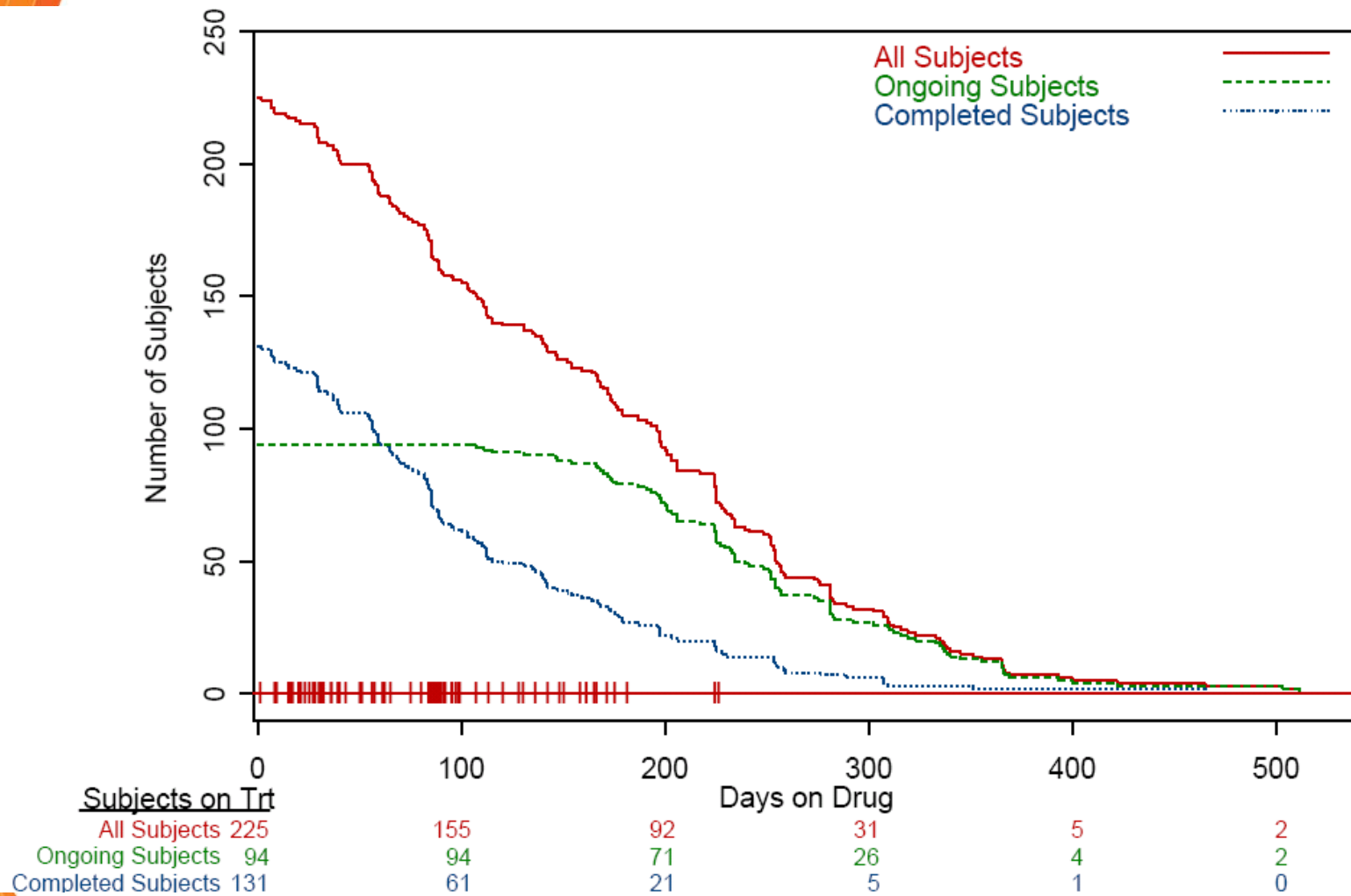
How many for how long and at what dose?

- What is the exposure underlying the safety profile
- Tabular summaries are useful....

Summary of Exposure

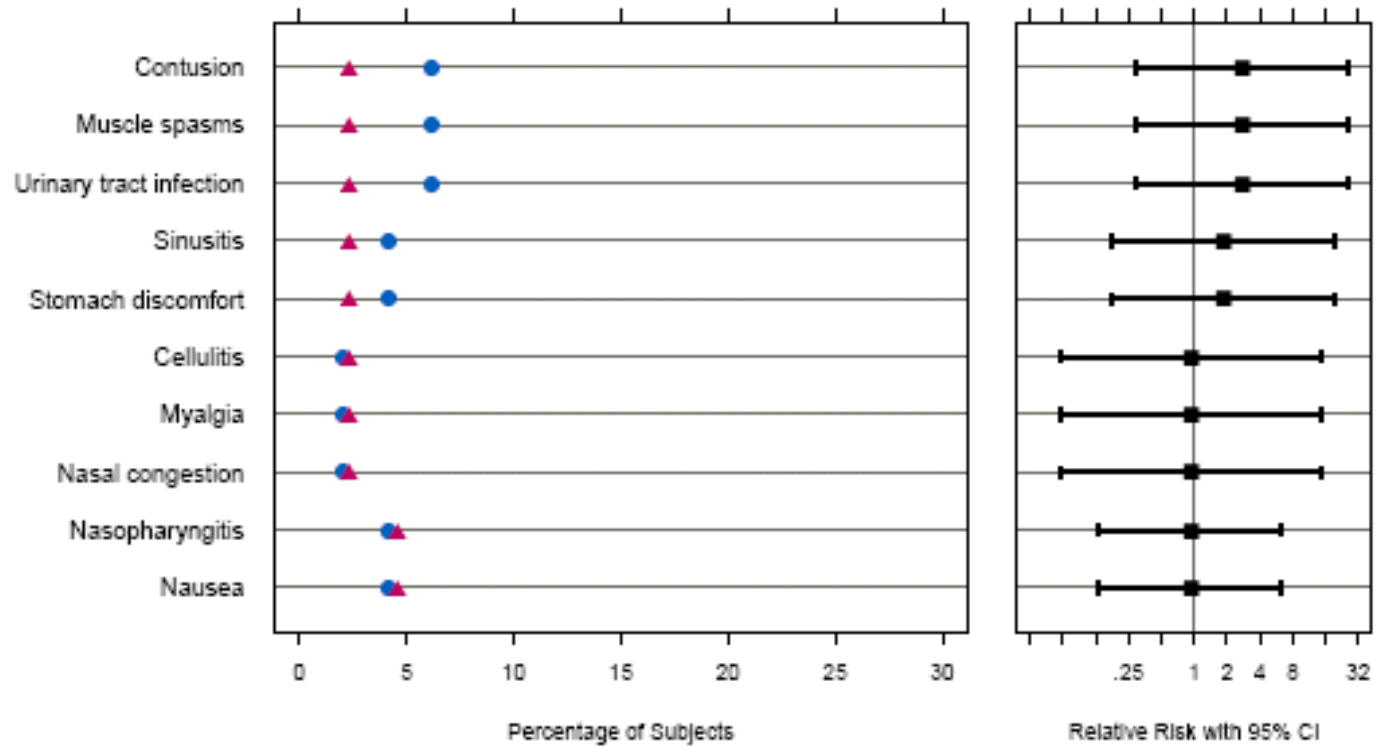
| | Exposure (Days) |
|--------|--------------------|
| N | 225 |
| Mean | 198 |
| Median | 187 |
| Min | 7 |
| Max | 500 |

Summary of Exposure



A screening tool for AEs

Figure 9.02
Most Frequent On-Therapy Adverse Events Sorted by Relative Risk



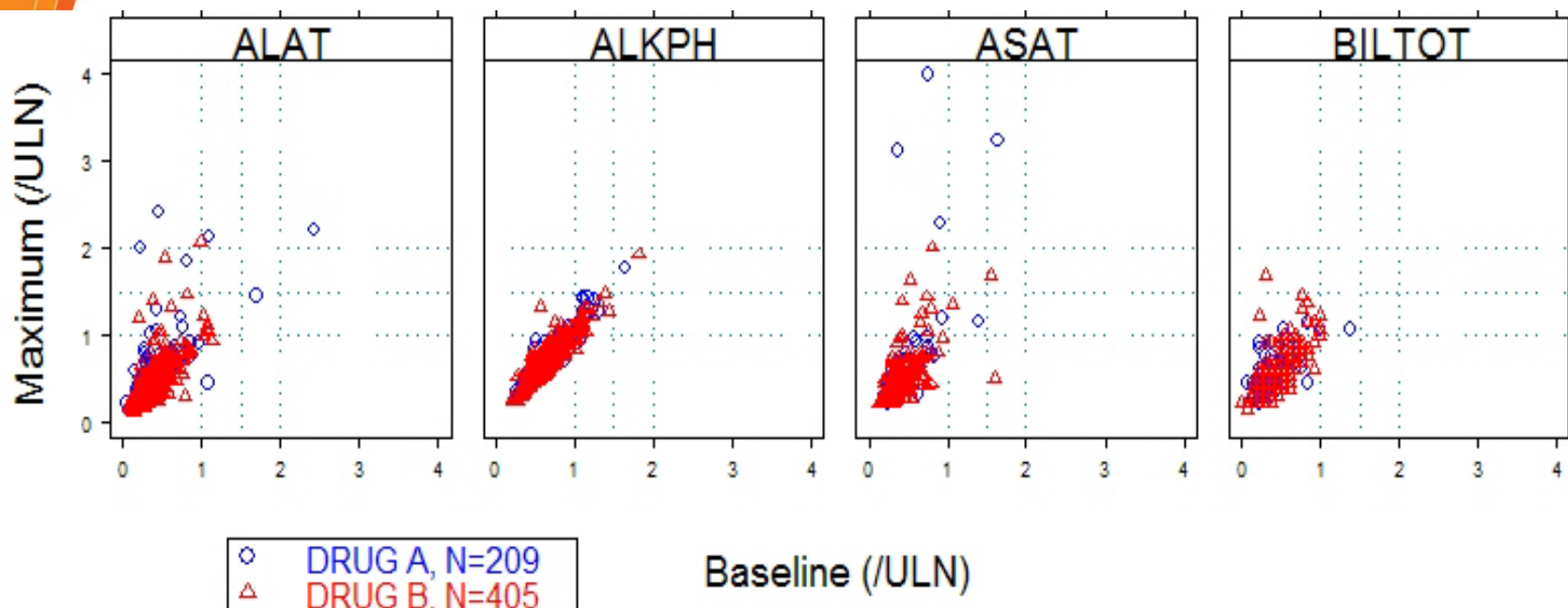
Lab Data

Routine Summary Statistics for Liver Function

| | Any Elevation | Elevations > 3XULN |
|------------------|---------------|-----------------------|
| ALT(n=200) | 40% | 15% |
| AST(n=200) | 35% | 12% |
| Bilirubin(n=200) | 25% | 2% |

This tabular summary does not tell the whole story

Consider a Simple Graph



For ASAT, ALKPH, and ALAT, the Clinical Concern Level is 2 ULN;
For BILTOT, the CCL is 1.5 ULN;
where ULN is the Upper Level of Normal Range

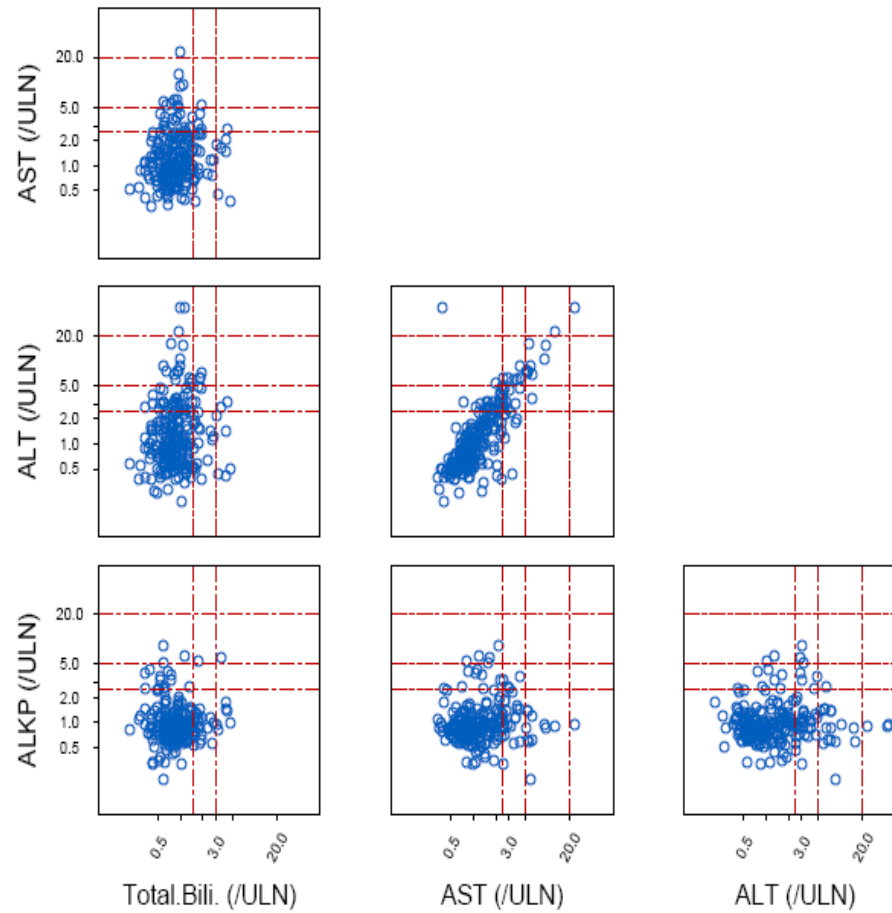
Graphical Style

- Graphical equivalent of a “shift table”
- Reference lines at clinically important levels
- Focus on upper left quadrant of each panel
- Position legend in unused part of graph with statement of numbers of patients
- May need legend for each panel to account for varying patient numbers
- Plot control group last to more readily identify Tx effect
- Consider displaying on log scale to account for skewed distribution

Some Relevant Questions

- Do ALT and AST track together?
- Are there simultaneous elevations in ALT and Bilirubin?
- ...

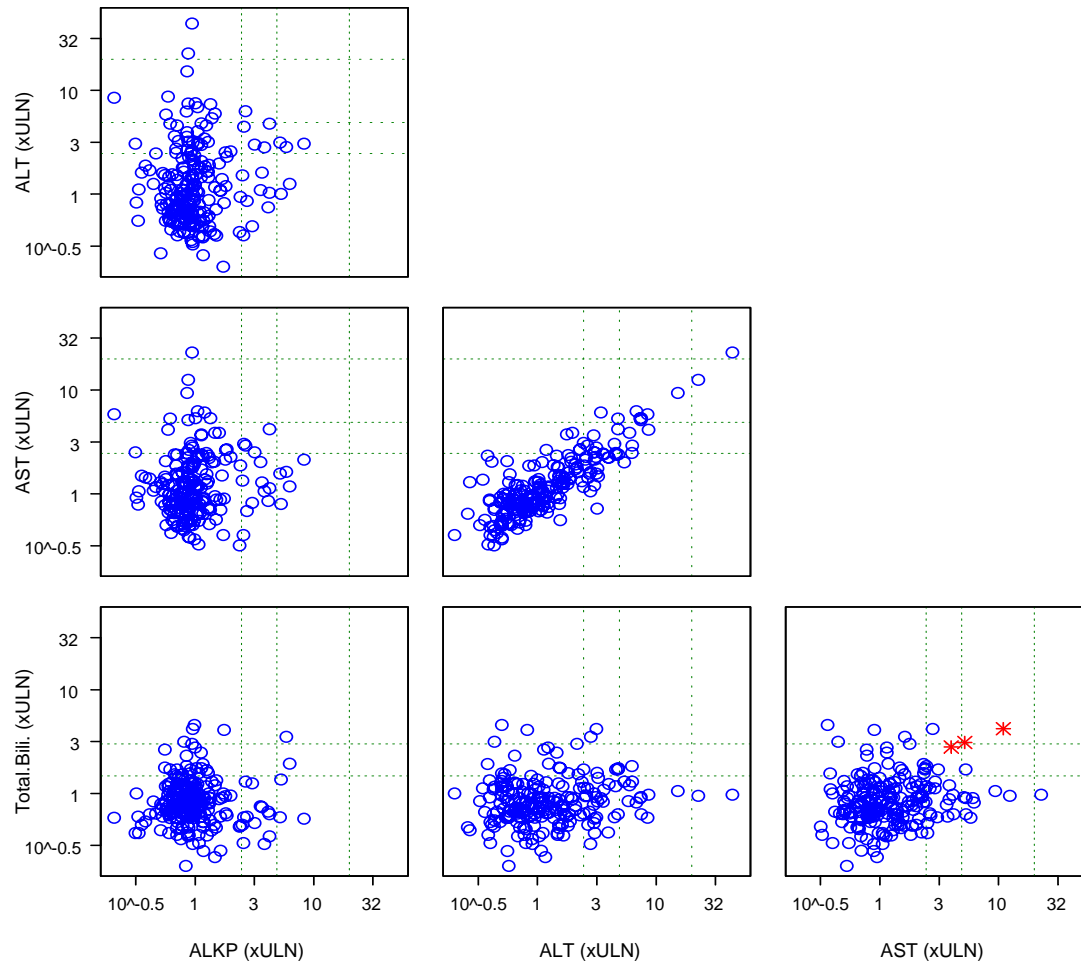
Another Simple Scatter Matrix



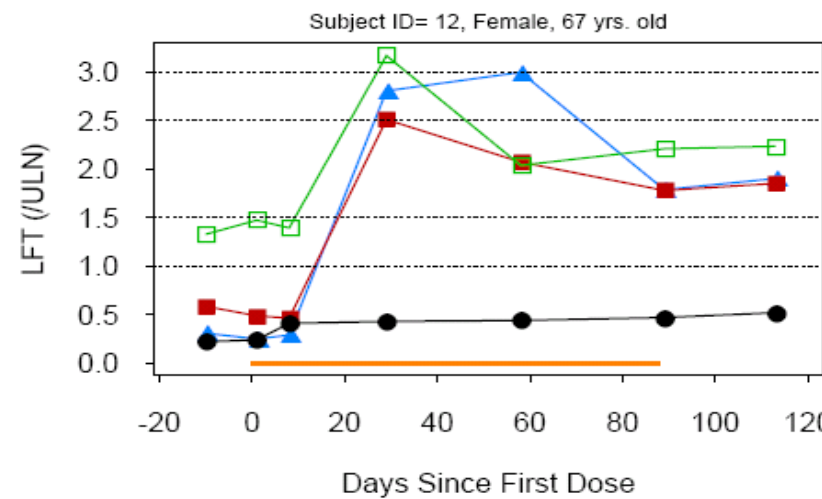
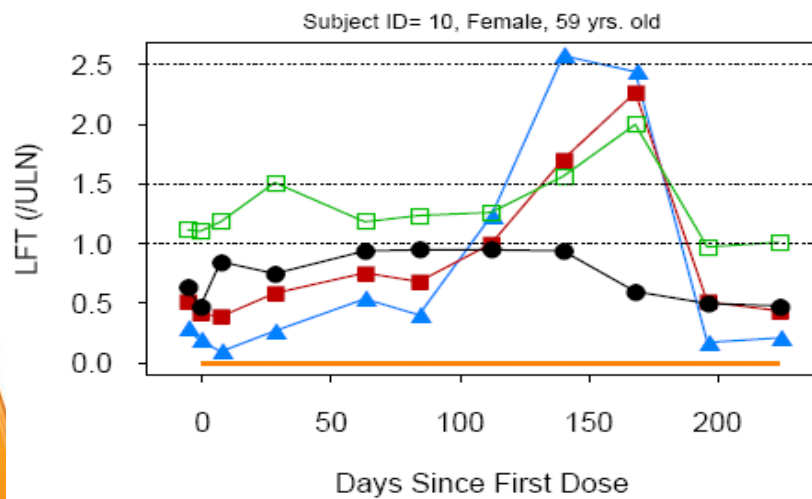
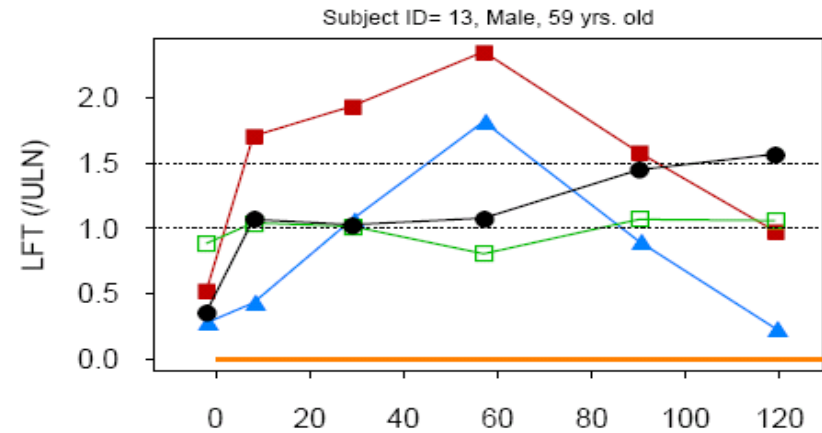
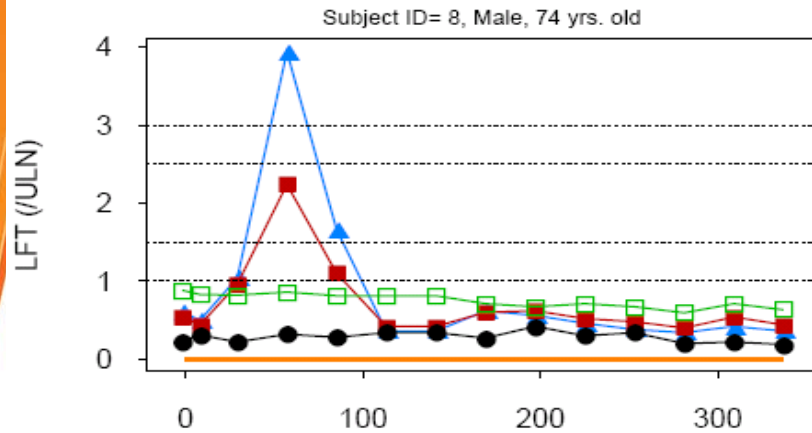
Hy's Law

- “Hy’s Law” was developed by Hyman Zimmerman as criteria for evaluating drug induced liver injury
- The signal for potential for severe drug-related hepatotoxicity has three components:
 - 1. Elevation of transaminases ≥ 3 ULN: ALT AST
 - 2. Concomitant elevation of Bilirubin
 - 3. Absence of other etiology
- “Hy’s Law” could be evaluated as part of the scatter matrix by generating different symbols for subjects who meet the criteria

Another version of the Scatter Matrix – Some Hypothetical Data



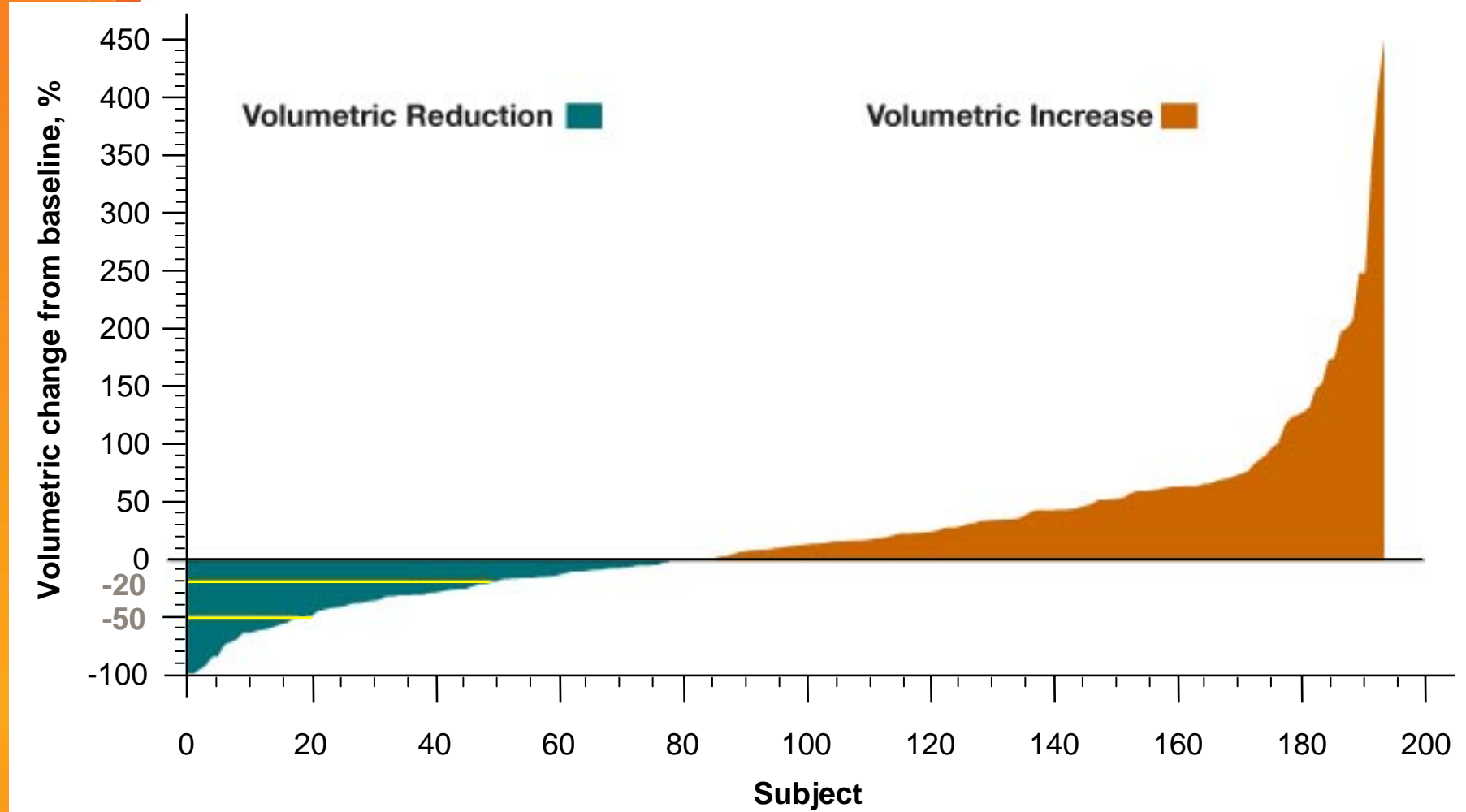
Patient Profiles



□ ALKP ■ AST
▲ ALT ● Total.Bili.

Waterfall Plot for Evaluating Changes from Baseline

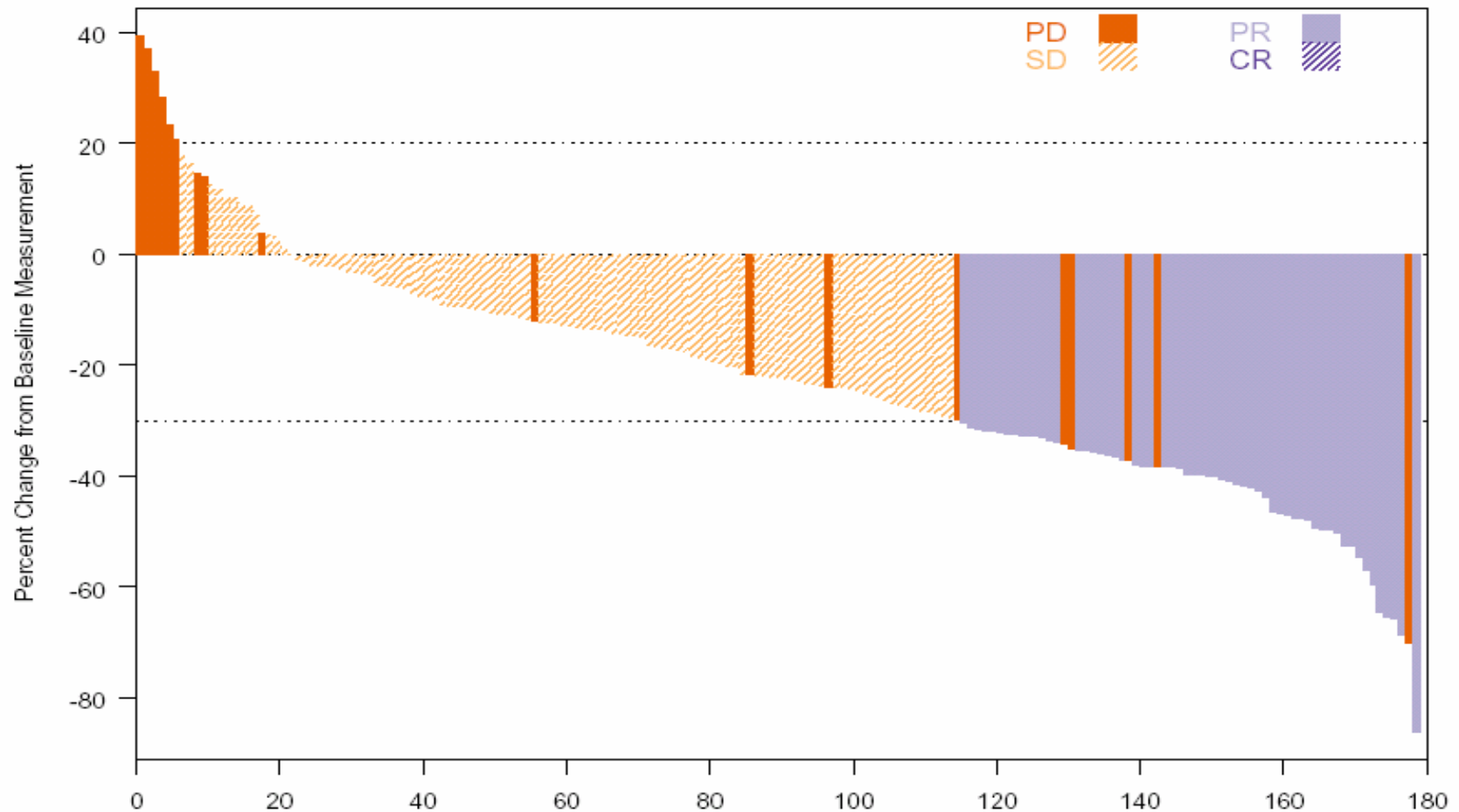
Waterfall plot showing best volumetric reduction of brain tumors



Lin et al, ASCO 2007

N=194

Independent-Reviewer Assessed Percent Reduction in Tumor Measurement at 12 Weeks From Baseline



Hutson et al, ASCO 2007

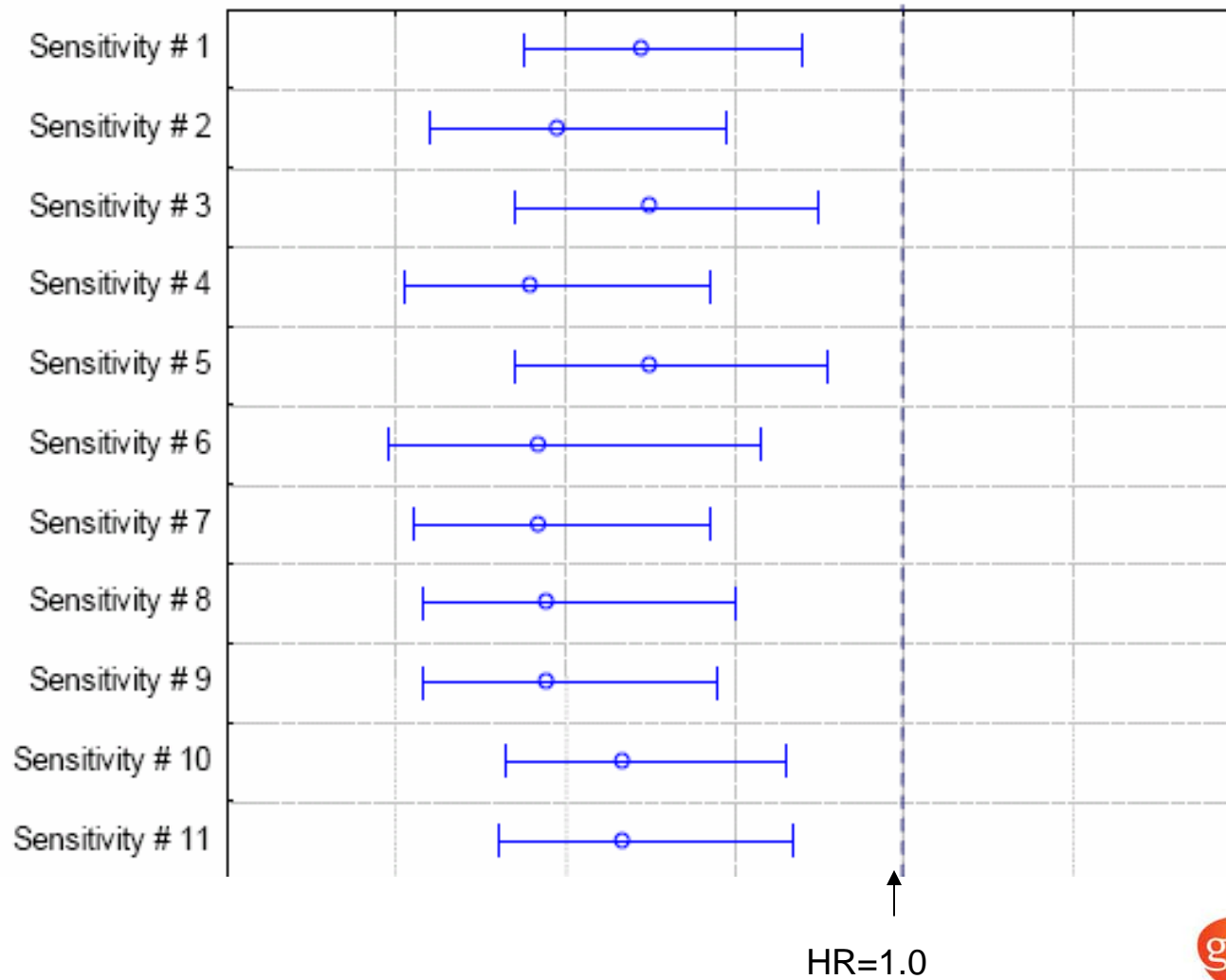
N=225

Graphical style of “waterfall” plot

- A method for looking at tumour shrinkage
- Can be adapted for other data
- Displays the distribution by looking at the order statistics
- Color and patterns to differentiate magnitude of changes
- Can display distributional location shifts in a comparative setting
 - Beware if randomization is not 1:1

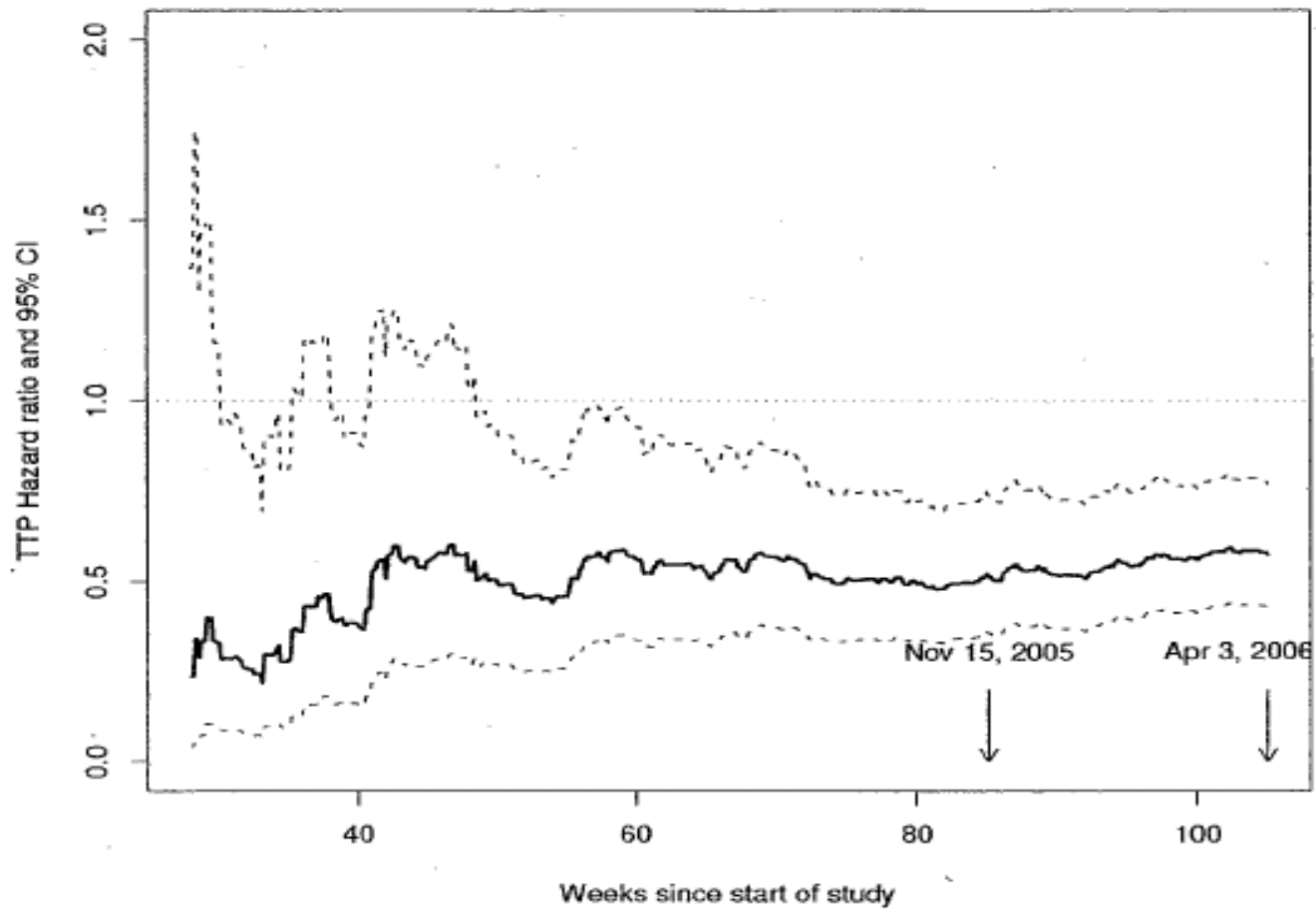
Some examples from regulatory review

A forest plot to make a point



Skyline Plot, examination of time course of hazard ratio

Figure 3 * Hazard Ratio and 95% CI for IRC Time to Progression Over Time



From FDA statistical review summary of Lapatinib

Summary and Conclusions

- Lake Blanche on Sunday
- Exposure critical first step in safety analysis
- Evaluation of patient safety from clinical trials
 - summary stats alone of limited value
 - graphics must provide identification of outliers
 - careful examination of individual patient data
- Waterfall plots valuable for change data
- Skyline plots indicate the *maturity* of an estimate

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References

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3. A. Di Leo, H. Gomez, Z. Aziz, Z. Zvirbule, M. Arbushites, M. Koehler, L. S. Williams, J. Dering, R. S. Finn. Lapatinib With Paclitaxel Versus Paclitaxel as First-Line Treatment for Patients With Metastatic Breast Cancer: A Phase III Randomized, Double-blind Study in 580 Patients, ASCO, 2007
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