A Case Study of Graphics in Clinical Trials:

The Role of Statistical Graphics in the Recent Submission/Approval of GSK's Votrient™ in the US

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Joint Statistical Meetings, Aug 3rd, 2010

Outline

- Background
- Safety Graphics
  - Patient level
  - Study Level
- Efficacy Graphics
- Conclusion
- Acknowledgements

Background

History of Votrient™, VEG105192

Background

- Votrient™ (also known as Pazopanib)
  - Oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit for the treatment of multiple cancer types.
- Phase I and Phase II data indicated promising results for the treatment of subjects with metastatic Renal Cell Carcinoma (RCC)
- Phase III study initiated to further investigate: VEG105192
  - 2:1 randomized, double-blind, placebo-controlled, multicenter
  - to evaluate efficacy and safety of Pazopanib compared to placebo in subjects with locally advanced and/or metastatic renal cell carcinoma (mRCC) (advanced RCC).
  - The primary endpoint was progression-free survival (PFS); the principal secondary endpoint was overall survival (OS).
  - 435 subjects in the final efficacy population (290 Paz, 145 Placebo)

Safety Graphics

Background: Liver Function Tests (LFTs)

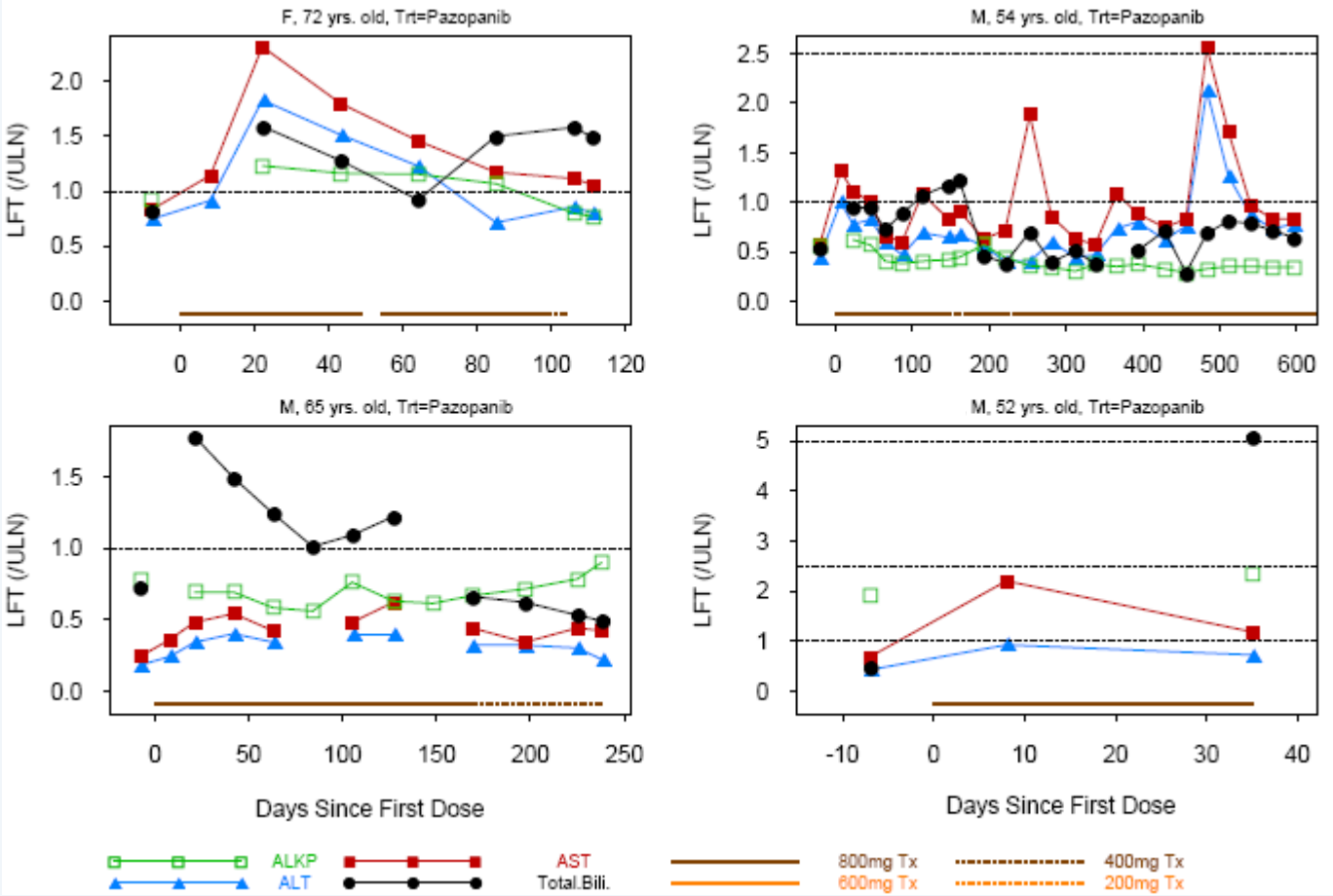
- Safety and tolerability of interest in all trials
  - Oncology
  - Emergent data
- Four main liver function tests:
  - ALT : *alanine aminotransferase*
  - AST: *aspartate aminotransferase*
  - Tot. Bili: *total bilirubin*
  - Alk. Phos: *alkaline phosphatase*
- Time to liver elevation
- Hy's Law:
  - 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

Typical Safety Plots

- 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
  - May include additional information such as adverse events or concomitant medications
  - LFTs scaled by ULN

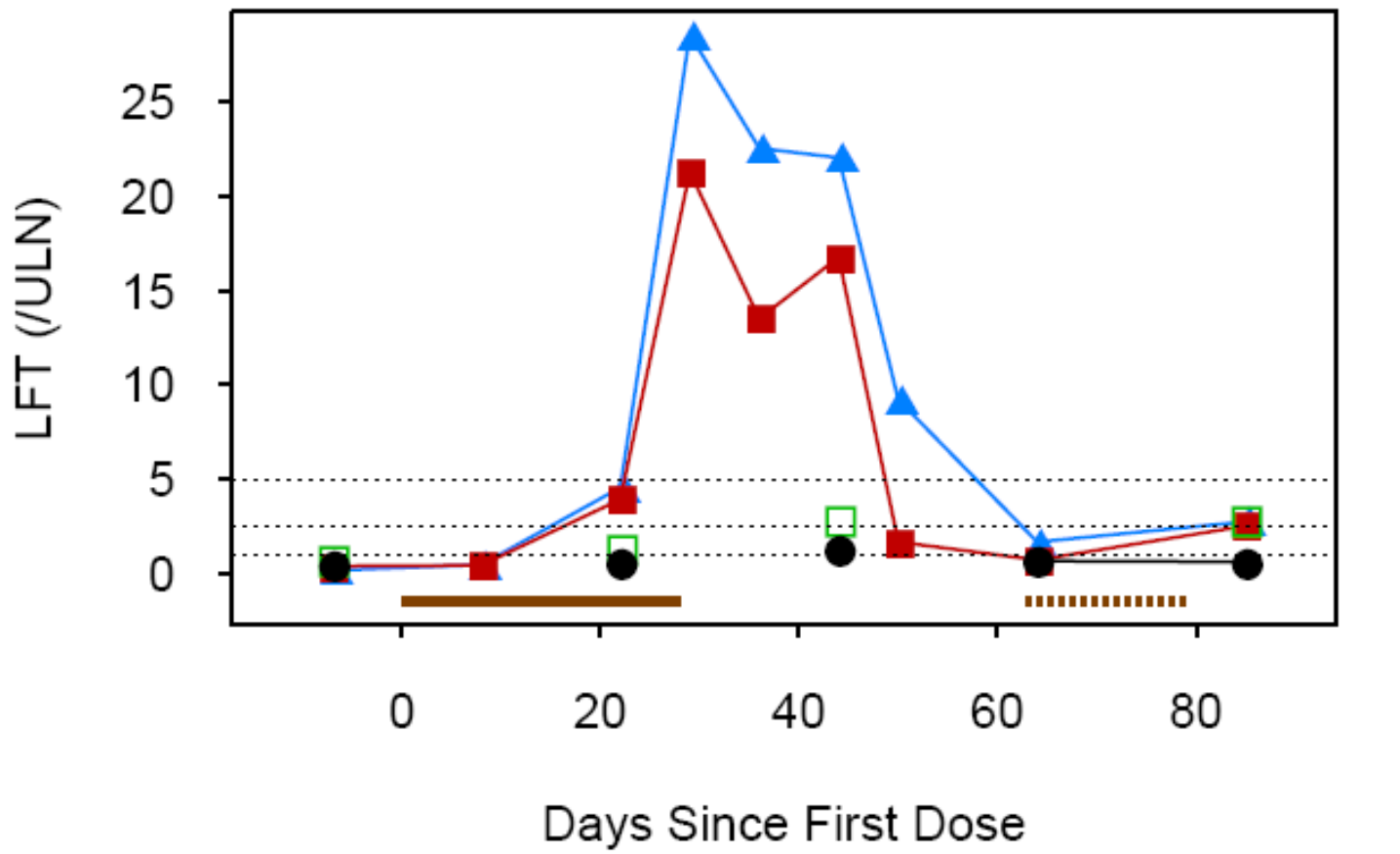
Liver Function Patient Profile plots

Safety



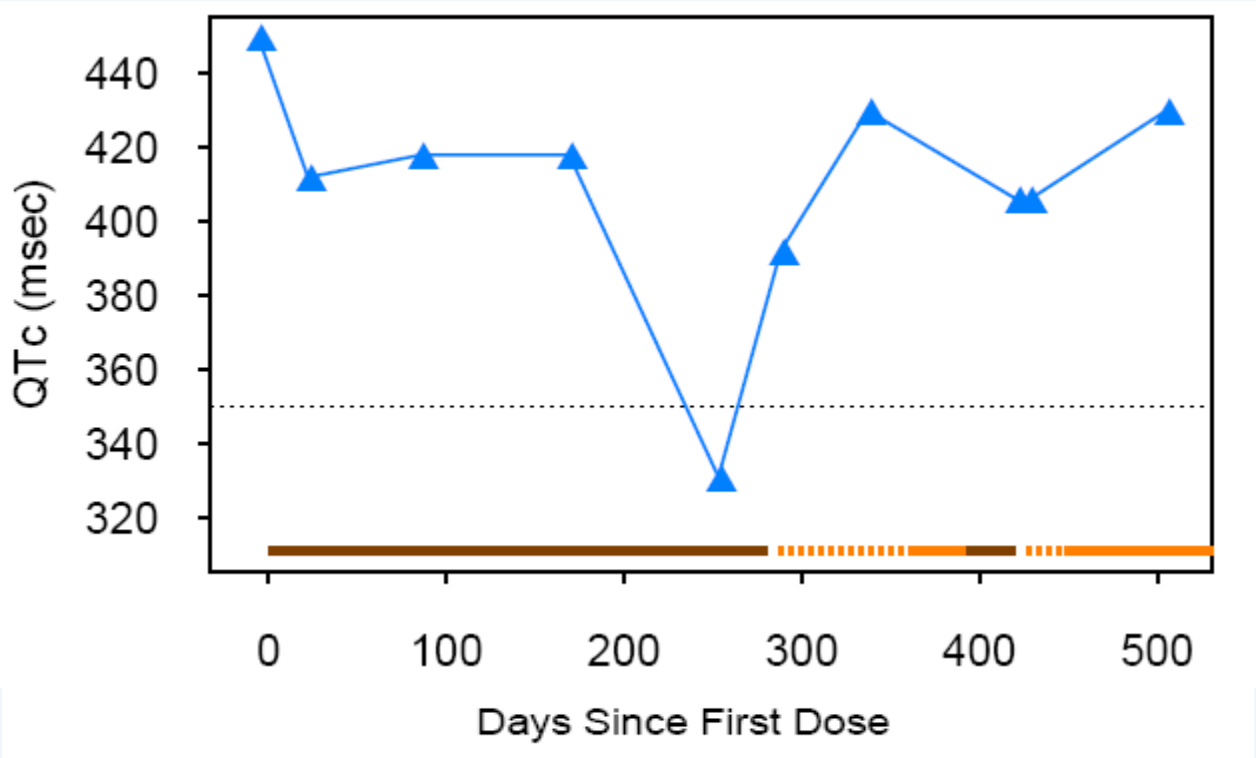
Liver Function Patient Profile plots

Safety



QTc Patient Profile plots

Safety



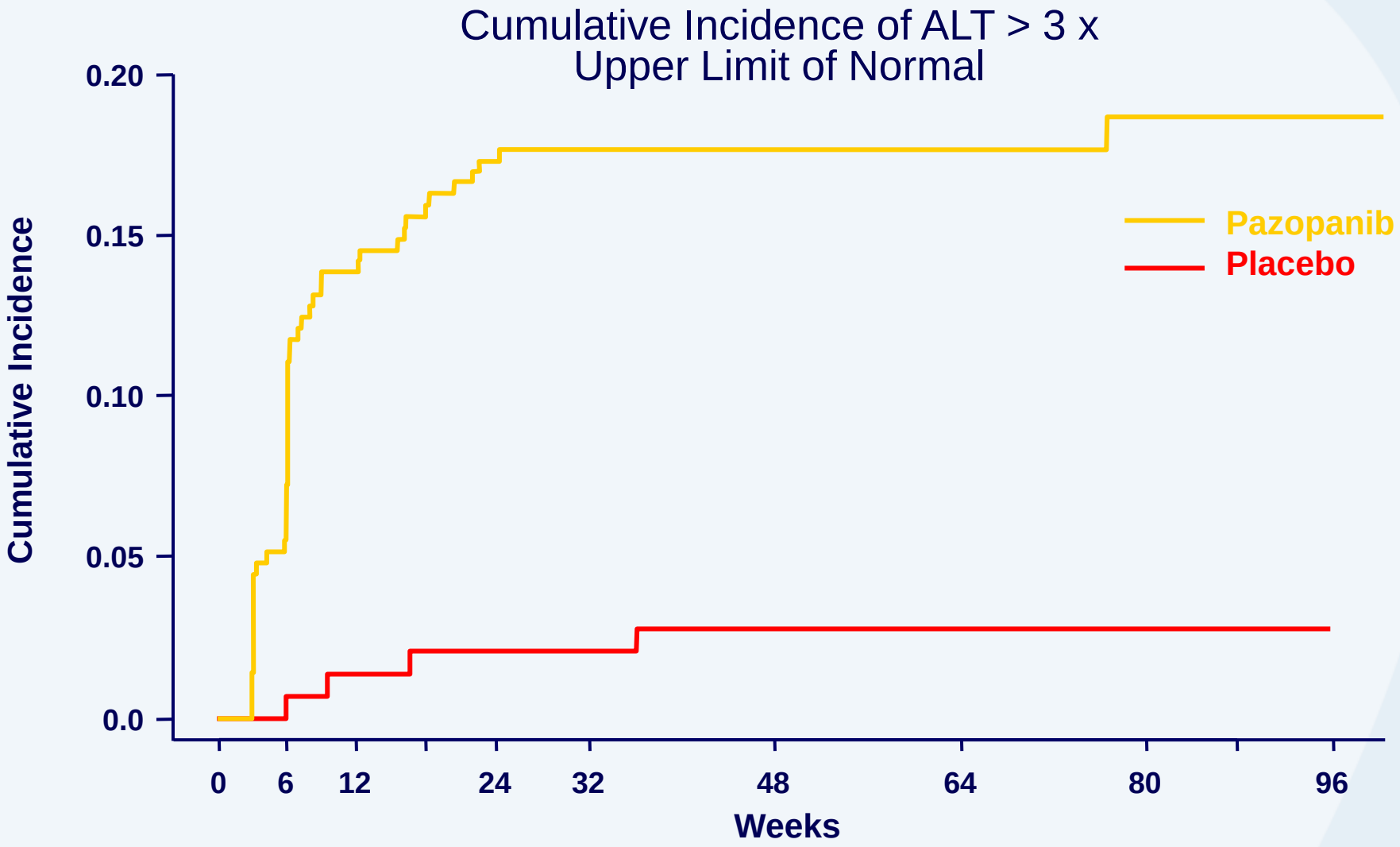
800mg Tx 600mg Tx 400mg Tx 200mg Tx

Typical 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, etc.

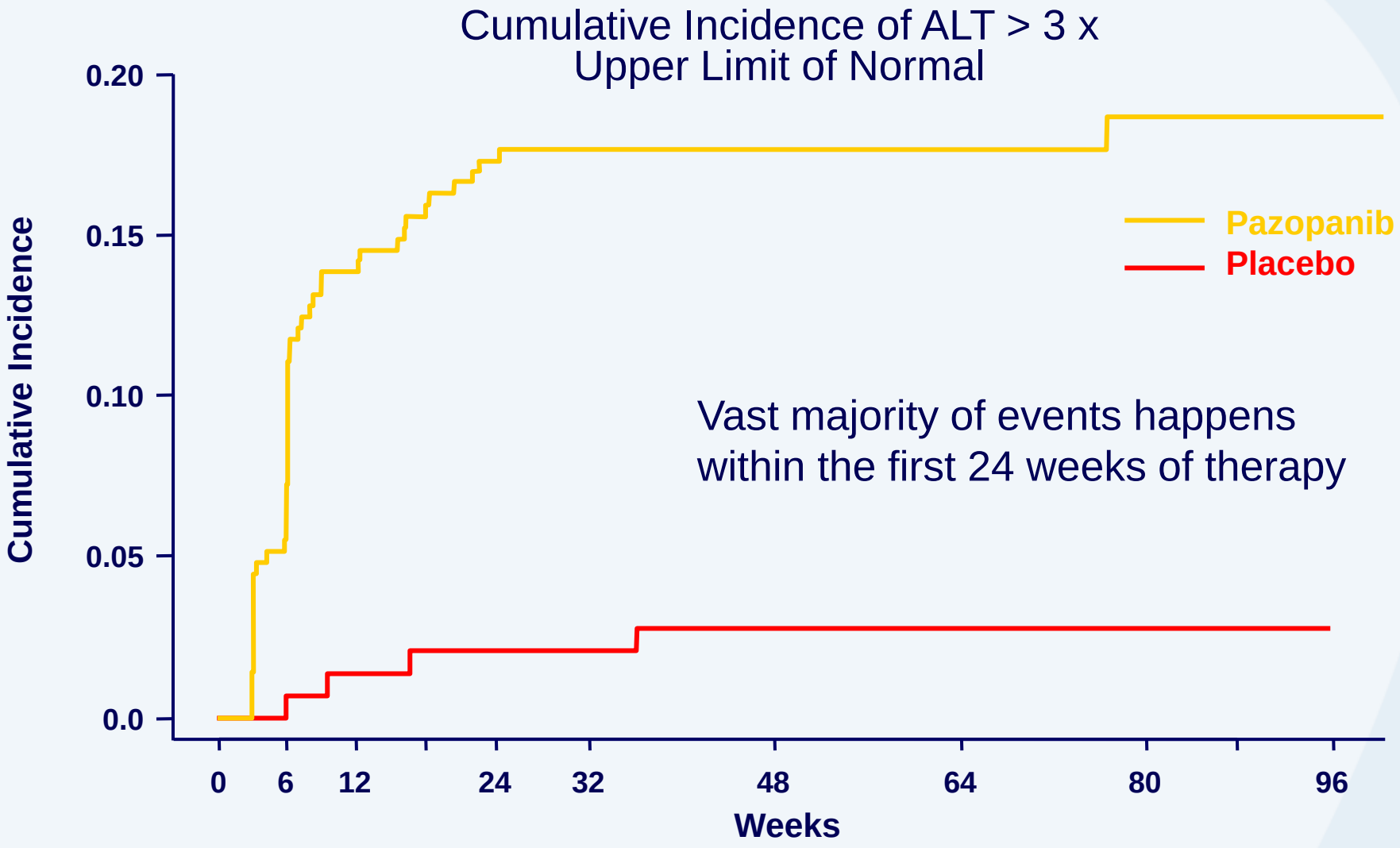
Cumulative Incidence for LFT Elevations

Safety



Cumulative Incidence for LFT Elevations

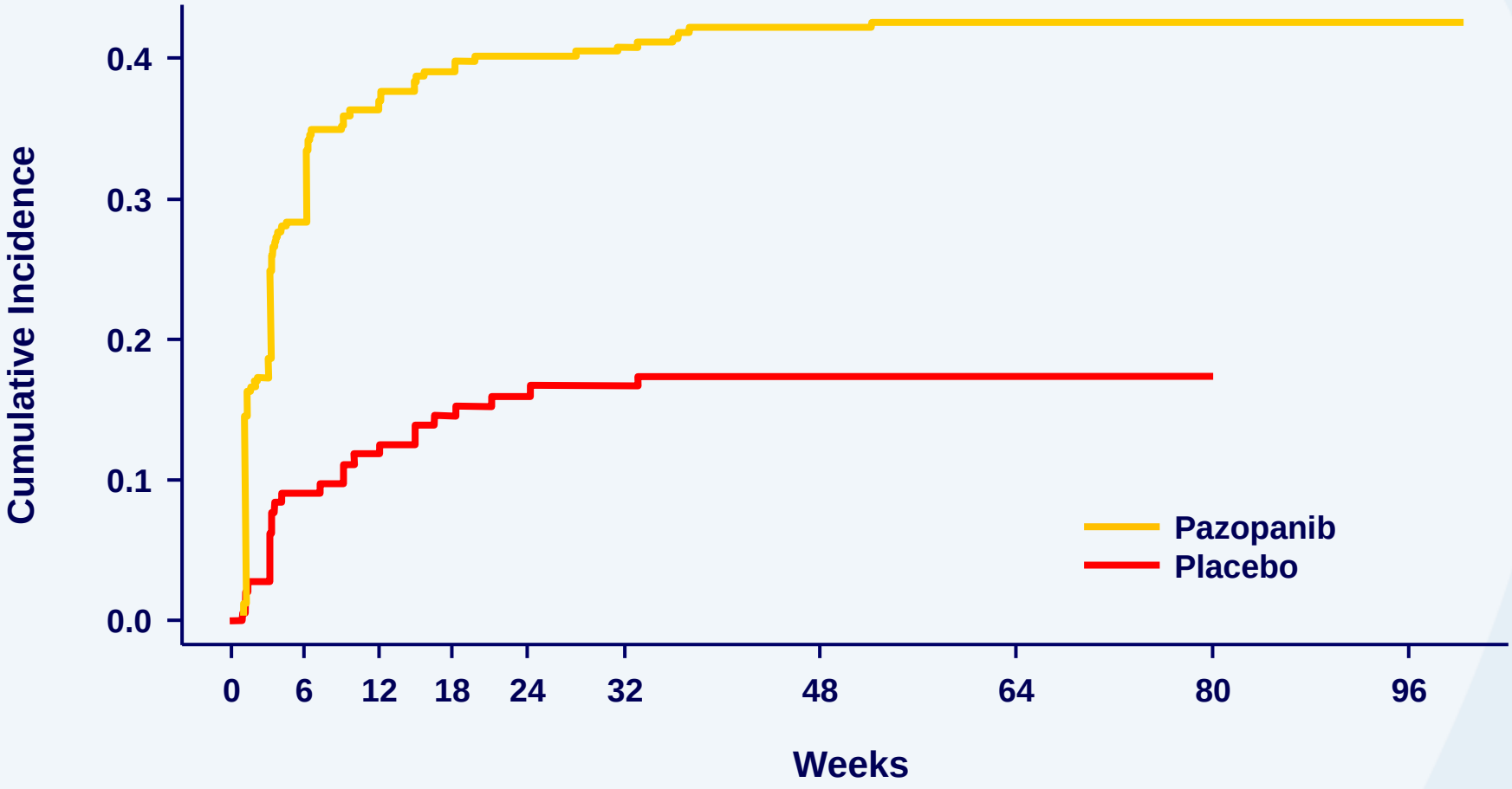
Safety



Cumulative Incidence for AEs of interest

Safety

Cumulative Incidence of Hypertension in Study VEG105192

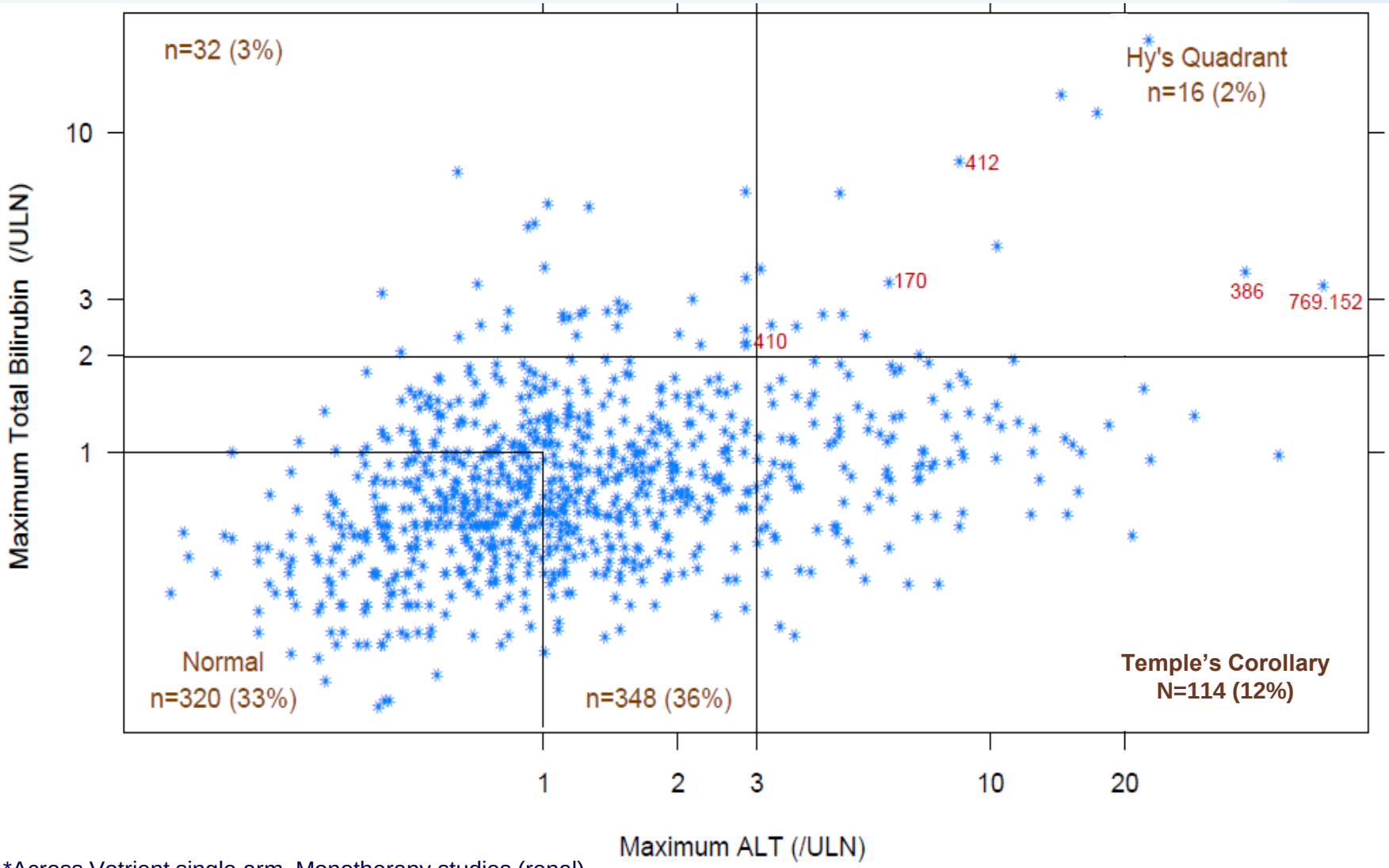


Typical Safety Plots

- Drug Induced Liver Injury Plots (‘DILI’)
  - Variation of scatter plot
  - Allows observer to easily identify the set of patients who demonstrate a clinically meaningful outcome
  - Hy’s Quadrant

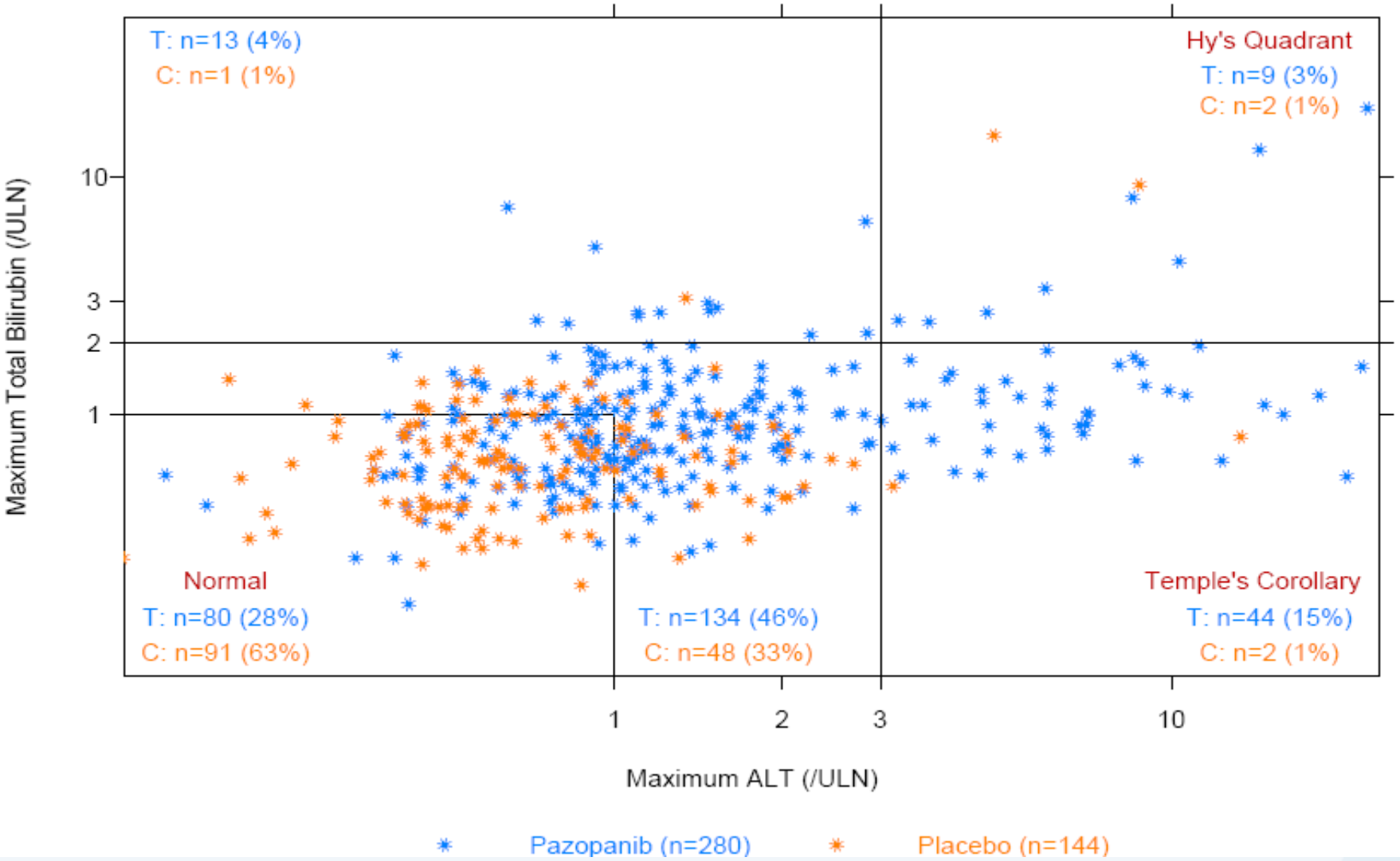
DILI Plots for Votrient Single Arm Studies (Renal)

Safety



*Across Votrient single arm, Monotherapy studies (renal)

DILI Plots for VEG105192



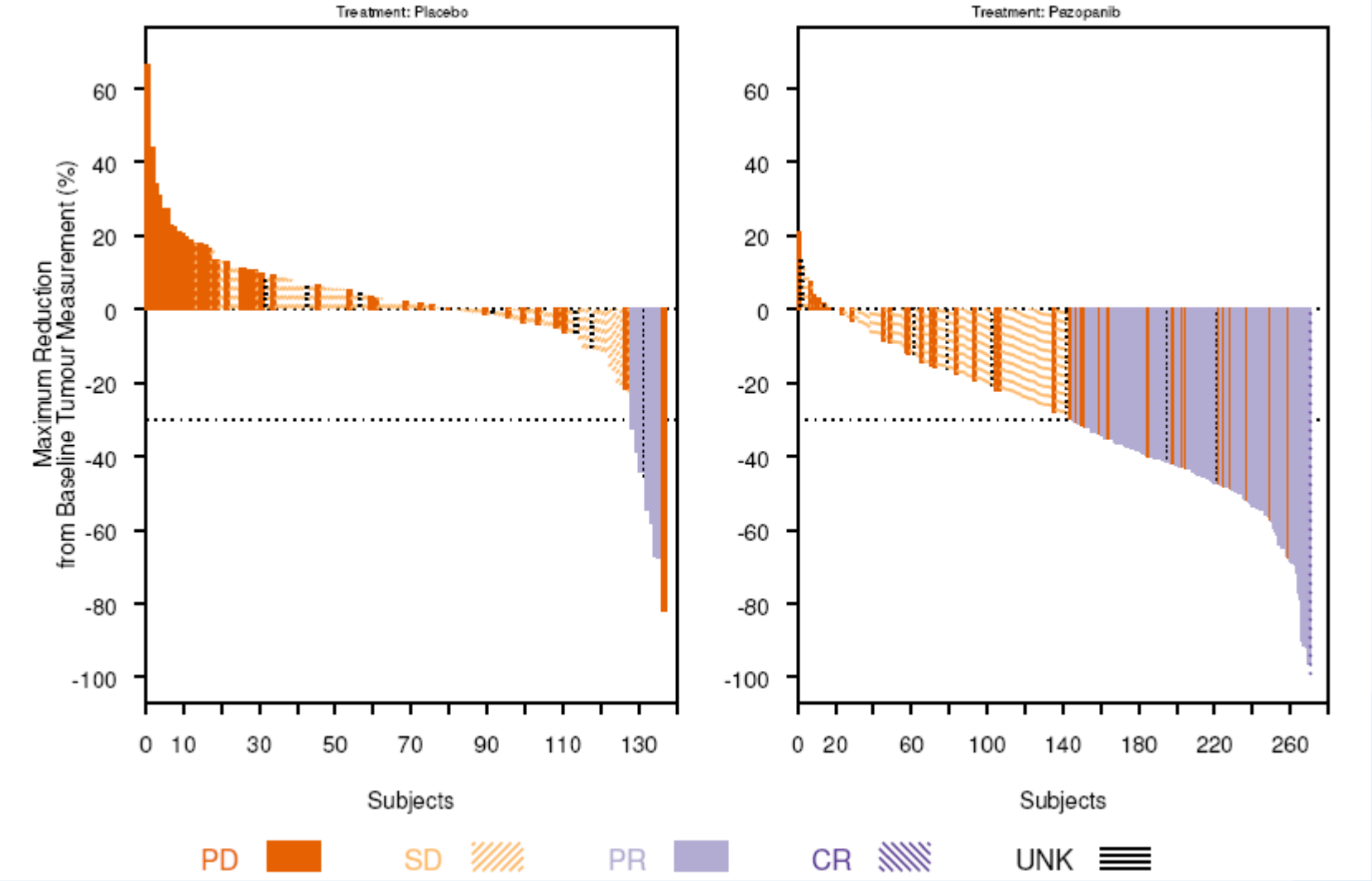
Efficacy Graphics

Typical Efficacy Plots

- ‘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

Waterfall Plot

Efficacy

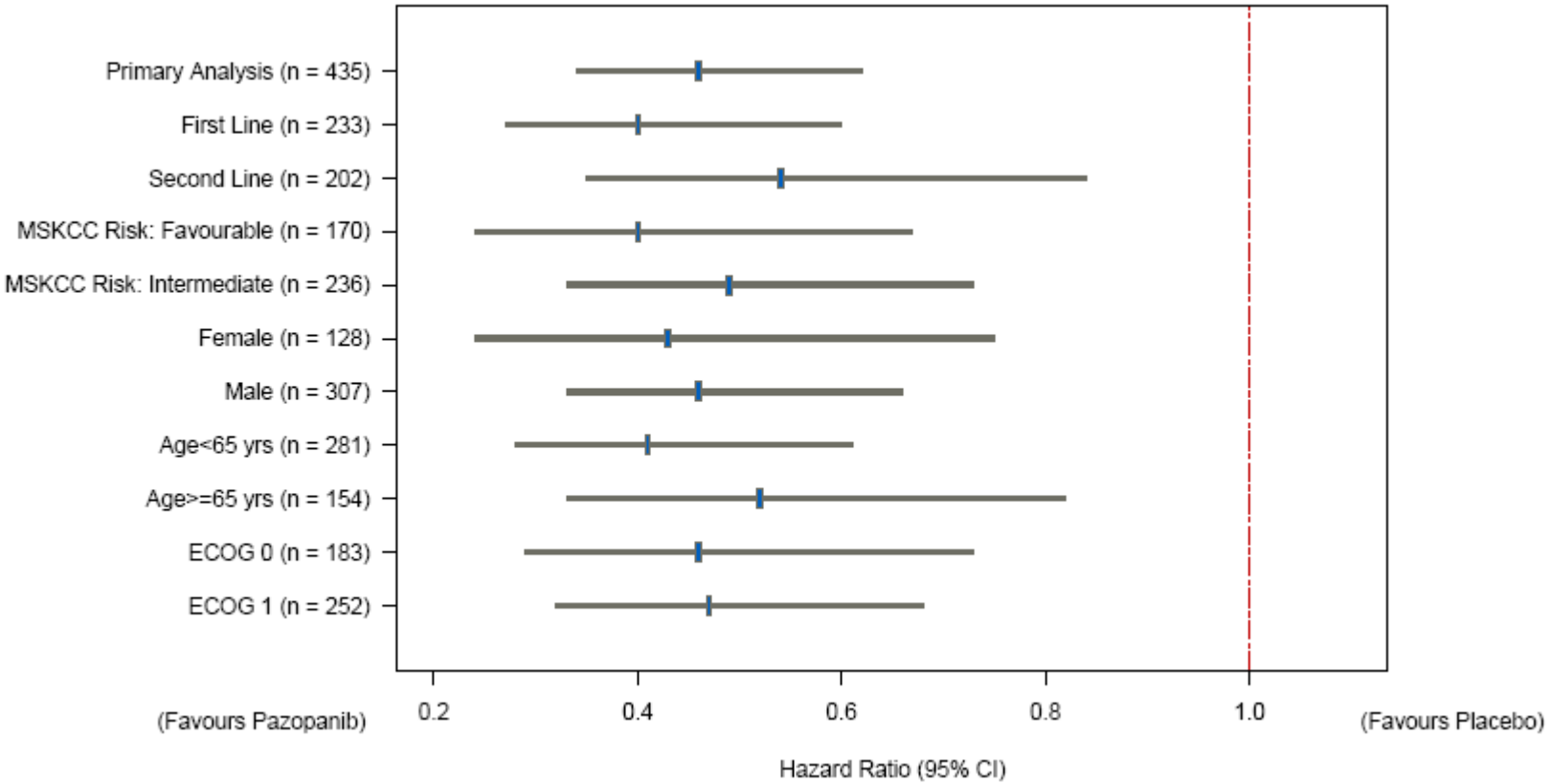


Typical Efficacy Plots

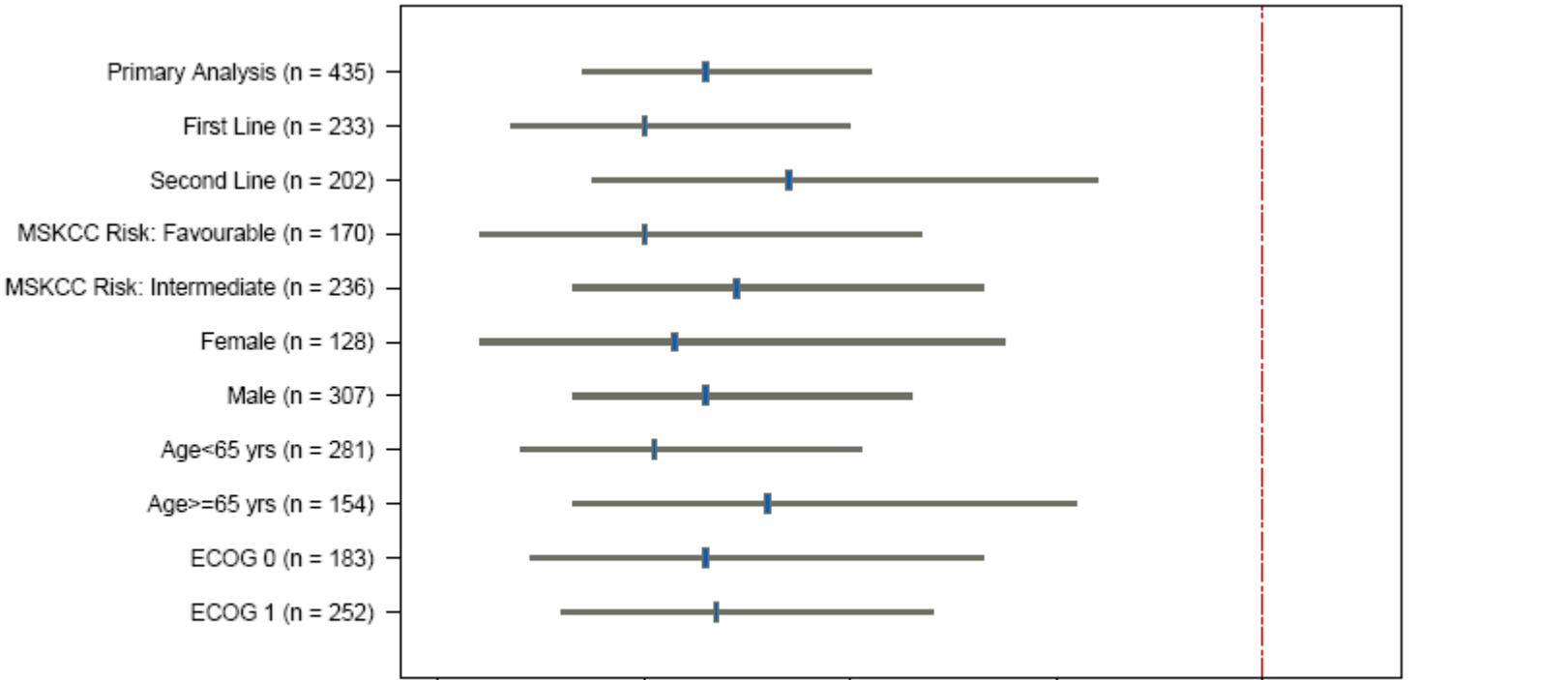
- Forest Plots
  - Simply summarizes the relative treatment effects of many separate analysis in one display
  - Allows for key indirect comparisons to be made
  - Subgroup analyses

Forest Plot of Hazard Ratios (PFS)

Efficacy

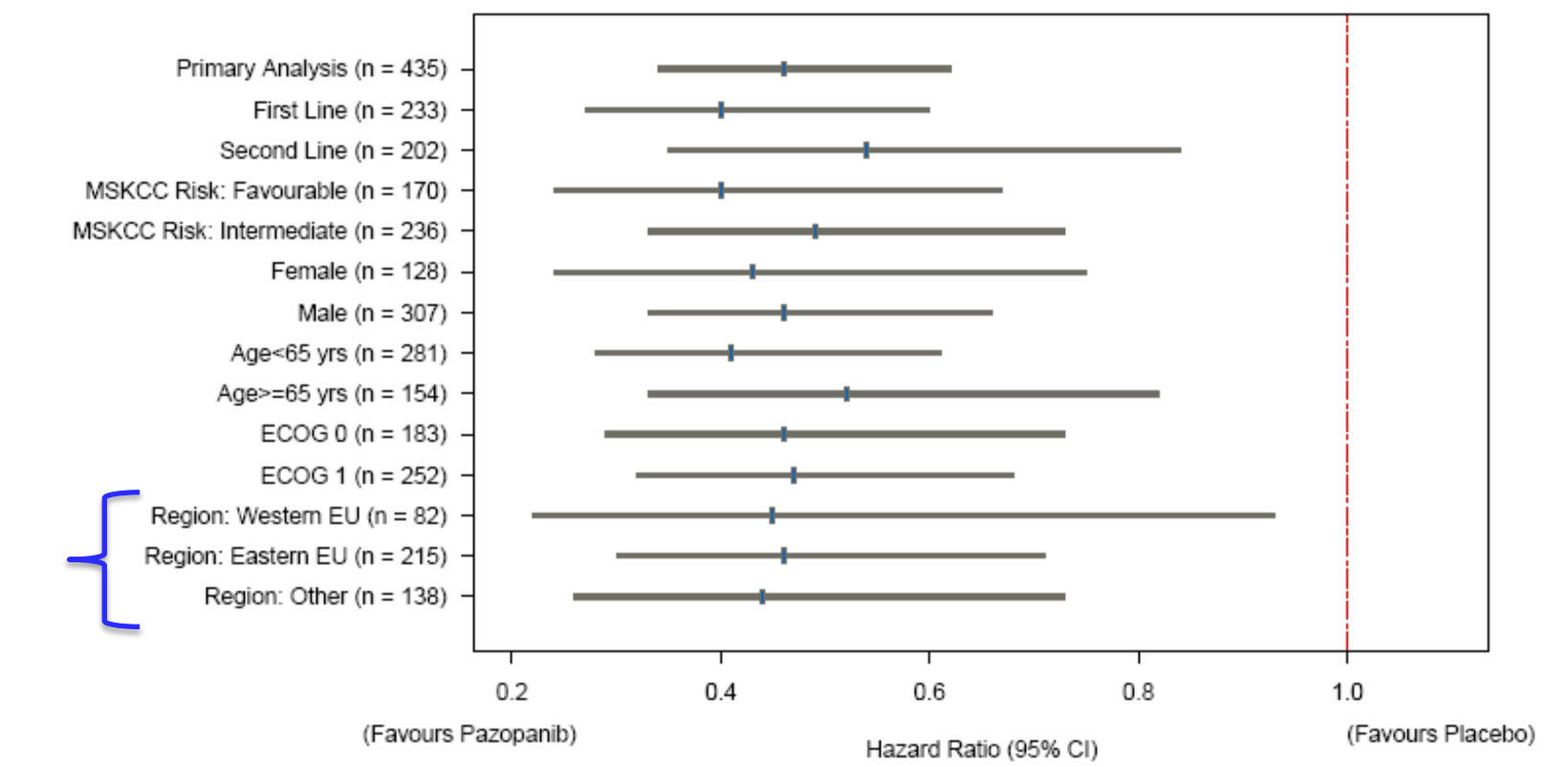


Forest Plot of Hazard Ratios (PFS)



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

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.

Conclusion

Graphics were…

- Integral in defining the risk-benefit
- Useful in generating the Risk Management Profile
- Helpful in providing clear answers to regulatory inquiries
- Part of a successful approval

Acknowledgements

- Thanks to the GSK Votrient Clinical team for all of their efforts and guidance:
  - Lini Pandite
  - Vicki Goodman
  - Mei Chen
- Special thanks to Ohad Amit, Karrie Wang, and Lauren McCann for their contributions to this presentation

Questions?

Thank You!