

Adverse Event Data over Time

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Whilst at GSK he developed an increasing passion for teaching and taught SAS Graphics to SAS Programmers, Statisticians and Scientists. Since then Kriss has moved on to become an independent Statistical Programmer and is now consulting at Eli Lilly supporting early phase Oncology. He has used SAS® for more than 10 years.

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Paper #AS02

Agenda

- ▶ Show an alternative way to visualise Adverse Events over Time
- ▶ Probability of Being in Response Function (Nancy Temkin)

Convention

- ▶ Adverse Events (AE's) are usually summarized like this:

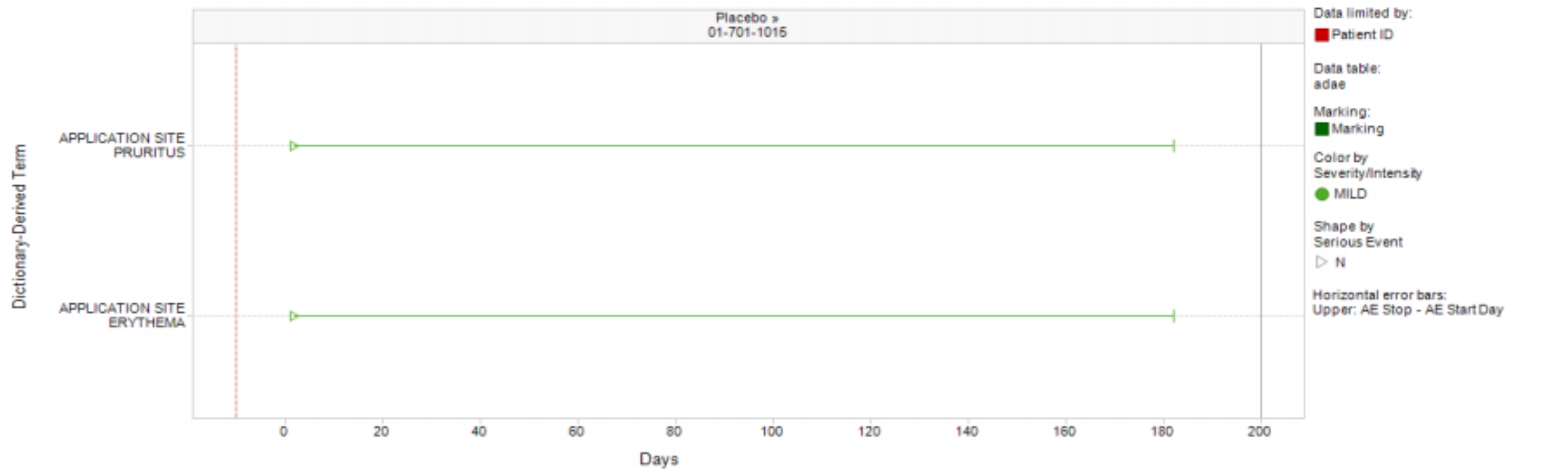
Table 14.3.2.2
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

1

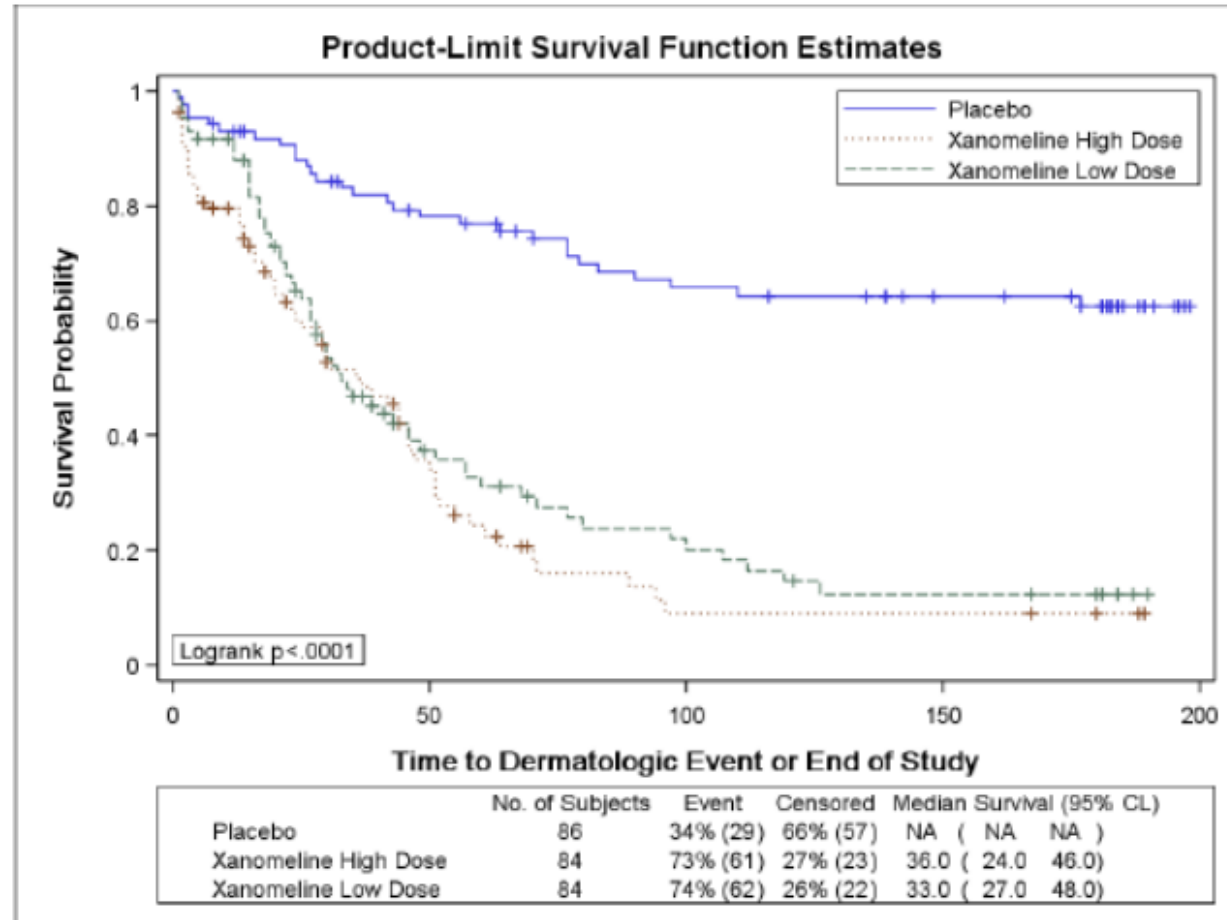
Category	Placebo (N=86) n (%)	Xanomeline Low (N=84) n (%)	Xanomeline High (N=84) n (%)
Subjects with any TEAE	34 (39.5)	65 (77.4)	68 (81.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
APPLICATION SITE PRURITUS	6 (7.0)	22 (26.2)	22 (26.2)
APPLICATION SITE ERYTHEMA	3 (3.5)	12 (14.3)	15 (17.9)
APPLICATION SITE DERMATITIS	5 (5.8)	9 (10.7)	7 (8.3)
APPLICATION SITE IRRITATION	3 (3.5)	9 (10.7)	9 (10.7)
APPLICATION SITE VESICLES	1 (1.2)	4 (4.8)	6 (7.1)
FATIGUE	1 (1.2)	5 (6.0)	5 (6.0)
OEDEMA PERIPHERAL	2 (2.3)	1 (1.2)	2 (2.4)
APPLICATION SITE SWELLING	0	1 (1.2)	2 (2.4)
APPLICATION SITE URTICARIA	0	2 (2.4)	1 (1.2)
CHILLS	1 (1.2)	1 (1.2)	1 (1.2)

Profile Plot

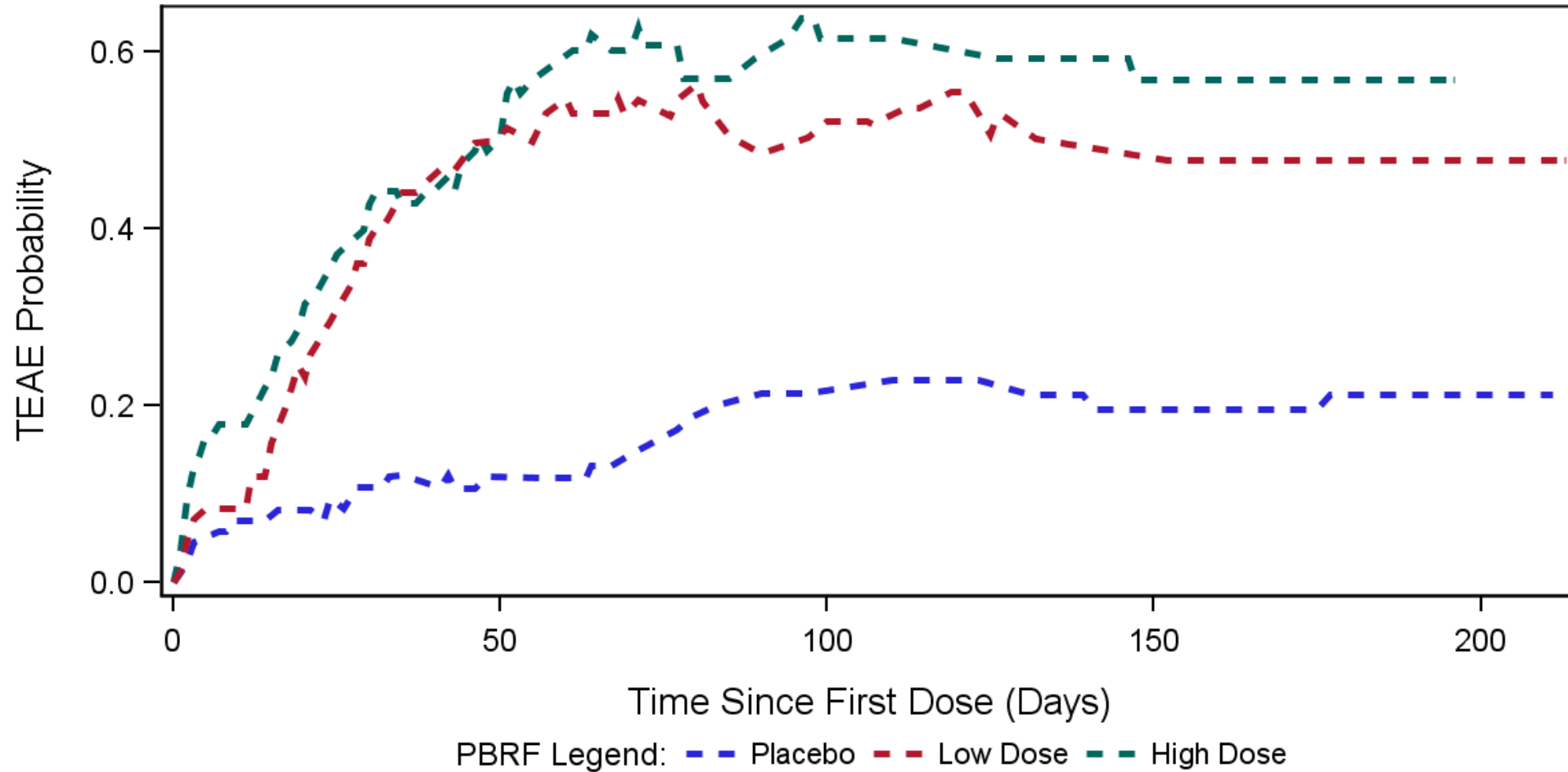
Figure 2: Treatment Emergent Adverse Event timeline for subject 1015



Occasionally a KM plot is used



Alternative Way PBRF Figure



Differences between PBRF and Kaplan-Meier

- ▶ Kaplan Meier The Kaplan-Meier estimator of the survivorship function (or survival probability) $S(t) = P(T > t)$ is:

$$\begin{aligned}\hat{S}(t) &= \prod_{j:\tau_j \leq t} \frac{r_j - d_j}{r_j} \\ &= \prod_{j:\tau_j \leq t} \left(1 - \frac{d_j}{r_j}\right)\end{aligned}$$

- ▶ PBRF $\hat{P}(x) = \hat{P}(x_{i-1})f(x_i) + \hat{G}(x_i;2)[G(x_{i-1};1) - \hat{G}(x_i;1)]$

Differences between PBRF and Kaplan–Meier in layman terms

- ▶ The PBRF takes into account more when a subject finishes a trial without an AE – censoring.
- ▶ The PBRF also takes into account when an AE is resolved.

PBRF Method

Input Data

Subject Identifier	Actual Treatment	Duration of treatment (days)	TEAE Relative End Day	Stop day	TEAE present	Is TEAE Date Censored?	TEAE Relative Start Day	TEAE Relative End Day /Subject Relative End Day
1015	Placebo	182		182	1	1	2	182
1023	Placebo	28	26	29	1	0	3	26
1047	Placebo	26		46	0	0		46

Input Data

ADSL

Subject Identifier	Actual Treatment	Duration of treatment (days)	TEAE Relative End Day	Stop day	TEAE present	Is TEAE Date Censored?	TEAE Relative Start Day	TEAE Relative End Day /Subject Relative End Day
1015	Placebo	182		182	1	1	2	182
1023	Placebo	28	26	29	1	0	3	26
1047	Placebo	26		46	0	0		46

Stop day is the relative day that the subject discontinued study =
Date subject discontinued the study – Date of First Treatment =
DM.RFENDT – ADSL.TRTSDT + 1

Input Data

ADAE

Subject Identifier	Actual Treatment	Duration of treatment (days)	TEAE Relative End Day	Stop day	TEAE present	Is TEAE Date Censored?	TEAE Relative Start Day	TEAE Relative End Day /Subject Relative End Day
1015	Placebo	182		182	1	1	2	182
1023	Placebo	28	26	29	1	0	3	26
1047	Placebo	26		46	0	0		46

Input Data

ADTTE

Subject Identifier	Actual Treatment	Duration of treatment (days)	TEAE Relative End Day	Stop day	TEAE present	Is TEAE Date Censored?	TEAE Relative Start Day	TEAE Relative End Day /Subject Relative End Day
1015	Placebo	182		182	1	1	2	182
1023	Placebo	28	26	29	1	0	3	26
1047	Placebo	26		46	0	0		46

Is TEAE Date Censored?:

If TEAE present = 0 (ADTTE.CNSR = 1) then 0

If TEAE present = 1 and TEAE Relative End Day (AE.AENDY) is missing then 1
Else 0.

Input Data

Subject Identifier	Actual Treatment	Duration of treatment (days)	TEAE Relative End Day	Stop day	TEAE present	Is TEAE Date Censored?	TEAE Relative Start Day	TEAE Relative End Day /Subject Relative End Day
1015	Placebo	182		182	1	1	2	182
1023	Placebo	28	26	29	1	0	3	26
1047	Placebo	26		46	0	0		46

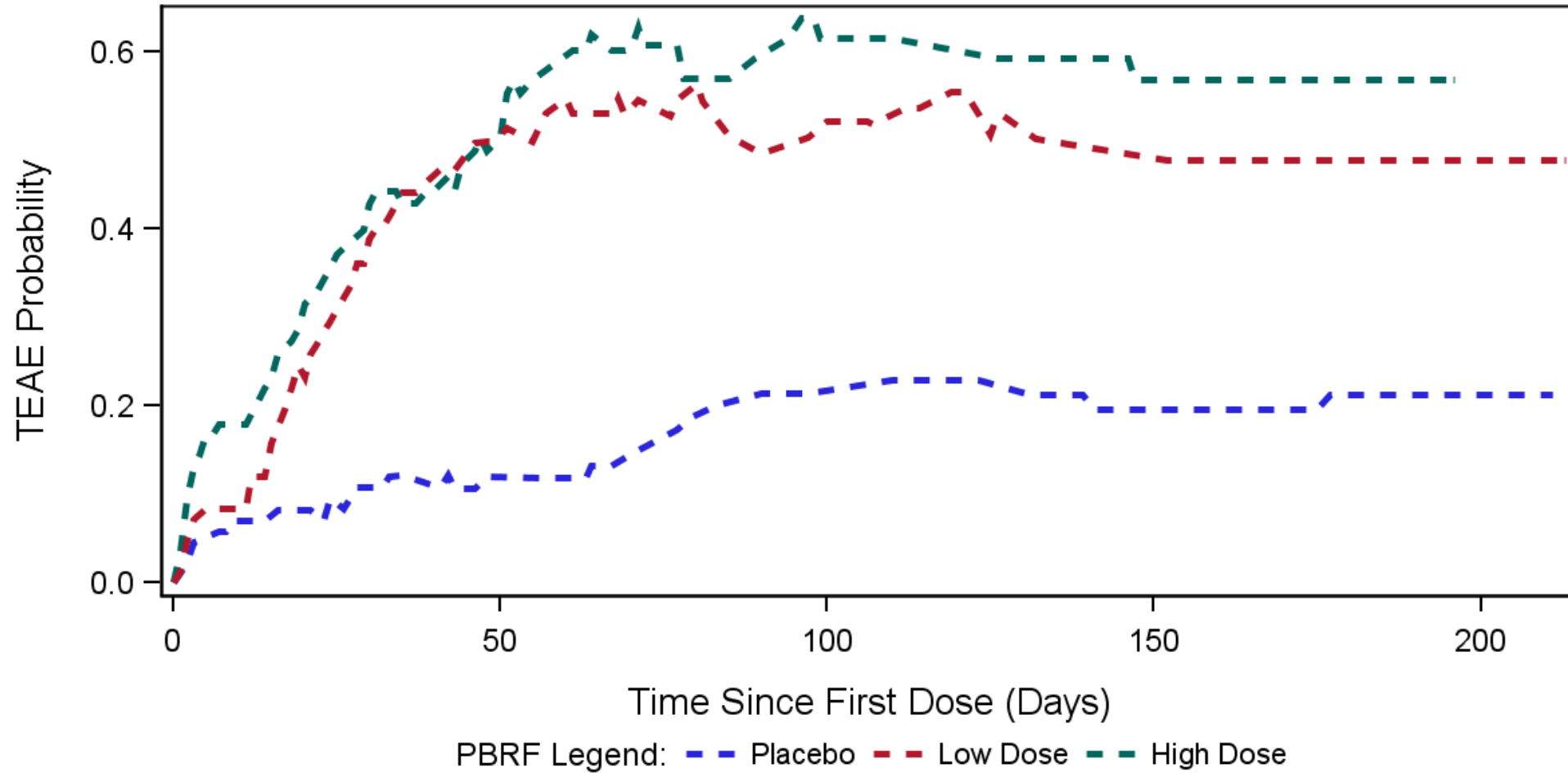
If TEAE present = 0 then ADTTE.AVAL

If TEAE present = 1 and TEAE Relative End Day is missing then Stop Day
Else TEAE Relative End Day.

Subset of PBRF Calculations

Actual Treatment	T_i (1)	P_i (2)	R_i (3)	L_i (4)	S_i (5)	W_i (6)	Number of subjects in Treatment Group	M_i (7)	N_i (8)	LG_{2i}	BG_{2i}	LG_{1i}	BG_{1i}	F_i	$P(T_i)$
Placebo	0	0	0	0	0	0	86	86	0	1		1	1	1	0
Placebo	1	0	1	0	0	0	86	86	0	1	1	0.9884	0.9884	1	0.0116
Placebo	2	0	1	0	0	0	86	85	1	1	1	0.9882	0.9767	1	0.0233
Placebo	3	0	2	0	0	0	86	84	2	1	1	0.9762	0.9535	1	0.0465
Placebo	7	0	1	0	0	0	86	82	4	1	1	0.9878	0.9419	1	0.0581
Placebo	8	1	0	0	0	0	86	81	5	0.9877	0.9877	1	0.9419	1	0.0581
Placebo	9	0	1	0	0	0	86	80	5	1	0.9877	0.9875	0.9301	1	0.0698
Placebo	12	1	0	0	0	0	86	79	6	0.9873	0.9873	1	0.9301	1	0.0698
Placebo	13	1	0	0	0	0	86	78	6	0.9872	0.9747	1	0.9301	1	0.0698
Placebo	14	1	0	0	0	0	86	77	6	0.9870	0.9744	1	0.9301	1	0.0698
Placebo	16	0	1	0	0	0	86	76	6	1	0.9870	0.9868	0.9178	1	0.0818
Placebo	21	0	1	0	1	0	86	75	7	1	1	0.9867	0.9056	0.8571	0.0824

PBRF Figure



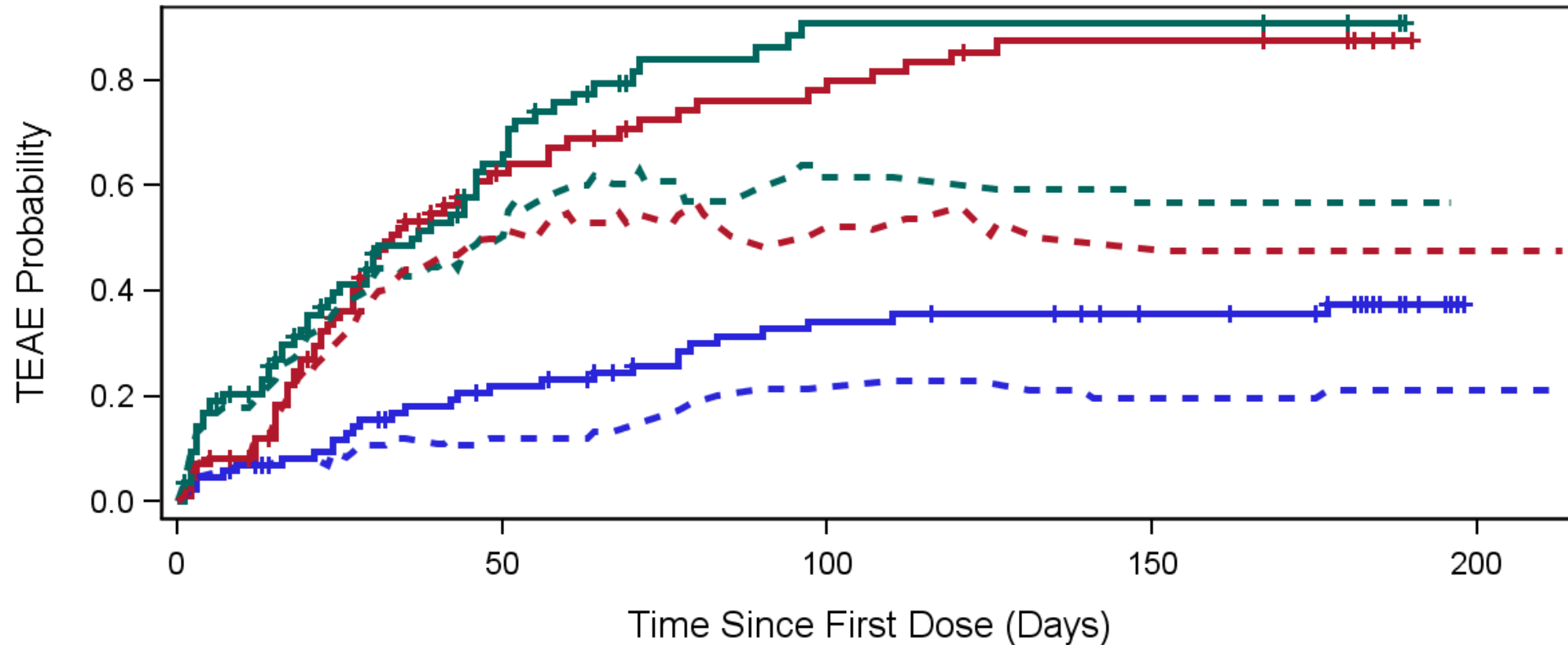
Snippet of the GTL code

```
layout overlay / xaxisopts = (label = "Time Since First Dose (Days)")
                    yaxisopts = (label = "TEAE Probability") walldisplay = all;

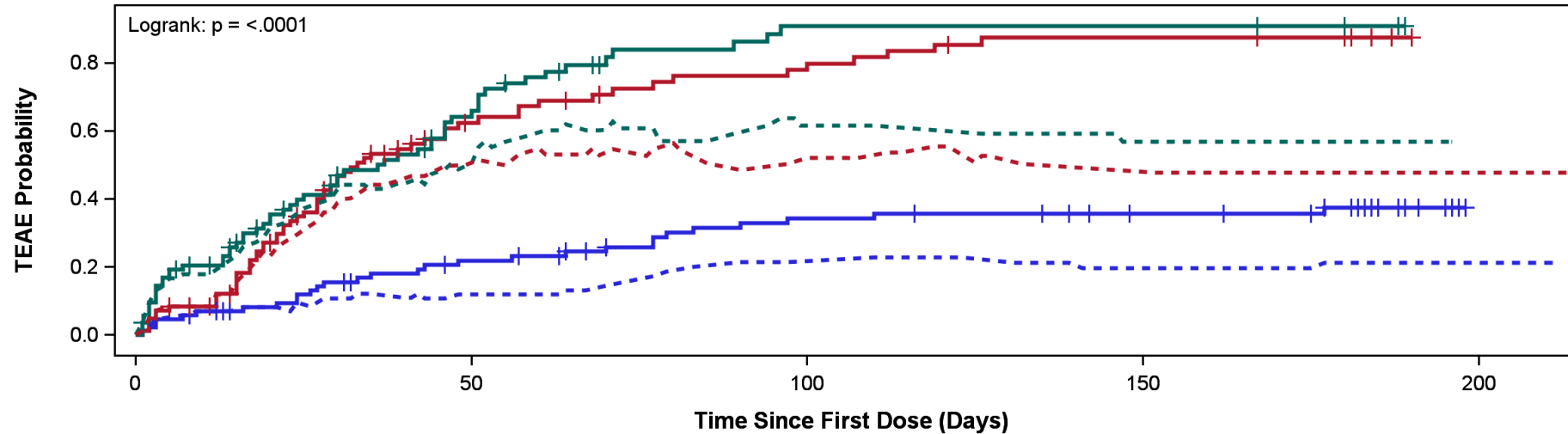
seriesplot x = ti y = p / group = id_pbrf grouporder = ascending name =
    "PBRF" legendlabel = "PBRF" lineattrs=(thickness = 2px pattern = 2);

layout gridded / columns =2 rows=2 location =outside border=false;
    entry ""; entry "";
    entry "PBRF Legend: ";
    discretelegend "PBRF" / itemsize = (linelength = 16px ) location =
        outside;
endlayout;
endlayout;
```

PBRF Figure with KM



PBRF Figure with KM and Summary Statistics



Subjects at Risk:								
Placebo	86	69	59	49	45	40	35	0
Low Dose	84	42	20	13	8	6	5	0
High Dose	84	38	14	6	4	4	3	0

Arm	No. of Subjects	Events	Censored	Median AE time (95% C.I.)
Placebo	86	29 (33.7%)	57 (66.3%)	(. - .)
Low Dose	84	62 (73.8%)	22 (26.2%)	33.0 (27.0 - 48.0)
High Dose	84	61 (72.6%)	23 (27.4%)	36.0 (23.0 - 46.0)

Conclusions

- ▶ Adverse events are typically reported as tables of incidence rates and a sometimes using a Kaplan–Meier time to event figure or patient profile plot.
- ▶ Currently apart from using a Kaplan Meier plot there are not many ways of visualizing TEAE's over time.
- ▶ Temkin's approach is helpful since it allows a visual of the probability that a patient has a given TEAE at any point in time, which is given by the curve, and the area under the curve is the expected duration of an TEAE which can be also useful in comparing treatments

Material

- ▶ The full code which creates the PBRF dataset and plots is found here:
http://www.krissharris.co.uk/pharmasug/2017/SP06/pg/figures/f_pbr.sas.
- ▶ The datasets needed for the PBRF is located here:
<http://www.krissharris.co.uk/pharmasug/2017/SP06/data/ads/ADaMs.zip>.

Contact Information

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References

- ▶ Allison, P. D. (2012). Logistic Regression Using SAS: Theory and Application (Second Edition ed.). Cary, NC: SAS Institute Inc.
- ▶ Cao, D., & He, X. (2011). Statistical Analysis of Adverse Events in Randomized Clinical Trials Using SAS. Nashville: PharmaSUG. Retrieved from <http://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP07.pdf>
- ▶ CDISC. (2013). SDTM/ADaM Pilot Project. Retrieved June 2015, from http://www.cdisc.org/system/files/members/article/application/zip/updated_pilot_submission_package.zip

More References

- ▶ CDISC Pilot Project. (2006). Final CSR. Ellis, S., Carroll, K. J., & Pemberton, K. (2008). Analysis of duration of response in oncology trials. *Contemporary Clinical Trials*, 29, 456–465.
- ▶ Gillespie, B., & Scott, C. (2008). USING SAS SOFTWARE FOR ESTIMATING THE PROBABILITY OF BEING IN RESPONSE . SUGI 88.
- ▶ ICH. (1994, October 27). CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING. Retrieved July 31, 2015, from E2A:
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline .
- ▶ Temkin, N. R. (1978). An Analysis for Transient States with Application to Tumor Shrinkage. *Biometrics*, 34(4), 571– 580.