PharmaSUG 2016 - Paper SP03

Programming Support for Exposure-Response Analysis in Oncology Drug Development

Peter Lu and Hong Yan

Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

ABSTRACT

Over the last decade Exposure-Response (ER) analysis has become an integral part of clinical drug development and regulatory decision-making. It plays an increasingly important role in the identification of early evidence of drug efficacy and safety and thus can support internal and external decision-making processes for evaluating drug benefit-risk and optimizing trial design. Unlike population pharmacokinetics analysis, however, the regulatory guidance and industry recommendations for ER analysis are still lacking in terms of the details of statistical modeling approaches, including multivariate logistic regression, linear mixed effects, nonlinear regression, and non-parametric or parametric Cox proportional-hazards regression. To ensure a successful ER analysis, quality SAS programming is essential in data preparation and presentation. Due to the nature of ER analysis, ER programming often faces challenges: Programming may start without a formal ER (PK/PD) analysis plan; the source data may not be fully available (primary endpoints of efficacy and safety); and studies may have different data standards and dictionary versions (e.g., AE or Concomitant medication). The purpose of this paper is to share ways in which SAS programmers can provide flexible, timely, and efficient support for ER analysis, and includes examples to elaborate the relevant ER programming processes and considerations.

INTRODUCTION

Exposure-Response (ER) analysis is a powerful tool which can be used to capture and quantify signals of interest in a clinical trial as well as to support the optimization of study design for late phase trials, based on the available data for the compound or drug class. Quantitative assessment of ER relationships is especially important in oncology clinical trials and can provide useful early evidence of drug safety and efficacy for internal and external decision-making. The knowledge gained from ER analysis may also help to reduce time and cost in drug development and to increase the success rate in subsequent pivotal studies.

As the scope of ER analysis may be broadly defined, this paper follows a narrow sense of ER analysis as given by Overgaard et al. (2015). The main focus is on ER analysis performed by statistical regression methodologies; time-course population pharmacokinetics (pop-PK) and pop-PK/PD are not considered. The statistical methodologies used for ER analysis may include linear mixed effects regression, logistic regression, nonlinear regression, and non-parametric or parametric Cox proportional-hazards regression. However industry recommendations and regulatory guidance are still lacking in comparison to the relatively mature pop-PK analysis approaches.

Appropriate identification of exposure and response variables as well as covariates is important to ensure a successful ER analysis. Exposure variables may include the area under curve (AUC) and its variants, Cmax, Cmin, trough concentration, steady-state trough concentration, and the geometric means of these PK-related exposure variables, while response variables may be clinical outcomes or endpoints of interest, for example, adverse events of interest, QT prolongation, tumor size change, time to events, surrogates or biomarkers, progression free survival, and overall survival. Response variables can be continuous, categorical, or time-to-event data.

ER analysis includes PK-Safety, PK-Efficacy, or both. PK-Safety analysis can be performed for PK-QT, PK-AE (e.g., clinical significant events for the compound), and PK-LAB (e.g., liver toxicity); PK-Efficacy analysis can be performed on exposure (e.g., AUC, Cmax, or trough concentration) compared to efficacy endpoints (e.g., the best overall response, the change of tumor size, progression free survival, and overall survival). Derivation of ER analysis

datasets from disparate sources is generally complex and outputs often include customized figures (e.g., boxplots, logistic plots, nonlinear regression plots and/or Kaplan-Meier plots) and tables.

ER analysis often involves different phase of trials or pooling of data from multiple clinical trials in order to have a broader dose range. However, exposure data from all patients may not be available at the time of analysis. ER programmers therefore face various challenges such as dealing with uncleaned or incomplete data or the lack of an analysis plan. To provide adequate programming support requires a specialist programming skill-set and knowledge-base. The focus of this paper is to share our perspectives on how ER (SAS) programmers can provide flexible, timely, and efficient support to ER analysis in oncology drug development.

ER PROGRAMMING CHALLENGES AND STRATEGIES

Some of the particular challenges which we have experienced during ER analysis programming are as follows:

1. Unlike clinical study report (CSR) programming, the statistical analysis plan (SAP) is not finalized when ER analysis is requested. The ER-SAP might be only a draft scope without detailed analysis information, and the statistician or modeler may still be exploring the feasibility of different analyses and potential models based on the early evidence.
2. The ER-SAP could keep evolving till to the due date for the deliverables and the timelines are usually tight for internal decision-making or for submission.
3. The required study level analysis datasets are not available or are delivered late (e.g., for early phase trials, the CSR SAP is not even finalized) and ER programmers may sometimes need to extract information directly from uncleaned source data.
4. The use of multiple disparate input datasets could lead to prolong programming time and require efforts to sort out data issues/programming issues.
5. Pooled ER analyses, including data drawn from studies across different phases, may have different data standards or different version of dictionaries and CTC toxicity grades. Also, PK data collection/trough concentration/steady state trough can vary from study to study.
6. The imputation of missing data can be complex and time consuming for oncology trials (e.g., impute/expand the dosing records from summary dose collection, excluding exposure records after the dose change/interruption/discontinuation).

We started an ER programming group and programmers were trained to develop expertise in handling different types of ER analyses. In addition to good SAS skills, we found the following to be key factors for success:

1. Understanding the ER analysis and study data: The ER programmer is not a trial programmer, and has to know from where to gather information and to be able to rapidly understand it.
2. Effective and transparent communication across the different line functions and multiple stakeholders (e.g., ER statisticians, ER modelers, trial programmers, trial data managers, trial statisticians, pharmacokinetists and clinicians).
3. Prioritization of multiple requests based upon company objectives and the ability to negotiating timelines.
4. A clearly written programming dataset specification (PDS) for ER analysis. This should be updated to reflect the most recent changes of ER-SAP, and the ER statistician/modeler should review and approve it.
5. Acting proactively and rapid action in response to ER requests. It is also essential to seek clarification from the statistician/modeler in timely manner when in doubt to avoid ambiguities and rework.
6. A good understanding of statistical regression modeling analysis and the principles of clinical pharmacology

EXAMPLES OF ER ANALYSIS

EXAMPLE 1: EXPOSURE-ECG (PK-QT) ANALYSIS

PK-QT analysis characterizes the relationship between drug concentration and the QT change from baseline, and investigates intrinsic and extrinsic covariates that may influence this relationship.

The ER dataset for PK-QT analysis usually includes drug concentrations and matched QT measurements, and covariates needed for model analysis. Figure 1 shows a PK-QT dataset for two subjects (covariates such as age, sex, BMI, etc. are not shown for simplicity). Each observation represents a unique and matched pair, and each subject has multiple PK-QT matched observations.

Notable variables in the PK-QT dataset in Figure 1 are:
QTCF : Corrected QT interval – Fridericia
QTCF_BASE: Baseline QTCF
QTCF_CHG: Change from baseline QTCF
ECGDT : ECG measurement date and time
STM_ECG : Scheduled time point for ECG measurement (hours)
PKSMPDT : PK drug sampling date and time
STM_PK : Scheduled time point for PK drug sampling (hours)
PKCONC : PK drug concentration
MATCH : Flag for matched pair of PK-ECG records, 1 – matched, 0 – otherwise

QTCF	QTCF_BASE	QTCF_CHG	ECGDT	STM_ECG	PKSMPDT	STM_PK	PKCONC	MATCH	ID
443.7	435.5	8.166667	15JUL2015:09:09:00	1	15JUL2015:08:54:00	0.500	68.6	1	06
443.7	435.5	8.166667	15JUL2015:10:09:00	2	15JUL2015:10:20:00	2.000	1310	1	06
438	435.5	2.5	15JUL2015:11:09:00	3	15JUL2015:11:20:00	3.000	1240	1	06
442.7	435.5	7.166667	15JUL2015:12:09:00	4	15JUL2015:12:21:00	4.000	969	1	06
429.7	435.5	-5.83333	15JUL2015:14:09:00	6	15JUL2015:14:24:00	6.000	562	1	06
433.7	435.5	-1.83333	15JUL2015:16:10:00	8	15JUL2015:16:24:00	8.000	468	1	06
430.3	435.5	-5.16667	22JUL2015:09:10:00	1	22JUL2015:09:21:00	1.000	468	1	06
433	435.5	-2.5	22JUL2015:10:09:00	2	22JUL2015:10:20:00	2.000	1340	1	06
438	435.5	2.5	22JUL2015:11:09:00	3	22JUL2015:11:20:00	3.000	1200	1	06
437.3	435.5	1.833333	22JUL2015:12:09:00	4	22JUL2015:12:20:00	4.000	1040	1	06
428.7	435.5	-6.83333	22JUL2015:14:09:00	6	22JUL2015:14:24:00	6.000	552	1	06
430	435.5	-5.5	22JUL2015:16:09:00	8	22JUL2015:16:21:00	8.000	472	1	06
427	435.5	-8.5	29JUL2015:09:09:00	1	29JUL2015:09:21:00	1.000	186	1	06
427	435.5	-8.5	29JUL2015:10:09:00	2	29JUL2015:10:20:00	2.000	808	1	06
430.7	435.5	-4.83333	29JUL2015:11:09:00	3	29JUL2015:11:22:00	3.000	791	1	06
423.3	435.5	-12.1667	29JUL2015:12:09:00	4	29JUL2015:12:20:00	4.000	647	1	06
411	435.5	-24.5	29JUL2015:14:09:00	6	29JUL2015:14:22:00	6.000	419	1	06
411.7	435.5	-23.8333	29JUL2015:16:09:00	8	29JUL2015:16:20:00	8.000	367	1	06
431.7	435.5	-3.83333	05AUG2015:09:05:00	1	05AUG2015:09:17:00	1.000	37.5	1	06
429.3	435.5	-6.16667	05AUG2015:10:05:00	2	05AUG2015:10:19:00	2.000	183	1	06
421.7	435.5	-13.8333	05AUG2015:11:05:00	3	05AUG2015:11:19:00	3.000	364	1	06
419.3	435.5	-16.1667	05AUG2015:12:05:00	4	05AUG2015:12:20:00	4.000	369	1	06
410	435.5	-25.5	05AUG2015:14:05:00	6	05AUG2015:14:16:00	6.000	315	1	06
423	435.5	-12.5	05AUG2015:16:05:00	8	05AUG2015:16:19:00	8.000	278	1	06
407	411.5	-4.5	15JUL2015:08:45:00	1	15JUL2015:08:30:00	0.500	55.5	1	11
401.7	411.5	-9.83333	15JUL2015:09:45:00	2	15JUL2015:09:56:00	2.000	260	1	11
403.7	411.5	-7.83333	15JUL2015:10:45:00	3	15JUL2015:10:57:00	3.000	192	1	11
404.3	411.5	-7.16667	15JUL2015:11:45:00	4	15JUL2015:11:56:00	4.000	227	1	11
395.7	411.5	-15.8333	15JUL2015:13:45:00	6	15JUL2015:13:56:00	6.000	188	1	11
388.7	411.5	-22.8333	15JUL2015:15:45:00	8	15JUL2015:16:00:00	8.000	125	1	11
401	411.5	-10.5	22JUL2015:08:45:00	1	22JUL2015:08:58:00	1.000	28.6	1	11
389.3	411.5	-22.1667	22JUL2015:09:45:00	2	22JUL2015:09:58:00	2.000	63.7	1	11
392.7	411.5	-18.8333	22JUL2015:10:45:00	3	22JUL2015:10:57:00	3.000	65.7	1	11
396	411.5	-15.5	22JUL2015:11:45:00	4	22JUL2015:11:56:00	4.000	73	1	11
399	411.5	-12.5	22JUL2015:13:45:00	6	22JUL2015:13:57:00	6.000	101	1	11
392.3	411.5	-19.1667	22JUL2015:15:45:00	8	22JUL2015:15:58:00	8.000	64.6	1	11
395	411.5	-16.5	29JUL2015:08:45:00	1	29JUL2015:08:57:00	1.000	502	1	11
398	411.5	-13.5	29JUL2015:09:45:00	2	29JUL2015:09:57:00	2.000	594	1	11
396.3	411.5	-15.1667	29JUL2015:10:45:00	3	29JUL2015:10:56:00	3.000	437	1	11
398.3	411.5	-13.1667	29JUL2015:11:45:00	4	29JUL2015:11:56:00	4.000	380	1	11
395.3	411.5	-16.1667	29JUL2015:13:45:00	6	29JUL2015:13:57:00	6.000	263	1	11
379.7	411.5	-31.8333	29JUL2015:15:45:00	8	29JUL2015:15:57:00	8.000	186	1	11

Figure 1: A sample of a PK-QTcF dataset from a cross-over study.

The main challenge is to match the closest QTcF change from baseline values with the drug concentration. We often see more than one record within a time window and so need to find the closest match to the concentration; the

algorithm should therefore be defined clearly in ER-SAP. PROC SQL is used to perform the matching as given in Figure 2.

```
** Get all matched pairs within a time window of 30 minutes;
proc sql noprint;
    create table pkecg01 as
    select  a.ID, a.QTCF, a.QTCF_BASE, a.QTCF_CHG, a.ECGDT, a.STM_ECG,
            b.PKSMPDT, b.STM_PK, b.PKCONC, round((a.ECGDT-b.PKSMPDT)/60,0.001) as TIMDF_PKECG,
            b.min(abs(round((a.ECGDT-b.PKSMPDT)/60,0.001))) as MIN_TD_PKECG
    from AECG as a, PKCONC as b
    where a.ID=b.ID and abs(a.ECGDT-b.PKSMPDT)/60 le 30
    group by a.ID, a.ECGDT
    order by a.ID, a.ECGDT;
quit;

** Get the closest mathced pairs;
proc sort data=pkecg01 out=pkecg02;
   by ID ECGDT MIN_TD_PKECG descending TIMDF_PKECG;
   where abs(TIMDF_PKECG) eq MIN_TD_PKECG;
run;

** Keep the matched pair with ECG measurement after PK drug sampling for multiple closest pairs;
data pkecg03;
   set pkecg02;
   by ID ECGDT MIN_TD_PKECG descending TIMDF_PKECG;
   if first.MIN_TD_PKECG;
run;
```

Figure 2: A code snippet for preparing a PK-QT analysis dataset.

A linear mixed effects model is usually used to explore the relationship between QTcF and drug concentration. PROC SGPLOT was used to generate the output shown in Figure 3, showing a regression line (data from PROC MIXED) superimposed on the observations.

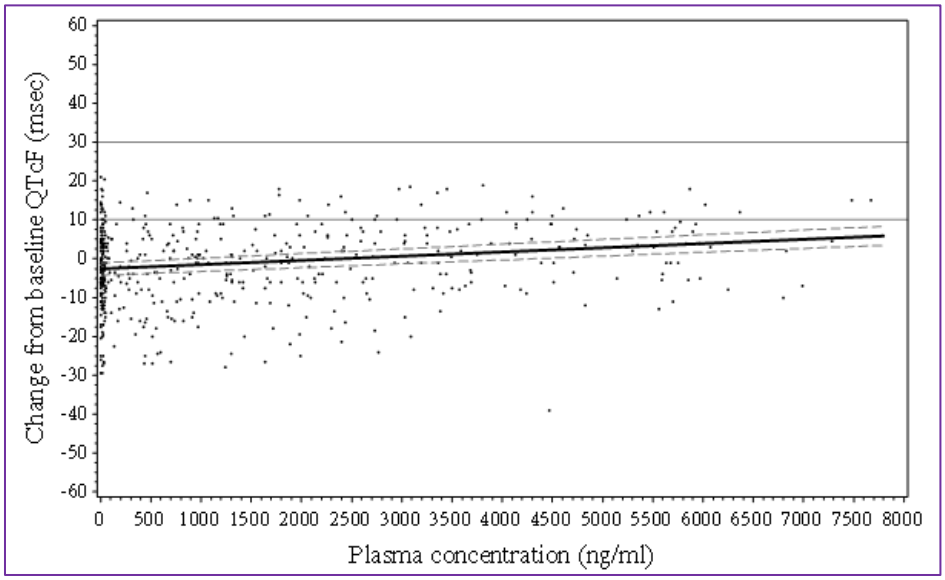

Figure 3: Scatter plot, regression line, and 90% CI of change from baseline QTcF vs. plasma concentration.

EXAMPLE 2: EXPOSURE AND CLINICAL SIGNIFICANT ADVERSE EVENTS (PK-AE) ANALYSIS

PK-AE analysis assesses the relationship between drug exposure and clinically significant adverse events, with or without adjusting for covariates. The analysis can be based on the presence/absence of events (Yes/No) or time to events

The PK-AE dataset usually contains drug exposure variables, censored flag and time to event, etc. Figure 4 shows a time to event ER dataset (AE and lab) in ADaM format: Each subject has multiple observations for standard and extended Cox models.

Notable variables in the PK_AE dataset in Figure 4 are:

AVAL : Analysis Value, time to event for the standard Cox model (DTYPE=”Fixed covariate”); Set to missing for the extended Cox model (DTYPE=”Time-dependent covariate”) as the time-dependent analysis requires two analysis variables AVAL1 and AVAL2."

CNSR : Censor variable for the standard Cox model (DTYPE=”Fixed covariate”), and direct copy for the extended Cox model (DTYPE=”Time-dependent covariate”) if AVAL2 is the study day of event/censoring. Set to 1 if AVAL2 is not the study day of event/censoring.

DTYPE : For the standard Cox model, set to DTYPE=”Fixed covariate”. For the extended Cox model (time-dependent analysis), set to DTYPE=”Time-dependent covariate”.

TNCMIN1 : For the standard Cox model (DTYPE=”Fixed covariate”), first calculate the cumulative projected Cmin (from ADPCEXP) from Day 1 to the day of event/censoring (including the projected Cmin on the day of event/censoring). Secondly divide this value by (day of onset/censoring; Day 1 + 1). For the time-dependent analysis (DTYPE=”Time-dependent covariate”), set to missing.

AVAL1 : For the standard Cox model (DTYPE=”Fixed covariate”), set to missing. For the extended Cox model (DTYPE=”Time-dependent covariate”), do the following: For the first row of each patient set to 0. Each time a subject’s projected Cmin changes, create a new row with AVAL1 set to the study day on which the projected Cmin changes – 1.

AVAL2 : For the standard Cox model (DTYPE=”Fixed covariate”), set to missing. For the extended Cox model (DTYPE=”Time-dependent covariate”), do the following: Set the value to the study day of next projected Cmin change – 1 or study day of event/censoring depending on whichever occurred first.

	PARCAT1	PARCAT1N	PARCAT2	PARCAT2N	PARAM	PARAMN	PARAMCD	AVALC	AVAL	CNSR	EVNTDESC	DTYPE	TNCMIN1	DI1	DI2	DI3	AVAL1	AVAL2	PROJCMIN	ID
18	Adverse event	1	Depressed mood disorders and disturbances (HLGT)	11	Time to first Depressed mood disorders and disturbances (HLGT) (At least grade 2)	5	TTEDEPR2		.	1	No post-baseline assessment	Time-depe covariate	.	.	.	.	108	109	91.559983	198
19	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2	109	109	1	No post-baseline assessment	Fixed covariate	671.2723	94.5	57.1	78.6	.	.	91.559983	198
20	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	0	1	1E-6	198
21	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	1	2	129.24978	198
22	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	2	104	704.15204	198
23	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	104	105	468.24624	198
24	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	105	106	311.37386	198
25	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	106	107	207.05704	198
26	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1		Time-depe covariate	.	.	.	.	107	108	137.68856	198
27	Adverse event	1	Anxiety disorders and symptoms (HLGT)	12	Time to first Anxiety disorders and symptoms (HLGT) (At least grade 2)	8	TTEANX2		.	1	No post-baseline assessment	Time-depe covariate	.	.	.	.	108	109	91.559983	198
28	Laboratory abnormality	2	Alanine aminotransferase (ALT) or Alanine aminotransferase (AST)	13	Time to first Alanine aminotransferase (ALT) or Alanine aminotransferase (AST) (At least grade 2)	11	TTEASLT2	109	109	1	Death	Fixed covariate	671.2723	94.5	57.1	78.6	.	.	91.559983	198
29	Laboratory abnormality	2	Alanine aminotransferase (ALT) or Alanine aminotransferase	13	Time to first Alanine aminotransferase (ALT) or Alanine aminotransferase (AST) (At least	11	TTEASLT2		.	1		Time-depe covariate	.	.	.	.	0	1	1E-6	198

Figure 4: Section of a dataset showing time to first AE of interest.

Figure 5 illustrates an example of a survival analysis using Kaplan-Meier curves with subjects in two groups categorized by the median of an exposure variable (geometric mean trough, using a different time to event dataset shown in Figure 4). The plot was generated using PROC SGPLOT with input data from PROC LIFETEST. Customized legends and a table of number of subjects at risk can be added as well using scatter plot statements (or TEXT statement) and XAXISTABLE if required.

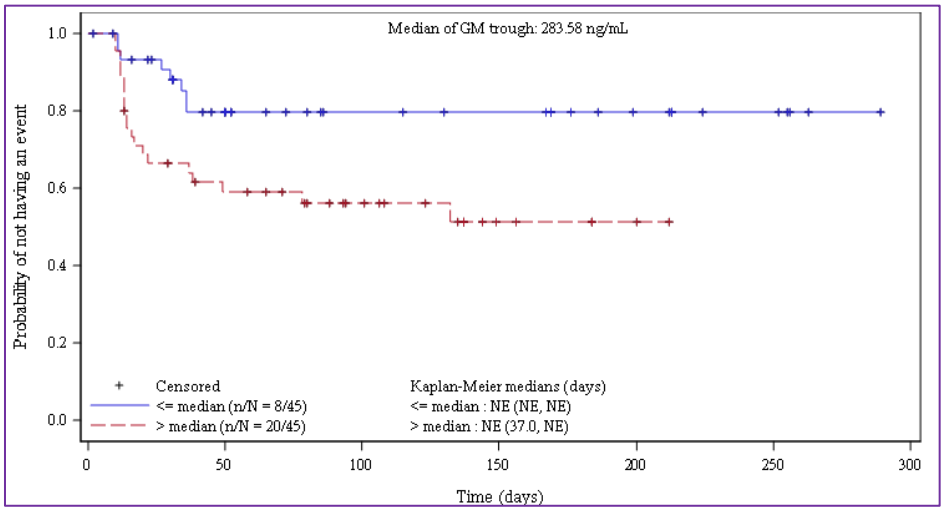

Figure 5: Kaplan-Meier plot of time to rash G2+ by median of geometric mean trough concentration

A nonlinear regression model was performed (Figure 6 with the same dataset as in Figure 5) to fit the observed proportions of an AE of interest (rash G2+) against an exposure GM trough concentration, as well as to determine the estimated probability and its 90%CI. PROC SGPLOT was used with input data generated from PROC NLMIXED. The observed proportions (2/22, 6/23, 10/22, 10/23) are the fraction of subjects with the AE (rash G2+) over the total subjects within their quartiles, Q1 (<25%), Q2 (<=25% and <50%), Q3 (<=50% and <75%), and Q4 (>=75%) of geometric mean trough concentration, respectively. All four fractions are aligned at their medians of GM trough concentration in each quartile. In addition, information regarding the exposure level can be added above the x-axis.

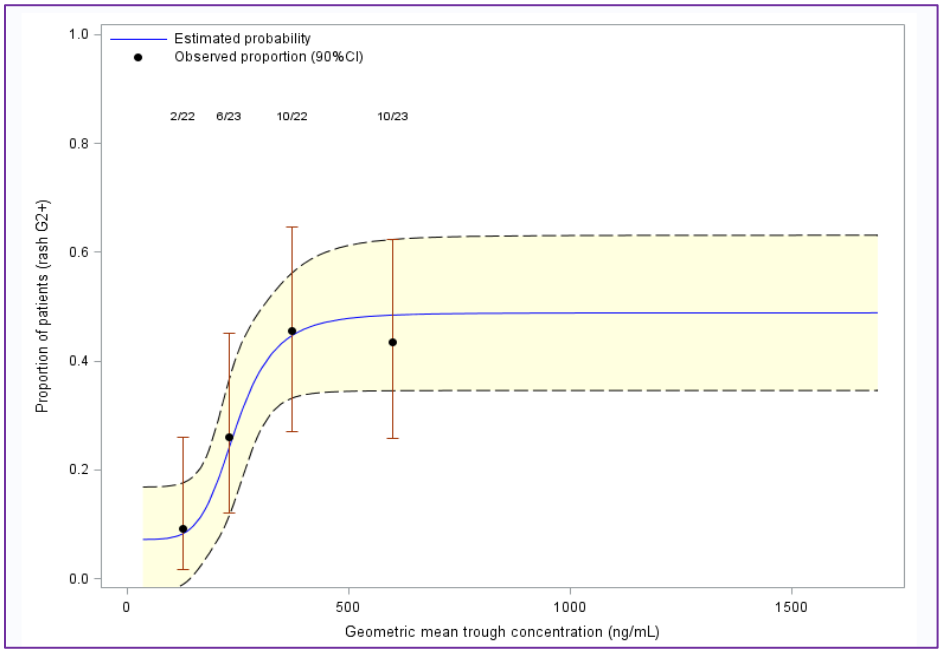

Figure 6: A nonlinear regression fit for an AE (rash with grade 2+) and its 90%CI overlaid with observed proportions vs. an exposure metric (GM trough concentration).

EXAMPLE 3: EXPOSURE AND CLINICAL RESPONSE (PK-EFFICACY) ANALYSIS

PK-Efficacy analysis aims to evaluate the relationship between drug exposure and an efficacy endpoint such as best overall response or percent change of target tumor size compared to baseline.

Depending on the specific objectives of the SAP, the PK-Efficacy dataset may have different structures. There are three types of structure commonly encountered in ER analysis. The first is per-observation per-subject for the time to the first event, or binary/nominal/ordinal tumor categorical response used in logistic regression. The event, for example, can be defined as the best overall response, responder/non-responder, progression-free survival (disease-free survival), or overall survival. The second type of structure is multiple observations per subject for recurrent event survival analysis. The third is one observation per subject per visit for efficacy assessment. Further ER analysis dataset structures are also possible, determined by the specific ER-SAP. An example of a PK-Efficacy dataset with per-observation per-subject is shown here in Figure 8.

Notable variables in PK_Efficacy dataset in Figure 8 are:
RESP : Binary response variable, Yes/No
RESPN : Binary response variable (num), 1='Yes', 2='No'
BORAVALC: Best overall response
PARMCD : Parameter code, GM_TROUGH = geometric mean of steady-state trough concentration
GMAVAL : Geometric steady-state trough concentration
BSTPCB : Best percent change of target tumor size from baseline

ID	RESP	RESP	BORAVALC	PARAMCD	PARAMN	GMAVAL	GMAVALU	BSTPCB
1001	No	2	PD	GM_TROUGH	1	317.867	ng/mL	-0.2333333
1002	Yes	1	PR	GM_TROUGH	1	166.411	ng/mL	-0.7471264
1003	No	2	PD	GM_TROUGH	1	675.456	ng/mL	0.22222222
1004	No	2	PD	GM_TROUGH	1	1301.519	ng/mL	0.14285714
1005	No	2	SD	GM_TROUGH	1	1116.748	ng/mL	-0.125
1006	No	2	SD	GM_TROUGH	1	675.244	ng/mL	-0.4951456
1007	Yes	1	PR	GM_TROUGH	1	920.36	ng/mL	-0.6185567
1008	Yes	1	PR	GM_TROUGH	1	752.288	ng/mL	-0.6333333
1009	No	2	SD	GM_TROUGH	1	530.849	ng/mL	0.16666667
1010	No	2	SD	GM_TROUGH	1	630.635	ng/mL	0

Figure 8: A portion of a PK-Efficacy dataset.

The geometric mean of the steady-state trough concentration is used as the exposure metric in the example. To identify whether a pre-dose concentration (after the first study treatment) is a trough in steady-state, the clear definition/criterion should be set out in the ER-SAP. In this example, the sample must have been taken before the next dose on the same day and within 20 to 28 hours after the leading dose, and the subject must have taken the dose as planned for at least 5 consecutive days prior to the sample being taken.

A logistic regression analysis was performed to fit the observed proportions of the confirmed best overall response (BOR) with their 90%CI (Figure 9). The plot was generated using PROC SGPLOT with input data from PROC LOGISTIC.

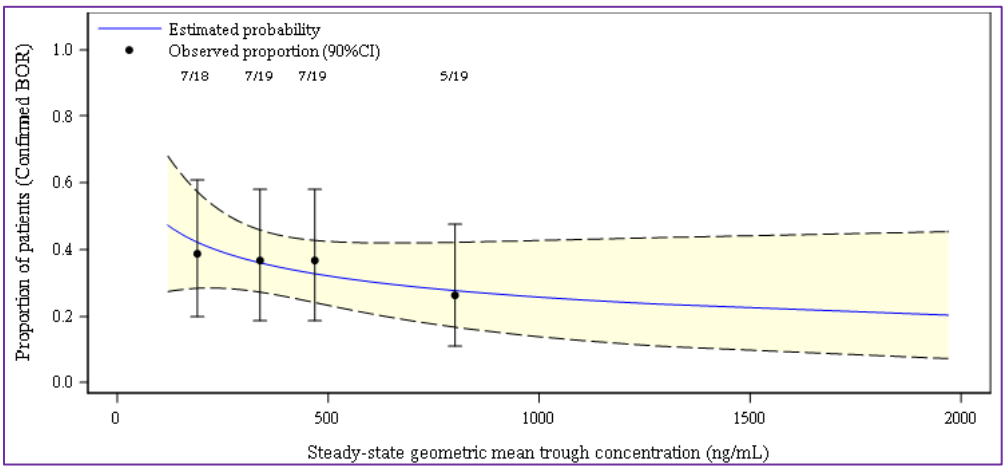

Figure 9: Logistic regression of confirmed best overall response (BOR).

SUMMARY

This paper shares our perspectives on programming support for ER analysis in oncology drug development. We have presented examples of challenges and also ways to provide flexible, timely and efficient programming support. ER programmers need to be trained in special technical and soft skills and to be aware of the challenges that may significantly impact ER programming efficiency. Three working examples of PK-Safety and PK-Efficacy analyses have been demonstrated with detailed dataset descriptions, key derivation steps for some exposure variables, and customized figure outputs.

Quality checks for ER analysis datasets and outputs are critical. A high-level data review validation from the ER modeler and statistician is important to make sure that data for analysis are correct from the scientific perspective (e.g., to confirm that an unusual outlier is not due to programming errors). Whether or not double or independent programming validation processes are required will depend on the requirements of the team members involved in the ER analysis and where the results may go. A well-maintained programming dataset specification (PDS) based on ER-SAP is indispensable for performing the validation and will ensure the quality of deliverables.

ACKNOWLEDGMENTS

We thank our colleague Danny Tuckwell for his review and editorial comments in the preparation of this paper.

REFERENCES

R.V. Overgaard, S.H. Ingwersen, and C.W. Tornoe, *Establishing Good Practices for Exposure-Response Analysis of Clinical Endpoints in Drug Development,* CPT Pharmacometrics Syst. Pharmacol., 2015, 4, 565-575.

FDA, *Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*, 2003

FDA, *Guidance for Industry: Population Pharmacokinetics*, 1999

Sharmeen Reza, *Growing Needs in Drug Industry for NONMEM Programmers Using SAS*, PharmaSUG2015 (Paper SP07)

Jixian Wang, *Exposure-Response Modeling: Methods and Practical Implementation*, Chapman and Hall/CRC, 1st Edition, 2015

Tong Lu, et al., *Survey of methodologies for exposure-response analysis of oncology drugs approved in FDA from 2010 to 2015*, American Conference on Pharmacometrics (ACoP6), Crystal City, VA, USA, 2015

K Venkatakrishnan, et al., *Optimizing oncology therapeutics through quantitative translational and clinical pharmacology: Challenges and Opportunities.* Clin. Pharmacol*,* Ther. Vol. 97, No. 1, 37-54, 2014

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Name: Peter Lu
Enterprise: Novartis Pharmaceuticals Corporation,
Address: One health plaza, East Hanover, New Jersey 07936-1080
E-mail: peter.lu@novartis.com

Name: Hong Yan
Enterprise: Novartis Pharmaceuticals Corporation,
Address: One health plaza, East Hanover, New Jersey 07936-1080
E-mail: hong.yan@novartis.com