

Programming standard rigidity vs study protocol flexibility

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ABSTRACT

Early clinical development (ECD) trials represent the transition between the preclinical and the clinical full development. The main objective of our trials is to determine the best dose of a new compound. Because the data generated in these studies, are often the “first in human (FIH)” clinical data available, the clinical team is also interested in exploring efficacy/PK/PD results. Instead of planning several Phase I trials to investigate the drug, a single flexible study protocol is written to address multiple objectives and to extend and adapt the trial with multiple scenarios up front.

The goal is to avoid protocol amendments and to set-up a CRF/Database able to handle these case scenarios. The preliminary results of FIH studies are used for internal decisions (move or not to full development) and/or for external communications.

As such, being a programmer in ECD requires dealing with flexible study designs, reporting multiple analyses, several times before the database is fully cleaned and locked. Your programs must be standard (provided the analysis requested is), ready after the first data transfer available and, robust and flexible to be run at any time. The challenge for a programmer is to use or adapt standard programs in an exploratory domain.

INTRODUCTION

In Oncology, one of the main goals of a compound is to decrease/remove the tumor(s) of a patient as well as preventing the appearance of new lesions and prolonging the life expectancy. Since ECD trials are the first studies in man, patients with different (and multiple) indications are selected for a single trial - a single trial may have adult patients with solid tumors in breast, colon, lung, or in any others indications. The first objective is to define a dose that is well tolerated by all patients (MTD=Maximum Tolerated Dose). Once this dose is found, then an extension phase will allow knowing more about efficacy, PK/PD data, and risk assessments to ensure a solid Proof Of Concept for further clinical development.

Therefore, most of the studies starts with a dose escalation phase (phase I) and are followed by a dose expansion or Phase II part in which the MTD or the recommended phase II dose (which could be lower than MTD) is given to a selected population.

BACKGROUND

FLEXIBLE PROTOCOL VS STANDARD ANALYSIS PLAN

The aim of the flexible protocol is to avoid multiple amendments and to allow

- (1) Flexibility in the dose selection, the dosing regimen, the dosing formulation,
- (2) Optional dose cohorts depending on the preliminary results
- (3) Adaptation of the schedule (removal/addition of arms/assessments), CRF and so database

Let's take an example:

The protocol plans that all patients receive an oral daily dose until disease progression. It also plans for a separate cohort receiving a single oral dose of drug followed by a 2-day washout period and then restarting the dosing (Cohort2).

Six dose groups are tested before the team decides to test for another dosing schedule. The protocol allows testing for a b.i.d. regimen: 3 doses cohort are tested. After that, a new formulation of the drug has been approved and is now available. The team decides to switch all patients to this new formulation. Moreover, it seems that the exposure in Cohort 2 is similar to the other groups. The team decides not to enroll anymore patients in this arm.

The aim of the analysis plan is to describe how data will be analyzed. This plan must be ready before the first patient first visit. With this kind of protocol, we do not know

- (1) How many dose groups we will have,
- (2) How many arms/indications we will have,

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(3) If different dosing schedules (once daily, twice daily,...) /formulations (capsule, sachet, tablet,) will be pooled or reported together.

How can we anticipate what has not happened yet? Of course at the end of the study, the clinical team will know exactly what has occurred during the study and the analysis will be clear. But since these data are the first clinical data available, the team needs to get them immediately in order to make internal decisions, write new protocols, update regulatory documents or publish results.

REPORTING LIVE DATA: CHALLENGES

- (1) The analysis plan may not be final/amended or may simply not contain the required analysis
- (2) Since the data are live, the programs must be robust enough to deal with data issues/ inconsistencies, to flag those having an impact on the analysis and to share the finding with the clinical team
- (3) Since the assessments are flexible, the programs must handle different case scenario to take into account the different modifications occurring during the study.

You may start the programming reporting 3 doses groups and, by the time of the CSR, you can have 15+ dose groups. The initial plan was to report all dose groups separately, but at the end of the study, you know that with the exception of PK, you will have to pool dose groups no matter the dosing schedule (once daily and twice daily doses show no difference) but to report separately according to the formulation.

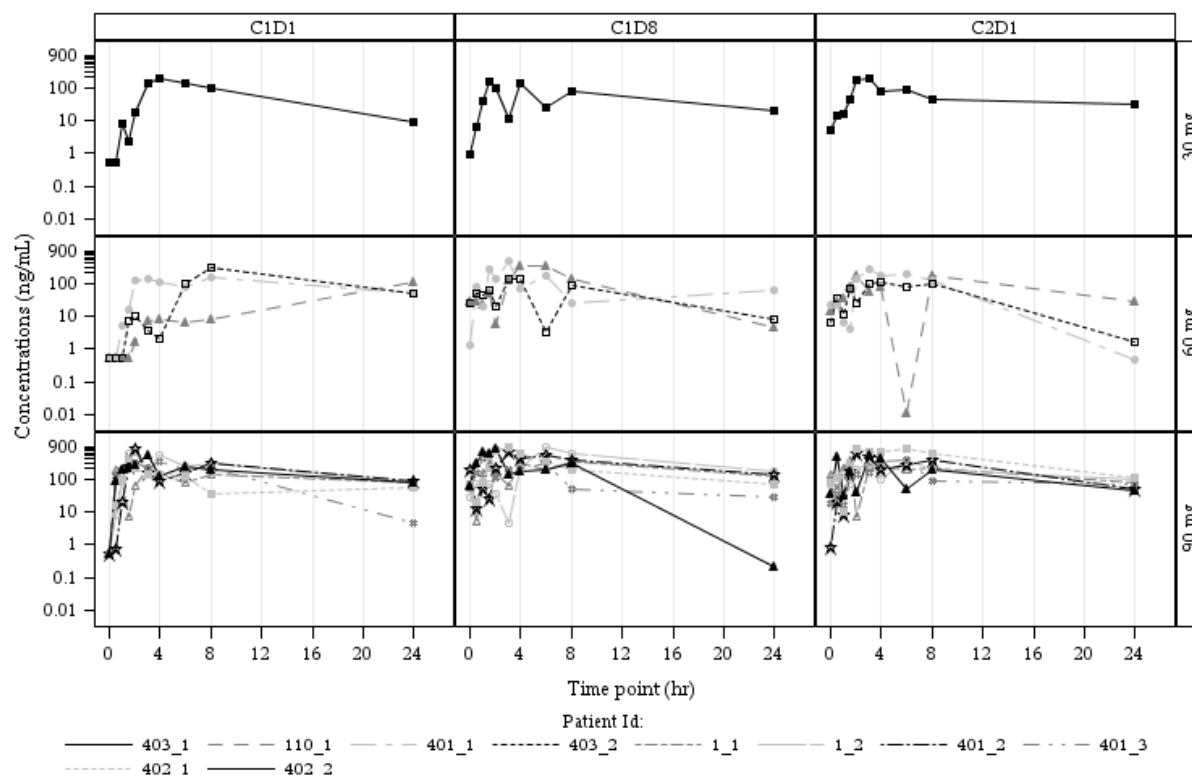
Additional data driven analysis could also be required if for example, patients with a specific indication have shown a better response.

PRACTICAL EXAMPLES

PHARMACOKINETICS RESULTS

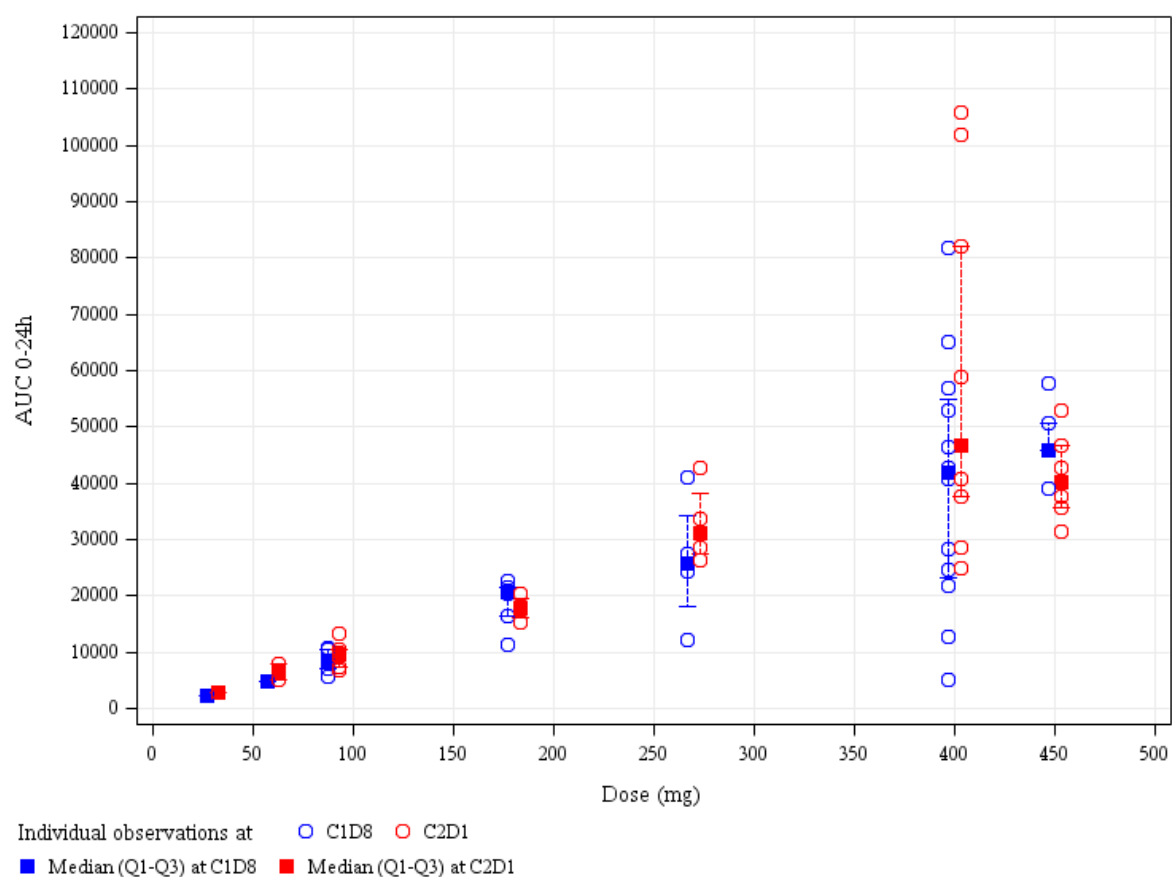
The pharmacokinetics is a good example to highlight the difference between reporting at the start of the study and during /at the end of the study when the data are more mature.

The first delivery is an update of regulatory documents. 10 patients are enrolled in the study. The team wants to have an overview of the concentration over the time for the first doses tested.



A few months later, 50 patients divided into 7 doses groups are on study. The team decides to present results to a conference and they want to show the exposure of the drug according to the dose at steady state. This plot is not planned in the analysis plan.

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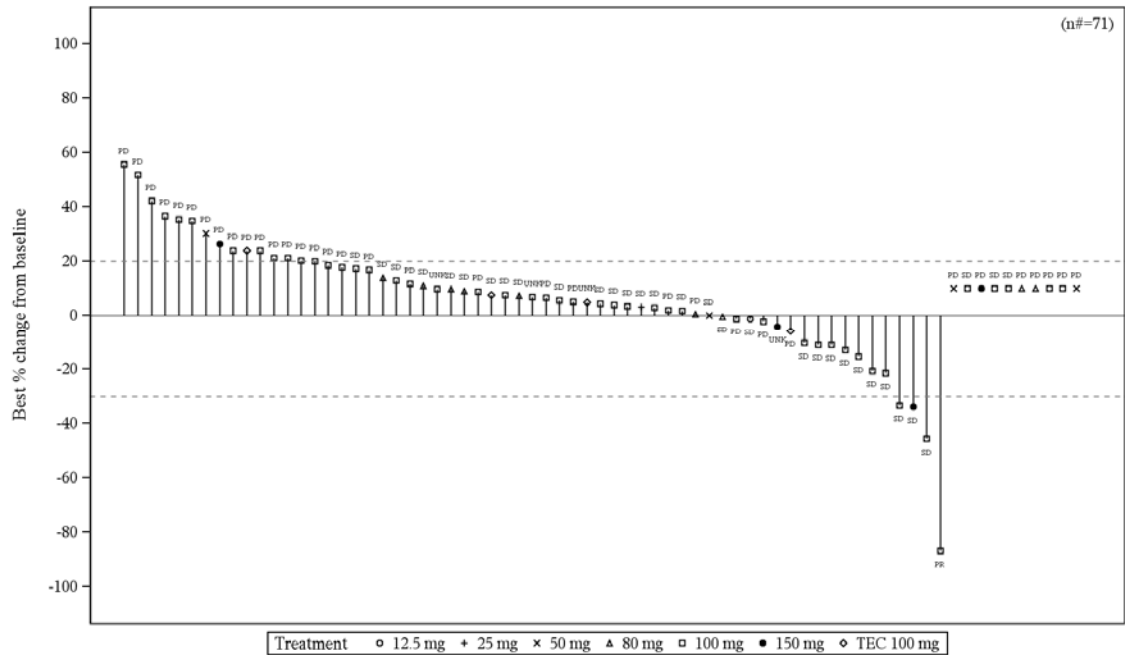


From Individual concentrations	To individual exposure at steady state
<pre>proc sgpanel data= pkconc ; panelby day trt / layout=lattice novarname columns=3 rows=3 COLHEADERPOS=top; series x=timep y=conc / group=patid lineattrs=(thickness=1) NAME='SERIE' ; scatter x=timep y=conc/ group=patid MARKERATTRS=(size=8pt) NAME='SCATTER'; rowaxis label="Concentrations (ng/mL)" type=log LOGBASE= 10 LOGSTYLE= LINEAR; colaxis label="Time point (hr)" values=(0 to 26 by 2) FITPOLICY=THIN grid; discretelegend ...;</pre>	<pre>proc sgplot data=par;; scatter x=trt1d8 y=_meld8/ MARKERATTRS=(COLOR=BLUE symbol= squarefilled ...) NAME='SCATTER1' YERRORLOWER= lo1 YERRORUPPER= up1 ERRORBARATTRS=(COLOR=BLUE PATTERN = 29) LEGENDLABEL='Median (Q1-Q3) at C1D8'; scatter x=trtn2d1 y=_me2d1 / MARKERATTRS=(...) LEGENDLABEL='Median (Q1-Q3) at C2D1'; scatter x=trt1d8 y=_val1d8 / MARKERATTRS=(symbol=circle COLOR=BLUE SIZE=8PT) NAME='SCATTER3' LEGENDLABEL='C1D8'; scatter x=trtn2d1 y=_val2d1 / MARKERATTRS=(symbol=circle COLOR=RED SIZE=8PT) NAME='SCATTER4' LEGENDLABEL='C2D1'; yaxis ...; xaxis label="Dose (mg) "values=(0 to 500 by 50); discretelegend "SCATTER3" "SCATTER4"/ noborder title="Individual observations at " position=bottomleft location=outside ; discretelegend "SCATTER1" "SCATTER2"/noborderposition = bottomleft location=outside ;</pre>

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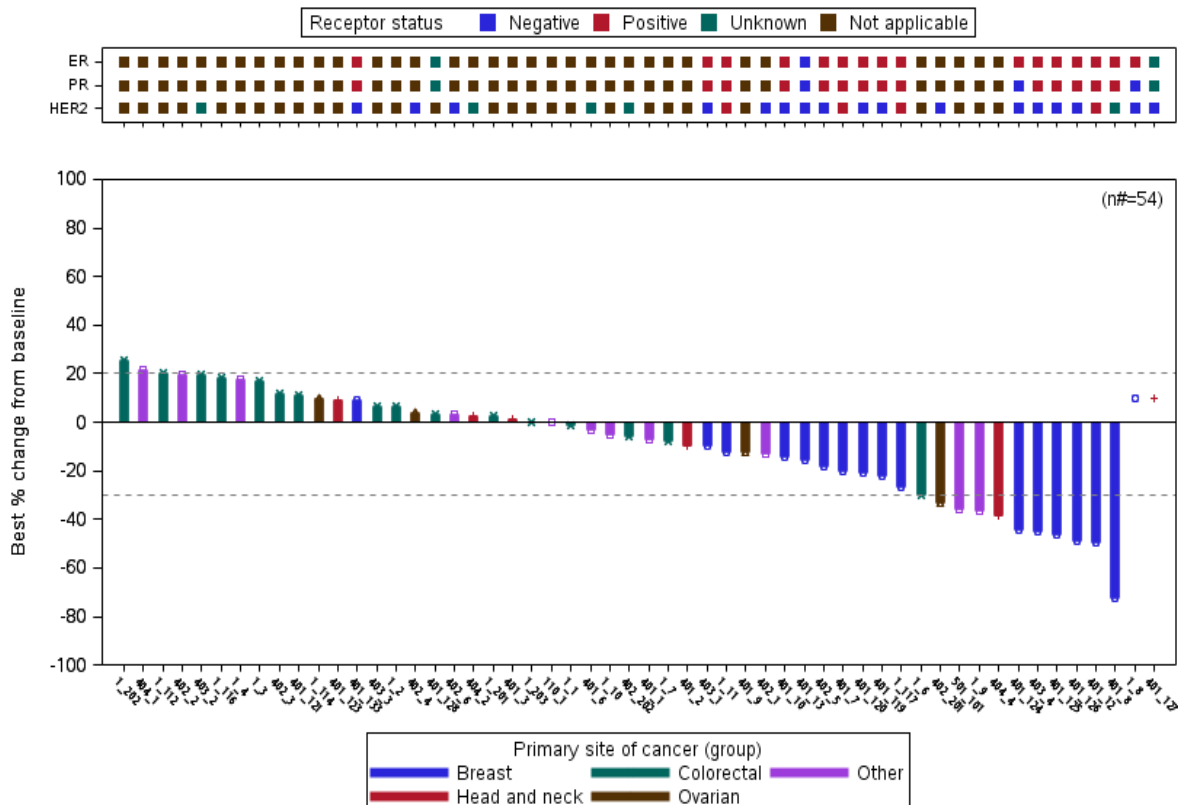
EFFICACY RESULTS

The standard plot shows the individual best percentage from baseline and the best overall response (BOR) (per RECIST) by treatment group.



However, it seems that patients with Breast Cancer (ER+ status) show a better response than patients with other types of cancer.

The team decides to report the best percentage change by indication and to show information on the hormonal status. Since most of the patients are still ongoing and/or have not yet a confirmed best overall response, the team does not want to display the best overall response



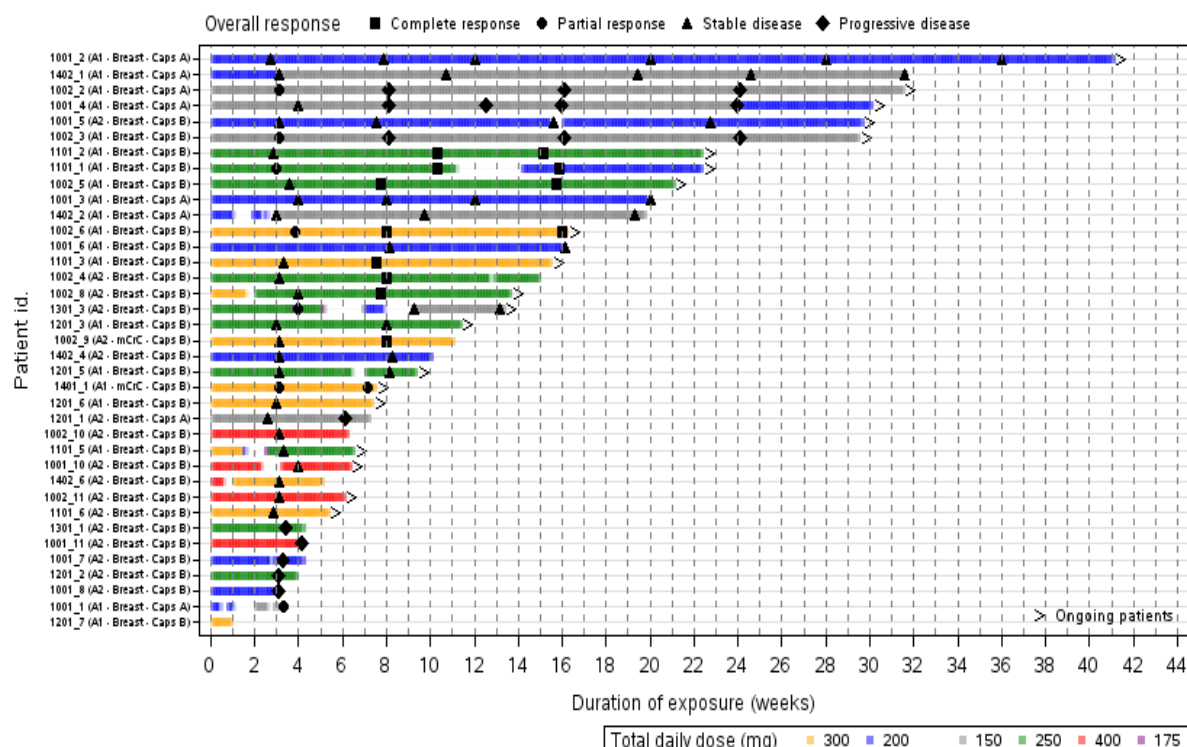
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From standard plot (CSR requirement)	to customized plot for publication
<pre> define statgraph waterfall; begingraph ; layout overlay / xaxisopts = (&__xaxisopt) yaxisopts = (&__yaxisopt) ScatterPlot X=patid Y=bpct1 / primary=true Group=trt NAME="SCATTER" MARKERATTRS=(size=4pt ...); NeedlePlot X=patid Y=bpct2 / NAME="NEEDLE" lineattrs=(pattern=1 ...) group=trt; ScatterPlot X=xlab Y=ylob / Group=trt MARKERCHARACTER=BOR ; /*refline;*/ DiscreteLegend "SCATTER" "NEEDLE" / ...; Endlayout; </pre>	<pre> layout lattice / columns=1 rows=2 rowweights=(&_mapsize &_watsize); layout overlay / cycleattrs=true xaxisopts=(...) yaxisopts=(...) ; ScatterPlot X=&_xvar Y=yheat_fmt / primary=true Group=&_heatval Markerattrs=(....) LegendLabel=" " NAME="S1"; DiscreteLegend "S1" / border=1 Location=outside valueattrs=(size= 10pt) titleattrs=(size= 10pt) ;; endlayout; </pre>

SAFETY/EFFICACY RESULTS

For other publications, the team would like to explore graphically the exposure to the study drug. They want to see the interruptions and/or the change of dosing for each patient and to cross check this information with the RECIST overall response.

No standard outputs exist for this kind of analysis. The team meets, the needs are clarified, and the specifications are established.



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BEGINGRAPH;

/*Define map color for each doses*/
discreteattrmap name="dosegroup" / ignorecase=true;
    value " " /markerattrs=(color=white );
    value "0" /markerattrs=(color=white );
    value "150" /markerattrs=(color=grey );
    value "175" /markerattrs=(color=purple );
    value "200" /markerattrs=(color=blue );
    value "250" /markerattrs=(color=green );
    value "300" /markerattrs=(color=orange );
    value "400" /markerattrs=(color=red );
enddiscreteattrmap;

DiscreteAttrVar attrvar=_group var=_GROUP1 attrmap="dosegroup";

/*DEFINE LAYOUT*/
LAYOUT OVERLAY / XAXISOPTS = ( type = linear
                                Linearopts = ( tickvaluelist=( &tick)
                                                  viewmin=0
                                                  viewmax=%eval(&nbcyc*28) ))
                YAXISOPTS = ( griddisplay = on
                                Label="Patient id."
                                type=discrete
                                display=(LABEL LINE TICKS ) );

/******ALL BELOW SCATTER REQUIRED AT LEAST ONE NON MISSING VALUE FOR (X;Y)*****/
/*PLOT DAILY EXPOSURE FOR EACH PATIENT*/
SCATTERPLOT X = EXP1N Y = PATID / NAME="SCATTER"
                                PRIMARY=TRUE
                                GROUP=_GROUP
                                MARKERATTRS=(SYMBOL=SQUAREFILLED ...)
                                DATATRANSAPARENCY=0.5
                                LEGENDLABEL="Total daily dose (mg)" ;

/*ANNOTATE ONGOING STATUS*/
SCATTERPLOT X = X_ONGO Y = YVAR / NAME="ONGO";
                                PRIMARY=TRUE
                                MARKERATTRS=( SYMBOL=GREATERTHAN
                                                  COLOR=BLACK)
                                DATATRANSAPARENCY=0
                                LEGENDLABEL="Ongoing patients" ;

/*ANNOTATE EACH TYPE OF OVERALL RESPNS*/
SCATTERPLOT X = X_CR Y = PATID / NAME="CR"
                                MARKERATTRS=( SYMBOL= SQUAREFILLED COLOR=BLACK)
                                LEGENDLABEL="Complete response" ;

SCATTERPLOT X = X_PR Y = PATID / NAME="PR"
                                MARKERATTRS=( SYMBOL= CIRCLEFILLED COLOR=BLACK)
                                LEGENDLABEL="Partial response" ;

SCATTERPLOT X = X_SD Y = PATID / NAME="SD"
                                MARKERATTRS=( SYMBOL= TRIANGLEFILLED COLOR=BLACK)
                                LEGENDLABEL="Stable disease" ;

SCATTERPLOT X = X_PD Y = PATID / NAME="PD"
                                MARKERATTRS=( SYMBOL= DIAMONDFILLED COLOR=BLACK)
                                LEGENDLABEL="Progressive disease" ;

SCATTERPLOT X = X_UK Y = PATID / NAME="UK"
                                MARKERATTRS=( SYMBOL= HASH COLOR=BLACK)
                                LEGENDLABEL="Unknown" ;

/*... REFERENCE LINES IF REQUIRED...*/

/*LEGENDS STARTS*/

*Actual dose legend;
DISCRETELEGEND " SCATTER " / LOCATION=OUTSIDE
                                HALIGN= RIGHT VALIGN=BOTTOM;

*Ongoing status;
DISCRETELEGEND "ONGO" / LOCATION=INSIDE
                                HALIGN=RIGHT VALIGN=BOTTOM;

/*IF OVERALL RESPONSE EXIST - LEGEND THEM */
DISCRETELEGEND "CR" "PR".../ LOCATION=OUTSIDE
                                HALIGN=RIGHT VALIGN=BOTTOM
                                TITLE="OVERALL RESPONSE" .....

ENDLAYOUT;
ENDGRAPH;

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CONCLUSION

In this paper, we have shown how easy it is to go from a standard output to a non standard one.

Working with flexible protocol means that you and your programs have to be flexible. You have to expect the unexpected! But you also have to be a good negotiator to ensure that standards programs are used where they can, and to try sometimes reigning the creativity from your clinical team, in order to save resources and time.

But the reverse can also happen; a non standard program developed for a publication could become a standard if the team wants to include it in the CSR.

In our case, the exposure/RECIST figure tends to become a standard figure for all publications and the clinical team is now thinking to include it in the CSR. If it is the case, we will have to think how to summarize the same information, but to the CSR requirements (black and white plot).

ACKNOWLEDGMENTS

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REFERENCES

<http://support.sas.com/>