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Efficacy endpoints in Oncology

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ABSTRACT

The evaluation of efficacy in oncology studies, in particular for solid tumors, is pretty standard and well defined by several regulatory guidance (e.g. EMA and FDA), including some specific cancer type guidance (e.g. NSCLC from FDA).
Although some references will be also given for non-solid tumors, the paper will mainly focus on solid tumors efficacy endpoints.
Overall Survival, Best Overall Response as per RECIST criteria, Progression Free Survival (PFS), Time to Progression (TTP), Best Overall Response Rate are some of the key efficacy indicators that will be discussed.

INTRODUCTION

Initially tumor response rate was sufficient for FDA approval of oncologic drugs. When in early '80 FDA started to request demonstration of improvement in survival, Overall survival (OS) became the gold standard endpoint to measure efficacy for most of the oncology indications as it is the only endpoint which demonstrate a "direct" clinical benefit to patients.

When in 1992 the FDA adopted the "accelerated drug approval" regulation, pharmaceutical industries increased the use of surrogate endpoints to speed the market arrival of new agents with the potential to save or extend lives. Thus, the use of Objective Response Rate (ORR), Time to Progression (TTP), Disease Free Survival (DSF), Progression Free Survival (PFS), increased in the application for new oncology drug approval; in particular ORR with or without TTP was used in almost 50% of the application (from Jan 90 to Nov 2002) [1].

SURROGATE ENDPOINTS

A "surrogate endpoints" is an alternative endpoint (e.g. biological markers, physical sign, etc.) that if validated allows conclusions to be made about the effect of an intervention on a true endpoint (e.g. a clinical meaningful endpoint), often requiring shorter "observation" period. An example in oncology is the use of objective response rate (ORR) and progression-free survival (PFS).

As stated above a surrogate endpoint needs to be validated. In oncology this means it should demonstrate to be an adequate substitute of OS, the endpoint to 'predict'; it also needs to be associated with the disease (cancer) and the treatment. Moreover it is also important to note that a surrogate endpoint may be valid for a particular indication (e.g. a particular intervention for colon cancer) and not for others.

EVALUATING TUMOR RESPONSE TO TREATMENT

BEST OVERALL RESPONSE (BOR) FOR SOLID TUMORS

In solid tumors[1], tumor response measures the changes in tumor mass, growth (progression) or shrinkage (response) and it is often assessed using the RECIST criteria (Response Evaluation Criteria in Solid Tumor) [2]. Although it is still the object of criticism (e.g. the definition of cut-off used to define the response and the progression), RECIST provides a simplified set of criteria for evaluating tumors response via an anatomical approach using an unidimensional measure of tumor burden.

In RECIST tumor lesions are classified as being Target (or measurable) or non-Target (or not measurable). Each existing lesion is identified prior to study entry (baseline) and classified accordingly and lesions characteristics such as location, measures (mm) and method used to assess the lesion are collected. Then, at regular time-points during the study, lesions assessed prior to study entry are re-evaluated (measured) and any new identified lesion are also evaluated (new with respect to baseline assessment).

Then, based on all lesions assessed, target, non-target and new lesions at each time-point (if any), the (overall) response is evaluated by looking at either progression (increase in sum of all target lesions or increase in size in any of the non-target lesions or any new lesion detected) or response (decrease in the sum of all target lesions with respect to baseline and disappearance of all non-target lesions). As per RECIST, latest version 1.1, the overall tumor response at each time-point is defined as follows:

- Complete Remission or Response (CR)
    - Disappearance of all lesions (target and non-target)
    - No new lesions diagnosed

[1] Cancer involving solid tumor typically originates in a specific body organ, such a lung, breast, ovarian, etc. Types of solid tumors includes sarcomas, carcinomas, adenocarcinomas, blastomas, carcinoid tumors

    - Sustained at least four weeks, when confirmation is required
- Partial Remission or Response (PR)
    - Greater than 30% decrease in the sum of the longest diameters of target lesions taking the baseline sum as reference
    - No evidence of progression in any of the non-target lesions diagnosed at baseline
    - No new lesions diagnosed.

- Progressive Disease (PD)
    - Greater than 20% increase in the sum of the longest diameters of target lesions taking the smallest sum as reference, where the smallest sum should be more than 5mm or
    - The progression of a non-target lesion or
    - The appearance of a new lesion.

In all other cases the tumor response, if evaluable, is defined as Stable (SD).

Then the Best Overall Response (BOR) is defined as follows:

- For randomized trials the BOR is the best among all overall responses (CR is better than PR that is better than SD)
- For non-randomized trials a confirmation is required within a pre-define time-frame, for example 6 weeks (this needs to be defined in the protocol).

Of note the confirmation was required for any kind of trial in RECIST version 1.

Table 1 summarizes the criteria for confirmation (when required):

Overall response at previous time-point	Overall response at current time-point	Best Overall Response
CR	CR	CR
CR/PR	PD	SD provided that criteria for minimum SD duration are met. Otherwise PD
PR	CR	PR
PR	PR	PR
SD	CR/PR	SD
SD	Any	SD, provided that criteria for minimum SD duration are met. Otherwise either PD or NE

Table 1: Criteria for Best Overall Confirmation with RECIST 1.1.

Of note table 1 is a revised version of the table reported in the paper presenting RECIST 1.1 as it does not include other combinations such as CR followed by a PR or SD, PR followed by SD; such a combination where for example initial CR are claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point, may require the change of previous CR assessment and therefore should not be considered as a confirmation without further checks (when confirmation is required).

Figure 1 in the next page shows an example of response assessment of a subject with both target and non-target tumor lesions assessed at baseline.

Assessing tumor response in oncology and in particular the use of RECIST criteria, have been the topic of several technical presentations in the past [3] [4] [5].

Related to the BOR, additional efficacy endpoints can be also derived and analyzed:

- Best Overall Response Rate or Objective Response Rate (ORR): the presence of at least one confirmed CR or confirmed PR
- Disease Control Rate: the presence of at least one confirmed CR or confirmed PR or SD

OTHER RESPONSE CRITERIA FOR NON SOLID TUMORS: EXAMPLE ACUTE MYELOID LEUKEMIA (AML)

Achieving a complete response, or complete remission, it is also the goal of oncology therapies in other type of cancer. As an example similarly with was done for solid tumors with RECIST, an International Working Group (IWG) has established a standard set of criteria for evaluating response for Acute Myeloid Leukemia (AML) [6]. Like for solid tumors the response status is also here assessed at regular time-points by the investigator and it is based on complete blood count usually performed on a weekly base.

Table 2 in next page summarizes the criteria for response assessment based on the IWG.

Type of Lesion	Lesion Number	Measure (mm)
BASELINE	Random Date:12JAN2013	CT-Scan Date: 10JAN2013
Target	T1	10
Target	T2	15
Target	T3	25
Non Target	NT1	
So overall at baseline using a CT-Scan as a method for the assessment, four lesions were detected with three of them being measurable (target) with sum of **50 mm**.		
ON TREATMENT ASSESSMENT 1 → OVERALL ASSESSMENT RESPONSE=SD		CT-Scan Date: 10FEB2013
Target	T1	5
Target	T2	10
Target	T3	25
Non Target	NT1	Present
Overall on the first assessment post treatment, using the same method as at baseline (CT-Scan), while there was confirmation of no new lesions and no change in the non-target lesion (neither response/disappearance or progression), the sum of lesions decrease to **40 mm with a % decrease of 20% (10/50)**, not qualifying for either CR or PR.		
ON TREATMENT ASSESSMENT 2 → OVERALL ASSESSMENT RESPONSE=PR		CT-Scan Date: 10MAR2013
Target	T1	5
Target	T2	10
Target	T3	10
Non Target	NT1	Present
At the second assessment post treatment, while keeping constant the status of non-target lesions, the sum of target lesions decrease to **25mm which is 50% of decrease** with respect to baseline.		
ON TREATMENT ASSESSMENT 3 → OVERALL ASSESSMENT RESPONSE=PR		CT-Scan Date: 10MAY2013
Target	T1	7
Target	T2	10
Target	T3	10
Non Target	NT1	Present
At the third assessment post treatment, the conditions observed at assessment nr. 2 were confirmed although a small (2mm) increase was seen in lesion T1 with respect to previous assessment, but overall the decrease of the sum of lesions seen at baseline was still qualifying for partial response, thus **confirming the PR observed at previous assessment**.		
ON TREATMENT ASSESSMENT 4 → OVERALL ASSESSMENT RESPONSE=PD		CT-Scan Date: 10JUL2013
Target	T1	10
Target	T2	15
Target	T3	10
Non Target	NT1	Present
At the fourth assessment post treatment, despite no change in the non-target lesion status and no new lesions were observed, the sum of target lesions increased of **more than 20% with respect to best sum** of target lesions prior to this assessment (visit 2 was best prior assessment, where sum of target lesions was 25).		
Best Overall Response (A): PR the 10MAR2013 Progression Free Survival (B): event observed the 10JUL2013, PFS Time=180 days (measured from date of randomization) Duration of Response: (B-A)+1=123 days		

Figure 1: Deriving best overall response process: an example where confirmation is required

Type of Response	Neutrophils Count (cells/uL)	Platelets (plt/UL)	Bone Marrow Blast (%)
Leukemia Free State	NA	NA	<5
CR Complete Remission	>1000	≥100000	<5
CRp CR with incomplete platelet recovery	>1000	≥30000 to <100000	<5
Cri CR with incomplete blood count recovery	≤1000	<100000	<5
PR Partial Remission	>1000	≥100000	Decrease of ≥50% to a value between 5% and 25%
Recurrence	Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥5 blasts in the bone marrow not attributable to any other causes		
Treatment Failure	Persistent AML in blood or bone marrow or death prior to response assessment		

Table 2: Response Criteria for AML

Efficacy endpoints based on the above response criteria could be then summarized as follows:

- CR rate
- Combined CR rate (CR+CRp+CRi)
- OR rate (CR+CRp+Cri+PR)

Based on the above response criteria, some time to event endpoints can be derived in addition to Overall Survival:

- Event Free Survival (EFS): time from randomization to Recurrence or death from any cause
- Relapse Free Survival (RFS): defined only for subjects achieving CR and it is measured from the date of Leukemia Free State was achieved until the date of the recurrence or death

TIME-TO-EVENT ENDPOINTS FOR SOLID TUMORS

The Duration of the event, or censoring if no events occurred, are usually calculated from the date of randomization or from first drug administration (if study is not randomized), to the date of the event; the general formula to be applied is usually (Date of Event/Censoring-Date of Randomization)+1.

Censoring methods and censoring date to be used may vary depending on the type of event. Table 3 summarizes the key features and starting / event date of some of the most used time-to-event endpoints.

Endpoint	Event Date	Censoring
Overall Survival (OS)	Date of death from any cause	Last date subject was seen alive
Time to Progression (TTP)	Date of Radiological Progression	Last tumor assessment performed
Progression Free Survival (PFS)	Date of Progression or death if occurred before progression	Last tumor assessment performed
Time to Treatment Failure (TTF)	The earliest date among the following events: • Progression • Discontinuation of treatment due to progression or Adverse Event • Start of any new anticancer therapy • Withdrawal of consent • Death within a specific timeframe from last tumor assessment	Last tumor assessment performed

Table 3: Possible time to event endpoints

OVERALL SURVIVAL (OS)

As previously mentioned, OS is the gold standard for measuring efficacy in Oncology. The event of interest in this case is the death from any cause and subjects without the event are censored to the last date of follow-up (last date the subject was proven to be alive). Although OS can be easily and unambiguously measured, the disadvantage is that a long observation period is required. Moreover the effect of the experimental treatment may be obscured when subjects in the control arm switch to the experimental arm after progression.

PROGRESSION FREE SURVIVAL (PFS)

Progression Free Survival (PFS) is often the primary endpoint of most of solid tumor cancer trials as requested by regulatory agencies [7] [8], although for most of the indications pivotal phase III may require OS. PFS is a composite event and it is defined as the time from randomization (or 1st drug administration for non-randomized trial) to one of the following events (whichever came first):

- radiological confirmed progression (e.g. imaging date)
- death from any cause

The definition of PFS may vary among studies. For example deaths occurred after a pre-defined time period after last tumor assessment without progression are not considered event and therefore censored at the last tumor assessment (death after more than one missed assessment or after an extended lost-to-follow-up time). Example of pre-defined period could be "within 12 weeks from last tumor assessment".

If no events are observed, or if death without previously documented progression is not observed within the pre-defined period, then the PFS is censored at the time of last tumor assessment or date of randomization (or date of 1st study drug administration in case of non-randomized trials), whatever comes later. If no assessment at baseline is available, PFS is to be censored at the date of randomization (or date of 1st study drug administration).

OTHER TYPE OF TIME-TO-EVENT ENDPOINTS

Other possible time to event efficacy endpoints include but are not limited to:

- Time to Progression (TTP), similar to PFS but only radiological progressions are considered
- Time to Clinical Progression (TTPc), where in addition to radiological progression, other events of clinical interest are evaluated, such as worsening in performance status or the start of a subset of medications that could be symptom of a progression (e.g. the use of Opioids). This later condition, if not appropriately collected in the eCRF, may require an ad-hoc post data collection medical assessment if TTPc can be not derived programmatically from the collected data
- Time to Treatment Failure (TTF), where the event of interest is the first occurrence of one of the following events:
  - progression assessed by the investigator
  - discontinuation of treatment due to PD
  - discontinuation of treatment due to an AE

    - start of any new anticancer therapy, or withdrawal of consent or death within 12 weeks from last tumor assessment or randomization (assuming 12 weeks is defined in the protocol)
- Duration of Response (DR), it is applicable to subject with BOR either CR or PR and it is defined as time from the first assessment of CR or PR until the date of the first occurrence of PD, or until the date of death (if occurred within predefined time period). In case of censored event, the duration of response is censored on the date of last tumor assessment or randomization (whichever occurs last)
- Duration of Stable Disease, measured from the randomization date (or first drug administration in non-randomized trials) until progression

MODIFIED VERSION OF PFS

For certain type of cancer a modified version of PFS can be used as a primary endpoint; for example the PCWG2 criteria for Prostate Cancer [9] and the mRECIST criteria for Hepatocellular Carcinoma [10].
As an example Prostate Cancer modified PFS versions is here described.

Prostate Cancer (PCWG2)
With this modified version, objective radiographic disease progression is defined as the presence of at least one of the following conditions:

- Bone lesion progression (appearance of 2 or more new bone lesions compared to baseline)
- Soft-tissue lesion progression according to RECIST (see above)
- Presence of skeletal events

One of the complication here is to make sure in the eCRF bone lesions, usually collected in the RECIST form, are collected in a separate form with additional criteria for data collection (e.g. collecting the nr. of new lesions at each assessment, evaluate whether or not the new lesions were symptomatic).

Other secondary endpoints specific to prostate cancer may include: PSA response defined as a 50% decrease in PSA from baseline for 2 consecutive evaluations, duration of PSA response, time to PSA response, analysis on bone lesions (e.g. number of new lesions from randomization).

MAIN COVARIATES

The note for guidance on statistical principles for clinical trials (ICH E9) briefly addresses the problem of adjustment for covariates. It advises experimenters to identify the covariates expected to have an important influence on the primary outcome and to specify how to account for them in the analysis in order to improve precision and to compensate for any lack of balance between groups. A baseline covariate is usually defined as a qualitative factor or a quantitative variable measured or observed before a subject starts taking study medication (usually before randomization) and expected to influence the primary variable to be analyzed.

There are many types of baseline covariates and their nature depends upon the context of the study. They may be demographic variables such as age or weight, disease characteristics such as duration or severity, commonly accepted prognostic factors, or factors such as center or investigator.

In oncology trials the use and selection of covariates in the multivariate analysis (e.g. Cox) may also differs from an indication to another; beside standard covariates such as age, sex, performance status, stage, tumor response to prior therapies and country / region (e.g. eastern vs western countries), depending on the type of cancer and setting (e.g. type of previous therapies, line of treatment, etc.), additional covariates can be added to the model to further control for confounders or to investigate potential treatment effects within specific subgroups of patients; this could also include biomarkers validated for the specific indication (e.g. CTC for Castrate Prostate Cancer or KRAS for NSCLC).

Table 4 provides some examples.

Indication	Possible additional covariates
Colorectal	Tumor location e.g. left vs right side Site of Metastasis (for Colorectal Advanced Cancer)
Prostate	Gleason Score PSA at baseline
Lung Cancer	Histology Smoking History
Breast	Receptorial Status Site Number of Metastasis (for Advanced Breast Cancer)
Melanoma	Exposure to sunlight

Table 4: Main covariates used in multivariate model

ANALYSIS

STATISTICAL ANALYSIS

Survival Analysis for Time to Event Endpoint

Figure 2 shows a possible way of summarizing key results from a survival analysis, where descriptive statistics of number events, median survival, number of subjects at risk at each time-point of interest and Hazard Ratio together with its confidence intervals, in this case unadjusted, are presented. The below example is just a possible way of summarizing results and of course the layout may change if you want to include more details such as the reason for the event (and censoring) in the case of composite endpoint such as PFS, or details from multivariate analysis (e.g. results in the single subgroups). Whatever layout you will choose, if you use for example SAS® you will need to get data from the standard SAS procedure for survival analysis, that is usually PROC LIFETEST® and PROC PHREG® (for Cox multivariate analysis).

An example of Cox model and how to retrieve the needed results from procedure is shown in figure 3.

Characteristic	Statistics	Placebo (N=22)	50mg (N=24)	500mg (N=28)
Number of Events		17 (77.3%)	18 (75.0%)	23 (82.1%)
Hazard Ratio[95% CI]; p-value		0.86 [0.31; 1.15] p=0.660	0.60 [0.45; 1.66] p=0.124	
Progression Free Survival Median(Months) [95 % CI]		2.8 [2.4; 4.1]	4.3 [2.8; 5.6]	2.8 [2.7; 3.3]
Nb of subjects at risk / Progression-free Rates up to [95 % CI] &	6 Months	1 / 6% [0%; 22%]	4 / 28% [11%; 49%]	3 / 18% [5%; 37%]
	12 Months	1 / 6% [0%; 22%]	2 / 21% [6%; 42%]	1 / 12% [2%; 31%]
	18 Months	0 /	0 /	0 /
	24 Months	0 /	0 /	0 /

Date cut-off: 30AUG2013

Figure 2: Example of a possible standard layout to present summary statistic of survival analysis

```
ods output ParameterEstimates=OutCox;
proc phreg data=ADTTE(where=(PARMCD='PFS'));
  class TRT01PN (ref="0");
  model AVAL*CNSR(1)=TRT01PN/ties = discrete rl ;
run;
```

Figure 3: Example SAS 9.3 code to retrieve results from a PHREG model

For an introduction on survival analysis see also [11].

Proportion for Overall Response Rate

Objective Response Rate is often analyzed by mean of rate per treatment arm (and/or groups). The SAS code in figure 4 illustrates how to retrieve rate and its confidence intervals using ODS OUTPUT from a PROC FREQ® call.

```
ods output BinomialProp=prop(where=(name1 in('_BIN_' 'XL_BIN' 'XU_BIN'))
                                   keep= TRT01PN name1 nvalue1);
ods output OneWayFreqs=freqs(where=(resp=1)
                                   keep= TRT01PN frequency percent AVALC);
proc freq data=ADRS(where=(PARAMCD="OBJRESP"));
  by TRT01PN;
  table AVALC/ binomial alpha=0.05;
run;
```

Figure 4: Obtaining Objective Response Rate and its Confidence Interval

GRAPHICAL REPRESENTATION

Kaplan Meier Plot or Forest Plot

Because of the nature of the efficacy endpoints used in oncology, the obvious way of presenting graphically the results is the Kaplan Meier plot. In addition, whenever a subgroup analysis also used, a good way of making a graphical synthesis is the use Forest plot (see an example in figure 5), where Hazard Ratio within each subgroup and its confidence intervals are reported and presented graphically together with other information (e.g. median survival, events/censored, etc.).

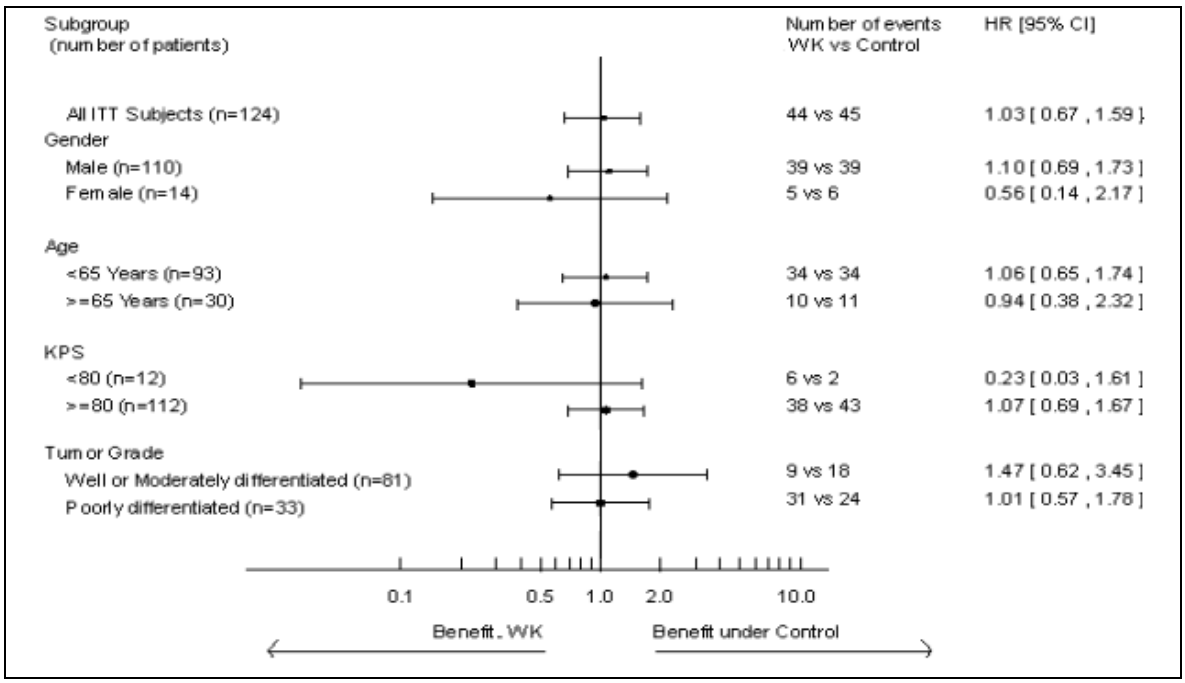

Figure 5: Forest Plot for Subgroups Analysis

Several papers have discussed technical implementation of Forest Plot with either ad-hoc solutions or SAS solutions using the recent added features of Statistical Graphics Procedures and Graph Template Language [12].

Waterfall plot of Tumor Shrinkage

Waterfall plot is a data visualization technique that depicts how a value increases or decreases for parameter of interest and is gaining recognition for the reporting of several types of clinical data [13]. In oncology it is often used to display tumor shrinkage that is the best observed % change of sum of target lesions from baseline. This 'measure' provides an additional (visual) indication of the treatment effect in reducing the tumor mass. In the example in figure 6 each vertical line represents the tumor shrinkage of each single subject enrolled into the study in the two different arms.

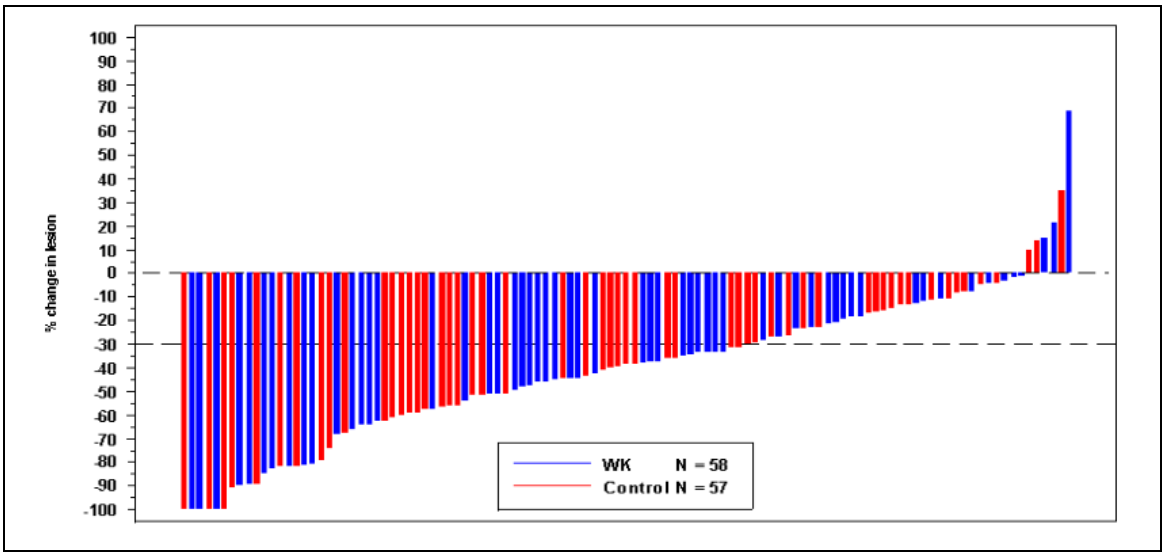

Figure 6: Waterfall Plot showing tumor shrinkage

SENSITIVITY ANALYSIS

Sensitivity analyses may be considered and will serve to evaluate potential bias. For example in a randomized trial efficacy endpoints are usually evaluated on the Intention to Treat (ITT) population, that is the set of all randomized subjects. As a sensitivity analysis you may decide to repeat the analysis of the primary efficacy endpoint, if not all, based on the Per Protocol (PP) Population; in this subset, subjects randomized but not treated as well as subjects with major protocol violations prior to study entry or during the study (e.g. insufficient drug exposure / dose intensity), are not included in the analysis. Whenever PFS is used, a possible sensitivity analysis could be the use of different methods for censoring PFS and the use of an Independent Review Committee (IRC).

The use of Independent Review Committee (IRC)
The purpose of an Independent Review Committee (IRC) is to review all the images (e.g. CT-Scan) 'generated' and used by the Investigator to make an assessment of the tumor response. An IRC is often required when response and /or any time-to-event endpoint based on tumor response assessment (e.g. PFS) are the primary endpoint of the study, especially with pivotal phase III studies.

The IRC should act independently and in a blinded manner (e.g. they will not know the assessment made by Investigator); also usually the review of the images is done in parallel by two independent reviewers (e.g. usually radiologist) and any discrepancy will be re-conciliated by a third evaluator who will act as an "adjudicator" (e.g. he/she will decide what will be the correct assessment). Basically the reviewers will replicate the assessment made by the Investigator and reported in the eCRF; they will therefore identify, classify and measure baseline tumor lesions, then they will repeat the assessment at each further time-point, thus evaluating overall response. Of note, in some trials the outcome (overall response) of the IRC may be used as a primary endpoint.

One challenge in handling IRC is the duplication of the source (investigator vs IRC); usually the information from the IRC assessment came from independent vendor in a separate set of datasets / files. The statistical programmer is then asked to treat the IRC data the same way as for the investigator assessment data and eventually pool the two sources in one set of datasets. For example the new oncology SDTM domains, TU, TR and RS, have standard variables to identify the source of the evaluation (XXEVAL and XXEVALID).

Other Sensitivity Analysis
Other potential sensitivity analysis 'correction' for PFS could be but not limited to:

- accounting for intermittent missing time points of assessment, where for subjects with progression the event date is backdated if the assessment documenting the progression was not performed within the pre-define time-frame (e.g. every 6 weeks)
- accounting for subsequent therapies, where censored subjects are censored on the last tumor assessment date prior to the start of subsequent therapies
- including late deaths such as death occurred after the planned number of weeks from last tumor assessment (usually 12 weeks.)

DATA ISSUES

Several issues in collecting and handling efficacy data in oncology can lead to improper evaluation if not promptly managed. Data should be monitored accurately and checks should be put in place to promptly identify inconsistencies in the collected data. As an example in the evaluation of tumor response when RECIST criteria are used, it is important to check that all the different information used in the evaluation of the response are consistent, so if we have an assessment of the investigator saying the target response was PD, in the clinical database we need to have documentation of such a progression by either having a new lesion recorded in correspondence of the time-point assessed as progression or an increase of at least 20% in the sum of target lesions with respect to nadir or a progression in any of the non-target lesions collected at baseline. Without any surprise you will discover that often this information does not match [14].

A more sophisticated assessment of the appropriateness of the data can be achieved by putting in place periodic medical and statistical supervision. The aim of such a process is to identify potential source of bias that could lead to an incorrect assessment of the efficacy endpoints. For example in a trial where PFS is the primary efficacy endpoint, it is important to monitor the number of PFS events and the tumor assessment schedule, so that we are able to detect early in advance Investigator sites where incorrect schedule occurred more frequently and put in place corrective actions for future enrolled subjects and/or future tumor assessments.

It is of course important in study where OS is one of the efficacy endpoints that follow-up date are keep up to date until the subjects will experience the event or withdrawn the study.

CDISC IMPLEMENTATION

Introduced with SDTM version 3.1.3 [15], "Oncology Disease-specific Therapeutic Area Supplement" contains mapping specifications for three new oncology SDTM domains:

- TU Tumor Identification
- TR Tumor Results
- RS Response

These three domains allow the mapping of tumor assessment information as per RECIST criteria, but the structure could also support the mapping of other methods/criteria.

No specific ADaM CDISC guidance has been released yet. However the ADaM Basic Data Structure for Time-to-event analysis – ADTTE [16], contains specific examples on how to derive and map composite time to event endpoints such as Progression Free Survival.

OTHER POSSIBLE TOPICS

Other possible topics in the evaluation of efficacy endpoints in oncology are but not limited to:

- competing risk analysis [17]
- biomakers analysis

- quality of life and the use of Time to Symptomatic event. For example the LCSS [18]

CONCLUSION

Despite the complexity of the disease, efficacy endpoints in most of the oncology indications are commonly accepted and based on standard criteria.

Managing, deriving and analyzing efficacy endpoints require a clear understanding of the disease and in particular the concept of response / progression.

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RECOMMENDED READING

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