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Efficacy ADaMs in Oncology – Step by Step (Dataset by Dataset)

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ABSTRACT

The CDISC ADaM team has designed the Analysis Data Model (ADaM) standards to support submission to regulatory agencies such as the U.S. Food and Drug Administration (FDA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). Pharmaceutical companies are required to follow the ADaM standards for analysis datasets to ensure a successful submission. The design of analysis datasets is generally driven by the scientific and medical objectives of the clinical trial.

In oncology, efficacy endpoints can be classified as 'with' or 'without' censoring. ADaM guidance recommends storing analysis results for censoring parameters and non-censoring parameters separately; therefore, there is a need to have two ADaM datasets with derived subject-level parameters. This article sheds light on creating analysis datasets for oncology efficacy (specifically for solid tumors) with step-by-step techniques and examples. The proposed methodology can be used for various evaluation criteria.

STUDY PROTOCOL, STATISTICAL ANALYSIS PLAN (SAP), TABLES-LISTINGS-GRAPHICS (TLG) SHELLS

Every clinical trial requires a protocol, which specifies study endpoints. Here are some of the most common efficacy endpoints for clinical trials in oncology (FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", December 2018):

- Overall Survival (OS)
- Time to Progression (TTP)
- Progression Free Survival (PFS)
- Objective Response Rate (ORR)

Most of oncology efficacy endpoints require censoring, but ORR (and some other endpoints) does not.

Statistical analysis plan (SAP) provides detailed descriptions of the study endpoints, their derivation and censoring rules, and the corresponding analysis. The SAP is usually accompanied by Tables, Listings, Graphics (TLG) shells. It clearly identifies how the results of the study, including derived efficacy parameters, are expected to be presented.

SDTM DOMAINS FOR DATA COLLECTION

To capture all relevant information on tumor lesions and the disease response, CDISC has developed a standard data structure, which is described in the Study Data Tabulation Model Implementation Guide (SDTM IG). The respective tumor package includes three SDTM domains: TU, TR, and RS. Although they are all related, each domain has its own distinct purpose, serving to represent the data collected in clinical trials.

- The Tumor Identification (TU) domain stores data that uniquely identifies tumors, which were tracked during the course of a study.

- The Tumor Results (TR) domain contains information about tumors identified in the TU domain in the form of quantitative measurements (e.g. diameter of the lesion in case of solid tumors) and/or qualitative assessments (e.g. results of assessment of non-target or new lesions). These measurements are taken at baseline and at each subsequent timepoint to support the response evaluations. In case of solid tumors, this domain also contains the summation of diameters of Target Lesions.

- The Disease Response (RS) domain holds the results of timepoint response evaluations, determined from domain TU and TR.

ADAM DATASETS REQUIREMENTS

The design of analysis datasets is generally driven by the scientific and medical objectives of the clinical trial. A fundamental principle is that the structure and content of the analysis datasets must support clear, unambiguous communication of the scientific and statistical aspects of the clinical trial. The purpose of ADaM is to provide a framework that enables analysis of the data, while at the same time allowing reviewers and other recipients of the data to have a clear understanding of the data lineage from collection to analysis to results.

ADaM datasets are the authoritative source for all data derivations used in statistical analyses. Standardized analysis datasets and metadata provide great benefits to recipients of the data beyond clear communication and transparency. ADaM datasets incorporate derived and collected data (from various SDTM domains, other ADaM datasets, or any combination thereof) into one dataset that permits analysis with little or no additional programming.

Analysis datasets must be accompanied by metadata and be analysis-ready, i.e. analysis datasets should have a structure and content that allows statistical analysis to be performed with minimal programming ("one proc away").

Survival analysis is a widely used class of statistical methods for studying the occurrence and timing of events. In many clinical studies, an outcome of interest is the time to an event. The unique feature of survival data is that at the end of the observation period, the event of interest may not have occurred for all subjects. Therefore, the time to event for these subjects is said to be censored (i.e., right-censored) and subjects can be censored for various reasons. ADaM standards suggest using a set of Time-to-Event Variables to capture the censoring status for a certain event of interest, the date of censoring, and the reason. This ADaM TTE (time-to-event) analysis dataset structure is designed to support commonly employed time-to-event analysis methods, such as the Kaplan-Meier Estimation and Cox Proportional Hazard Model.

ANALYSIS DATASET ADTR (TUMOR RESULTS)

This ADaM dataset resembles SDTM domain TR (one observation per subject per timepoint per tumor per response assessment criteria per evaluator). After the identification of baseline lesions (Target and Non-Target) at screening, the information about each new lesion reported post baseline is stored in TU. This is represented in ADTR by a pair of records - for date/timepoint of initial appearance and for date/timepoint of unequivocal assessment. Since it is possible for the timepoint of initial appearance of new lesion to be different from the timepoint of unequivocal assessment, two parameters related to New Lesion are recommended. Suggested parameters (if evaluation criteria is RECIST ver 1.1) include:

- 'Longest Diameter (mm)'
- 'Short Axis Diameter (mm)'
- 'Tumor State - Non-Target Lesion'
- 'Tumor State - New Lesion - Initial Appearance'
- 'Tumor State - New Lesion - Unequivocal Assessment'

SDTM domain TR also contains information about sum of diameters of target lesions at each timepoint. The keeping of this type of information (which is timepoint level information) is preferable in the following ADaM dataset – ADTRS. (Please see Appendix 1 for example of ADTR)

ANALYSIS DATASET ADTRS (TIMEPOINT RESPONSES)

This dataset contains timepoint level results. It has one observation per subject per timepoint per parameter per response assessment criteria per evaluator. Possible parameters include:

- 'Timepoint Sum of Target Lesion Diameters: Lymph Nodes (mm)'
- 'Timepoint Sum of Target Lesion Diameters: Non-Lymph Nodes (mm)'
- 'Timepoint Sum of all Target Lesion Diameters (mm)'
- 'Timepoint Target Lesions Response'
- 'Timepoint Non-Target Lesions Response'
- 'Initial Appearance of New Lesions'
- 'Timepoint Overall Response'

Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters (Example: Time point Overall Response by Independent Reviewer).
For the first three parameters above, the result is numeric, so the variable AVAL should be used. For the last four parameters, the result is a character value, so the variable AVALC should be used.

It is important to identify whether specific observations are used in or excluded from the future analysis. The ADaM methodology is to use analysis flags (ANLzzFL, where zz is a two digit numerical numbers, for example, 01, which assigned sequentially to cover different analysis) to indicate observations that fulfill specific requirements for one or more analyses – this is based on methodology provided by the SAP.

For example, based on SAP instruction about censoring rules, the following timepoint evaluations should not be taken into consideration for derivation of PFS and other endpoints:

- if they are after new anti-cancer treatment started
- if they are that are after a certain number of days post last dose date (specified by the SAP)
- if they are after more than one missing adequate assessment
- if they are after the initial response of PD.

Except these cases, the value of analysis flag ANL01FL should be "Y", for the associated records, where ANL01FL is for analysis based on SAP censoring rules.

Sensitivity analyses are commonly performed for the same efficacy endpoints where the censoring rules might be different from those of the primary analysis. In these cases, additional analysis flags are required to capture the records that are included in each sensitivity analysis.

For example, ANL02FL can be created for sensitivity analysis, where the derivation of PFS is determined by different censoring rule of including in derivation the overall time-point evaluations, occurred after more than one missing adequate assessment. Another analysis flag, ANL03FL, can be created for a sensitivity analysis where selection of timepoints results participated in derivation, is done according to the Immune-Related Response Evaluation Criteria.

Another major set of analysis flags is recommended to identify the first occurrence of response of a responder (complete or partial response – 'CR' or 'PR'). Before populating these flag variables, it is important to check the SAP to determine whether confirmation of response is required and what the criteria for confirmation is. For example, if confirmation is required, in the case of a subject with post-baseline sequence of timepoint overall responses of {'SD', 'PR', 'SD', 'SD', 'PR', 'PR', …}, where 'SD' refers to "Stable Disease", the fifth post-baseline evaluation should be marked with such flag (because this is the first confirmed response). For another subject with post-baseline timepoint overall responses of {'SD', 'PR', 'PD'}, no records will be marked because the 'PR' is not confirmed and this subject cannot be considered a responder according to the SAP. Similar to these analysis flags, the additional analysis flags can be created (if needed) for different sensitivity analyses.

It is also recommended to derive an additional variable, PCHG (Percent Change from Baseline), for the parameter 'Timepoint Sum of all Target Lesion Diameters (mm)' for each post-baseline timepoint. It may be used later in the Analysis Dataset for Efficacy (ADEF) for the derivation of Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir (the lowest point), which is presented in a widely used waterfall plot. (Please see Appendix 2 for example of ADTRS)

ANALYSIS DATASET ADEF

This BDS dataset should contain the results of derived efficacy parameters where the censoring is irrelevant. This dataset is created as one observation per subject per subject-level parameter per response assessment criteria per evaluator. Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters (Example: Best Overall Response by Independent Reviewer).

The most common subject level parameters qualified for this ADaM dataset are 'Best Overall Response' (BOR) and 'Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir'. The first parameter is derived for all intent-to-treat subjects. The second parameter is derived only for subjects having baseline and at least one post-baseline measurements of sum of target lesions diameters in ADTRS marked with the corresponding analysis flag. The values of these parameters will be kept correspondingly in variables AVAL or AVALC. The algorithm for derivation of Best Overall Response should be described in the SAP and is not covered in this article. Sometimes, a study requires the calculation of BOR with and without confirmation of response or using different evaluation criteria. In such cases, more than one parameter should be reserved in this dataset. The value of BOR is needed for derivation of ORR, which is a commonly used efficacy endpoint. Previously created ADTRS cannot be used as a substitution for ADEF in derivation of BOR, because in cases of early SD (i.e. subject has an 'SD' as the only post-baseline assessment, which is assessed too early to be count as BOR of 'SD'), absence of post-baseline evaluations, or only one post-baseline evaluation 'PR' when confirmation of response is required. For such cases, the value of BOR can differ from the results of any of the timepoint assessments. Similarly, in case of use of several evaluation criteria, several parameters for 'Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir' (one parameter per criteria) are expected.

Additionally, Disease Control Rate (DCR) is normally included in the study as exploratory endpoint. DCR is the proportion of subjects among Analysis Set, who have the BOR of 'CR', 'PR', or 'SD' (stable disease). In order to calculate ORR or DCR, two more custom flags, EFORFL (Objective Response Flag) and EFDCFL (Disease Control Flag) are suggested to be populated only for the parameter of 'Best Overall Response'. It is also recommended to have one additional variable BORDESC (Best

Overall Response Description) that is populated only for the parameter(s) Best Overall Response and provides the rationale behind assigning the Best Overall Response (examples of possible values: 'Confirmed CR', 'Unconfirmed PR', 'Early SD', etc.). (Please see Appendix 3 for example of ADEF)

The reason for having the EFCBFL (Clinical Benefit Flag) in ADTTE instead of ADEF is explained in the next section.

ANALYSIS DATASET ADTTE

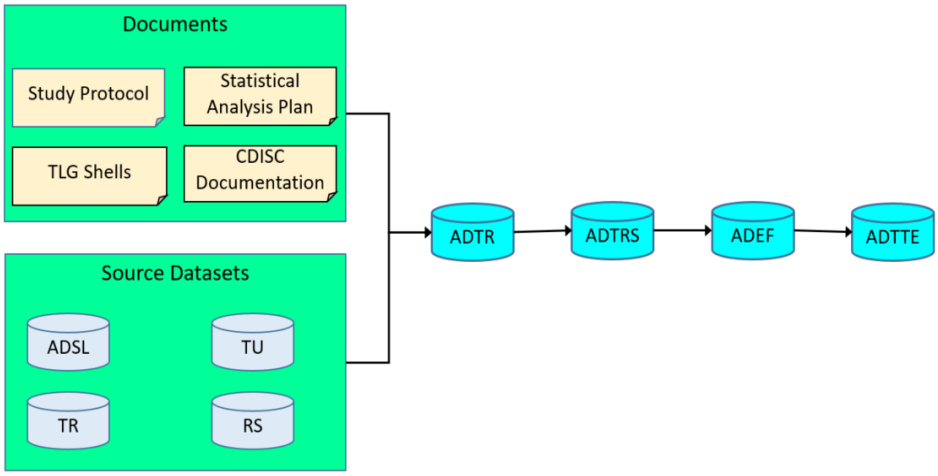
The ADTTE dataset should contain the efficacy parameters requiring censoring. The presence of such parameters is one of the main characteristics of oncology clinical trials. This dataset is created as one observation per subject per time-to-event subject-level parameter per response assessment criteria per evaluator. Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters (Example: Progression Free Survival (months) by Investigator).

As mentioned previously, most efficacy endpoints on oncology are time-to-event with censoring. As an example, there are three commonly used parameters, "Overall Survival Time (Months)", "Progression Free Survival Time (Months)", and "Duration of Response (Months)". The first two parameters are derived for all intent-to-treat subjects and the third one is derived only for subjects having BOR of 'CR' or 'PR' in ADaM dataset ADEF (subjects with EFORFL value of 'Y' in ADEF). Sometimes, a study requires the calculation of time-to-event parameters using different evaluation criteria or using rules according to sensitivity analysis. In such cases, more than one separate parameters should be reserved in this dataset. The values of these parameters will be kept in variables AVAL and CNSR (Censor), following CDISC Guidance "ADaM Basic Data Structure for Time-to-Event Analysis. Version 1.0". Other important variables that should be present in the ADTTE are ADT (Analysis Date), STARTDT (Time to Event Origin Date for Subject), EVNTDESC (Event or Censoring Description), and CNSDTDSC (Censor Date Description). The algorithm for derivation of all these parameters should be described in the SAP and is not covered in this article.

If CBR (Clinical Benefit Rate - the proportion of subjects who have the BOR of 'CR', 'PR', or having durable stable disease among Analysis Set) is one of the study endpoints, it is suggested creating two custom flags, EFDUSDFL (Durable SD Flag) and EFCBFL (Clinical Benefit Flag), for the parameter of 'Progression Free Survival Time'. Durable SD is declared only for subjects having BOR as 'SD' with a duration of SD ≥ xx weeks (where xx should be defined by protocol and SAP). Further, duration of SD is a time-to-event concept using the same PFS censoring rule. In other words, duration of SD equals the progression free survival time for subjects with a BOR of SD. To be noted, EFDUSDFL should be created only for subjects with a BOR of 'SD', and EFCBFL is marked with 'Y' if the subject has value ADEF.EFORFL of 'Y' or value EFDUSDFL of 'Y'. (Please see Appendix 4 for example of ADTTE)

Figure 1 lists the source documents and datasets and the dependency of creating efficacy ADaMs.

Figure 1 Source and Order of Generating Efficacy ADaMs



CONCLUSION

By applying the techniques described in this paper and referencing the source documents (Study Protocol, SAP, TLG shells), and CDISC ADaM Guidance, all required subject-level efficacy parameters in oncology clinical trials cab be derived and stored, regardless of the need for censoring. It is very important to follow the proposed order in creating ADaM datasets for efficacy — ADTR → ADTRS → ADEF → ADTTE — as each dataset in this sequence uses results from the previous ones. This article also describes how to establish several analysis and occurrences flags in ADTRS that aids in the selection of needed timepoint evaluations using different response criteria. The ideas provided in this article are not limited to RECIST criteria, and can be easily adjusted to any tumor-specific evaluation criteria.

APPENDICES

APPENDIX 1. EXAMPLE OF ADTR DATASET

In this example, SDTM TR and TU domains are used as the source data. Each new lesion has break into two records – initial appearance and unequivocal assessment. All tumor assessments are based on independent imaging review per RECIST 1.1. Optional variables EVAL, EVALID, ACPTFL, CRIT can be used for other assessment (e.g. investigator assessment) and criteria.

USUBJID (Unique Subject Identifier)	**ATPT** (Analysis Timepoint)	**TRLNKID** (LinkID)	**PARAM** (Parameter)	**ADT** (Analysis Date)	**AVAL** (Analysis Value)	**AVALC** (Analysis Value (C))	**EVAL** (Evaluator)	**EVALID** (Evaluator Specified)	**ACPTFL** (Accepted Record Flag)	**CRIT** (Criterion)
1111	SCREENING	TNL1	Longest Diameter (mm)	2017-01-01	20		INDEP.	READER1	Y	RECIST1.1
1111	SCREENING	TL1	Short Axis Diameter (mm)	2017-01-02	15		INDEP.	READER1	Y	RECIST1.1
1111	SCREENING	NT1	Tumor State - Non-Target Lesion	2017-01-01		Present	INDEP.	READER1	Y	RECIST1.1
1111	WEEK 6	TNL1	Longest Diameter (mm)	2017-02-15	18		INDEP.	READER1	Y	RECIST1.1
1111	WEEK 6	TL1	Short Axis Diameter (mm)	2017-02-15	13		INDEP.	READER1	Y	RECIST1.1
1111	WEEK 6	NT1	Tumor State - Non-Target Lesion	2017-02-16		Present	INDEP.	READER1	Y	RECIST1.1
1111	WEEK 6	NEW1	Tumor State - New Lesion - Initial Appearance	2017-02-16		Yes	INDEP.	READER1	Y	RECIST1.1
1111	WEEK 12	TNL1	Longest Diameter (mm)	2017-04-01	0		INDEP.	READER1	Y	RECIST1.1
1111	WEEK 12	TL1	Short Axis Diameter (mm)	2017-04-01	17		INDEP.	READER1	Y	RECIST1.1
1111	WEEK 12	NT1	Tumor State - Non-Target Lesion	2017-03-31		Absent	INDEP.	READER1	Y	RECIST1.1
1111	WEEK 12	NEW1	Tumor State - New Lesion - Unequivocal Assessment	2017-03-31		Present	INDEP.	READER1	Y	RECIST1.1
1111	SCREENING	TNL1	Longest Diameter (mm)	2017-01-01	21		INDEP.	READER2		RECIST1.1
1111	SCREENING	TL1	Short Axis Diameter (mm)	2017-01-02	16		INDEP.	READER2		RECIST1.1
1111	SCREENING	NT1	Tumor State - Non-Target Lesion	2017-01-01		Present	INDEP.	READER2		RECIST1.1
1111	WEEK 6	TNL1	Longest Diameter (mm)	2017-02-15	20		INDEP.	READER2		RECIST1.1
1111	WEEK 6	TL1	Short Axis Diameter (mm)	2017-02-15	15		INDEP.	READER2		RECIST1.1
1111	WEEK 6	NT1	Tumor State - Non-Target Lesion	2017-02-16		Present	INDEP.	READER2		RECIST1.1
1111	WEEK 12	TNL1	Longest Diameter (mm)	2017-04-01	0		INDEP.	READER2		RECIST1.1
1111	WEEK 12	TL1	Short Axis Diameter (mm)	2017-04-01	10		INDEP.	READER2		RECIST1.1
1111	WEEK 12	NT1	Tumor State - Non-Target Lesion	2017-03-31		Absent	INDEP.	READER2		RECIST1.1

APPENDIX 2. EXAMPLE OF ADTRS DATASET

In this example, the subject according to protocol should be evaluated once in 6 weeks. However, the subject has more than one missing assessment between Week 6 and Week 24 evaluations. Therefore, results of timepoint evaluation from Week 24 (2017-09-20) cannot be marked with Analysis Flag 01, and as a result of it, the '1st Occurrence of Response' Flag (ANL51FL) cannot be assigned to this timepont, even if the Timepoint Overall Response is 'PR'. ANL02FL and ANL52FL are flags for sensitivity analysis in which we include time-point evaluations occurred after more than one missing adequate assessment, Accordingly, the Timepoint Overall Response of 'PR' on 2017-09-20 is marked with ANL52FL. Again, a set of variables of, ACPTFL, and CRIT from the example of ADTR can be added to ADTRS for different tumor assessment and criteria. Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters.

USUBJID (Unique Subject Identifier)	**ATPT** (Analysis Timepoint)	**PARAM** (Parameter)	**ADT** (Analysis Date)	**AVAL** (Analysis Value)	**AVALC** (Analysis Value (C))	**PCHG** (Percent Change from Baseline)	**ANL01FL** (Analysis Flag 01)	**ANL51FL** (1st Occur of Response Flag)	**ANL02FL** (Analysis Flag 02)	**ANL52FL** (1st Occur of Response – Sensitivity Flag)
2222	SCREENING	Timepoint Sum of all Target Lesion Diameters (mm) by Investigator	2017-04-01	50			Y		Y	
2222	WEEK 6	Timepoint Sum of all Target Lesion Diameters (mm) by Investigator	2017-05-15	40		-20.0	Y		Y	
2222	WEEK 6	Timepoint Target Lesions Response by Investigator	2017-05-15		SD		Y		Y	
2222	WEEK 6	Timepoint Non-Target Lesions Response by Investigator	2017-05-15		Non-CR / Non-PD		Y		Y	
2222	WEEK 6	Initial Appearance of New Lesions by Investigator	2017-05-15		No		Y		Y	
2222	WEEK 6	Timepoint Overall Response	2017-05-15		SD		Y		Y	
2222	WEEK 24	Timepoint Sum of all Target Lesion Diameters (mm) by Investigator	2017-09-20	30		-40.0			Y	
2222	WEEK 24	Timepoint Target Lesions Response by Investigator	2017-09-20		PR				Y	
2222	WEEK 24	Timepoint Non-Target Lesions Response by Investigator	2017-09-20		Non-CR / Non-PD				Y	
2222	WEEK 24	Initial Appearance of New Lesions by Investigator	2017-09-20		No				Y	
2222	WEEK 24	Timepoint Overall Response by Investigator	2017-09-20		PR				Y	Y

APPENDIX 3. EXAMPLE OF ADEF DATASET

This example follows the previous example of ADTRS where two analysis flags were used. EFORFL and EFDCFL flags are generated for each parameter of BOR. EVAL and CRIT can be added to ADEF for different tumor assessment and criteria. However, the acceptance flags ACPTFL are not needed as only the accepted independent imaging review records are used for ADEF. Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters.

USUBJID (Unique Subject Identifier)	**PARAM** (Parameter)	**AVAL** (Analysis Value)	**AVALC** (Analysis Value (C))	**BORDESC** (Best Overall Response Description)	**EFORFL** (Objective Response Flag)	**EFDCFL** (Disease Control Flag)
2222	Best Overall Response by Investigator		SD	Observed SD		Y
2222	Best Overall Response – Sensitivity Analysis by Investigator		PR	Observed PR	Y	Y
2222	Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir by Investigator	-20.0				
2222	Percent Change in Sum of Target Lesion Diameters from Baseline to Post-baseline Nadir - Sensitivity Analysis by Investigator	-40.0				

APPENDIX 4. EXAMPLE OF ADTTE DATASET

This example follows the previous examples of ADTRS and ADEF. This subject has Last Known Alive Date of 2018-10-10 as it presented in the first record of the following table. The death was not recorded for this subject. ANAL01FL in ADTRS is used to mark timepoint evaluations participating in making decision according to SAP. For PFS (according to SAP), this subject is censored due to 'More than one missing adequate assessment'; ANAL02FL in ADTRS is used to mark timepoint evaluations participating in making decision according to the requirement of sensitivity analysis. For PFS (according to the requirements of sensitivity analysis) that subject is also censored but due to 'No Death or PD at Time of Data Cut-off'. Duration of Response is only generated for subject with Best Overall Response of 'PR' and 'CR', therefore, this subject only has one parameter of 'Duration of Response – Sensitivity Analysis (months)'. In this example, durable SD is defined as subjects having BOR as 'SD' with a duration of SD ≥ 23 weeks. Therefore, EFDUSDFL and EFCBFL are not marked with 'Y' for PFS (days) as the duration of SD falls short. EFCBFL='Y' for PFS – Sensitivity Analysis (months) because subject has BOR - Sensitivity Analysis of 'PR' and the derivation of durable stable disease is irrelevant for this subject (it should be derived only in case BOR = 'SD'). Because the qualifiers (like information about Evaluator) are not allowed in BDS structure, this information is now part of parameters.

USUBJID (Unique Subject Identifier)	**PARAM** (Parameter)	**AVAL** (Analysis Value)	**CNSR** (Censor)	**STARTDT** (Time to Event Origin Date for Subject)	**ADT** (Analysis Date)	**EVNTDESC** (Event or Censoring Description)	**CNSDTDSC** (Censor Date Description)	**EFDUSDFL** (Durable SD Flag)	**EFCBFL** (Clinical Benefit Flag)
2222	Overall Survival (months)	18.23	1	2017-04-04	2018-10-10	No Death at Time of Data Cut-off	Last Known Alive Date		
2222	Progression Free Survival (months) by Investigator	1.38	1	2017-04-04	2017-05-15	More than one missing adequate assessment'	Date of the Last Adequate Overall Tumor Assessment by SAP		
2222	Progression Free Survival – Sensitivity Analysis (months) by Investigator	5.59	1	2017-04-04	2017-09-20	No Death or PD at Time of Data Cut-off	Date of the Last Adequate Overall Tumor Assessment by requirements of Sensitivity Analysis		Y
2222	Duration of Response – Sensitivity Analysis (months) by Investigator	0.03	1	2017-09-20	2017-09-20	No Death or PD at Time of Data Cut-off	Date of the Last Adequate Overall Tumor Assessment by requirements of Sensitivity Analysis		

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