PharmaSUG 2019 - Paper PO-130

When Biomarker Drives Primary Endpoint: An Oncology Case Study of SDTM Design Using Multiple Myeloma.

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ABSTRACT

Oncology studies are often driven by imaging, which led to the creation of the tumor-specific TU and TR domains in the SDTM IG 3.1.2, where the capture of the scan details and results is described. These domains usually are linked to the RS Domain, which contains the overall tumor response in an oncology study. There are, however, a few oncology conditions like multiple myeloma, which are not driven by imaging but by specific biomarkers. This information would be captured in the LB Domain, in contrast to TU and TR.

Biomarkers play an important role in indicating normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In multiple myeloma, serum free light chain (SFLC), serum and urine protein electrophoresis (SPEP and UPEP), and immunofixation are the key biomarker-related tests that define the standard response criteria.

In this paper, we would like to share how we have mapped the efficacy biomarker tests in the LB SDTM domain, as well as the safety-related tests, while maintaining a clear demarcation between both by using LBCAT or LBSCAT, and other additional variables allowed under the findings observation class (SDTM v1.4). This helps to maintain the distinction and also ease the design of the efficacy- and safety-related ADaM datasets. At the SDTM level, we have also leveraged the RELREC to create traceability between the efficacy data in the LB to that captured in the RS Domain.

INTRODUCTION

About 30,700 patients will be diagnosed, in the United States this year, with multiple myeloma (MM) and 1 in 132 has a lifetime risk of developing this disease (The American Cancer Society medical and editorial content team, n.d.). In general, plasma cells make the antibodies (also called immunoglobulins) that help the body attack and kill germs, thus protecting from us from infections. Plasma cells are found mainly in the bone marrow. But, if these plasma cells become cancerous and proliferate out of control, the disease is called multiple myeloma.

In this paper we would like to discuss how multiple myeloma disease markers are different from other cancers, where the bulk of the response information is captured using lab tests in LB. We plan to illustrate how the link is established between LB and RS using RELREC, to establish transparency and aid in better ADaM design.

HOW IS MM DIFFERENT FROM OTHER CANCERS?

Unlike solid tumors (which fall under RECIST Criteria) that are usually diagnosed mainly by imaging (CT scan, PET scan), multiple myeloma involves the following array of tests:

Tests that are part of usual routine in any clinical trial but of significance in MM:

- Blood counts
- Calcium levels
- Kidney function tests

Test results that are specific to MM, unlike other cancers:

- Smoldering multiple myeloma (SMM): People with SMM are at risk for developing MM
- Light chain amyloidosis
- Waldenstrom macroglobulinemia (WM)

Along with the above tests, bone marrow biopsy and imaging to an extent help keep track of MM. As seen in Table 1, the response criteria depend on various laboratory tests as per the guidelines of International Myeloma Working Group, which are captured in LB. As you can see, the LB domain would not only contribute to Safety but heavily to Efficacy, as well.

Standard Response Criteria	Serum and Urine Protein Electrophoresis and Immunofixation	Serum Free Light Chains (FLC)	Bone Marrow	Plasmacytoma or Bone Lesions
Stringent CR	Negative immunofixation of serum and urine	Normal FLC ratio (0.26-1.65)	Absence of clonal plasma cells by IHC (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)	Disappearance of any soft tissue plasmacytomas
Complete Response (CR)	Negative immunofixation of serum and urine	In patients whose only measurable disease is abnormal serum FLC level, normal FLC ratio (0.26-1.65)	< 5% plasma cells	Disappearance of any soft tissue plasmacytomas
Very Good Partial Response (VGPR)	Serum and urine M-component detectable by immunofixation but not by electrophoresis ***or*** ≥ 90% reduction in serum M-component ***and*** urine M-component < 100 mg/24 h	In patients whose only measurable disease is abnormal serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels	n/a	If present at baseline >90% decrease in the SPD of a soft tissue plasmacytoma compared with baseline
Partial Response (PR)	≥ 50% reduction of serum M-protein ***and*** Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 h	If serum and urine M-protein are not measurable, a decrease of ≥ 50% in the difference between involved and uninvolved FLC levels	If serum and urine M-protein and serum FLC are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline plasma cell percentage was ≥ 30%	If present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is required
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M protein ***and*** Reduction in 24-hour urine M-protein by 50%-89%	n/a	n/a	If present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or PD			
Progressive Disease (PD)	Increase of 25% from lowest confirmed response value in: Serum M-component (absolute increase must be ≥ 0.5 mg/dL). If serum M-component is ≥ 5 mg/dL at baseline increase of ≥ 1 g/dL from baseline ***and/or*** Urine M-component (absolute increase must be ≥ 200 mg/24 h)	In patients without measurable serum and urine M-protein levels, increase of 25% from lowest confirmed response value in difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)	If serum and urine M-protein and serum FLC are not measurable, increase of 25% from lowest response value in bone marrow plasma cell percentage (absolute increase must be ≥ 10%)	Definite development of new bone lesions or soft tissue plasmacytomas ***or*** ≥50% increase from nadir in SPD of >1 lesion ***or*** ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis

Table 1. International Myeloma working Group (IMWG) Mapping Response Criteria (Kumar, et al., 2016)

LB

In the LB domain, we are mapping different biomarker tests for the subject ABC-001. In Table 2 below, the biomarker tests including serum and urine protein electrophoresis and electrophoresis, Serum free light chains, bone marrow aspirate analytics, which play a vital role in establishing the efficacy, are captured. The LBGRPID variable helps us in grouping the relevant tests that contribute to Efficacy. Please note that the records with LBCAT value of “Chemistry” do not have the LBGRPID value generated so that these Safety related tests are distinguished from those contributing to Efficacy.

DOMAIN	LBTEST	LBTESTCD	LBCAT	LBSCAT	LBORRES	LBORRESU	VISIT	LBDTC	LBNRIND
LB	Monoclonal Protein spike	MSPIKE	Electrophoresis	SPEP	2.7	g/dL	Baseline	2019-01-01	ABNORMAL
LB	Monoclonal Protein spike	MSPIKE	Electrophoresis	SPEP	5.2	g/dL	Cycle 1	2019-01-15	ABNORMAL
LB	Urine Monoclonal Protein spike	MSPIKE	Electrophoresis	UPEP	2.7	g/dL	Baseline	2019-01-01	ABNORMAL
LB	Urine Monoclonal Protein spike	MSPIKE	Electrophoresis	UPEP	5.2	g/dL	Cycle 1	2019-01-15	ABNORMAL
LB	Serum Kappa Light Chain	KLCFR	Immunology	SFLC	91.8	mg/L	Baseline	2019-01-01	ABNORMAL
LB	Serum Kappa Light Chain	KLCFR	Immunology	SFLC	142.8	mg/L	Cycle 1	2019-01-15	ABNORMAL
LB	Serum Lambda Light Chain	LLCFR	Immunology	SFLC	5.9	mg/L	Baseline	2019-01-01	ABNORMAL
LB	Serum Lambda Light Chain	LLCFR	Immunology	SFLC	2.9	mg/L	Cycle 1	2019-01-15	ABNORMAL
LB	Serum Light Chain Ratio	S-LCR	Immunology	SFLC	15.559	RATIO	Baseline	2019-01-01	ABNORMAL
LB	Serum Light Chain Ratio	S-LCR	Immunology	SFLC	49.241	RATIO	Cycle 1	2019-01-15	ABNORMAL
LB	Urine Protein Random	PROT	Electrophoresis	UPEP	40	mg/dL	Baseline	2019-01-01	HIGH
LB	Urine Protein Random	PROT	Electrophoresis	UPEP	28	mg/dL	Cycle 1	2019-01-15	HIGH
LB	Bone Marrow	BNMRW	Bone marrow local	BM ASPIRATE	75	%	Baseline	2019-01-01	
LB	Bone Marrow	BNMRW	Bone marrow local	BM ASPIRATE	90	%	Cycle 1	2019-01-15	

Table 2: LB SDTM domain with various response biomarker tests

RS

The RS SDTM domain is rather simple, as shown in Table 3. It consists of the confirmed response as captured in the CRF. However, RSDTC was not captured in the CRF and is derived in this example as the earliest date of all the efficacy-relevant tests done for the subject, at a visit. So, we pick the earliest date of all the tests in LB with LBGRPID matching with the RSLNKGRP in RS, which in this example is 2019-01-15. Usually TU and TR domains are interlinked to RS and contribute to RSDTC derivation but in this example LB is used to derive RSDTC.

DOMAIN	RSLNKGRP	RSTEST	RSSTRESC	VISIT	RSDTC
RS	2	Confirmed Response	Progressive Disease	Cycle 1	2019-01-15

Table 3: RS SDTM domain with various responses, including the biomarker test responses

RELREC

RELREC is the most underplayed domain in SDTM although it is the key which unlocks and interconnects the rest of the SDTM domains. In the RS domain shown in Table 3, the RSDTC was derived using the data captured in LB. In Table 4, the variables IDVAR and RELTYPE illustrate how they act as a key that connects these two domains, with a one-to-many relationship.

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
LB		LBGRPID		Many	A
RS		RSLNKGRP		One	A

Table 4: RELREC establishing the link between LB and RS

ADRS

In the ADRS example shown in Table 5, we have created new parameters based on the analysis needs to show the transparency that was missing, on how the investigators have derived the response of “Progressive Disease” in Table 3. Also, the parameters “Current sflc status” and “Current spep status” show the different individual responses derived under the IMWG response criteria. For example, as per the criteria for SFLC, we have calculated absolute difference and percentage change of difference between kappa and lambda serum light chains. Based on the calculated absolute and percentage values, we eventually derive the response values under the current SFLC status (CSFLC) PARAM. In a similar way, we have also generated current SPEP and UPEP status values. Thus, ADRS is created by using the relevant tests in LB and showing how it translates into the overall response captured in RS.

PARAM	PARCAT1	AVAL	AVALC	AVISIT	ADT
SERUM KAPPA LIGHT CHAIN	IMMUNOLOGY	9.18		Baseline	1-Jan-19
SERUM LAMBDA LIGHT CHAIN	IMMUNOLOGY	0.59		Baseline	1-Jan-19
SERUM LIGHT CHAIN RATIO	IMMUNOLOGY	15.559		Baseline	1-Jan-19
ABSOLUTE DIFFERENCE IN INVOLVED AND UNINVOLVED	IMMUNOLOGY	8.59		Baseline	1-Jan-19
PERCENT CHANGE FOR DIFFERENCE IN INVOLVED AND UNINVOLVED	IMMUNOLOGY	0		Baseline	1-Jan-19
SERUM KAPPA LIGHT CHAIN	IMMUNOLOGY	14.28		Cycle 1	15-Jan-19
SERUM LAMBDA LIGHT CHAIN	IMMUNOLOGY	0.59		Cycle 1	15-Jan-19
SERUM LIGHT CHAIN RATIO	IMMUNOLOGY	15.559		Cycle 1	15-Jan-19
ABSOLUTE DIFFERENCE IN INVOLVED AND UNINVOLVED	IMMUNOLOGY	13.99		Cycle 1	15-Jan-19
PERCENT CHANGE FOR DIFFERENCE IN INVOLVED AND UNINVOLVED	IMMUNOLOGY	62.9		Cycle 1	15-Jan-19
CURRENT SFLC STATUS	IMMUNOLOGY		PD	Cycle 1	15-Jan-19
MONOCLONAL PROTEIN SPIKE	ELECTROPHORESIS	0.93		Baseline	1-Jan-19
MONOCLONAL PROTEIN SPIKE	ELECTROPHORESIS	1.23		Cycle 1	15-Jan-19
CURRENT SPEP STATUS	ELECTROPHORESIS		SD	Baseline	1-Jan-19
CURRENT SPEP STATUS	ELECTROPHORESIS		SD	Cycle 1	15-Jan-19
MONOCLONAL PROTEIN SPIKE, 24 HRS	ELECTROPHORESIS	500		Baseline	1-Jan-19
MONOCLONAL PROTEIN SPIKE, 24 HRS	ELECTROPHORESIS	620		Cycle 1	15-Jan-19
CURRENT UPEP STATUS	ELECTROPHORESIS		PR	Cycle 1	15-Jan-19
OVERALL CONFIRMED RESPONSE	RESPONSE		PD	Cycle 1	15-Jan-19

Table 5: ADRS with various new parameters showing how the 'overall response' was determined

CONCLUSION

We would like to conclude that it is important to understand the intricacies of the data before mapping the CRF variables to SDTM domains rather than being constrained by the generic guidelines of the SDTM IG. In this paper, we have used the LB domain to capture most of the response-related biomarker tests rather than using the IG-specified TR and RS domain, but we did maintain the traceability between RS and LB domains, using the RELREC. Thus, RELREC acts as a bridge that can connect various domains so that the FDA reviewer or statistician can combine the domains, if required to get the complete picture.

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ACKNOWLEDGEMENTS

We would like to acknowledge Avani Kaja and Balavenkata Pitchuka for their valuable suggestions to this paper.

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