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Analysis of Oncology Studies for Programmers and Statisticians

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ABSTRACT
Compared to other therapeutic studies, oncology studies are generally complex and difficult for programmers and statisticians. There is more to understand and to know such as different clinical study types, specific data collection points and analysis. In this paper, programmers and statisticians will learn oncology specific knowledge in clinical studies and will understand a holistic view of oncology studies from data collection, CDISC datasets, and analysis. Programmers and statisticians will also find out what makes oncology studies unique and learn how to lead the programming and statistical teams.

The paper will cover three different sub types and their response criteria guidelines. The first sub type, Solid Tumor study, usually follows RECIST (Response Evaluation Criteria in Solid Tumor) or irRECIST (immune-related RECIST). The second sub type, Lymphoma study, usually follows Cheson. Lastly, Leukemia studies follow study specific guidelines (e.g., IWCLL for Chronic Lymphocytic Leukemia).

Programmers and statisticians will learn how to create SDTM tumor specific datasets (RS, TU, TR), what SDTM domains are used for certain data collection, and what Controlled Terminology (e.g., CR, PR, SD, PD, NE) will be applied. They will also learn how to create time to event ADaM datasets from SDTM domains and how to use ADaM datasets to derive efficacy analysis (e.g., OS, PFS, TTP, ORR, DFS).

Finally, the paper will show how standards (e.g., response criteria guidelines and CDISC) will streamline clinical trial artefacts development in oncology studies and how end to end clinical trial artefacts development can be accomplished through this standards-driven process.

INTRODUCTION OF ONCOLOGY CLINICAL TRIAL STUDIES
Oncology studies are complex and difficult for programmers and statisticians to conduct since oncology studies demand different way of collecting, measuring and analyzing data. Oncology studies are different from other studies in the following area.

- Tumor measurements and their response to drug
- Oncology-specific measurements for response criteria (e.g., Liver and Spleen Enlargement, Bone Marrow Infiltrate and Blood Counts)
- Oncology-dagnosis measurements (e.g., immunophenotype, performance status on ECOG, staging)
- Toxicity (Lab and AE)
- Time to Event Analysis (e.g., OS, PFS, TTP and ORR)

There are three types of oncology clinical trial studies.

- Solid Tumor
- Lymphoma
- Leukemia Response

The solid tumor studies usually follow RECIST 1.0 or 1.1 on tumor response evaluation criteria. Lymphoma studies usually follow Cheson 1997 or 2007. Leukemia studies have four different types and each type follow different response evaluation criteria - Acute Lymphoblastic Leukemia (ALL) following National Comprehensive Cancer Network (NCCN) Guideline versions 1 2012, Acute Myeloid Leukemia (AML) following IWAML 2003, Chronic Lymphocytic Leukemia (CLL) following IWCLL 2008, Chronic Myeloid Leukemia (CML) following CML ESMO Guideline. This paper will use Chronic Lymphocytic Leukemia as an example. In addition, immunotherapy follow irRECIST (immune related RECIST) 2008.

ONCOLOGIC SPECIFIC CDISC STANDARDS
CDISC recently developed Oncology-related standards both in SDTM, ADaM and Control CT.

SDTM
- TU: Tumor Identification
- TR: Tumor Results
- RS: Response
ADaM
  • ADTTE: Time to Event ADaM datasets

CT
  • Response Criteria
    o CR – Complete Response
    o PR – Partial Response
    o SD – Stable Disease
    o PD – Progression Disease
    o NE – Not Evaluable
    o NonCR/NonPD - Non Complete Response/Non Progressive Disease
  • Tumor Measurements
    o LDIAM – Longest Diameter
    o SUMDIA – Sum of Diameter
    o LPERP – Longest perpendicular of Diameter
    o AREA – Area
    o SUMAREA – Sum of Area
    o TUMSTATE – Tumor State
  • Response
    o TRGRESP – Target Response
    o NTRGRESP – Non-target Response
    o NEWLPROG – New Legion Progression
    o OVRLRESP – Overall Response
    o BESTRESP – Best Response

SOLOID TUMOR DATA COLLECTION AND SDTM IMPLEMENTATION

INTRODUCTION OF SOLID TUMOR
Solid Tumor are masses of abnormal tissue that originate in organs or soft tissues that typically do not include fluid areas and cysts (e.g., breast cancer, liver cancer, pancreatic cancer and melanoma)

INTRODUCTION OF RECIST
RECIST is Response Evaluation Criteria in Solid Tumor and there are two versions - 1.0 and 1.1. Most recent studies follow the recent version, RECIST 1.1, released on October 2008. The paper will follow RECIST 1.1.

SOLID TUMOR SPECIFIC MEASUREMENT
A lesion is any abnormality in the tissue of an organism and can be described as a cut, an injury, an infected area or a tumor. In oncology study, lesions are tumors. They are divided into three types for the purpose of their measurements.
  • Target lesions
  • Non-target lesions
  • New lesions

TARGET LESIONS
In clinical trials following RECITS 1.1, target lesions selection at baseline follows as
  • Measurable
  • 5 lesions total
  • Maximum of 2 lesions per organ
  • Representing all involved organs
  • Quantitative measurements
    o Longest diameter of lesions
    o Short axis of Lymph nodes
    o Sum of diameters (both lesions and lymph nodes)

NON TARGET LESIONS
Non-target lesions selection at baseline follows as
  • All other lesions beside target lesions
  • Qualitative measurements – present, absent or unequivocal progression.
NEW LESIONS
New lesions at post-baseline follow as
- Any lesions that are newly found at post-baseline.
- Either quantitative or qualitative measurements.

RESPONSE ASSESSMENT AT GIVEN VISIT ACCORDING TO RESIST 1.1
A response of the drug at given cycle will be determined by the followings.
- SUMDIA of target lesions (TR)
- Non-target lesions assessment (TR)
- New lesions (TR)

Examples of response assessment at given visit according to RECIST 1.1 are introduced in Table 1 and 2.

Table 1 - SDTM TR (Tumor Response) dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>TRGRID</th>
<th>TRLINKID</th>
<th>TRTESTCD</th>
<th>TRTEST</th>
<th>TRORRES</th>
<th>TRORRESU</th>
<th>VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-01-001</td>
<td>Target</td>
<td>T01</td>
<td>LDIAM</td>
<td>Longest Diameter</td>
<td>10</td>
<td>mm</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>Target</td>
<td>T02</td>
<td>LDIAM</td>
<td>Longest Diameter</td>
<td>10</td>
<td>mm</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>Target</td>
<td>T03</td>
<td>LDIAM</td>
<td>Longest Diameter</td>
<td>15</td>
<td>mm</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>Target</td>
<td>SUMDIAM</td>
<td></td>
<td>Sum of Diameter</td>
<td>35</td>
<td>mm</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>Non-Target</td>
<td>NT01</td>
<td>TUMSTATE</td>
<td>Tumor State</td>
<td>PRESENT</td>
<td>Cycle 1</td>
<td></td>
</tr>
<tr>
<td>001-01-001</td>
<td>Non-Target</td>
<td>NT02</td>
<td>TUMSTATE</td>
<td>Tumor State</td>
<td>PRESENT</td>
<td>Cycle 1</td>
<td></td>
</tr>
<tr>
<td>001-01-001</td>
<td>Non-Target</td>
<td>NT03</td>
<td>TUMSTATE</td>
<td>Tumor State</td>
<td>PRESENT</td>
<td>Cycle 1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - SDTM RS (Response) dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>RSTESTCD</th>
<th>RSTEST</th>
<th>RSCAT</th>
<th>RSORRES</th>
<th>VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-01-001</td>
<td>TRGRESP</td>
<td>Target Response</td>
<td>RECIST 1.1</td>
<td>PR</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>NTRGRESP</td>
<td>Non-target Response</td>
<td>RECIST 1.1</td>
<td>NonCR/NonPD</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>NEWLPROG</td>
<td>New Lesion Progression</td>
<td>RECIST 1.1</td>
<td>N</td>
<td>Cycle 1</td>
</tr>
<tr>
<td>001-01-001</td>
<td>OVRLRESP</td>
<td>Overall Response</td>
<td>RECIST 1.1</td>
<td>PR</td>
<td>Cycle 1</td>
</tr>
</tbody>
</table>

Key points to note in the table 1 and 2 are:
- Row 4 of table 1 determines row 1 of table 2
- Row 5 to 8 of table 1 determines row 2 of table 2
- No indication of new lesion of table 1 determines row 3 of table 2
- In table 2, row 1 to 3 will determine row 4.

LYMPHOMA DATA COLLECTION AND SDTM IMPLEMENTATION

INTRODUCTION OF LYMPHOMA
Lymphoma is cancer that starts in lymph node.

INTRODUCTION OF CHESON
An international working group (IWG) published guidelines for response measurements on non-Hodgkin’s Lymphoma (NHL) in 1999. In 2007, Cheson 2007 was published with the recommendations from other lymphoma studies and with the addition of more advanced diagnosis.

LYMPHOMA SPECIFIC MEASUREMENT
In lymphoma clinical trials, lesions are enlarged lymph nodes, nodal masses and extra nodal masses, and a lymph node lesion is considered measurable if its length of longest diameter is greater than 15 mm or that of its greatest perpendicular axis is greater than 10 mm by CT scan.

Lymphoma studies following Cheson 2007 will collect the following measurements.
- Tumor measurements in CT / MRI
- Lymph Node, Nodal Masses and Extra Nodal Masses
- PET scan on lesions (to distinguish viable tumor from fibrosis)
• Bone Marrow Assessment
• Spleen and Liver Enlargement Assessment

SDTM IMPLEMENTATION ON CHESON 2007 MEASUREMENT
Cheson 2007 measurements are implemented in follow SDTM domains.
• Tumor measurement in SPD by CT SCAN (TR)
• Tumor assessment by PET (TR)
• Bone Marrow Infiltrate (LB and FA)
• Spleen and Liver Enlargement (PE)
These measurements will be assessed to determine a response (RS) at each cycle.

LEUKEMIA DATA COLLECTION AND SDTM IMPLEMENTATION
INTRODUCTION OF LEUKEMIA
Leukemia is a cancer that usually begins in the bone marrow and result in high numbers of abnormal white blood cells (lymphocytes).

There are four types of Leukemia:
• Acute Lymphoblastic Leukemia (ALL) - a rapid increase in the number of immature white blood cells.
• Acute Myeloid Leukemia (AML) - a rapid increase in the number of abnormal white blood cells in bone marrow that interfere with the production of normal blood cells.
• Chronic Lymphocytic Leukemia (CLL) - excessive buildup of relatively mature, but still abnormal, white blood cells
• Chronic Myeloid Leukemia (CML) - the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

The paper will focus only on CLL and the progress of CLL follows as.
1. Mutation of stem cells in bone marrow
2. Abnormal WBC (CLL cells) are formed
3. CLL cells increase in bone marrow
4. CLL cells increase in blood

INTRODUCTION OF IWCLL
IWCLL 2008 defines the diagnosis of CLL.
• Blood: > 5 x 10^9 B lymphocytes/L (5000 / uL) in blood.
• Immunophenotype (flow cytometry) of Lymphocytes:
  o A presence of T-cell antigen CD5
  o A presence of B-cell surface CD19, CD20, CD23
  o Low surface immunoglobin CD20, CD79b

LEUKEMIA SPECIFIC MEASUREMENT
The following will be collected according to IWCLL 2008.
• Tumor measurements in CT / MRI – Lymph Node
• Blood Lymphocytes
• Bone Marrow Assessment
• Spleen and Liver Enlargement Assessment
• Blood Count Assessment – Neutrophils, Platelets and Hemoglobin
• Immunophenotype (flow cytometry)
• Performance Status by ECOG (Eastern Cooperative Oncology Group)
• Staging – Assessment of disease progress for treatment plan
  o Rai: 0 (low risk), 1 & 2 (intermediate risk), 3 (high risk)
  o Binet: A, B, C
Immunophenotype, ECOG and staging measurements are considered additional since they don’t determine response at each cycle.

SDTM IMPLEMENTATION ON IWCLL 2008 MEASUREMENT
IWCLL 2008 measurements are implemented in follow SDTM domains.
- Tumor measurement in SPD by CT SCAN (TR)
- Bone Marrow Infiltrate (LB and FA)
- Spleen and Liver Enlargement (PE)
- Blood Counts (LB)
These measurements will be assessed to determine a response at given visit.

**ONCOLOGY SPECIFIC ENDOPOINTS AND TIME-TO-EVENT ADAM IMPLEMENTATION**

The most common efficacy end points in oncology studies are

- OS (Overall Survival)
  - Primary
  - Time from randomization until death
  - Intent-to-treat population
- PFS (Progression Free Survival)
  - Primary
  - Time from randomization until objective tumor progression or death
  - Death is NOT censored.
  - Often the preferred end points in lymphoma studies (i.e., incurable histologic subtypes).
- TTP (Time to Progression)
  - Time from randomization until objective tumor progression
  - Death is censored.
- ORR (Objective Response Rate)
  - Rate of partial and complete responses to non-responses.
  - Until 1970s, FDA usually approved cancer drugs based on ORR.
  - Usually used in Phase II trials of novel new agents.
- Response Duration
  - Time from CR or PR until relapse or progression

ORR, DFS, PFS, TTP, ORR and Response Duration are based on tumor assessments. The oncology specific endpoints are expressed in ADaM Time to Event datasets as in Table 3.

Table 3 - ADTTE dataset with Progression Free Survival (PFS) parameter

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>TRTP</th>
<th>PARAM</th>
<th>AVAL</th>
<th>STARTDT</th>
<th>ADT</th>
<th>CNSR</th>
<th>EVNTDESC</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-01-001</td>
<td>Study Drug</td>
<td>Progression Free Survival (Days)</td>
<td>452</td>
<td>2011-01-01</td>
<td>2011-03-01</td>
<td>0</td>
<td>PROGRESSIVE DISEASE</td>
</tr>
<tr>
<td>001-01-002</td>
<td>Control</td>
<td>Progression Free Survival (Days)</td>
<td>338</td>
<td>2011-02-01</td>
<td>2011-01-05</td>
<td>1</td>
<td>LOST OT FOLLOW-UP</td>
</tr>
<tr>
<td>001-01-003</td>
<td>Control</td>
<td>Progression Free Survival (Days)</td>
<td>212</td>
<td>2011-02-05</td>
<td>2011-09-05</td>
<td>0</td>
<td>DEATH</td>
</tr>
<tr>
<td>001-01-004</td>
<td>Study Drug</td>
<td>Progression Free Survival (Days)</td>
<td>463</td>
<td>2011-03-20</td>
<td>2012-06-25</td>
<td>1</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>001-01-005</td>
<td>Study Drug</td>
<td>Progression Free Survival (Days)</td>
<td>67</td>
<td>2011-03-26</td>
<td>2011-06-01</td>
<td>0</td>
<td>PROGRESSIVE DISEASE</td>
</tr>
</tbody>
</table>

Key points to note in the table 3 is:
- Row 1, 3, 5 are NOT censored.

**STANDARDS DRIVEN ONCOLOGY STUDIES**

**ONCOLOGY SPECIFIC STANDARDS**

The paper introduces oncology specific standards.

- Response Criteria guidelines
  - RECIST 1.1
  - Cheson 2007
  - IWCLL 2008
- Data Collection
  - Tumor measurement
  - Bone Marrow Assessment
- Spleen and Liver Enlargement Assessment
- Blood Counts
- Response Assessment
- CDISC
  - SDTM: TU, TR, RS
  - ADaM: TTE
  - CT: CR, PR, PD, SD, LDIAM, SUMDIA, LPERP, AREA, SUMAREA, TUMSTATE TRGRESP, NTRGRESP, NEWLPROG
- Analysis: OS, PFS, TTP, ORR, DFS

Since we can standardize response criteria guidelines, data collection, SDTM, ADaM and Analysis, we can create oncology-specific end to end clinical trial artefacts development process. As seen in Figure 1, Lymphoma studies will select standards from each process and those interlinked standards will create standards in the next process. So, oncologic specific standards can drive clinical trial artefacts from protocol, collection, SDTM, ADaM and analysis.

CONCLUSION
CDISC introduces the new tumor domains in SDTM and Time to Event datasets in ADaM, but it is also very important for programmers and statisticians to understand therapeutic characteristics and methods in Oncology. Response criteria such as RECIST 1.1, Cheson 2007, IWCLL 2008 introduce how to collect oncology specific data and analyze responses in oncology studies. The combination of response criteria and CDISC can streamline the end to end standards-driven oncology clinical trial process.

REFERENCES
New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)
Revised Response Criteria for Malignant Lymphoma (Cheson 2007)
Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines (IWCLL 2008)
ADaM Implementation Guide, Version V 1.1
Analysis Data Model, Version 2.1 (ADaM 2.1)
ADaM Basic Data Structure for Time-to-Event Analyses
SDTM Version 1.3
SDTM Implementation Guide Version 3.2
CDER Guidance for Industry – Clinical Trial Endpoints for the approval of Cancer Drugs and Biologics
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