Science For A Better Life

Deconstructing ADRS

Tumor Response Analysis Data Set

Steve Almond / November 2016

Agenda

- Introduction
- Basic Analysis Needs
- Different Response Criteria and Assessors
- Summary of Derived Parameters and Missing Data
- From SDTM to Derived ADaM Parameters
- Other Considerations
- Conclusions … and Epilogue

Introduction

- Efficacy analyses in oncology trials include responder and time-to-event endpoints
- SDTM domains for tumor-related data
  - Tumor Identification (TU), Tumor Results (TR), Disease Response (RS)
- Purpose: to describe an ADaM data set which supports responder type of analysis, i.e., based on some response algorithm (RECIST v1.0 or v1.1, mRECIST, Cheson, etc.)

Basic Analysis Needs: Summary & Data

- Primary analysis: objective tumor response rate (ORR)

	Treatment A (N=XX)		Treatment B (N=XX)	
	n (%)	[95% CI]	n (%)	[95% CI]
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]

SUBJID	TRTP	AVALC
1	Treatment A	Responder
2	Treatment A	Non Responder
3	Treatment B	Responder
4	Treatment B	Non Responder
⋮	⋮	⋮

Objective Response Explained

- Objective response: subject is “Responder” if best overall response (BOR) is complete response (CR) or partial response (PR)

- Other types of response: subject is “Non Responder” if BOR is one of:
  - stable disease (SD)
  - progressive disease (PD)
  - not evaluable (NE)

Summarizing ORR and BOR

- Primary analysis: objective tumor response rate (ORR)
- Secondary analysis: best overall response (BOR)

	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Best Overall Response				
Complete Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Partial Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Stable Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Progressive Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Not Evaluable	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]

Data: Objective Response and Best Overall Response Observations

SUBJID	PARAMCD	PARAM	AVAL	AVALC
1	OBJRESP	Objective Response	9	Responder
1	BESTRESP	Best Overall Response	1	Partial Response
2	OBJRESP	Objective Response	9	Responder
2	BESTRESP	Best Overall Response	0	Complete Response
3	OBJRESP	Objective Response	10	Non Responder
3	BESTRESP	Best Overall Response	2	Stable Disease
4	OBJRESP	Objective Response	10	Non Responder
4	BESTRESP	Best Overall Response	3	Progressive Disease
⋮	⋮	⋮	⋮	⋮

More Specific Analysis: Different Response Criteria

- Primary analysis: objective tumor response rate (ORR) *according to mRECIST*
  - subjects evaluated against two criteria: modified RECIST for hepatocellular carcinoma (HCC) and RECIST 1.1

Response with respect to mRECIST	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]

Response with respect to RECIST 1.1	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Best Overall Response				
Complete Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Partial Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Stable Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Progressive Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Not Evaluable	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]

Data: Different Response Criteria

SUBJID	RSCAT	PARAMCD	AVAL	AVALC
1	mRECIST HCC	OBJRESP	9	Responder
1	mRECIST HCC	BESTRESP	1	Partial Response
1	RECIST 1.1	OBJRESP	10	Non Responder
1	RECIST 1.1	BESTRESP	2	Stable Disease
2	mRECIST HCC	OBJRESP	9	Responder
2	mRECIST HCC	BESTRESP	0	Complete Response
2	RECIST 1.1	OBJRESP	9	Responder
2	RECIST 1.1	BESTRESP	1	Partial Response
3	mRECIST HCC	OBJRESP	10	Non Responder
3	mRECIST HCC	BESTRESP	2	Stable Disease
3	RECIST 1.1	OBJRESP	10	Non Responder
3	RECIST 1.1	BESTRESP	2	Stable Disease
4	mRECIST HCC	OBJRESP	10	Non Responder
4	mRECIST HCC	BESTRESP	3	Progressive Disease
4	RECIST 1.1	OBJRESP	10	Non Responder
4	RECIST 1.1	BESTRESP	2	Stable Disease
⋮	⋮	⋮	⋮	⋮

More Specific Analysis: Different Assessors

- Primary analysis: objective tumor response rate (ORR) according to mRECIST *by independent assessment*
  - subjects evaluated against two criteria: mRECIST for HCC and RECIST 1.1, *both by independent assessor and investigator*

Response with respect to mRECIST – Independent Assessment	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
⋮	⋮	⋮	⋮	⋮

Response with respect to RECIST 1.1 – Independent Assessment	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
⋮	⋮	⋮	⋮	⋮

Response with respect to mRECIST – Investigator	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
⋮	⋮	⋮	⋮	⋮

Response with respect to RECIST 1.1 – Investigator	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
⋮	⋮	⋮	⋮	⋮

Data: Different Assessors

SUBJID	RSEVAL	RSCAT	PARAMCD	AVALC
1	INDEPENDENT ASSESSOR	mRECIST HCC	OBJRESP	Responder
1	INDEPENDENT ASSESSOR	mRECIST HCC	BESTRESP	Partial Response
1	INDEPENDENT ASSESSOR	RECIST 1.1	OBJRESP	Non Responder
1	INDEPENDENT ASSESSOR	RECIST 1.1	BESTRESP	Stable Disease
1	INVESTIGATOR	mRECIST HCC	OBJRESP	Non Responder
1	INVESTIGATOR	mRECIST HCC	BESTRESP	Stable Disease
1	INVESTIGATOR	RECIST 1.1	OBJRESP	Non Responder
1	INVESTIGATOR	RECIST 1.1	BESTRESP	Stable Disease
2	INDEPENDENT ASSESSOR	mRECIST HCC	OBJRESP	Responder
2	INDEPENDENT ASSESSOR	mRECIST HCC	BESTRESP	Complete Response
2	INDEPENDENT ASSESSOR	RECIST 1.1	OBJRESP	Responder
2	INDEPENDENT ASSESSOR	RECIST 1.1	BESTRESP	Partial Response
2	INVESTIGATOR	mRECIST HCC	OBJRESP	Responder
2	INVESTIGATOR	mRECIST HCC	BESTRESP	Partial Response
2	INVESTIGATOR	RECIST 1.1	OBJRESP	Responder
2	INVESTIGATOR	RECIST 1.1	BESTRESP	Partial Response
3	INDEPENDENT ASSESSOR	mRECIST HCC	OBJRESP	Non Responder
3	INDEPENDENT ASSESSOR	mRECIST HCC	BESTRESP	Stable Disease
3	INDEPENDENT ASSESSOR	RECIST 1.1	OBJRESP	Non Responder
3	INDEPENDENT ASSESSOR	RECIST 1.1	BESTRESP	Stable Disease
3	INVESTIGATOR	mRECIST HCC	OBJRESP	Non Responder
3	INVESTIGATOR	mRECIST HCC	BESTRESP	Stable Disease
3	INVESTIGATOR	RECIST 1.1	OBJRESP	Non Responder
3	INVESTIGATOR	RECIST 1.1	BESTRESP	Stable Disease
⋮	⋮	⋮	⋮	⋮

Derived Parameters – Summary

- Another derived parameter: Disease Control (PARAMCD='DISCTRL')
  - Best overall response = CR or PR or SD
- Total number of derived observations = 12N
  - PARAMTYP = 'DERIVED'

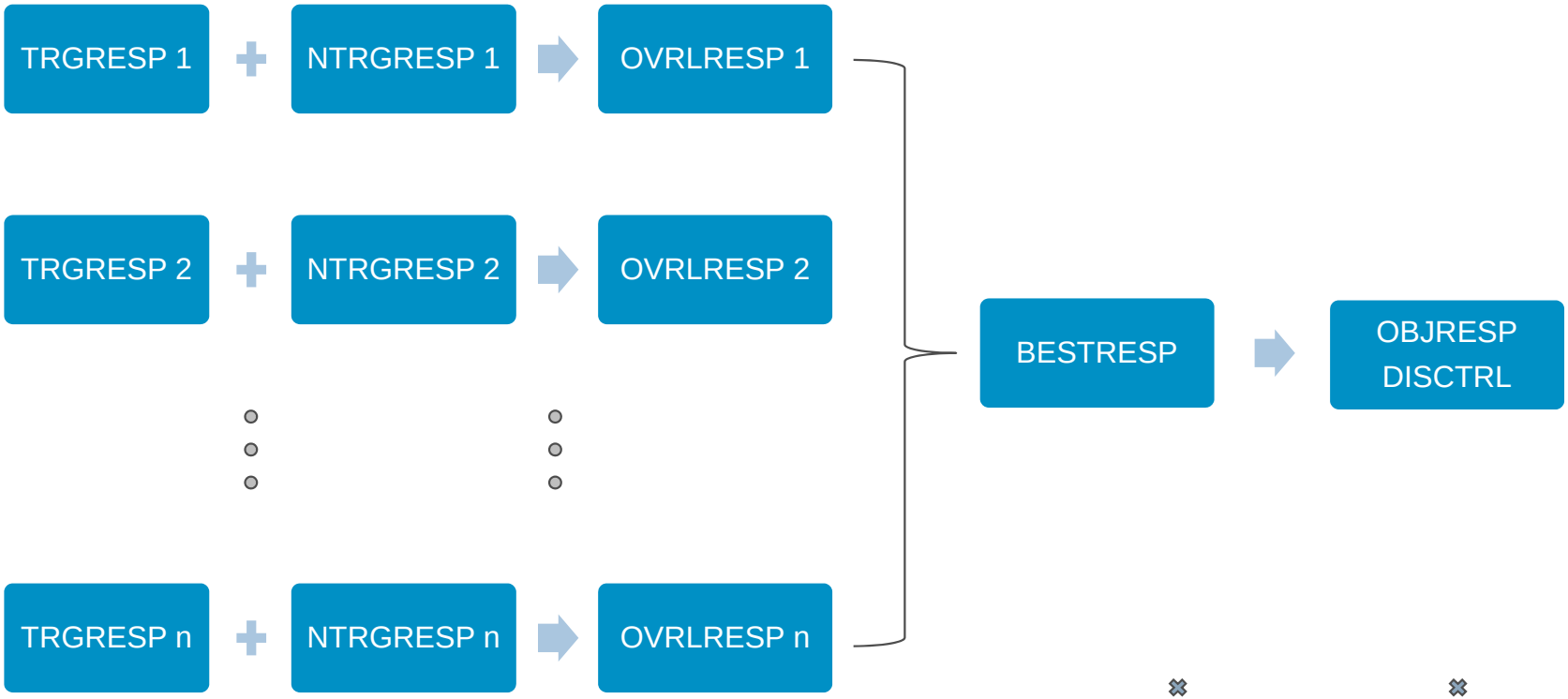
Missing Data

- Include dummy observations if missing response data
  - i.e., no on-treatment assessments available
  - BESTRESP → AVALC='Missing'
  - OBJRESP, DISCTRL → AVALC='Non Responder'

	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Best Overall Response				
Complete Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Partial Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Stable Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Progressive Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Not Evaluable	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Missing	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]

From SDTM to Derived ADaM Parameters

- Target Response (TRGRESP), Non-target Response (NTRGRESP), and Overall Response (OVRLRESP) *by visit* also included in ADRS from SDTM RS



RSEVAL

Data: All Observations for a Subject

SUBJID	RSEVAL	RSCAT	VISIT	PARAMCD	PARAMTYP	AVALC
1	INDEPENDENT ASSESSOR	mRECIST HCC		OBJRESP	DERIVED	Responder
1	INDEPENDENT ASSESSOR	mRECIST HCC		BESTRESP	DERIVED	Partial Response
1	INDEPENDENT ASSESSOR	mRECIST HCC		DISCTRL	DERIVED	Responder
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 2	TRGRESP		SD
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 2	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 2	OVRLRESP		SD
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 4	TRGRESP		PR
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 4	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 4	OVRLRESP		PR
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 6	TRGRESP		PR
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 6	NTRGRESP		PD
1	INDEPENDENT ASSESSOR	mRECIST HCC	CYCLE 6	OVRLRESP		PD
1	INDEPENDENT ASSESSOR	RECIST 1.1		OBJRESP	DERIVED	Non Responder
1	INDEPENDENT ASSESSOR	RECIST 1.1		BESTRESP	DERIVED	Stable Disease
1	INDEPENDENT ASSESSOR	RECIST 1.1		DISCTRL	DERIVED	Responder
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 2	TRGRESP		SD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 2	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 2	OVRLRESP		SD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 4	TRGRESP		SD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 4	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 4	OVRLRESP		SD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 6	TRGRESP		SD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 6	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	RECIST 1.1	CYCLE 6	OVRLRESP		SD
1	INVESTIGATOR	mRECIST HCC		OBJRESP	DERIVED	Non Responder
1	INVESTIGATOR	mRECIST HCC		BESTRESP	DERIVED	Stable Disease
1	INVESTIGATOR	mRECIST HCC		DISCTRL	DERIVED	Responder
1	INVESTIGATOR	mRECIST HCC	CYCLE 2	TRGRESP		SD
1	INVESTIGATOR	mRECIST HCC	CYCLE 2	NTRGRESP		NonCR/NonPD
1	INVESTIGATOR	mRECIST HCC	CYCLE 2	OVRLRESP		SD
1	INVESTIGATOR	mRECIST HCC	CYCLE 4	TRGRESP		PD
1	INVESTIGATOR	mRECIST HCC	CYCLE 4	NTRGRESP		PD
1	INVESTIGATOR	mRECIST HCC	CYCLE 4	OVRLRESP		PD
1	INVESTIGATOR	mRECIST HCC	CYCLE 6	TRGRESP		PD
1	INVESTIGATOR	mRECIST HCC	CYCLE 6	NTRGRESP		PD
1	INVESTIGATOR	mRECIST HCC	CYCLE 6	OVRLRESP		PD
1	INVESTIGATOR	RECIST 1.1		OBJRESP	DERIVED	Non Responder
1	INVESTIGATOR	RECIST 1.1		BESTRESP	DERIVED	Stable Disease
1	INVESTIGATOR	RECIST 1.1		DISCTRL	DERIVED	Responder
1	INVESTIGATOR	RECIST 1.1	CYCLE 2	TRGRESP		SD
1	INVESTIGATOR	RECIST 1.1	CYCLE 2	NTRGRESP		NonCR/NonPD
1	INVESTIGATOR	RECIST 1.1	CYCLE 2	OVRLRESP		SD
1	INVESTIGATOR	RECIST 1.1	CYCLE 4	TRGRESP		SD
1	INVESTIGATOR	RECIST 1.1	CYCLE 4	NTRGRESP		NonCR/NonPD
1	INVESTIGATOR	RECIST 1.1	CYCLE 4	OVRLRESP		SD
1	INVESTIGATOR	RECIST 1.1	CYCLE 6	TRGRESP		PD
1	INVESTIGATOR	RECIST 1.1	CYCLE 6	NTRGRESP		NonCR/NonPD
1	INVESTIGATOR	RECIST 1.1	CYCLE 6	OVRLRESP		PD

Other Considerations: Independent Assessors

- Multiple independent assessors, whose interpretations may differ
- Variable RSEVALID differentiate between independent readers
  - e.g., “READER 1” vs. “READER 2”
- If adjudication necessary, the flag RSACPTFL=‘Y’ is used to identify which assessor the adjudicator agrees with
- Data from a single assessor used for the derived parameters (BESTRESP, OBJRESP, DISCTRL)

Data: Multiple Independent Assessors

SUBJID	RSEVAL	RSEVALID	RSACPTFL	RSCAT	VISIT	PARAMCD	PARAMTYP	AVALC
1	INDEPENDENT ASSESSOR			mRECIST HCC		OBJRESP	DERIVED	Responder
1	INDEPENDENT ASSESSOR			mRECIST HCC		BESTRESP	DERIVED	Partial Response
1	INDEPENDENT ASSESSOR			mRECIST HCC		DISCTRL	DERIVED	Responder
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 2	TRGRESP		SD
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 2	TRGRESP		SD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 2	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 2	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 2	OVRLRESP		SD
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 2	OVRLRESP		SD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 4	TRGRESP		PR
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 4	TRGRESP		SD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 4	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 4	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 4	OVRLRESP		PR
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 4	OVRLRESP		SD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 6	TRGRESP		PR
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 6	TRGRESP		SD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 6	NTRGRESP		PD
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 6	NTRGRESP		NonCR/NonPD
1	INDEPENDENT ASSESSOR	READER 1	Y	mRECIST HCC	CYCLE 6	OVRLRESP		PD
1	INDEPENDENT ASSESSOR	READER 2	N	mRECIST HCC	CYCLE 6	OVRLRESP		SD
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
1	INVESTIGATOR			RECIST 1.1	CYCLE 6	OVRLRESP		PD
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Other Considerations: Interim Analyses

- While subject is still ongoing, adjudication is only carried out under certain circumstances (e.g., if disease progression in question); otherwise this occurs once subject participation is complete

- SAP should specify how to handle, e.g., use the “worst” independent assessment
  - Include flag in data set to indicate which observations used in such a case
  - Later adjudication may select different observation

Other Considerations: Variations in Response Criteria

- Different criteria types (RECIST v1.0, RECIST v1.1, mRECIST, etc.)
- Confirmation may or may not be needed for CR & PR, depending on criteria type and primary endpoint
- Even if confirmation required, summaries may include BOR of “Unconfirmed” CR and PR

	Treatment A (N=XX)		Treatment B (N=XX)	
Objective Tumor Response Rate				
Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Non Responder	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Best Overall Response				
Complete Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Unconfirmed Complete Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Partial Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Unconfirmed Partial Response	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Stable Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Progressive Disease	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Not Evaluable	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]
Missing	xx (xx.x%)	[xx.x%,xx.x%]	xx (xx.x%)	[xx.x%,xx.x%]

Conclusions

- Primary analysis for an oncology trial might involve numerous qualifiers on the endpoint being used
  - Underlying ADaM data set contains many observations used for similar, supporting analyses
- Qualifying variables follow from SDTM domain, but important to understand the relationship between RS records and the derived ADRS parameters
- Consider basic analysis needs first to focus on the elements required from ADRS and then expand as necessary depending on other aspects of study design

Epilogue

- Improper use of PARCAT1 in paper
- PARAMCD / PARAM vs. qualifying variables
- Variations in data from assessors, e.g.,
  - best overall response might be provided in RS domain
  - adjudication may be distinct set of observations
- Therapy area user guides
  - breast cancer (TAUG-BrCa), prostate cancer (TAUG-PrCa)

- CDISC Webinar – January 12, 2017

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Thank you!

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