

Adapting to Adaptive

Angelo Tinazzi, Ashish Aggarwal, Steve Wong - Cytel Inc

ABSTRACT

The use of Adaptive designs is becoming quite popular and well-perceived by the regulatory agencies such as the FDA in the US. “Adaptation” can occur in different fashion and potentially make studies more efficient (e.g. shorter duration, fewer patients) more likely to demonstrate an effect of the drug if one exists, or more informative.

The aim of this presentation is to illustrate a case where an adaptive design was used in a Phase III oncology pivotal study having Overall Survival as a primary end-point. The particular adaptation implemented was an un-blinded Sample Size Re-estimation (SSR) that applied a promising zone approach. The main focus will be how the adaptive design impacted the SDTM modelling, the design of some ADaM datasets (i.e. those containing the time-to-event endpoints and therefore using ADTTE ADaM model) and later on how some mapping and analysis decisions were described in both the study and analysis reviewer guide.

WHAT IS AN ADAPTIVE DESIGN

An *adaptive design clinical study* is defined as a study that includes a *prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study* (FDA)¹.

What can be adapted?

- Eligibility Criteria
- Randomization Allocation Ratio
- Doses in Dose Finding Studies or Arm Removal / Addition
- Sample Size
- Early Trial Termination for Efficacy or Futility

Practical Implications of Changes due to use of Adaptive Design⁷:

- Data Collection and Cleaning to allow data availability for Interim Analysis
- Protocol Amendments
- Changes in EDC and/or Randomization System
- Simulations and Predictions
- Avoid «Operational Bias» by making sure only ‘corrected’ people are unblinded
- Availability of an Independent Statistical Committee and Data Monitoring Committee

IMPACT OF CHANGES IN SDTM TRIAL DESIGN MODEL

- It may require a change in any Trial Design Model (TDM)
- Current SDTM-TDM includes TA (Trial Arms), TE (Trial Elements), TV (Trial Visits), TI (Trial Inclusion / Exclusion), TS (Trial Summary)

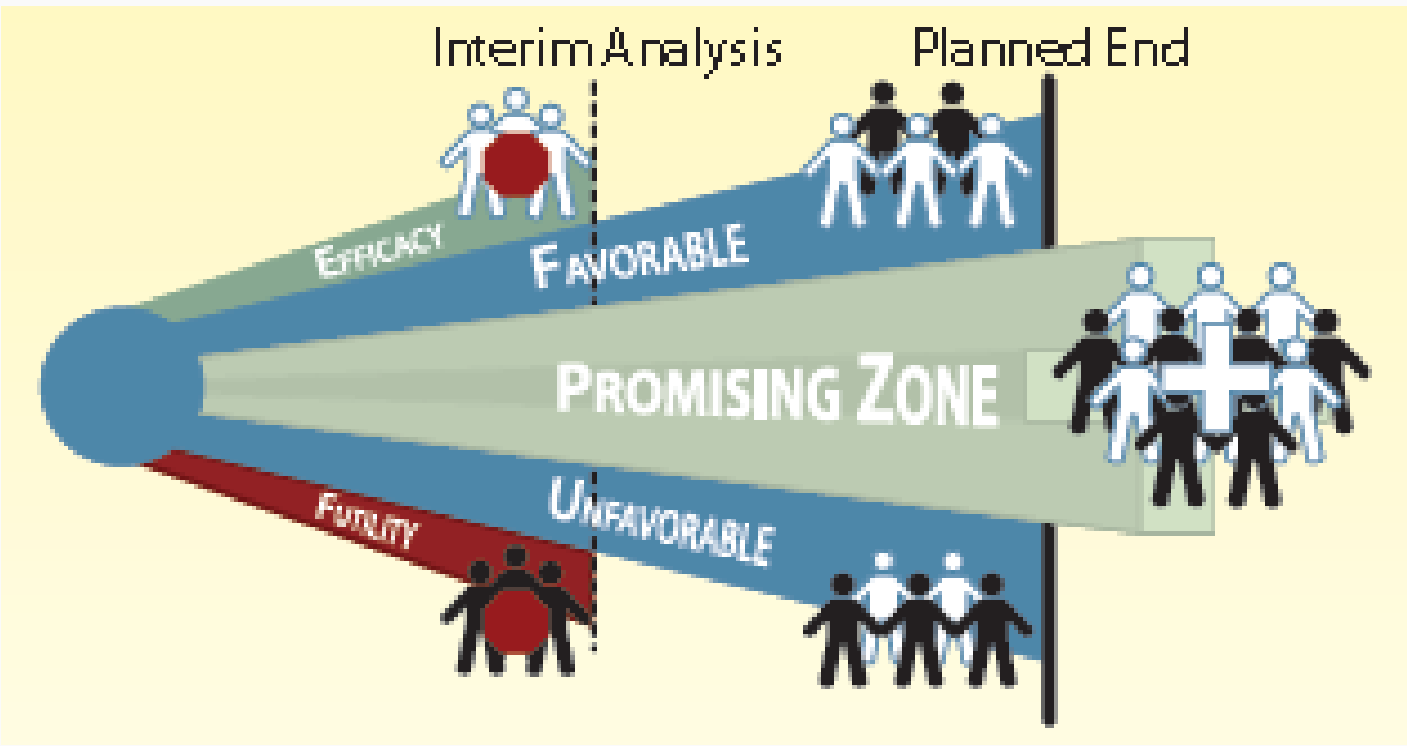
TDM	Adaptation Example 1 Arm(s) Addition	Adaptation Example 2 Change Eligibility Criteria for Age
TA	<u>YES</u> Addition of new arm(s)	<u>NO</u>
TE	<u>YES</u> New elements for added arm(s)	<u>NO</u>
TV	<u>NO</u> if New arm(s) has same schedule	<u>NO</u>
TI	<u>NO</u> if New arm(s) has same eligibility criteria	<u>YES</u> New eligibility/version of age criteria
TS	<u>YES</u> Information about new arm(s)	<u>YES</u> Change in Age Span



Except for TIVERS in TI domain, it is not possible to *clearly identify to what the study looked like at the time of enrolment*⁸

CASE: A PHASE III DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL FOR FIRST-RELAPESED OR REFRACTORY MYELOID LEUKEMIA (AML) – ‘PLANNED’ ADAPTATION OF SAMPLE SIZE

- Overall Survival (OS) as primary endpoint
- Power study to detect 0.71 HR Ctrl / Trt (sample size N=450)
- Interim Analysis when 50% of required events occurred
 - If sample size increase is required type-1 error should be controlled by using Cui, Hung and Wang⁶ weighted statistic modified for survival data
 - In this model the estimate (log-rank) at stage 1 (interim analysis) is combined with estimate at stage 2 (final analysis) by a pre-specified weight



- HR at interim analysis ≤ 0.74 NO CHANGE
- HR at interim analysis **0.74-0.86 INCREASE SAMPLE SIZE**
- HR at interim analysis ≥ 0.86 NO CHANGE

«Adapting» CDSIC-SDTM

SUPPDM					
	USUBJID	QNAM	QLABEL	QVAL	QORIG
1	-101-101001	AGEGROUP	IVRS Age Group	< 60 years	eDT
2	-101-101001	DISSTAT	IVRS Disease Status	Refractory	eDT
3	-101-101001	DMCFL	Patient in 2012 efficacy analysis	Y	eDT
4	-101-101001	LOCATION	IVRS Location	US	eDT

A DM supplemental qualifier item ‘flagging’ patients included in the ‘sample’ analyzed during interim analysis

«Adapting» CDSIC-ADaM

ADEFFTTE										
	SUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC	CNSDTS	
1	101001	Overall Survival (Months)	OS	16.8310...	15AUG2011	07JAN2013	0	DEATH		
2	101001	Overall Survival as per Interim analysis cut-off (Months)	OSI	12.0644	15AUG2011	15AUG2012	1	NO EVENT	CUT OFF DATE APPLIED AT INTERIM ANALYSIS	
3	101002	Overall Survival (Months)	OS	8.44838...	12SEP2011	25MAY2012	0	DEATH		
4	101002	Overall Survival as per Interim analysis cut-off (Months)	OSI	8.44838...	12SEP2011	25MAY2012	0	DEATH		

An ADaM BDS-TTE⁹ dataset with two OS (Overall Survival) parameters, Overall Survival as per final analysis cut-off (PARAMCD=OS) and Overall Survival as per interim-analysis cut-off (PARAMCD=OSI)

«Adapting» Output Programming

$T2$ (the adjusted log-rank test statistics Cui formula) = $\sqrt{t1} \underline{Z1} + \sqrt{(1-t1) \{ \sqrt{t2^*} \underline{Z2^*} - \sqrt{t1_{actual}} \underline{Z1} \} / \sqrt{t2^* - t1_{actual}}}$

The SAS code for Kaplan Meier Survival Method used

```
ods output trendtests=<Output Dataset>(where=(test='Log-Rank')) ;
proc lifetest data=ADAM.ADEFFTTE(where=(PARAMCD="<OS | OSI>"))
  method=KM alphaqt=0.05;
  time AVAL*CNSR(1) ;
  strata /group=TRT01PN trend;
run;
```

- $\underline{Z1}$ log-rank statistics based on all data at the interim analysis (PARAMCD=‘OSI’)
 - $\underline{Z2^*}$ log-rank statistics based on all data at final analysis (PARAMCD=‘OS’)
- The outputs of the two models (the log-Rank Z statistics) are then combined and weighted by a pre-defined weight:
- $t1$: 0.5
 - $t1^*$: Actual Number of Events for Interim Analysis (based on final data)
 - $t2^*$: Final Number of Events / Planned Number of events

«Adapting» Reviewer Guide

Study Data Reviewer Guide (SDRG): explain the reviewer how to identify patients analyzed during the interim analysis

Section 3: Subject Data Description

For the re-creation of the primary endpoint as per re-calculated interim analysis, patients included in 2012 interim analysis can be identified with SUPPDM where QNAM=“DMCFL” (Patient in 2012 efficacy analysis) and QVAL=“Y”

Analysis Data Reviewer Guide (ADRG): explain the reviewer which analysis dataset and records have to be used to re-calculate the ‘estimate’ as per interim analysis cut-off and as per final analysis cut-off

Section 5: Analysis Dataset Descriptions

OSI / Overall Survival as per Interim analysis cut-off (Months) – This is the *primary efficacy endpoint as per interim analysis cut-off. This is applicable only to the 382 patients part of the 2012 interim analysis (ADSL.DMCFL). It is re-calculated using data available at the time of final db lock but applying the cut-off date applied at the time of the interim analysis (15AUG2012)*

CONCLUSIONS

- Operational implications of Adaptive Designs should be carefully evaluated
- Current SDTM IG does not fully support changes during the course of the study i.e. linking subjects to a specific version of the protocol
- Other adaptations such as those required by our study can be ‘easily’ implemented with a bit of ‘imagination’ without breaking the rules
- Documentation is a key to maintain traceability

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