Creating a Synthetic Control Arm (SCA) from Previous Clinical Trials: Applications to Establishing Early Endpoints as Indicators of Overall Survival in Relapsed/Refractory Acute Myeloid Leukemia

Donald Berry,[1] Steven Blotner,[2] Lin-Chi Chen,[2] Somnath Sarkar,[2] PJ Allen,[3] Philip Beineke,[3] Mark Chandler,[3] Ruthanna Davi,[3] Michael Elashoff,[3] David Lee,[3] Steven Schwager,[3] Salome Zan[3]
[1] Department of Biostatistics, The University of Texas MD Anderson Cancer Center and Berry Consultants; [2] Roche Innovation Center - New York; [3] Medidata Solutions

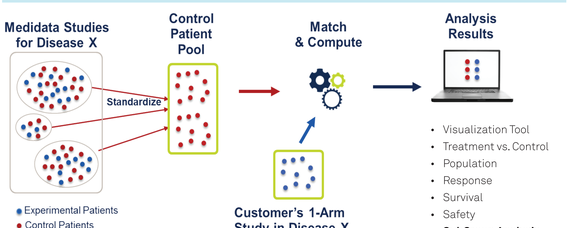
Contact
Ruthanna Davi
rdavi@mdsol.com

Introduction to SCA

Clinical trials are hampered by absence of control group

- Single-arm efficacy trials are often necessary, especially early phase, because of
  - Ethical or practical reasons
  - Difficult oncology indications
  - Rare diseases or populations (e.g., pediatrics)
- Expensive "go" decisions are often made on meager evidence
  - Published papers with few metrics and unknown statistical bias from patient baseline characteristics and response definitions; unique features of historical trials; differences in time period and location
- This contributes to later-phase failure rate

SCA leverages prior control patient data to improve evaluation of outcomes of single-arm trials



SCA has benefits across the development cycle

- Reduced scientific uncertainty in evaluating efficacy in early-phase trials
  - Arms are precisely matched at subject level
  - Control group can be large (2-10 X size of treatment group)
  - Bias from time, site, and study-specific effects is minimized
  - Exploratory subgroup analysis is enabled
- Improved selection of compounds for next phase
- Improved design of subsequent trials
- Reduced failure rates in phase II and III
- While there is no perfect substitute for a randomized control arm, SCA is a customized historical control

Objectives

- To assess the feasibility of constructing an appropriate control arm data set, a Synthetic Control Arm (SCA), by aggregating patient-level data from historical clinical trials.
- To reduce biases common to historical control studies by using the SCA in estimation of the treatment effect.
- To evaluate response association with survival as an exploratory analysis.

Experimental Arm Characteristics

Expansion cohort of idasanutlin in RR-AML

- 16 Response Evaluable RR-AML Patients out of 21 Enrolled
- Prespecified primary efficacy endpoint is confirmed CR/CRi
  - Confirmed CR: Achieved CR and the next response (minimum of 28 days after) was also CR
  - Unconfirmed CR: Achieved CR but did not meet definition of Confirmed CR
  - Confirmed CRi: Did not achieve CR, achieved CRi and the next response (minimum of 28 days after) was also CRi
  - Unconfirmed CRi: Did not achieve CR, Achieved CRi but did not meet definition of Confirmed CRi
- ≤2 Prior Regimens (induction + consolidation = one regimen)
- Age ≥18
- ECOG = 0 or 1

Methods for SCA

Patient-level data selected from standardized data repository of over 3000 historical trials in many therapeutic areas are used for constructing SCAs

Oncology data available for SCA (May 2017)

Indication	Subjects	Studies
Lung Cancer	27,252	67
Breast Cancer	19,520	39
Prostate Cancer	12,660	46
Colorectal Cancer	11,965	27
Multiple Myeloma	9,301	52
Kidney Cancer	7,388	31
Lymphoma	6,854	46
Other Oncology Indications[1]	102,374	583
Total	**197,314**	**891**

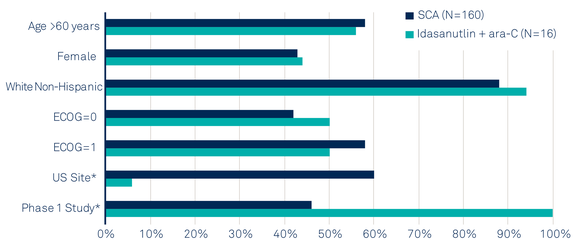
1. Other Oncology Indications includes: Leukemia, Liver Cancer, Melanoma, Brain Cancer, Gastric Cancer, Neutropenia, Myelodysplastic Syndrome, Ovarian Cancer, Oral Cancer, Pancreatic Cancer, Sarcoma, Esophageal Cancer, Mesothelioma, Mucositis, Head and Neck Cancer, Bladder Cancer, Squamous Cell Carcinoma, Biliary Tract Cancer, Endometrial Cancer, Thyroid Cancer, Bone Metastases, Neuroblastoma, Multiple Conditions, and Other

340 patients from 7 historical AML trials available

- 10 SCA patients were selected (while blinded to outcome) to match each of the 16 Idasanutlin + ara-C treated patients on ≥ 4 of 6 baseline criteria at the individual patient level
  - Age above or below 60 years
  - Sex
  - White non-Hispanic or not
  - ECOG score
  - US site or not
  - Phase of study
- Historical trial patients from both standard of care & experimental arms were used to increase sample size
  - Historical experimental therapies had no apparent effect compared to standard of care

Results

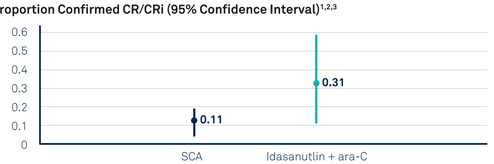
Comparison of Baseline Demographics between Experimental Arm and SCA



* No relationships between US Site or Phase 1 Study status and outcome were evident.

Efficacy Results

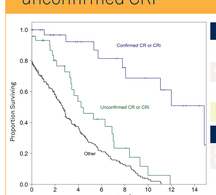
Proportion Confirmed CR/CRi (95% Confidence Interval)[1,2,3]



1. Exploratory analysis not intended to show statistical comparison
2. Response Evaluable Population displayed; ITT response for Idasanutlin + ara-C arm is 24%
3. CI calculated using bootstrap methods

Sensitivity analyses using alternative matching methods yielded consistent results

Patients who achieved confirmed CR or confirmed CRi had better overall survival than those who achieved unconfirmed CR or unconfirmed CRi[1]

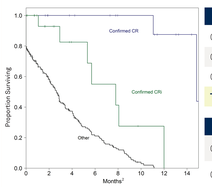


	N	Events	Median
Confirmed CR or Confirmed CRi	39	9	14.8
Unconfirmed CR or Unconfirmed CRi	47	25	4.2
Other	254	172	2.6
Total	340	206	

	Hazard Ratio (95% CI)
Confirmed CR or Confirmed CRi vs. Unconfirmed CR or Unconfirmed CRi	0.10 (0.04, 0.27)
Confirmed CR or Confirmed CRi vs. Other	0.09 (0.04, 0.21)
Unconfirmed CR or Unconfirmed CRi vs. Other	0.54 (0.35, 0.84)

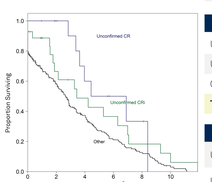
1. Includes all available patients: 340 patients from 7 historic AML trials
2. Long term follow-up began after the treatment period, at study day 56

Patients who achieved confirmed CR had better overall survival than those who achieved confirmed CRi[1]



	N	Events	Median
Confirmed CR	16	2	14.8
Confirmed CRi	23	7	7.8
Other	254	172	2.6
Total	293	181	

	Hazard Ratio (95% CI)
Confirmed CR vs. Confirmed CRi	0.03 (0.001, 0.75)
Confirmed CR vs. Other	0.02 (0.002, 0.14)
Confirmed CRi vs. Other	0.24 (0.10, 0.54)



	N	Events	Median
Unconfirmed CR	19	7	5.7
Unconfirmed CRi	28	18	3.5
Other	254	172	2.6
Total	301	197	

	Hazard Ratio (95% CI)
Unconfirmed CR vs. Unconfirmed CRi	0.76 (0.29, 2.01)
Unconfirmed CR vs. Other	0.43 (0.20, 0.93)
Unconfirmed CRi vs. Other	0.61 (0.37, 1.02)

1. Includes all available patients: 340 patients from 7 historic AML trials
2. Long term follow-up began after the treatment period, at study day 56

Conclusions

SCAs provide enhanced context for interpretation of uncontrolled experimental results, enabling

- Quantitative estimation of treatment effect size
- More reliable decision making in early phases
- Exploratory analyses exploiting large sample size
- Construction of more efficient and informative clinical trials
- Methodology applicable to other indications

Response (CR/CRi) is positively associated with improved OS in relapsed/refractory AML

- Confirmation of the CR/CRi is further associated with improved OS
- Median OS in patients with CR is longer than in patients with CRi

References

Kantarjian, H et al, 2017, Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab, Blood 129:1275-1283

Walter, RB et al, 2010, Effect of Complete Remission and Responses Less Than Complete Remission on Survival in Acute Myeloid Leukemia: A Combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M. D. Anderson Cancer Center Study, JCO 28:1766-1771