Results of a randomized control arm are replicated by a synthetic control arm (SCA); a case study in non small cell lung cancer (NSCLC)

Ruthie Davi[1], Andrea Ferris[2], David Lee[1], Antara Majumdar[1], Mark Stewart[3], Larry Strianese[1], Elizabeth Stuart[4], Xiang Yin[1], Antoine Yver[5]
[1]Medidata Solutions (Acorn AI);[2] LUNGevity Foundation;[3] Friends of Cancer Research;[4] Johns Hopkins University;[5] Daiichi-Sankyo

Abstract number
9108

acorn ai
a Medidata company

Contact
Ruthie Davi
rdavi@medidata.com

The Problem

Absent / Compromised Concurrent Randomized Control

Confirmatory trials after accelerated approval

- Availability of investigational product or a similar product on the market may compromise a randomized trial
  - trial recruitment more difficult
  - control arm retention more challenging
  - control arm compliance more problematic

Single-arm efficacy trials

- Many accelerated approval phase 2 trials in difficult oncology indications
- Ethical or practical reasons
- Rare diseases or special populations (e.g., pediatrics)

Early phase single arm trials

Examples of the Challenges

BRAVO study — large randomized trial of PARP inhibitor stopped early because trial is unlikely to produce data that is interpretable

- Large randomized trial of PARP inhibitor in BRCA positive breast cancer
- Unusually high rate of censoring especially in control arm
- Early discontinuation likely related to the desire of control patients to be treated with a newly approved PARP inhibitor similar to the experimental therapy during conduct of the trial

RCT of sunitinib malate influenced by treatment cross-over, fails to demonstrate OS benefit after clear and large demonstration of PFS benefit

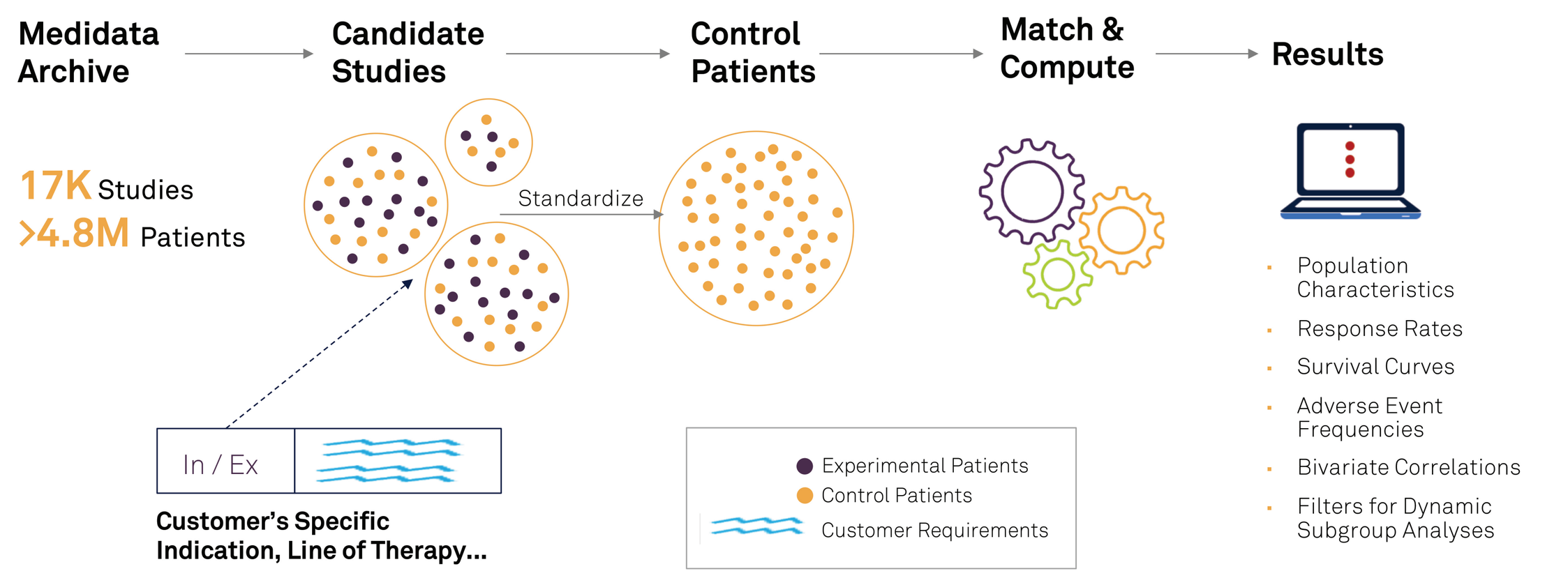
- Large randomized trial of sunitinib malate versus placebo in gastrointestinal stromal tumor
- Interim analysis demonstrates large positive effect on PFS (HR=0.33, 95% CI (0.24, 0.47))
- 84% of patients on placebo accepted treatment with sunitinib malate after the interim analysis
- At final analysis no difference in OS was observed (HR=0.88, 95% CI (0.68, 1.1))
- Absence of effect likely a result of the treatment "cross-over" in the placebo arm

The Proposal — A Synthetic Control Arm

Well-matched patient-level data from historical clinical trials to augment or replace the randomized control

- Utilize historical clinical trials conducted before the experimental product or similar products available so that 'cross-over' effect is not present
- Patients from historical trials selected to statistically match the baseline characteristics of experimentally treated patients using propensity scores to provide a fair comparison akin to a randomized comparison

Creation of a synthetic control arm



SCA leverages patient data from prior trials to improve evaluation of outcomes of trials with absent or compromised control arms

Assessment of Validity of SCA: NSCLC Case Study

Objective

- To determine whether a synthetic control arm can mimic the results of a randomized control arm
- Explore the potential applications of historical clinical trials data to RCTs
  - Aim of minimizing the number of patients assigned to control
  - Provide better understanding of experimental therapy independent of the effect of treatment cross-over

Data Sources

- Project Data Sphere[1]: control patient level data from three large randomized trials in NSCLC
- MEDS[2]: patient level data from multiple clinical trials in NSCLC

Building the Synthetic Control Arm

Features of Historical Clinical Trials

- Open label and blinded phase 2 & 3 trials
- Multinational
- Timespan of starts of trial (2004 to 2013)
- Overall survival measured

Target Randomized Control

One of the three historical trials provided by Project Data Sphere is designated as the 'Target Randomized Control'

- Case study was repeated by defining a second historical trial from Project Data Sphere as the target (results not shown but were consistent with the results described here)
- Third trial from Project Data Sphere was not chosen as a target due to limited size and unreliable recording of some baseline characteristics

Eligibility Criteria for Selection of Candidate SCA Patients from All Other Historical Trials

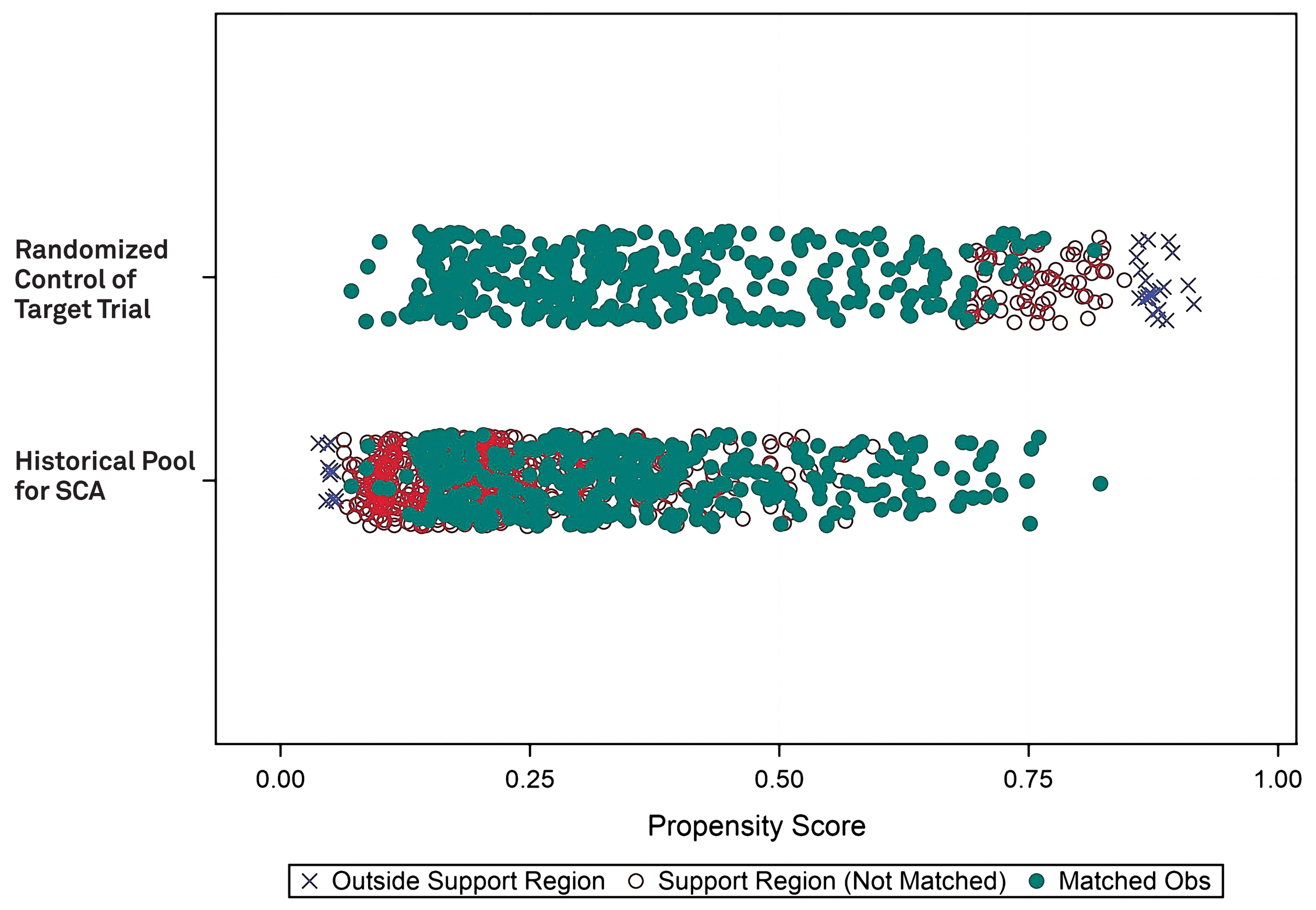
- Inclusion in a historical clinical trial accessible within this project
- NSCLC at stage III or IV
- Received prior platinum-based chemotherapy
- Men and women ≥ 18 years of age
- ECOG performance status of ≤ 2
- Measurable disease
- Received treatment with docetaxel

Propensity Score Matching

Greedy 1:1 Nearest Neighbor matching on propensity score was used and the following baseline characteristics were included as covariates in the propensity score model:

- Age at baseline (continuous)
- Years from cancer diagnosis (continuous)
- Race (White vs Others)
- Sex (Female vs Male)
- Smoking (Current vs Former vs Never)
- Histology (Squamous vs Non-squamous)
- Stage (III vs IV)
- ECOG (0 vs 1 vs 2)
- Prior surgery (Yes/Maybe vs No)
- EGFR/KRAS mutation (Positive vs No/Unknown)

Propensity scores rely on an assumption of no unmeasured confounders; Historical data more likely to be appropriate if strong confounders are all observed and available for adjustment.

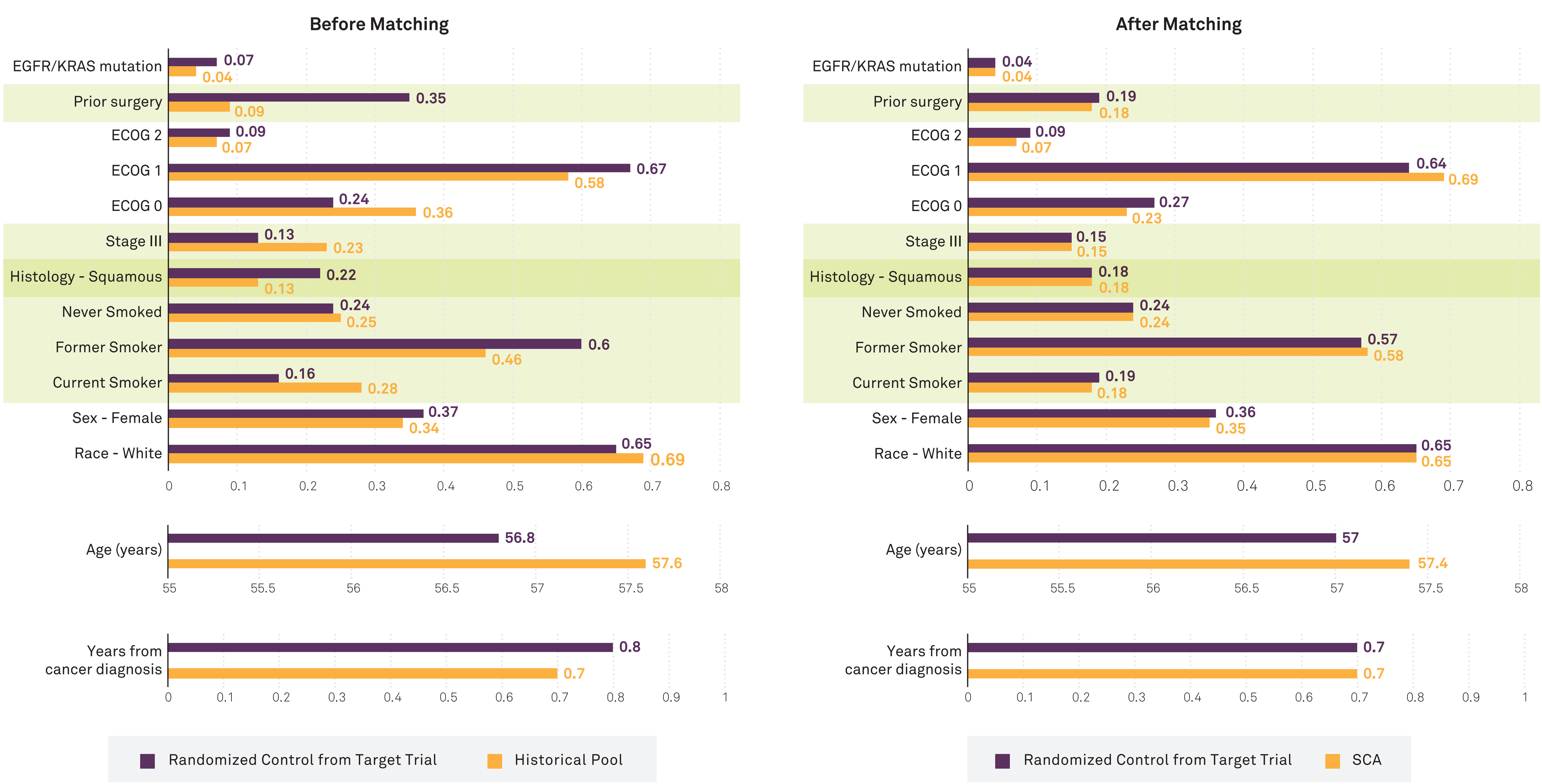


High degree of overlap in propensity scores between the two groups indicates it is possible to create a well matched comparator

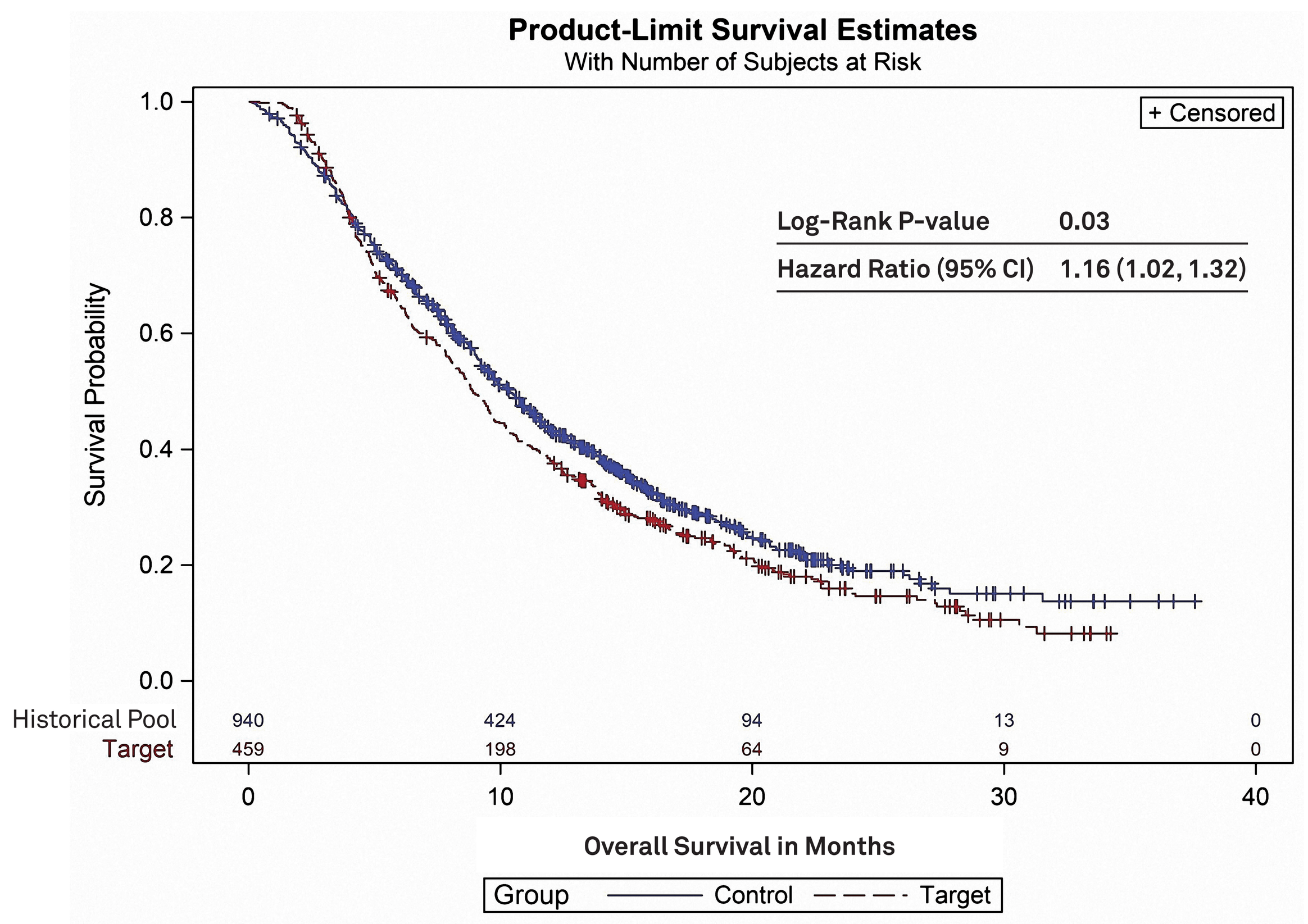
- 80% of target randomized control is matched with nearest neighbor greedy matching
- Exclusion of patients from the target enhances balance between groups rather than threatens it as would be the case with exclusions from the ITT group in a randomized controlled trial

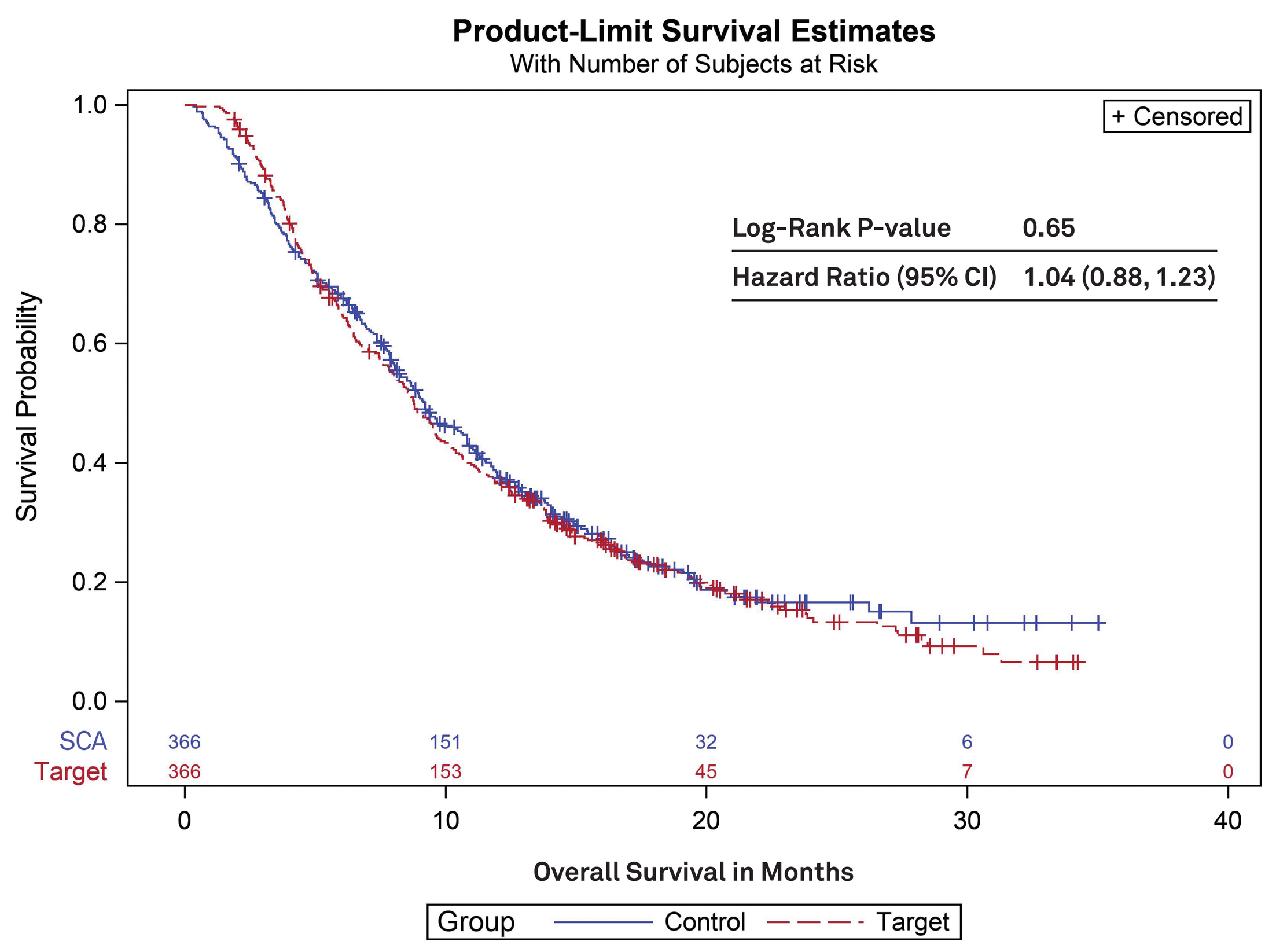
Results

Baseline Demographic & Disease Characteristics Well Balanced After Matching



Overall Survival in SCA is Similar to Target Randomized Control





Conclusions

- Comparable balance in observed baseline characteristics of the SCA and Target Randomized Control was achieved
- Overall survival (OS) in Target Randomized Control was replicated by SCA
  - The Kaplan Meier curves for OS in the SCA and Target Randomized Control visually overlap
  - Log rank test (p=0.65) and hazard ratio of 1.04 (95% CI: (0.88, 1.23)) were not statistically significant
- In some settings, SCA can augment or replace a randomized control, mitigating many of the recruitment, retention, and cross-over challenges when enrolling or maintaining a concurrent control

Future Work

- Assessment of whether the treatment effect can be replicated with the use of SCA
- Examine effect of unobserved covariates on treatment group comparisons
- Exploration of tweaks to the matching methods to reduce the proportion of patients who are not matched
- Expand to additional indications

References

White paper available at Friends of Cancer Research website: www.focr.org/sites/default/files/SCA%20White%20Paper.pdf

Sunitinib malate capsule prescribing information. 2006. Available online: http://labeling.pfizer.com ShowLabeling.aspx?id=607

Tesaro press release. 2017. Available online: http://ir.tesarobio.com/news-releases/news-release-details/tesaro-announces-expanded-development-program-niraparib-focused

Footnotes

1. Project Data Sphere is a platform where the research community can share historical patient level data from academic and industry phase 3 cancer clinical trials. The analyses in this case study are at least partially based on research using information obtained from www.projectdatasphere.org, which is maintained by Project Data Sphere, LLC. Neither Project Data Sphere, LLC nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this work.
2. Medidata Enterprise Data Store is a collection of thousands of previous clinical trials conducted by the pharmaceutical industry for drug or medical product development with patient level data recorded through the Medidata electronic data capture system. Per the legal agreements with the sponsors of these historical clinical trials and Medidata, these data are available for use in deidentified (i.e., patients and original sponsor of the trial cannot be identified) and aggregated (i.e., every analysis must include data from two or more sponsors) form.