Strategies to improve clinical development journey with external control arm using historical clinical data

8th-Dec-2023

Today's Presenter

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Solution Consultant

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MEDIDATA

DASSAULT SYSTEMES

Agenda

- What is External Control?
- Medidata AI Data Coverage
- Evidence of External Control Arm
- Use Case of External Control Arm
- Q&A

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What is External Control?

What is the challenges?

e.g. Rare diseases
Regenerative medicine
Gene therapy
Life-threatening diseases

Source: 薬事申請に Real World Data を外部対照と して利用する際の留意点 (日本製薬工業協会 医薬品評価委員会 データサイエンス部会)

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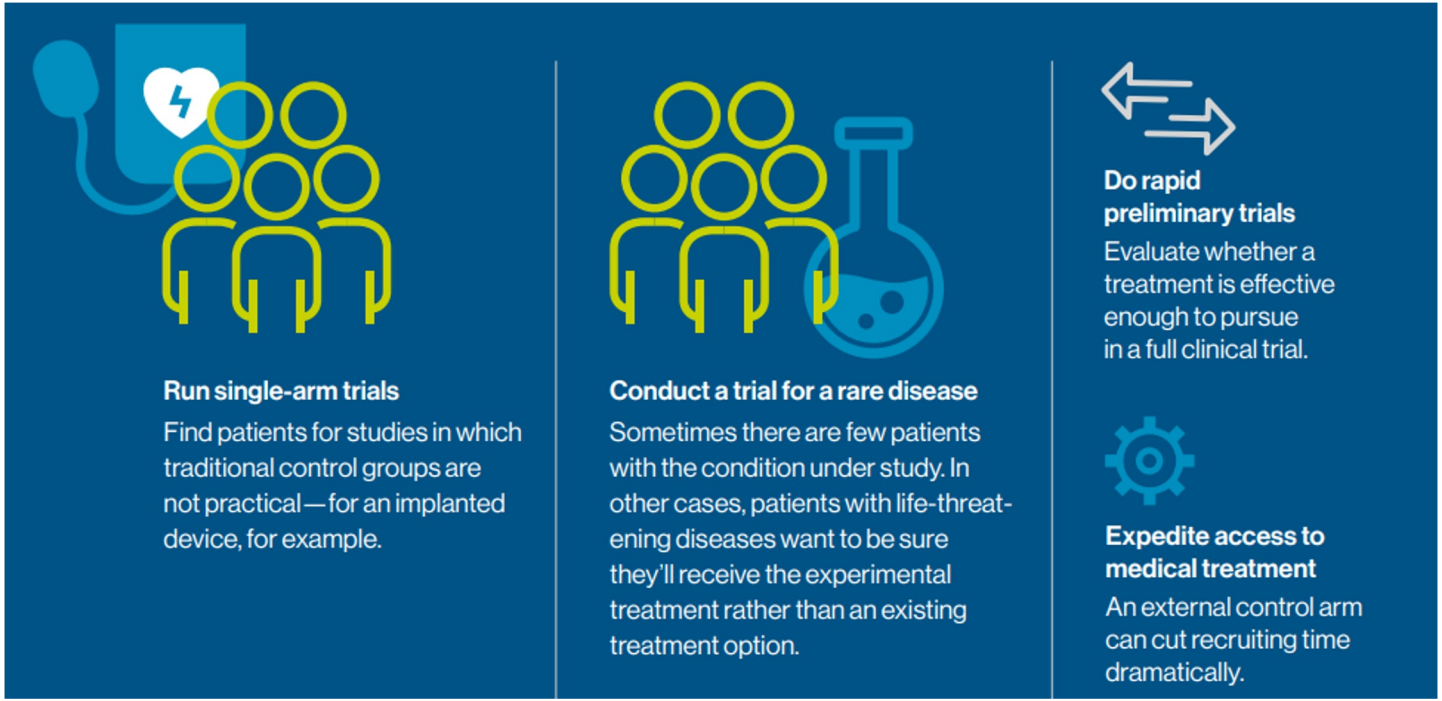
Why use External Control Arm?

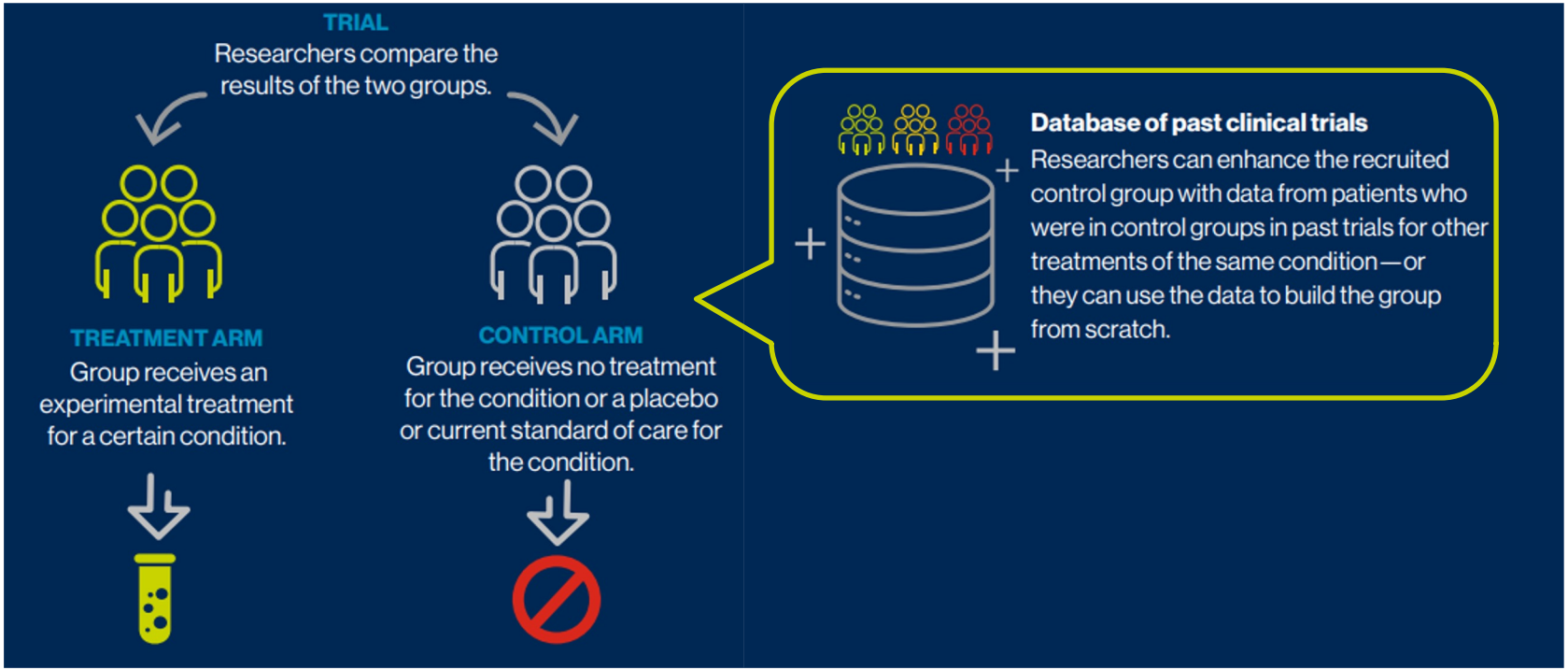
Under certain circumstances, researchers might create a control group using patient data from past clinical trials instead of recruiting a new control group. They might need to do the following:



Source: MIT Technology Review Insights; based on information from the US Library of Medicine

How External Controls work

Under certain circumstances, researchers might create a control group using patient data from past clinical trials instead of recruiting a new control group. They might need to do the following:



Source: MIT Technology Review Insights; based on information from the US Library of Medicine

Medidata AI Data Coverage

Our Data

The Medidata Platform holds the industry's largest scientific and operational dataset

30,000+
Studies Run

8,000+
Active Studies

9,000,000+
Trial Subjects

145+
Indications ready-to-go with predictive models

1,000,000
Study-sites, standardized to 33,000+ Facilities

145+
Countries

Medidata AI Has the World's Largest Historical Clinical Trial Database, With 2 Distinct Flavors of Historic Clinical Trial Data

Medidata Archive

30K+ Studies

9M+ Patients

Operational Data

Study, country and site level data with associated investigator names

35+ metrics spanning enrollment, quality, congestion and cycle times

True performance metrics based on actual events with real-time data capture

Example use cases:

- Analyze trial landscape in real-time
- Identify and rank countries and sites
- Forecast and re-forecast enrollment
- Generate ongoing, live study insights

Clinical Data

Study and patient-level data

100+ clinical fields, covering

- Primary & secondary outcomes
- Study & concomitant treatments
- Inclusion and exclusion criteria
- Adverse events

Rapid, precise meta-analysis at the subject level

Example use cases

- Synthetic Control Arm®
- Select patient populations
- Select comparators
- Validate endpoints
- Simulate outcomes using "virtual patients"

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Medidata has curated the world's largest dataset from past trials

Largest patient-level data from past trials in existence

30,000+ trials run on the Medidata Rave platform

8,000+ ongoing trials on Rave

9M+ patients from 150+ countries

Continuously growing with new data added as trials are completed

Coverage representative of drug development in the industry

- ❑ Oncology (13,000+)
- ❑ Cardiovascular (4,000+)
- ❑ Immunology (3,000+)
- ❑ Respiratory (2,000+)
- ❑ CNS (1,500+)
- ❑ Metabolic (1,500+)
- ❑ Nephrology (500+)
- ❑ Dermatology (500+)
- ❑ Medical Devices (1,000+)

Deep, structured data captured directly from case report forms

ENDPOINTS

Traditional endpoints used in clinical trials and major covariates captured directly with no derivation or estimation

PURPOSE

Data captured for research and evaluation purposes by leading investigators at prestigious medical centers

PATIENT HISTORY

Detailed patient history including prior lines of therapies, comorbidities, concomitant medications

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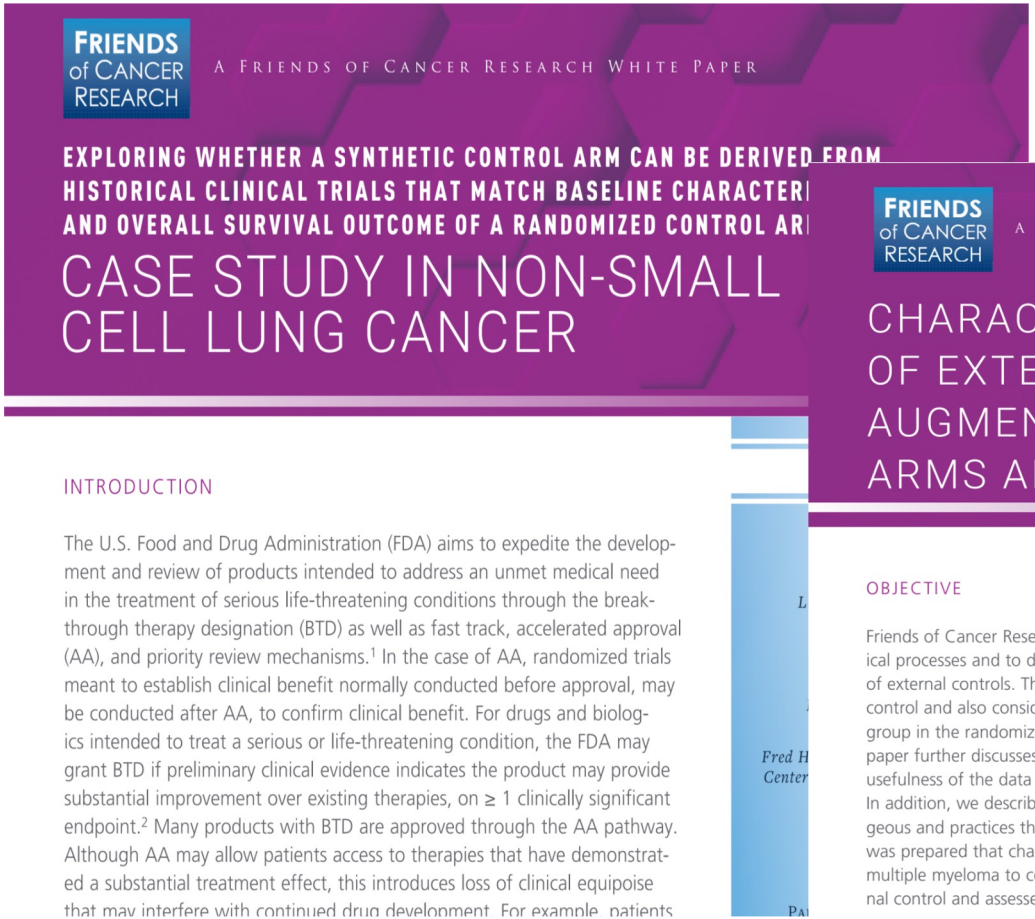
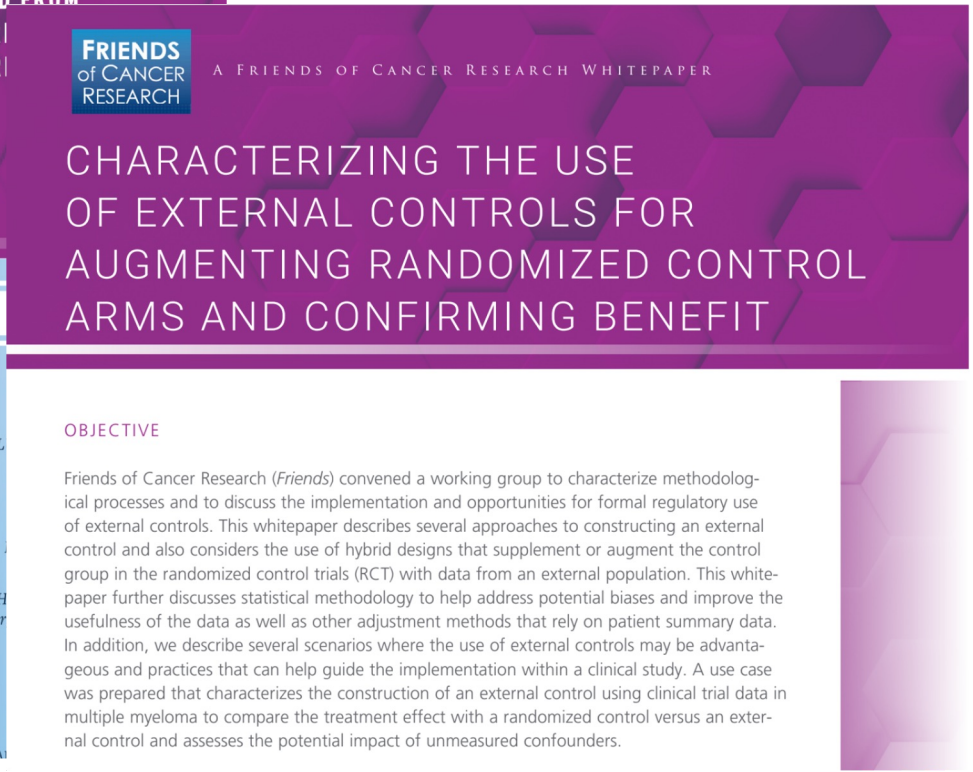
Evidence of External Control Arm

Friends of Cancer Research- Case study in NSCLC, Multiple Myeloma





Friends of Cancer Research- Case study in NSCLC

Data Sources

- Project Data Sphere[1]
- Medidata Enterprise Data Store (MEDS)[2]

Trial Characteristics

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

SCA Patient Eligibility Criteria

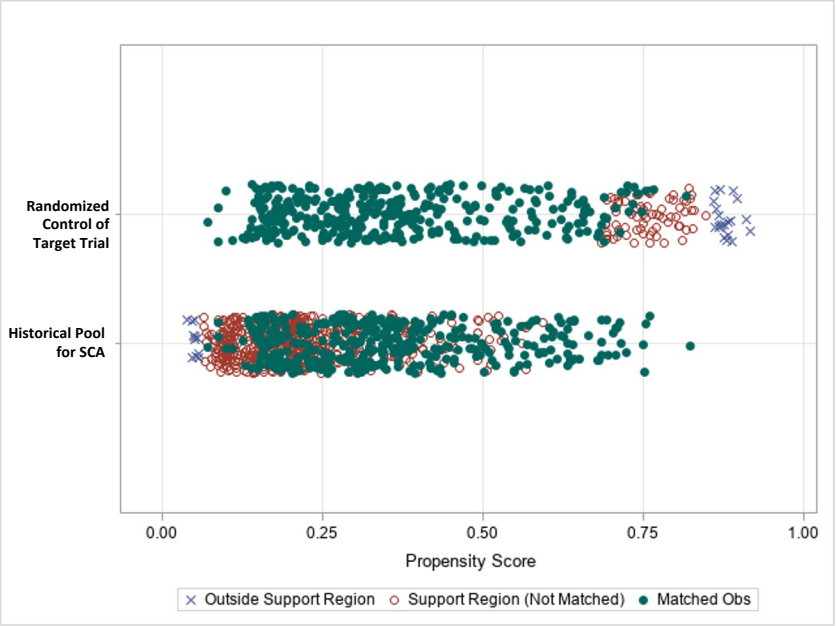
- Inclusion in a historical clinical trial accessible within this project
- NSCLC at stage III or IV
- Received prior platinum-based chemotherapy
- Men and women ≥ 18 years of age
- ECOG performance status of ≤ 2
- Measurable disease
- Received treatment with docetaxel

1. These analyses are 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 web site have contributed to, approved or are in any way responsible for the contents of this work.
2. Includes 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. Legal agreements permit 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.

Prespecified Propensity Score Matching

Baseline Characteristics for Matching

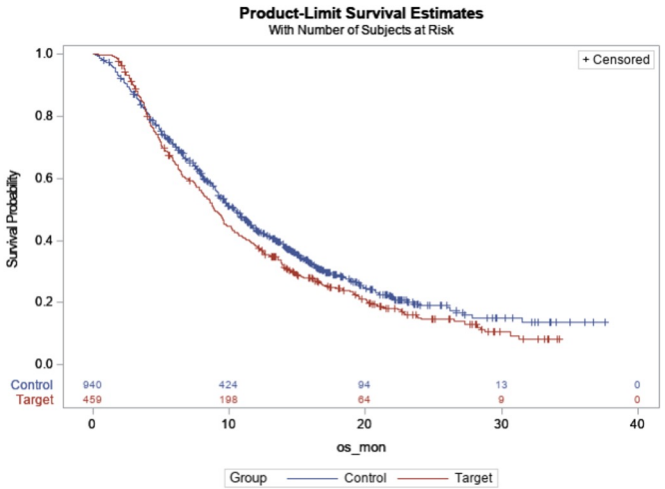
- Age at baseline (continuous)
- Years from cancer diagnosis (continuous)
- Race (White vs Others)
- Sex (Female vs Male)
- Smoking (Current vs Former vs Never)
- Histology (Squamous vs Non-squamous)
- Stage (III vs IV)
- ECOG (0 vs 1 vs 2)
- Prior surgery (Yes/Maybe vs No)
- EGFR/KRAS mutation (Positive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



External Control Arm Case Study

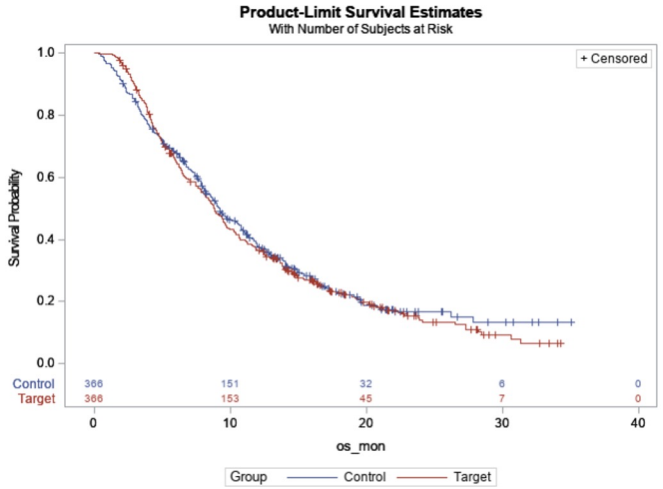
Our data and matching algorithms closely replicated target randomized control (NSCLC)

Before Matching



Before Matching	
Log-Rank P-value	0.03
Hazard Ratio (95% CI)	1.16 (1.02, 1.32)

After Matching



After Matching	
Log-Rank P-value	0.65
Hazard Ratio (95% CI)	1.04 (0.88, 1.23)

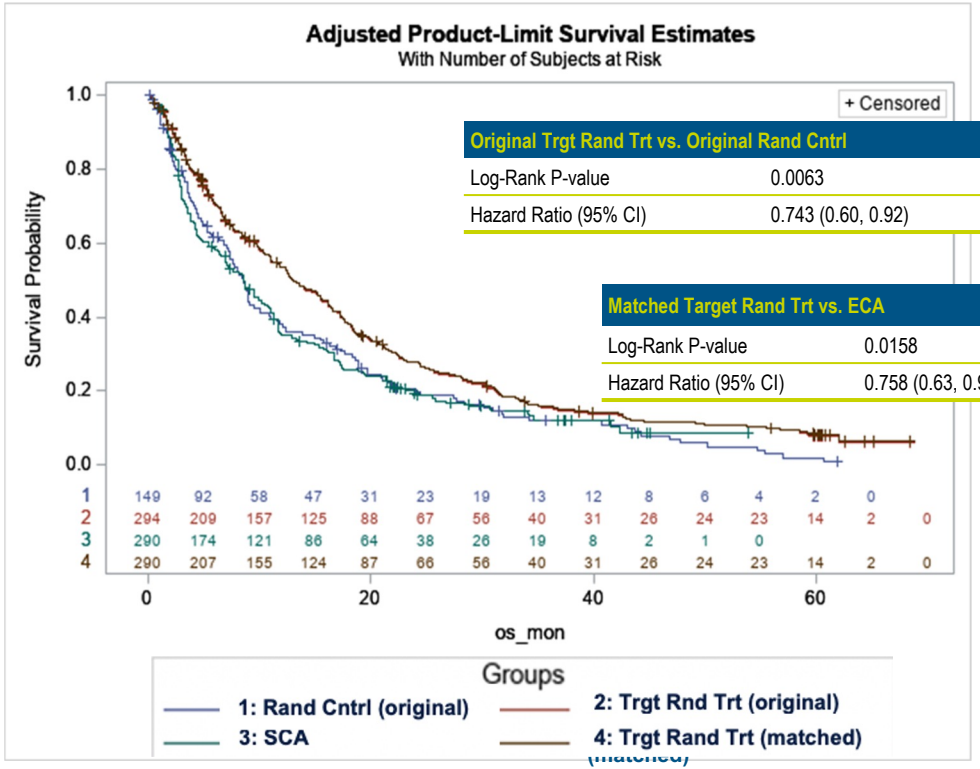
RESULTS

What it means

- **ECA successfully replicated the overall survival in the control arm** of the target trial
- Important step in understanding how **ECA may mitigate challenges faced with a concurrent control arm** in difficult-to-study indications

External Control Arm Case Study

Multiple Myeloma Results — Treatment Effect relative to ECA Mimics that of Randomized Control in Terms of OS



- Investigational arm of the Target Randomized Trial (red)
- Randomized control arm of the Target Randomized Trial (blue)
- Matched investigational arm of the Target Randomized Trial (brown)
- SCA (teal)

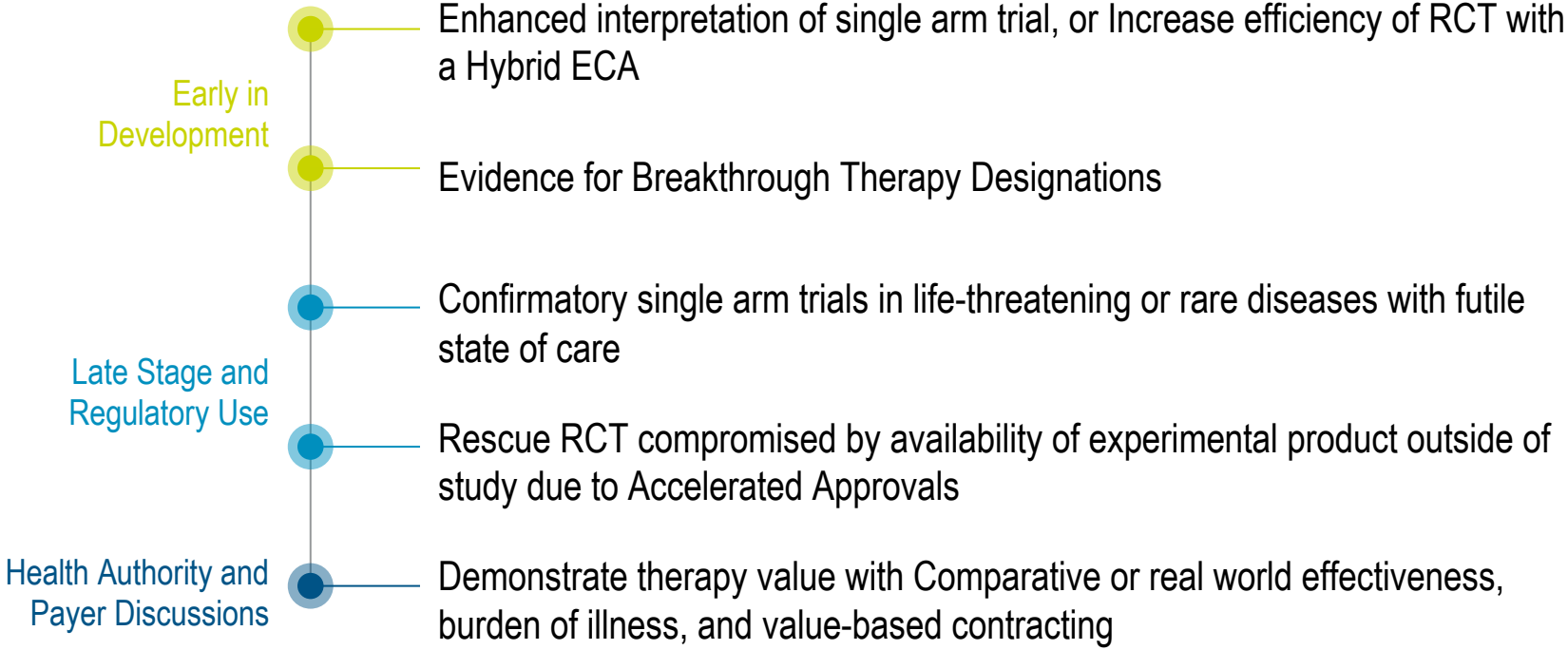
RESULTS

What it means

- **ECA successfully replicated the overall survival in the control arm** of the target trial
- Comparison of ECA to matched investigational arm successfully **replicated trt effect on overall survival** from randomized target trial
- Body of evidence is building demonstrating how ECA may **mitigate challenges faced with a concurrent control arm in difficult-to-study indications**

Use Case of External Control Arm

What are the typical applications of a External Control Arm?



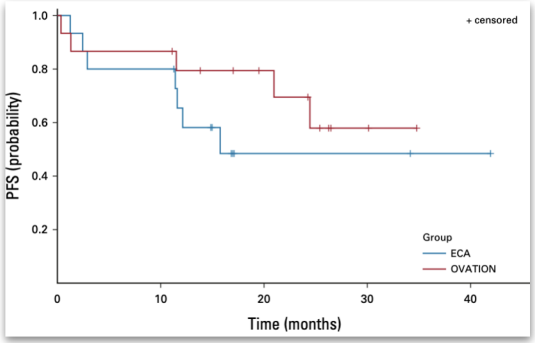
Early Development Application of a External Control Arm

Early in Development

Late Stage and Regulatory Use

Health Authority and Payer Discussions

- ECA to **enhance the interpretation of a Phase I single arm trial** showed strong PFS treatment effect
- Analyses justified a **20 patient sample size reduction** in the Phase II study execution
  - *Savings due to lower patient recruitment is estimated at **$1.5 million****



Yin X, Davi R, Lamont EB, Thaker PH, Bradley WH, Leath III CA, Moore KM, Anwer K, Musso L, Borys N. Historic Clinical Trial External Control Arm Provides Actionable GEN-1 Efficacy Estimate Before a Randomized Trial. JCO Clinical Cancer Informatics. 2023 Jan;7:e2200103.

*"**We are extremely impressed with the high quality of the matched data from the Medidata ECA**," said Michael H. Tardugno, Celsion's chairman, president and chief executive officer. **"They were able to provide near-perfect matches for patient characteristics in our Phase Ib OVATION I Study."***

*"This preliminary evidence of a strong treatment effect trend supports our commitment to the GEN-1 program, and **we will aggressively explore means of accelerating its development with regulatory agencies and our investigators.**"*

- Dr. Nicolas Borys, Imunon's Chief Medical Officer.

(March 27, 2020) The full press release can be viewed here.

** The Medidata PICAS database is the clinical benchmark and cost database of previously negotiated investigator grants with a store of more than 320,000 grants and contracts and 29,500 protocols for over 1,800 indications.*

Abstract #1025

Phase IB Trial Efficacy Estimates via a Clinical Trial Synthetic Control Arm

Xiang Yin, PhD[1]; Ruthie Davi, PhD[1]; Elizabeth Lamont, MD, MS, MMSc[1]; Premal Thaker, MD, MS[2]; William Bradley, MD[3], Charles Leath, MD, MSPH[4]; Kathleen Moore, MD[5]; Khursheed Anwer, PhD, MBA[6]; Lauren Musso[6]; Nicholas Borys, MD[6]

[1]Acorn AI, at Medidata, a Dassault Systèmes company; 2 Siteman Cancer Center, Washington University in St Louis; [3] Medical College of Wisconsin; [4] O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham; [5] University of Oklahoma Health Sciences Center/Sarah Cannon Research Institute; and [6]Celsion Corporation

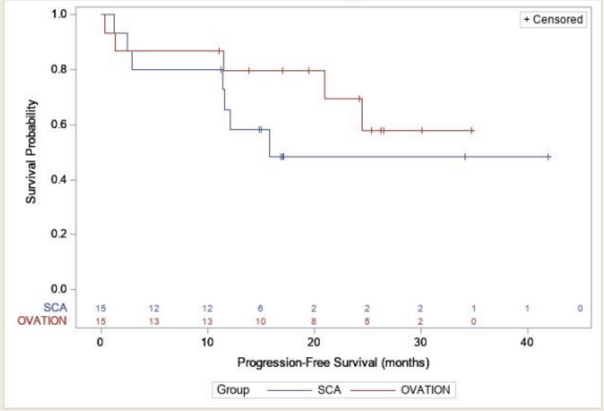
AACR American Association for Cancer Research

- Phase Ib dose-escalating OVATION I Study (NCT02480374), GEN-1 in Stage III/IV ovarian cancer patients
- Standardized and integrated patient-level MEDS data (N=41) from phase I-III trials (enrollment years 2015-2016) with patient-level OVATION-1 data (N=18)
- Used standard propensity score methods to identify MEDS patients who appeared similar to OVATION-1 patients to create ECA

Table. Attributes of OVATION-1 and Historic Clinical Trial Patients

	Before Matching		After Matching	
	OVATION-1	Historic Trial	OVATION-1	SCA
Variables	**N=18**	**N=41**	**N**	
ECOG=0*	6 (33%)	20 (49%)		
White Race	15 (83%)	34 (83%)	1	
Stage III	12 (67%)	25 (61%)		
Age (mean, +/- SD)	64.5 +/- 7.5	62.2 +/- 11.1	62.	
BMI (mean, +/- SD)	30.4 +/- 6.6	27.6 +/- 7.4	29.	
ln(CA-125) (mean, +/- SD)	6.4 +/- 0.9	6.7 +/- 1.1	6.	
Days Since Dx (mean, +/- SD)	10.1 +/- 4.8	16.9 +/- 11.4	8.	

Figure 2. PFS of Matched OVATION-1 and SCA Patients (N=30)



*Patient ECOG scores were ≤ 2

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

GEN-1 in Combination with Neoadjuvant Chemotherapy for Patients with Advanced Epithelial Ovarian Cancer: A Phase I Dose-escalation Study

Premal H. Thaker[1], William H. Bradley[2], Charles A. Leath III[3], Camille Gunderson Jackson[4], Nicholas Borys[5], Khursheed Anwer[5], Lauren Musso[5], Junko Matsuzaki[6], Wiam Bshara[6], Kunle Odunsi[6], and Ronald D. Alvarez[7]

ABSTRACT

Purpose: GEN-1 (phIL-12-005/PPC), an IL12 plasmid formulated with polyethyleneglycol-polyethyleneimine cholesterol lipopolymer, has preclinical activity when combined with platinum-taxane intravenous chemotherapy and administered intraperitoneally in epithelial ovarian cancer (EOC) models. OVATION I was a multicenter, nonrandomized, open-label phase IB trial to evaluate the safety, preliminary antitumor activity, and immunologic response to GEN-1 in combination with neoadjuvant chemotherapy (NACT) carboplatin-paclitaxel in patients with advanced EOC.

Patients and Methods: A total of 18 patients with newly diagnosed stage IIIC and IV EOC were enrolled. A standard 3+3 dose-escalation design tested four GEN-1 doses (36, 47, 61, 79 mg/m^2) to determine the maximum tolerated dose and dose-limiting toxicities (DLTs). GEN-1 was administered in eight weekly intraperitoneal infusions starting at cycle 1 week 2 in combination with three 21-day cycles of NACT carboplatin AUC 6 and weekly paclitaxel 80 mg/m^2.

Results: The most common treatment-emergent adverse events at least possibly related were nausea, fatigue, abdominal pain/cramping, anorexia, diarrhea, and vomiting. Eight patients experience grade 4 neutropenia attributed to NACT. No DLTs occurred. A total of 14 patients were evaluable for response and 12 (85.7%) had radiological response (two complete response and 10 partial response) prior to debulking; nine were R0 at debulking and one patient had complete pathologic response. IL12 and its downstream cytokine, IFNγ, increased in peritoneal washings but not as much in blood. Increased levels of myeloid dendritic cells and T-effector memory cells in peritoneal fluid, plus elevated CD8$^+$ T cells and reduced immunosuppression within the tumor microenvironment were found. A median time to treatment failure of 18.4 months (95% confidence interval, 9.2–24.5) was observed in the intention-to-treat population.

Conclusions: Adding GEN-1 to standard NACT is safe, appears active, and has an impact on the tumor microenvironment.

Regulatory Application of a External Control Arm

MEDICENNA™

Early in Development

Late Stage and Regulatory Use

Health Authority and Payer Discussions

- **Medicenna used a Medidata ECA** to demonstrate efficacy in a single-arm Phase II trial, with the goal of using the results to design a Phase 3 ECA-based registrational trial
- The ECA demonstrated large efficacy effect size in all-comers subjects and subjects expressing high levels of IL4R.
- For the first time, the **FDA approved the use of hybrid ECA** in a Phase III study design in Recurrent Glioblastoma resulting in a **66% reduction in the required randomized control arm**

*"We are extremely impressed with the Medidata AI team for providing a **scientifically rigorous rationale for the design of an innovative registration trial incorporating an external control arm** for the treatment of recurrent glioblastoma (rGBM) with MDNA55.*

The FDA's acceptance of this unique design, will expedite completion of the Phase 3 trial in rGBM allowing earlier access of MDNA55 for a disease with poor prognosis and high unmet need,"

-Dr. Fahar Merchant, President and CEO of Medicenna.

(October 15, 2020) **The full press release can be viewed here.**

Medicenna Updates Efficacy Results from Phase 2b Recurrent GBM Trial at ASCO 2020

Medicenna Updates Efficacy Results from Phase 2b Recurrent GBM Trial at ASCO 2020

NEWS PROVIDED BY
Medicenna Therapeutics Corp. ➞
May 29, 2020, 08:05 ET

-Tumor control achieved in 76% of evaluable subjects irrespective of IL4R expression resulting in mOS, mPFS and PFS-12 of 15.0 months, 4.6 months and 33%, respectively-
-In the Proposed Population (all IL4R High subjects and IL4R Low subjects receiving high dose), mOS increased by up to 126% when compared to a Synthetic Control Arm (SCA)-

Table 1

Eligibility-Matched Groups	N	mOS	Improvement in mOS	Hazard Ratio (HR)	OS-12
MDNA55 All-comers	44	12.4	61%	0.58	53%
SCA All-comers	81	7.7			25%
MDNA55 IL4R High	21	15.8	155%	0.54	62%
SCA IL4R High	17	6.2			24%

Table 2

Propensity-Weighted Groups	N	mOS	Improvement in mOS	HR
MDNA55 All-comers	43	12.4	72%	0.63
SCA All-comers	40.8	7.2		
MDNA55 IL4R High	17	13.2	116%	0.52
SCA IL4R High	16.8	6.1		

"Further refinement of new and previously reported data ***using a rigorous propensity-matching methodology*** to remove any potential selection bias further bolsters this belief. … The Company plans to ***submit an end of Phase 2 meeting package for MDNA55 to the FDA in Q2 2020.”***

Late Stage Application of a External Control Arm

Early in Development

Late Stage and Regulatory Use

Health Authority and Payer Discussions

- The ZUMA-3 trial of KTE-X19 in relapsed/refractory (r/r) adult B-cell precursor acute lymphoblastic leukaemia (B-ALL) utilizes a single arm design.
- To contextualize these results, a externalcontrol (EC) study derived from individual patient-level data (IPD) sampled from Medidata's historical clinical trials (CTs) data repository was constructed.
- This comparative study demonstrated a clinically relevant improvement of OCR24 and OS following KTE-X19 vs available therapies and provides strong evidence for its use in adult patients with R/R B-ALL

ASH Annual Meeting & Exposition

3844 The Comparison of Kte-X19 to Current Standards of Care: A Pre-Specified Synthetic Control Study Utilizing Individual Patient Level Data from Historic Clinical Trials (SCHOLAR-3)

Program: Oral and Poster Abstracts
Session: 704. Cellular Immunotherapies: Clinical: Poster III
Hematology Disease Topics & Pathways:
Clinical Trials, Lymphoid Leukemias, ALL, Biological, Clinical Research, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Clinically Relevant, Diseases, Therapies, Lymphoid Malignancies

Monday, December 13, 2021, 6:00 PM-8:00 PM

Bijal D. Shah, MD[1], *Imi Faghmous*[2*], *James Whitmore, PhD*[2*], *Behzad Kharabi Masouleh, MD*[3*] *and Hairong Xu, MD, PhD*[3*]

[1]*H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*
[2]*Kite, A Gilead Company, Santa Monica, CA*
[3]*Kite, a Gilead Company, Santa Monica, CA*

Background: The ZUMA-3 trial of KTE-X19 in relapsed/refractory (r/r) adult B-cell precursor acute lymphoblastic leukaemia (B-ALL) utilizes a single arm design. To contextualize these results, a synthetic control (SC) study derived from individual patient-level data (IPD) sampled from historical clinical trials (CTs) was constructed.

Aims: To compare the overall survival (OS) and objective complete response rate at week 24 (OCR24) results of the ZUMA-3 pivitol study using a matched (SC) derived from IPD from CTs.

Methods:

This study had two distinct phases: firstly, CTs from which patients were sampled were identified using the medidata enterprise data store (MEDS). The second phase of this study constructed SCs to the ZUMA-3 population, one SC for patients naïve to blinatumomab (blin) or inotuzuamab (ino) therapy (SCA-1) and one in blin or ino pre-treated patients (SCA-2). All analysis were pre-specified and conducted by an external third party to Kite Pharma.

3844 The Comparison of Kte-X19 to Current Standards of Care: A Pre-Specified Synthetic Control Study Utilizing Individual Patient Level Data from Historic Clinical Trials (SCHOLAR-3)

Methods: SCA-1 for patients naïve to blinatumomab (blin) or inotuzuamab(ino)/SCA-2 in blin or ino pre-treated patients from MEDS. **The propensity score was derived as a function of the number of previous lines of therapy, prior allo-SCT, age, sex, ECOG, Philadelphia chromosome status, percentage bone marrow blasts and extramedullary disease.**

Table 1 Objective complete response rate at week 24 and Odds ratio between SCA and ZUMA-3

Type	SCA-1 (20)	ZUMA-3 (20)
OCR24	35.0% (95% CI 15.4, 59.2)	85% (95% CI 62.1, 96.8)
Odds ratio	10.5 (95% CI 2.3, 48.7; p-value 0.0031)	

Table 2 Post hoc analysis to further contextualize the OCR24 rate

Type	SCA-3 (HCTs)	ZUMA-3
OCR24	35.8% (95% CI 23.1, 50.2)	69.8% (95% CI 55.7, 81.7)
Odds ratio	4.1 (95% CI 1.8, 9.3) p-value 0.0009.	

Table 3 Overall survival between all matched ZUMA-3 and all SCA

Type	ZUMA-3	SCA-3
Med. OS	18.20 months (95% CI 12.22, NE m)	5.49 months (95% CI 3.32, 9.23 m)

"ZUMA-3 patients had a 64% lower risk of death with a hazard ratio 0.36 (95% CI 0.20, 0.66) p-value 0.0005"

DASSAULT SYSTEMES

Summary

- **ECA created from historical clinical trials data successfully replicated the control arm** of the target trial
  - Non-small cell lung cancer case study
  - Relapsed refractory multiple myeloma case study
- Important step in understanding how **ECA may save time and cost and mitigate challenges faced with a concurrent randomized controls**

Q&A

Thank you!