



Evaluating External Control Arms: Results from a Collaborative Pilot Study

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Pilot results presented on behalf of the ECA Project Working Group

Friends Real-World Evidence Portfolio

Broad Goal: Develop and establish methodology for using real-world data (RWD) to inform clinical trial designs, evaluate therapies, and support regulatory decision-making

2017

2026

Pilot 1.0

Established standardized definitions and protocols to enable reliable real-world endpoint capture across data sources

Pilot 2.0

Evaluated the internal consistency of rw-datasets by applying randomized controlled trial inclusion/exclusion criteria

rw-Response

Developed a framework to evaluate rw-response across multiple sources

ECA Pilot

Define a robust process for external control arm (ECA) construction using RWD and prior clinical trial data

Evaluating External Control Arms

The Promise

- ECAs enable treatment effect estimation when randomized trials are infeasible or enrollment is insufficient, particularly in rare cancers and settings with high unmet need.
- Leverage external data sources to evaluate treatment effects
 - Potential to accelerate evidence generation and support regulatory decision-making

The Challenge

- Key uncertainties in ECA construction and interpretation:
- Variability in data sources, availability, and completeness
 - Approach to operationalizing eligibility criteria and handling missing data
 - Unclear thresholds for determining when an ECA is “fit-for-purpose”

Our Approach

- Establish a multi-stakeholder collaboration to evaluate ECAs by:
- Implementing a shared statistical analysis plan
 - Independently constructing ECAs
 - Comparing reproducibility, attrition, baseline balance, and outcome estimates
 - Generating practical, evidence-based insights

ECA Pilot Project Approach

9 Participating Partners Contributed Patient Data from External Sources

Target Trial–Aligned Population

RESOLVE Control Arm (metastatic PDAC gemcitabine + nab-paclitaxel)

External Data Cohorts

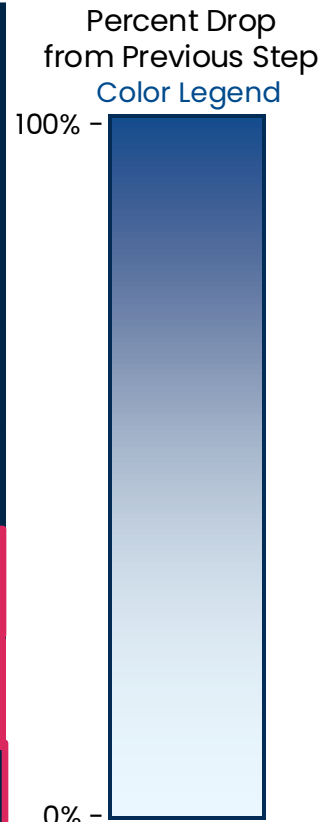
Adults with metastatic PDAC receiving first-line gemcitabine + nab-paclitaxel

Pilot Objectives

1. **Evaluate reproducibility:** Assess whether independently constructed ECAs can approximate the same trial control arm
2. **Characterize variability:** Identify how data sources and methodological choices impact comparability of ECA to target trial
3. **Define fit-for-purpose use:** Establish practical criteria for when ECAs can support decision-making

ECA Pilot Cohort: Clinical Eligibility Criteria

Eligibility Criteria	Eligible Patients in Cohort (n, % excluded from previous step)							
	A	B	C	D	E	F	G	H
Adults (≥18) with mPDAC, 1L nab-paclitaxel + gemcitabine (May 2013–Jul 2021)	1232 0%	236 0%	125 0%	746 0%	5477 0%	386 0%	1117 0%	3274 0%
Pts with adenocarcinoma histology	1231 0%	233 1%	125 0%	746 0% (NC)	5477 0%	386 0%	1076 4%	3274 0%
Pts with no brain or leptomeningeal disease before index	1230 0%	232 0%	122 2%	745 0%	5469 0%	386 0%	1070 1%	3274 0%
Pts with no stroke or intracranial hemorrhage in prior 6 months	1222 1%	231 0%	122 0%	745 0% (NC)	5402 1%	386 0%	1024 4%	3274 0%
Pts with no other primary cancer in past 3 years (except NMSC/CIS)	1195 2%	229 1%	122 0%	745 0% (NC)	5402 0% (NC)	379 2%	949 7%	3163 3%
Pts with no surgery within 4 weeks of index (except PDAC biopsy, infusion placement)	1188 1%	219 4%	120 2%	729 2%	5397 0%	379 0%	928 2%	3163 0% (NC)
Pts with no prior systemic therapy for PDAC	901 24%	166 24%	57 53%	620 15%	3836 29%	349 8%	750 19%	2540 20%
Pts with no adjuvant radiotherapy within 6 months of mPDAC diagnosis	899 0%	166 0%	54 5%	620 0% (NC)	3836 0% (NC)	349 0%	733 2%	2540 0% (NC)



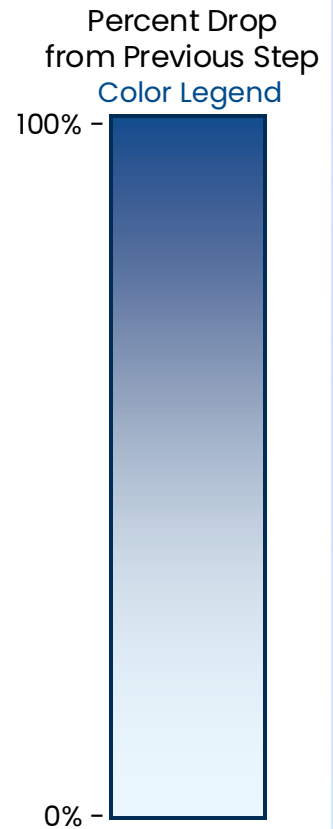
NC = not captured

Understanding why patients were excluded—whether due to abnormal values or missing data—and where data are not structurally captured is essential for interpreting attrition patterns and assessing whether a data source is fit-for-use in constructing a credible ECA.

ECA Pilot Cohort: Lab Eligibility Criteria

Eligible Patients in Cohort (n, % excluded from previous step)

Eligibility Criteria	Eligible Patients in Cohort (n, % excluded from previous step)							
	A	B	C	D	E	F	G	H
Lab eligibility: hematologic function	899	166	54	620	3836	349	733	2540
Labs in timeframe	397	161	NC	620	3682	349	728	2292
Available and completed labs	351	125	NC	598	3583	349	578	2328
Pts with adequate hematologic function	351 61%	109 34%	54 0% (NC)	517 16%	2531 34%	349 0%	551 25%	1557 39%
Pts with no transfusions or growth factor use within 30 days	351 0%	106 3%	54 0% (NC)	517 0% (NC)	2422 4%	347 1%	550 0%	1530 2%
Lab eligibility: hepatic & renal function								
Labs in timeframe	178	106	NC	517	2319	347	535	1328
Available and completed labs	50	104	NC	517	2282	347	447	1328
Pts with adequate hepatic and renal function	50 86%	67 37%	54 0% (NC)	399 22%	1643 32%	347 0%	372 32%	791 48%
Pts with ECOG 0-1 or KPS ≥70 , or no PS recorded	39 22%	57 15%	52 4%	351 12%	1357 17%	347 0%	305 18%	677 14%



NC = not captured

Laboratory-based eligibility criteria shape cohorts through both biological thresholds and operational constraints, making it important to distinguish true clinical differences from trial-real-world mismatches.

Pre-balance Demographic Characteristics

DEMOGRAPHICS	RESOLVE TRIAL	B	D	E	F	G	H
N (number of patients)	213	57	351	1,357	347	305	677
Age categories at index:							
<65 years	55.9	29.8	25.9	26	51	32.1	27.5
>= 65 years	44.1	70.2	74.1	74	49	67.9	72.5
Sex:							
Female	43	32	48	46	43.8	45	46
Male	57	68	52	54	56.2	55	54
Race:							
White	67	80.7	0	66	83	80.3	73.4
Black or African American	3	5.3	0	8.2	4.3	11.1	7.8
Asian	28	0	0	1.6	3.2		1.9
Unknown/Missing	2	3.5	100	12	5.8	6.9	16
Ethnicity:							
Hispanic	5	22.8	0	4.3	6.1	2.3	2.4
Non-Hispanic	93	71.9	0	73	88.5	59.3	78
Unknown/Missing	2	5.3	100	23	5.5	38.4	19.5

Percent of Patients
in Each Category

Color Legend



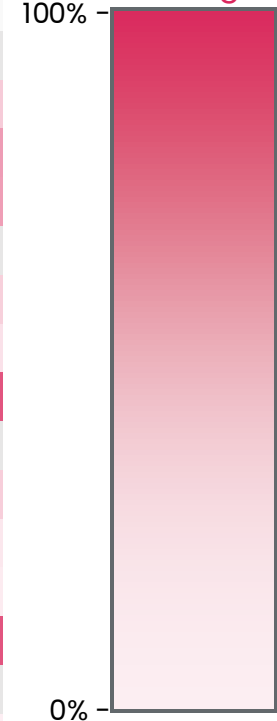
Demographic characteristics are broadly similar across cohorts, with some differences observed relative to the RESOLVE control arm prior to balancing.

Pre-balance Clinical Characteristics

CLINICAL CHARACTERISTICS	RESOLVE TRIAL	B	D	E	F	G	H
N (number of patients)	213	57	351	1,357	347	305	677
Performance Status (KPS)							
100/90	69						
80/70	31						
Performance Status (ECOG)							
0		40.4	37.3	29	43.2	34.1	18
1		54.4	62.7	56	56.8	59.6	41.5
Unknown		3	0	0	0	6.3	40.5
Liver Metastasis Status							
Present	80	71.9	72.4	0	83.3	75.4	15.5
Absent	20	28.1	25.1	0	16.7	22.3	6.7
Unknown	0	0	2.6	100	0	2.3	77.8
Number of Sites of Metastases							
1	37.1	59.6	59.8	0	30.3	63	16.5
2	39.9	28.1	29.1	0	31.7	23.3	4
>2	22.1	12.3	6.8	0	37.2	11.4	1.6
Unknown	0	0	3.1	100	0.8	2.3	77.8
Prior Cancer Therapies							
Surgical Intervention	14	0	0	9	6.1	6.2	0
Radiation Therapy	3	0	0	0	0		0
Chemotherapy	0.5	0	0	0	0		0
None	82.5	100	0	0	93.9	93.8	0
Unknown	0	0	100	91	0	0	100

Percent of Patients in Each Category

Color Legend



Methodological Approach to Construct ECAs

Assess & Impute Missing Data

What information is missing across datasets, and can we address these gaps in a consistent and reliable way?

- Assess extent and pattern of missing covariates
- Impute missing values using multiple imputation

Propensity Score Balance

Can we identify and characterize patients in external data sources who are comparable to the RESOLVE control arm?

- Estimate patient-level control probabilities using flexible models
- Document model type, covariates

Matching/Weighting

After adjustment, how well can we balance baseline characteristics between patients in external data sources and the trial population?

- Apply matching/weighting as needed
- Assess covariate balance with standardized mean differences

Methodological Approach Characteristics

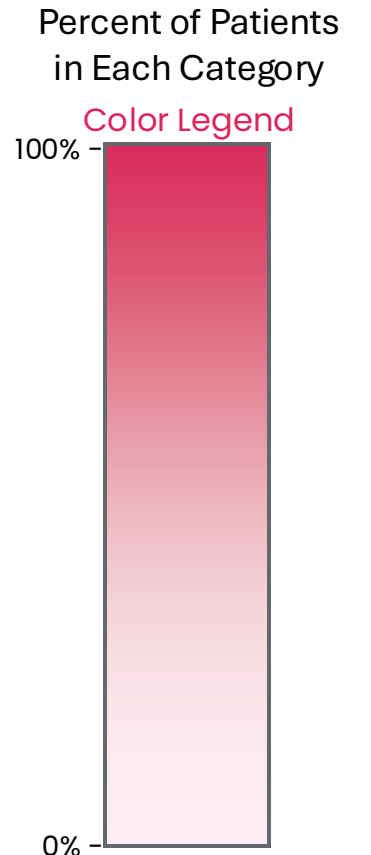
		Covariates					
		B	D	E	F	G	H
Demographics	Age	X	X	X	X	X	X
	Sex	X	X	X	X	X	X
	Race	X		X	X	X	
	Ethnicity	X		X	X		X
Clinical Characteristics	KPS/ECOG	X	X	X	X	X	X
	Liver Metastases	X	X		X	X	X
	Metastatic Sites	X	X		X	X	
	Prior Chemotherapy	X			X		
	Prior Radiation	X			X		
	Prior Surgery	X		X	X	X	
	Time from diagnosis to index	X	X	X	X	X	X
	Time from Stage IV to Dx	X	X	X	X	X	

	B	D	E	F	G	H
Model Type	Logistic regression	Logistic regression	Covariate Balancing PS	Logistic regression	Logistic regression	Logistic regression
Method	ATT Weighting	ATT weighting	Full matching	ATT weighting	ATT weighting	1:1 nearest neighbor matching
Number of Imputations	5	5	5	5	5	5
Matched / Weighted Patients	57	210 (210–210)	759 (754–768)	188	199 (194–210)	198 (197–200)
Covariates Balanced (SMD < 0.1)	12/20 (60%)	8/9 (88.9%)	36/36 (100%)	18/20 (90%)	8/9 (88.9%)	15/20 (75%)

A common SAP ensured methodological consistency, while dataset-specific choices reflect the realities of working with heterogeneous real-world and historical clinical data sources

Post-balance Demographic Characteristics

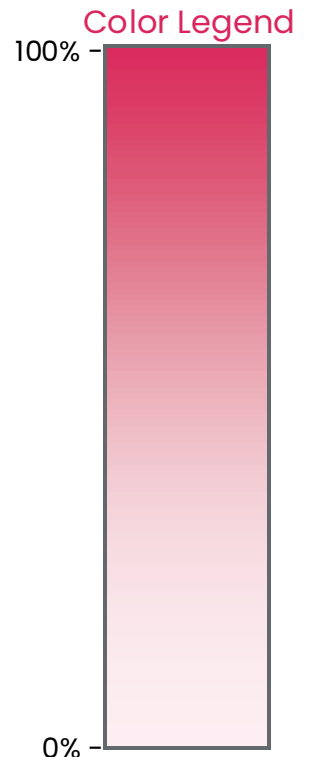
DEMOGRAPHICS	RESOLVE TRIAL	B	D	E	F	G	H
N (number of patients)	213	57	203.4	759	188	199.6	197.6
Age categories at index							
<65 years	55.9	29.8	53.8	53.8	49.3	41.6	27.5
>= 65 years	44.1	70.2	46	45	50.7	58.4	72.5
Sex: N(%)							
Female	43	31.6	41.7	46	44.8	44.1	46
Male	57	68.4	58.3	54	55.2	55.9	54
Race: N(%)							
White	67	80.7	0	67	69.6	73.6	73
Black or African American	3	5.3	0	3.1	3.7	19	8
Asian	28	0	0	28	24.1	2.1	2
Other	0	10.5	0	0	0.2	5.4	0
Unknown/Missing	2	3.5	100	2.7	2.4	0	16
Ethnicity: N(%)							
Hispanic or Latino	5	22.8	0	5.7	3.7	8.1	2
Not Hispanic or Latino	93	71.9	0	92	93.2	91.9	78
Unknown/Missing	2	5.3	100	2.7	3.2	0	20



Post-balance Clinical Characteristics

CLINICAL CHARACTERISTICS	RESOLVE TRIAL	B	D	E	F	G	H
N (number of patients)	213	57	203.4	759	188	199.6	197.6
Performance Status (KPS)							
100/90	69						
80/70	31						
Performance Status (ECOG)							
0		43.9	41.2	39	35.8	67.8	40.2
1		56.1	58.8	61	64.2	32.2	59.8
Liver Metastasis Status							
Present	80	71.9	78	0	82.2	77.3	81.4
Absent	20	28.1	22	0	17.8	22.7	18.6
Unknown	0	0	0	100	0	0	0
Number of Sites of Metastases							
1	37.1	60	33.1	0	36.9	32.2	70.1
2	39.9	28	29.7	0	28	29.7	16.5
>2	22.1	12	37.2	0	35.2	38.1	13.4
Unknown	0	0	0	100	0	0	0
Prior Cancer Therapies							
Surgical Intervention	14	0	0	15	8.2	11.3	0
Radiation Therapy	3	0	0	0	0	0	0
Chemotherapy	0.5	0	0	0	0	0	0
None	82.5	100	0	0	91.8	88.7	0
Unknown	0	0	100	85	0	0	100

Percent of Patients in Each Category

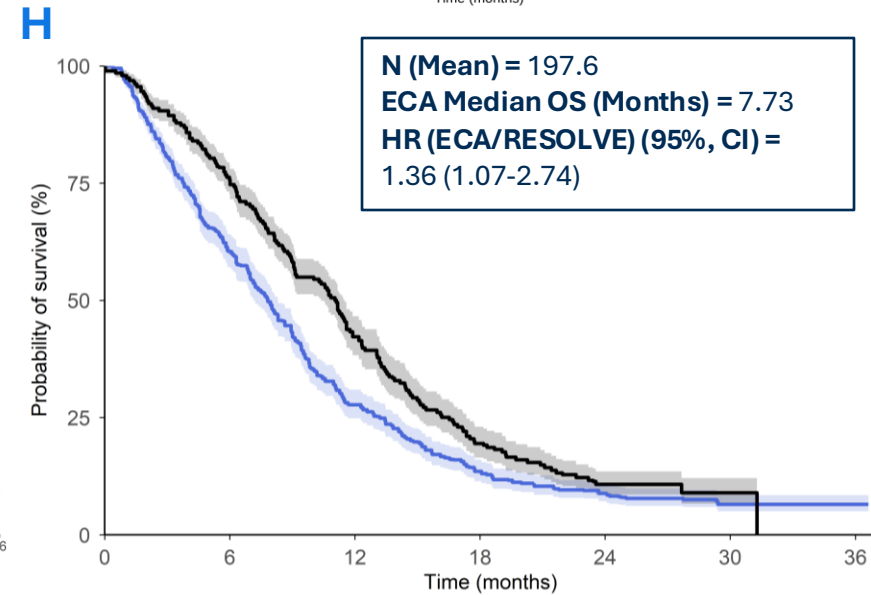
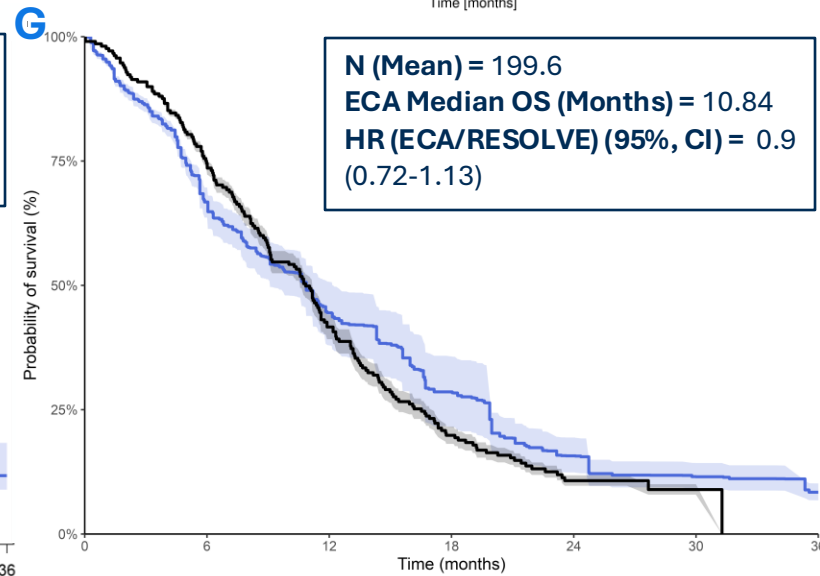
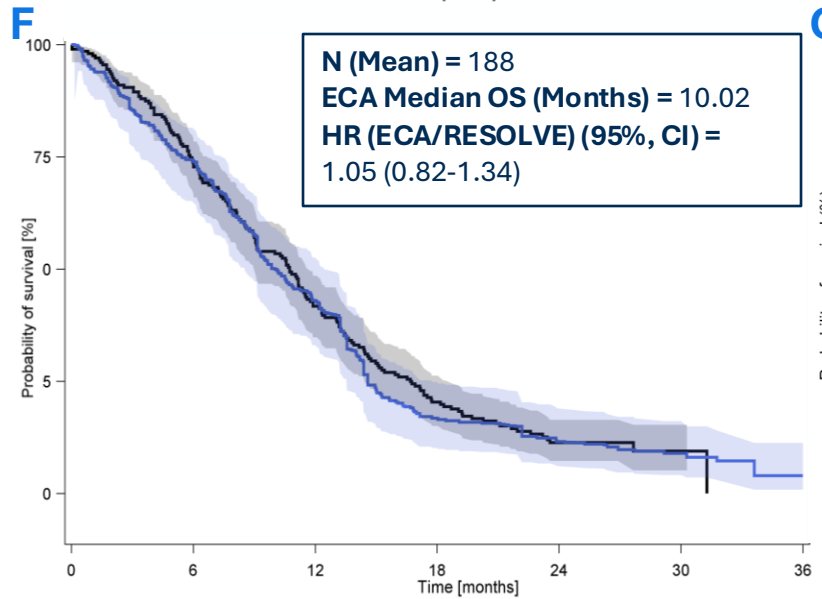
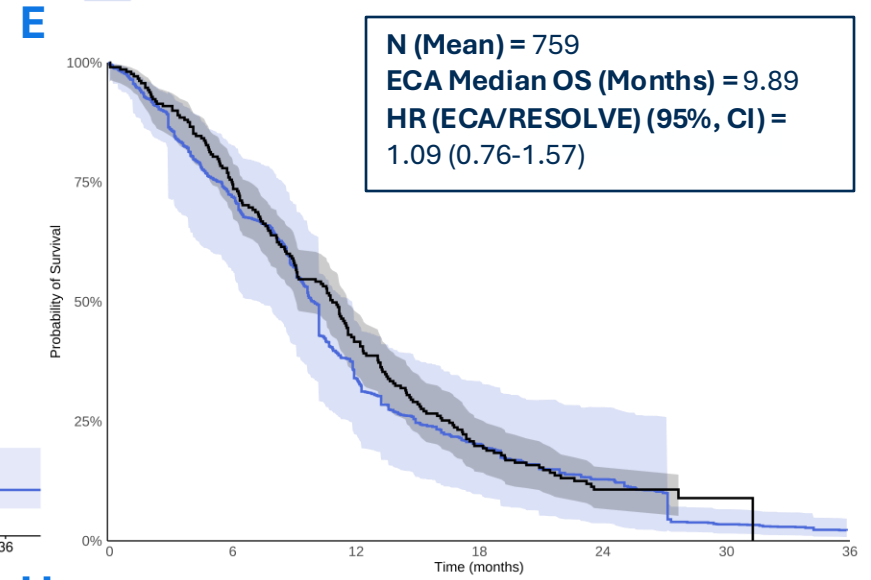
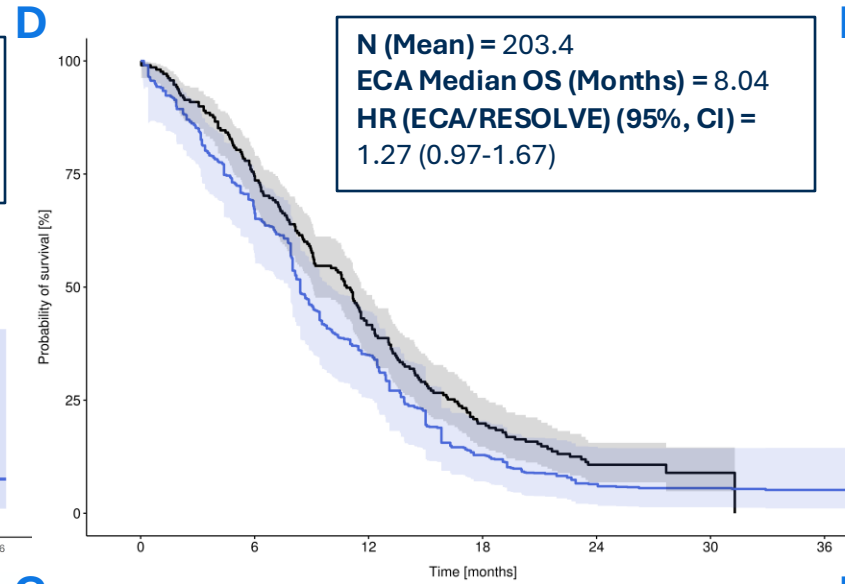
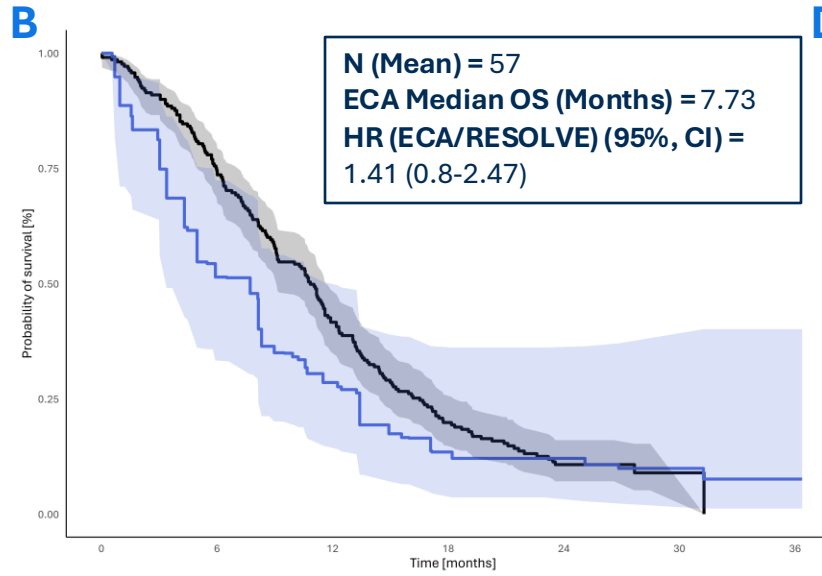


Estimation of Overall Survival (OS)

RESOLVE Median OS (Months) = 10.78

FRIENDS
of CANCER
RESEARCH

— RESOLVE Trial Control Arm
— External Comparator Arm



Preliminary Takeaways

- Independent construction of ECAs across heterogeneous external data sources is feasible under a shared statistical analysis plan
- Trial eligibility criteria and data availability substantially shape cohort composition
- Baseline covariate comparability can be achieved using appropriate matching and weighting approaches
- Outcome estimates vary across ECAs, reflecting differences in data sources and methodological choices
- Transparent documentation of data, eligibility implementation, and analytic decisions is essential

Future Directions

- Conduct additional sensitivity analyses to better distinguish the effects of data source differences, missingness, sample characteristics, and analytic methods
- Explore approaches to assess comparability between ECAs and the control arm of the target trial, including direction, magnitude, and uncertainty of effect estimates
- Evaluate the impact of more standardized methodological choices across sources, including matching vs. weighting and covariate selection
- Further assess how data completeness and balance of key prognostic variables influence alignment with the target trial

ECA Pilot Project Data Partners

- AbbVie
- American Society of Clinical Oncology (ASCO)
- ConcertAI
- Flatiron Health
- Guardian Research Network
- IQVIA
- iOMEDICO
- Medidata
- Ontada
- Pancreatic Cancer Action Network (PanCAN)
- Tempus AI
- Verana Health (COTA)

We thank the data partners and working group members for their valuable contributions throughout the project.