

## Background

- External control arms (ECAs) may strengthen evidence generation in oncology settings where randomized trials are infeasible, inefficient, or difficult to conduct.
- ECAs may be particularly relevant in rare cancers, high unmet need settings, or contexts where enrollment into traditional control arms is challenging.
- However, confidence in ECAs depends on whether external data sources can reliably identify patients comparable to a target clinical trial population and generate outcomes that approximate the randomized control arm.
- Friends of Cancer Research led a multi-stakeholder pilot project to evaluate whether independently constructed ECAs, developed using a shared statistical analysis plan across diverse real-world and historical clinical trial data sources, could approximate the control arm of a randomized oncology trial.

## Methods

- A multi-stakeholder partnership developed a common protocol and statistical analysis plan to guide independent construction of ECAs across data sources and achieve the following objectives:
  - Evaluate reproducibility:** assess whether independently constructed ECAs could approximate the same randomized trial control arm.
  - Characterize variability:** identify how data sources, eligibility implementation, missingness, and methodological choices impacted comparability between ECAs and the target trial.
  - Identify fit-for-purpose considerations:** generate practical insights into when ECAs may be sufficiently reliable to support evidence generation and regulatory decision-making
- Nine external data partners (ConcertAI, COTA, Flatiron Health, Guardian Research Network/IQVIA, iOMEDICO, Medidata, Ontada, Pancreatic Cancer Action Network, and Tempus) identified and analyzed external cohorts of patients with metastatic pancreatic ductal adenocarcinoma receiving first-line gemcitabine plus nab-paclitaxel to approximate the control arm of the RESOLVE randomized clinical trial, as defined by the criteria specified below.

## CONSORT Diagram

Eligibility Criteria	Eligible Patients in Cohort (n, % excluded from previous step)								
	A	B	C	D	E	F	G	H	I
Adults (≥18) with mPDAC, 1L nab-paclitaxel + gemcitabine (May 2013–Jul 2021)	1333	236	125	746	5477	386	1117	3274	308
Pts with adenocarcinoma histology	1332	233	125	746	5477	386	1076	3274	296
Pts with no brain or leptomeningeal disease before index	1330	232	122	745	5469	386	1070	3274	296
Pts with no stroke or intracranial hemorrhage in prior 6 months	1320	231	122	745	5402	386	1024	3274	282
Pts with no other primary cancer in past 3 years (except NMSC/CIS)	1288	229	122	745	5402	379	949	3163	267
Pts with no surgery within 4 weeks of index (exp. PDAC biopsy, infusion placement)	1278	219	120	729	5397	379	928	3163	267
Pts with no prior systemic therapy for PDAC	988	166	57	620	3836	349	750	2540	177
Pts with no adjuvant radiotherapy within 6 months of mPDAC diagnosis	984	166	54	620	3836	349	733	2540	155

Eligibility Criteria	Eligible Patients in Cohort (n, % excluded from previous step)								
	A	B	C	D	E	F	G	H	I
Lab eligibility: hematologic function	984	166	54	620	3836	349	733	2540	155
Lab eligibility: hepatic & renal function	344	106	NC	517	2319	347	535	1328	147
Pts with adequate hematologic function	374	109	54	517	2531	349	551	1657	147
Pts with no transfusions or growth factor use within 30 days	371	106	54	517	2422	347	550	1630	147
Lab eligibility: hepatic & renal function	192	67	54	399	1643	347	372	791	82
Pts with ECOG 0–1 or KPS ≥70, or no PS recorded	158	57	52	351	1357	347	305	677	81

**Trial eligibility criteria could be implemented across external data sources, but attrition varied by source and was largely driven by prior treatment, laboratory criteria, and missing or non-captured data, highlighting eligibility operationalization as a key source of ECA variability.**

## 1. Pre-balanced Cohort Characteristics

DEMOGRAPHICS	RESOLVE TRIAL	B	D	E	F	G	H
<b>N (number of patients)</b>	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

CLINICAL CHARACTERISTICS	RESOLVE TRIAL	B	D	E	F	G	H
<b>N (number of patients)</b>	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	15	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	0
Chemotherapy	0.5	0	0	0	0	0	0
None	82.5	100	0	0	93.9	93.8	0
Unknown	0	0	100	91	0	0	100

Demographic and clinical characteristics of the external cohorts were broadly similar to the RESOLVE control arm, though variability was observed across key prognostic factors, including age, race/ethnicity, performance status, liver metastases, and number of metastatic sites. Numbers indicate the proportion of patients in each category. Pink shading is used to denote the proportion of patients for each category (light pink: lower proportion, dark pink: higher proportion).

## 2. Methodological Approach Characteristics

Available Covariates		B	D	E	F	G	H	
Demographics	Age (continuous)	X	X	X	X	X	X	
	Age (categorical)	X	X	X	X	X	X	
	Sex	X	X	X	X	X	X	
	Race	X		X	X	X	X	
	Ethnicity	X		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	X	
	Prior Treatment	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	X		

Propensity Score Model Characteristics and Covariate Balance Across Data Partners						
	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
Matched / Weighted Patients	57	210 (210–210)	759 (754–768)	188	199 (194–210)	198 (197–200)
PS covariates available n (% of 10)	10/10 (100%)	8/11 (72.7%)	9/11 (81.8%)	11/11 (100%)	11/11 (100%)	10/11 (90.9%)
PS covariate subcategories balanced % of subcategories used	57.9%	88.8%	100%	90%	83.3%	100%

**A shared statistical analysis plan aligned eligibility criteria, baseline covariates, and analytic approaches across partners, while differences in available covariates, data completeness, and dataset-specific operational decisions shaped cohort construction and analytic feasibility.**

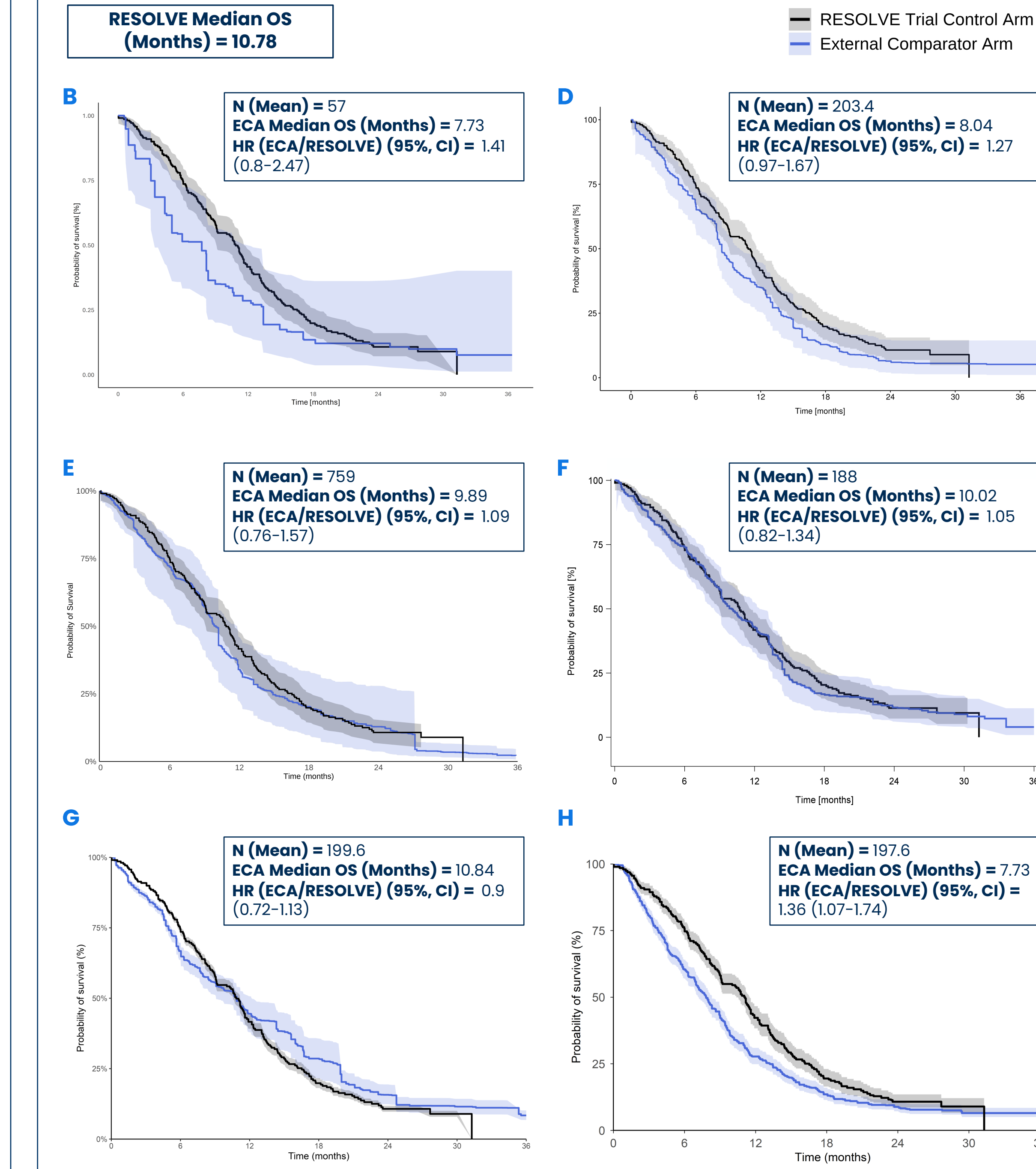
## 3. Post-balanced Cohort Characteristics

DEMOGRAPHICS	RESOLVE TRIAL	B	D	E	F	G	H
<b>N (number of patients)</b>	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

CLINICAL CHARACTERISTICS	RESOLVE TRIAL	B	D	E	F	G	H
<b>N (number of patients)</b>	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

**Propensity score adjustment improved alignment with the RESOLVE control arm, but covariate balance depended on data completeness, cohort size, and availability of key prognostic factors, underscoring the need to assess data fitness before interpreting ECA results.**

## 4. Estimation of Overall Survival (OS)



**Median OS estimates across ECAs ranged from ~7.7 to 10.8 months compared with 10.8 months in the RESOLVE control arm, demonstrating that external cohorts could generate survival estimates broadly aligned with the target trial.**

**Hazard ratio (HR) estimates ranged from ~0.9 to 1.4 versus RESOLVE, with greater divergence in cohorts with smaller sample sizes, greater missingness, or less complete covariate balance.**

## Conclusions & Future Directions

- Independent ECA construction was feasible across heterogeneous external data sources using a shared statistical analysis plan.
- Differences in eligibility implementation, covariate availability, missingness, and analytic choices may have affected cohort construction, baseline balance, and OS estimates.
- Propensity score methods improved alignment with the RESOLVE control arm, but balance depended on the availability and completeness of key prognostic factors.
- Outcome estimates were broadly comparable to the RESOLVE control arm, but variability across ECAs underscores the need to interpret results in the context of data fitness and analytic implementation.
- Transparent documentation of operational and analytic decisions is essential for interpreting ECA results and assessing whether an ECA is fit-for-purpose.
- Additional analyses could assess how standardizing methodological choices, including covariate selection, matching versus weighting, and handling of missing data, affects ECA comparability.

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