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A Framework for Accelerating Clinical Development with Real-World External Control Arms (ECA) in Phase 2 trials

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Why External Control Arms (ECA) for Phase 2 Trials?

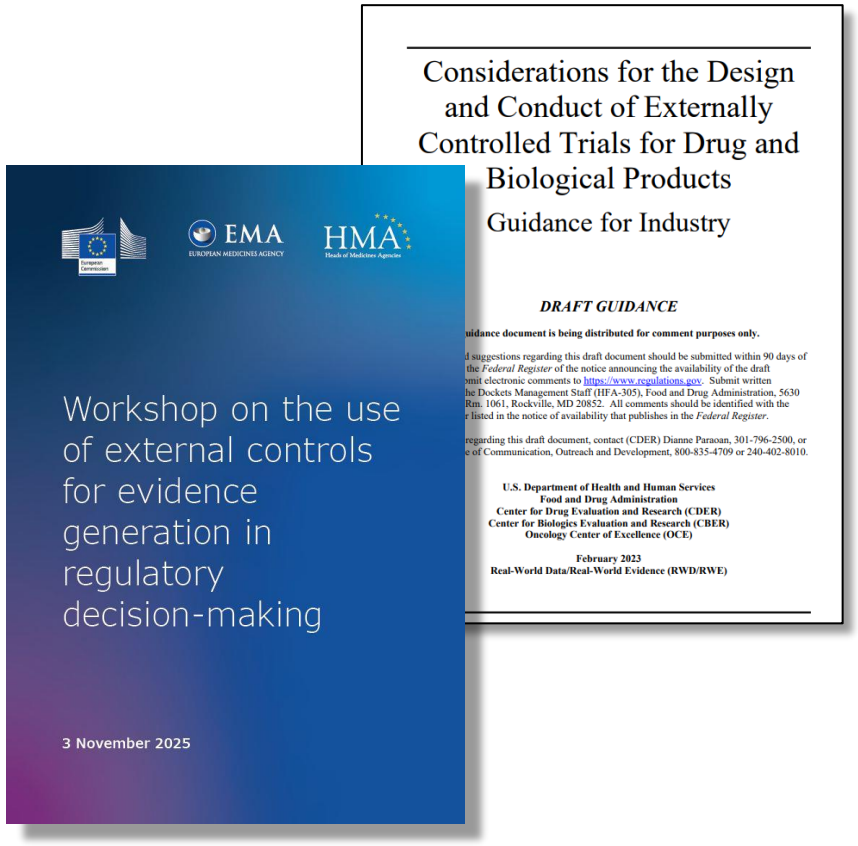
ECAs derived from real world data are increasingly accepted in Phase 3 trials to support regulatory decision making

- Greater understanding of optimal settings for application
- Maturing methodologies

Phase 2 trials face unique challenges:

- Small sample sizes
- Limited comparator context
- Early signal interpretation is critical for go/no-go decisions

Opportunity: Can we extend state-of-the-science ECA design earlier upstream in clinical development in the setting of a Phase 2 single arm trial?



A Framework for ECA Methods Extended to Phase 2 Single Arm Study Design

Objective:
Design a contemporaneous ECA for an *in–progress* Phase 2 trial with the goal of rapidly generating research-grade evidence to support clinical development

1	**Fit for purpose data selection & provenance**
2	**Trial emulation design**
3	**Trial eligibility emulation**
4	**Confounding control**
5	**Sensitivity analysis & simulation**

Fit for Purpose Data Selection & Provenance: The McKesson Oncosystem

SCRI Sarah Cannon Research Institute

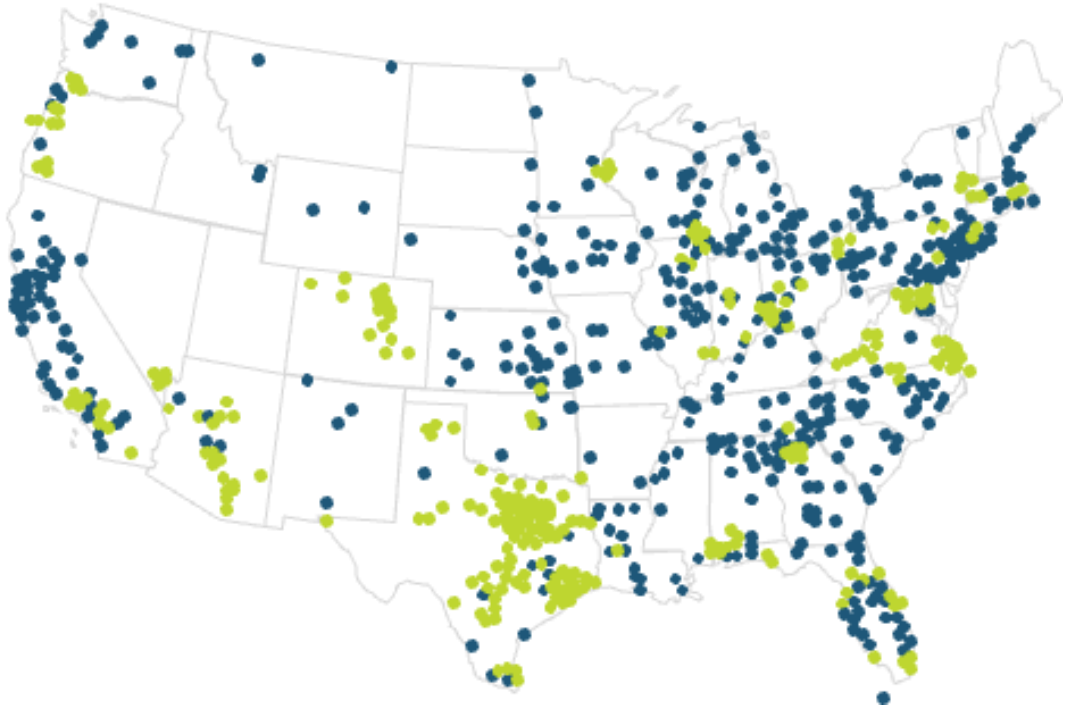
Global Leader in Clinical Trials

- **850 first in human trials** since inception
- Contributed to pivotal research leading to the majority of new cancer therapies **FDA approved** today
- Former a **joint venture with the US Oncology Network** in 2022

The US Oncology Network

Largest Community Oncology Network

- Over **2,700** oncology providers across the US
- Neraly **1 in 4 U.S. cancer patients** treated with The Network
- 15-year longitudinal data from near real-time, linked EHR, molecular, and outcomes data
- Fully **traceable** data
- Contributed to **100+ FDA approvals**



The US Oncology Network Practice

McKesson Provider Solutions Oncology Practice

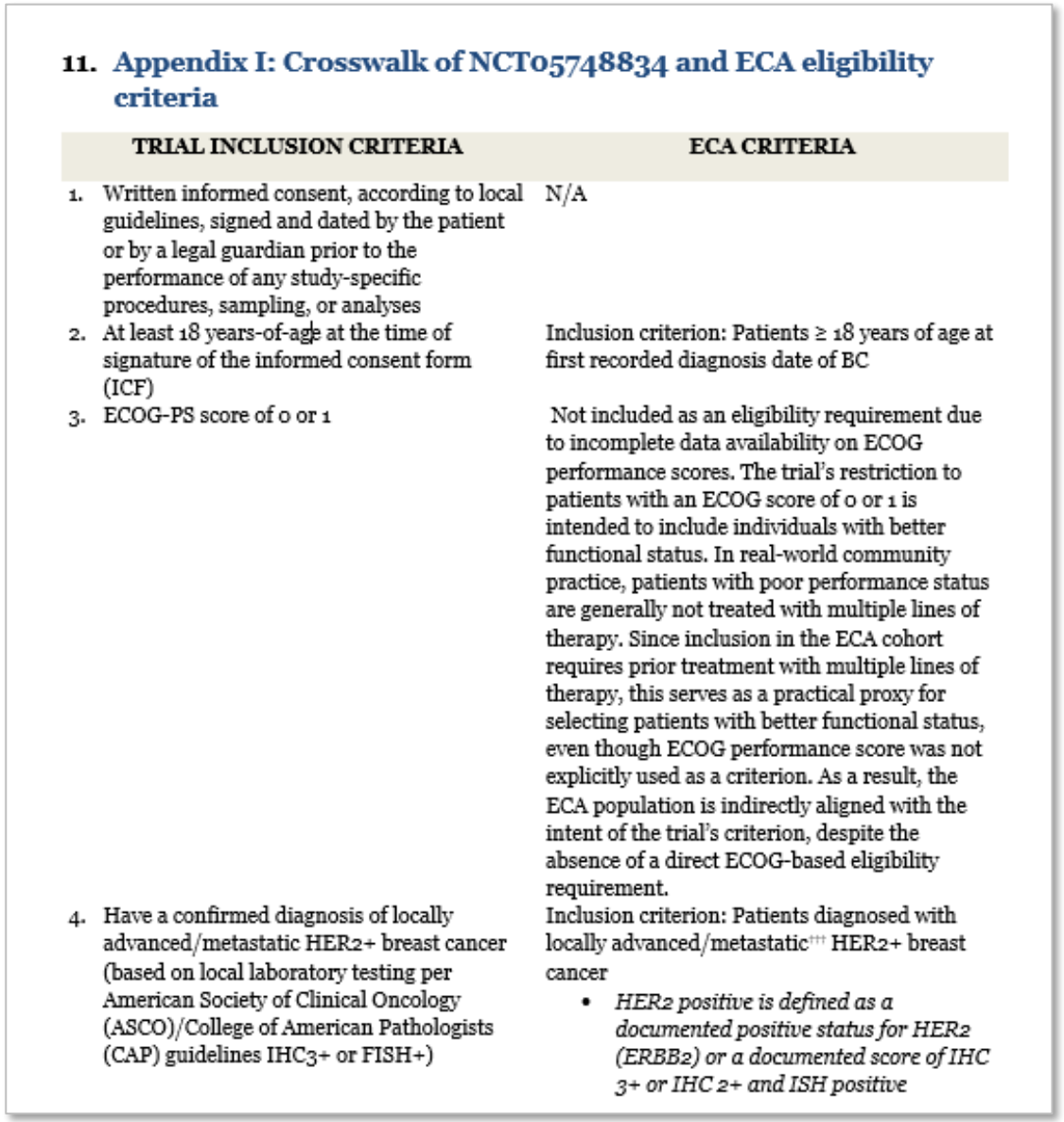
	Phase 2 Single Arm Open Label Trial (NCT05748834: PI: Erika Hamilton MD)	Real-World External Control Arm
P	Participants with HER2+ breast cancer with >1 line of anti-HER2therapy for locally advanced/metastatic disease or relapsed <6 mos of completion of anti-HER2 adjuvant therapy. Target sample size of **36 patients**.	Patients treated within The US Oncology Network and diagnosed with advanced/metastatic HER2+ BC who initiated at least one subsequent SOC line of therapy following anti-HER2 therapy received within the advanced/metastatic setting
I	Tucatinib 300mg 2x/day in combination with Doxil 40mg/m2 givenIV on day 1 of each 28 day cycle	Qualifying standard of care (SOC) treatment in ≥ 2L following the receipt of at least one prior line of anti-HER2 therapy
C	No Comparator: single arm, open label	N/A
O	**Primary**: Objective response rate (ORR) via RECIST v1.1; **Secondary**: Progression free survival (PFS), tx-related AE's	**Primary**: physician-reported objective response rate (PR-ORR): **Secondary**: physician-reported PFS (PR-PFS)
T	**Index**: Trial enrollment; **Follow up**: to 40 months	**Index:** initiation of a standard-of-care treatment regimen; **Follow up**: variable (date of last contact, date of death or end of observation period)

Trial eligibility emulation strategy

1. **Exact emulation** using available real-world data sources with adequate completeness
   - When not possible, a **proxy** was developed with a team of medical oncologists and epidemiologists
   - Priorities:
     1. Alignment with **prognostically significant information**
     2. Real world data **completeness**

2. **Timeframes** for assessment adapted to allow for realistic alignment with routine care

3. **Structured data** elements prioritized where possible



11. Appendix I: Crosswalk of NCT05748834 and ECA eligibility criteria

	TRIAL INCLUSION CRITERIA	ECA CRITERIA
1.	Written informed consent, according to local guidelines, signed and dated by the patient or by a legal guardian prior to the performance of any study-specific procedures, sampling, or analyses	N/A
2.	At least 18 years-of-age at the time of signature of the informed consent form (ICF)	Inclusion criterion: Patients ≥ 18 years of age at first recorded diagnosis date of BC
3.	ECOG-PS score of 0 or 1	Not included as an eligibility requirement due to incomplete data availability on ECOG performance scores. The trial's restriction to patients with an ECOG score of 0 or 1 is intended to include individuals with better functional status. In real-world community practice, patients with poor performance status are generally not treated with multiple lines of therapy. Since inclusion in the ECA cohort requires prior treatment with multiple lines of therapy, this serves as a practical proxy for selecting patients with better functional status, even though ECOG performance score was not explicitly used as a criterion. As a result, the ECA population is indirectly aligned with the intent of the trial's criterion, despite the absence of a direct ECOG-based eligibility requirement.
4.	Have a confirmed diagnosis of locally advanced/metastatic HER2+ breast cancer (based on local laboratory testing per American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines IHC3+ or FISH+)	Inclusion criterion: Patients diagnosed with locally advanced/metastatic††† HER2+ breast cancer • *HER2 positive is defined as a documented positive status for HER2 (ERBB2) or a documented score of IHC 3+ or IHC 2+ and ISH positive*

Confounder Selection & Propensity Score Model

- Covariate selection was defined *a priori* based on ***subject matter knowledge*** with a committee of data scientists, informaticians, oncologists and epidemiologists
  - Prioritize variables that could inform treatment selection and primary and secondary outcomes based on literature and expert clinical input

Age at baseline	Line of therapy at index date (1, 2, 3, 4+)	Number of metastatic sites (0, 1, 2, etc)
Disease Free Interval (days)	Hormone Receptor Status (positive/negative)	Prior exposure to tucatinib (yes/no)
	Previous exposure of neratinib or enhertu (none, either, both)	

Goal: Contemporaneous ECA assembly; interim exploration of feasibility of adequate sample and covariate balance

Trial:

Target enrollment: n=36
12 currently enrolled

60 simulated patients from Phase 2 trial (1 original sample and 4 bootstrap subsamples)

ECA:

2-stage sampling:
Structured data (n=150) followed by unstructured data

Target: up to n=108 (3:1)

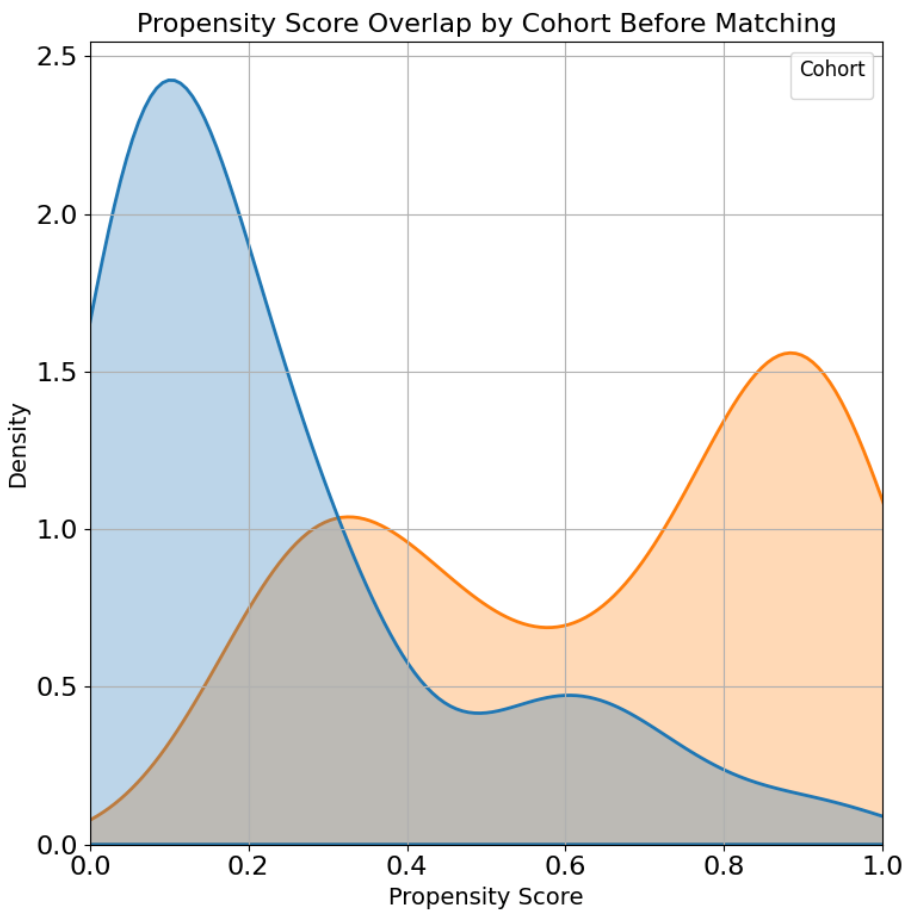
Index: initiation of a standard-of-care treatment regimen

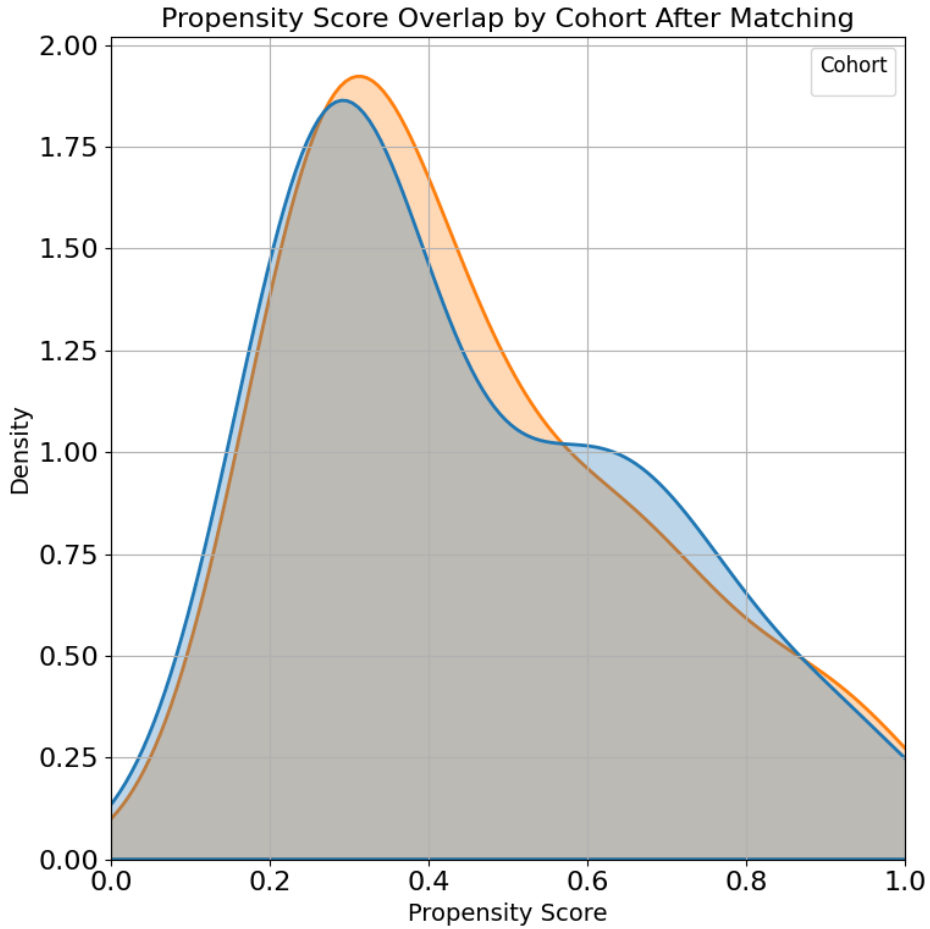
Analysis Methods:

PS matched analysis included 33 matched pairs

PS-weighted analysis included n=12 trial and n=74 ECA patients

Distribution of the Propensity Score Before and After Matching





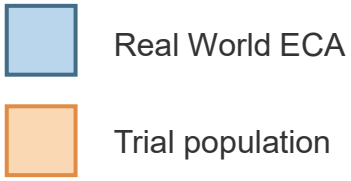


Table 1: Baseline characteristics of ECA and Trial patients after PS Matching

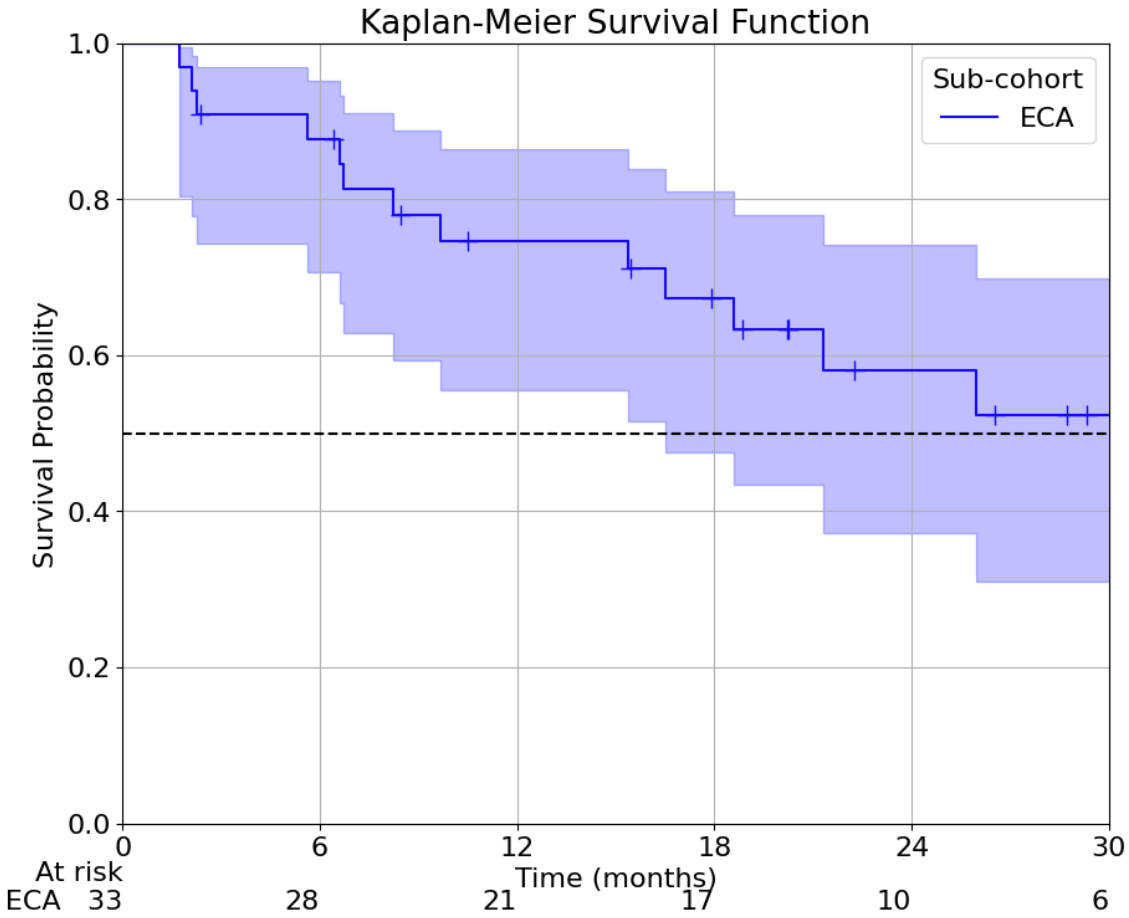
	External Control Arm (n=33)	Trial Arm (n=33)	p value
Age (years)			0.75
Mean (SD)	63.5 (13.0)	64.1 (9.8)	
Line of therapy at index			0.75
Mean (SD)	2.6 (1.2)	2.6 (1.0)	
Median (IQR)	3 (2, 4)	2 (2, 3)	
Number of metastases at index			0.78
Mean (SD)	2.5 (1.4)	2.5 (1.4)	
Median (IQR)	2 (1, 3)	3 (2, 3)	
Disease free interval (days)			0.93
Mean (SD)	986 (1926)	992 (1577)	
Prior exposure to Enhertu, N (%)	16 (49%)	16 (49%)	1
Prior exposure to Tucatinib, N (%)	12 (36%)	11 (33%)	1
Prior exposure to Neratinib, N (%)	4 (12%)	4 (12%)	1

Table 2: Baseline characteristics of ECA and Trial patients after IPW (ATT approach)

	External Control Arm (n=91)	Trial Arm (n=60)	p value
Age (years)			0.79
Mean (SD)	67.4 (10.2)	66.7 (10.4)	
Line of therapy at index			0.41
Mean (SD)	3.1 (0.97)	2.8 (1.0)	
Median (IQR)	3 (2, 4)	2.5 (2, 4)	
Number of metastases at index			0.78
Mean (SD)	1.8 (1.1)	1.7 (1.4)	
Median (IQR)	1 (1, 2)	2 (0, 3)	
Disease free interval (days)			0.47
Mean (SD)	809 (1663)	1066 (1530)	
Prior exposure to Enhertu, N (%)	56 (75%)	31 (52%)	0.01
Prior exposure to Tucatinib, N (%)	35 (47%)	22 (37%)	0.57
Prior exposure to Neratinib, N (%)	6 (8%)	4 (7%)	0.88

ECA Outcome Data Available Before Trial Completion:

Time to OS for ECA Cohort among ECA Patients (n=33) Matched to Trial Cohort



Summary: A Framework for ECA Methods Applied to Phase 2 Single Arm Study Design

1	**Fit for purpose data selection**	Data sourced from a large community oncology network (full traceability) overlapping trial catchment population; Secondary use of data sourced from an EHR & supplemented with custom chart abstraction
2	**Trial emulation design**	Contemporaneous external control arm (ECA) cohort study design; coordination with trial PI; heavy subject matter involvement
3	**Trial eligibility emulation**	Data scientist, epidemiologist, informatician, biostatistician and medical oncologist collaboration to adapt trial eligibility to real-world setting
4	**Confounding control**	Subject matter driven; matching on Propensity Score
5	**Sensitivity analysis & simulation**	Bootstrap simulation to address small trial sample sizes; Iterative refinement as trial accrues, independent of outcome data; IPTW PS methods as sensitivity

Conclusions and Next Steps

1

Accelerate Early Phase Development:

Contemporaneous ECA development - without trial outcome data - to accelerate availability of contextual evidence

2

Advanced techniques to cope with Ph 2 design:

Simulation stabilized matching in small trial sizes

Subject matter expertise is critical (as always!)

3

Extension:

Robustness of these methods warrants further exploration

As trial completes enrollment, reassess patient balance & generate primary & secondary outcome data

Scale framework to other indications

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Thank you!

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