De Novo Request for

IceCure Medical Ltd.'s ProSense Cryoablation System

U.S. Food & Drug Administration

Center for Devices and Radiological Health

General and Plastic Surgery Devices Panel Meeting

November 7, 2024

Agenda

Background

Steven Nagel, M.D. & Jinfeng Tian, Ph.D.

ICE3 Study

Steven Nagel, M.D. & Xu Zhang, Ph.D.

Systematic Literature Review of Standard of Care Outcomes

Areej Hamid Haj Ali Idris, M.P.H.

Benefit-Risk Considerations

Jessica Carr, Ph.D.

Clinical Background

Steven Nagel, M.D., FACS

Clinical Context: Breast Cancer

Breast cancer is the most commonly diagnosed cancer among U.S. women, excluding nonmelanoma skin cancer.

- **1 in 8 women** will develop breast cancer in the U.S. during their lifetime.
- It is estimated there will be **310,720 new cases in 2024** of female breast cancer.
- **Invasive ductal carcinoma is the most common** type, representing 70-80%.

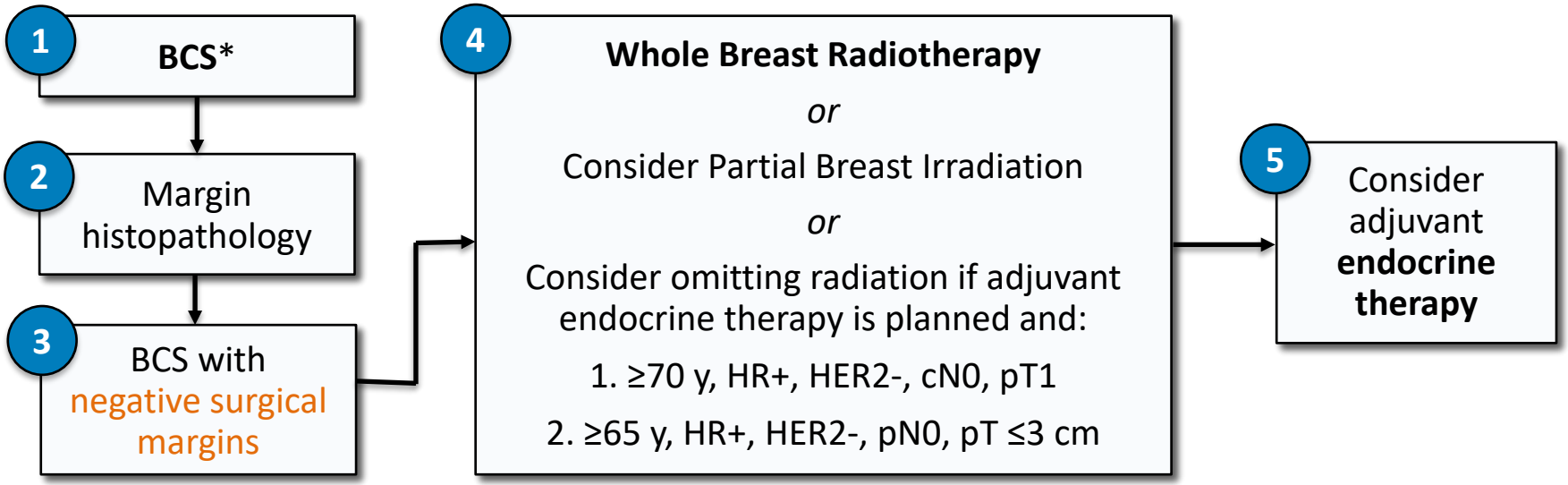
Factors Impacting Clinical Prognosis

Factor	Favorable Prognosis	Adverse Prognosis
Patient Age	Older women may have less aggressive disease at diagnosis	Younger women more aggressive disease, more likely to recur
Anatomic Features	Low to intermediate grade (T1 N0 M0) less aggressive, lower recurrence rates	High grade, lobular carcinoma, multifocality, extensive intraductal component, lymphovascular invasion
Receptor Status	Hormone Receptor positive (ER+ or PR+) less aggressive disease	HER2 overexpression (HER2+) more aggressive disease
Luminal Subtype	Luminal A Lowest recurrence rate, develops recurrence late	High Ki-67 index aggressive disease

The ProSense System is intended for early stage, low-risk patients:
≥60 years, Histological Grade 1-2, tumor size ≤1.5 cm, N0, ER+, PR+/-, HER2-

Treatment Per Clinical Guidelines

Locoregional treatment for cT1, N0, M0, HR+, HER2- breast cancer is **Breast Conserving Surgery (lumpectomy) followed by Radiotherapy**



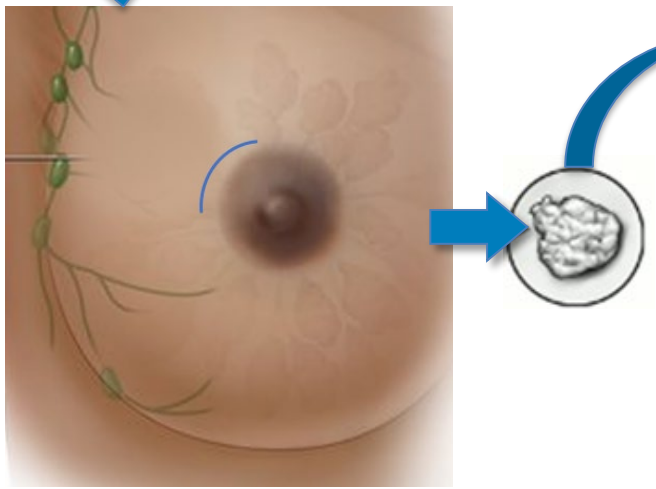
*Mastectomy may be indicated for certain patients

2024 National Comprehensive Cancer Network® Version 5.2024 – October 15, 2024

Breast Conserving Surgery (lumpectomy)

Lumpectomy for a 1.5 cm tumor:

- can be performed under general anesthesia, light sedation, or local anesthesia
- outpatient procedure
- 15-40 minutes from incision to bandage



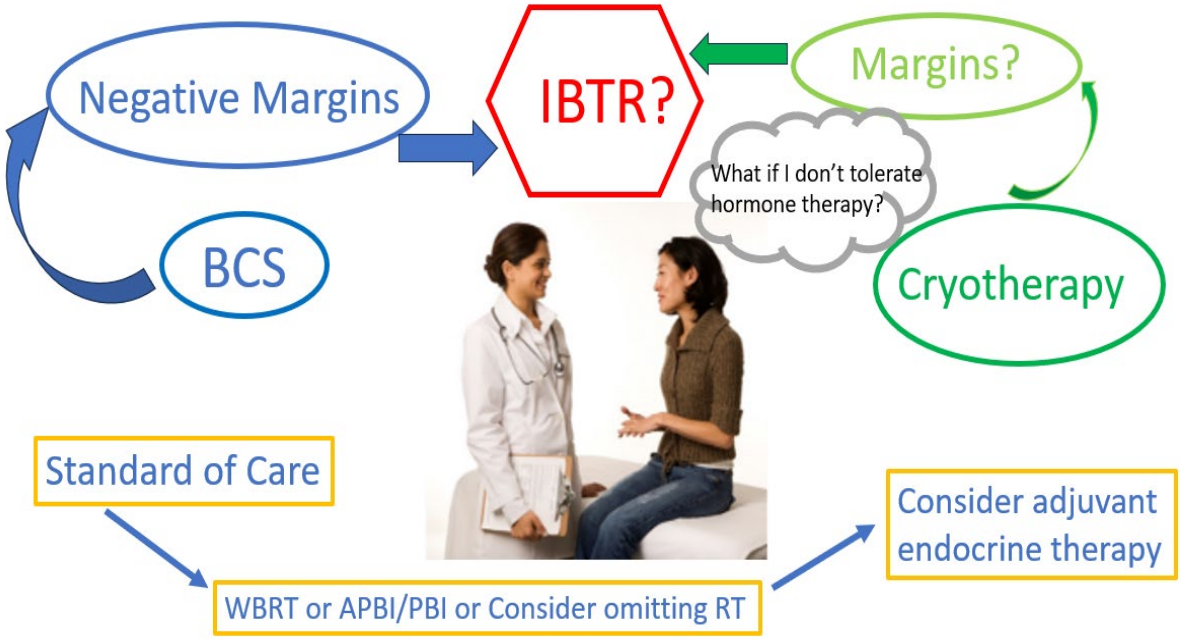
Processes to facilitate negative margins:

- specimen radiograph
- cavity shave margins
- intraoperative pathology assessment

Modified images from NIH (cancer.gov) and American Cancer Society (cancer.org)

Importance of Surgical Margins

Negative margins reduce the odds of recurrence.
With cryoablation, there is no surgical specimen for evaluation of treatment success.



The panel will be asked to comment on the risk of breast cancer recurrence with ProSense

Regulatory Background

Jinfeng Tian, Ph.D.

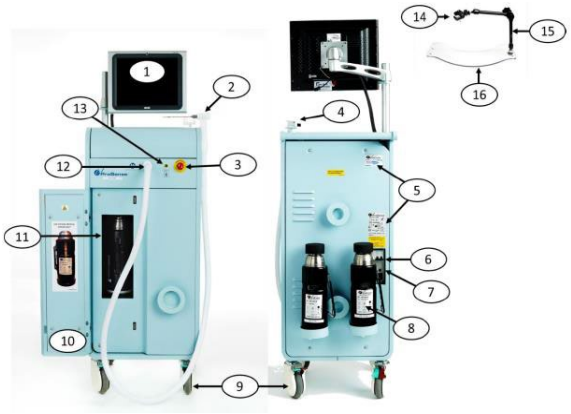
Regulatory Context: Cryosurgical Devices

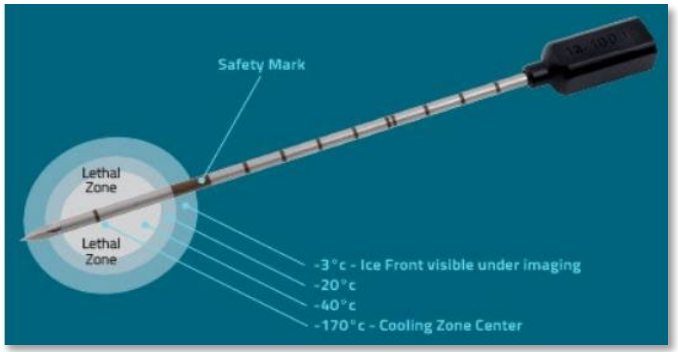
No devices have FDA marketing authorization for the treatment of breast cancer, e.g., in lieu of lumpectomy.

- Cryosurgical technology has been **marketed and used** in the U.S. since **before 1976**.
- Marketing authorization to date is for **cryogenic destruction** of tissue, including **ablation** of tumors and benign breast lesions.
- **For ablation indications**, **bench testing is typically sufficient** to validate specifications and substantially equivalent performance with marketed devices.

ProSense Cryoablation System

Prior clearances:	Use as a cryosurgical tool in multiple surgical fields, including general surgery for breast fibroadenomas
Mechanism:	A cryoprobe is inserted through a small skin incision and cooled using liquid nitrogen to create extremely low temperatures that ablate tissue
Monitoring:	Ultrasound monitors the ice ball size in real time during treatment





cryoprobe schematic

Proposed Indications for Use (IFU)

Treatment of patients with <u>early stage, low risk breast cancer</u> with adjuvant endocrine therapy

- Unifocal tumor, size ≤ 1.5 cm
- Clinically lymph node negative
- Patients ages ≥60 years
- Infiltrating ductal carcinoma
- ER+, PR+/-, HER2-
- Histological Grade 1-2

Excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion

De Novo Submission Evaluation

IceCure Medical submitted a De Novo request for the new IFU.

- A De Novo sets the stage for future similar products by establishing “special controls” imposed on all subsequent devices of that type.

- Your perspectives will be incorporated into FDA’s decision regarding:
  - **Assessment of probable benefits**
  - **Assessment of probable risks**
  - **Assessment of additional factors, including:**
    - **Uncertainty**
    - **Patient perspectives**
    - **Addressing unmet medical need**

The panel will be asked to vote on whether the benefits outweigh the risks

ICE3 Study Overview

Steven Nagel, MD FACS

‘Ablate and Resect’ Background Data

Single-Arm Literature Studies	
Study method	Ablate and resect
Device	Argon gas & LN2-based systems (ProSense System was not used)
No. subjects	9-99, depending on the cohort
Tumor size	Up to 2 cm
Tumor type	IDC / DCIS
Time to resection	14-30 days
Major findings	Complete tumor necrosis ranging from 79% (T≥1cm) to 100% (T<1cm)
Reported limitations	Evaluating tumor extent prior to cryoablation and treatment effectiveness afterwards; negative predictive value of MRI was 81%

Roubidoux et al. 2004, Sabel et al. 2004, Simmons et al. 2016 (ACOSOG Z1072), Manenti et al. 2011

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The panel will be asked to comment on the ability of standard of care imaging technology to accurately characterize tumor size and extent prior to surgery.

Roubidoux et al. 2004, Sabel et al. 2004, Simmons et al. 2016 (ACOSOG Z1072), Manenti et al. 2011

ICE3 Pivotal Study Overview

Design	**Non-randomized, single-arm study**
Investigational sites	19 U.S. clinical sites
Population	206 women with early stage, low risk breast cancer and target tumor size ≤1.5 cm
Primary Endpoint: **IBTR rate at 5-years**	IBTR is "evidence of invasive or in situ breast cancer in the ipsilateral breast or chest wall." Biopsy was required to confirm diagnosis of suspicious lesions.

FDA did not provide input on study design, endpoints, or analysis plan prior to study initiation.

ICE3 Study Performance Goal

Protocol-defined success criterion for the Primary Endpoint:
95% CI upper bound at 5-years is **<10%**

IceCure literature IBTR rate (5%)* + reference margin (5%) = 10% Goal

Some articles included patients with higher risk factors for recurrence than the intended population, e.g.:

- tumors >1.5 cm
- tumor grade 3
- ER-
- Cohorts with no patients receiving radiotherapy

The panel will be asked to comment on the strengths and limitations of the single-arm, nonrandomized study design with a literature-based performance goal.

ICE3 Study Secondary Endpoints

- Adverse Events
- NCCN Distress Thermometer (patient survey at baseline and 6 months)
- Cosmetic satisfaction (5-point scale; patient and provider at each follow-up)
- Regional invasive breast tumor recurrence rate
- Distant metastases rate including contralateral breast cancer
- Disease-Free Survival (DFS)
- Overall Survival (OS)
- Breast Cancer Survival (BCS)

The protocol definition of DFS included:

- *local (DCIS or invasive), regional, or distant breast cancer recurrence*
- *second primary cancer*
- *DCIS or invasive contralateral breast cancer, or*
- *death due to any cause*

ICE3 Enrollment Criteria

Key Inclusion Criteria

1. Diagnosis of invasive ductal breast carcinoma by core needle biopsy, meeting the following criteria:
   a. Unifocal primary disease
   b. Tumor size ≤1.5 cm in greatest diameter
   c. Nottingham score 1-2; **nuclear & mitotic scores ≤ 2**
   ~~**d. Ki-67 < 14%**~~
   e. ER positive and/or PR positive
   f. HER2 negative
   g. Lymph node negative (N0)
2. Age **≥** ~~**65**~~ 50 (Local IRB), Age ≥ ~~**65**~~ 60 (WCG IRB)
3. Breast size adequate for safe cryoablation

Key Exclusion Criteria

1. Presence of lobular carcinoma
2. Presence of luminal B pathology
3. Nottingham score of 3
4. Presence of microinvasion, or invasive breast carcinoma, extensive intraductal component (EIC)
5. Presence of multifocal and/or multicentric breast cancer
6. Presence of multifocal calcifications
7. Presence of prior or concurrent neo-adjuvant chemotherapy for breast cancer

Modifications during the study:
(1) Removal of Ki-67<14%; (2) Addition of nuclear & mitotic score ≤ 2; (3) Reduced age cut-off

ICE3 Study Procedures

1. **Imaging**
by mammography, ultrasound, and in some cases MRI to ensure eligibility

2. **Treatment with cryoablation therapy**
under local anesthesia and ultrasound visualization.

Default treatment:

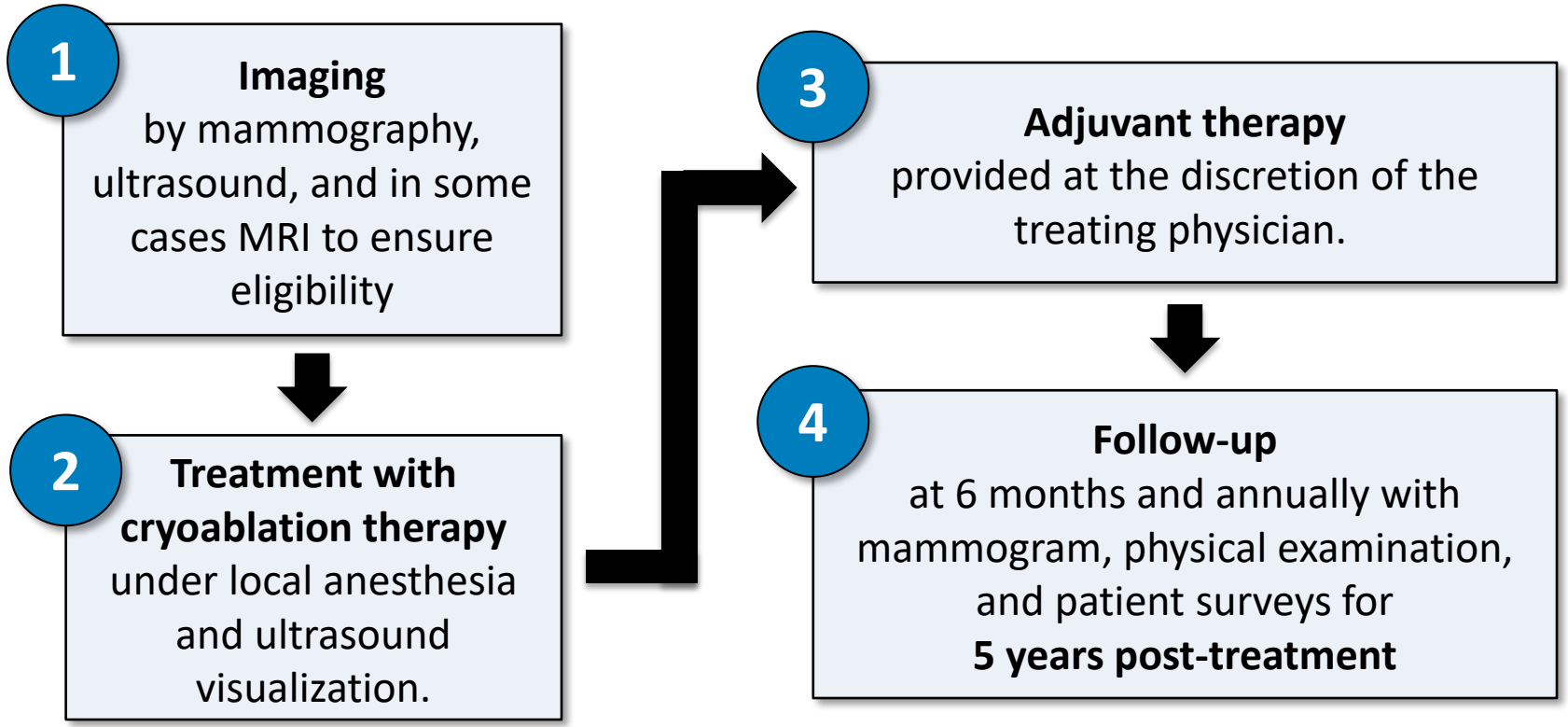
9-minute 1st freeze
8-minute 1st thaw
9-minute 2nd freeze
Short 2nd thaw

Treatment times were adjusted to target ice ball width:

- >35 mm at end of 1st freeze
- >40 mm at end of 2nd freeze

Average procedure time: 34.9 min.

ICE3 Study Procedures



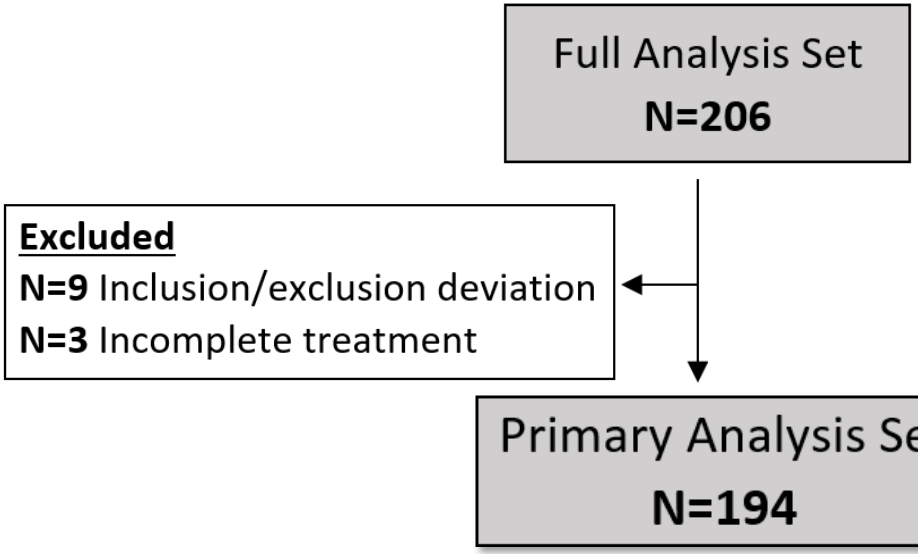
ICE3 Study Patient Population

Full Analysis Set
N=206

All subjects enrolled and treated in the study, including partial treatment.

- FDA evaluates safety for all treated patients
- FDA reports IBTR rate of the full analysis set

ICE3 Study Subject Disposition



All subjects enrolled and treated in the study, including partial treatment.

- FDA evaluates safety for all treated patients
- FDA reports IBTR rate of the full analysis set

All subjects enrolled and treated in the study **except for 12 excluded**.

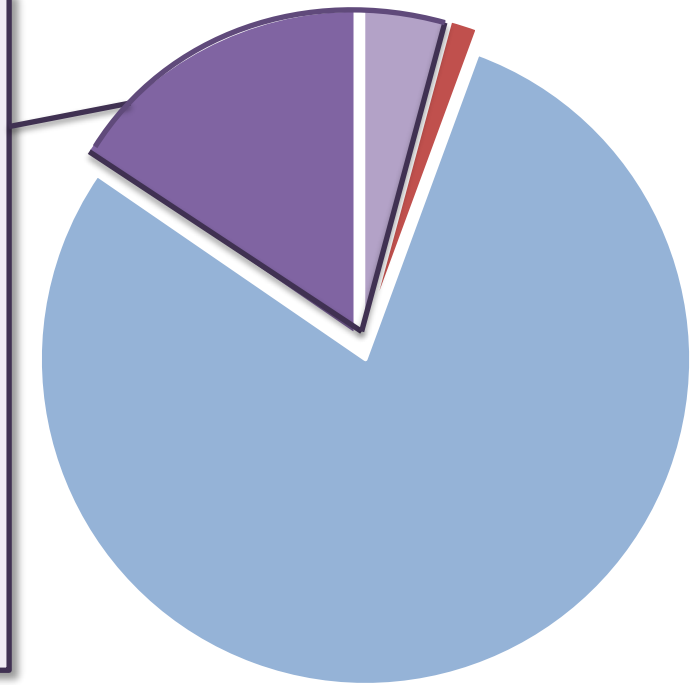
- IceCure Medical reported IBTR rate based on the primary analysis set

Exclusions from the Primary Analysis Set

44 subjects had major protocol deviations related to inclusion/exclusion criteria.

9 of 44 were excluded from IceCure Medical's Primary Analysis Set due to:

(5) Tumor >1.5 cm
e.g., 1.7 cm, 1.8 cm, 2.3 cm
(2) Neoadjuvant hormone Tx
(1) Baseline multifocal tumor
(1) Baseline DCIS 40%



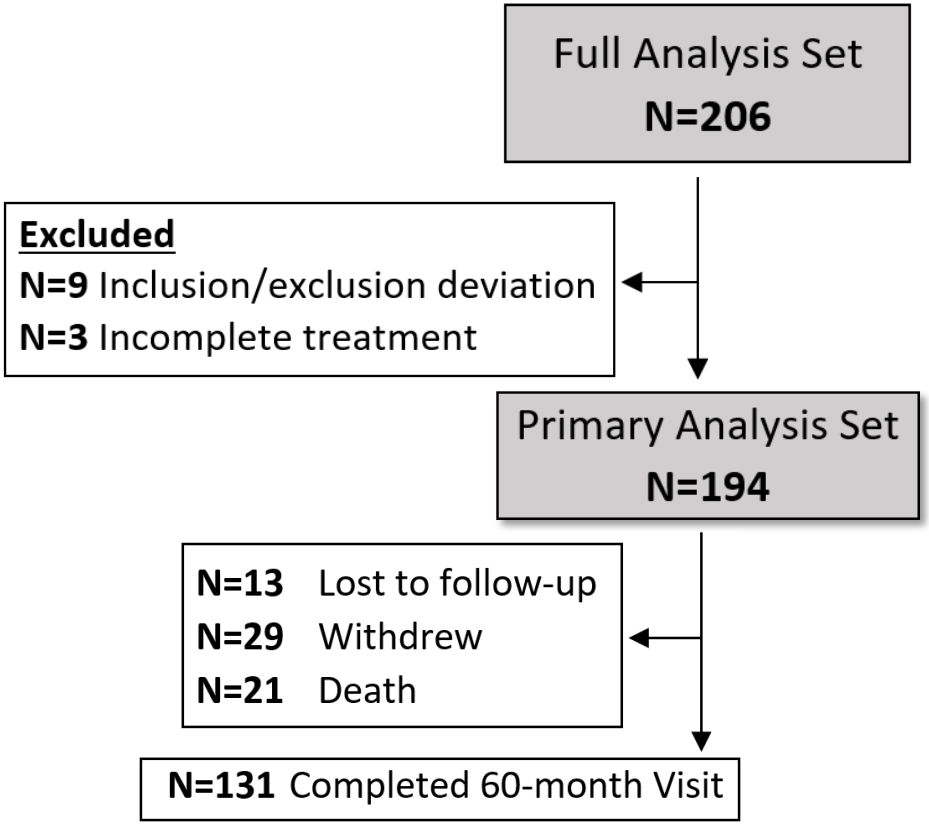
N = 206 treated subjects

12 exclusions from the Primary Analysis Set (n=194):

- 9 Inclusion/exclusion criteria deviations
- 3 inadequate treatment time

IBTR occurred in 5 of the 12 subjects. 4 of these subjects were excluded after recurrence.

ICE3 Study Subject Disposition



All subjects enrolled and treated in the study, including partial treatment.

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All subjects enrolled and treated in the study **except for 12 excluded**.

- IceCure Medical reported IBTR rate based on the primary analysis set

ICE3 Study Patient Characteristics

Full analysis set (N=206)

Adjunctive Treatment		
Hormone therapy only	132	64%
Radiation only	3	1.5%
Hormone and radiation therapy	25	12%
Hormone, radiation, and chemotherapy	1	0.5%
No adjunctive treatment or other	40	19.5%
Unknown	5	2.5%

Type of Tumor		
Luminal A	200	97%
Luminal B	3	1.4%
Unknown	3	1.4%

Ki-67		
Ki-67 < 14%	99	48%
Ki-67 ≥ 14%	41	20%
Unknown	66	32%

All subjects were Hormone Receptor positive, HER2 negative and Nottingham Grade 1 or 2

ICE3 Study Patient Characteristics

Full analysis set (N=206)

Age		
55 to 60 years	4	2%
61 to 70 years	49	24%
71 to 80 years	105	51%
81 to 90 years	46	22%
91 to 94 years	2	1%

Ethnicity		
African American	15	7%
Asian	1	0.5%
Caucasian	169	82%
Hispanic	14	7%
Native American	2	1%
Unknown	5	2%

ICE3 Study Patient Characteristics

Full analysis set (N=206)

Age		
55 to 60 years	4	2%
61 to 70 years	49	24%
71 to 80 years	105	51%
81 to 90 years	46	22%
91 to 94 years	2	1%

Ethnicity		
African American	15	7%
Asian	1	0.5%
Caucasian	169	82%
Hispanic	14	7%
Native American	2	1%
Unknown	5	2%

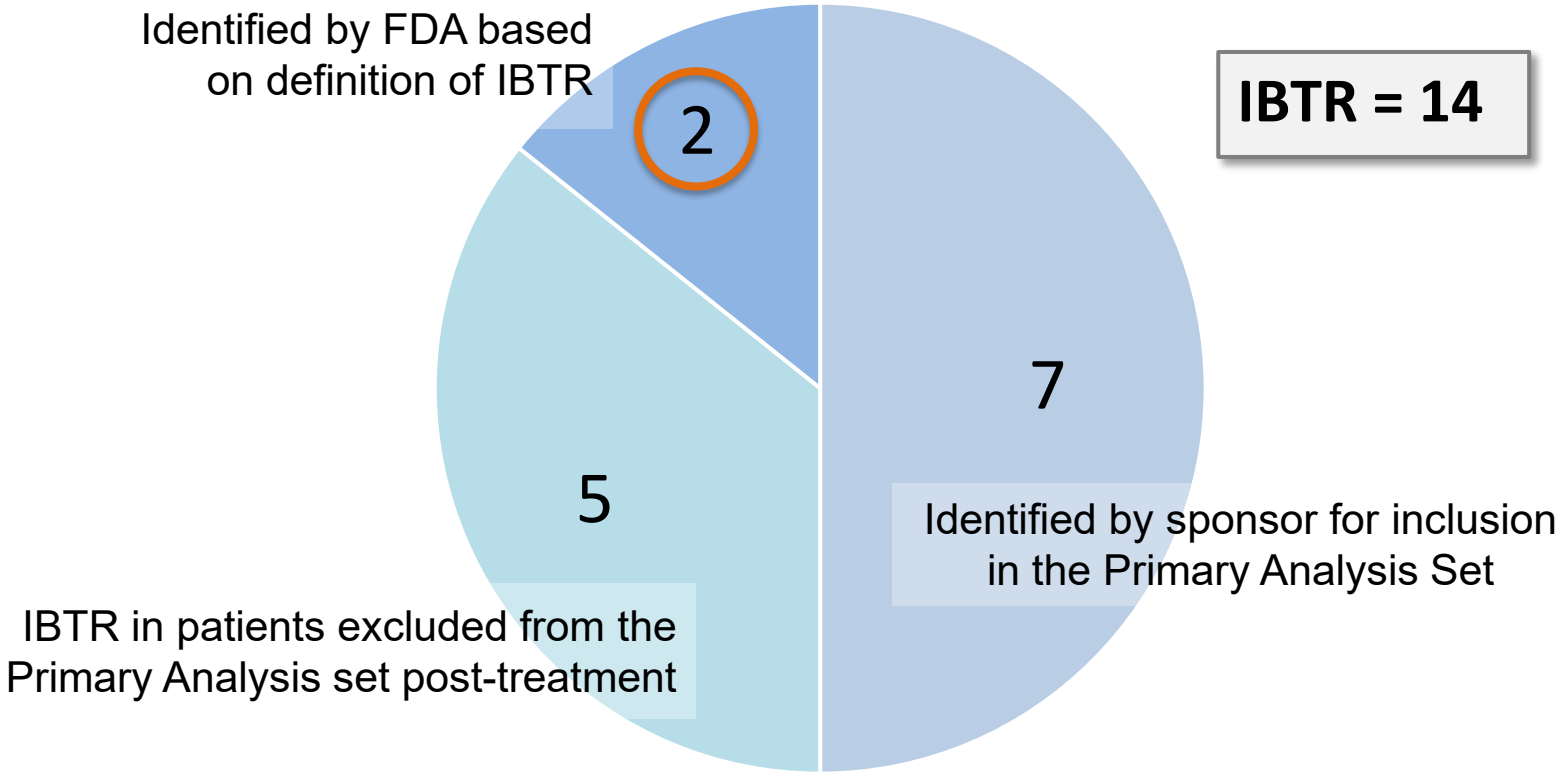
The panel will be asked to comment on the reproducibility of the patient population with respect to relevant risk factors for local recurrence (IBTR).

ICE3 Study Results and Clinical Discussion

Steven Nagel, MD FACS

Identification of IBTRs in the ICE3 Study

Full Analysis Set (N=206)



Two of Fourteen IBTR Identified by FDA

Case 1: New ipsilateral tumor with same histology and molecular subtype, but different location

- Primary breast cancer located at 8:00-9:00, 4-5 cm FN
  - Newly diagnosed breast cancer at 12:00, 5 cm FN
- Same histology (Grade 2 invasive ductal carcinoma)
- Same molecular subtype (ER+, PR+, HER2-)

Case 2: Mammographic density adjacent to cryoablation site identified as concerning for recurrence

- Investigator identified a suspicious lesion, but the patient declined biopsy

IBTR protocol definition: "*evidence of invasive or in situ breast cancer in the ipsilateral breast*"
Second primary breast cancer: evidence of invasive or in situ breast cancer *in the contralateral breast*

Primary Endpoint Results

Full Analysis Set (N=206)

Primary Endpoint	Event Type	# of events	Kaplan-Meier Rate (95% CI)	Cumulative Incidence Function Rate (95% CI)
IBTR	Local recurrence	14	9.5% (5.7 – 15.7%)	8.7% (5.2 – 14.5%)

The mean time to recurrence was 47.2 months

The median time to recurrence was 51.6 months

Secondary Endpoints: 5-Year Outcomes

Full Analysis Set (N=206)

Secondary Endpoint	Event Type	# of events	Kaplan-Meier Rate (95% CI)
DFS	Local recurrence	14	75.2% (67.7 – 81.2%)
	Distant recurrence	2	
	2nd primary BC	3*	
	2nd primary non-BC	8	
	Death due to any cause	20	
	Total patients with events	41	
OS	Death due to any cause	20	88.6% (82.8 – 92.5%)
Breast Cancer Survival	Death due to breast cancer	2	96.6% (92 – 98.6%)
	Unknown cause of death	3	

*FDA classified 1 case as IBTR that IceCure Medical identified as 2nd primary breast cancer

5-year Outcomes by Analysis Population

5-year Outcome	Subjects	Rate (KM) (95% CI)	Rate (CIF) (95% CI)
ICE3 Full Analysis Set (N = 206)			
IBTR	**14**	9.5% (5.7-15.7%)	**8.7%** (5.2-14.5%)
DFS	41	75.2% (67.7-81.2%)	---
OS	20	88.6% (82.8-92.5%)	---
Breast Cancer Survival	5	96.6% (92-98.6%)	---
ICE3 Primary Analysis Set (N = 194)			
IBTR	**9**	6.8% (3.6-12.8%)	**6.2%** (3.2-11.7%)
DFS	36	77.3% (70-83.1%)	---
OS	20	88.4% (82.6-92.4%)	---
Breast Cancer Survival	5	96.6% (92-98.6%)	---

Supportive Secondary Endpoints

Endpoint	NCCN Distress Thermometer	Cosmetic Satisfaction
Scale	1-10 *10 = extreme distress* *0 = no distress*	1-5 *5 = very satisfied* *1 = very dissatisfied*
Outcome	0.7-point improvement *at 6 months compared to baseline*	28% satisfied/70% very satisfied *at 6 months through 5 years*
Limitations	No evaluation of distress following recurrence events. Single-arm design does not allow direct comparison with SoC.	15% of subjects did not complete the survey at a given visit. Single-arm design does not allow direct comparison with SoC.

Serious Adverse Events

Primary Analysis Set (N=194)

- 133 SAEs reported in 65 subjects (33.5% of subjects)
- 21 Deaths

SAEs may be related or unrelated to the device.
Any recurrence: *SAE*
IBTR: *device-related SAE*

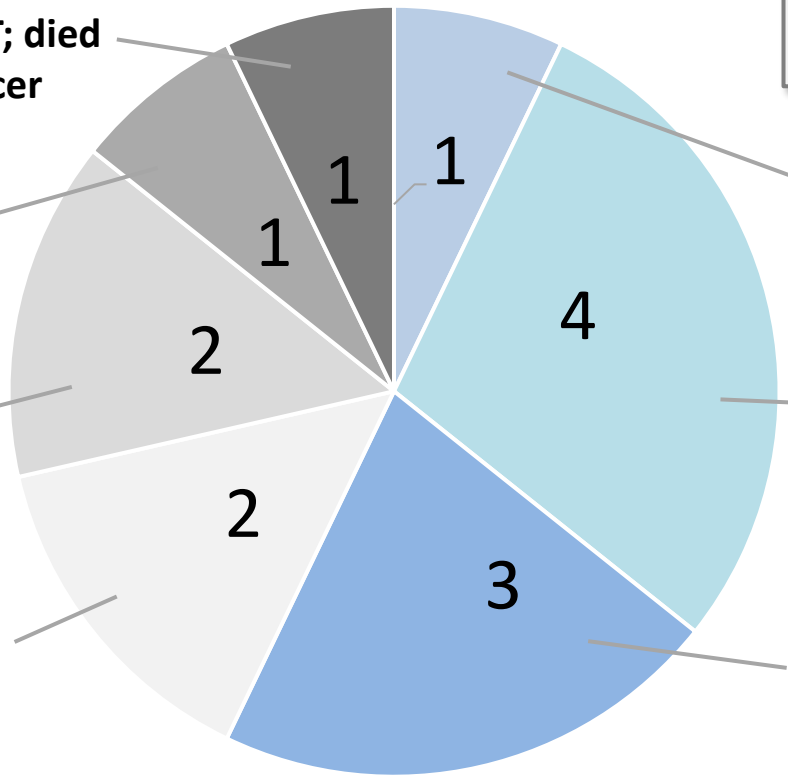
Full Analysis Set (N=206)

- 14 IBTR (5 IBTR among the 12 patients excluded from the Primary Analysis Set)

Event	N (%)
Deaths	21 (10.2%)
Deaths not due to breast cancer	16 (7.8%)
Deaths due to breast cancer	2 (1.0%)
Deaths due to unknown cause	3 (1.5%)
Distant recurrences	2 (1.0%)
Local recurrences	14 (6.8%)
Second primary non-breast cancer	8 (3.9%)
Second primary breast cancer	3 (1.5%)

Sequelae of Local Recurrence

Full Analysis Set (N=206)



IBTR = 14

Underwent lumpectomy + RT; died due to metastatic breast cancer

Underwent lumpectomy but died due to unknown causes

Underwent lumpectomy or partial mastectomy and survived for full duration of 5-year study*

Declined further work-up or conservative follow-up only and survived for full duration of 5-year study*

No information available (subject excluded before study completion)

Underwent lumpectomy or total/bilateral mastectomy and excluded before study completion

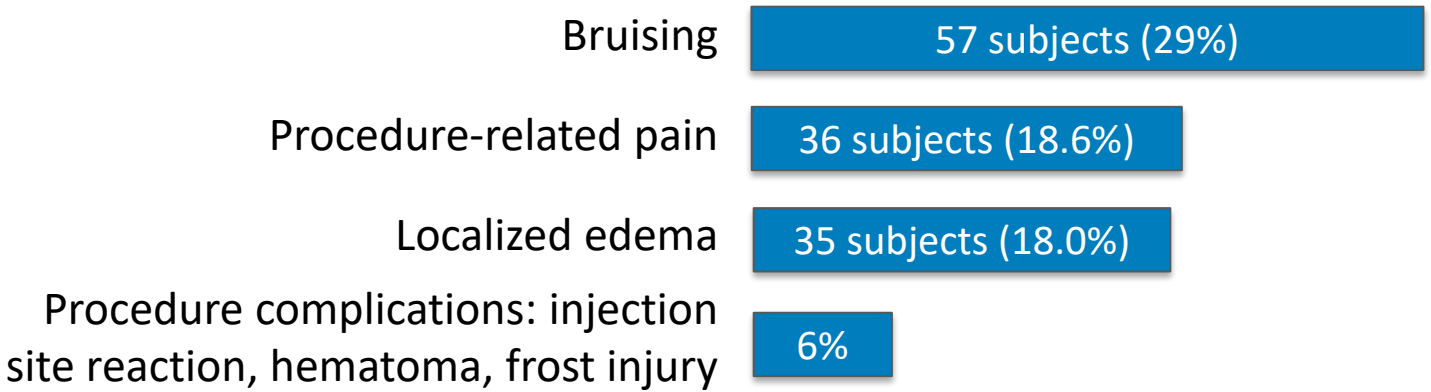
Underwent partial mastectomy and withdrew early

*Includes 1 of the 2 cases classified by FDA as IBTR

Adverse Events

140 subjects (72.2%) reported 517 AEs
93 subjects (48.0%) reported **180 procedure-related AEs**

The **most prevalent procedure-related* AEs** in the Primary Analysis Set were:



Procedure-related AEs were reported within 30-days, but duration of the AEs are not reported

Statistical Considerations

Xu Zhang, Ph.D.

ICE3 Study Analysis Plan (Per Protocol)

Hypothesis	$H_0: p \geq 10\%$ $\quad vs \quad$ $H_A: p < 10\%$ where p is the proportion of patients with IBTR at 5 years
Sample size determination	• Assumed IBTR rate of 5% • A sample size of 150 subjects was estimated to achieve a ± 5% level of accuracy
Analysis method for IBTR rate at 5 years	Kaplan-Meier (KM)

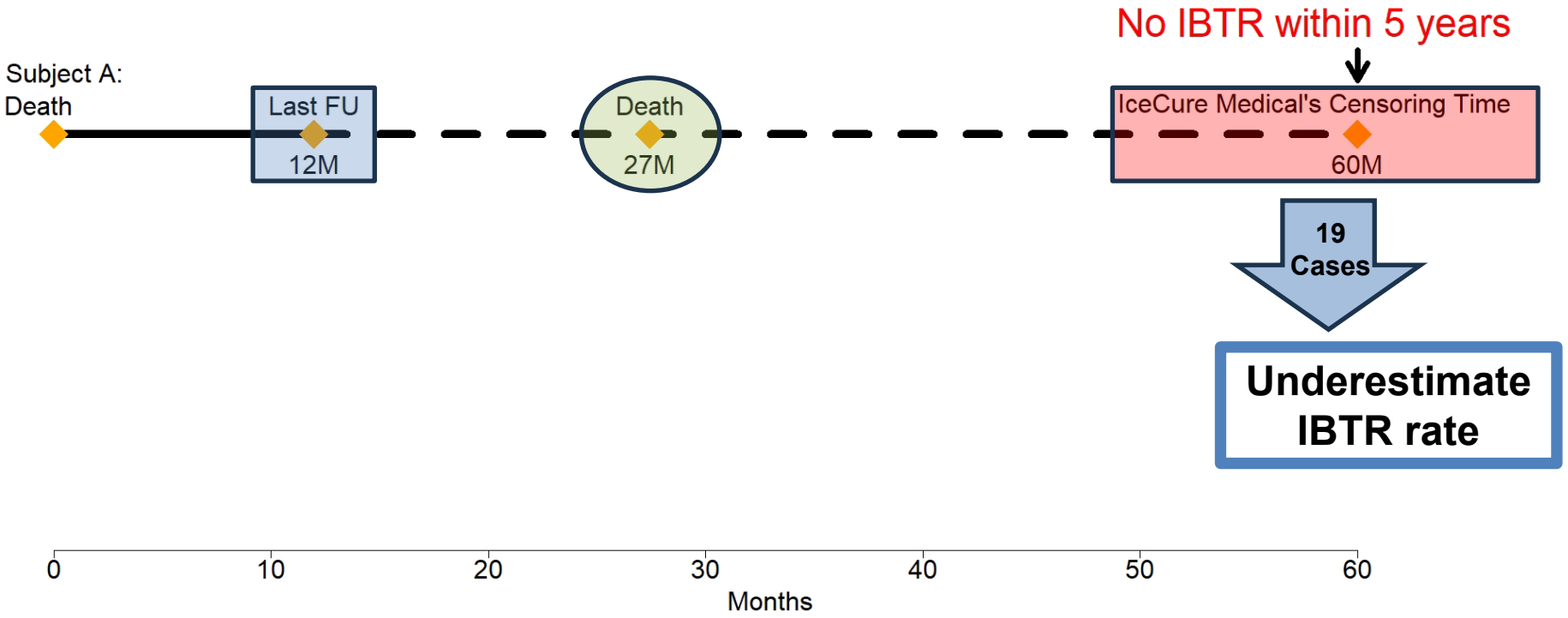
Censoring Time in Kaplan-Meier

- **In the ICE3 study, censored subjects include:**
  - Subjects who died without IBTR
  - Subjects lost to follow-up (LTFU) or withdrawal without IBTR
- **Conventional censoring time:**
  - Last follow-up date for which a subject is known to be IBTR-free
  - FDA uses this method
- **IceCure Medical's censoring approach for IBTR**:

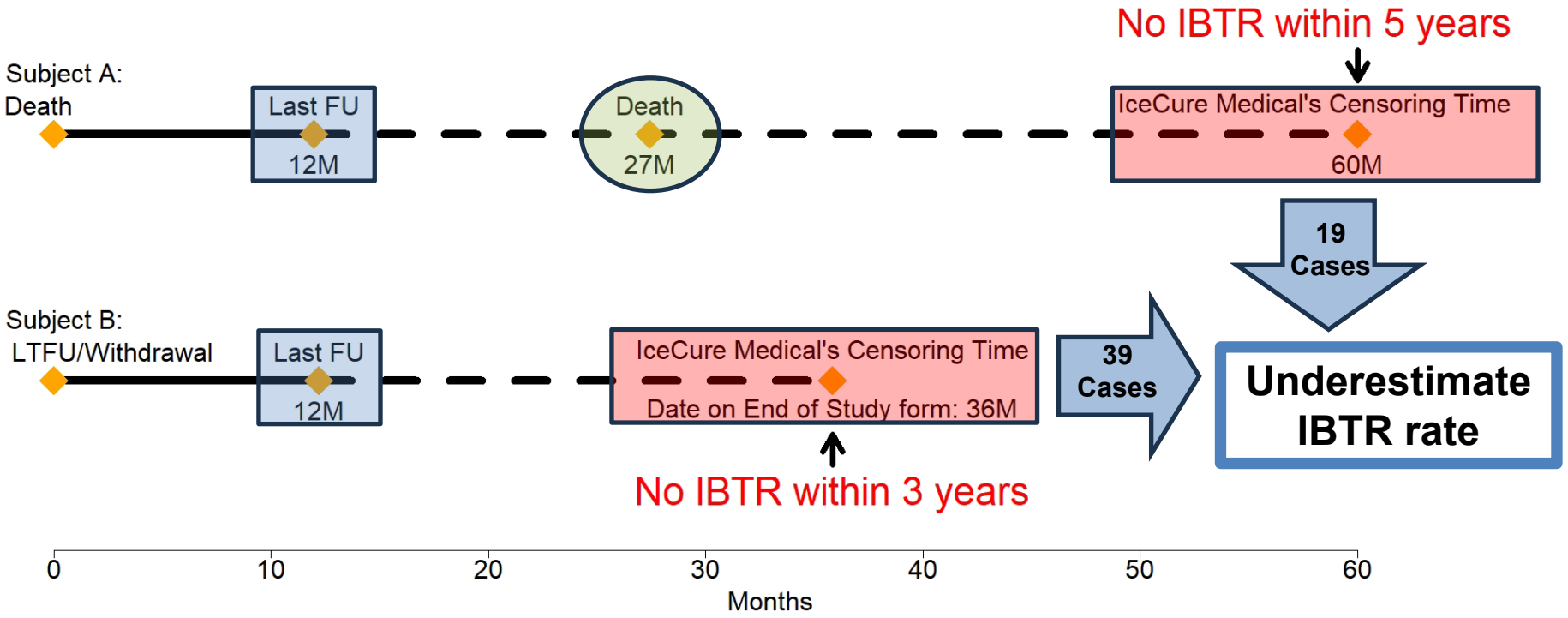
LTFU/Withdrawal	Death
Date on End of Study form or 60 months	60 months

Note: Censoring methods were not pre-specified in the ICE3 study protocol.

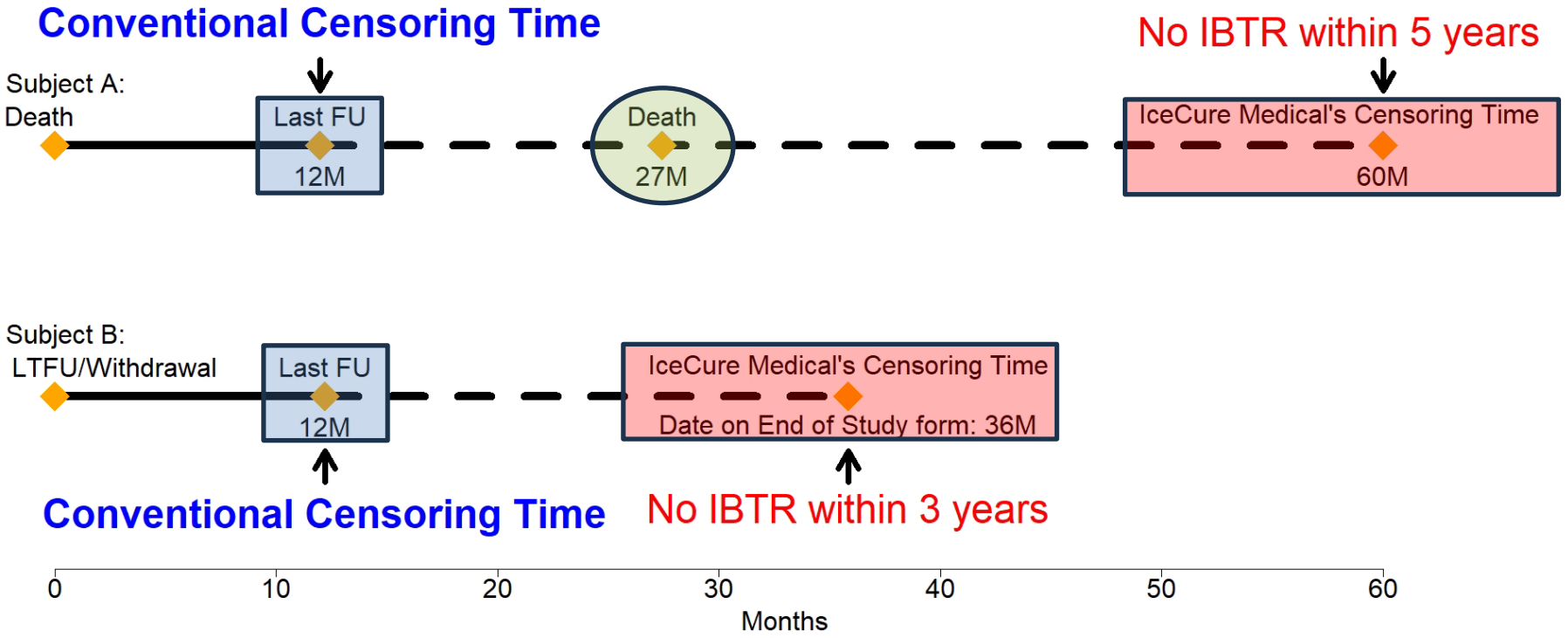
IceCure Medical's Censoring Approach



IceCure Medical's Censoring Approach



Conventional Censoring Approach



Comparison of KM Results by Censoring Approach

IBTR results for the Primary Analysis Set (**N=194**) using IceCure Medical's count of 7 local recurrences shows **underestimation of the event rate** by IceCure Medical's KM censoring methods compared with conventional KM censoring methods.

Number of IBTR *(identified by IceCure Medical)*	**IBTR Rate with IceCure Medical censoring (95% CI)**	**IBTR rate with conventional censoring (95% CI)**
7	4.3% (2.1-8.7%)	5.2% (2.5-10.7%)

Note: The IceCure Medical proposed performance goal was 10% for the primary endpoint IBTR rate

Censoring Approach for Secondary Endpoints

IceCure Medical's censoring time for subjects without an event of interest in the KM calculation for other 5-year endpoints is shown below:

Outcome	Censoring Time	
	LTFU/Withdrawal	Death
IBTR	Date on End of Study form *or* 60 months, whichever comes first	60 months
"Distant Metastases"		60 months
DFS (protocol definition)		N/A (death considered event)
DFS (NCI definition interpreted by sponsor)[+]		60 months

[+]IceCure Medical's interpretation of DFS per the NCI definition did not include 18 non-Breast Cancer deaths.

Full versus Primary Analysis Set

Subjects with inclusion/exclusion (I/E) deviations

	# of Subjects with I/E deviations	# of IBTR in subjects with I/E deviations	%
Full analysis Set (N=206)	44	8	18%
Included in Primary Analysis Set (N=194)	34	3	8.8%
12 Excluded Subjects	10*	5	50%

**one subject has both an inclusion/exclusion (I/E) deviation and an inadequate procedure time*

IBTR Results for Two Analysis Sets under Conventional Censoring

Analysis Set	# of IBTR	KM Rate (95% CI)	CIF Rate (95% CI)
Full Analysis Set N=206	14	9.5% (5.7-**15.7%**)	8.7% (5.2-**14.5%**)
Primary Analysis Set N=194	9	6.8% (3.6-**12.8%**)	6.2% (3.2-**11.7%**)

In all cases, the ICE3 results did not meet IceCure Medical proposed 10% performance goal

Statistical Considerations in the ICE3 Study

- IceCure Medical censoring approach may underestimate IBTR rate

- Exclusion of 12 subjects by IceCure Medical may lead to underestimation of IBTR rate

Post-Hoc Sub-Population Analyses

Steven Nagel, MD FACS

Generalizability of ICE3 Patient Population

FDA suggested exploring post-hoc subpopulations to:

- Evaluate the outcomes for a potential patient subgroup with hormone therapy
- Facilitate comparison with similar representative patient populations in the literature

ICE3 Full Analysis Set – Adjunctive Treatments		
Hormone therapy only	132	64%
Radiation only	3	1.5%
Hormone and radiation therapy	25	12%
Hormone, radiation, and chemotherapy	1	0.5%
No adjunctive treatment or other	40	19.5%
Unknown	5	2.5%

Adjunctive treatment has a significant impact on recurrence rate

Many large literature cohorts have specific treatment regimens

LUMINA study

Whelan et al. 2023

N=500, Invasive BC

Age ≥ 55 years

Tumor size < 2cm

Hormone Therapy

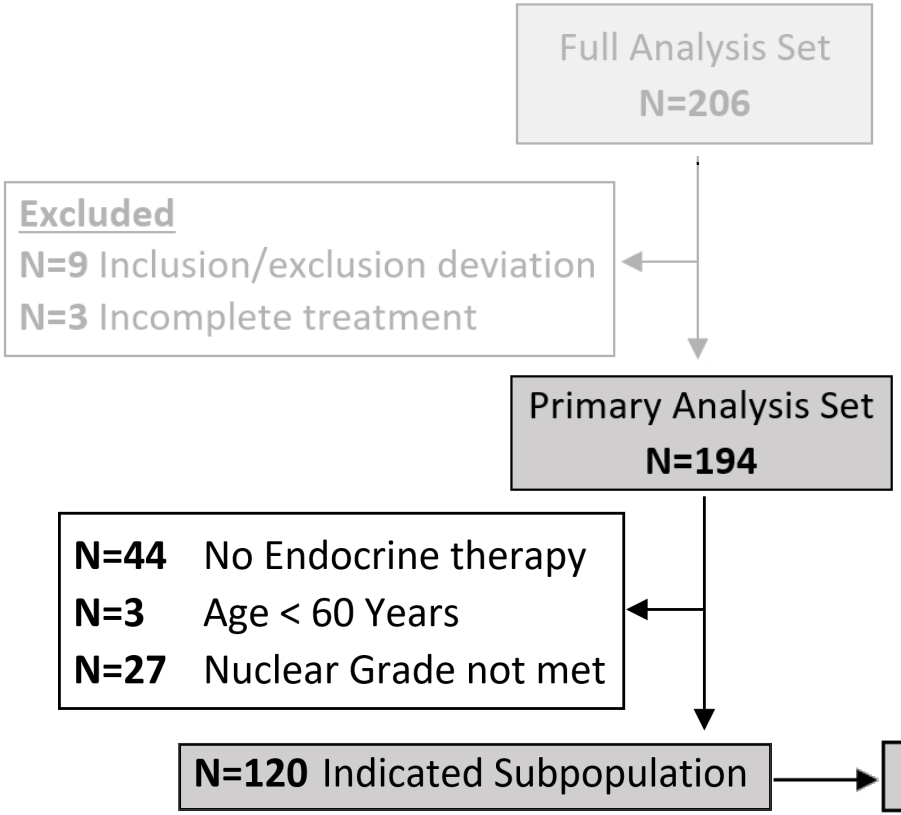
No Radiation

Grade 1-2

ER+, PR+, HER2-

Luminal A, Ki-67<13.25%

Post-Hoc Indicated Subpopulation



An **Indicated Subpopulation** was defined post-hoc based on the proposed IFU statement criteria: all patients receiving adjunctive endocrine therapy.

- Nuclear grade was also required to be 1-2 per to the ICE3 protocol criteria.
- Ki-67 was not used as a criterion.

ICE3 Study Patient Characteristics

Indicated Subpopulation (N=120)

Age		
55 to 60 years	0	0%
61 to 70 years	30	25%
71 to 80 years	67	56%
81 to 90 years	23	19%
91 to 94 years	0	0%

Ki-67		
Ki-67 < 14%	56	47%
Ki-67 ≥ 14%	20	16%
Unknown	44	37%

Adjunctive Treatment		
Hormone therapy only	98	81.5%
Hormone and radiation therapy	21	17.5%
Hormone, radiation, and chemotherapy	1	1%

Ethnicity		
African American	8	7%
Asian	0	0%
Caucasian	99	83%
Hispanic	9	7%
Native American	0	0%
Unknown	4	3%

All subjects were Hormone Receptor positive, HER2 negative and Nottingham Grade 1 or 2

ICE3 Study Patient Characteristics

Indicated Subpopulation (N=120)

Age		
55 to 60 years	0	0%
61 to 70 years	30	25%
71 to 80 years	67	56%
81 to 90 years	23	19%
91 to 94 years	0	0%

Ki-67		
Ki-67 < 14%	56	47%
Ki-67 ≥ 14%	20	16%
Unknown	44	37%

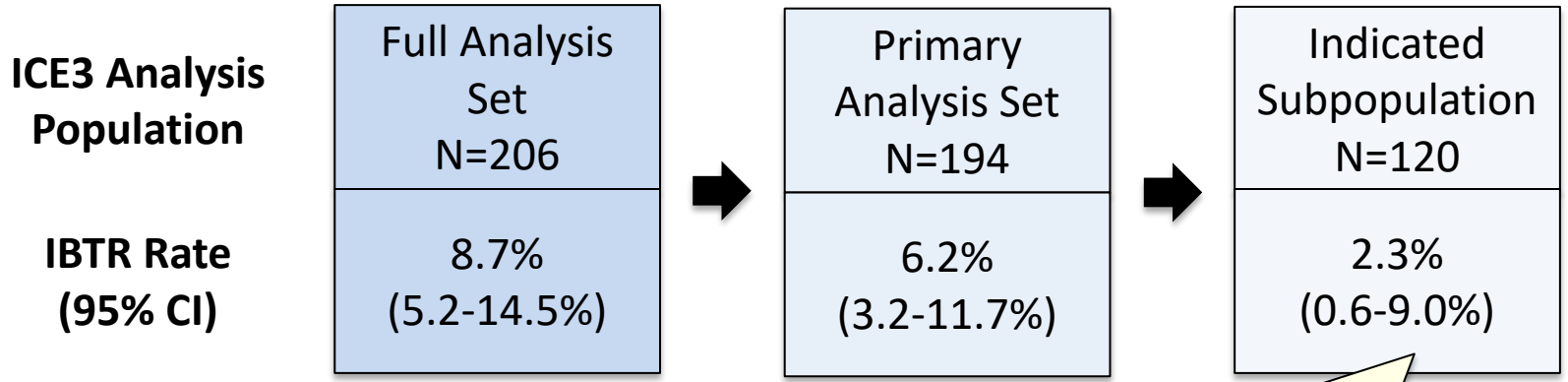
Adjunctive Treatment		
Hormone therapy only	98	81.5%
Hormone and radiation therapy	21	17.5%
Hormone, radiation, and chemotherapy	1	1%

Ethnicity		
African American	8	7%
Asian	0	0%
Caucasian	99	83%
Hispanic	9	7%
Native American	0	0%
Unknown	4	3%

The panel will be asked to comment on the generalizability of subjects with respect to risk factors for recurrence.

Results of the ICE3 Indicated Subpopulation

There were **2 IBTR events** identified in the Indicated Subpopulation.

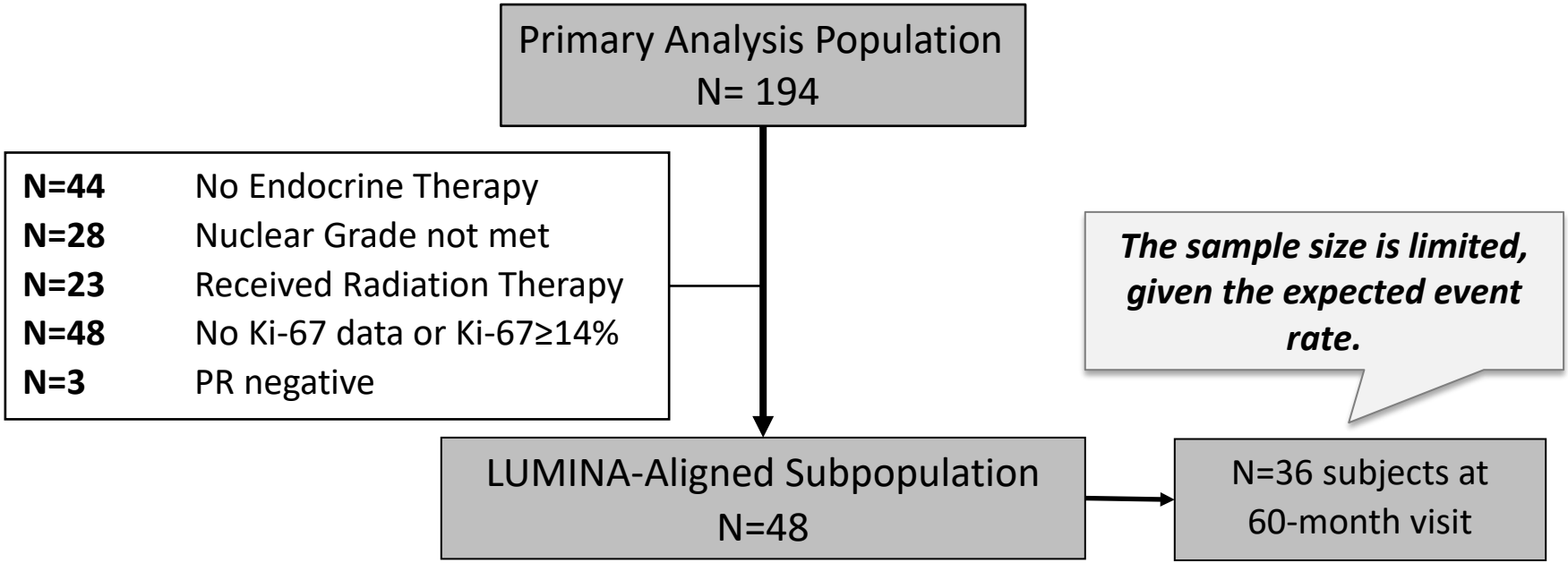


Rates are shown based on CIF (not KM) for direct comparison with literature rates

The panel will be asked to comment on the sample sizes and corresponding uncertainty in the different analysis populations.

Post-Hoc LUMINA-Aligned Subpopulation

A **LUMINA-aligned subpopulation** was defined post-hoc to allow comparison between ICE3 study patients and the LUMINA study N=500 (Whelan et al. 2023)



Systematic Literature Review of Low-Risk Patients Receiving Standard Surgical Treatment

Areej Idris, MPH

Goal of FDA SLR

Background: Need for Historical Benchmark	**ICE3 clinical study:** Single-arm study evaluating ProSense System
	
	➢ IceCure Medical provided an estimated IBTR rate for patients treated with lumpectomy based on an SLR and meta-analysis
	➢ The SLR and meta-estimate were limited by:
	  ➢ Selecting studies with mixed-risk populations; subjects could differ from the selection criteria by up to 25%
	  ➢ Weighting of rates based on alignment with selection criteria
	  ➢ Exclusion of patients with radiotherapy

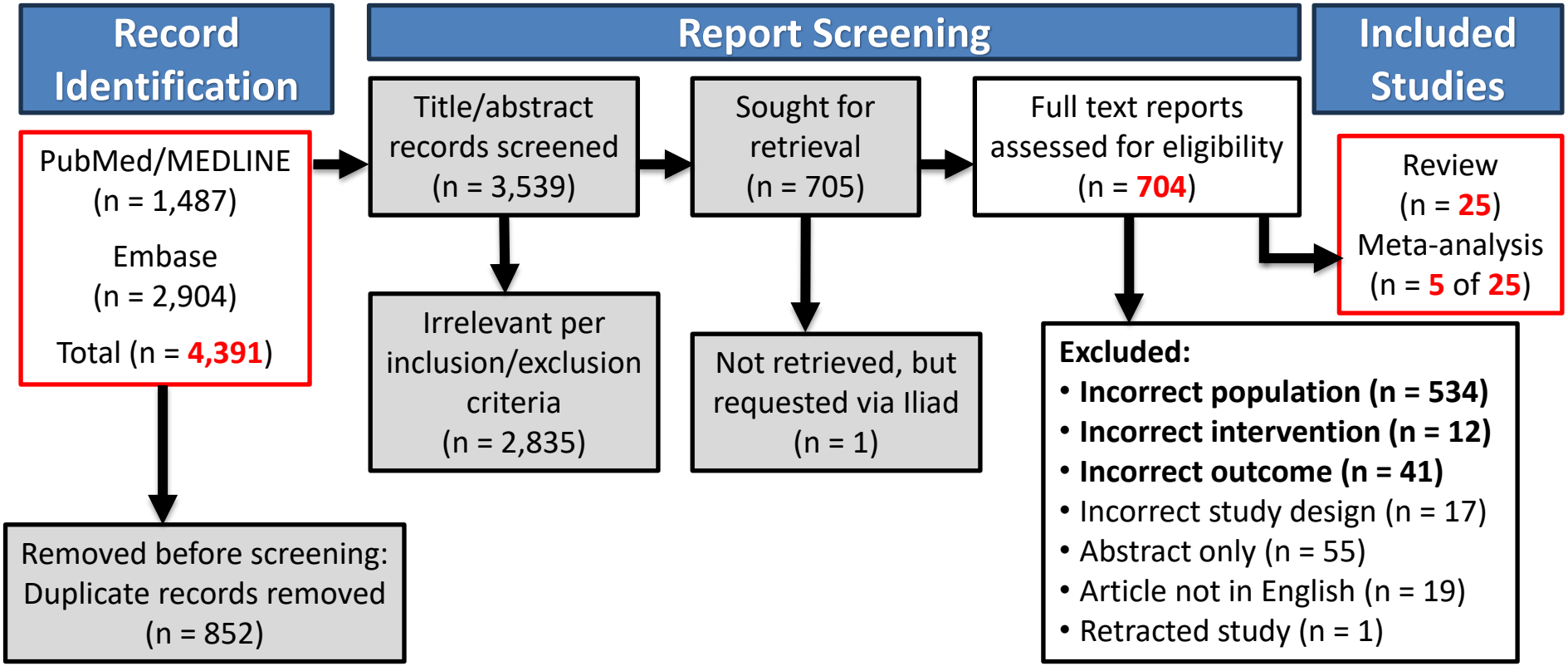
FDA's Independent SLR	**Goal:** ➢ Estimate IBTR rate for standard surgical treatment of the indicated subpopulation

SLR Methodology

SLR Protocol	PRISMA guidelines and Cochrane Handbook for Systematic Reviews of Interventions*	
Eligibility Criteria	**Inclusion**	✓ Female patients ≥50 years ✓ Tumor: ≤2 cm, Nottingham grade 1-2, ER+, PR+, HER2-, Ki-67<14% (if reported) ✓ Node-negative ✓ Published since 2004
	Exclusion	Lobular carcinoma, high grade, multifocal, lymphovascular invasion
SLR Search Strategy	**Databases**	PubMed/MEDLINE and Embase
	Search Date	August 6, 2024
	Search Terms	➢ Breast cancer-specific terms (e.g., "breast neoplasms", "breast tumor") ➢ Surgical intervention terms (e.g., "breast-conserving surgery", "lumpectomy") ➢ Recurrence-related terms (e.g., "ipsilateral breast tumor", "IBTR") ➢ Stage and risk-related terms (e.g., "Early Stage", "Low Risk", "Nottingham Grade") ➢ Specific criteria terms (e.g., "≤1.5cm", "Luminal A", "Ki67")
	Controlled vocabulary (e.g., MeSH terms) and diverse synonyms	

* Please see full panel pack for exact methods

Literature Screening Flow Diagram



Based on the "PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only"

Description of the 25 studies in the SLR

Total Studies in the SLR	**25**	
Total SLR Sample Size	**15,281** patients	Smallest: 12 patients (Liao 2011) Largest: 2,109 patients (Carleton 2021)
Treatment Modalities	**Radiotherapy**: 21 studies, **Hormone therapy**: 23 studies, **Both:** 19 studies	
Study Designs	**Randomized controlled trials**: 8, **Observational** studies: 17	
Geographic Distribution	**U.S.:** 9 studies, **UK**: 4 studies, **Italy**: 3 studies, Other countries: 9 studies	
Follow-up Duration	≥ 10 years follow-up: 4 studies	
	≥ 5 years median follow-up: 15 studies	
Five-year IBTR Rates	**20 studies** reported an explicit 5-year IBTR rate: **5 studies** reported **0%** rates **9 studies** reported rates of **1% or lower** **12 studies** reported rates of **2% or lower** **15 studies** reported rates of **3% or lower** **17 studies** reported rates of **4% or lower** **19 studies** reported rates of **5.9% or lower** **One study** (Dhan 2020) reported rates of 12% (no therapy), 1.5% (radiation), and 4.2% (hormone therapy).	

Studies Selected for Meta-Analysis

25 SLR Studies

20 excluded

5 studies in meta-analysis with **6** cohorts

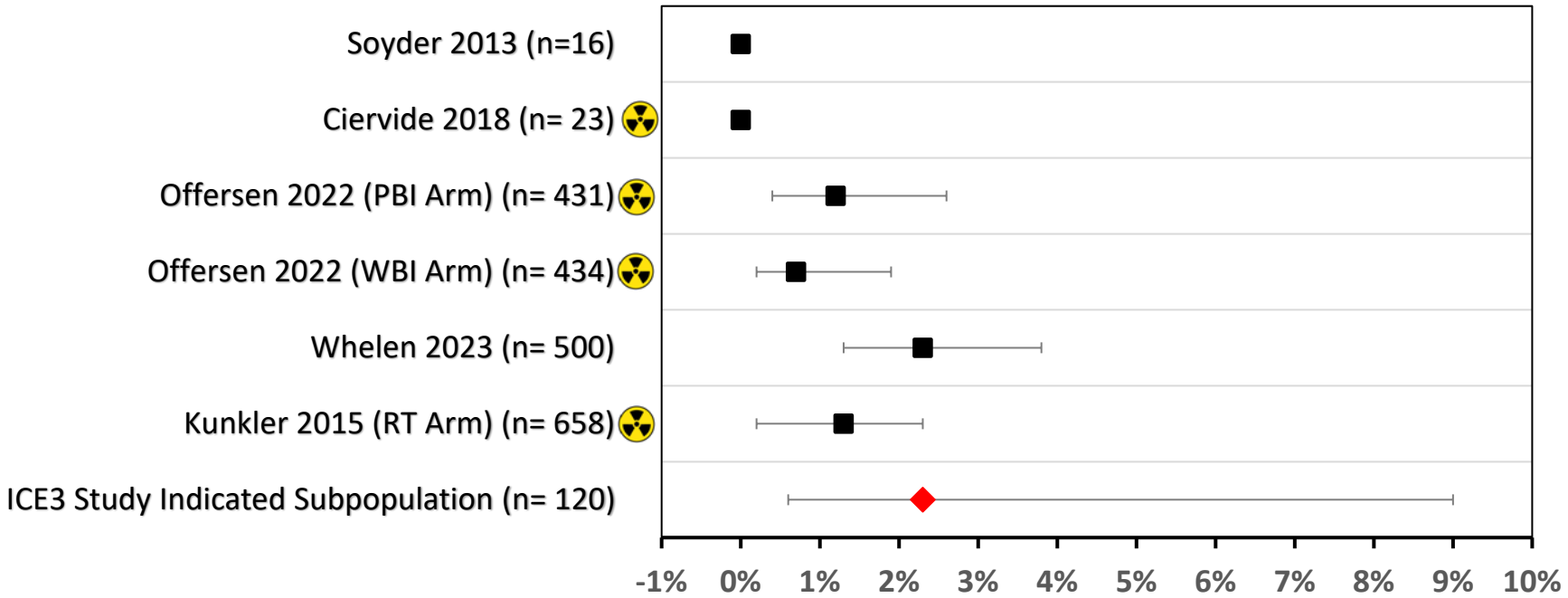
Cohort	Sample Size	At Risk 5 yrs	Events 5 yrs	IBTR 5 yr Rate
Soyder 2013	16	11	0	0.0%
Ciervide 2018	23	16	0	0.0%
Offersen 2022[1]	431	379	5	1.2%
Offersen 2022[2]	434	396	3	0.7%
Whelan 2023	500	246	10	2.3%
Kunkler 2015[3]	658	324	5	1.3%

[1]Partial Breast RT arm; [2]Whole Breast RT arm; [3]RT arm

Reason for Exclusion	Cohorts Excluded
Presence of T size >2cm	12
HR negative or unknown	12
Presence of chemotherapy	9
HER2 positive or status unknown	7
Presence of Grade 3 tumor	6
Presence of node positive	5
Presence of lobular carcinoma	5
Lymphovascular invasion	5
Age range too broad	5
Presence of DCIS	3
Mastectomy patients included	1
Luminal B	1

Note: Most studies had multiple reasons

Forest Plot of the Meta-analysis Studies



Cohort with any type of Radiotherapy

ICE3 Study IBTR rate compared to FDA's SLR

ICE3 Study Results

ICE3 Analysis Population	Full Analysis Set N=206	Primary Analysis Set N=194	Indicated Subpopulation N=120
IBTR Rate (95% CI)	8.7% (5.2-14.5%)	6.2% (3.2-11.7%)	2.3% (0.6-9.0%)

SLR Meta-Analysis Results

ICE3 Study SLR-derived Performance Goal	FDA SLR Meta-Analysis
~5% IBTR rate 95% CI UB <10%	Min. 0%, Max. 2.3%

ICE3 Study IBTR rate compared to FDA's SLR

ICE3 Study Results

ICE3 Analysis Population	Full Analysis Set N=206	Primary Analysis Set N=194	*ProSense System* Indicated Subpopulation N=120
IBTR Rate (95% CI)	8.7% (5.2-14.5%)	6.2% (3.2-11.7%)	2.3% (0.6-9.0%)

SLR Meta-Analysis Results

Early stage, low-risk patients treated with hormone therapy (with/without radiotherapy)

Lumpectomy FDA SLR Meta-Analysis
Min. 0%, Max. 2.3%

ICE3 Study IBTR rate compared to FDA's SLR

ICE3 Study Results

ICE3 Analysis Population	Full Analysis Set N=206	Primary Analysis Set N=194	*ProSense System* Indicated Subpopulation N=120
IBTR Rate (95% CI)	8.7% (5.2-14.5%)	6.2% (3.2-11.7%)	2.3% (0.6-9.0%)

SLR Meta-Analysis Results

The panel will be asked to discuss the overall clinical significance of the ICE3 effectiveness results compared with the SLR

Early stage, low-risk patients treated with hormone therapy (with/without radiotherapy)

Lumpectomy FDA SLR Meta-Analysis
Min. 0%, Max. 2.3%

Benefit-Risk

Jessica Carr, Ph.D.

Probable Benefits

Invasive surgery avoidance
• Minimally invasive method with no excision • Performed under local anesthesia • High rate of cosmetic satisfaction of patient and provider respondents

Breast cancer treatment outcomes

• ICE3 full analysis set:
  • IBTR rate 8.7% (5.2-14.5%)
  • DFS 75.2% (67.7-81.2%)
  • OS 88.6% (82.8-92.5%)
  • Breast Cancer Survival 96.6% (92-98.6%)
• ICE3 Indicated subpopulation:
  • IBTR rate 2.3% (0.6-9.0%)

No data is available that directly compares AEs or cosmetic outcomes of lumpectomy of 1.5 cm tumors under local anesthesia with treatment using the ProSense System.

Probable Risks

No surgical specimen for pathology evaluation

Risk of inadequate diagnostic characterization of the tumor
(reliance on core biopsy results only)
- Variability in receptor status
- Insufficient tissue

Risk of incomplete treatment
- No confirmation of complete ablation
- Reliance on follow-up imaging for recurrence detection

IBTR rates

ICE3 Indicated subpopulation: 2.3% (0.6-9.0%)

SLR meta-analysis: Min. 0%, Max. 2.3%

Recurrence impacts patient health, QoL, and financial burden.

Procedure-related risks

Risks of pain, bruising, and edema

Limitations and Uncertainty

1

Without a control arm of the ICE3 study with a similar distribution of patient characteristics, it is difficult to compare the results to standard treatment outcomes.

- **Adjuvant treatment:**
  18% of ICE3 intended subpopulation received radiotherapy
  4 of 6 cohorts received radiotherapy in FDA's meta-analysis
  No cohorts received radiotherapy in IceCure Medical's SLR

- **Age:**
  Intended use age ≥60 years, ICE3 median age 74.5 years, FDA SLR age >50 years

- **Protocol deviations:**
  Enrollment criteria modified, 45 enrollment criteria violations, 12 subjects excluded

Limitations and Uncertainty

1

Without a control arm of the ICE3 study with a similar distribution of patient characteristics, it is difficult to compare the results to standard treatment outcomes.

2

Availability of a literature comparator

- FDA identified 25 studies similar to the intended patient population
- Only 6 cohorts were selected with the closest alignment to the IFU

Limitations and Uncertainty

1. **Without a control arm of the ICE3 study with a similar distribution of patient characteristics, it is difficult to compare the results to standard treatment outcomes.**

2. **Availability of a literature comparator**

3. **Variability due to limited sample size in ICE3**

ICE3 Full Analysis Set:	206 treated subjects	**CI: 5.2-14.5%**
Indicated Subpopulation:	120 subjects matching IFU	**CI: 0.6-9.0%**

20% missing data rate (LTFU, withdraw)

Limitations and Uncertainty

1. **Without a control arm of the ICE3 study with a similar distribution of patient characteristics, it is difficult to compare the results to standard treatment outcomes.**
2. **Availability of a literature comparator**
3. **Variability due to limited sample size in ICE3**
4. **Unknown complete ablation rate**

Accurate imaging needed to characterize lesion size and confirm complete ablation

Summary

Benefit

Minimally invasive method
Performed under local anesthesia
Invasive surgery avoidance
Cosmetic satisfaction

Risk

Risk of inadequate diagnostic characterization
Risk of incomplete treatment
Pain, bruising, and edema

The panel will be asked to comment on the QoL benefits of surgery avoidance versus QoL risks of recurrence for the indicated population.

Uncertainty

Study population generalizability
Comparability with literature
Wide confidence intervals
Unknown complete ablation rate

The panel will be asked to comment on the overall benefit-risk profile of the device for the proposed indications for use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ADMINISTRATION

Reference Slides

ICE3 Study Protocol Deviations

There were 448 protocol deviations for 157 subjects; 56 were major deviations.

Type of Deviation	Major		Minor	
	Events	Subjects	Events	Subjects
Violation of Inclusion/Exclusion Criteria	45	44	0	0
Missed Visit	0	0	20	16
Visit Out of Window	0	0	203	113
Follow Up Procedural Deviation	2	2	160	69
Informed Consent Deviations	2	2	2	2
Other (*e.g., use of neoadjuvant hormone blockage, inadequate procedure time, incomplete treatment)*	7	7	6	8

Exclusions from the Primary Analysis Set

Subj.	Reason for exclusion
1	Prior lumpectomy and radiation in addition to baseline multifocal tumor
2	Baseline tumor size 2.3 x 1.1 cm per re-measuring the index lesion
3	DCIS 40% on baseline pathology
4	Lesion size 1.7 x 1.4 x 1.5 cm
5	Lesion size 1.5 x 1.7 x 1.7 cm
6	Lesion size 1.8 x 1.5 x 1.4 cm
7	Larger lesion size on mammography (size not specified)
8	Lesion measured on mammography as 1.6 cm. Patient treated with neoadjuvant hormone blockage. Lesion re-evaluated before cryoablation as 1.1 x 0.8 cm.
9	Lesion measured as 1.9 cm on sonography. Patient treated with neoadjuvant hormone blockage. Lesion re-evaluated before cryoablation as 1.2 x 0.9 x 1.1 cm.
10-12	Short treatment protocol, 1 due to machine malfunction

Of the 12 excluded subjects, 5 had IBTR and were withdrawn from the study after recurrence was identified.

ICE3 Study Indicated Subpopulation

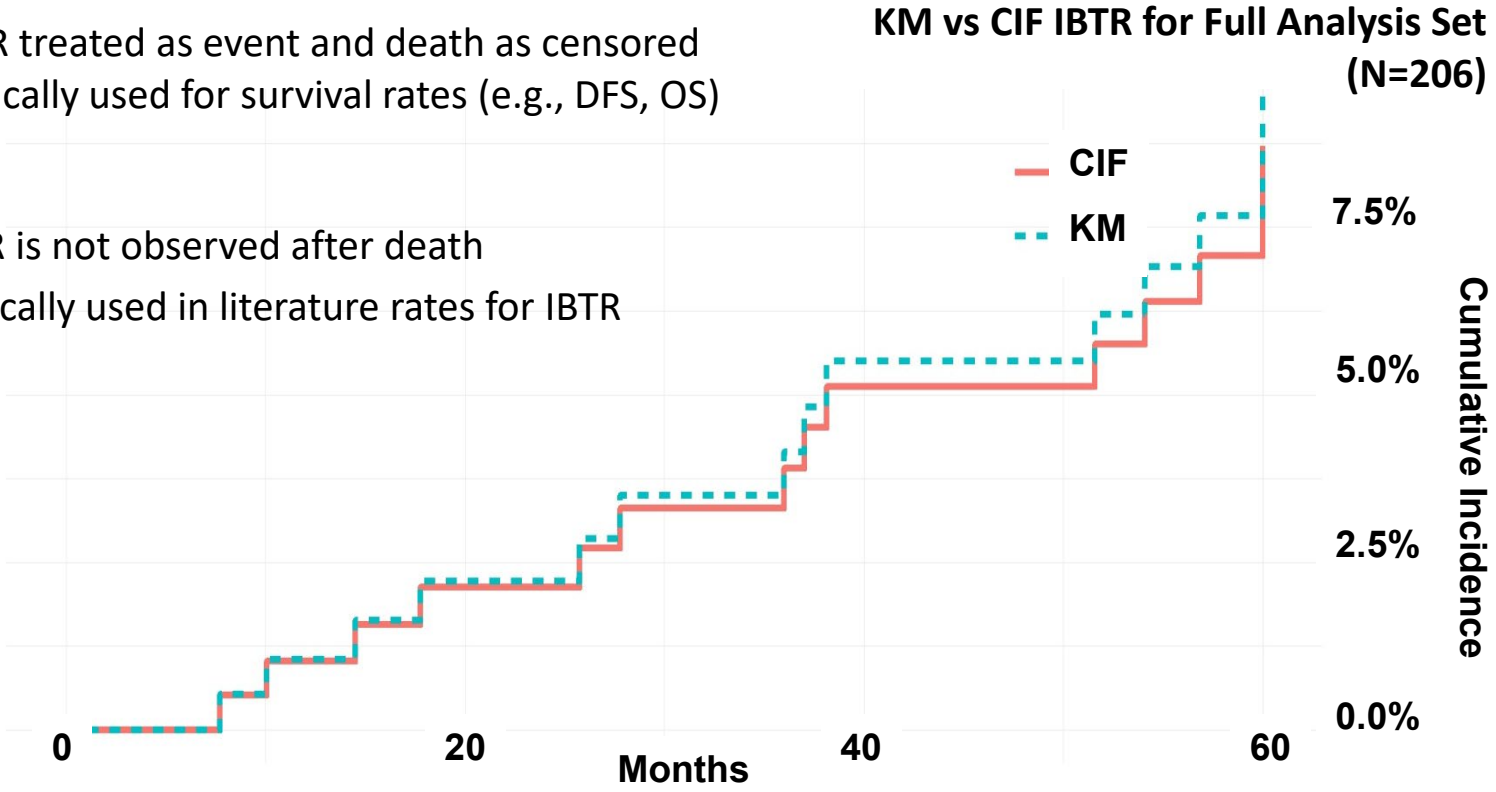
Inclusion Criteria	Exclusion Criteria
Unifocal invasive ductal breast carcinoma	Presence of lobular carcinoma, microinvasion or invasive breast carcinoma with extensive intraductal component, lymphovascular invasion, multifocal and/or multicentric breast cancer, multifocal calcifications
Age ≥ 60 years	Age < 60 years
Nottingham grade 1-2; specifically, nuclear and mitotic scores must be ≤2*	Nottingham grade of 3; specifically nuclear and/or mitotic score >2*
Node negative	Node positive
ER positive and/or PR positive, HER2 negative	ER and PR negative, or HER2 positive; presence of luminal B pathology
Tumor size ≤1.5 cm in greatest diameter	Tumor size > 1.5 cm in greatest diameter
Must receive adjuvant endocrine therapy	No adjuvant endocrine therapy

ICE3 Study Analysis Populations

Population	Subjects	Description
Full analysis set	N = 206	All subjects enrolled and treated in the study, including partial treatment.
Primary analysis set	N = 194	All subjects enrolled and treated in the study *except* for those excluded due to: ▪ violations of the inclusion/exclusion criteria (N=9), or ▪ incomplete treatment (N=3).
Indicated subpopulation *(post-hoc)*	N = 120	Subpopulation of the primary analysis set defined post-hoc based on the proposed IFU statement criteria; all patients received adjunctive hormone therapy.

Cumulative Incidence Function vs. KM

- **KM**
  - IBTR treated as event and death as censored
  - Typically used for survival rates (e.g., DFS, OS)
- **CIF**
  - IBTR is not observed after death
  - Typically used in literature rates for IBTR



Meta-Analysis Methods and Outcomes

Aspect	Methodology	Statistical Outcome
Model Specification	Random-effects model via GLIMMIX procedure in SAS	Overall IBTR rate: 0.61% (95% CI: 0.10% to 3.50%)
Weighting Strategy	1. Standard inverse-variance weighting for most studies 2. Adjusted weights for zero-event studies 3. Continuity correction applied to account for zero events	Inclusion of all studies in the analysis, including those with zero events All studies included in analysis (n=5) and all cohorts (n=6), including zero-event studies (n=2)
Heterogeneity Evaluation	Q statistic, I^2 index, and Tau^2	Q statistic: 63316.1996 ($p < 0.0001$), I^2 index: 99.99%, Tau^2: 2.6000 - indicating very high heterogeneity
Subgroup Analysis	by radiation treatment status	No radiation: 0.47% (95% CI: 0.00% to 35.91%); With radiation: 0.68% (95% CI: 0.15% to 2.94%)
Sensitivity Assessment	Leave-one-out analysis	$I^2 > 99\%$ in all iterations
Publication Bias Evaluation	Funnel plot visualization	Asymmetry observed in the funnel plot

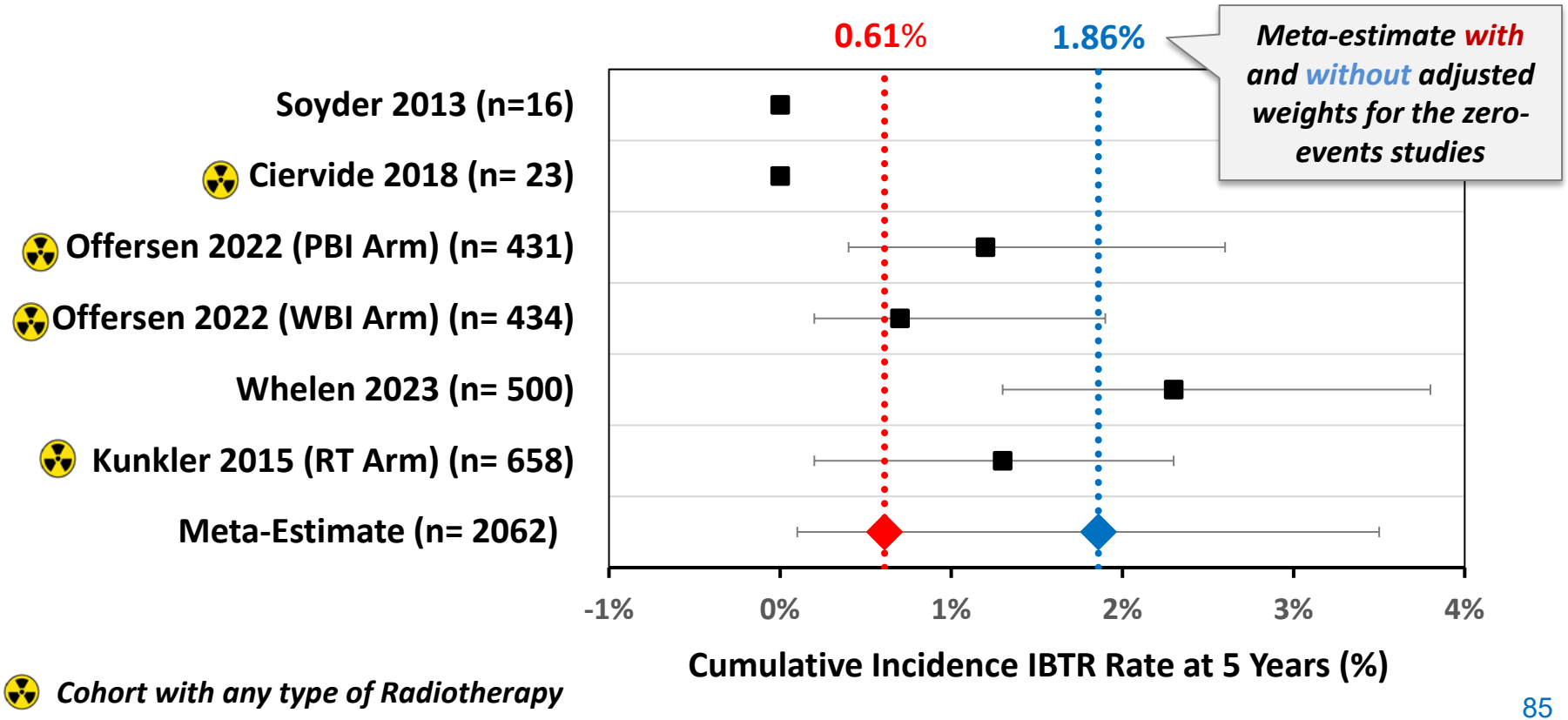
Meta Studies Breakdown by Exclusion Criteria

Exclusion Criteria	Kunkler 2015* (RT Arm) (n= 658)	Whelen 2023 (n= 500)	Ciervide 2018 (n= 23)	Offersen 2022 (WBI Arm) (n= 434)	Offersen 2022 (PBI Arm) (n= 431)	Soyder 2013 (n=16)
Female < 50 years	-	-	-	-	-	-
Tumor > 2 cm	(1/74)*, 11%	-	-	-	-	-
Nottingham grade 3	(0/13)*, 2%	-	-	-	-	?
ER negative	(0/55)*, 8%	-	-	-	-	-
PR negative	?	-	-	-	-	-
HER2 positive	?	-	-	2 (0%)	1 (0%)	?
Node-negative	-	-	-	-	-	-
Ki-67 >14% (if reported)	-	-	Ki 67 < 25%	-	-	-
Lobular carcinoma	-	-	-	3 (1%)	1 (0%)	-
multifocal	-	-	-	-	-	-
lymphovascular Invasion	(0/27)*, 4%	-	-	-	-	-

? No reported information

*Number of patients with local recurrence/total number

Random effect model meta-estimate



Cohort with any type of Radiotherapy