Sponsor's Executive Summary

IceCure Medical, Ltd.

ProSense™ System

DENXXXXXX

General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

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Abbreviations Used

ACOSOG	American College of Surgeons Oncology Group
AE	Adverse Event
APBI	Accelerated Partial Breast Irradiation
ASBrS	American Society of Breast Surgeons
BCL2	B cell lymphoma 2
BCS/BCT	Breast Conserving Surgery/Therapy (i.e., Lumpectomy)
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
C:	Confidence Interval
CIP	Clinical Investigation Plan
CK	Cytokeratins
CT	Computed tomography
DB	Database
DCIS	Ductal Carcinoma in Situ
DFS	Disease-Free Survival
DSMB	Data Safety Monitoring Board
ENT	Ear, Nose, Throat
ER	Estrogen Receptor
erbB3 and erbB4	Luminal A subtype: ER-positive and/or PR-positive with negative HER2 and low Ki67
EUSOMA	European Society of Breast Cancer Specialists
FDA	Food and Drug Administration
FOXA1	hepatocyte nuclear factor 3 alpha
FU	Follow-up
GATA3	GATA binding protein 3
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
IBTR	Ipsilateral Breast Tumor Recurrence
IQR	Interquartile Range
ISO	International Organization for Standardization
IRB	Institutional Review Board
Ki67	Proliferating cell nuclear antigen
KM	Kaplan-Meier
LB	Lower Bound
LTFU	Long Term Follow-up
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NSR	Non-significant Risk
PG	Performance Goal
PMA	Premarket Approval
PMS	Post Market Surveillance
PPI	Patient Preference Information

PR	Progesterone Receptor
PRO	Patient Reported Outcome
PRISMA	Preferred Reporting Items for Systemic Reviews and Meta-Analyses
RT	Radiotherapy
QOL	Quality of Life
SAE	Serious Adverse Events
SD	Standard Deviation
SOC	Standard of Care
SLNB	Sentinel Lymph Node Biopsy
TNM	Tumor, Node, Metastasis staging criteria
UB	Upper Bound
US	United States
WBI	Whole Breast Irradiation

1. SUMMARY

This executive summary is for the De Novo application submitted by IceCure Medical for ProSense™ Cryoablation System. **IceCure is seeking an expansion of indications for the FDA-cleared ProSense™ Cryoablation System to include treatment of early stage, low-risk breast cancer with adjuvant endocrine therapy.**

This executive summary provides an overview of the ProSense™ device and as a minimally invasive treatment option supporting information submitted by IceCure Medical in its De Novo application.

IceCure Medical appreciates your participation in the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee and asks that you review the provided materials with the following clinical and regulatory context:

- **The ProSense™ Cryoablation System is Already FDA Cleared for Tumor Ablation**

  The ProSense™ Cryoablation System is intended for cryogenic destruction of tissue during surgical procedures by the application of extreme cold temperatures. The IceCure ProSense™ Cryoablation System has been FDA-cleared since 2007 (K072883, K102360, K183213) and is commercially available in the United States for ablation of tumors in the fields of urology, oncology, dermatology, gynecology, ENT, general and thoracic surgery, and proctology. The ProSense™ Cryoablation system has also been FDA-cleared for the ablation of breast fibroadenomas. Outside of the United States, ProSense™ Cryoablation System is authorized in other countries and has been used successfully in the treatment of breast cancer since 2014.

- **The Current Standard-of-Care for the Indicated Patient Population is Surgical Tumor Removal (Lumpectomy)**

  Lumpectomy is the standard-of-care treatment for patients with early stage, low-risk breast cancer that is endocrine-receptor positive. Lumpectomy is performed as an outpatient procedure where an incision is made over the tumor site for resection of the tumor, ensuring sufficient tissue is removed to achieve clear tumor margins to reduce chances of recurrence. The surgery is invasive, requiring a 1-to-2 inch incision and the procedure typically takes 1-2 hours. Outcomes of lumpectomy with adjuvant endocrine therapy are widely published and reported rates of 5-year cancer recurrence range from 0%-10.5% in the indicated population[1, 2.] Lumpectomy is considered safe and effective for the treatment of breast cancer; however, it is still an invasive surgical procedure. While most patients are discharged the same day, recovery following the surgery may take up to two weeks, with surgical side effects seen in up to 9% of patients up to 6 years after the procedure. Following lumpectomy, patients are treated with adjuvant therapies, such as endocrine therapy according to physician discretion.

- **The Clinical Community Favors De-escalation of Breast Cancer Treatment for Low Risk Patients in order to Minimize Patient Risks and Enhance Quality of Life**

  Current treatment options such as surgery (mastectomy, lumpectomy, etc.), chemotherapy, radiation, and other drug therapies have demonstrated efficacy in reducing morbidity but can have a detrimental effect on the quality of life of the patient. Patients with early-stage,

low-risk breast cancer that is endocrine-receptor positive (ER+, PR+ or PR-) have the best prognosis and are at lowest risk for recurrence and cancer related morbidity; the 5-year relative survival rate (compared to those who do not have breast cancer) in the U.S. of localized (early stage) breast cancer is 99%[3]. Accordingly, these patients are appropriate candidates for minimizing risk exposure during therapy without detrimental cost to recurrence and morbidity rates.

As described in detail in these materials, data from the company's multicenter ICE3 clinical study support the safety and effectiveness of the ProSense™ Cryoablation System for treatment of women aged 60 and over with early stage, low risk breast cancer receiving adjuvant endocrine therapy. The data further demonstrate that this minimally invasive treatment option presents improved benefits for the indicated patients and fewer risks compared to the standard of care treatment.

- **Data from the ICE3 Clinical Study Demonstrate a Reasonable Assurance of Effectiveness and Safety for ProSense™ for Treatment of Low Risk Breast Cancer**
  - **Effectiveness.** The ICE3 study met the pre-specified effectiveness performance goal. The ProSense™ Cryoablation System primary analysis population outcomes demonstrates 100% of patients are recurrence free through 2-years follow-up and >95% of patients are recurrence free through 5-years follow-up, nearly 97% when treated per the proposed indications for use.
  - **Safety.** Cryoablation procedure related adverse events (edema, bruising, hematoma), hypothermic damage to nearby tissue and postoperative pain, occurred acutely and the majority of events were mild in severity[4]. These procedure-related events are common to all cryoablation procedures and are less severe than the standard of care lumpectomy surgical-procedure related risks[5, 6].

    Breast cancer related risks include risk of incomplete treatment, risk of recurrence and risk of breast cancer related death and are common to all breast cancer treatments. Less than 5% of ICE3 patients experienced tumor recurrence. Two (2) patients died as a result of breast cancer (1.03%). Risk of incomplete treatment is sufficiently mitigated through real-time visualization of tumor ablation during treatment and recurrence or residual tumor is sufficiently identified through routine annual mammography. All alternate treatment methods are available to the patient in the case of incomplete treatment or tumor recurrence.
  - **Benefit/ Risk.** Cryoablation is a minimally invasive alternative to breast conserving surgery (BCS) that reduces morbidity along with providing benefits to the patient with regard to the psychosocial and cosmetic impact of breast cancer therapy[4, 5, 7]. The minimally invasive nature of treatment with ProSense™ allows for treatment without the need for general anesthesia, shorter recovery times, and improved cosmesis of the scar site and also due to lack of excision of breast tissue. Patients

and physicians reported significant quality of life benefits with use of ProSense™ Cryoablation System in the ICE3 study: patients experience near immediate recovery to normal activity (median 1 day recovery time) and 99.1% of patients and 97% of physicians who responded were 'satisfied' or 'very satisfied' with the breast cosmetic outcome at 5 years follow-up.

- **Comparison of ICE3 Outcomes to SOC Lumpectomy Confirms Positive Benefit/ Risk**

  The ProSense™ Cryoablation System demonstrated benefit of treatment of early-stage breast cancer in patients with the lowest risk for recurrence with similar effectiveness to standard-of-care and significantly fewer and less severe adverse events and risks. Sub-group analyses evaluating outcomes based on adjuvant treatment or biologic characteristics confirmed the favorable IBTR outcomes of patients treated with ProSense™. In all analyses, ICE3 patients treated with cryoablation using ProSense™ experienced a similar rate of recurrence as patients treated with lumpectomy, while avoiding risks and side effects of lumpectomy, including those associated with general anesthesia as well as scarring, infection, bleeding, damage to nearby tissue, pain and swelling that may last for months, nerve damage, poor cosmesis and depression.

1.1.Disease State and De-escalation of Treatment

Breast cancer is a disease in which the cells in the breast grow unregulated, forming a malignant tumor with potential to spread if left untreated and metastasize[8]. Endocrine receptor positive (c ER+, PR+ or PR-) and HER2- is a surrogate for the Luminal A subtype, the most common molecular subtype of breast cancer that accounts for 68% of all cases. This subtype tends to be slower-growing and less aggressive than other subtypes and responds to endocrine therapy[9]. Patients with this breast cancer subtype have a good prognosis and the local recurrence rate is significantly lower than the other subtypes[10].

Patients with early-stage, low-risk breast cancer that is endocrine-receptor positive have the best prognosis and are at lowest risk for recurrence and cancer related morbidity; the 5-year relative survival rate (compared to those who do not have breast cancer) in the U.S. of localized (early stage) breast cancer is 99%[3].

Standard-of-care treatment for patients with early stage, low-risk breast cancer that is endocrine-receptor positive is lumpectomy, which involves surgical excision of the tumor, followed by adjuvant endocrine therapy. Lumpectomy is performed as an outpatient procedure where an incision is made over the tumor site for resection of the tumor, ensuring sufficient tissue is removed to achieve clear tumor margins to reduce chances of recurrence. Outcomes of lumpectomy with adjuvant endocrine therapy are widely published and reported rates of 5-year cancer recurrence range from 0%-10.5% in the indicated population[1, 2].

Surgical resection may have a detrimental effect on the quality of life of the patient, such as lingering physical scarring and disfigurement of the breasts, fatigue, and lymphoedema. Many women demonstrate delayed onset of psychological struggles including reflecting on fears (e.g., survival, recurrence) and existential issues once the focus on treatment has abated[11, 12].

Breast cancer treatment has seen many advances in recent decades, lessening the morbidity to patients, while improving outcomes[13]. Central to these gains has been the introduction of breast conserving surgery (BCS) allowing for removal of tissue at the tumor site alone instead of radical mastectomy in low risk patients. BCS is considered safe and effective for the treatment of breast cancer. However, it is still an invasive surgical procedure, performed under general anesthesia that requires, at minimum, a 1-to-2-inch incision and takes several hours. Recovery can be a prolonged process and surgical side effects can last for years after the procedure. Risks and side effects of the surgery include those associated with general anesthesia as well as scarring, infection, bleeding, damage to nearby tissue, pain and swelling that may last for months, nerve damage, and depression. Positive margins and incomplete removal of cancerous tissue are also considered as risks.

There is considerable interest from the clinical community in further de-escalation of the treatment of breast cancer to minimize risks. Patients at lowest risk for recurrence and cancer related morbidity are appropriate candidates for minimizing risk exposure during therapy without detrimental cost to recurrence and morbidity rates.

1.2.Device Description

The ProSense™ Cryoablation System is intended for cryogenic destruction of tissue by the application of extreme cold temperatures. The IceCure ProSense™ Cryoablation System has been FDA-cleared since 2007 (K072883, K102360, K183213) and is commercially available in the United States for ablation of tumors in the fields of urology, oncology, dermatology, gynecology, ENT, general and thoracic surgery, and proctology. The ProSense™ Cryoablation system has also been FDA-cleared for the ablation of breast fibroadenomas. Outside of the United States, ProSense™ Cryoablation System has been used successfully in the treatment of breast cancer since 2014.

The ProSense™ Cryoablation System comprises a small diameter probe and a cryotherapy generator which allows for delivery of cryotherapy directly to the tumor site in a minimally invasive approach. The delivered treatment is intended to destroy tissue by cooling the selected target to extremely low temperatures, using a closed system with pressurized liquid nitrogen and a disposable cryoprobe.

When used in the treatment of low risk breast cancer, the procedure is performed outpatient under local anesthesia. The tumor dimensions are measured in all planes (sagittal, transverse, anterior-posterior) prior to treatment and the cryoprobe is inserted through a 3mm incision created by a

surgical scalpel along the longest axis possible in the radial view. Insertion and treatment is performed under direct ultrasound (US) visualization. The cryoprobe cooling zone center is placed into the middle of the lesion. Cryoprobe position is checked by confirming the cryoprobe is centered in the anti-radial view. The cancerous tissue is then frozen to sub-zero temperatures within minutes by utilizing liquid nitrogen which flows through and is contained within the probe. The quick-freezing cycle causes ice crystals to form an ice ball within the margins of the tumor, resulting in death of the tumor cells. Healthy tissue adjacent to the cancerous tissue is left unaffected. Tumors are typically ablated in two freeze-thaw cycles during which cryoprobe tip temperature should reach at least -150°C. During the freeze-thaw-freeze cycles, ice ball width growth is monitored with real time imaging via ultrasound. After the first and second freeze, ice ball width and length are measured to ensure complete lesion engulfment with desired margins (1cm).

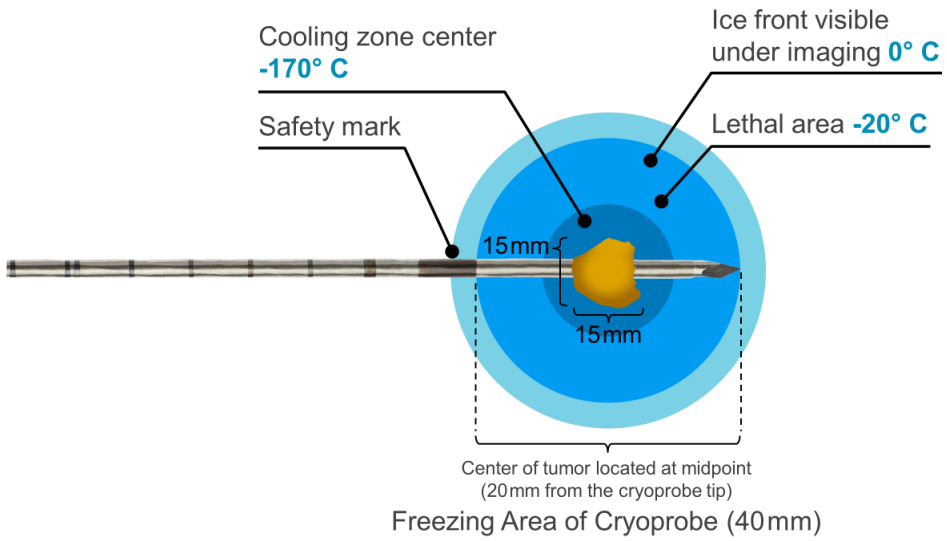


Figure 1-1: Schematic diagram of cryoprobe, cooling zone, and lethal area during cryoablation procedure.

1.2.1. Indications for Use

The IceCure ProSense™ Cryoablation System has been FDA 510(k) cleared since 2007 for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ENT, gynecology, oncology, proctology, and urology. The subject of this Advisory Panel Meeting is the expansion of the indications for use to include treatment of breast cancer:

ProSense™ Cryoablation System is indicated for treatment of patients with early stage, low risk breast cancer with adjuvant endocrine therapy.*

**Patients with early stage, low-risk breast cancer are patients ⩾60 years of age with prognostic stage 1A defined as unifocal tumor size ⩽1.5cm, ER+/PR+/-, HER2-, histological grade 1-2 infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0).*

1.3. Regulatory History of ProSense™ Cryoablation System for Treatment of Low Risk Breast Cancer

The IceCure ProSense™ Cryoablation System has been CE marked and commercially available in markets outside the U.S. for breast cancer treatment for more than a decade with more than 1,600 cryoablation treatments performed worldwide.

FDA granted ProSense™ Cryoablation System Breakthrough Device Designation in March 2021 for the proposed breast cancer treatment indication, on the basis of reasonable expectation that ProSense™ Cryoablation System provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or condition.

In October of 2022, IceCure Medical submitted a De Novo application for ProSense™ Cryoablation System providing the interim results of the ICE3 study. The initial dataset has subsequently been updated with the final study data including 5 year follow-up data on patients.

1.4. ICE3 Supporting Clinical Evidence

Cryoablation for breast cancer treatment has been demonstrated in clinical practice and in prospective studies published in the literature as a suitable alternative to BCS that offers patients a less invasive procedure for an effective and favorable treatment option for patients with early-stage low-risk breast cancer.

Cryoablation for treatment in breast cancer has been studied and outcomes have been published over the past several decades[14]. Studies that performed cryoablation followed by surgical resection demonstrate effective treatment of breast cancer confirmed by pathological results. For treatment in breast cancer, cryoablation is a short (1 hour) outpatient procedure that does not require general anesthesia. In terms of quality of life, women who received cryoablation treatment reported better financial and psychosocial well-being compared to women who received BCS[5]. ICE3 Clinical Study Design

The ICE3 clinical study by IceCure Medical is a multicenter (19 sites in the United States), prospective, single arm, nonrandomized clinical trial using cryoablation to remove malignant breast cancer tissues with adjuvant treatment per physician discretion in women aged 60 and over

conducted between October 2014 and March 2024. The study was approved by the Institutional Review Board (IRB) to be conducted as a non-significant risk study under IRB oversight. An Independent Data and Safety Monitoring Board (DSMB) routinely reviewed the study data to provide safety oversight.

The primary objective of the ICE3 clinical study is to evaluate the safety and effectiveness, of cryoablation with IceCure Medical's ProSense™ Cryoablation System for the treatment of early stage, low-risk breast cancer in women 60 years or older as measured by Ipsilateral Breast Tumor Recurrence (IBTR) rate.

The primary endpoint, Ipsilateral Breast Tumor Recurrence (IBTR) rate, was analyzed using the Kaplan-Meier (KM) method.

Key secondary endpoints include:

- Distant metastases rate including contralateral breast cancer.
- Disease-free Survival (DFS) until first disease event.
    - Protocol defines as local (Ductal Carcinoma In Situ (DCIS) or invasive), regional, or distant breast cancer recurrence, contralateral breast cancer, DCIS or invasive, second primary cancer (non-breast), or death due to any cause.
    - National Cancer Institute defines as local (Ductal Carcinoma In Situ (DCIS) or invasive), regional, or distant breast cancer recurrence.
- Breast cancer survival until death from breast cancer or unknown cause.
- Overall survival until death from any cause.
- Breast cosmetic satisfaction.
- Adverse events related to study device or procedure rate.

The protocol specified that the final analysis be performed 5 years from the last patient enrollment in the study. **The ICE3 clinical study has completed 5-year follow-up and final study outcomes are provided in this summary.**

IceCure Medical designed the ICE3 clinical study as a single arm clinical study for a number of reasons:

- The standard of care for the removal of early-stage malignant breast cancer tissues is lumpectomy, which has been well documented in the literature regarding its rate of recurrence and clinical outcomes.
- A blinded or randomized clinical study design was not deemed reasonable for this investigation.
    - Based on the differences in treatments compared to the standard of care methods for the indicated population, lumpectomy, blinding of patients or physicians in the trial would be impossible.

  - Randomization was not deemed appropriate for patients in a trial studying the ProSense™ Cryoablation System due to questions of equipoise and different treatment providers (breast surgeon versus breast surgeon or interventional radiologist) performing lumpectomy and cryoablation.
- Given that a blinded or randomized clinical study design is not possible, a literature control based on treatment of >3,500 patients is more robust than would be expected of a prospectively enrolled control.
- Given similar outcomes presented across the preponderance of clinical studies in the literature, development of a performance goal based on the thousands of patients treated with lumpectomy is a valid scientific method for assessment of the safety and effectiveness of the ProSense™ Cryoablation System. In addition, sufficient level of detail exists in the literature to assess various subpopulations of interest in comparison to the ICE3 study data.

1.4.1. Analysis Populations

- **All Treated Population (N=206)**: all patients treated in the ICE3 study. Supplemental safety analyses are performed on this population.
- **Primary Analysis Population (N=194)**: all treated population excluding DSMB excluded patients. Primary effectiveness and safety analyses are performed on this population.

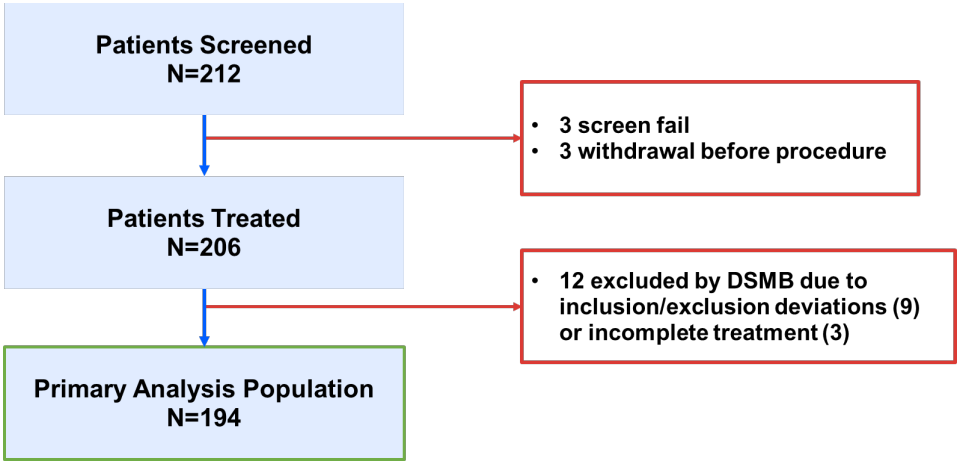


Figure 1-2. Analysis Population Flowchart

Follow-up compliance at 5-years follow-up is >80%. Mean study follow-up is 54.2 months (SD 13.1). 5-year outcome data are available on 155 patients; the remaining 39 patients contributed data to the survival analysis through mean 34.8 months, primarily due to loss to follow-up and patients withdrawing from the study. This high rate of follow-up over the course of a 5-year study provides a strong foundation for the overall results of the clinical study.

The mean age of the patients was 74.9 ±6.9 years (range, 55–94 years), and the mean BMI was 28.8±6.3 kg/m^2. In alignment with the inclusion criteria detailed above, the enrolled patient population consisted of females (100%), ER positive (100%), PR positive (93%), and with a Nottingham score of ≤2 (100%).

1.4.2. ICE3 Primary Endpoint

Based on the long history of lumpectomy, considered the gold standard of care for treatment of the indicated population, and the wealth of published literature on breast cancer recurrence outcomes, FDA agreed that literature can serve as an appropriate comparator to the ICE3 clinical study results. IceCure Medical pre-specified a comparator rate for 5-year IBTR outcome among patients in the ICE3 clinical study based on literature-reported rates for the standard-of-care, lumpectomy.

- **Pre-Specified Literature-Based Performance Goal**: If the upper limit of the 95% confidence interval for IBTR at the 5-year time point is less than 10%, the study will be considered successful.

The ICE3 5-year Ipsilateral Breast Tumor Recurrence (IBTR) rate (n=194) was 4.3% with upper bound of 95% confidence interval of 8.7%, meeting the pre-specified primary endpoint of a recurrence rate of less than 10%.

1.4.3. Secondary Effectiveness Outcomes

Secondary effectiveness endpoints in the Primary Analysis Set at 5 years demonstrated a 96.7% breast cancer survival rate and a 92.8% disease-free survival rate using the NCI definition. Overall survival rate exceeds the actuarial survival rate for people age 74, the mean age of the ICE3 study population. In addition, 82.9% of subjects returned to full activities within 48 hours after the procedure and median time to resume normal activities was 1 day (range 0-8 days). 99.1% of patients and 97% of physicians who responded were ‘satisfied’ or ‘very satisfied’ with the breast cosmetic outcome at 5 years follow-up.

1.4.4. ICE3 Safety Outcomes

The ICE3 clinical study outcomes demonstrate reasonable assurance of safety for ProSense™ Cryoablation System based on the safety data from the primary analysis population (n=194).

Procedure-related adverse events (edema, bruising, hematoma), hypothermic damage to nearby tissue and postoperative pain, occurred acutely and the majority were mild in severity. These procedure-related events are common to all cryoablation procedures and are less severe than surgical-procedure related risks. Breast cancer related risks include risk of incomplete treatment, risk of recurrence and risk of breast cancer related death and are common to all breast cancer treatments.

The Data Safety Monitoring Board (DSMB) conservatively classified a total of four (4) serious adverse events in three (3) patients (1.5%) to be possibly related to the cryoablation procedure, due to user error. In two cases, the DSMB determined two patients received suboptimal treatment (one with 5 minute treatment cycles and one with 7 minute treatment cycles resulting in ice balls <35mm at the end of first freeze and <40mm at the end of the second freeze) and one (1) patient experienced probe mispositioning (not centered or deep enough in tumor) during cryoablation.

A total of 21 deaths (10.8%) were observed in the ICE3 study, 20 deaths occurred within 5-years of cryoablation treatment. Of these, two (2) patients died as a result of breast cancer (1.03%).

1.5.FDA-Requested Supplemental Analyses

FDA requested IceCure perform a series of analyses to evaluate ICE3 outcomes versus alternate literature comparators and in sub-populations of ICE3 clinical study patients based on adjuvant treatment and/ or biological characteristics. The literature search was updated in accordance with FDA-recognized literature review standards per the PRISMA methodology to reflect the current treatment standard of care.

These FDA-requested analyses and ICE3 and comparator groups are summarized in Table 1-1.

Table 1-1: Summary of ICE3 Analysis Populations and Respective Literature Comparators

Characteristics of Interest	ICE3		Comparator	
	Sub-Population	IBTR Outcome	Literature Analysis	IBTR Outcome
Alternate Comparator				
Full primary analysis population versus alternate comparator	Primary Analysis Population (N=194)	4.3% (95% CI UB: 8.7%)	IceCure PRISMA Meta-analysis	3.52% (95% CI UB: 5.77%)
Sub-Populations Intended to Align with LUMINA				
Endocrine therapy only	Sub-population with endocrine therapy without radiation (N=124)	3.7% (95% CI UB: 9.6%)	IceCure PRISMA sensitivity (lumpectomy with endocrine therapy)	2.82% (95% CI UB: 4.83%)
Endocrine therapy only, Further restricted to ICE3 patients with available Ki67 score and Ki67<14; excludes PR-	Sub-population aligned w/ LUMINA (N=56)	2.17% (95% CI UB: 14.4%)	LUMINA study (lumpectomy with endocrine therapy)	2.3% (95% CI UB 4.1%)
Endocrine therapy only, Further restricted to ICE3 patients with available Ki67	Sub-population aligned w/ LUMINA and	2.56% (95% CI UB: 16.8%)	LUMINA study (lumpectomy with endocrine therapy)	2.3% (95% CI UB 4.1%)

Characteristics of Interest	ICE3		Comparator	
	Sub-Population	IBTR Outcome	Literature Analysis	IBTR Outcome
score and Ki67<14; excludes PR- and nuclear grade ≤ 2	nuclear grade ≤ 2 (N=48)			
Sub-Populations Intended to Align with Proposed Indication				
Endocrine +/- other adjuvant treatments **17% with adjuvant radiotherapy*	Sub-population aligned w/ indications (N=147)	3.08% (95% CI UB: 8.0%)	IceCure PRISMA sensitivity (lumpectomy with endocrine therapy) **excludes adjuvant radiotherapy*	2.82% (95% CI UB: 4.83%)
Endocrine +/- other adjuvant treatments Age ≥ 60, nuclear grade ≤ 2 **17% with adjuvant radiotherapy*	Sub-population aligned w/ indications and nuclear grade ≤ 2 (N=120)	1.95% (95% CI UB: 7.6%)	IceCure PRISMA sensitivity (lumpectomy with endocrine therapy) **excludes adjuvant radiotherapy*	2.82% (95% CI UB: 4.83%)
Sub-Population Intended to Evaluate Impact of Adjuvant Radiotherapy				
Radiation +/- other adjuvant treatments	Sub-population with radiation (N=29)	0%	FDA PRISMA sensitivity (lumpectomy with radiation)	Range: 0-1.2%

Cryoablation treatment does not interfere with or preclude adjuvant treatments. As with lumpectomy, physicians can proceed with additional concomitant therapies as appropriate for the specific patient. When looking at the ICE3 data in subpopulations stratified by adjuvant therapy, there were minor, expected differences in recurrence rates of subpopulations treated with adjuvant endocrine therapy alone, endocrine therapy with or without other adjuvant treatments, and adjuvant radiotherapy alone. Similar subpopulation analyses were performed based on biological characteristics. In all of the subpopulation analyses, ICE3 recurrence rates were comparable to the corresponding literature comparator.

Both the pre-specified primary endpoint and the various analyses of ICE3 sub-populations as compared to PRISMA and literature outcomes confirmed favorable IBTR outcomes in the ICE3 study population. In all analyses, ICE3 patients treated with cryoablation using ProSense™ experienced a similar rate of recurrence as patients treated with lumpectomy. Importantly, the subpopulation aligned with the proposed indications, indicated by the black box, shows improved

recurrence outcomes as compared to the overall population with nearly 97% of patients free from recurrence.

1.6. Benefit/Risk Evaluation

The ProSense™ device has demonstrated benefits in the treatment of early-stage, low risk breast cancer, which outweigh the risks of treatment. Further the benefit/risk profile of the device compares favorably to the standard of care.

The data from the ICE3 clinical study demonstrate that ProSense™ Cryoablation System provides immediate ablation of cancerous breast tissue without recurrence through 2-years post-treatment and an overall low rate of recurrence 5 years post-treatment; the 5-year IBTR rate is similar to that of lumpectomy.

Additionally, ProSense™ Cryoablation System cryoablation treatment of early-stage, low-risk breast cancer was shown to have fewer and less severe adverse events and risks (**Table 1-2**) compared to the standard of care. These benefits significantly impact on the patient's treatment experience and quality of life. The treatment modality alone further offers improved patient benefits due to the minimally invasive approach, as reflected in patient reported outcomes in ICE3 with regard to procedure-related risks, recovery time, pain, and cosmesis.

Table 1-2. Comparison of Benefits and Risks of Lumpectomy and Cryotherapy

Lumpectomy	Cryotherapy (ICE3)
Clinical Experience • Outpatient – general (75%) or local anesthesia[15, 16] • Surgery prep + 1-2-hour procedure + recovery from general anesthesia[17] • 1"-2" long incision (minimum) • Up to 2-week recovery for normal activities[18]	**Clinical Experience** • Outpatient – only local anesthesia • 30 min – 2 hour procedure[19] • Needle-hole as cryoprobe is inserted, no incision (3mm) • Near immediate recovery to normal activity median 1 day (range 0-8 days) recovery time (ICE3)
Quality of Life (QOL) • Literature reports up to 30-40% dissatisfied with appearance of breasts[20, 21] • 60% less likely to believe they were healthier and more likely to fear recurrence if asymmetric breasts[22] • Increased depression (43%)[22] • Reduced feeling of sexual attractiveness[22, 23]	**Quality of Life (QOL)** • Satisfactory cosmetic result (95%)[24] • High percentage of patients and physician responders satisfied with cosmetic results (99.1% of patients and 97% of physician responders 'satisfied' or 'very satisfied' at 5 years in ICE3) • Significant improvement in distress thermometer at 6 months relative to baseline in ICE3 clinical study

Lumpectomy	Cryotherapy (ICE3)
• Breast reconstruction associated with reduced, short-term QOL[1]	• No breast reconstruction needed
Adverse Events/Side Effects • Surgical side effects seen in up to 9% of patients up to 6 years after the procedure[25] • Surgical Scars[24] • 18% of the women experience their breast scars are worse than expected, and about 10-30% are dissatisfied with the appearance of their scar[26, 27]. • Breast disfigurement/asymmetry[20, 21] • General anesthesia risks and side effects[28-32] • Infection (0.5%-23.5%)[2, 19, 25, 33-38] • Bleeding (resulted intraoperative or post-operative transfusion (0.07%)[33] • Hematoma (3.7%)[37] • Seroma (32.6%)[39] • Fat necrosis (4.3%)[40] • Nerve damage[1] and neuropathic pain in 31% of patients following breast-conserving surgery[41]. • Postoperative effects may linger for months: pain tenderness, swelling, bruising[19, 21, 42] • 78.8% experiences post-surgical related pain lasting six months or more (40% moderate to worst possible)[20] • 33% report chronic post-treatment pain up to 12 months post-surgery[43] • Risk of incomplete tumor removal[44, 45] • Reoperation (23.2%)[46] and re-excision (21.7%)[47]	**Adverse Events/Side Effects** • Minimal scarring • No disfigurement • No general anesthesia • No observations of procedure-related infection • No observations of procedure-related bleeding • Less invasive/less tissue damage • Hypothermic damage to nearby tissue possible (2.1%) • Mild-moderate pain (19.1%) • Mild-moderate edema (18.6%) • Mild-moderate bruising (27.8%) • Risk of incomplete ablation. • Theoretical risk of seeded tumors upon cryoprobe removal if incomplete ablation (not observed in ICE3)

The evidence demonstrates a reasonable assurance of safety and effectiveness of ProSense™ Cryoablation System when used in the treatment of early-stage, low-risk breast cancer, the breakthrough nature of the device and significant patient need, as well as assurance of risk mitigation through routine annual mammography and suitability of all alternate treatment measures, ProSense™ Cryoablation System benefit-risk assessment indicates the benefits of the

device outweigh the risks for the proposed indicated population of patients with early-stage, low-risk breast cancer.

- **Data from the ICE3 Clinical Study Demonstrate a Reasonable Assurance of Effectiveness and Safety for ProSense™ for Treatment of Low Risk Breast Cancer**

  The ICE3 clinical study by IceCure Medical is a multicenter (19 sites in the United States), prospective, single arm, nonrandomized clinical trial using cryoablation to remove malignant breast cancer tissues in women aged 60 and over. The ProSense™ Cryoablation System overall study cohort outcomes demonstrate >95% of patients are recurrence free through 5-years follow-up, nearly 97% when treated per the proposed indications for use.

  - **Effectiveness.** The ProSense™ Cryoablation System overall study cohort outcomes demonstrate >95% of patients are recurrence free through 5-years follow-up, nearly 97% when treated per the proposed indications for use.
  - **Safety.** Cryoablation procedure related adverse events (edema, bruising, hematoma), hypothermic damage to nearby tissue and postoperative pain, occurred acutely and the majority of events were mild in severity. These procedure-related events are common to all cryoablation procedures and are less severe than the standard of care lumpectomy surgical-procedure related risks[5, 6].

    Breast cancer related risks include risk of incomplete treatment, risk of recurrence and risk of breast cancer related death and are common to all breast cancer treatments. Less than 5% of ICE3 patients experienced tumor recurrence. Two (2) patients died as a result of breast cancer (1.03%). Risk of incomplete treatment is sufficiently mitigated through real-time visualization of tumor ablation during treatment and recurrence or residual tumor is sufficiently identified through routine annual mammography. All alternate treatment methods are available to the patient in the case of incomplete treatment or tumor recurrence.
  - **Benefit/ Risk.** Cryoablation is a minimally invasive alternative to breast conserving surgery (BCS) that reduces morbidity along with providing benefits to the patient with regard to the psychosocial and cosmetic impact of breast cancer therapy. The minimally invasive nature of treatment with ProSense™ allows for treatment without the need for general anesthesia, shorter recovery times, and improved cosmesis of the scar site and also due to lack of excision of breast tissue. Patients and physicians reported significant quality of life benefits with use of ProSense™ Cryoablation System in the ICE3 study: patients experience near immediate recovery to normal activity (median 1 day recovery time) and 99.1% of patients and 97% of physicians who responded were ‘satisfied’ or ‘very satisfied’ with the breast cosmetic outcome at 5 years follow-up.

- **Comparison of ICE3 Outcomes to SOC Lumpectomy Confirms Positive Benefit/ Risk**

  The ProSense™ Cryoablation System demonstrated benefit of treatment of early-stage breast cancer in patients with the lowest risk for recurrence with similar effectiveness to standard-of-care and significantly fewer and less severe adverse events and risks. Sub-group analyses evaluating outcomes based on adjuvant treatment or biologic characteristics confirmed the favorable IBTR outcomes of patients treated with ProSense™. In all analyses, ICE3 patients treated with cryoablation using ProSense™ experienced a similar rate of recurrence as patients treated with lumpectomy, while avoiding risks and side effects of lumpectomy, including those associated with general anesthesia as well as scarring, infection, bleeding, damage to nearby tissue, pain and swelling that may last for months, nerve damage, poor cosmesis and depression.

- **The totality of evidence demonstrates safety, efficacy, and positive benefit/ risk profile of ProSense™ Cryoablation System for treatment of early-stage, low-risk breast cancer. Cryotherapy with ProSense™ Provides Clinically Appropriate De-escalation of Breast Cancer Treatment to Minimize Patient Risks and Improve Quality of Life During Treatment.**

2. DISEASE STATE AND UNMET CLINICAL NEED

Summary

- The indicated population is patients with early-stage, low-risk breast cancer that is ER+ and HER2-. These patients are at lowest risk for recurrence and cancer related morbidity. This population has the best prognosis and is the most receptive to endocrine therapy.
- Existing breast cancer treatment options, including radiotherapy and surgical resection, are associated with health risks and may have a detrimental effect on the quality of life of the patient.
- For decades, the clinical community of breast cancer surgeons and treatment providers has pushed for de-escalation of care to lessen the morbidity of treatment to patients with low-risk breast cancer.
- Recent highly influential, peer-reviewed studies, CALGB 9343 and PRIMEII, evaluated outcomes following treatment with lumpectomy with and without radiotherapy. These studies concluded that despite 3% to 8-9% differences in 5-year and 10-year recurrence outcomes, there was essentially no difference in overall survival.
- Despite differences in local recurrence rate, the clinical community is recommending de-escalation of care. Further, these studies demonstrated that the risk of local recurrence does not equate to the risk of overall survival.
- Early stage, low risk breast cancer patients are most appropriate for further de-escalation of care to eliminate the need for surgery and associated tissue resection and treatment-related risks.

2.1. Breast Cancer Subtypes

In 2024, an estimated 310,720 new cases of invasive breast cancer will be diagnosed in women[9]. Breast cancer is a disease in which the cells in the breast grow unregulated, forming a malignant tumor with potential to spread if left untreated and metastasize[8]. Breast cancer is a heterogeneous complex of diseases, a spectrum of many subtypes with distinct biological features that lead to differences in response patterns to various treatment modalities and clinical outcomes.

Traditional classification systems consider biological characteristics, such as tumor size, lymph node involvement, histological grade, patient's age, and molecular characteristics, including estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2 or c-erbB2) status[48].

Tumors can be classified based on Tumor, Node, Metastasis (TNM) staging criteria. Tumor (T) describes the diameter of the tumor. Node (N) describes whether the cancer has spread to the lymph nodes. Metastasis (M) describes whether the cancer has spread to a different part of the body.

Lowest Risk → Highest Risk

Tumor Size (T)	T1: Tumor size <2 cm	T2: Tumor size 2-5 cm	T3: Tumor size >5 cm	T4:Tumor extends to skin or chest wall
Lymph Nodes (N)	N0: No lymph node metastasis	N1: Metastasis to ipsilateral, movable axillary LNs	N2: Metastasis to ipsilateral fixed axillary, or IM LNs	N3: Metastasis to infraclavicular/supraclavicular LN, or to axially and IM LNs
Metastasis (M)	M0: No distant metastasis	M1: Distant metastasis		

Figure 2-1. TNM Staging Criteria with ProSense™ Cryoablation System Indicated Population Characteristics Outlined in Green

Breast cancer is further classified by molecular characteristics that are associated with clinical presentation, response to therapy, and prognosis. The four broad molecular subtypes are Luminal A, Luminal B, basal-like, and HER2-enriched. These subtypes were originally defined by gene expression profiling but are often approximated based on simpler tests that determine ER, PR, and HER2 status. Hormone receptor positive (HR+) cancers are those that test positive for ER or PR, or both.

HR+ and HER2- is a surrogate for the Luminal A subtype, the most common molecular subtype of breast cancer that accounts for 68% of all cases. This subtype tends to be slower-growing and less aggressive than other subtypes and responds to endocrine therapy[9]. Patients with this breast cancer subtype have a good prognosis and the local recurrence rate is significantly lower than the other subtypes[10].

The patient population for discussion in this panel meeting is biologically categorized as T1N0M0 and molecularly categorized as ER+/HER2-. This is the same population included in the ICE3 study and is the indicated population for the use of ProSense™.

2.2.Early-Stage Standard of Care – Lumpectomy without Radiation

The standard-of-care treatment for early-stage breast cancer is lumpectomy (also known as breast conserving surgery [BCS/BCT]) and is considered safe and effective for the treatment of breast cancer. However, lumpectomy is still an invasive surgical procedure, most often performed under general anesthesia that requires, at minimum, a 1-to-2-inch incision and takes 1-2 hours. While most patients are discharged the same day, recovery following the surgery may take up to two weeks, with surgical side effects seen in up to 9% of patients up to 6 years after the procedure. Risks and side effects include those associated with general anesthesia as well as scarring, infection, bleeding, damage to nearby tissue, pain and swelling that may last for months, nerve damage, and depression. Positive margins and incomplete removal of cancerous tissue are also considered as risks. There are significant and potentially long-term effects on the quality of life and body image of patients undergoing surgery for breast cancer due to cosmetic results; literature

has cited as many as 30-40% of lumpectomy patients are dissatisfied with the cosmetic outcome[20, 21]. Reconstructive surgery may alleviate long-term quality of life effects but is associated with detrimental and significant short-term effects on quality of life.

Following lumpectomy, additional adjuvant treatments may be considered based on the original tumor characteristics. Radiation therapy, including whole breast irradiation (WBI) and accelerated partial breast irradiation (APBI), is often performed after surgical excision of the tumor ranging from 6 to 12 weeks post procedure. However, as will be described in Section 2.3, recent study results and society recommendations support that lumpectomy without radiotherapy should be considered the standard of care treatment for elderly patients with early stage T1 invasive breast cancer. This includes the 2024 NCCN updated guidelines, which incorporated an option for omission of radiation therapy following breast conserving surgery (BCS) in women aged 65 years and older with stage I, estrogen receptor-positive breast cancer who planned to receive endocrine therapy. For this reason, lumpectomy without radiation is considered the standard-of-care comparator.

Endocrine therapy is recommended as standard of care by the NCCN treatment guidelines for treatment of hormone receptor positive tumors. Endocrine therapy (also called hormonal therapy, hormone treatment, or hormone therapy) slows or stops the growth of hormone-sensitive tumors by blocking the body's ability to produce hormones or by interfering with effects of hormones on breast cancer cells. Tumors with presence of ER and/or PR and the absence of HER2 (i.e., luminal-A) present a high response rate to endocrine therapy (tamoxifen or aromatase inhibitors). Endocrine therapy is typically recommended to be continued for 5 to 10 years post lumpectomy procedure.

2.3.De-escalation of Treatment of Breast Cancer

Breast cancer treatment has seen many advances in recent decades, lessening the morbidity to patients, while improving outcomes[13]. Less aggressive treatment is feasible because of earlier diagnosis and smaller tumor size at diagnosis. Progress in breast cancer genomics has increased the understanding of tumor prognosis, allowing for patient-specific management. Patients who may benefit from less aggressive surgery and adjuvant therapies are able to be identified from tumor biology[49].

In 2016, the Society of Surgical Oncology initiated the 'Choosing Wisely' campaign to encourage doctors and patients to question the need for commonly used tests and treatments, including recommendations to consider less axillary surgery and less radiation. In particular, radiation therapy can cause side effects such as fatigue, skin irritation, and breast swelling, and in a subset of patients more severe and long-term risks such as skin telangiectasia, breast pain, induration, and retraction that can adversely affect cosmesis and quality of life. Breast radiotherapy can even cause second cancers and cardiac diseases.

Further de-escalation of breast cancer treatment, specifically to omit radiotherapy, has been evaluated in several clinical trials including:

- The CALGB 9343 study *(NEJM, 2004)* evaluated outcomes following treatment with lumpectomy plus Tamoxifen with or without radiotherapy (RT) in women age >70 years with ER+, Stage 1 carcinoma. The 10-year outcomes of this study showed a statistically significant difference in IBTR survival (98% with RT, 90% without RT); however, there was essentially no difference in overall survival (67% with RT, 66% without RT). The study concluded that the addition of radiotherapy provided no benefit in terms of overall survival, distant disease-free survival, and ultimate breast preservation. This study also demonstrated that the risk of local recurrence does not equate to the risk of overall survival[50].

- The PRIMEII study *(NEJM, 2023)* evaluated outcomes following treatment with lumpectomy plus endocrine therapy with or without radiotherapy in women age >65 years with HR+ tumors sizes 3cm or smaller. The 5-year and 10-year IBTR recurrence rates showed 2.8% and 8.6% difference between patients treated with and without radiotherapy; however, there were no differences in distant metastases, contralateral breast cancer, or overall survival, or new breast cancers in patients treated with or without radiotherapy. The authors concluded that the 5-year rate of ipsilateral breast tumor recurrence of 4.1% is low enough for omission of radiotherapy to be considered for some patients[51].

The conclusions of these studies and society recommendation, including American Breast Cancer Society encouragement of de-escalation of therapy, supports that despite differences in local recurrence rate, the clinical community is recommending de-escalation of care to omit adjuvant radiotherapy. Further, these studies demonstrated that the risk of local recurrence does not equate to the risk of overall survival. A reasonable next step would be to determine a subset of early-stage breast cancer patients who could potentially forgo surgical intervention based on their tumor biology.

3. CRYOABLATION FOR BREAST CANCER TREATMENT

Summary

- Cryoablation effectively kills cancer cells through the processes of osmotic injury, mechanical injury, vascular injury, coagulative necrosis, and immunogenic response.
- For the treatment of breast cancer, cryoablation is performed under the guidance of real-time imaging to monitor tumor margins and ensure the destruction of the entire tumor mass.
- Prior research in cryoablation in breast cancer (dating back to the 1960s) demonstrates that cryoablation is an effective alternative to BCS for disease control.
- The patient experience for BCS and cryoablation differ greatly. The BCS experience includes increased preparation, procedure duration, and recovery. Cryoablation offers a less invasive treatment option with a faster recovery and the same treatment benefits.

Cryoablation has emerged as a minimally invasive alternative to BCS that reduces morbidity along with the psychosocial and cosmetic impact of breast cancer therapy. Using a needle-like, handheld cryoprobe and liquid-nitrogen, tumors are typically ablated in two freeze-thaw cycles achieving a core temperature of -170°C. A schematic diagram of a breast cancer cryoablation procedure is shown in Figure 3-1.

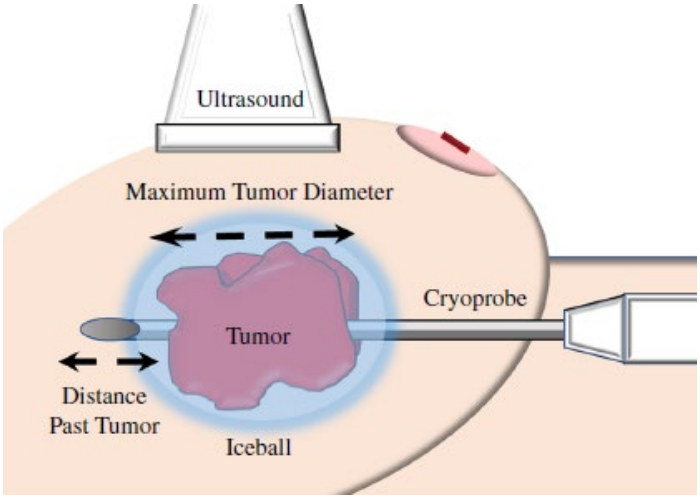


Figure 3-1. Schematic diagram of a breast cancer cryoablation procedure. The maximum tumor diameter is identified by ultrasound in two orthogonal views and the cryoprobe is inserted through the tumor for appropriate location for complete ice ball zone tumor destruction. From Khan et al 2023[5].

The cryoprobe is guided by CT or ultrasound in real time to promote complete cryoablation of the cancerous mass and limit unnecessary cryoablation of healthy surrounding tissue. Skin injury is

prevented by repeated injection of saline under the dermis to maintain separation between the skin and the underlying frozen mass. The architecture of the tissue of the breast is preserved due to the fact that the tumor tissue is not removed, it is internally destroyed and replaced with fibrotic tissue. Additionally, the skin incision to allow introduction of the cryoprobe is minimal, 3mm in comparison to surgical removal of the tumor, 1-2 inches. Therefore, cryoablation is expected to provide a more satisfactory cosmetic outcome, which has implications for the quality of life of the patients.

3.1.Cryoablation Mechanism of Action

Cryoablation always involves a first freeze, a passive thaw, and a second freeze. The freezing is repeated because tissue that has been damaged conducts cold temperatures more efficiently, thus expanding the area of necrosis. The freeze-thaw times depend on the device, the size of the targeted lesion, and the desired ablation margin. Intuitively, the larger the lesion, the longer the freeze time. Additionally, cancers require longer freeze times than fibroadenomas. The lethal cold isotherm (colder than -30°C) resides within 5mm of the ultrasound-visible ice margin; therefore, the goal in breast cancer cryoablation is to create a 1-cm margin of ice on all sides of the cancer to best accomplish complete tumor ablation. Slow passive thawing is thought to be more important to achieve effective cryoablation than the rapidity of the freeze cycles. The longer the duration of the thaw, the greater the damage to the cells from prolonged oxidative stress, solute effects, and ice crystal growth and restructuring, which create shearing forces that disrupt tissues[52].

The extremely cold temperatures created during cryoablation result in cell death by direct and indirect mechanisms. Osmotic injury and mechanical injury are direct results of cryoablation; vascular injury, coagulative necrosis, and immunogenic response are indirect results of cryoablation.

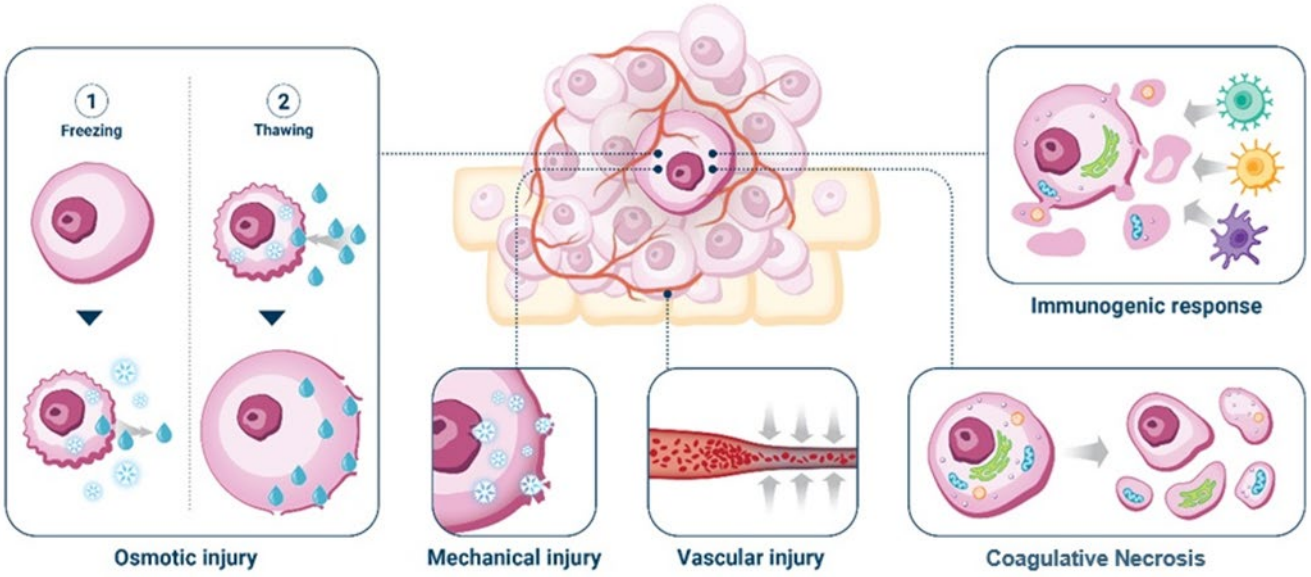


Figure 3-2. Five Key Mechanisms of Cryoablation

1. Osmotic Injury

Rapid and sustained freezing causes ice crystal formation in the extracellular space that leads to tumor cell dehydration through creation of an osmotic gradient. When the tumor cells dehydrate and shrink, cracks in the tumor cell membrane are formed.

During the thawing phase, the ice crystals that formed in the extracellular space melt to form water. The hypotonicity of the extracellular space causes water to flow back into the intracellular space of the previously dehydrated cells. The flow of water causes the cells to swell and rupture, leading to cell death. The high salt concentration in the dehydrated cells impairs cellular function, leading to apoptosis.

2. Mechanical Injury

The freezing process causes the formation of ice crystals inside the tumor's cells. These crystals directly damage the walls of the intracellular organelles like the DNA-containing nuclei and energy-creating mitochondria and induce pore formation in the plasma membranes. The damage results in permanent dysfunction of the cellular transport systems and leakage of cellular components.

3. Vascular Injury

Intracellular ice crystal formation damages cell lining of the blood vessels and causes vasoconstriction of the blood vessels supplying the tumor, depriving the tumor of oxygen and nutrients. With the thawing of the cryoablation zone, blood flow is restored, and free radicals

are released. Free radicals re-injure the blood vessel lining and cause blot clot formation. This process leads to apoptosis due to blood/oxygen restriction.

4. Coagulative Necrosis

The warmer outer portion of the ice ball does not reach low, direct tumor killing temperatures. These warmer temperatures can activate enzymes within the tumor cells that destroy intracellular proteins and DNA. Tumor cells experience coagulative necrosis 8-12 hours after the freezing injury.

5. Immunogenic Response

Cryoablation may have an additional role beyond tumor destruction. Through the immunogenic response, the patient's own immune system is able to be harnessed to fight the cancer. The cryoablation procedure induces the systemic antitumor response where abnormal tumor cell proteins (DAMP/PAMPs released) activate an immune response to kill the tumor cells.

3.2.Prior Work and Foundational Studies

The history of cryosurgery dates back to 1851 with the use of a mixture of salt and crushed ice to induce extreme cold locally for the destruction of tissue[53]. Cryoablation for the treatment of breast cancer has been studied for decades, dating back to the 1960s for procedures with palliative intent and the 1980s for procedures with curative intent[4] The following decades early studies of cryoablation treatment of breast cancer demonstrated good technical and cosmetic results.

Cryoablation systems use the same mechanism of action to freeze and thaw tissue and cause cell death (Joule-Thomson effect). Given the similarities in cryoablation systems, importantly, the ability to achieve cell death through extreme cold locally, conclusions of prior studies on similar devices are applicable to the ProSense™ device.

Early studies of cryoablation treatment of breast cancer, as detailed in **Figure 3-3**, resulted in key conclusions that informed later work including the ICE3 study:

- Ultrasound guidance offers sufficient visualization of ice ball formation.
- Invasive components of small tumors can be treated using cryoablation but DCIS components can be challenging as DCIS is often not well visualized on ultrasound.
- Best clinical results were achieved when small (<1.5cm) ductal tumors were treated with an ice ball larger than the tumor (i.e., with an ~1cm margin around the tumor to endure the tumor is engulfed without causing frost injury).
- Positive outcomes of cryoablation and resection studies motivated the use of cryoablation for curative treatment without the need for resection.

Cryoablation for breast cancer treatment is a suitable alternative to BCS that offers patients a less invasive procedure in the form of non-operative care. The research on the success of cryoablation in treatment of breast cancer and the benefits to the patient show cryoablation can be an effective and favorable treatment option for patients with early-stage low-risk breast cancer.

The ProSense™ System has been used in studies for the treatment of breast cancer around the world as outlined in **Figure 3-4**.

Figure 3-3. Summary of Studies of Cryoablation for Treatment of Breast Cancer

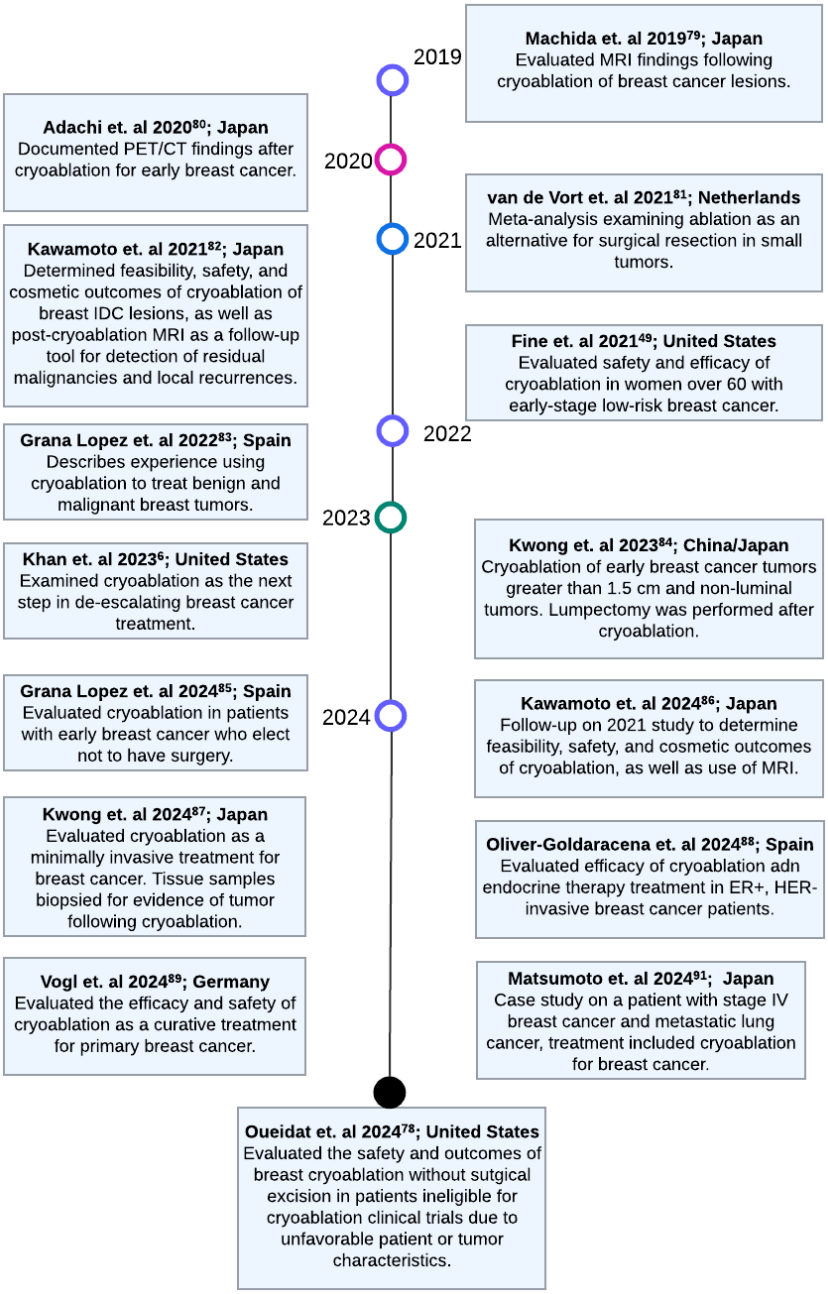


Figure 3-4. Breast Cancer Cryoablation Studies with ProSense™ System

3.3.Impact on Patient Experience

The standard of care, lumpectomy, is a surgical procedure that creates a higher patient burden compared to cryoablation. For lumpectomy, pre-surgical screening is required weeks and days in advance of the procedure and many patients require medical clearance to undergo a surgical procedure. Patients must fast prior to the procedure and may need to adjust medication doses. The lumpectomy procedure typically lasts 1-2 hours but because of the general anesthesia most patients undergo, patients will spend an hour or more in the recovery room. Due to the anesthesia, patients may experience pain, nausea, and vomiting and will be required to find a caregiver who can provide transportation home from the hospital. During recovery, patients may experience pain, potential continued nausea from anesthesia, and may be at higher risk of post-operative bleeding or seroma. Following lumpectomy 14%-20% of patients will have to undergo re-excision due to unclear margins, repeating the surgical process[54]. Cancer is one of the most expensive medical conditions to treat in the United States, the financial difficulty associated with cancer treatment is known as financial toxicity. Financial toxicity has clinically relevant outcomes related to quality of life, symptom burden, compliance, and patient survival. Because of the high costs of cancer treatment, patients without insurance may prioritize treatments based on cost[5]. The cost of lumpectomy results in patients reporting lower financial and psychosocial well-being.

For a cryoablation procedure, there is a pre-procedure screening, but no fasting is required prior to the procedure. Cryoablation is done under local anesthesia, so there are no unwanted side effects associated with general anesthesia. The procedure takes 1 hour from start to finish and patients can drive themselves to and from the appointment. A small incision is made that can be covered with a small bandage so there are no concerns about cleaning the excision site or managing surgical drains post-procedure. The procedure is essentially painless due to the analgesic effect of the tumor freezing process. Most patients are able to return to their normal non-strenuous activities the very next day, resulting in less time missed from work[7]. Patients who received cryoablation report higher financial and psychosocial well-being compared to those who received lumpectomy[5].

Comparing the processes of prepping for, undergoing, and recovering from lumpectomy and cryoablation shows that cryoablation, while providing the same treatment benefits is less burdensome on the patient throughout the entire course of care. Cryoablation could be an appropriate treatment option for patients.

4. PROSENSE™ CRYOABLATION SYSTEM

- The ProSense™ Cryoablation System is FDA-cleared.
- The safety and effectiveness of ProSense™ Cryoablation System in destruction of tissue has been established and is not the focus of this summary or Advisory Committee Panel Meeting.
- The ProSense™ cryoablation procedure is minimally invasive (3mm incision) and performed under local anesthesia.
- The cryoablation procedure is performed under real-time ultrasound or CT guidance and physician user has control over ice ball size through control of freeze duration.

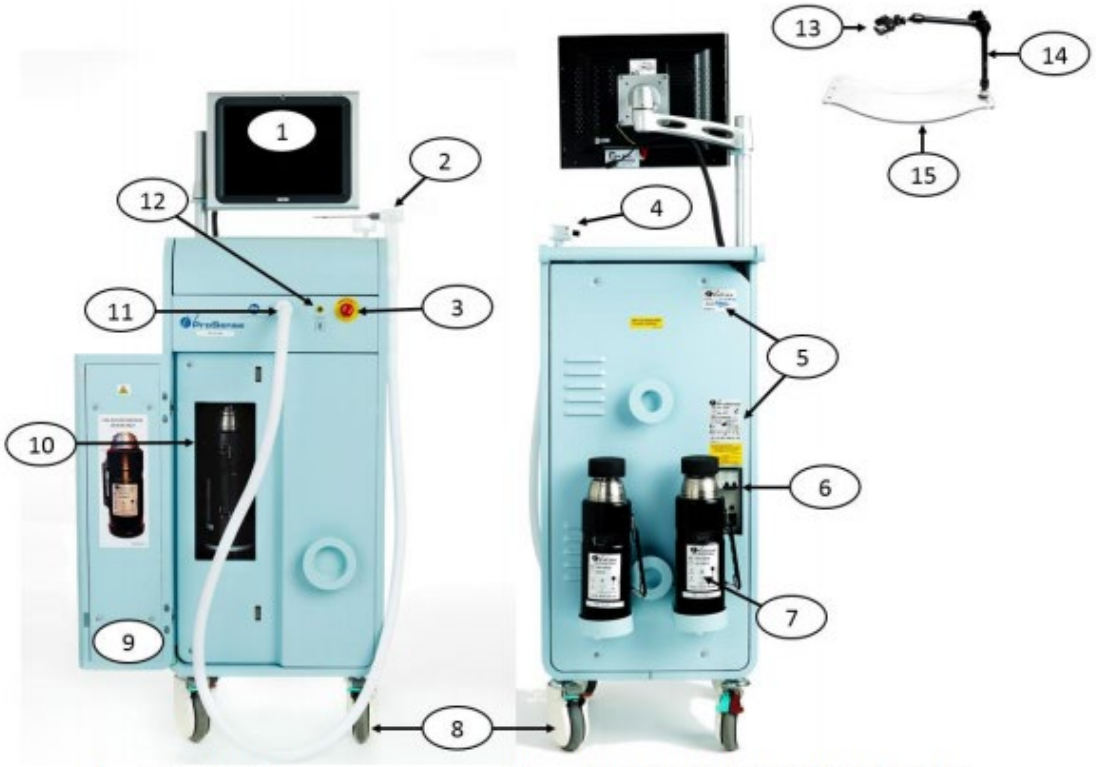
4.1. Device Description

The ProSense™ System by IceCure (FDA-cleared under K072883, K102360, K183213) is intended to destroy tissue by cooling the selected target to extremely low temperatures, using a closed system pressurized liquid nitrogen and a disposable cryoprobe. The cryoprobe is inserted through a 3mm incision to the target tumor. The cancerous tissue is then frozen to sub-zero temperatures within minutes by utilizing liquid nitrogen while the tumor remains under direct visualization with ultrasound.

The ProSense™ Cryoablation system includes:

- Main chassis – ProSense™ cryoablation system is housed within a chassis mounted on four rollers for ease of movement. Each roller is equipped with directional and rotational brakes for system immobilization. Located on the top of the chassis are a touch screen control panel and a cryohandle cradle. On the right upper part of the chassis is the Emergency Stop button – a round red button that shuts down the system immediately in an emergency situation. On the back of the chassis are two hooks used for hanging the electric cable, and a grip handle for ease of system transportation.
- Adjustable touch screen – the touch screen is located on top of the main chassis and allows for the operating and monitoring of the system. It is designed for users and technicians. Users are instructed to not connect any signal input/output port to the touch panel PC except certified equipment provided by IceCure Medical.
- External accessories: introducers, temperature sensor, liquid nitrogen Dewar, holder, foot pedal for control of cryotherapy delivery, and single use cryoprobes available in straight and 90° configurations to increase maneuverability.

The following figure (**Figure 4-1**) illustrates external features of the cryoablation system.



1. Touch screen
2. Cryohandle
3. Emergency Stop button
4. Cryoprobe cradle
5. System labels
6. ON-OFF switch
7. Dewar vessels
8. Rollers
9. Dewar positioning door/Elevator door
10. Dewar elevator compartment
11. Flexible hose connection
12. Temperature sensor port
13. Holder gripper
14. Holder adjustable arm
15. Holder base

Figure 4-1: Front and back view of ProSense™ cryoablation system with numbered components

4.2.Procedure for Use

Prior to cryoablation treatment the tumor's dimensions in all planes (sagittal, transverse, anterior-posterior) are measured. The cryoprobe is inserted through a small opening in the skin (~3mm) created by a surgical scalpel along the longest axis possible in the radial view. The cryoprobe cooling zone center is placed into the middle of the lesion. Cryoprobe position is checked by confirming the cryoprobe is centered in the anti-radial view. The cancerous tissue is then frozen to sub-zero temperatures within minutes by utilizing liquid nitrogen. The quick-freezing cycle causes ice crystals to form an ice ball within the margins of the tumor, effectively destroying the tissue. Healthy tissue adjacent to the cancerous tissue is left unaffected. Tumors are typically ablated in two freeze-thaw cycles during which cryoprobe tip temperature should reach at least -150°C. During the freeze-thaw-freeze cycles ice ball width growth is monitored with real time

imaging via ultrasound. After the first and second freeze, ice ball width and length are measured to ensure complete lesion engulfment with desired margins.

The cryoablation technique used in the ICE3 study was described in detail by Fine, et al[49].

4.3.Indications for Use

The company is seeking authorization for the following indications:

> ProSense™ cryoablation system is indicated for treatment of patients with early stage, low risk breast cancer* with adjuvant endocrine therapy.
>
> *Patients with early stage, low-risk breast cancer are patients ≥60 years of age with prognostic stage 1A defined as unifocal tumor size ≤1.5cm, ER+/PR+/-, HER2-, histological grade 1-2 infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0).

IceCure ProSense™ cryoablation system has been FDA cleared (K072883, K102360, K183213) since 2007 for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ENT, gynecology, oncology, proctology, and urology. The complete cleared indications for use statement is provided below:

ProSense™ cryoablation system is also indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, thoracic surgery, gynecology, oncology, proctology, urology as detailed below.

- **Urology** - ablate prostate tissue in cases of prostate cancer and benign prostatic hyperplasia (BPH).
- **Oncology** - ablation of cancerous or malignant tissue and benign tumors and palliative intervention.
- **Dermatology** - ablation or freezing of skin cancers and other cutaneous disorders. Palliation of tumors of the skin. Destruction of warts or lesions.
- **Gynecology** - ablation of malignant neoplasia or benign dysplasia of the female genitalia.
- **ENT (Ear, Nose, Throat)** - Palliation of tumors of the oral cavity and ablation of leukoplakia of the mouth.
- **General Surgery -** Ablation of tumors, breast fibroadenomas, leukoplakia of mouth, angiomas, sebaceous hyperplasia, basal cell tumors of the eyelid or canthus area, ulcerated basal cell tumors, dermatofibromas, small hemangiomas, mucocele cysts, multiple warts, plantar warts, hemorrhoids, anal fissures, perianal condylomata, pilonidal cysts actinic and seborrheic keratoses, cavernous hemangiomas, recurrent cancerous lesions. Palliation of tumors of the rectum, hemorrhoids, anal fissures, pilonidal cysts, and recurrent cancerous lesions.

Destruction of warts or lesions. Palliation of tumors of the oral cavity, rectum, and skin.

- **Thoracic Surgery** - ablation of arrhythmic cardiac tissue and cancerous lesions.
- **Proctology** - ablation of benign or malignant growths of the anus and rectum and hemorrhoids.

4.4.Regulatory and Marketing History

4.4.1. Regulatory History

The IceCure ProSense™ cryoablation system has been FDA cleared (K072883, K102360, K183213) since 2007 for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ENT, gynecology, oncology, proctology, and urology.

Between 2018 and 2022, IceCure Medical submitted a series of pre-submissions to FDA to discuss the appropriate regulatory pathway, plans for interim analysis, and totality of evidence generated in the ICE3 clinical study in support of use of ProSense™ Cryoablation System for treatment of early-stage, low-risk breast cancer.

FDA granted ProSense™ Cryoablation System Breakthrough Device Designation in March 2021 for indication of treatment of breast cancer, on the basis that ProSense™ Cryoablation System provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or condition.

In October of 2022, IceCure Medical submitted a De Novo application for ProSense™ Cryoablation System including an interim analysis of the ICE3 clinical study. FDA's request for additional information was received in December 2022 and IceCure Medical submitted a response including the requested comparative PRISMA Systematic Review and Meta-analysis in June 2023. In September 2023, FDA declined to grant IceCure Medical's De Novo based on the interim ICE3 study dataset.

In January 2024 following a successful appeal to reopen the De Novo submission for further FDA consideration, FDA requested IceCure submit new information, including the full dataset from the ICE3 clinical study and the final analysis comparing the results of ICE3 clinical study with the LUMINA study. Additionally, FDA requested updated Indications for Use be specified. IceCure responded to all FDA requests and submitted the final clinical study report with complete 5 year patient follow up to FDA in April 2024.

4.4.2. Marketing History

The IceCure ProSense™ Cryoablation System was previously FDA-cleared (K072883, K102360, K183213) for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ENT, gynecology, oncology, proctology, and urology.

The IceCure ProSense™ Cryoablation System has been CE marked and commercially available in markets outside the U.S. for more than a decade with more than 1,600 cryoablation treatments performed worldwide for the treatment of breast cancer.

Countries/regions with ProSense™ indication for use including cryoablation for breast cancer include: EU, Israel, Greece, Turkey, India, Thailand, Australia, Brazil, Hong Kong, Singapore and South Africa. Countries/ regions with ProSense™ indication for use without breast cancer include: Costa Rica, China, Taiwan, Japan, Mexico, Colombia.

5. ICE3 CLINICAL STUDY DESIGN

Summary

- Prospective, single-arm study with follow-up through 5-years after cryoablation treatment with ProSense™ Cryoablation System and pre-specified comparison to literature-reported IBTR rates for standard-of-care lumpectomy.
- Designed and conducted according to FDA guidelines, Code of Federal Regulations (CFR) Title 21, and ICH Good Clinical Practice.
- ICE3 was conducted in the United States at 19 clinical sites; investigators include breast surgeons and interventional radiologists.
- The study was approved by the Institutional Review Board (IRB) to be conducted as a non-significant risk study under IRB oversight. An independent Data and Safety Monitoring Board (DSMB) provided oversight during the course of the study.
- The objective of this study was to evaluate the safety and effectiveness of cryoablation with IceCure Medical's ProSense™ device for the treatment of early stage, low-risk breast cancer in women 60 years or older as measured by Ipsilateral Breast Tumor Recurrence (IBTR) rate.
- The primary endpoint, IBTR rate, was estimated using the Kaplan-Meier (KM) method. The protocol specified that if the upper limit of the 95% confidence interval for IBTR rate at the 5-year time point is less than 10%, the study will be considered successful.
- Per FDA request, additional comparisons have been performed to evaluate IBTR rate from the ICE3 clinical study versus a comparator rate derived from a PRISMA Systematic Review and Meta-analysis of all applicable literature as well as evaluation of an ICE3 subpopulation as compared to outcomes of the LUMINA study[55].

5.1.Study Overview

The ICE3 clinical study by IceCure Medical is a multicenter (19 sites in the United States), prospective, single arm, nonrandomized longitudinal clinical trial using ProSense™ cryoablation to remove malignant breast cancer tissues in women aged 60 and over. The trial began in October 2014 and 5 year follow up was completed in March 2024.

This study was conducted in accordance with all applicable regulations set forth under 21CFR, The Medical Device Directive and in accordance with the ICH Good Clinical Practice and local laws and regulations relevant to medical devices.

Table 5-1. Study Synopsis

Study Title	Cryoablation of Low-Risk Breast Cancers less than 1.5 cm: An evaluation of local recurrence (ICE3 Trial)	
Study Period	Initiation Date: 27-Oct-2014	Last patient completed: 15-Mar-2024
Investigational Device	ProSense™	

Study Sites and Participants	212 patients / 19 sites in the United States
Device Description	IceCure Medical's ProSense™ cryogenic system (also branded as ICESENSE3™) is intended for cryogenic destruction of tissue (utilizes Liquid Nitrogen) during surgical procedures (minimally invasive image-guided), by the application of extreme cold temperatures. The ProSense™ system is FDA-cleared for use as a cryosurgical tool in the fields of general surgery (including breast fibroadenomas), dermatology, neurology, thoracic surgery, ENT, gynecology, oncology, proctology, and urology.
Study Design and Duration	Multi-centered, single arm, non-randomized clinical trial. Total study duration is about 10 years.
Study Objectives	The goal of this study was to evaluate the safety and efficacy, in terms of Ipsilateral Breast Tumor Recurrence (IBTR) rate of cryoablation using IceCure medical's ProSense™ device for the treatment of low-risk early breast cancer in women 60** years or older.
Study Endpoints	Primary endpoint: Local Ipsilateral Breast Tumor Recurrence (IBTR) rate. Secondary endpoints: • Complete ablation of primary tumor rates up to 60 months after cryoablation. • Improvement or maintenance of patient's quality of life at 6 months compared to baseline. • Breast cosmetics satisfaction. • Regional Invasive breast tumor recurrence rate. • Distant metastases rate including contralateral Breast cancer. • Disease–free Survival (DFS) from date of complete ablation of the primary tumor, until the first disease event where the disease event is defined as 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. • Overall survival from the date of the cryoablation until the date of death from any cause or up to the 60 months follow up visit. • Breast Cancer Survival from the date of cryoablation until the date of death from breast cancer or up to the 60 months follow-up visit. Patients who died without a specified cause will be considered as events (i.e., due to breast cancer). • Adverse events related to study device or procedure rate.
Study Population	Women aged 60** or older, with low-risk breast carcinoma, less than or equal to 1.5 cm in diameter, will be enrolled into the study.

Eligibility Criteria	1. Competent to sign informed consent 2. 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 grade 1-2. Specifically, nuclear and mitotic scores must be less than or equal to 2.* d. Estrogen receptor positive, and or progesterone receptor positive, HER2 negative, 3. Age ≥ 50 (Local IRB**), Age ≥ 60 (WCG IRB), 4. Breast size adequate for safe cryoablation. 5. Lesion must be sonographically visible at the time of treatment. 6. History of previously treated ipsilateral or contralateral breast carcinoma is not an exclusion criterion if the investigator is certain newly diagnosed carcinoma is a new unifocal primary tumor.
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 with extensive intraductal component (EIC) 5. Presence of multifocal and/or multicentric in breast cancer 6. Presence of multifocal calcifications 7. Presence of prior or concurrent neoadjuvant chemotherapy for breast cancer 8. Presence of prior en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer

*The investigators and DSMB agreed that eligibility should be based on composite Nottingham grade and not on component scores. This determination is aligned with acceptable guidelines indicating that *all invasive breast carcinomas should be assigned a histologic grade. The Nottingham combined histologic grade (Nottingham modification of the SBR grading system) is recommended and is stipulated for use by NCCN SEER as well as the recent Lumina study*[56, 57]. All cases of nuclear or mitotic score components > 2 are documented as protocol deviations.
**Local IRB inclusion criteria was age ≥50, WCG IRB inclusion criteria was age ≥60. Only two patients were under 60 years of age.

The protocol specifies that the final analysis will be performed 5 years from the last patient enrollment in the study. **The ICE3 clinical study has completed 5-year follow-up and final study outcomes are provided in this summary.**

5.2.Study Oversight

IRB Approval of Non-significant Risk (NSR) Study

The study was approved by the Institutional Review Board (IRB) to be conducted as a NSR study under IRB oversight.

DSMB Oversight

An Independent Data and Safety Monitoring Board (DSMB) met annually, or as needed, to review the results of the study and to evaluate any safety or efficacy issues that may arise during the study. The results of the study were submitted to the DSMB at least once a year. The ICE3 DSMB is comprised of five members with relevant expertise.

The Board performed periodic data review and informed the study Principal Investigator and IceCure when the sequential monitoring has reached a stopping boundary. The DSMB was charged with recommending termination of the study at any time should prospective ethical or safety guidelines not be met.

DSMB reports were submitted to IRBs as periodic safety reports.

5.3.Study Treatment and Follow-Up

The study included up to 9 visits at the clinic: 1 screening, 1 treatment, and 7 follow-up visits.

Following enrollment and providing written informed consent, each patient underwent a single cryoablation treatment session without subsequent excision as described in Section 4.2 The cryoablation procedure was performed under ultrasound visualization. The ProSense™ cryoablation system was used per the User Manual.

In case of close tumor proximity to the skin, sterile saline was injected between the skin and the forming ice ball, increasing the distance between the ice ball and dermis, thereby protecting the skin from thermal injury. A minimum of 5 mm distance between the ice ball and the dermal layer of skin was recommended to prevent injury.

The treating investigator documented baseline lesion sizes, procedure data, and ice ball measurements in the study data records. Additionally, the treating investigator evaluated and recorded any observed and reported adverse events. Patients were generally discharged same day per institutional protocols.

Post cryoablation adjuvant treatment (endocrine therapy, chemotherapy and/or radiation therapy) was provided at the discretion of the treating physician.

A phone call follow-up (FU) visit was conducted up to 1-month post-procedure. All patients were asked to return to the clinic for follow-up visits at 6, 12, 24, 36, 48, and 60 months following

treatment. The treating investigator performed a physical examination, evaluated and recorded imaging results and any adverse events, and documented patient and physician satisfaction, at each follow-up visit until 60 months from the procedure date.

5.4.Study Methods

FDA has asked you to consider the design of the ICE3 trial, specifically the single arm study design and sample size.

The ICE3 clinical study was designed as a single-arm study to demonstrate the safety and effectiveness of the ProSense™ Cryoablation System for cryoablation to remove malignant breast cancer tissues in women aged 60 and over. IceCure Medical designed the ICE3 clinical study as a single arm clinical study for a number of reasons:

- The standard of care for the removal of early-stage malignant breast cancer tissues is lumpectomy, which has been well documented in the literature regarding its rate of recurrence and clinical outcomes.
- A blinded or randomized clinical study design was not deemed reasonable for this investigation.
    - Based on the differences in treatments compared to the standard of care methods for the indicated population, lumpectomy, blinding of patients in the trial would be impossible.
    - Randomization was not deemed appropriate for patients in a trial studying the ProSense™ Cryoablation System due to questions of equipoise and different treatment providers (breast surgeon versus interventional radiologist) performing each of the treatments.
- Given that blinded or randomized clinical study design is not possible, a literature control based on treatment of >3,500 patients is more robust than would be expected of a prospective control.
- Given similar outcomes presented across the preponderance of clinical studies in the literature, development of a performance goal based on the thousands of patients treated with lumpectomy is a valid scientific method for assessment of the safety and effectiveness of the ProSense™ Cryoablation System. In addition, sufficient level of detail exists in the literature to assess various subpopulations of interest in comparison to the ICE3 study data. The pre-specified performance goal will be described in detail in Section 5.4.3.

The study sample size is justified in Section 5.4.1. It is important to note that ICE3 builds on the large body of work described in Section 3.2. These prior studies established the technical and clinical success of treatment of breast cancer with cryoablation as well as the ideal condition for use, small ductal tumors treated with an iceball larger than the tumor. The positive outcomes of the cryoablation and resection studies informed the design of the ICE3 study and IBTR estimate used to determine the study sample size.

5.4.1. Sample Size Justification

The sample size was calculated for the primary efficacy endpoint, local invasive or in situ breast tumor recurrence rate at 5 years, to estimate the ipsilateral breast tumor recurrence rate with a ±5% level of accuracy. For a two-sided 95% exact Clopper-Pearson confidence interval, a binomial proportion whose true value is 5%, a sample size of 150 yields a half-width of at most 5% with a conditional probability of over 99%. Therefore, a sample size of 150 patients with complete ablation of the primary tumor is required.

The clinical protocol pre-specified enrollment of 150-200 patients to ensure a sufficient sample size, accounting for loss-to-follow-up.

A total of 212 patients were screened for enrollment in the study. Of these, three (3) were screen failures and 209 were enrolled in this study at 19 investigational sites. Three (3) patients withdrew consent prior to procedure. A total of 206 patients were enrolled and treated.

5.4.2. Pre-Specified Analysis Populations

- **All Treated Population (N=206)**: all patients treated in the ICE3 study. Supplemental safety analyses are performed on this population.
- **Primary Analysis Population (N=194)**: all treated population excluding DSMB excluded patients. Primary effectiveness and safety analyses are performed on this population.

The DSMB excluded a total of twelve (12) patients, nine (9) due to deviation from inclusion/ exclusion criteria and three (3) incomplete treatment, resulting in the Primary Analysis Set of N=194.

- Patients excluded due to incomplete treatment resulting from extremely short treatment protocol (short treatment cycle times 1 min 22 sec – 2 min 24 sec) or single freeze cycle. A sensitivity analysis including patients excluded due to incomplete treatment is provided in Section 6.10.2. This analysis shows no impact of these patients on the overall 5-year recurrence rate.
- Patients excluded due to deviation from inclusion/ exclusion criteria were due multi-focal disease or tumor size larger than 1.5cm. Based on prior studies described in Section 3.2, patients with multi-focal disease and large tumors are known to have greater risk for recurrence. This population is not the focus of ICE3 and were therefore excluded by DSMB. Similarly, these patients do not meet the proposed indication and were excluded or down-weighted in the literature comparators. A sensitivity analysis including patients excluded due to deviation from inclusion/ exclusion criteria or incomplete treatment is provided in Section 6.10.3.

The “Primary Analysis Set” was used for the primary measurement of safety and effectiveness. Supplemental safety analyses were performed in the ‘All Treated Population’ (Section 6.10).

5.4.3. Pre-Specified Primary Endpoint

5.4.3.1. Kaplan-Meier Survival Analysis

The primary endpoint, IBTR rate, was estimated using the Kaplan-Meier (KM) method.

In Kaplan-Meier survival analyses, patients contribute data until the event of interest occurs or patients are 'censored'. In the ICE3 study and analyses shown in this executive summary, patients were censored at the time of completion of the study exit form. The literature commonly handles censoring of patients who withdraw from the study or are lost-to-follow-up in this manner. Patients who died without recurrence were considered non-recurrence through 60 months.

See **Appendix H** for additional detail on censoring and sensitivity analyses using analysis methods and methods of censoring.

5.4.3.2. Literature-Based Performance Goal

The protocol specified that if the upper limit of the 95% confidence interval for IBTR rate at the 5-year time point is less than 10%, the study will be considered successful.

A reference rate for local recurrence rate at 5 years was originally evaluated through a literature review that produced estimates of the local occurrence around 5.0%.

Based on this review, for sample size determination, it was assumed that the local recurrence rate for patients receiving the device would be equal to the literature review rate of 5.0%. Therefore, the performance goals for success of the Overall Population were calculated as shown below:

> The performance goal (PG) was determined by adding a pre-specified non-inferiority reference margin of 5% to the reference rate. Therefore, the performance goal is 5.0% + 5.0% = 10.0%.

The primary effectiveness hypothesis is that the success rate for the investigational device is less than the performance goal of 10.0%. Formally, the hypothesis to be tested is:

> H_O: The expected proportion of patients with local recurrence at Year 5 (p_T) is greater than or equal to the performance goal (PG) of 10.0%.
>
> H_A: The expected proportion of patients with success at Year 5 (p_T) is less than the performance goal (PG) of 10.0%.

These hypotheses may be symbolically represented as:

> H_O: $p_T \geq PG = 10.0\%$
>
> H_A: $p_T < PG = 10.0\%$
>
> Where p_T is the success rate for patients treated with the investigational device.

5.5.Disease Outcomes and Definitions

The protocol-specified definitions of disease outcomes are detailed below.

The protocol pre-specified that diagnosis of a first breast cancer recurrence or second primary cancer diagnosis be made only when both the clinical and laboratory findings (biopsy) confirm the presence of disease. Suspicious findings do not constitute criteria for breast cancer recurrence. Any recurrence of malignant disease should be proven by biopsy or excision.

Local Recurrence
Local recurrence is defined as evidence of invasive or in situ breast cancer in the ipsilateral breast or chest wall. Patients who develop clinical evidence of tumor recurrence in the remainder of the breast or chest wall must have a biopsy of the suspicious lesion to confirm the diagnosis. Given the challenges of defining a reliable definition of local recurrence versus new primary, all recurrences in the ipsilateral breast will be considered in the analysis of the primary endpoint.

Please note: during the course of the study, the DSMB Chair advised, based on clinical practice in the breast surgery field, that a new ipsilateral tumor in a different quadrant or at least 5cm distant from the original tumor should be considered as a second primary breast cancer.

Additional disease outcomes and definitions can be seen below. For additional details refer to **Appendix F**.

Table 5-2: Additional Disease Outcomes and Definitions

Regional Occurrence	Tumor in ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or soft tissue of ipsilateral axilla
Distant Metastases	Tumor in any area of the body except those defined as local or regional
Disease Free Survival (ICE3 Protocol Definition)	Freedom from disease events including local (DCIS or invasive), regional or distant breast cancer recurrence, second primary breast cancer, DCIS or invasive contralateral breast cancer, second primary non-breast cancer and death due to any cause
Disease Free Survival (National Cancer Institute (NCI) Definition)	Freedom from disease events including local (DCIS or invasive), regional or distant breast cancer recurrence, second primary breast cancer, DCIS or invasive contralateral breast cancer *Please note: The NCI definition excluding primary non-breast cancer and death is the most common definition of DFS reported in the literature.*
Overall Survival	Freedom from death due to any cause

Breast Cancer Survival	Freedom from death due to breast cancer or unknown cause *Please note: The literature most commonly reports only deaths known to be due to breast cancer. The ICE3 protocol definition is more conservative as it includes deaths due to unknown cause.*

5.6.Safety Outcomes and Definitions

Per the study protocol, an adverse event is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a patient that appears or worsens during a clinical study. An adverse event may be not related to the investigational device, or the drug therapy prescribed as part of the study protocol. All adverse events are classified according to Common Terminology Criteria for Adverse Events v.4.0 (CTCAE):

A **serious adverse event (SAE)** is defined in the protocol as a medical occurrence, which results in one of the following outcomes:

a) Death
b) Serious deterioration in the health of the patient, users, or other persons as defined by one or more of the following:
1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function including chronic diseases, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan (CIP), without serious deterioration in health, is not considered a serious adverse event.

Intensity of the adverse event is defined as follows:

- Mild: A sign or symptom, which is usually transient, no special treatment is required, and generally not interfering with usual activities.
- Moderate: A sign or symptom, which may be ameliorated by simple therapeutic measures, and may interfere with usual activity.
- Severe: A sign or symptom that is intense or debilitating and that interferes with usual activities.

The **relationship of the adverse event to the study device or procedure** is defined as follows:

- Probable: An adverse event has a strong temporal relationship to study device or recurs on re-challenge, and another etiology is unlikely or significantly less likely.

- Possible: An adverse event has a strong temporal relationship to study device, and an alternative etiology is equally or less likely compared to the potential relationship to study device.
- Probably not: An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
- Not related: An adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

Events with 'probable' or 'possible' relatedness to the study device or procedure are categorized as 'procedure-related'.

6. ICE3 CLINICAL STUDY RESULTS

Summary

- Patient accountability was high with >80% follow-up at the 5-year endpoint; this follow-up rate is considerable given the advanced age of the study population and duration of study follow-up.
- ICE3 5-year IBTR rate met the pre-specified performance goal.
- ICE3 outcomes demonstrate benefit of treatment of low-risk breast cancer with similar effectiveness to standard-of-care and significantly fewer and less severe risks.
    - The ICE3 clinical study outcomes demonstrate >95% of patients are recurrence free through 5-years follow-up, nearly 97% when treated per the proposed indications for use.
    - Risks to health posed by ProSense™ System when used for the treatment of early stage, low-risk breast cancer include risks that are common to all cryoablation systems, including ProSense™ System when used per the cleared indications. All serious, procedure-related events are mitigated by treatment according to approved labeling.
    - Patients and physicians report significant quality of life benefits: patients experience near immediate recovery to normal activity (median 1 day recovery time) and 99.1% of patients and 97% of physicians who responded were 'satisfied' or 'very satisfied' with the breast cosmetic outcome at 5 years follow-up.
    - ICE3 clinical study met the pre-specified primary endpoint.
- The totality of evidence demonstrates safety, efficacy, and positive benefit/risk profile of ProSense™ Cryoablation System for the treatment of early-stage, low-risk breast cancer.

As shown below in **Figure 6-1**, a total of 212 patients were screened for enrollment in the study. Of these patients, 3 were screen failures and 209 were enrolled in this study at 19 investigational sites. Three (3) patients withdrew consent prior to procedure. A total of 206 patients were enrolled and treated.

The DSMB excluded a total of twelve (12) patients, nine (9) due to deviation from inclusion/ exclusion criteria and three (3) incomplete treatment, resulting in the Primary Analysis Set of N=194.

- Patients excluded due to incomplete treatment resulting from extremely short treatment protocol (short treatment cycle times 1 min 22 sec – 2 min 24 sec) or single freeze cycle. A sensitivity analysis including patients excluded due to incomplete treatment is provided in Section 6.10.2. This analysis shows no impact of these patients on the overall 5-year recurrence rate.

- Patients excluded due to deviation from inclusion/ exclusion criteria were due multi-focal disease or tumor size larger than 1.5cm. Based on prior studies described in Section 3.2, patients with multi-focal disease and large tumors are known to have greater risk for recurrence. This population is not the focus of ICE3 and were therefore excluded by DSMB. Similarly, these patients do not meet the proposed indication. A sensitivity analysis including patients excluded due to deviation from inclusion/ exclusion criteria or incomplete treatment is provided in Section 6.10.3.

The final analysis includes 5-year outcome data, including known death, recurrence or non-recurrence, on 80% (155/194) of patients. This amount of known data is considerable given the advanced age of the study population and duration of study follow-up.

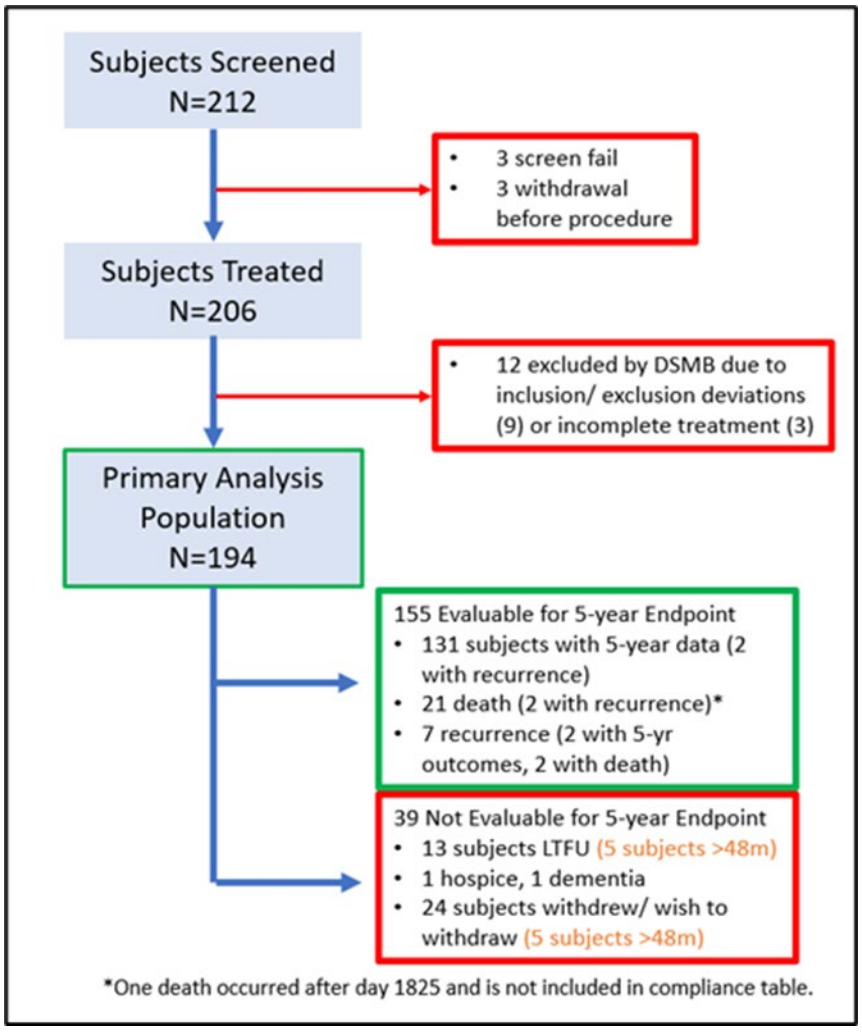


Figure 6-1. ICE3 Clinical Study Patient Disposition Flowchart

The results presented in **Section 6** are for the primary analysis population unless specified otherwise. Results for the defined sub-populations are presented in **Section 6.10.2**.

6.1.Patient Accounting

The patient accounting and follow-up compliance is shown in **Table 6-1** for the primary analysis set with definitions following.

Follow-up compliance at 5-years follow-up is >80%. Mean study follow-up is 54.2 months (SD 13.1). 5-year outcome data are available on 155 patients; the remaining 39 patients contributed data to the survival analysis through mean 34.8 months. This high rate of follow-up over the course of a 5-year study provides a strong foundation for the overall results of the clinical study.

Table 6-1: ICE3 Clinical Study Follow-Up Compliance

	Year 1 (Day 365)	Year 2 (Day 730)	Year 3 (Day 1095)	Year 4 (Day 1460)	Year 5 (Day 1825)
(1) Theoretical follow-up	194	194	194	194	194
(2) Cumulative Death	5	7	14	19	20
(3) Cumulative Local Recurrence	0	0	2	3	7
(4) Cumulative Death and Local Recurrence	5	7	16	21*	25*
(5) Expected Due [(5)=(1)-(4)]	189	187	178	173	169
(6) Patients with any clinical data at time point	179	160	147	141	131
(7) Patients N-start per survival analysis for local IBTR*	192	190	184	173	162
(8) Study compliance [(8) = (6) / (7)]	93.2%	84.2%	79.9%	81.5%	80.9%

*Two subjects with recurrence at any time through year 5 also experienced death.

Follow-up Compliance Definitions:

- **Theoretically due:**
  - A patient must be treated at least 1825 days before the database (DB) Lock (2024-03-17) to be considered theoretically due. All patients in the ICE3 clinical study are theoretically due.
- **Expected due:**
  - Patients are considered expected due if they are theoretically due, have not died, and have not had a recurrence. This number does leverage theoretically due.
  - Please note, contribution to the primary endpoint is not contingent on being expected due. Patients who die or experience a recurrence are known to have the primary endpoint and are included in the primary endpoint statistics.
- **Patients with clinical data:**
  - These are the patients that have been evaluated for year 5, have died through 1825 days, or have recurrence within 1825 days.

- **Patients with N-start per survival analysis**
  - For the purposes of evaluation of the survival analysis, 'N Start' quantifies the number at risk in each interval. That is 'N Start' is the number of patients not yet died, recurred, or terminated early (documented long-term follow-up [LTFU] or withdrew) and exited the prior interval.

6.2.Protocol Modifications and Deviations

The ICE3 protocol was modified in 2015 to eliminate Ki67 enrollment criteria, allow for inclusion of PR-, allow for inclusion of previously treated breast carcinoma if new unifocal primary tumor, and specify that Nottingham nuclear or mitotic component scores be ≤2. Subsequent to this change, the only substantive modifications to the study protocol were to decrease the required age to 60 at all sites and decrease the required age to 50 at sites under Local IRB. All other protocol version changes (through version 27) were routine updates to clinicaltrials.gov to update recruitment status, study status, contacts/ locations and provide requested information related to study outcomes.

Table 6-2. Protocol Modifications During ICE3 Enrollment and Follow-Up

Protocol 13	Protocol 15	Protocol 16	Protocol 17 (Local IRB ONLY)
11 MAY 14	23 MAR 15	1 MAR 17	28 JUN 17
Protocol version at study start	2c. added 'nuclear or mitotic component score must be ≤2' 2d. Removed Ki67 criteria, allowed for PR negative 6. History of previously treated ipsilateral or contralateral breast carcinoma is not an exclusion criteria if the investigator is certain newly diagnosed carcinoma is a new unifocal primary tumor.	3. Age modified from ≥65 to ≥60	3. Age modified from ≥60 to ≥50

IceCure Medical reported a total of 448 protocol deviations for 157 subjects, of which 56 were categorized as major deviations. As described above, the DSMB excluded a total of twelve (12) patients, nine (9) due to major deviation from inclusion/ exclusion criteria including 2 patients in this group with multifocal disease, 1 with DCIS, and the remaining 6 with tumor sizes greater than 1.5 cm and three (3) incomplete treatment where the device was not used for the full treatment protocol (short treatment cycle times 1 min 22 sec – 2 min 24 sec or single freeze cycle). There were 45 deviations from the pre-specified inclusion/exclusion criteria for 44 patients.

Majority of the remaining deviations were due to out of window visits or follow-up procedural deviations, many due to the COVID-19 emergency.

Table 6-3. Summary of Protocol Deviations by Type and Classification

Deviation Category	Major		Minor		Total	
	Events	Subj.	Events	Subj.	Events	Subj.
Missed Visit	0	0	20	16	20	16
Visit Out of Window	0	0	203	113	203	113
Violation of Inclusion/Exclusion Criteria	45	44	0	0	45	44
Follow Up Procedural Deviation	2	2	160	69	162	69
Informed Consent Deviations	2	2	2	2	4	4
Other (e.g., use of neoadjuvant hormone blockage, inadequate procedure time, incomplete treatment)	7	7	6	8	13	15

6.3.Demographics and Baseline Characteristics

The patient demographics and cryoablation procedure data are shown in the sections below for the Primary Analysis Set. Patient demographic and operative data are presented as categorical and continuous variables as shown below in **Table 6-4** and **Table 6-5**.

The mean age of the patients was 74.9 ±6.9 years (range, 55–94 years). In alignment with the inclusion criteria detailed above, the enrolled patient population consisted of females (100%), ER positive (100%), PR positive (93%), and with a Nottingham score of <2 (100%).

As discussed in Section 2.1, HR+ and HER2- is commonly used as a surrogate for Luminal A. The investigator's clinical impression of all patients based on histologic evaluation was consistent with Luminal A; however; three (3) patients were determined to have luminal-B type tumor (2%) based on genomic evaluation.

The baseline demographic categorical variables for the primary analysis set are shown below in **Table 6-4**.

Table 6-4: ICE3 Clinical Study Baseline Demographics - Categorical Variables Primary Analysis Set (N=194)

	n	%
Gender		
Male	0	0%
Female	194	100%
Ethnicity		
African American	14	7%
Asian	1	1%
Caucasian	160	85%
Hispanic	12	6%
Native American	2	1%
ER (Estrogen Receptor)		
Positive	194	100%
Negative	0	0%
PR (Progesterone Receptor)		
Positive	180	93%
Negative	14	7%
HER-2neu		
Positive	0	0%
Negative	194	100%
Nottingham Grade		
1	96	49%
2	98	51%
>2	0	0%
Type of tumor		
Luminal A	188	98%
Luminal B	3	2%

Table 6-5: ICE3 Clinical Study Baseline Demographics – Continuous Variables Primary Analysis Set (N=194)

	N	Mean	SD	Med	Min	Max
Age (years)	194	74.9	6.9	74.5	55.0	94.0
BMI (kg/m^2)	136	28.8	6.3	27.9	15.0	47.6
Source: Table 2_1 Baseline Demo_Continuous.sas; Analyzed: 21MAR2024						

6.4.Medical History

The medical history of the patients enrolled in the ICE3 clinical study including previous breast cancer history and tumor characteristics are shown below in **Table 6-6** and **Table 6-7**.

As would be expected of an older population, most patients presented with one or more comorbidities.

Table 6-6: ICE3 Clinical Study Medical History (Breast/Uterus/Ovaries) Categorical Variables - Primary Analysis Set (N=194)

	n	%
Past history of Malignant Breast/Uterus/Ovaries Diseases or Abnormalities?		

	n	%
Yes, Breast Cancer	22	11%
Yes, Other	10	5%
Breast surgery in the past? Yes.	45	23%
If yes, Breast treated in the past?		
Contralateral	24	53%
Ipsilateral	15	33%
Bilateral	5	11%
Not Specified	1	2%
Family history of breast cancer? Yes.	67	35%
Family history of ovarian cancer? Yes.	4	2%
Past history of malignant breast disease or abnormalities?	22	11%
Past history of malignant uterus diseases or abnormalities?	9	5%
Past history of malignant ovaries diseases or abnormalities?	1	1%
OCP oral contraception pills? Yes.	53	27%
Fertility treatment? Yes.	1	1%
Hormonal replacement therapy? Yes.	56	29%
Current Breast Cancer		
Breast Deformation?		
Yes, Bulging	2	1%
Yes, Other	5	3%
Yes, Bulging and Other	0	0%
Palpable? Yes.	29	15%
Breast Skin Characteristics? Yes.	7	4%

Table 6-7: ICE3 Clinical Study Medical History (General) Categorical Variables - Primary Analysis Set (N=194)

	n	%
Coagulopathies or thrombocytopenia? Yes.	5	3%
Other hematological diseases? Yes.	9	5%
Hypertension? Yes.	109	56%
Hyper/dys lipidemia? Yes.	66	34%
CHF congestive heart failure? Yes.	8	4%
Cardiac arrythmia? Yes.	22	11%
Unspecified heart disease? Yes.	38	20%
History of stroke or TIA? Yes.	12	6%
COPD chronic obstructive pulmonary disease? Yes.	19	10%
Asthma? Yes.	12	6%
Other pulmonary disease? Yes.	24	12%
Diabetes mellitus? Yes.	34	18%
Thyroid disease? Yes.	38	20%
ESRD (end stage renal disease)? Yes.	0	0%
Dementia? Yes.	4	2%
Other neurological deficits (unable to understand)? Yes.	9	5%

	n	%
Arthritis? Yes.	57	29%
Other musculoskeletal diseases? Yes.	38	20%
Tobacco?		
Yes	14	7%
Former	62	32%

6.5.Cryoablation Procedure Details

The cryoablation procedure details for the Primary Analysis Set are shown below in **Table 6-8**. The mean tumor sagittal dimension was 0.81 cm (range, 0.25 –1.49 cm), the mean tumor transverse dimension was 0.74 cm (range, 0.28–1.4 cm), and the mean tumor anterior-posterior dimension (A-P) was 0.63 cm (range, 0.1-1.4 cm).

Table 6-8: ICE3 Clinical Study Cryoablation Procedure – Continuous Variables Primary Analysis Set (N=194)

	N	Mean	SD	Med	Min	Max
Tumor Dimensions						
Sagittal (cm)	193	0.81	0.29	0.80	0.25	1.49
Transverse (cm)	194	0.74	0.27	0.70	0.28	1.40
Anterior/Posterior (cm)	194	0.63	0.26	0.60	0.10	1.40
Freeze Duration						
First (minutes)	194	8.5	1.9	8.5	2.8	13.0
Second (minutes)	194	8.5	2.1	8.2	4.0	13.8
Total (minutes)	194	17.0	3.8	16.8	7.6	26.2
Thaw (minutes)	193	7.9	1.6	8.0	2.9	17.0
Final Iceball Dimension						
Width (mm)	194	36.9	5.1	36.8	24.5	61.0
Length (mm)	194	46.9	6.8	48.2	36.0	65.5
Source: Table 3_1 Cryoablation Procedure_Continuous.sas; Analyzed: 02APR2024						

Adjuvant treatment was provided following the procedure based on the physician's discretion. A majority of patients (78.9%, 153/194) received adjuvant treatment:

- Endocrine therapy only: 63.9% (124/194)
- Radiation only: 1.5% (3/124)
- Endocrine and radiation therapy: 12.9% (25/194)
- Endocrine, radiation and chemotherapy: 0.5% (1/194)

6.6.Primary Effectiveness Endpoint

As shown in the following tables, ProSense™ Cryoablation System demonstrated an estimated local IBTR five-year recurrence rate of 4.3%, at a mean follow-up period of 54.16 ± 13.07 months, with 2-sided 95% confidence interval upper bound of 8.7%. (**Table 6-9** and **Figure 6-2**).

Please note: One patient returned late for their five-year visit (63 months post-treatment) and was observed to have recurred. Typically, Kaplan Meier survival analysis truncates the data contribution at the 5-year anniversary (Month 60 or Day 1825) and would not have included this event. The analysis shown in Table 6-9 conservatively includes this recurrence observed during the 5-year visit which occurred after the 5-year treatment anniversary.

At the 36-month and 48-month time points, the IBTR rate was 0.6% (1 recurrence event; 95% CI, 3.9%;) and 1.7% (3 recurrence events; 95% CI, 5.3%), respectively.

Table 6-9: ICE3 Clinical Study Local IBTR Rate - Primary Analysis Set (N=194) Including Additional Recurrence Beyond 5-Year Anniversary

Time	N start*	At Risk**	Cumulative Recurrence	Survival Estimate†	Recurrence Estimate†	1-sided 95% CI UB	2-sided 95% CI LB	2-sided 95% CI UB
Operative	194	194	-	-	-	-	-	-
Month 6	194	192	0	100.0%	0.0%	0.0%	0.0%	0.0%
Year 1	192	190	0	100.0%	0.0%	0.0%	0.0%	0.0%
Year 2	190	184	0	100.0%	0.0%	0.0%	0.0%	0.0%
Year 3	184	173	1	99.4%	0.6%	2.8%	0.1%	3.9%
Year 4	173	162	3	98.3%	1.7%	4.4%	0.6%	5.3%
Year 5	162	133	7	95.7%	4.3%	7.8%	2.1%	8.7%

*N start: number of patients at the beginning of the follow-up time interval.
**At risk: number of patients that completed the follow-up time interval with no IBTR event.
†Kaplan-Meier (product-limit) estimate with 1-sided 95% CI upper bound (UB) and 2-sided 95% lower and upper bounds (LB and UB).
Source: Table 4_1 Local IBTR_FAS.sas; Analyzed: 21MAR2024

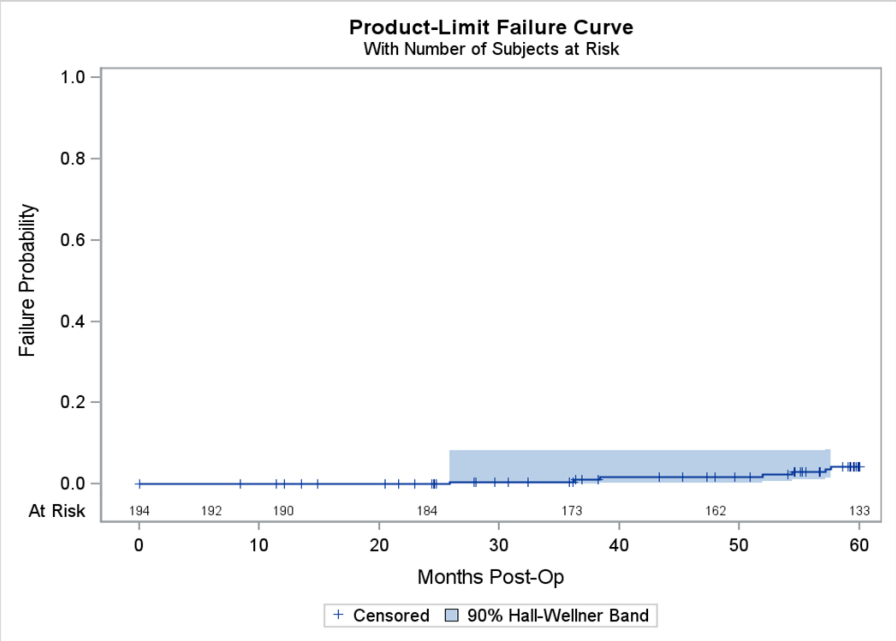


Figure 6-2: ICE3 Clinical Study Local IBTR Recurrence Rate - Primary Analysis Set (N=194) Including Additional Recurrence Beyond 5-Year Anniversary

The characteristics of the seven patients who experienced recurrence are shown in **Table 6-10**. The mean time to recurrence was 46.72 months (range 25.88–63.15 months). The mean baseline tumor size, at the largest dimension, was 0.87 cm (range, 0.58–1.38 cm). After the second freeze, the ice ball length was 4.93 cm (range, 4.0–5.8 cm), and the ice ball width was 3.75 cm (range, 2.98–4.39 cm). Three of the seven recurrences received no adjuvant treatment; this is not consistent with the proposed indication for use with adjuvant endocrine therapy. The remaining four received endocrine therapy alone.

Please note: FDA has included two additional recurrence events in their analysis of IBTR. Both cases have been closely evaluated with the DSMB who do not believe either case is confirmed local recurrence which was defined as confirmed through biopsy or cytology and should not be included in the IBTR rate. Additionally, neither patient received adjuvant treatment in line with the indicated patient population for treatment with this device.

- *In one case, the patient had a new ipsilateral tumor that was identified in a different quadrant (the primary breast cancer was located at the LOQ 8:00-9:00, 4-5cm FN, and the newly diagnosed breast cancer at the UIQ 12:00, 5cm FN). Both the investigator and DSMB Chair determined this case to be second primary breast cancer. The DSMB Chair advised that this case follows clinical practice in the breast surgeon field to define a new ipsilateral tumor in a different quadrat or at least 5cm distant from the original tumor as a second primary breast cancer.*
- *In the second case, the patient was documented as 'BI-RADS 2' based on mammography (62.2 months after the cryoablation treatment), which indicates a benign finding in a breast imaging test. The investigator identified this as a suspicious lesion; however, the patient refused to undergo biopsy or further assessment. The DSMB determined that in absence of a biopsy to evaluate the suspicious lesion, an annual mammogram is recommended to be performed at year 6 and there is no clear indication of recurrence at year 5.*

It is widely published that despite successful initial treatment, some cancer cells may remain in the body and these cells can eventually grow and lead to a recurrence[55, 58].This is a known risk common to all breast cancer treatments, including surgical resection with confirmed margins, and is considered to be a natural course of the disease.

Table 6-10: ICE3 Clinical Study Characteristics of Patients with Local Recurrence

Patient characteristics	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G
Age	73	67	72	72	86	79	70
Time to recurrence (months)	54.38	51.90	25.88	36.20	38.38	57.16	63.15
Nottingham grade	2	2	2	2	2	2	2
Estrogen receptor	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Progesterone receptor	Positive	Positive	Positive	Negative	Positive	Positive	Positive
Lumina Type	A	A	A	B	A	A	A
Max Tumor size on procedure day (cm)	0.99	0.60	0.58	0.58	1.30	1.38	0.64
Ice ball length (cm)	5.0	4.0	5.0	4.0	5.8	5.69	5.0
Ice ball width (cm)	4.08	3.1	3.31	2.98	4.15	4.22	4.39
SLNB	No	No	No	No	No	No	No
Adjuvant radiation (Y/N)	No	No	No	No	No	No	No
Adjuvant chemotherapy (Y/N)	No	No	No	No	No	No	No
Adjuvant endocrine therapy (Y/N)	Yes	No	No	Yes	Yes	No	Yes

SLNB sentinel lymph node biopsy

6.7.Evaluation of Pre-Specified Performance Goal

The estimated local IBTR recurrence rate for the Primary Analysis Set was 4.3% at 5-year follow-up. The upper bound is 8.7%. Therefore, the 10% pre-specified performance goal based on the original literature review was met.

6.8.Secondary Effectiveness Endpoints

The ICE3 clinical study evaluated secondary clinical endpoints from a number of relevant domains (i.e., Complete Ablation of Primary Tumor, Quality of Life, Breast Cosmetic Satisfaction, Regional Invasive Breast Tumor Recurrence Rate, Distant Metastases (Including Contralateral Breast Cancer), Disease-Free Survival (DFS), Overall Survival, and Breast Cancer Survival (including patients who died without cause).

Overall, patients treated with ProSense™ Cryoablation System in the Primary Analysis Set exhibited improvement and numerically favorable rates of success across the broad spectrum of secondary analyses.

6.8.1. Survival Analyses

The protocol-specified definitions of disease outcomes are detailed in **Section 5.5**.

Table 6-11. ICE3 Clinical Study Summary of Secondary Effectiveness Endpoints – Survival Analyses – Primary Analysis Set (N=194)

Secondary Effectiveness Endpoint *(see outcome definition in Section 5.5)*	Event Count	Year 5 Survival Rate	2-sided 95% CI LB - UB
Regional Recurrence Survival Estimate	0	100.0%	-
Distant Metastases Survival Estimate *Includes events observed beyond 5 year anniversary*	6	96.4%	92.2% - 98.4%
Disease Free Survival - Protocol Definition* *Includes events observed beyond 5 year anniversary*	35	79.8%	73.0% - 85.1%
Disease Free Survival - NCI Definition *Includes events observed beyond 5 year anniversary*	12	92.8%	87.6% - 95.8%
Overall Survival Estimate	20	88.6%	82.9% - 92.5%
Breast Cancer Survival Estimate	5	96.7%	92.2% - 98.6%

*Includes all deaths and second primary non-breast cancer as failure events

As shown above, the overall survival at 5-years follow-up was 88.6%. This survival rate exceeds the actuarial survival rate for persons aged 74 in 2014, indicating that the ICE3 population had fewer deaths than are expected for a similarly aged population. There was a 96.7% breast cancer survival rate for the Primary Analysis Set. Of the five (5) cumulative deaths, two were verified as related to breast cancer (1.03%) and the remaining three (3) patients died for unknown reasons. See **Appendix A** for more information on reason for death.

6.8.2. Quality of Life Evaluations

Time to Resume Normal Activities

Patients treated with cryoablation were quick to resume normal activities. Data are available for 181 patients, out of which 150 (82.87%) returned to full activities within 48 hours after the procedure and median time to resume normal activities was 1 day (range 0-8 days).

NCCN Distress Thermometer

Quality of Life was measured using the NCCN Distress Thermometer. The Distress Thermometer is a validated tool used worldwide as an effective means of analyzing quality of life measures that are affected by a clinical trial. This evaluation demonstrated a statistically significant improvement in distress at 6 months as compared to baseline.

Breast Cosmetic Satisfaction

Breast Cosmetic Satisfaction was recorded at 6 months follow-up and annual visits thereafter. Both the patient and treating physician were asked to rate satisfaction with the breast cosmetic outcome of the procedure according to a 5 point scale ranging from very satisfied to very dissatisfied as shown in **Table 6-12**.

As shown below, 99.1% of patients and 97% of physicians who responded were 'satisfied' or 'very satisfied' with the breast cosmetic outcome at 5 years follow-up. The remainder of responders were 'somewhat satisfied' with the cosmetic outcome at 5 years (**Table 6-12**).

Similarly high rates of satisfaction were reported at earlier timepoints with only one patient reporting dissatisfaction at any timepoint and three (3) physician reports of dissatisfaction. For one patient, both the patient and doctor reported dissatisfaction at 24 month follow up due to fat necrosis consistent with the cryoablation site. This patient struggled with multiple comorbidities and healing of the cryoablation site was impaired. Another physician reported dissatisfaction at 48-month follow-up due to general fibrosis and hyperpigmentation, likely due to adjuvant radiation therapy. Hyperpigmentation is not a known side effect of cryoablation. A third physician reported dissatisfaction at 24-month follow-up, but details were not provided. Importantly, no patients or physicians reported dissatisfaction in breast cosmetic outcome at Year 5.

Table 6-12: ICE3 Clinical Study Breast Cosmetic Satisfaction – Primary Analysis Set (N=194)

	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Patient satisfaction						
Very Satisfied	125 (70.6%)	115 (68.5%)	99 (69.2%)	83 (64.8%)	73 (64.6%)	73 (65.8%)
Satisfied	50 (28.2%)	50 (29.8%)	40 (28%)	45 (35.2%)	39 (34.2%)	37 (33.3%)
Somewhat Satisfied	2 (1.1%)	3 (1.8%)	3 (2.1%)	0 (0%)	2 (1.8%)	1 (0.9%)
Dissatisfied	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Very Dissatisfied	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)

	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Physician satisfaction						
Very Satisfied	87 (49.4%)	79 (47.6%)	68 (48.2%)	56 (43.8%)	52 (48.6%)	50 (49%)
Satisfied	87 (49.4%)	87 (52.4%)	68 (48.2%)	72 (56.3%)	55 (50.09%)	49 (48%)
Somewhat Satisfied	2 (1.1%)	0 (0%)	3 (2.1%)	0 (0%)	0 (0%)	3 (2.9%)
Dissatisfied	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Very Dissatisfied	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)	0 (0%)

6.9.Safety Results

Non-procedure related and procedure related adverse events are summarized below in **Table 6-13** and **Table 6-14**.

Table 6-13: ICE3 Clinical Study Non-Procedure Related Adverse Event Summary - Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	**Subjs‡**	**%°**
Non-Procedure Related Adverse Events	337	99	51.0%
Non-Procedure Related Serious Adverse Events	123	56	28.9%
Non-Procedure Related Adverse Events by Severity			
Mild	175	60	34.3%
Moderate	74	40	20.6%
Severe	88	43	22.2%
Serious Non-Procedure Related Adverse Events by Severity			
Mild	5	3	1.5%
Moderate	32	22	11.3%
Severe	86	42	21.6%

† Total number of events without regard to length of follow-up.
‡ Number of subjects experiencing event without regard to length of follow-up.
° Percentage of subjects experiencing specific event without regard to length of follow-up.
Procedure relationship: Remotely, Possible, Probable, Unknown.
Source: Table 5_1 AE Summary_FAS v2.sas; Analyzed: 09JUN2024

Table 6-14: ICE3 Clinical Study Procedure Related Adverse Event Summary – Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
Procedure Related Adverse Events	180	93	47.9%
Procedure Related Serious Adverse Events	4	3	1.5%
Procedure Related Adverse Events by Severity			
Mild	158	83	42.8%
Moderate	18	15	7.7%
Severe	4	4	2.1%
Serious Procedure Related Adverse Events by Severity			
Mild	0	0	0.0%
Moderate	3	3	1.5%
Severe	1	1	0.5%

† Total number of events without regard to length of follow-up.
‡ Number of subjects experiencing event without regard to length of follow-up.
° Percentage of subjects experiencing specific event without regard to length of follow-up.
Procedure relationship: Remotely, Possible, Probable, Unknown.
Source: Table 5_1 AE Summary_FAS v2.sas; Analyzed: 09JUN2024

There were 337 non-procedure related adverse events reported by 99 patients and 180 procedure related adverse events reported by 93 patients. Of the procedure-related events, four (4) were serious; three (3) being local recurrence and one (1) being metastatic breast cancer. The majority of procedure-related events were mild in severity.

In total, there were 21 deaths (10.8%) during the follow-up period; two were verified as related to breast cancer (1.03%). This rate of breast cancer survival is similar to what is reported in the literature for lumpectomy: a range of 0% to 6.3% of patients treated with lumpectomy were reported to have died from breast cancer within 5 years of treatment[50, 51, 55, 59, 60].

Please note, only 20 deaths occurred within 5-years of cryoablation treatment. See **Appendix A** for more information on reason for death.

As shown below in **Table 6-15**, six procedure-related adverse event types occurred in greater than two percent (2%) of patients. Importantly, all adverse event types are expected procedure-related adverse events common to all cryoablation procedures.

Table 6-15: ICE3 Clinical Study - Procedure-Related Events that Occurred in > 2% of Patients – Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
Bruising	57	57	29.4%
Pain	38	36	18.6%
Localized Edema	37	35	18.0%
Injection site reaction	11	10	5.2%
Hematoma	9	9	4.6%
Frost Injury	4	4	2.1%

† Total number of events without regard to length of follow-up.
‡ Number of subjects experiencing event without regard to length of follow-up.
° Percentage of subjects experiencing specific event without regard to length of follow-up.
Procedure relationship: Remotely, Possible, Probable, Unknown.
Adverse events with missing date are analyzed as relative day 1.

Majority of procedure-related adverse events occurred within 1 month of surgery (91.1%) with many events reported on the day of the procedure. Most procedure-related adverse events were mild in severity (87.8%); 10% were moderate and the remaining 4 events (2.2%) were conservatively categorized as severe and serious as described below. All non-serious procedure-related adverse events resolved without residual effects.

The DSMB conservatively classified a total of four (4) serious adverse events in three (3) patients to be possibly related to the study procedure/device, due to physician user error. The DSMB determined that two patients received suboptimal treatment (one with 5 minute treatment cycles and one with 7 minute treatment cycles resulting in ice balls <35mm at the end of first freeze and <40mm at the end of the second freeze) and one (1) patient experienced probe mispositioning (not centered or deep enough in tumor) during cryoablation. One (1) of the patients that had a serious adverse event possibly related to the study procedure/device had both local recurrence and distant recurrence; this patient was reviewed by the DSMB retrospectively and believed not to be eligible based on MammaPrint results, which suggested luminal-B pathology. All four events occurred greater than 2-years post-cryoablation. The DSMB classified three of the events as moderate in severity and one as severe. Two of the serious, procedure related adverse events resolved without residual effect, and the remaining two serious, procedure related adverse events resulted in treatment of local recurrence and death due to metastatic disease.

Table 6-16. Summary of Serious Procedure-Related Adverse Events

Pt	SAE	Possible Cause per DSMB	Severity	Outcome
1	Local Recurrence	Possibly related due to probe malpositioning	Moderate	Resolved without effect
2	Local Recurrence	Possibly related due to violation of treatment protocol	Moderate	Resolved without effect
3	Local Recurrence	Possibly related due to violation of treatment protocol	Moderate	Death

Pt	SAE	Possible Cause per DSMB	Severity	Outcome
	Metastatic Breast Cancer		Severe	

Additional safety results can be found in **Appendix C.**

FDA's safety analysis considers all events of recurrence to be device-related serious adverse events. Given the ICE3 protocol definition of AE relationship, DSMB recommendation and regulatory and clinical precedent set by recent clinical drug trials, IceCure believes that FDA's categorization of local recurrence, distant recurrence, second primary cancer (breast and non-breast) as related to the cryoablation device/ procedure is not clinical reasonable and is not consistent with regulatory and clinical precedent. Additional information is provided in **Appendix H**.

6.10. Sensitivity Analyses

6.10.1. Supplemental Safety Analysis: All Treated Population

As a supplemental analysis for safety, data was compiled on all subjects treated with the ProSense™ Cryoablation System (the "All Treated Population") as part of the ICE3 study (n=206). As shown below in **Table 6-17**, 150 patients reported 541 adverse events. There were 192 procedure related adverse events reported by 100 patients and 65 patients reported 133 serious adverse events. There were five (5) serious procedure related adverse events, four (4) being local recurrence and one (1) being metastatic breast cancer. The majority of procedure-related events were mild in severity.

In total, there were 21 deaths (10.8%) during the follow-up period; two were verified as related to breast cancer (1.03%). See **Appendix A** for more information on reason for death.

Table 6-17: ICE3 Clinical Study Adverse Event Summary – Overall Population (N=206)

	ICECURE (N= 206)		
	Events†	**Subjs‡**	**%°**
Adverse Events			
All	**541**	**150**	**72.82%**
Procedure Related	**192**	**100**	**48.54%**
Serious Adverse Events			
All	**133**	**65**	**31.55%**
Procedure Related	**5**	**4**	**1.94%**
Adverse Events by Severity			
Mild	**346**	**115**	**55.83%**
Moderate	**99**	**55**	**26.70%**
Severe	**96**	**51**	**24.76%**

	ICECURE (N= 206)		
	Events†	**Subjs‡**	**%°**
Serious Adverse Events by Severity			
Mild	**5**	**3**	**1.46%**
Moderate	**38**	**28**	**13.59%**
Severe	**90**	**45**	**21.84%**
Deaths			
All	**21**	**21**	**10.19%**

† Total number of events without regard to length of follow-up.
‡ Number of subjects experiencing event without regard to length of follow-up.
° Percentage of subjects experiencing specific event without regard to length of follow-up.
Procedure relationship: Remotely, Possible, Probable, Unknown.

6.10.2. Supplemental Primary Effectiveness Analysis: Primary Analysis Set with Incomplete Treatment

The IBTR rate for the primary analysis set including the three subjects with incomplete treatment is provided in **Table 6-18**. As shown below, there is no impact of addition of these subjects on the overall 5-year recurrence rate.

Table 6-18. Local IBTR Recurrence Rate – Primary Analysis Set with Three (3) Subjects with Incomplete Treatment and Including Additional Recurrence Beyond 5-Year Anniversary

Time	N start*	At Risk**	Cumulative Recurrence	Survival Estimate†	Recurrence Estimate†	1-sided 95% CI UB
Operative	197	197	-	-	-	-
Month 6	197	193	0	100.0%	0.0%	0.0%
Year 1	193	190	0	100.0%	0.0%	0.0%
Year 2	190	184	0	100.0%	0.0%	0.0%
Year 3	184	173	1	99.4%	0.6%	2.8%
Year 4	173	162	3	98.3%	1.7%	4.4%
Year 5	162	133	7	95.7%	4.3%	7.8%

*N start: number of patients at the beginning of the follow-up time interval.
**At risk: number of patients that completed the follow-up time interval with no IBTR event.
†Kaplan-Meier (product-limit) estimate with 1-sided 95% CI upper bound (UB).
Source: Table 4_1 Local IBTR_FAS_Sensitivity.sas; Analyzed: 04APR2024

6.10.3. Supplemental Primary Effectiveness Analysis: Full Analysis Set

The ICE3 protocol pre-specified that the per-protocol analysis set excluding patients with any major protocol deviation and with data available for the analysis would serve as the main analysis set for performance assessments.

Table 6-19 shows various analyses of 5-year IBTR, starting with recurrence in the 'all treated' population including two additional events classified by FDA as recurrence. FDA's evaluation of recurrence including patients treated outside of inclusion/ exclusion criteria with biologic features known to have a greater risk of recurrence as well as addition of recurrence in a different quadrant as well as unconfirmed recurrence results in a "worst case" analysis of the potential recurrence rate. Of note, the literature used for comparison did not consider recurrence using these "worst case" classification methods or include subjects with recurrence identified beyond the 5-year anniversary. As a result, FDA's "worst case" analyses should be reviewed with this context.

IceCure believes the DSMB's assessment of 7 recurrence cases in the primary analysis population, conservatively including recurrence observed >60 months, is more reflective of the ICE3 study outcome. Further, the analysis of 3 recurrences in 147 patients treated with adjuvant endocrine therapy is most representative of the strict 5-year IBTR rate in the indicated population.

The 5-year 'freedom from recurrence' rates of these populations is shown in Table 6-19. As shown below, the indicated population experienced a <3% rate of IBTR.

See **Appendix H** for additional information.

Table 6-19. Sensitivity analyses for effect of various analysis methods on primary efficacy analysis of IBTR in the ICE3 trial.

	Column 1	Column 2	Column 3	Column 4
	KM (IceCure censoring)†	**KM (Censored at time of death) †**	**CIF (KM) (Censored at time of death) †**	**CIF (Competing Risk*) (Censored at time of death) †**
ICE3 All Treated (n=206, n=14 recurrence)	92.0% (86.8%-95.2%)	91.5% (86.1%-94.9%)	91.5% (86.5%-95.2%)	92.1% (87.5%-95.5%)
Exclude 1 unconfirmed recurrence Exclude 1 different quadrant recurrence				
ICE3 All Treated (n=206, n=12 recurrence)	93.3% (88.4%-96.1%)	92.8% (87.6%-95.9%)	92.8% (88.2%-96.1%)	93.3% (88.9%-96.4%)

	Column 1	Column 2	Column 3	Column 4
	KM (IceCure censoring)†	**KM (Censored at time of death) †**	**CIF (KM) (Censored at time of death) †**	**CIF (Competing Risk*) (Censored at time of death) †**
Exclude major deviations from inclusion/exclusion: 9 subjects with multifocal or >1.5 cm tumor or DCIS: 40%				
ICE3 All Treated (excluding major inc/exc dev but with incomplete treatment) (n=197, n=7 recurrence)	95.7% (91.2%-97.9%)	95.3% (90.4%-97.8%)	95.3% (91.1%-98.0%)	95.7% (91.8%-98.1%)
Exclude recurrence >M60				
ICE3 All Treated (excluding major inc/exc dev but with incomplete treatment) (n=197, n=6 recurrence)**	96.4% (92.1%-98.4%)	96.0% (91.4%-98.2%)	96.0% (92.0%-98.4%)	96.4% (92.7%-98.5%)
Exclude subjects to align ICE3 study population with the proposed indicated population.				
ICE3 Indicated population (n=147, n=3 recurrence)**	97.7% (93.2%-99.3%)	97.6% (92.6%-99.2%)	97.6% (93.5%-99.3%)	97.7% (94.0%-99.4%)

† 'IceCure censoring' refers to censoring method described in Section 5.4.3.1; subjects who withdrew or were lost-to-follow-up were censored at the time of completion of the study exit form and patients who died without recurrence were considered to be non-recurrence through 60 months. Alternate death censoring is shown in columns 2-4 with censoring at the time of death. See Appendix H for additional detail.
*Competing risk of death due to any cause.
**Excludes one recurrence observed >M60.

7. FDA-REQUESTED SUPPLEMENTAL ANALYSES

Summary

- FDA requested that IceCure conduct a PRISMA systematic literature review and meta-analysis to define the comparator rate and replace the original performance goal.
- The ICE3 recurrence rate was found to be similar to the PRISMA derived lumpectomy comparator.
- FDA requested additional analyses to evaluate subpopulations of the ICE3 clinical study patients based on adjuvant treatment and/ or biological characteristics.
- In all analyses, ICE3 patients treated with cryoablation using ProSense™ experienced a similar rate of recurrence as patients treated with lumpectomy, while avoiding risks and side effects of lumpectomy.

7.1. ICE3 Population versus PRISMA Systematic Literature Review

In May 2023, FDA recommended following PRISMA guidelines to conduct a literature review and meta-analysis to define the comparator rate and replace the original literature review from which the performance goal IBTR rate of 5.0% was derived. IceCure agreed to perform an updated literature search in accordance with FDA-recognized literature review standards per the PRISMA methodology to reflect the current treatment standard of care.

The eligibility criteria outlined below were developed according to PICO (Population, Intervention, Outcome, Comparator) guidelines to offer a robust comparison to the ICE3 population. To be included in the review and meta-analysis, the population described by the published article must include patients treated with breast-conserving surgery (i.e., lumpectomy) without adjunctive radiation in the cohort of interest.

IceCure's PRISMA literature review selected lumpectomy without adjuvant radiotherapy as the cohort of interest for the following reasons: (1) the conclusions of recently published clinical trials (i.e., CALGB 9343, PRIME II) and guidelines (i.e., NCCN, NICE, St. Gallen International Consensus Guidelines, EUSOMA) to de-escalate care, omitting adjuvant radiotherapy in patients ≥ 65 or ≥ 70 years of age receiving adjuvant endocrine therapy for low-risk tumors[61] and (2) reflect the ICE3 patient population where a majority of patients (85.6%) of patients did no received radiotherapy per physician discretion. Due to the well-documented impact of adjunctive therapies on local recurrence rates, the population of interest that offers the best comparison to the ICE3 clinical study population is treated with BCS with or without adjunctive endocrine but not radiation therapy.

The screening criteria for the PRISMA literature review are outlined in **Table 7-1**. Low risk of breast cancer recurrence is defined as patients having early-stage tumors that are <2cm in diameter (T1), node negative (N0), ER/PR positive, and HER2 negative.

Table 7-1: PRISMA Systematic Review and Meta-analysis Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Articles were **included** if all of the following criteria were met: • Breast-conserving surgery (i.e., lumpectomy) procedure without adjunctive radiation • Cancer type (low risk, lymph node negative, • ER/PR positive, HER2 negative) • Age >50 • Greater than or equal to approximately 100 patients • More than one study site • IBTR evaluable and extractable • English • Full text available	Articles were **excluded** if any of the following criteria were met: • Not breast-conserving surgery (i.e., lumpectomy) procedure **OR** breast-conserving surgery (i.e., lumpectomy) with adjunctive radiation • Cancer type (high risk, lymph node positive, HER2 positive, ER/PR negative) • Age < 50 • Less than approximately 100 patients • Single site study • Book chapters, letters, dissertations, and conference proceedings • IBTR data unavailable/ not extractable • Not English language • Full text unavailable • Duplicate article or population

Relevant published scientific literature was searched in multiple databases including the PubMed, Ovid/Medline, and Embase databases and internet searches of clinical research sites (i.e., ClinicalTrials.gov). Multiple databases were searched to provide comprehensive coverage of the literature related to the target population and intervention.

IceCure submitted the protocol including search criteria to FDA in May 2023.

The included articles were appraised individually with regard to their relevance and contribution to the objectives of this systematic review. The criteria for determining the quality and scientific validity of each piece of data, relevance to the systematic review, and how to weight the contribution of each piece of data were pre-specified.

In June 2023, IceCure provided FDA the requested PRISMA Systematic Review and Meta-analysis to support the comparator rate for the ICE3 clinical study, which is based on the IBTR rate reported in the literature for the standard of care, lumpectomy, in the target patient population. The PRISMA Systematic Review and Meta-analysis included clinical trials of postmenopausal females (≥50 years) who underwent a breast-conserving surgical intervention without adjuvant radiation. The cancer type included is low risk, early stage (T1), node negative (N0), local (M0), ER/PR positive, and HER2 negative breast cancers. The PRISMA Systematic Review and Meta-analysis was updated in March 2024, to include all relevant studies published documenting outcomes following treatment with standard-of-care, lumpectomy without radiation, published through the date of the search.

Based on this review, the estimated 5-year literature-derived IBTR rate is 3.52% (95% CI UB 5.77%). The IBTR rate from the ICE3 clinical study was then compared to this rate.

Additional detail on PRISMA methods and results is provided in **Appendix C**.

7.1.1. PRISMA-Selected Articles

A listing of articles included in the PRSIMA analysis and a summary of how they compare to the ICE3 clinical study is provided below in **Table 7-2**. Articles with patient population with at least >75% alignment with regard to tumor characteristics were included in the meta-analysis. Article contributions were then downweighed in the meta-analysis based on alignment. Articles with "ideal" (>90%) alignment were not downweighed, and the entire at risk sample size was considered in the meta-analysis. Articles with "sufficient" (<90% and >75%) alignment were downweighed, and the at-risk sample size was reduced by 25%. This approach avoids introducing bias by excluding relevant data while limiting its impact on the results in recognition of the between-study heterogeneity.

Table 7-2: Articles Included in PRISMA Systematic Review and Meta-analysis

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
ICE3	**194**	**75.7 (55-94)**	**4.3%**	
Studies without Adjuvant Endocrine Therapy				
Author: Stenmark Tullberg (2021)[62] Citation: Stenmark Tullberg et al. Immune Infiltrate in the Primary Tumor Predicts Effect of Adjuvant Radiotherapy in Breast Cancer; Results from the Randomized SweBCG91RT Trial. Clin Cancer Res. 2021 Feb Trial: SweBCG91RT Trial	84	Median age: 60 (32-78)	15.4%	• Younger patient population than ICE3. • Larger percentage of patients staged as PR+. • No adjuvant endocrine therapy. **The authors performed a subgroup analysis of patients ≥65 year of age with T1N0 ER+ breast cancer. The recurrence rate in this subgroup was presented.** **Limitations** - **Average age of the subgroup unknown (all patients ≥ 60 years of age)** - **HER2 status not reported** - **PR status not reported in subgroup** - **Adjuvant chemotherapy 2.2% of patients in overall group** ***This article was excluded from the PRISMA Sensitivity Analysis.***
Author: Wickberg (2018)[63] Citation: Wickberg et al. Influence of the subtype on local recurrence risk of breast cancer with or without radiation therapy. Breast. 2018 Dec	49	61	10.5%	• Younger patient population than ICE3. • Larger percentage of patients staged as PR+. • Luminal-A patient population. • No adjuvant endocrine therapy.

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
				The authors performed a subgroup analysis of patients with Luminal-A tumors. The recurrence rate in this subgroup was presented. **Limitations** - **Definition of IBTR*** - **Average age unknown (all patients ≥ 55 years of age)** - **Tumor grade unknown (all patients Luminal-A)** - **Small samples size (article was initially included as the sample size was ≥100 patients. The Luminal-A subgroup determined to be more appropriate was significantly smaller)** ***Please note: IBTR was defined as recurrence in the surgical field, new primary cancers in quadrants outside the surgical field, metastases in intramammary lymph node or recurrence in the cuticular tissue. This definition is broader than that of ICE3.** ***This article was excluded from the PRISMA Sensitivity Analysis.***
Author: Blamey (2013)[64] Citation: Blamey et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis:	Treatment Arm (a): 95	57 (33-69)	Treatment Arm (a): 13.1%	• Younger patient population than ICE3 trial. • Clear excision margins confirmed microscopically.

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
British Association of Surgical Oncology (BASO) II trial. Eur J Cancer. 2013 Jul Study: British Association of Surgical Oncology (BASO) II Trial				**Limitations** - **Younger patient population compared to ICE3 (average age 57 years)** - **HER2 status unknown** - **ER/PR status known (all patients Nottingham Prognostic Index (NPI) ≤2.4 indicative of "excellent prognosis"** ***This article was excluded from the PRISMA Sensitivity Analysis.***
Studies with Adjuvant Endocrine Therapy				
Author: Fastner (2020) [65] Citation: Fastner et al. Endocrine therapy with or without whole breast irradiation in low-risk breast cancer patients after breast-conserving surgery: 10-year results of the Austrian Breast and Colorectal Cancer Study Group 8A trial. Eur J Cancer. 2020 Mar Trial: 8 A trial of the Austrian Breast and Colorectal Cancer Study Group	430	66.1 (46-80)	3.6%	• Younger patient population than ICE3. • Smaller percentage of patients staged as T1, PR+, HER2-. • All patients treated with endocrine therapy. **Limitations** - **T2 tumors (8.6%)** - **Undetermined grade (6.0%)** - **Patient age <50 (1.2%)** - **ER- (1.2%)** - **PR- (18.8%)** - **KI 67 > 20 or Her2neu positive (9.2%)** **Article contribution was down weighted in the meta-analysis.**
Author: Fyles (2004)[59]	305	68[(b)]	5.8%	• Younger patient population than ICE3.

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
Citation: Fyles et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep				• Patients who had undergone BCS with confirmed negative margins. • Larger percentage of patients staged as PR+. • All patients treated with endocrine therapy. **The authors performed a subgroup analysis on "women with good prognosis" defined as those with T1 tumors that either were positive for hormone receptors or had an unknown hormone-receptor status. The recurrence rate in this subgroup was presented.** **Limitations** - **Younger patient population compared to ICE3 (all patients ≥50 years of age)** - **Unknown hormone receptor status (14.1%)** - **HER2 status unknown**
Author: Hughes (2013)[50] Citation: Hughes et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013 Jul Trial: Cancer and Acute Leukemia Group B (CALB) 9343	319	>75	4.8%	• Smaller percentage of patients staged as PR+. • All patients treated with endocrine therapy. **Limitations** - **ER- (1.3%)** - **PR- (21.0%)** - **T2 tumor (2.8%)** - **HER2 status unknown**

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
				Article contribution was down weighted in the meta-analysis.
Author: Kunkler (2023)[51] Citation: Kunkler et al. Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer. N Engl J Med. 2023 Feb	593	70.8 (67-73)	3.9%	• Younger patient population than ICE3. • Patients who were treated with BCS and axillary staging, sentinel-node biopsy, or axillary-node clearance and were node-negative. • Clear excision margins (≥ 1mm). • Had received adjuvant or neoadjuvant endocrine therapy. • Smaller percentage of patients staged as T1. • All patients treated with endocrine therapy. **The authors performed a subgroup analysis of patients ER-high status tumors. The recurrence rate in this subgroup was presented.** **Limitations** - **Tumor size 2.1-3.0cm (12.6%)** - **Grade 3 (3.4%)** - **Lymphovasuclar invasion (4.8%)** **Article contribution was down weighted in the meta-analysis.**
Author: Fisher (2002)[66] Citation: Fisher et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after	334	>50[(c)]	10.5%	• Clear excision margins via pathologic examination. • Axillary lymph nodes negative via histologic examination.

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol. 2002 Oct				• All patients treated with endocrine therapy. • Smaller percentage of staged as ER+. **Limitations** - **Younger patient population than ICE3 (52.1% <60 years of age)** - **ER- (12.9%)** **Article contribution was down weighted in the meta-analysis.**
Author: Blamey (2013)[64] Citation: Blamey et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. Eur J Cancer. 2013 Jul Study: British Association of Surgical Oncology (BASO) II Trial	Treatment Arm (b): 106	57 (33-69)	Treatment Arm (b): 2.0%	• Younger patient population than ICE3 trial. • Clear excision margins confirmed microscopically. • All patients treated with endocrine therapy. **Limitations** - **Younger patient population compared to ICE3 (average age 57 years)** - **HER2 status unknown** - **ER/PR status known (all patients Nottingham Prognostic Index (NPI) ≤2.4 indicative of "excellent prognosis"**
Author: Jagsi (2024)[60] Citation: Jagsi R et al. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low	200	62 (50-69)	3.40% 0.00%	• Younger patient population than ICE3. • BCS margins ≥ 2mm. • Luminal-A patient population.

Study Citation	Number of Patients Treated [(a)]	Avg. Age (Range) [Yrs]	5 Year IBTR	Comments on Comparison to ICE3 Clinical Study Population
Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol. 2024 Feb Trial: Individualized Decisions for Endocrine therapy Alone) IDEA				• Larger percentage of patients staged as PR+. • All patients treated with endocrine therapy. **Limitations** - **Younger patient population compared to ICE3 (mean age 62 years)** - **Lobular carcinoma (10%)** - **Poorly differentiated tumor (3%)** - **Lymphovascular invasion (8%)**
Author: Whelan (2023)[55] Citation: Whelan et al. Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. N Engl J Med. 2023 Aug	500	67.1 (62.9-71.6)	2.3%	• Younger patient population than ICE3. • BCS margins ≥ 1mm. • Negative axillary nodes determined by sentinel-lymph-node biopsy or axillary-node dissection. • Luminal-A patient population. • All patients treated with endocrine therapy. **Limitations** - **Younger patient population compared to ICE3 (average age 67.1 years)**
Author: Rodin (2023)[67] Citation: Rodin et al. Impact of Non-Adherence to Endocrine Therapy on Recurrence Risk in Older Women with Stage I Breast Cancer After Breast-Conserving Surgery	703	74 (69-74)	2.80%	• All patients treated with endocrine therapy. **Limitations** - **High grade tumor (6.1%)** - **ER+ and PR+ (90%)** - **HER2 status unknown (36.8%)**

(a) Number of patients treated within treatment arm and subgroup of interest (if applicable)
(b) Fyles 2004 reported median age
(c) Fisher 2002 did not provide an average age for the treatment cohorts of interest; however, based on the inclusion/exclusion criteria of the study, the average age was > 50 years

7.1.2. Comparison to ICE3 Primary Analysis Set IBTR Rate

IceCure conducted a PRISMA Systematic Review and Meta-analysis to support the comparator IBTR rate for the ICE3 clinical study. The PRISMA comparator is based on the IBTR rate reported for studies published in the peer-reviewed literature for the standard of care, lumpectomy, in a target patient population comparable to the ICE3 clinical study population.

The predefined eligibility criteria ensure a homogenous patient population with a specific cancer diagnosis (i.e., low risk, early stage, node negative (T1, N0, ER/PR positive, and HER2 negative) treated with a single intervention (i.e., lumpectomy). In total, eleven (11) unique articles reporting clinical studies containing data from 3,718 patients were included and analyzed in this review and meta-analysis.

The results from the PRISMA Systematic Review and Meta-analysis represent the established and accepted outcomes of the existing standard of care treatment lumpectomy without radiotherapy and constitute a valid reference rate for comparison to investigational treatments. The PRISMA derived comparator rate resulted in an **estimated 5-year IBTR rate of 3.52% with a 95% CI from 2.08% to 5.77%.**

The meta-analysis interval provided a two-sided 95% CI of 2.08% to 5.77%. The true overall survival rate can be as small as 2.08% or as large as 5.77%. The CI was calculated using a Monte-Carlo (MC) approach to generate the 95% interval defined as the 2.5% and 97.5% percentiles from 10,000 sample.

The IBTR rates of from the PRISMA selected literature and the ICE3 clinical study are summarized in Figure 7-1**.** All articles were published in the last 25 years (oldest published in 2002), with 58.3% (7/12) published in the 5 years.

A full report of the methods, analysis, and results from the PRISMA Systematic Review and Meta-analysis is summarized in **Appendix D**.

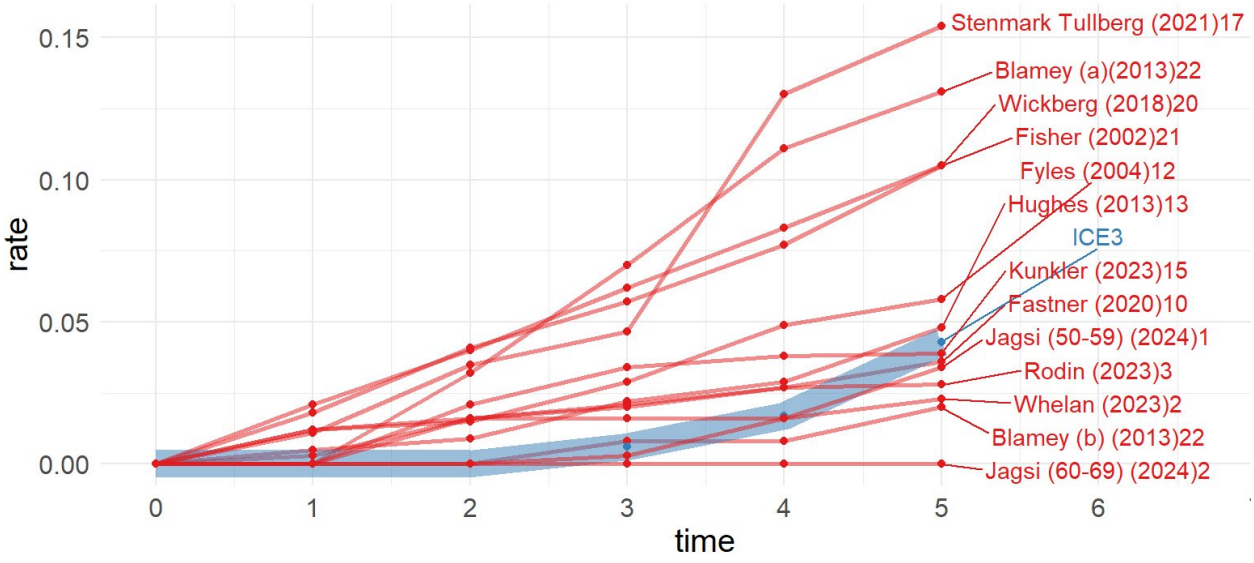


Figure 7-1. Ipsilateral Breast Tumor Recurrence (IBTR) Rate Up to 5-years for the ICE3 Clinical Study and Each Study Included in the PRISMA Systematic Review and Meta-analysis

Table 7-3: Comparison of ICE3 Primary Analysis Set and PRISMA Derived Comparator

	5-Year IBTR	95% CI UB
ICE3 Primary Analysis Set	4.3%	8.7%
PRISMA Derived Comparator	3.52%	5.77%

The ICE3 clinical study primary outcome is acceptable when compared to the PRISMA derived comparator.

7.2.ICE3 Subpopulations versus Literature Comparators

FDA requested IceCure perform analyses to evaluate outcomes in sub-populations of ICE3 clinical study patients to align with the LUMINA study[55] and the proposed indications based on adjuvant treatment and/ or disease characteristics as follows:

1. Sub-populations intended to align with LUMINA
    a. **ICE3 Subpopulation with Adjuvant Endocrine Therapy, without Adjuvant Radiotherapy:** Includes 124 patients from the ICE3 study treated with adjuvant endocrine therapy but without adjuvant radiotherapy.
    b. **ICE3 Subpopulation Aligned with the LUMINA Study and Nuclear Score ≤ 2:** Includes 56 patients from the ICE3 clinical study. Excludes patients who do not meet the LUMINA study criteria, specifically patients with adjuvant radiation, without adjuvant endocrine therapy, without Ki67 index (not required in ICE3) and/ or Ki67 >14, and PR-.
    c. **ICE3 Subpopulation Aligned with the LUMINA Study and Nuclear Score ≤ 2:** Includes 48 patients from the ICE3 clinical study. Excludes patients who do not

meet the LUMINA study criteria, specifically patients with adjuvant radiation, without adjuvant endocrine therapy, without Ki67 index (not required in ICE3) and/ or Ki67 >14, and PR-. Additionally excludes patients without Nottingham component scores available for analysis or nuclear score ≥ 2.
Please note: nuclear subcomponent criteria is not part of proposed indication.

2. Sub-populations intended to align with proposed indications
    a. **ICE3 Subpopulation with Adjuvant Endocrine therapy with or without adjuvant radiotherapy:** Includes 147 patients from the ICE3 clinical study. Excludes patients who do not meet the proposed indication, specifically patients <60 years of age and/ or without adjuvant endocrine therapy.
    b. **ICE3 Subpopulation Aligned with Proposed Indications and Nuclear Score ≤ 2:** Includes 120 patients from the ICE3 clinical study. Excludes patients who do not meet the proposed indication, specifically patients <60 years of age and/ or without adjuvant endocrine therapy. Additionally excludes patients without Nottingham component scores available for analysis or nuclear score ≥ 2.
    Please note: nuclear subcomponent criteria is not part of proposed indication.
3. Sub-population intended to evaluate impact of adjuvant radiotherapy
    a. **ICE3 Subpopulation with Adjuvant Radiotherapy:** Includes 29 patients from the ICE3 clinical study treated with adjuvant radiotherapy.

These FDA-requested sub-populations are compared various literature populations as summarized below. Additional detail is provided in **Appendix G**.

Table 7-4: Summary of FDA-Requested ICE3 Sub-populations and Respective Literature Comparators

Characteristics of Interest		ICE3		Comparator	
		Sub-Population	IBTR Outcome	Literature Analysis	IBTR Outcome
Sub-Populations Intended to Align with LUMINA					
1(a)	Endocrine therapy only	Sub-population with endocrine therapy without radiation (N=124)	3.7% (95% CI UB: 9.6%)	IceCure PRISMA sensitivity (lumpectomy with endocrine therapy)	2.82% (95% CI UB: 4.83%)
1(b)	Endocrine therapy only, Further restricted to ICE3 patients with available Ki67 score and Ki67<14; excludes PR-	Sub-population aligned w/ LUMINA (N=56)	2.17% (95% CI UB: 14.4%)	LUMINA study (lumpectomy with endocrine therapy)	2.3% (95% CI UB 4.1%)

Characteristics of Interest		ICE3		Comparator	
		Sub-Population	IBTR Outcome	Literature Analysis	IBTR Outcome
1(c)*	Endocrine therapy only, Further restricted to ICE3 patients with available Ki67 score and Ki67<14; excludes PR- and nuclear grade ≤ 2	Sub-population aligned w/ LUMINA and nuclear grade ≤ 2 (N=48)	2.56% (95% CI UB: 16.8%)	LUMINA study (lumpectomy with endocrine therapy)	2.3% (95% CI UB 4.1%)
Sub-Populations Intended to Evaluate Proposed Indication					
2(a)	Endocrine +/- other adjuvant treatments **17% with adjuvant radiotherapy*	Sub-population aligned w/ indications (N=147)	3.08% (95% CI UB: 8.0%)	IceCure PRISMA sensitivity (lumpectomy with endocrine therapy) **excludes adjuvant radiotherapy*	2.82% (95% CI UB: 4.83%)
2(b)*	Endocrine +/- other adjuvant treatments Age ≥ 60, nuclear grade ≤ 2 **17% with adjuvant radiotherapy*	Sub-population aligned w/ indications and nuclear grade ≤ 2 (N=120)	1.95% (95% CI UB: 7.6%)	IceCure PRISMA sensitivity (lumpectomy with endocrine therapy) **excludes adjuvant radiotherapy*	2.82% (95% CI UB: 4.83%)
Sub-Population Intended to Evaluate Impact of Adjuvant Radiotherapy					
3(a)	Radiation +/- other adjuvant treatments	Sub-population with radiation (N=29)	0%	FDA PRISMA sensitivity (lumpectomy with radiation)	Range: 0-1.2%

*FDA has agreed to the subpopulations with further restrictions based on nuclear grade ≤2 or no missing component scores.

When looking at the ICE3 data in FDA-requested subpopulations stratified by adjuvant therapy, there were minor, expected differences in recurrence rates of subpopulations treated with adjuvant endocrine therapy alone, endocrine therapy with or without other adjuvant treatments, and adjuvant radiotherapy alone. Similarly, we see minor differences in recurrence rates when restricted based on biological characteristics.

Ultimately, the various analyses of ICE3 sub-populations as compared to PRISMA and literature outcomes confirmed favorable IBTR outcomes in the ICE3 study population. In all analyses, ICE3 patients treated with cryoablation using ProSense™ experienced a similar rate of recurrence as patients treated with lumpectomy. Importantly, the subpopulation aligned with the proposed

indications, indicated by the black box, shows improved recurrence outcomes as compared to the overall population with nearly 97% of patients free from recurrence.

8. OTHER CLINICAL EXPERIENCE WITH PROSENSE™ FOR TREATMENT OF BREAST CANCER

As described in Section 4.4.2, ProSense™ Cryoablation System has been used in the treatment of breast cancer outside of the United States.

IceCure has compiled a summary of data available on use of ProSense™ Cryoablation System device for the treatment of breast cancer. The available data sources include data from independent clinical literature and post market surveillance (PMS) data. The PMS data are limited to safety data to support CE marking. The full text publications of the independent clinical studies are provided in **Appendix D**.

The clinical literature populations consist of patients with early stage, low risk breast cancer. However, it is important to note that the literature populations are not directly comparable to the ICE3 patient population. In many cohorts, the treated patients were younger than those in the ICE3 clinical study and/ or treated with adjuvant radiotherapy. Nonetheless, the observed outcomes are supportive of the safety, effectiveness, and positive benefit-risk profile of use of ProSense™ Cryoablation System device for treatment of early stage low-risk breast cancer.

The ProSense™ Cryoablation System or an equivalent cryoablation device was used in over 1,600 procedures for the treatment of breast cancer in independent clinical studies:

- Across the clinical literature, eighteen (18) cohorts of patients were treated in independent clinical studies in the United States, Japan, Spain, Germany, Romania, Italy, and the Netherlands with follow-up to 16 years.
- Ten (10) of the independent clinical studies reported local recurrence outcomes. In total, the clinical studies reported 22 recurrences in up to 1,366 patients (1.61%).
- No serious device or treatment related adverse events were reported in the independent clinicals studies. Two patients reported skin redness that resolved within two weeks and one patient reported alteration in skin pigmentation. One study reported a complication rate of 4.9% with no serious complications. The complications included self-limiting ecchymosis, seroma, nodular thickening, and hematoma or swelling at the cryoablation site. Another study reported a complication rate of 6.3%. The complication was hypothermia induced skin damage and was mild in all cases.

As part of the post market surveillance (PMS) requirements for the CE marking of ProSense™ Cryoablation System device for use in Europe, IceCure has collected safety and physician satisfaction data for procedures that are known to IceCure; however, these data do not represent all use cases.

PMS data were collected on 150 patients treated with ProSense™ Cryoablation System for breast cancer:

- In total, 4/140 (2.9%) of patients reported adverse events (1 hematoma, 2 minor skin burns, and 1 not specified).
- Physician satisfaction was graded as “Excellent” in 124/141 (88%) cases.
- Physician satisfaction was graded as “Good” in 15/141 (11%) cases.

- Physician satisfaction was graded as “Medium” in the remaining 2/141 (1%) cases.

9. BENEFIT - RISK

Summary

- The ICE3 Study has demonstrated that benefits of the ProSense™ device in treatment of early-stage, low risk breast cancer outweigh the risks of treatment.
    - Treatment benefit of immediate ablation of cancerous breast tissue with 100% freedom from recurrence through 2-years follow-up and >95% freedom from recurrence through 5-years follow-up.
    - Clinical experience benefits of minimally invasive procedure performed in an outpatient setting under local anesthesia resulting in fewer side effects and improved cosmesis.
    - Quality of life benefits including near immediate recovery and full return to activities after treatment as well as short and long term satisfaction with cosmetic results.
    - Overall more favorable patient journey as compared to standard-of-care, lumpectomy.
- Risks of ProSense™ are risks associated with cryoablation systems and breast cancer treatment; no new risks are introduced.
    - Procedure-related risks are common to all cryoablation procedures and less severe than surgical-procedure related risks of standard-of-care, lumpectomy.
    - Breast cancer related risks include risk of incomplete treatment, risk of recurrence and risk of breast cancer related death and are common to all breast cancer treatments.
    - Identified risks have been/are mitigated through completed testing, planned testing, labeling, and other necessary special and general controls.
- Demonstrated treatment, clinical experience, and quality of life benefits translate to significant advantages relative to the standard of care lumpectomy surgery.
- Totality of evidence supports reasonable assurance of safety and effectiveness for the device, and that the probable benefits outweigh the possible risks to patients.

9.1.1. Treatment Benefits

Clinical evidence from the multicenter prospective ICE3 clinical study demonstrates that the ProSense system results in immediate ablation of cancerous breast tissue. The procedure is performed under real-time ultrasound visualization allowing the physician visualization of the target tissue, helping to ensure complete treatment of the lesions.

As described in Section 6, the ProSense™ Cryoablation System primary analysis population outcomes demonstrates 100% of patients are recurrence free through 2-years follow-up and >95% of patients are recurrence free through 5-years follow-up. The ICE3 study met the pre-specified effectiveness performance goal. The recurrence rate was shown to be comparable to the recurrence rate of standard of care lumpectomy as reported in the literature.

Additionally, the ICE3 population demonstrated success in secondary outcome measures. No regional recurrence was observed and the distant recurrence rate was low at 3.6% at 5-years follow-up. The study overall survival rate exceeds the actuarial survival rate for people age 74, the mean age of the ICE3 study population.

Cryoablation treatment does not interfere with or preclude adjuvant treatments. As with lumpectomy, physicians can proceed with additional concomitant therapies as appropriate for the specific patient. When looking at the ICE3 data in subpopulations stratified by adjuvant therapy, there were minor, expected differences in recurrence rates of subpopulations treated with adjuvant endocrine therapy alone, endocrine therapy with or without other adjuvant treatments, and adjuvant radiotherapy alone. Similar subpopulation analyses were performed based on biological characteristics. In all of the subpopulation analyses, ICE3 recurrence rates were comparable to the corresponding literature comparator.

Importantly, the subpopulation aligned with the proposed indications, ICE3 patients ≥ age 60 treated with adjuvant endocrine therapy, a 3.08% recurrence rate was observed. The comparable PRISMA literature demonstrated a 2.82% recurrence rate. The recurrence rate is accordingly comparable to the current standard of care, demonstrating that cryotherapy is an acceptable effective alternative to lumpectomy.

9.1.2. Clinical Experience Benefits

The cryoablation procedure is an outpatient procedure performed using local anesthesia alone, without the need for general anesthesia and associated risks. The cryoablation procedure is performed in 30 – 120 minutes. While lumpectomy can be performed under local anesthesia, it is typically performed under general anesthesia with procedure times closer to 2 hours.

The ProSense™ cryoablation procedure is completed through a 3mm incision, with access only needed for the cryoprobe. Physicians often use the same incision used for tumor biopsy. Due to the minimally invasive nature, patients have a rapid return to full daily activities. In the ICE3 clinical study, 82.87% of the study population returned to full daily activities within 48 hours after the procedure following minimal side effects that did not require treatment intervention beyond post-procedure wound care. In comparison, lumpectomy requires an incision typically ranging from 25-50mm (~1-2 inches). Postoperative effects of pain, tenderness, swelling, infection, and bruising are reported for lumpectomy, consistent with surgical interventions with certain publications noting that 78.8% of patients experience post-surgical pain lasting six months or more (40%, moderate to worst possible) with 9% of patients still experiencing post-surgical issues 6 years after surgery[20].

ProSense™ presents a less invasive option compared to standard-of-care lumpectomy, further deescalating treatment of breast cancer.

The ability to perform the procedure with a minimally invasive approach and without the removal of breast tissue contributes to improved patient reported outcomes including reduced pain and improved cosmesis assessment. In the ICE3 trial, all patients tolerated the procedure with minimal

discomfort and no patients required pain medication other than over-the-counter pain relievers. This is a meaningful improvement as compared to lumpectomy, where post-operative pain control is key consideration in the treatment plan.

Additionally, a high percentage of patients and physicians were satisfied with cosmetic results:

- ≥97% of patients satisfied or very satisfied at 6 months – 5 years timepoints
- ≥96% of physicians satisfied or very satisfied at 6 months – 5 years timepoints

This is a significant improvement compared to patient-reported data presented in the literature following the current standard of care lumpectomy, with some studies reporting patient dissatisfaction with the appearance of their breasts following lumpectomy at rates of 30-40%[20, 21].

The minimally invasive nature of the procedure and the lack of removal of tissue also further reduces the potential for subsequent elective reconstructive surgeries and the potential risks associated with a second surgery.

9.1.3. Patient Journey Benefits

With lumpectomy, patients attend a pre-surgical screening in advance of the procedure and must receive medical clearance to undergo surgery. Patients must fast prior to the procedure and may need to adjust medication doses. Day of procedure, patients visit the radiology department for insertion of the localization device. This is followed by pre-surgical prep with the surgeon and anesthesiologist, and more waiting. Patients then undergo general anesthesia for the lumpectomy procedure, which usually lasts 2-3 hours while the tumor is surgically excised. Patients then must wait 2-3 hours in the recovery room while the anesthesia wears off. Side effects of the anesthesia include pain and nausea, and the patient must be driven home. Recovering at home after the procedure may require cleaning the excision site daily, managing surgical drains, wearing a compression bra, and limited movement for 1-2 weeks. In the end, 14-20% of patients may undergo re-excision after lumpectomy due to unclear margins, doomed to repeat the surgical process[54].

With cryoablation, patients attend a pre-procedure screening appointment in advance. On the day of procedure, patients can enjoy a healthy breakfast, there is no need for fasting as general anesthesia is not required. Patients are able to drive themselves to and from the cryoablation appointment, so there is no need to arrange transportation with a caregiver. The cryoablation procedure is 1 hour, takes place under local anesthesia, and the incision can be covered by a band-aid. No additional at home maintenance or limitations are required in recovery. A comparison of the steps of a lumpectomy procedure vs. a cryoablation procedure can be seen in Figure 9-1.

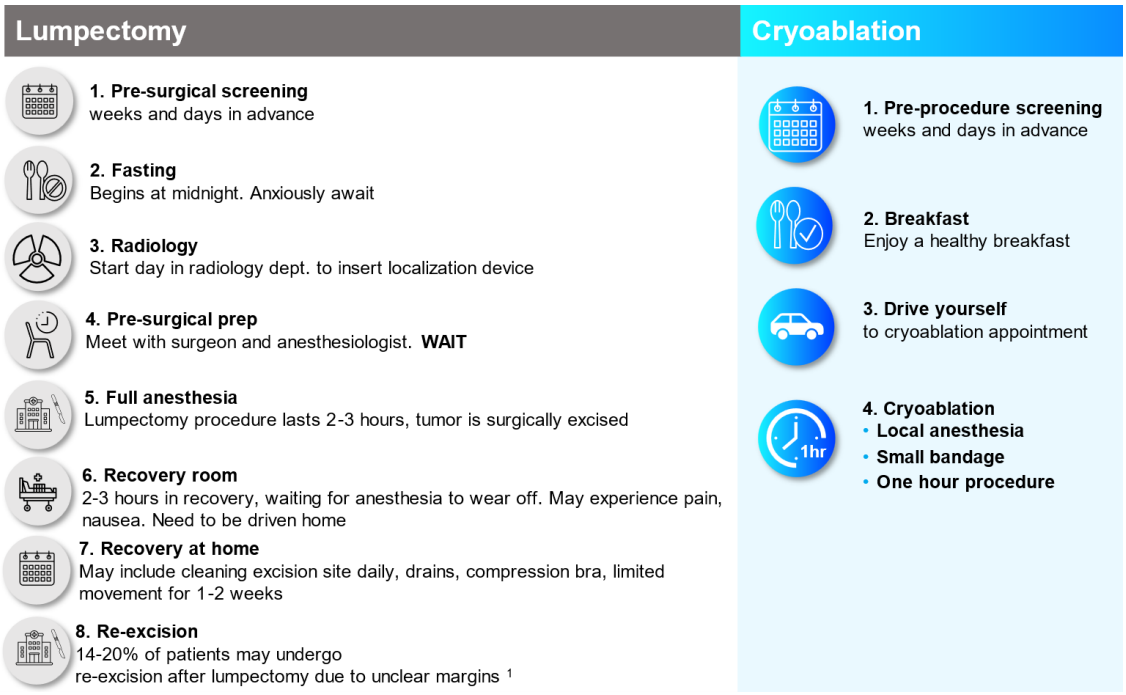


Figure 9-1: Comparison of Lumpectomy and Cryoablation Patient Journeys

As demonstrated in the ICE3 study, cryoablation offers meaningful quality of life benefits. 99.1% of patients in the primary analysis set and 97% of physicians who responded were 'satisfied' or 'very satisfied' with the breast cosmetic outcome at 5 years follow-up. Patients experienced near immediate recovery to normal activity following the cryoablation procedure, with an average 1-day (range 0-8 days) recovery time.

Cryoablation is able to offer disease control like lumpectomy, while eliminating the harsher aspects of the lumpectomy procedure. Cryoablation is able to provide improved quality of life benefits throughout the course of care.

9.2.Possible Risks

Risks to health posed by ProSense™ Cryoablation System when used for the treatment of low-risk breast cancer include risks that are common to all cryoablation systems, including ProSense™ Cryoablation System when used per the previously cleared indications. No new risks have been identified for use of the ProSense™ system in the treatment of breast cancer in addition to the typical risks associated with cryoablation devices and procedures. These risks include post-procedural pain, tenderness and swelling, frost injury, scarring or bleeding. In discussions with the FDA, the proposed indications for use are associated with risk of ineffective treatment of the life-threatening disease state. All risks identified have been, or will be, mitigated through already completed testing, planned testing, labeling, and other necessary general and special controls.

In addition the risks for treatment of low risk breast cancer patients are consistent with or less severe than the risk associated with standard of care lumpectomy treatments for the indicated population. All relevant risks to health are categorized and described below and are traced to general mitigation approaches.

Risk of Incomplete Ablation

Incomplete treatment is an adverse event which may occur due to device malfunction, aborted procedure poorly planned cryoablation procedure (lack of freezing time, early cryoprobe withdrawal), imprecise cryoprobe location, improper patient selection pertaining to the tumor size or allowed margins or any circumstances preventing sufficient tumor engulfment and proper completion of cryoablation procedure.

Incomplete treatment may be detected during cryoablation procedures or immediately after it, or at follow up visits (via imaging). Incomplete treatment may potentially lead to secondary risk of seeded tumors upon cryoprobe removal. Incomplete treatment may require additional cryoablation or other methods of treatment. If unrevealed, incomplete treatment may lead to residual malignancy and/ or death.

Risk of incomplete ablation is a known risk associated with the cleared ProSense™ Cryoablation System and is not a new or increased risk associated with the proposed indication for treatment of early stage, low-risk breast cancer. Of the 206 patients treated in the ICE3 clinical study, 3 (1.5%) were determined by the DSMB to have received incomplete treatment. The risk of incomplete treatment is mitigated by adherence to the instructions for use in patient selection ensuring that the tumor size can be encapsulated by an ice ball of 4cm, and monitoring the formation of the ice ball with ultrasound during the procedure to ensure that the margins of the tumor are encompassed. Subsequent imaging is available to the physician post treatment to evaluate cell death and shrinking of the tumor.

The validation activities and end user labeling related to this risk are unchanged from the cleared ProSense™ Cryoablation System.

The risks associated with incomplete treatment are consistent with the potential risks presented by lumpectomy in the cases of in incomplete margins.

Tumor Recurrence

Risk of tumor recurrence is a known risk associated with the cleared use of ProSense™ Cryoablation System. Tumor recurrence is also a primary risk of all breast cancer treatment, including cryoablation and breast conserving surgery. Based on the PRISMA Systematic Literature Review, there is a 3.53% risk of ipsilateral breast tumor recurrence following breast conserving surgery (lumpectomy) without radiotherapy and with or without endocrine therapy. However, it is important to note that risk of tumor recurrence in patients with low-risk breast cancer does not equate to risk to overall survival.

Tumor recurrence was specifically evaluated in the ICE3 clinical study by mammogram and physical examination at 6 months and annually thereafter for 5 years post-treatment. The estimated local IBTR recurrence rate for the primary analysis dataset was 4.3% at 5-years follow-up with 2-sided 95% confidence interval upper bound of 8.7%.

Death
Death is a known risk of breast cancer. Incomplete treatment of breast cancer or presence of more complex tumors including multi-focal disease may lead to residual malignancy and/or death.

Death due to any cause was collected and evaluated in the ICE3 clinical study. At the time of the final data analysis, the ICE3 clinical study had an overall survival rate of 88.6% at 5 years, with most deaths due to pre-existing comorbidities or unrelated to study or treatment. Overall survival rate exceeds the actuarial survival rate for people age 74, the mean age of the ICE3 study population.

An evaluation of breast cancer survival, including death due to breast cancer or unknown causes, resulted in a disease-free survival estimate of 96.7%. Two (2) patients died as a result of breast cancer (1.03%).

Procedure-Related Adverse Events
Procedure-related adverse events are a known risk of breast cancer treatment, including cryoablation and breast conserving surgery. Cryoablation procedure-related risks occur at a much lower rate and severity as compared to breast conserving treatment (lumpectomy) due to cryoablation's minimally invasive nature.

Procedure-related risks that were observed in the ICE3 clinical study are common to all cryoablation systems, including ProSense™ Cryoablation System when used per the cleared indications. No risks have been identified in addition to the typical risks associated with cryoablation devices and procedures.

Scarring
One patient reported breast twitching, one reported dimpling, and one reported tethering. All three events were reported within the first year of treatment and were mild in severity. All events resolved without residual effect.

Lumpectomy scars are usually small, typically 1-2 inches. Scars take time to settle after the procedure. The appearance of scars take 2-3 months to diminish, while redness and pigmentation can take 9-12 months to fade. Most scars become flat and pale after 12 months. Every surgery carries the risk of developing unfavorable scars. After oncologic breast surgery, 18% of the women experience their breast scars are worse than expected, and about 10-30% are dissatisfied with the appearance of their scar[26, 27].

Infection
There were no reports of procedure-related infection in the ICE3 study.

The literature report rates of infection of 0.5%-1.4% following lumpectomy[2, 19, 25, 33-35].

Bleeding
There were no reports of procedure-related bleeding. 57 patients (29.4%) experienced bruising post-procedure. Majority of the bruising events were mild (78.9%). All events occurred within one month of treatment and resolved without residual effect.

The literature report need for intraoperative or post-operative transfusion in 0.07% of patients treated with lumpectomy[33].

Nerve Damage
There were no reports of procedure-related nerve damage.

A systematic review and meta-analysis reported neuropathic pain in 31% of patients following breast-conserving surgery[41].

Hypothermic Damage to Nearby Tissue
Four patients (2.1%) experienced frost injury post-procedurally; all were reported within 1 month of treatment and were mild to moderate in severity. These four events resolved without residual effect.

Post-procedural Pain, Tenderness, Swelling
19.1% of patients experienced mild to moderate pain and 18.6% of patients experienced mild to moderate edema. Postoperative pain, tenderness, and swelling generally resolved within days without treatment.

Comparison to lumpectomy rates reported in the literature: 78.8% of patients treated with lumpectomy experienced post-surgical pain lasting six months or more (40%, moderate to worst possible)[20].

9.2.1. Risk Mitigation

The ProSense™ Cryoablation System qualifies as a Class II device based on its risk profile. No new risks have been identified in addition to the typical risks associated with cryoablation devices and procedures.

In discussions with the FDA, the proposed indications for use are associated with risk of ineffective treatment of the life-threatening disease state. Importantly, this risk is mitigated by the following:

- Tumor and ablation margins are evaluated real-time by ultrasound at the time of treatment.
- Patients undergo routine (annual) screening for breast cancer recurrence.
- All alternate treatment methods are available to the patient in the case of incomplete treatment or recurrence.

- Any uncertainty of long-term recurrence is mitigated by routine screening and treatment follow-up.

All risks identified have been, or will be, mitigated through already completed testing, planned testing, labeling, and other necessary special and general controls. The mitigation measures proposed in the De Novo submission support that general and special controls can provide reasonable assurance of safety and effectiveness and demonstrate that the probable risks to health are outweighed by probable benefits associated with the use of ProSense™ Cryoablation System.

9.3. Summary of Benefit Risk Comparisons Relative to Standard-of-Care Lumpectomy

The demonstrated treatment, clinical experience, and quality of life benefits translate to significant advantages relative to the standard of care lumpectomy surgery**.** These advantages include clinical advantages derived from a less invasive procedure, quality of life and cosmetic benefits, and minimized risk of adverse events.

The data presented throughout this submission supports that there is a reasonable assurance of safety and effectiveness for the device, and that the probable benefits outweigh the probable risks to patients

Table 9-1 provides a summary of the benefits and risks of the ProSense™ cryotherapy treatment for low risk breast cancer in comparison to lumpectomy, where benefits are shaded in green, and risks are shaded in red in **Table 9-1**.

Table 9-1: Benefit and Risk Considerations of Cryotherapy for Breast Cancer versus Standard of Care Lumpectomy

Risks & Considerations	Lumpectomy	Cryotherapy with ProSense™
Clinical Experience	General (75%) or occasionally local anesthesia[15, 16]	Only local anesthesia
	Surgery prep + 1-2-hour procedure + recovery from anesthesia[17]	30 min - 2 hours[19]
	Up to 2-week recovery for normal activities[18]	Near immediate recovery to normal activity with possibly mild pain/swelling for a few days. 1.7 days recovery time in ICE3
Quality of Life (QOL)	30-40% Dissatisfied with appearance of breasts[20, 21]	Satisfactory cosmetic result (95%)[24]; High percentage of patients and physician responders satisfied with cosmetic results (99.1% of patients and 97% of physicians 'satisfied' or 'very satisfied' at 5 years in ICE3) and minimal scaring.
	60% less likely to believe they were healthier and are more likely to fear recurrence if they have asymmetric breasts[22]	
	Increased depression (43% of patients) [22]	Significant improvement in distress thermometer at 6M relative to baseline in ICE3 clinical study
	Reduced feeling of sexual attractiveness[22, 23]	
	Breast reconstruction associated with reduced, short-term QOL[1]	No breast reconstruction needed
Adverse Events/Side Effects*	Surgical Scars[24] and Breast disfigurement/asymmetry[20, 21] 18% of the women experience their breast scars are worse than expected, and about 10-30% are dissatisfied with the appearance of their scar [26, 27]	Minimal scarring, no disfigurement
	Infection (0.5%-23.5%)[2, 19, 25, 33-38]	No observations of procedure-related infection in ICE3 clinical study
	Bleeding (resulted Intraoperative or post-operative transfusion) (0.07%)[33] Hematoma (3.7%)[37]	No observations of procedure-related bleeding in ICE3
	Nerve damage[1]	Less invasive/less tissue damage but nerves near ablation target may still be damaged No observations of nerve damage in ICE3

Risks & Considerations	Lumpectomy	Cryotherapy with ProSense™
	Neuropathic pain in 31% of patients following breast-conserving surgery [41]	
	Damage to nearby tissue	Hypothermic damage to nearby tissue possible Four mild - moderate burn occurred in ICE3 indicated population (2.1%)
	Postoperative effects may linger for months: Pain, Tenderness, Swelling, Bruising[19, 21, 42, 43]	Postoperative pain, tenderness, swelling, bruising generally resolved within days without treatment
	9% of patients still experienced post-surgical issues 6 years after surgery[20] 78.8% experienced post-surgical pain lasting six months or more (40%, moderate to worst possible)[20]	No surgery
	Risk of incomplete tumor removal[44, 45]	Risk of incomplete ablation Theoretical risk of seeded tumors upon cryoprobe removal if incomplete ablation
Follow-Up, Recurrence Mitigations	Adjuvant therapies: Radiation Therapy Endocrine Therapy (ER+) Chemotherapy Follow-Up: History/Physical examinations every 3-6 months for first 3 years, 6-12 months for year 4-5, annually thereafter. Mammograms 1 year after initial mammogram, 6 months after completing radiation therapy, and annually thereafter.	Likely identical recommendations to lumpectomy follow-up procedures and adjuvant therapies. Cryolesion may persist for 1 month and make physical examination and breast imaging difficult to interpret.
	5-year recurrence estimate of 2.82% (95% CI: 1.62% to 4.83%) based on PRISMA meta-analysis with adjunctive endocrine therapy. 5-year recurrence estimate of 2.3% (95% CI: 1.2% to 4.1%) Overall survival 84.3% identified in PRISMA literature (with adjunctive endocrine therapy) and 97.2% (90% CI, 95.9 to 98.4) in LUMINA.	5-year recurrence estimate is low (3.7% in ICE3 indicated population treated with adjuvant endocrine therapy) No regional recurrence in ICE3 Overall survival 89.5% in ICE3 indicated population

Risks & Considerations	Lumpectomy	Cryotherapy with ProSense™
	Disease Free survival 94.7%-99.7% identified in PRISMA literature (with adjunctive endocrine therapy) and 97.3 (90% CI, 95.9% to 98.4%) in LUMINA. Reoperation in up to 70% of lumpectomies[44].	Disease Free Survival 95.3% indicated population Distant recurrence rate is low (1.8% rate estimate in ICE3)

* 13-year (2003-2017) adjusted smoothed trend analysis of Surgical Complication Rates (lumpectomy), in nationwide breast cancer surgeries, showed no significant change

10. CONCLUSIONS

As described in detail in these materials, data from the company's multicenter ICE3 clinical study support the safety and effectiveness of the ProSense™ Cryoablation System for treatment of women aged 60 and over with early stage, low risk breast cancer receiving adjuvant endocrine therapy. The data further demonstrate that this minimally invasive treatment option presents improved benefits for the indicated patients and fewer risks compared to the standard of care treatment and therefore can provide an appropriate alternative minimally invasive treatment option for patients to consider in conjunction with their doctors.

- **Data from the ICE3 Clinical Study Demonstrate a Reasonable Assurance of Effectiveness and Safety for ProSense™ for Treatment of Low Risk Breast Cancer**

  The ICE3 clinical study by IceCure Medical is a multicenter (19 sites in the United States), prospective, single arm, nonrandomized clinical trial using cryoablation to remove malignant breast cancer tissues in women aged 60 and over. The ProSense™ Cryoablation System overall study cohort outcomes demonstrate >95% of patients are recurrence free through 5-years follow-up, nearly 97% when treated per the proposed indications for use.

  - **Effectiveness.** The ProSense™ Cryoablation System overall study cohort outcomes demonstrate >95% of patients are recurrence free through 5-years follow-up, nearly 97% when treated per the proposed indications for use.
  - **Safety.** Cryoablation procedure related adverse events (edema, bruising, hematoma), hypothermic damage to nearby tissue and postoperative pain, occurred acutely and the majority of events were mild in severity. These procedure-related events are common to all cryoablation procedures and are less severe than the standard of care lumpectomy surgical-procedure related risks.

    Breast cancer related risks include risk of incomplete treatment, risk of recurrence and risk of breast cancer related death and are common to all breast cancer treatments. Less than 5% of ICE3 patients experienced tumor recurrence. Two (2) patients died as a result of breast cancer (1.03%). Risk of incomplete treatment is sufficiently mitigated through real-time visualization of tumor ablation during treatment and recurrence or residual tumor is sufficiently identified through routine annual mammography. All alternate treatment methods are available to the patient in the case of incomplete treatment or tumor recurrence.
  - **Benefit/ Risk.** Cryoablation is a minimally invasive alternative to breast conserving surgery (BCS) that reduces morbidity along with providing benefits to the patient with regard to the psychosocial and cosmetic impact of breast cancer therapy. The minimally invasive nature of treatment with ProSense™ allows for treatment without the need for general anesthesia, shorter recovery times, and improved cosmesis of the scar site and also due to lack of excision of breast tissue. Patients and physicians reported significant quality of life benefits with use of ProSense™ Cryoablation System in the ICE3 study: patients experience near immediate recovery to normal activity (median 1 day recovery time) and 99.1% of patients and 97% of physicians who responded were 'satisfied' or 'very satisfied' with the breast cosmetic outcome at 5 years follow-up.

- **Comparison of ICE3 Outcomes to SOC Lumpectomy Confirms Positive Benefit/ Risk**

  The ProSense™ Cryoablation System demonstrated benefit of treatment of early-stage breast cancer in patients with the lowest risk for recurrence with similar effectiveness to standard-of-care and significantly fewer and less severe adverse events and risks. Sub-group analyses evaluating outcomes based on adjuvant treatment or biologic characteristics confirmed the favorable IBTR outcomes of patients treated with ProSense™. In all analyses, ICE3 patients treated with cryoablation using ProSense™ experienced a similar rate of recurrence as patients treated with lumpectomy, while avoiding risks and side effects of lumpectomy, including those associated with general anesthesia as well as scarring, infection, bleeding, damage to nearby tissue, pain and swelling that may last for months, nerve damage, poor cosmesis and depression.

- **Cryotherapy with ProSense™ Provides Clinically Appropriate De-escalation of Breast Cancer Treatment to Minimize Patient Risks and Improve Quality of Life During Treatment**

  Existing breast cancer treatment options, including radiotherapy and surgical resection, are associated with health risks and may have a detrimental effect on the quality of life of the patient. For decades, the clinical community of breast cancer surgeons and treatment providers has pushed for de-escalation of care to lessen the morbidity of treatment to patients with low-risk breast cancer. Early stage, low risk breast cancer patients are most appropriate for further de-escalation of care to eliminate the need for surgery and associated tissue resection and treatment-related risks. Cryoablation offers a needed alternative to surgical resection.

The ProSense™ Cryoablation System is FDA-cleared technology with an established safety and effectiveness profile for the destruction of cancerous tissue. The totality of evidence from the ICE3 5-year study, prior studies of cryoablation and other clinical experience with ProSense™, and comparison to outcomes of standard-of-care published in the literature demonstrate safety, effectiveness, and positive benefit/risk profile of ProSense™ Cryoablation System for the treatment of early-stage, low-risk breast cancer.

11. APPENDICES

A. Additional Detail on Reason for Deaths in ICE3 Study
B. ICE3 Full Safety Results
C. PRISMA Systematic Review and Meta-Analysis
D. Publications on use of ProSense™ Cryoablation System in Treatment of Breast Cancer
E. ProSense™ Cryoablation System Draft Instructions for Use
F. Disease Outcome Definitions in ICE3 Protocol
G. Supplemental Analyses of ICE3 Sub-Populations and Literature Comparators
H. Differences Between FDA and IceCure Analyses

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