Appendix H –Differences between FDA and IceCure Analyses

1. Censoring

In IceCure's data analysis, the primary endpoint, ipsilateral breast tumor recurrence (IBTR) rate, was pre-specified to be estimated using the Kaplan-Meier (KM) method. FDA has stated that the Cumulative Incidence Function (CIF) method to calculate the primary endpoint outcome primarily be relied upon and has presented the primary endpoint according to this method.

IceCure acknowledges FDA's questions regarding two analysis details used in the efficacy analysis of the ICE3 clinical trial: the use of Kaplan-Meier (KM) plots instead of Cumulative Incidence Figures (CIF), and the handling of censored observations for subjects who did not experience an IBTR event while on study, specifically subjects who died prior to a diagnosed ipsilateral breast tumor recurrence IBTR event.

IceCure presented analyses of time to event data such as IBTR and overall survival using the KM product-limit method. IceCure believes that the KM method is preferable in this context as it is the pre-specified method. It is also the most commonly used method for handling time to event data in literature and will be most recognized and most easily interpreted by the panelists.

For standard time to event data where there is only one event which either occurs or does not occur (and is thus censored) the CIF approach is very close to the complement of the KM survival estimate. Generally, the two methods will only differ when the analysis uses a competing risks (CR) analysis approach.

IceCure has conducted several sensitivity analyses to explore the impact of the various analysis methods discussed above on the primary efficacy conclusion of IBTR, to assess the impact of these analysis choices on the conclusions. The results of these sensitivity analyses are presented in **Table 1** and are summarized below.

The impact of using a KM analysis vs. a CIF analysis is minimal, as can be seen by comparing column 1 (KM using IceCure censoring) and column 3 (CIF using KM censoring [i.e. not competing risks approach] with patients censored at the time of death).

The impact of the death censoring approach is also minimal, as can be seen by comparing column 1 (KM using IceCure censoring) and column 2 (KM using censoring at time of death). In "IceCure censoring", 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.

Table 1. Sensitivity analyses for effect of various analysis methods on primary efficacy analysis of IBTR in the ICE3 trial

	KM (IceCure censoring)†	KM (Censored at time of death) †	CIF (KM) (Censored at time of death)†	CIF (Competing Risk*) (Censored at time of death) †
Primary Analysis Population (n=194, n=7 recurrence) 5-Year IBTR Rate	4.3% (2.1%-8.7%)	4.6% (2.2%-9.5%)	4.6% (2.0%-8.9%)	4.2% (1.9%-8.1%)

†'IceCure censoring' refers to 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.
*Competing risk is death from any cause

The upper bound of each of these confidence intervals is below 10%, indicating that the primary endpoint was met using any censoring method. In further exploring the robustness of the efficacy analysis results to the choice of censoring time is due to the fact that, in practice, the vast majority of censored observations were censored the same way as the FDA preference of using the date of the most recent known assessment visit. This is illustrated by the summary statistics of the difference between the two approaches. Of 194 subjects, 164 (84.5%) have a difference of within +/- 1 month, with the difference for many subjects being 0 months. The median difference is 0 months, the mean difference is 3 months, and the range is -8.6 months to 58.4 months; refer to the histogram showing the distribution in **Figure 1**.

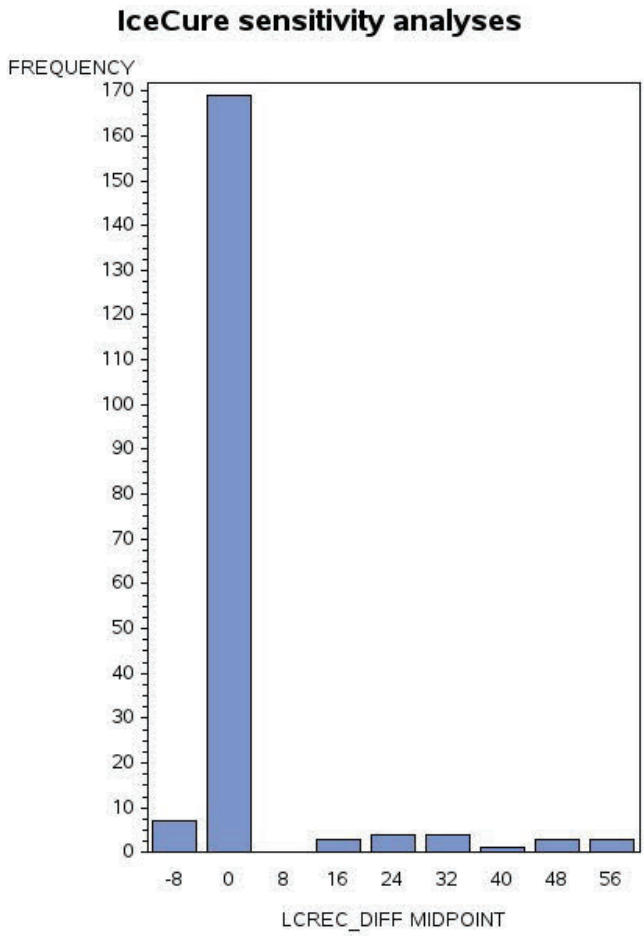

Figure 1. Histogram of the difference in event and censoring times between IceCure and FDA censoring method

An additional concern raised by FDA is the treatment of subjects who died as being censored through 60 months for estimating the time to IBTR. To address this concern, we have implemented a competing risks analysis which treats deaths due to any cause as a competing event rather than as a censoring event for the estimation of the time to IBTR. The impact of this analysis approach is minimal, as can be seen by comparing column 1 (KM using IceCure censoring) and column 4 (CIF using competing risks with IceCure censoring).

In summary, these sensitivity analyses reveal that the overall conclusion of the analyses is largely unchanged regardless of which censoring approach or analysis methodology is used, demonstrating that the results of this analysis are robust to the particular censoring choice and analysis method used. We believe that these sensitivity results show that, while FDA has raised concerns regarding theoretical risks of some of IceCure's statistical analyses being biased, when these risks are assessed, the data are robust to them as using alternative analysis choices does not appreciably change the conclusions of the trial with respect to 5-year IBTR.

2. Number of Recurrences

As pre-specified in the ICE3 protocol, diagnosis of a first breast cancer recurrence or second primary cancer diagnosis is 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 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.

IceCure observed, based on pre-specified protocol definitions and DSMB recommendation, a total of 6 recurrence events through month 60 and one additional (1) recurrence event that occurred in month 63 in the primary analysis set (N=194), resulting in 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%.

FDA's analysis of the primary endpoint in the Full Analysis Set resulted in an IBTR rate of 8.7% (95% CI: 5.2-14.5%) based on the cumulative incidence of local recurrences identified in 14 of the 206 treated subjects. FDA's analysis represents the worst-case recurrence rate.

FDA's total number of recurrence events (14/206) includes:

- 7 recurrence events observed in the ICE3 study in the primary analysis set (N=194)
- 2 additional events considered to be recurrence by FDA that were not considered to be recurrence by the ICE3 DSMB in the primary analysis set (N=194)
- 5 recurrence events observed in 12 patients excluded by DSMB (N=12)

The DSMB excluded a total of twelve (12) patients from the primary analysis set, nine (9) due to deviation from inclusion/ exclusion criteria and three (3) incomplete treatment.

- Patients excluded due to incomplete treatment experienced extremely short treatment protocol (short treatment cycle times 1 min 22 sec – 2 min 24 sec) or single freeze cycle.
- Patients excluded due to deviation from inclusion/ exclusion criteria were due multi-focal disease, DCIS or tumor size larger than 1.5cm. Based on prior studies, 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.

None of the three patients with 'incomplete treatment' had recurrence. Of the nine (9) patients excluded due to multi-focal disease, DCIS or large tumors, five (5) recurred. Based on prior

studies, patients with multi-focal disease, DCIS and large tumors are known to have greater risk of recurrence. This population is not the focus of ICE3 and were therefore excluded from the primary analysis set by the DSMB. Similarly, these patients do not meet the proposed indication.

Additionally, FDA included two additional cases that did not meet the ICE3 protocol's definition of recurrence. Importantly, 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.

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 viewed in 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 5-year IBTR rate in the indicated population.

The 5-year 'freedom from recurrence' rates of these populations is shown in **Figure 2**. As shown below, the indicated population experienced a <3% rate of IBTR.

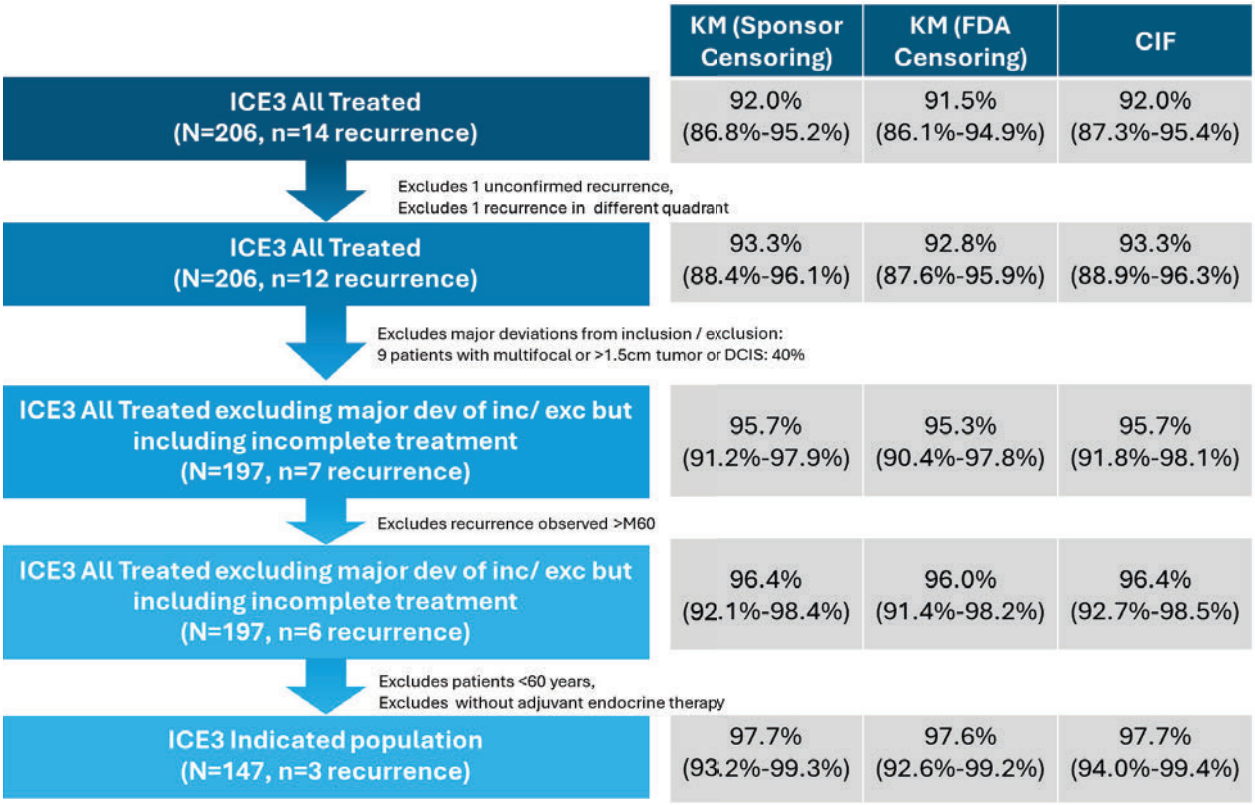

Figure 2. 'Freedom from Recurrence' at 5-Years Follow-up in Various ICE3 Populations using Various Analysis Methods

3. Safety Events

Drawing from the ICE3 protocol's definition of AE relationship, DSMB recommendation, and regulatory and clinical precedent set by recent clinical drug trials, IceCure believes that FDA's expectation that local recurrence be classified as 'Serious adverse events, device related' is clinically inappropriate and lacks consistency with regulatory and clinical precedent.

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.[1,2] Cancer cells can acquire new genetic mutations over time which may resist the effect of adjuvant therapy. Cancer cells may have spread to other parts of the body before or during the initial treatment. Even if the primary tumor is removed or treated, these metastatic cells can eventually grow into new tumors, causing a recurrence. This is a known risk common to all breast cancer treatments and is considered to be a natural course of the disease.

The DSMB reviewed all cases of recurrence as adverse events, per FDA request, and the DSMB classified three (3) cases of local recurrence and one (1) case of distant metastases as possibly related to the study device due to suboptimal treatment for a total of four (4) serious, related adverse events in a total of three (3) subjects ((b) (6) experienced local recurrence and metastatic breast cancer). Two patients received suboptimal treatment (one with 5-minute treatment cycles and one with 7-minute treatment cycles resulting in iceball sizes <35mm at the end of the 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.

The ICE3 study protocol defines the relationship of the adverse events to the study device 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 significant 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 much more likely alternative etiology.

Local recurrence stems from the presence of primary breast cancer before the initiation of treatment. The ProSense™ device is intended to destroy breast tumors, thereby treating cancer; however, the primary etiology remains the primary cancer. Furthermore, there is no significant temporal correlation, as the cryoablation procedure lasts less than an hour with no permanent

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[1] Whelan TJ, Smith S, Parpia S, Fyles AW, Bane A, Liu FF, et al. Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. N Engl J Med. 2023;389(7):612-9.

[2] Fattahi S, Mullikin TC, Aziz KA, Afzal A, Smith NL, Francis LN, et al. Proton therapy for the treatment of inflammatory breast cancer. Radiother Oncol. 2022;171:77-83.

implant, while tumor recurrence was observed to manifest much later during the follow-up period (>2 years post-treatment).

This perspective aligns with the clinical protocol documented in NCT02107703 "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without LY2835219, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer" approved in April 2014. The multicenter, randomized, double-blind, Phase 3 trial compared an investigational breast cancer treatment drug, LY2835219 plus fulvestrant, to a placebo plus fulvestrant in women with breast cancer. Endpoints included overall survival rates, pain and symptom burden endpoints, and safety and tolerability endpoints related to AE rates.

- Section 10.3.1. (pg. 46) of the NCT02107703 protocol states, "**Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect."**
    - The objective of the ICE3 is to evaluate the safety and efficacy, in terms of Ipsilateral Breast Tumor Recurrence (IBTR) rate of cryoablation using IceCure medical's ProSense™ device. As noted above, lack of intervention effect is not an adverse event related to the device, but rather related to the question of intervention effect being evaluated. Per FDA recommendation, all cases of recurrence and distant metastases are considered as serious adverse events.

- Further Section 10.3.1.1 (page. 48) of the protocol states, **"Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug."**
    - The DSMB evaluated all AEs and the recurrence cases in the ICE3 trial and did not classify ALL cases of local recurrence and cases of distant metastases as device related adverse events; instead, they classified events on a case-by-case basis and determined that a total of four (4) adverse events in a total of three (3) subjects (b) (6) (b) (6) experienced local recurrence and metastatic breast cancer) were serious and related to the study treatment.

Similarly, the clinical protocol published for NCT03167619 "Phase II Multicenter Study of Durvalumab (MEDIA4736) and Olaparib in Platinum Treated Advanced Triple Negative Breast Cancer" studied a population of women with triple negative breast cancer.

- Section 5.8 (pg. 64) provided insight into the handing of disease progression, **"Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. SAEs due to progression will be reported and classified as unrelated to treatment."**

Local recurrence in the ICE3 trial is most appropriately classified as a serious adverse event unrelated to the treatment (cryoablation). Conservatively, the DSMB classified four (4) events in

three (3) subjects as possibly related to treatment due to suboptimal treatment, not performed according to the study protocol.

The alignment with established clinical protocols, such as NCT02107703 and NCT03167619, underscores the appropriate classification of local recurrence as unrelated to the ProSense device in the ICE3 trial.

4. SLR

Inclusion Criteria – Adjuvant Therapies

This section details the differences between FDA and IceCure Medical's System Literature Reviews (SLR) for comparison to the results of the single-arm ICE3 study.

A key difference between FDA and IceCure Medical's SLRs was the inclusion of articles with use of specific adjuvant therapies. FDA included use of adjuvant radiotherapy, while IceCure explicitly excluded use of adjuvant radiotherapy.

IceCure does not recognize the local recurrence rate of BSC with adjuvant radiotherapy to be an adequate comparator to the ICE3 study for two primary reasons: (1) the conclusions of recently published clinical trials (i.e., CALGB 9343, PRIME II) and guidelines (i.e., NCCN, EUSOMA, NICE, St. Gallen International Consensus Guidelines) to de-escalate care, recommend omission of adjuvant radiotherapy in patients ≥65 receiving adjuvant endocrine therapy for low-risk tumors and (2) majority of the ICE3 patient population (85.6%) did not receive radiotherapy per physician discretion.

Use of adjuvant radiotherapy following breast conserving surgery (lumpectomy) has a well-characterized effect on local recurrence rates. Randomized, controlled, peer-reviewed studies, CALGB 9343 and PRIME II both concluded that omission of the use of adjuvant radiotherapy was associated with an increased incidence of local recurrence, but had no detrimental effect on distant recurrence or overall survival.[3,4,5]

Both FDA's and IceCure's SLR included used of endocrine therapy. Adjuvant endocrine therapy following breast conserving surgery has a well-characterized effect and is associated with decreased local recurrence in patients with hormone receptor positive tumors. In the ICE3 study, the majority (78.8%) received adjuvant endocrine therapy. Therefore, the inclusion criteria of Quadrantectomy is a breast-conserving surgery that removes a quarter of the breast, including the tumor, a 2- to 3-cm margin of healthy tissue, and sometimes the pectoralis fascia and overlying

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[3] Kunkler, I. H., et al. (2015). "Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial." Lancet Oncol 16(3): 266-273.

[4] Kunkler, I. H., et al. (2023). "Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer." N Engl J Med 388(7): 585-594.

[5] Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, Muss HB, Smith BL, Hudis CA, Winer EP, Wood WC. 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 1;31(19):2382-7. doi: 10.1200/JCO.2012.45.2615.

skin. This surgical technique involves greater tissue resection than lumpectomy. The majority of early-stage tumors do not necessitate a quadrantectomy; this technique is not standard of care treatment for low-risk, early-stage breast cancer.[6]

IceCure's SLR allowed breast conserving surgery (lumpectomy) with or without adjuvant endocrine therapy.

	FDA's SLR	IceCure's SLR
Surgical Procedure	Lumpectomy/Quadrantectomy	Lumpectomy
Adjuvant Radiotherapy	Included	Excluded
Adjuvant Endocrine Therapy	Included	Included

Weighting Criteria in the Meta-analysis

Both FDA's and IceCure Medical's SLR's utilized random effects meta-analysis models to account for between-study heterogeneity. A key difference in the meta-analysis methodology was the weighting scheme employed. FDA's SLR utilized inverse-variance weighting, which assigns the largest weight on the study with the least variance. In this context, this method of weighting placed the largest weights to the two studies with the least number of events as a result of the method FDA used to assign weights to the studies with no observed events. ICECURE contends that this method of weighting is concerning as it would weight studies based on outcome, placing the greatest weight on studies with outcome of no recurrence. In IceCure's review of FDA's meta-analysis methodology, it was observed that the two zero event studies (Soyder 2013 and Ciervide 2018) provide nearly 70% of the weight to the meta-analysis estimate. This is very concerning given the two studies of 16 patients and 23 patients, respectively, make up 1.89% of the total meta-analysis sample size (1,372) and both studies were rated by FDA as having serious risk of bias. ICECURE believes that using the same weighting system for these two studies would more accurately balance their influence in the study. ICECURE additionally notes that in FDA's sensitivity analysis, the impact of excluding either of these small studies results in nearly doubling the synthesized treatment estimate, which again highlights the over-reliance of the synthesized effect on these very small studies.

FDA's meta-analysis of patients without radiation includes a 500 patient study (Whelan 2023) with a 2.3% IBTR rate and a 16 patient study (Soyder 2013) with a 0% IBTR rate.[1,7] The meta-analysis rate of these two studies was determined by FDA to be 0.49% (0.00-34.99%).

To achieve this meta-analysis rate, the outcome of the 16 subjects in Soyder (2013) was weighted to be equivalent to the 1850 subjects in Whelan (2023). From this perspective, relative to sample size, the 16 subjects are given 116 times the weight they would have based on sample size.

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[6] Czajka ML, Pfeifer C. Breast Cancer Surgery. [Updated 2023 Feb 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553076/

[7] Soyder A, Ozbaş S, Koçak S. Locoregional Recurrence and Survival Rates after Breast-Conserving Surgery and Hormonal Therapy in 70-Year-Old or Older Patients with Stage I or IIA Breast Carcinoma. Breast Care (Basel). 2013 May;8(2):134-7. doi: 10.1159/000350776.

Weighted based on sample size, the estimate would be roughly 2.23% (or essentially no different than the Whelan 2023 paper on its own).

FDA's draft guidance "*Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry*" (2018) states on (Section V.B.):

> *"…Sparse data resulting from rare safety outcomes pose particular problems in a meta-analysis. The statistical methods chosen for the analysis should perform well when the number of outcome events is very small in one or more of the component trials or in one or more treatment groups within a trial. Some commonly used methods perform well when there are ample events, but not so well when events are sparse (Bradburn, Deeks et al. 2007).* ***For example, inverse variance weighting involves estimating risk with a weighted estimate of trial results, where weights are computed as the inverse of the trial level variance estimates. With sparse data, the estimated variances may not be well-determined, resulting in an unstable risk estimate. If some of the component trials have no events, the choice of methods is even more limited****."*

IceCure Medical's SLR employed a prespecified down weighting approach based on congruence of the studied patient population with the intended patient population in the ICE3 study. Articles similar, but not identical, to the intended patient population with respect to tumor characteristics were down-weighted in the IceCure meta-analysis.

This approach was prespecified due to the assumption that real world population would not be perfectly homogenous, and this approach was outlined in a SLR protocol submitted to FDA. In IceCure's SLR the random effects meta-analysis model was repeated with the number of subjects contributing from the applicable studies (i.e. the number at-risk) decreased by 25% (25% = 100% minus the lower bound of the P1(b) criteria)) (refer to weighting criteria in Appendix G). In other words, for each study reported as having "sufficient" (instead of "ideal") alignment with the ICE3 study instead of ideal (P1(b) instead of P1(a)), 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.

Finally, note that FDA's meta-analysis modelled recurrence as an odds ratio using only the data available at 5 years, whereas ICECURE's approach modelled recurrence for each year through 5 years. Weighting in a survival curve context is nuanced as the variance is a function of both the total number of events (i.e., the underlying event prevalence) and the number of subjects at risk for the given time-period, with the known behavior of the Greenwood variance estimator being non-decreasing over time as a study accumulates more events and more censored observations. Due to the multi-factor aspect of impacts on the variance, IceCure believes that weighting by sample size is preferable as it assigns more weight to studies which utilized more subjects. As noted above, the FDA's meta-analysis guidance cautions to carefully consider the specific methods used in a sparse event setting such as this low-risk population.

Article Section for the Pooled Meta-analysis

Appendix G of FDA's Executive Summary states that "*Only five of the 25 eligible studies had data that were suitable for pooling in a meta-analysis, due to slight heterogeneity in study population characteristics such as partial population use of adjuvant chemotherapy or tumor size modestly >2cm*.", but the exclusion criteria for each article are unclear. Moreover, these articles are cited in FDA qualitative synthesis as evidence. The selection process resulting in the five articles appears to be inconsistently applied. For example, Soyder 2013 was included in the meta-analysis despite unknown HER2 status in the studied population. However, other larger studies, including CALGB 9343 (Hughes 2013), were excluded from FDA's meta-analysis for this reason.

As another example of inconsistency in FDA's methods, Kunkler 2015 (PRIME II) published an RCT investigating the use of adjuvant radiotherapy and impact on outcomes. Two treatment arms were enrolled:

- *(1) Lumpectomy with adjuvant endocrine therapy and with radiotherapy*
- *(2) Lumpectomy with adjuvant endocrine therapy and without radiotherapy*

Patient demographic information and tumor characteristics were near identical between groups (See Table 1 and Table 2 of Kunkler 2015) as expected in a randomized controlled trial. After median follow-up of 5 years (IQR 3.84–6.05), ipsilateral breast tumor recurrence was 1.3% (95% CI 0.2–2.3) in women assigned to whole-breast radiotherapy and 4.1% (95% CI 2.4–5.7) in those assigned no radiotherapy (p=0·0002). However, FDA's SLR only included the radiotherapy-treated group (treatment arm (1)) in their meta-analysis. It is unclear why the data from the other randomized treatment arm (2) was not considered. As noted above, a cohort with 100% of patients receiving adjuvant radiotherapy is not an appropriate comparator to the ICE3 study as this is not reflective of standard-of-care treatment in early-stage, low-risk breast cancer and is not representative of >85% of the ICE3 study population.

Conversely, IceCure Medical included all SLR included studies in the meta-analysis.

IceCure Medical reviewed FDA's 25 selected articles against IceCure's defined inclusion/exclusion criteria, finding that fourteen (14) articles were excluded from IceCure's SLR due to radiotherapy use, two (2) were excluded due to quadrantectomy, and two (2) for small sample size and insufficient follow-up. Refer to **Table 2** for reason for exclusion or inclusion. Five (5) studies identified in FDA's SLR were included in IceCure's SLR. Two (2) studies in FDA's SLR met the inclusion/exclusion criteria of IceCure's SLR but were not identified in search methods. The 5-year IBTR recurrence rates in these two studies are higher than the rate reported in IceCure's meta-analysis and inclusion would be expected to have no impact or increase the overall meta-analysis rate.

Table 2. FDA SLR Included Studies

	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
1	**Abdelsattar (2020)**[8]	117	1.9% (IORT) 0% (WBRT)	Yes	No	
2	**Arvold (2011)**[9]	905	0.8% (95% CI, 0.4%-1.8%)	Yes	No	
3	**Benitez (2007)**[10]	36	0% WLE alone = 1.9% per annum	Yes	No	
4	**Blamey (2013)**[11]* **BASO II Trial**	1135	Radiotherapy alone = 0.7% per annum Tamoxifen only = 0.8% per annum	Yes for treatment group	No	FDA excluded from their meta-analysis due age. The study participants were mean age 57.
5	**Carleton (2021)**[12]	2109	1.2%	57.8% of patients	No	

[8] Abdelsattar JM, McClain K, Afridi FG, Wen S, Cai Y, Musgrove KA, Bailey K, Shaikh PM, Jacobson GM, Marsh W, Lupinacci K, Cowher MS, Jenkins HH. Intraoperative Radiation Therapy Versus Whole Breast Radiation for Early-Stage Breast Cancer Treatment in Rural Appalachia. Am Surg. 2020 Dec;86(12):1666-1671. doi: 10.1177/0003134820940735.

[9] Arvold ND, Taghian AG, Niemierko A, Abi Raad RF, Sreedhara M, Nguyen PL, Bellon JR, Wong JS, Smith BL, Harris JR. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol. 2011 Oct 10;29(29):3885-91. doi: 10.1200/JCO.2011.36.1105.

[10] Benitez PR, Keisch ME, Vicini F, Stolier A, Scroggins T, Walker A, White J, Hedberg P, Hebert M, Arthur D, Zannis V, Quiet C, Streeter O, Silverstein M. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. Am J Surg. 2007 Oct;194(4):456-62. doi: 10.1016/j.amjsurg.2007.06.010.

[11] Blamey RW, Bates T, Chetty U, Duffy SW, Ellis IO, George D, Mallon E, Mitchell MJ, Monypenny I, Morgan DA, Macmillan RD, Patnick J, Pinder SE. 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;49(10):2294-302. doi: 10.1016/j.ejca.2013.02.031.

[12] Carleton N, Zou J, Fang Y, Koscumb SE, Shah OS, Chen F, Beriwal S, Diego EJ, Brufsky AM, Oesterreich S, Shapiro SD, Ferris R, Emens LA, Tseng G, Marroquin OC, Lee AV, McAuliffe PF. Outcomes After Sentinel Lymph Node Biopsy and Radiotherapy in Older Women With Early-Stage, Estrogen Receptor-Positive Breast Cancer. JAMA Netw Open. 2021 Apr 1;4(4):e216322. doi: 10.1001/jamanetworkopen.2021.6322.

	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
6	**Cernusco (2016)**[13]	295	2%	Yes	No	
7	**Ciérvide (2021)**[14]	23	0%	Yes	Yes	IceCure is concerned that outcomes of this 23 patient study were disproportionately up-weighted by FDA's use of inverse variance weighting.
8	**Coles (2017)**[15] **IMPORT LOW Trial**	2018	0.89%	Yes	No	
9	**Dahn (2020)**[16]	460	Hormone and radiation therapy = 0.8% Radiation alone = 1.5% Hormone therapy alone = 4.2% No adjuvant therapy = 12.0%	Yes – 2 study arms	No	

[13] Cernusco NLV, Bianco PD, Romano M, Muraglia A, Rossi G, Giri MG, Guariglia S, Lombardi D, Pellini F, Cavedon C, Pollini GP, Mazzarotto R. Long-Term Outcomes Using Electron IOERT APBI for Early Stage Breast Cancer: The Verona University Hospital Experience. Clin Breast Cancer. 2022 Feb;22(2):e167-e172. doi: 10.1016/j.clbc.2021.05.015.

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[15] Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, Bhattacharya IS, Brunt AM, Ciurlionis L, Chan C, Donovan EM, Emson MA, Hamett AN, Haviland JS, Hopwood P, Jefford ML, Kaggwa R, Sawyer EJ, Syndikus I, Tsang YM, Wheatley DA, Wilcox M, Yarnold JR, Bliss JM; IMPORT Trialists. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet. 2017 Sep 9;390(10099):1048-1060. doi: 10.1016/S0140-6736(17)31145-5.

[16] Dahn H, Wilke D, Walsh G, Pignol JP. Radiation and/or endocrine therapy? Recurrence and survival outcomes in women over 70 with early breast cancer after breast-conserving surgery. Breast Cancer Res Treat. 2020 Jul;182(2):411-420. doi: 10.1007/s10549-020-05691-6.

	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
10	**De Paula (2016)**[17]	65	0%	Yes	No	
11	**Demirci (2012)**[18]	295	99% 10-year locoregional control	Yes	No	
12	**Eldredge-Hindy (2021)**[19]	158	2.17% (95% CI 0.58–5.78)	Yes	No	
13	**Fyles (2004)**[20]*	611	3.2% overall Tamoxifen and radiation arm = 0.4 Tamoxifen arm = 5.9%	Yes in RT arm	No	FDA excluded this article as they were unable to extract data on the target population. IceCure recommended extraction of the subgroup with T1, ER+ tumors. Subgroup outcomes are available in Figure 4 of Fyles (2004) manuscript. 5 year IBTR rate is 5.8%.
14	**Hughes (2004)**[21]* **CALGB 9343**	636	5-year IBTR: Tamoxifen only arm = 4.1%	Yes in RT arm	No	FDA excluded this article (CALGB 9343) based on lack of information on HER2 status and stated that target group could not be extracted as 2% had ER negative and 2% with size >2cm.

[17] DE Paula U, D'Angelillo RM, Barbara R, Caruso C, Gomellini S, Caccavari A, Costarelli L, Scavina P, Mauri M, Santini E, Antonaci A, Cavaliere F, LA Pinta M, Loreti A, Fortunato L. Once Daily Accelerated Partial Breast Irradiation: Preliminary Results with Helical Tomotherapy®. Anticancer Res. 2016 Jun;36(6):3035-9.

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[20] Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, Weir LM, Olivotto IA. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70. doi: 10.1056/NEJMoa040595.

[21] Hughes, K. S., et al. (2004). "Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer." N Engl J Med 351(10): 971-977.

	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
			Tamoxifen + RT arm = 1.3%			IceCure believes that this high-quality RCT study should have been included in FDA's meta-analysis. The 5-year IBTR rates were reported to be 4.1% in the no radiotherapy and 1.3% in the group with radiotherapy.
15	**Hughes (2013)[5]*** **CALGB 9343**	636	10-year IBTR: Tamoxifen arm IBTR-free survival = 91% (95% CI, 87-94) Tamoxifen and radiation arm IBTR-free survival group = 98% (95% CI, 96-99)	Yes in RT arm	No	
16	**Jagsi (2024)[22]***	186	50-59 age group = 3.3% 60-69 age group = 3.6%	No	No	
17	**Kahn (2013)[23]**	224	10-year local relapse-free survival 98% overall	Yes	No	
18	**Kirbky-Bott (2005)[24]**	121	11.57% Median time to recurrence 56 months	Not specified	No	

[22] Jagsi R, Griffith KA, Harris EE, Wright JL, Recht A, Taghian AG, Lee L, Moran MS, Small W Jr, Johnstone C, Rahimi A, Freedman G, Muzaffar M, Haffty B, Horst K, Powell SN, Sharp J, Sabel M, Schott A, El-Tamer M. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol. 2024 Feb 1;42(4):390-398. doi: 10.1200/JCO.23.02270.

[23] Khan AJ, Parikh RR, Neboori HJ, Goyal S, Haffty BG, Moran MS. The relative benefits of tamoxifen in older women with T1 early-stage breast cancer treated with breast-conserving surgery and radiation therapy. Breast J. 2013 Sep-Oct;19(5):490-5. doi: 10.1111/tbj.12150.

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	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
19	**Kunkler (2015)[3*]**	658	With Radiotherapy: 1.3% (CI: 0.2-2.3%). Without Radiotherapy: 4.1% (CI: 2.5-5.7%) *Please note: this group was excluded from FDA's meta-analysis*	Yes in radiotherapy group (Group selected by FDA)	Yes	FDA's meta-analysis includes the IBTR rate from the RCT treatment arm with radiotherapy only ('RT group'). The Sponsor has requested that FDA include outcomes from both treatment arms. The 5-year IBTR rate in the 'no RT' group was 4.1% (CI: 2.5-5.7%). This is significantly higher than FDA's current meta-analysis.
20	**Liao (2011)[25]**	12	0%	Yes	No	IceCure requested that FDA exclude this article as the treatment evaluated is quadrantectomy, not lumpectomy.
21	**Offersen (2022)[26]**	434 (WBI arm) 431 (PBI arm)	18 locoregional recurrences in total (6 in WBRT and 10 PBI) KM rate not provided	Yes	Yes	54 (12%) patients with nonductal, 3 (1%) patients with lobular. Reported locoregional recurrence with KM survival curve. Local recurrence was not reported with KM survival curve or rate so unclear how FDA has determined the local IBTR rate.
22	**Ohsumi (2022)[27]**	321	IBTR-free survival = 97%	No	No	

[25] Liao L, Han G, Li Y, Wang Z, Liu D, Pi Z. A primary experience of conventional fractionated three-dimensional conformal partial breast irradiation for early-stage breast cancer. Exp Ther Med. 2011 May;2(3):551-555. doi: 10.3892/etm.2011.223

[26] Offersen BV, Alsner J, Nielsen HM, et al. Partial Breast Irradiation Versus Whole Breast Irradiation for Early Breast Cancer Patients in a Randomized Phase III Trial: The Danish Breast Cancer Group Partial Breast Irradiation Trial. J Clin Oncol 2022;40(36):4189-4197. (In eng). DOI: 10.1200/JCO.22.00451.

[27] Masuda N, Ohsumi S, Nishimura R, et al. Combined analysis of the WORTH 1 and WORTH 2 studies of ipsilateral breast tumor recurrence after breast conservative surgery without radiotherapyusing the "5-mm thick slice and 5-mm free margin method". Cancer Research 2021;81(4) (Conference Abstract) (In English). DOI: 10.1158/1538-7445.SABCS20-PS1-01.

	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
23	**Soyder (2013)**[7]	16	0%	No	Yes	Concern with study design: Authors describe as a 'descriptive case series'. Authors do not describe follow-up or methods to identify recurrence – it is unclear if standard of care in Turkey is consistent with United States. Concern with population: No discussion of HER2 status. Unclear if T1N0M0 subgroup (n=16) excludes all patients with Grade 3 so unable to identify aligned subgroup. IceCure is concerned that outcomes of this 16 patient study were disproportionately up-weighted by FDA's use of inverse variance weighting.
24	**Tinterri (2009)**[28]	649	Lumpectomy only arm = 2.5% Lumpectomy and radiation arm = 0.7%	Yes in RT arm	No	This article should have been excluded; treatment evaluated is quadrantectomy, not lumpectomy.
25	**Whelen (2023)**[1]*	500	2.3%	No	Yes	The FDA and IceCure meta-analyses evaluate the overall rate of IBTR. The authors commented in response to a question in November 2023, that 5-year incidence of local recurrence in the ipsilateral breast among the 161 patients 64 years of age or younger was 1.4% (90% CI: 0.4-3.7%); the corresponding incidence among the 339 patients

[28] Tinterri C, Gatzemeier W, Zanini V, et al. Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: a prospective randomised multicentre trial. Breast 2009;18(6):373-7. (Article) (In English). DOI: 10.1016/j.breast.2009.09.013.

	Study Included in FDA SLR	Sample Size	IBTR Rate	Radiotherapy?	Included in FDA Meta-Analysis	IceCure Concern
						older than 64 years of age was 2.8% (90% CI: 1.5 – 4.8%).[29]

*Selected for inclusion in IceCure's PRISMA SLR and meta-analysis.

[29] Recht A. Omitting Radiotherapy in Luminal A Breast Cancer. N Engl J Med. 2023 Nov 2;389(18):1727. doi: 10.1056/NEJMc2310656. PMID: 37913518.