24 Hour Summary
General and Plastic Surgery Devices Panel
Advisory Committee Meeting
November 7, 2024

Introduction:

A meeting of the General and Plastic Surgery Devices Panel ("the Panel") of the Medical Devices Advisory Committee was convened on November 7, 2024, to discuss, make recommendations, and vote on clinical information related to a *De Novo* request for the ProSense Cryoablation System proposed by IceCure Medical Ltd.

On November 7, 2024, the Panel discussed the sponsor's proposed indication: "for use in the treatment of patients with early stage, low-risk breast cancer for the treatment of breast cancer with adjuvant endocrine therapy."

Invited Speakers:

The Panel heard presentations from external speakers invited by FDA. Dr. Monica Morrow, Dr. Julie Margenthaler, and Dr. Patricia Ganz presented on the history of pivotal changes in standard of care treatment of local breast cancer, recurrence risk in breast cancer treatment and the role of molecular subtypes and clinicopathologic risk factors, and quality of life considerations of breast cancer treatments, respectively.

Open Public Hearing (OPH):

In the OPH session, the Panel heard presentations from clinicians, patients, and other stakeholders. Dr. Diana Zuckerman spoke on behalf of the National Center for Health Research. Becky Finnick, Susan Tschirhart, and Muriel Smith spoke from patient experience. Dr. Kenneth Tomkovich spoke from a clinician perspective.

FDA Questions/Panel Deliberations:

Q1. Please comment on the strengths and limitations of standard of care imaging technology (e.g., mammography, ultrasound, MRI) to accurately characterize the tumor size and extent prior to surgical or cryoablation treatment in early stage, low-risk breast cancer patients.

The panel generally agreed that standard imaging technologies like mammography, ultrasound, and MRI are effective for characterization of tumor size for early-stage low-risk breast cancer, but with limitations. One panel member stated that imaging modalities such as ultrasound and mammography tend to underestimate the tumor size by a small amount, e.g., 2-3 mm, for small tumors, and other panelists agreed. Challenges are particularly evident in invasive lobular cancers, multifocal cases, and dense breast tissue. Some panel members noted that more advanced imaging might be necessary for determining which patients are appropriate to be treated with the ProSense System and indicated MRI may be a more accurate imaging tool for assessing tumor size and informing patient selection, and that active monitoring is important to ensure accurate disease assessment and to improve treatment decisions.

Q2. Please discuss the strengths and limitations of the single-arm, nonrandomized study design using a literature-derived performance goal for the primary endpoint IBTR rate. In particular, please comment on:

- **a. The 10% performance goal; and**
- **b. The reproducibility of the patient population in the ICE3 study with respect to relevant risk factors for local recurrence (IBTR).**

The panelists offered a variety of perspectives on the single-arm non-randomized study design, with a focus on the 10% performance goal for the IBTR rate and the reproducibility of patient populations. Several panel members indicated that a randomized controlled trial would be ideal or would have been helpful; however, the panel generally found a single-arm study design to be justified in this specific case. Some of the justifications provided by different panel members for the acceptability of the single-arm study design included the fact that the ProSense Cryoablation device is already available on the U.S. market and some patients can access treatment with the device without participating in the trial, and substantial data is available in the literature to serve as a benchmark.

Some panel members commented that at the time the study was initiated, the proposed IBTR rate of 5% within the performance goal was reasonable. A couple of panelists raised concerns regarding the reliability of the literature comparator and that several different recurrence rates for standard of care, ranging from 2-8%, had been cited by different panelists and speakers.

Several panel members commented that the size of the study relative to a low number of events and the analysis of the study data were more concerning than the single-arm design.

Regarding reproducibility of the patient population, one panelist commented that through advancements in technology over the years, there are more tools available now to define the patient population in terms of Ki-67 and genomic tests, in addition to standard histopathology assessments and tumor size. One panelist commented that Hispanic and African American patients tend to present with more advanced stage disease.

The consensus was a mix of recognition of the constraints of surgical trial designs while acknowledging that randomized controlled trials, if feasible, would provide stronger evidence. Concerns were raised over sample size, patient selection bias, and the variability of IBTR rates.

The panel chair concluded there was lack of uniformity on this question.

Q3. Please comment on the strengths and limitations of each analysis population and subpopulation for determining the benefit versus risk of the ProSense System for the proposed IFU. In particular, please comment on:

- **a. the relative heterogeneity of subjects with respect to risk factors for recurrence;**
- **b. alignment with the proposed indications for use;**
- **c. adequacy of the sample sizes and corresponding uncertainty**

The panel discussed the strengths and limitations of using analysis populations and subpopulations to assess the benefit-risk balance of the ProSense system. Some panelists noted the challenge of defining low-risk populations, with some panel members noting limitations due to missing data and the absence of breast cancer subtyping in earlier trials.

While alignment with the proposed indications was generally supported, there was a call for standardized follow-up protocols. Issues such as sample size, uncertainty in single-arm trials, and patient selection bias were acknowledged. The panel generally agreed that there are cohorts of patients in the low-risk category for whom this device may be appropriate, but several panelists raised concerns that the study does not provide information about all patients within the range of categories in the proposed indications for use. Multiple panelists raised specific concerns about the availability of data for women at younger ages, such as in their 60s. Concerns about the representativeness of samples, and potential technical success uncertainties were also raised. Overall, the ProSense system showed potential, but the need for more comprehensive data and clearer patient guidelines was emphasized.

Some panelists indicated that we now have more tools available to help define a low-risk patient population, in contrast to the study population in which there was missing Ki-67 data and not all subjects had genomic testing. Panelists noted that the heterogeneity in patients may be a reason for the range of results observed in the study, and that this may reflect real-world patients who would be considered for the treatment.

Study size and uncertainty were noted to be challenges but that a randomized controlled trial would also be challenging to complete. Several panelists raised concerns regarding the limitations of the statistical methods applied to the study data, including the censoring methods, and whether the selection of patients into the study represents the range of patients that will receive the device treatment.

Q4. Please discuss the overall clinical significance of the effectiveness results of the ICE3 study compared to the SLR and meta-analysis results.

While many panelists acknowledged the comparability of ICE3's results to existing data, they expressed concerns about the non-randomized nature of the study and the challenges this presents in fully assessing the population differences and recurrence rates. The panelists acknowledged that the systematic literature reviews had strengths and weaknesses and the ICE3 study population received a mix of adjunctive treatments (e.g., radiation, endocrine therapy), but with these caveats in mind, the IBTR rate from the indicated population seemed comparable to the findings of the Systematic Literature Review and analysis.

Some panelists additionally discussed that patient adherence to endocrine therapy would be important in selecting patients for de-escalation of surgical treatment to the use of cryoablation, because compliance to endocrine therapy is a known challenge in clinical practice and affects

recurrence rate. There was also recognition of the need for clear patient selection criteria based on factors like age, tumor aggressiveness, and adherence to systemic therapies. While the panel indicated that overall, the ICE3 results align with existing data in many respects, they stressed the importance of addressing these uncertainties through better patient selection, post-marketing data, and informed patient consent to ensure clinical relevance and safety. One panelist suggested that a registry could help track the outcomes of patients and a designated informed consent form could help patients. One panelist commented that surgeons and radiologists would know that certain patients, such as younger women who present with a higher Ki-67 and more aggressive tumors would not be a candidate for use of the device. Another panel member commented that as long as patients are properly informed, they could choose what they are willing to go through to achieve a certain local recurrence rate.

Q5. Please comment on how the adverse event data and cosmetic satisfaction surveys in the ICE3 study inform benefit and risk of the ProSense System.

The panel discussed how adverse event data and cosmetic satisfaction surveys from the ICE3 study inform the benefits and risks of the ProSense system. There was general agreement that the procedure is safe and well-tolerated, with low adverse effects reported, and that many patients had positive cosmetic outcomes. However, some panelists raised concerns about the methodology used to assess cosmetic satisfaction, noting that more formal instruments could have been employed to strengthen the data. While the results suggest that the ProSense system provides good cosmetic results, some panelists pointed out that lumpectomy, which is often seen as a minimally invasive option, also yields excellent cosmetic outcomes for many patients, particularly for small tumors. There was also discussion about the importance of patient education, highlighting the need for clear, concise information to support informed decision-making. The panel emphasized that patients should be well-informed about the potential risks, benefits, and uncertainties associated with the procedure, and that adequate guidance should be provided to help them make the best decision in partnership with their healthcare provider.

Q6. Please discuss the quality-of-life benefits of surgery avoidance relative to the quality-of-life risks of breast cancer recurrence for the intended patient population.

The panel discussed the quality-of-life benefits of avoiding surgery versus the potential risks of breast cancer recurrence for the intended patient population. Some panelists felt there was adequate information available for patients to make an informed decision, while other panelists raised concerns that the ICE3 study does not clearly elucidate the risk of recurrence. Many panelists agreed that surgery avoidance is highly appealing to patients, particularly in terms of the convenience and reduced downtime associated with the ProSense procedure. This is especially relevant for patients in rural areas who may have limited access to cancer care. However, some panelists noted the trade-off between avoiding surgery and the risk of needing additional imaging studies, such as MRIs, which could lead to further biopsies and interventions. Some panelists noted that the use of the ProSense system does not remove future surgical options from patients. For example, if a patient has a recurrence, they still have other standard options available, including excision. Multiple panelists noted that this treatment option may be trading surgery for additional imaging, such as MRIs, and potentially more biopsies long-term.

The importance of offering patients choices was emphasized, as individual preferences regarding surgery avoidance and certainty of treatment outcomes vary. Some patients may prioritize avoiding surgery even if it means accepting a higher risk of recurrence, while others might prefer the certainty of traditional surgery despite its associated risks and recovery time. The panel acknowledged that the data on recurrence risk from the ProSense system are not fully robust, which makes it difficult to estimate the precise risk of recurrence. This lack of clarity complicates informed decision-making, as patients may struggle to assess the trade-offs between the benefits of avoiding surgery and the potential for recurrence.

Overall, the panel stressed the need for clear communication with patients about the potential risks and benefits, including the uncertainties regarding recurrence rates. They agreed that this type of decision should be made collaboratively between patients and their healthcare providers, ensuring that patients are fully informed about their options and the possible outcomes.

Q7. Given the totality of evidence presented regarding the safety and effectiveness of the ProSense System, please comment on the overall benefit-risk profile of the device for the proposed indications for use in the treatment of early stage, low-risk breast cancer in lieu of lumpectomy.

The panel discussed the overall benefit-risk profile of the ProSense system for treating early-stage low-risk breast cancer, agreeing that while the technology holds promise, its effectiveness is not yet fully proven. There was consensus that the definition of "low-risk" breast cancer should be more specific, particularly regarding whether genomic data should be included. Concerns were raised about the lack of randomized controlled trials and the reliance on observational data, with some questioning the justification for the proposed age limitations of 60-65 years. Panelists had several suggestions for mitigating risk, including clearly defining low-risk breast cancer and standardizing the biopsy procedure prior to cryoablation. The panel emphasized the need for more rigorous studies, especially in younger patients and those with higher risk, to better understand recurrence rates and long-term outcomes. One panelist reiterated concerns about the lack of randomized controlled evidence to guide patient decision making. There were also discussions about the adequacy of biopsy samples for patient selection, with a call for standardization to ensure more reliable data. Overall, while the system shows potential, further clinical evidence is necessary to confirm its safety and effectiveness.

Panel Vote:

The Panel voted 9 Yes; 5 No; 0 Abstentions that the benefits of the ProSense Cryoablation System outweigh the risks for the proposed Indications for Use. Four of the eighteen voting members were not present for the vote. The total vote number represents the fourteen voting members present at the time the vote was held.

The panel members who voted "no" expressed concerns about uncertainties in patient selection and risk assessment, particularly around the variability in biopsy results and age range of patients included in the study. They emphasized the need for clearer criteria and more controlled data to accurately evaluate long-term risks, such as recurrence rates. There was also a call for additional safeguards, such as informed consent and post-market surveillance, especially for younger patients, and a desire for more data on excluded patient populations.

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Transcripts:

Transcripts may be downloaded from:
November 7, 2024: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting Announcement - 11/07/2024 | FDA

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