

## **Appendix F – Disease Outcomes Definitions in ICE3 Study Protocol**

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.*

### **Regional Recurrence**

Regional recurrence is defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular, and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after surgery. This can be confirmed with positive cytology or histologic biopsy.

### **Distant Recurrence**

Distant recurrence is evidence of tumor in any areas of the body, with the exception of those defined as local or regional recurrence above.

### **Second Primary Breast Cancer**

A second primary breast cancer is evidence of invasive or in situ breast cancer in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed histologically.

### **Second Primary Cancer (non-breast)**

Any non-breast second primary cancer will be considered as disease free survival. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

### **Disease-Free Survival**

Disease-free survival (DFS) is determined from date of cryoablation 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, and death due to any cause.

Alternate DFS Definition According to the NCI:

According to the National Cancer Institute (NCI), disease-free survival (DFS) is the amount of time a patient survives after cancer treatment without any signs or symptoms of the cancer. This definition is most commonly utilized in literature.

Importantly, this definition differs from the protocol-specified definition in that deaths and second primary non-breast cancer are not counted toward the DFS rate.

To allow for comparison to DFS rates reported in the literature (LUMINA included), DFS was also evaluated using the less strict NCI Definition

### **Overall and Breast Cancer Specific Survival**

Overall survival will be measured from the date of the cryoablation until the date of death from any cause or up to the 60 months follow up visit.

Women not known to be dead at the time of analysis will be censored at the date of last follow-up.

Breast cancer specific survival will be measured from the date of cryoablation until the date of death from breast cancer or up to the 60 months follow up visit. Women who die from other documented causes (i.e. cause is not breast cancer) will be censored at the time of death. All women not known to be dead at the time of analysis will be censored at date of last follow-up.