# LUMISIGHT™ and Lumicell™ Direct Visualization System (DVS) as Adjunct to Standard of Care to Identify Residual Cancer Within the Lumpectomy Cavity

## March 5, 2024

Lumicell

Medical Imaging Drugs Advisory Committee (MIDAC)

# Introduction

**Jorge Ferrer, PhD**

Chief Scientific Officer

Lumicell

# LUM System Is Real-Time, Intracavity, Fluorescence-Guided Imaging as Adjunct to Standard of Care (SoC)

## LUM System

### LUMISIGHT

***Find***

Optical imaging agent that produces fluorescence signal at sites of residual cancer

### Lumicell Direct Visualization System (DVS)

+

***Detect***

Hand-held imaging probe inserted into breast cavity to identify residual cancer

***Guide***

Real-time cancer detection software guides surgeon to remove residual cancer

# LUM System Developed to Fill Important Unmet Clinical Need

Lumpectomy meant to be minimally invasive alternative to mastectomy

Surgeons have no way to see full extent of cancer inside cavity

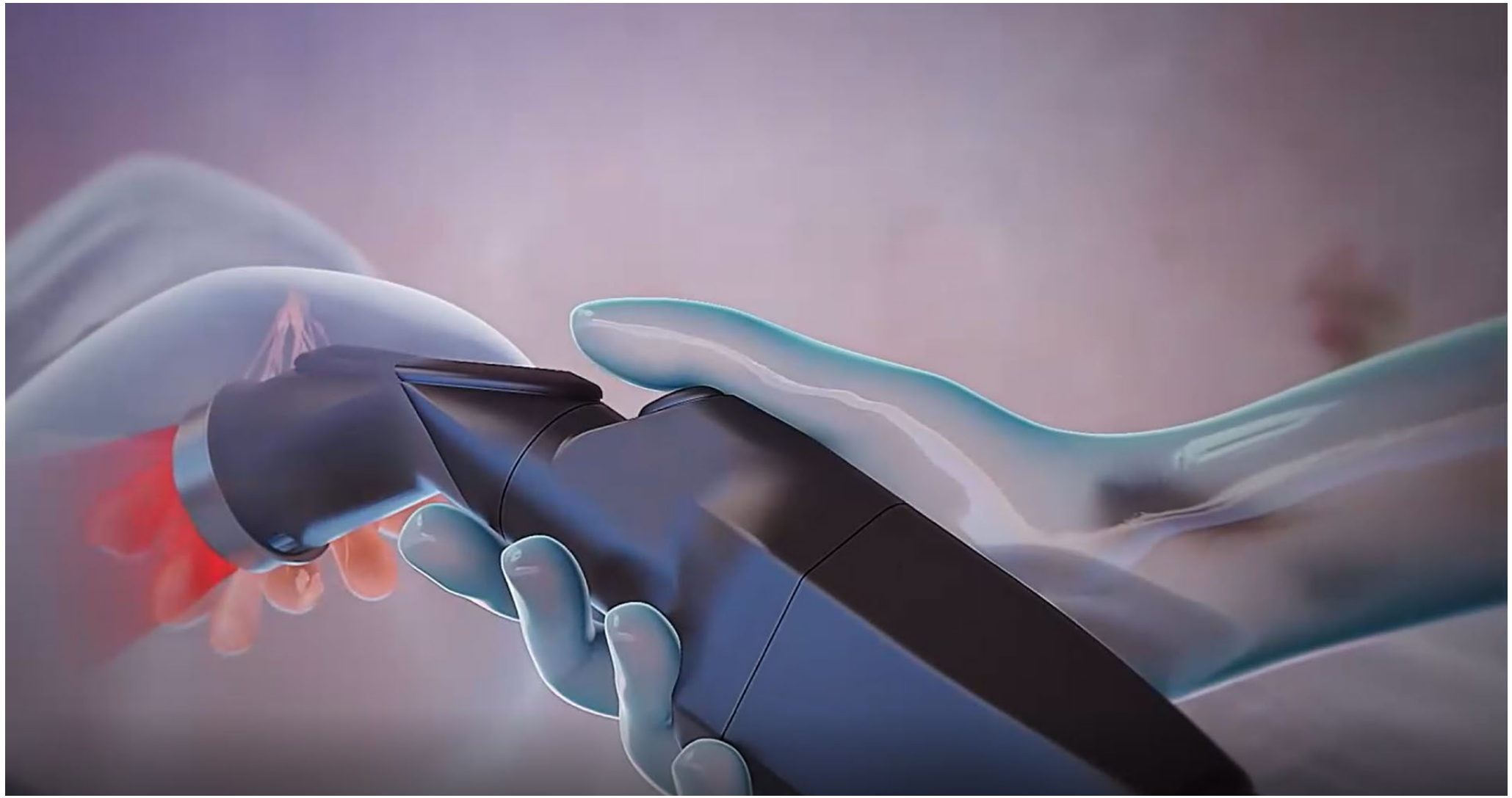
19% of negative margins have residual cancer remaining[1]

9% – 36% second surgeries[2,3]

**Clear unmet need for real-time, intracavity assessment to more effectively determine extent of tumor for more complete resection**

1. Tang et al. 2015; 2. Dupont et al. 2021; 3. Bundred et al. 2022

# LUM System in Action



# LUM System Clinical Development Program in Breast Cancer and Cardiovascular Safety

| Study ID | Phase / Design | Patients Injected with LUMISIGHT |
|---|---|---|
| DUK1-12-137 | Phase 1<br>Single site, nonrandomized, open label trial | 15<br>(3 breast, 12 sarcoma)<br>(6 at 0.5 mg/kg; 6 at 1 mg/kg;<br>3 at 1.5 mg/kg) |
| CLP00201 | Phase 1 Cardiovascular Safety Trial, healthy volunteers<br>Single site, randomized, double-blind, placebo controlled, dose-escalation | 24<br>32 enrolled<br>(8 in placebo-controlled arm) |
| LUM-015/2.6-001 | Feasibility Phase A<br>Single site, nonrandomized, open label trial | 10<br>(5 at 0.5 mg/kg; 5 at 1 mg/kg) |
| LUM-015/2.6-001 | Feasibility Phase B<br>Single site, nonrandomized, open label trial | 45<br>(1 mg/kg) |
| CL0006 | Feasibility Phase C<br>Multicenter, nonrandomized, open label trial | 234<br>(1 mg/kg) |
| CLP0008 | Feasibility in Patients Receiving Neo-Adjuvant Therapy<br>Multicenter, randomized, blinded trial | 12<br>(1 mg/kg) |
| CL0007 | Pivotal Study<br>Multicenter, 2-arm, randomized, blinded trial | 406<br>(1 mg/kg) |

# Data Supporting Efficacy and Safety of LUM System Published in NEJM Evidence

| Study ID | | | th LUMISIGHT |
|---|---|---|---|
| DUK1-12-137 | | | sarcoma)<br>at 1.0 mg/kg;<br>g/kg) |
| CLP00201 | | | led<br>trolled arm) |
| LUM-015/2.6-001 | | | at 1.0 mg/kg) |
| LUM-015/2.6-001 | | | g) |
| CL0006 | | | g) |
| CLP0008 | | | g) |
| CL0007 | Pivotal Study<br>Multicenter, 2-arm, randomized, blinded trial | 406<br>(1 mg/kg) | |

NEJM Evidence

Published April 27, 2023

DOI: 10.1056/EVIDoa2200333

ORIGINAL ARTICLE

## Intraoperative Fluorescence Guidance for Breast Cancer Lumpectomy Surgery

Barbara L. Smith, M.D., Ph.D.,[1] Kelly K. Hunt, M.D.,[2] David Carr, M.D.,[3] Peter W. Blumencranz, M.D.,[4] E. Shelley Hwang, M.D., M.P.H.,[5] Michele A. Gadd, M.D.,[1] Kimberly Stone, M.D.,[6] Donna L. Dyess, M.D.,[7] Daleela Dodge, M.D.,[8] Stephanie Valente, D.O.,[9] Nayana Dekhne, M.D.,[10] Patricia Clark, M.D.,[11] Marie Catherine Lee, M.D.,[12] Laila Samiian, M.D.,[13] Beth-Anne Lesnikoski, M.D.,[13] Lynne Clark, M.D.,[14] Kate Porta Smith, M.P.H., C.C.R.P.,[15] Manna Chang, Ph.D.,[15] Daniel K. Harris, Ph.D.,[15] Brian Schlossberg, Ph.D.,[15] Jorge Ferrer, Ph.D.,[15] Irene L. Wapnir, M.D.,[6] for the INSITE Study Team*

# Proposed Indication and Dosing

## Proposed Indication

- LUMISIGHT is indicated for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery (also known as breast-conserving surgery)

## Proposed Dosing

- For use only as a single dose of 1 mg/kg, 2-6 hours prior to imaging

# Benefits of LUM System Outweigh Risks

## Benefits

- Enables removal of residual cancer missed by SoC surgery and pathology
- Converts positive margins to negative, sparing potential second surgeries
- Does not appear to worsen cosmesis
- Provides real-time *in vivo* imaging to surgeons
- As adjunct to SoC, improves surgical outcomes

## Risks

- False positives can lead to unnecessary tissue removal
- 0.6% serious hypersensitivity or anaphylaxis risk (4 / 726 patients)

**Benefits of removing residual cancer left behind by SoC surgery outweigh any identified risks that can be managed in preoperative setting and with labeling**

# Sponsor-Proposed Risk Mitigation Strategies for LUMISIGHT Administration

- Clear Labeling
- Training Program
- Enhanced Pharmacovigilance
- Postmarket Study

# Agenda

| | |
|---|---|
| **Unmet Need** | **Kelly Hunt, MD, FACS, FSSO**<br>Professor and Chair, Department of Breast Surgical Oncology, Division of Surgery<br>MD Anderson Cancer Center<br>President, Society of Surgical Oncologists |
| **Efficacy** | **Shelley Hwang, MD, MPH**<br>Mary and Deryl Hart Distinguished Professor of Surgery<br>Vice Chair of Research Department of Surgery<br>Leader, Breast Cancer Disease Group<br>Duke University and Duke Cancer Institute |
| **Safety** | **Peter Blumencranz, MD, FACS**<br>Medical Director, BayCare Oncology Service Line<br>Medical Director, The Comprehensive Breast Care Center of Tampa Bay |
| **Allergic Reactions / Hypersensitivity** | **Tanya Laidlaw, MD, FAAAAI**<br>Director of Translational Research, Division of Allergy and Clinical Immunology<br>Chief, Section of Clinical and Translational Sciences, Div. of Allergy and Clinical Immunology<br>Brigham and Women's Hospital, Associate Professor, Harvard Medical School |
| **Risk Mitigation Strategies** | **Jorge Ferrer, PhD**<br>Chief Scientific Officer<br>Lumicell |
| **Clinical Perspective** | **Barbara Smith, MD, PhD**<br>Director, Breast Program, Massachusetts General Hospital<br>Massachusetts General Hospital Trustees Chair in Breast Surgery<br>Professor of Surgery, Harvard Medical School |

# Additional Experts

## Gheorghe Doros, PhD, MBA

Professor of Biostatistics
Boston University, School of Public Health
Director of Statistical Consulting
Baim Institute for Clinical Research

## Michael Whitworth, MD

American Board of Anesthesiologists
Managing Partner, Prn Anesthesia

## Simona Shaitelman, MD

Professor of Breast Radiation Oncology
Director, Division of Radiation Oncology Biomarker Strategic Initiative Laboratory
UT MD Anderson Cancer Center
Vice-Chair, ASTRO Partial Breast Irradiation Clinical Practice Guideline

## Dorothy Wong, MD

Chair of Pathology, Reg Med Center of San Jose, CA
Medical Director/Staff Pathologist, Dignity Health

# Unmet Need


## Kelly Hunt, MD, FACS, FSSO

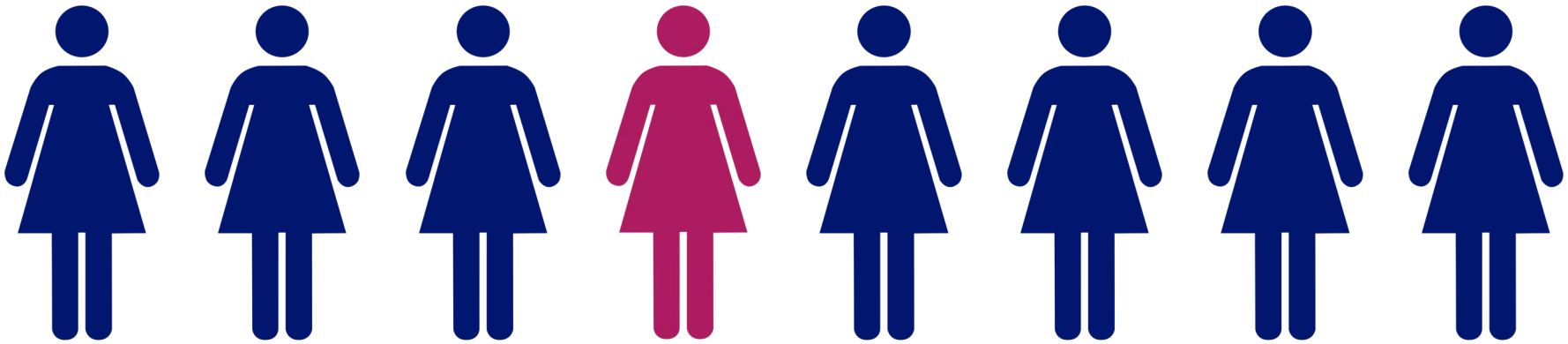
Professor and Chair, Department of Breast Surgical Oncology, Division of Surgery

MD Anderson Cancer Center

President, Society of Surgical Oncology

# Breast Cancer Is Most Common Cancer in Women

**1 in 8**



**women in United States will develop breast cancer in their lifetime[1]**

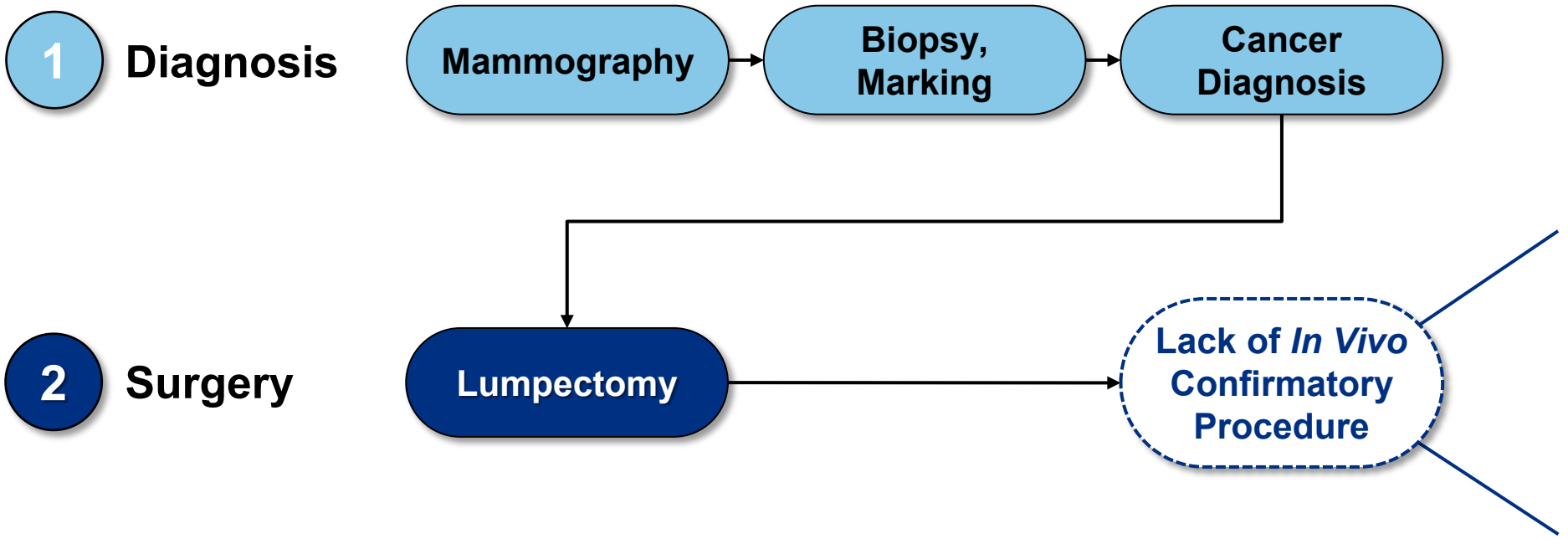
1. American Cancer Society, 2023

# Breast Cancer Is Life-Threatening Disease

| | |
|---|---|
| > 300,000 | women estimated to be diagnosed with breast cancer in US in 2023[1] |
| ~ 43,000 | patients will die from breast cancer each year in US[1] |
| 2nd | leading cause of cancer death in women in US[1] |
| > 180,000 | patients undergo lumpectomy each year in US[2] |

1. American Cancer Society, 2023; 2. National Cancer Database - Accessed 2023

# Caring for Patients with Breast Cancer Is Complex

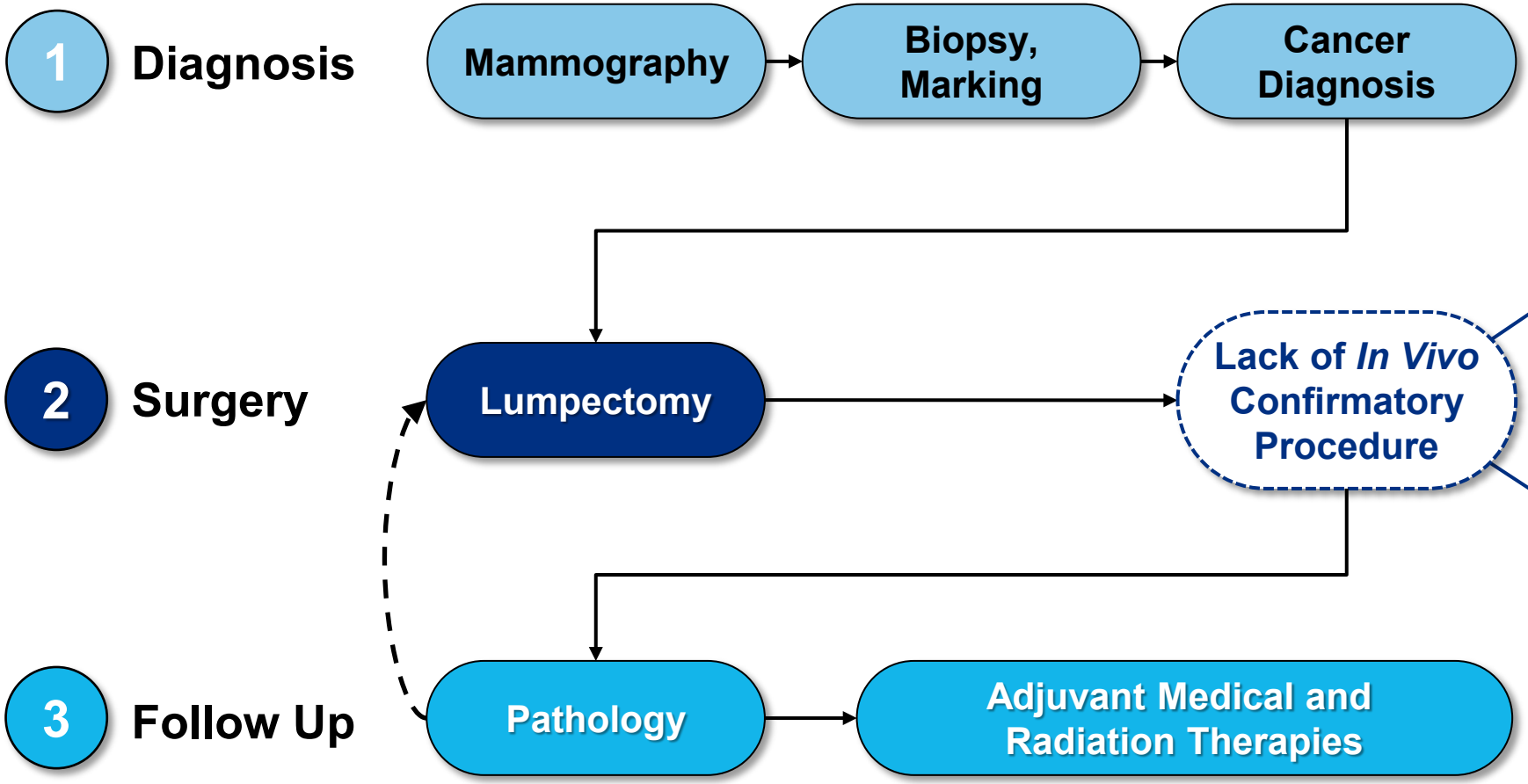



***Ex Vivo*** Approaches

- Radiofrequency spectroscopy
- Intraoperative X-ray
- Optical coherence tomography (OCT)

**No direct assessment of residual cancer in surgical cavity**

# Standard of Care Can Fail to Achieve Complete Resection




- Some negative margins known to have residual cancer[1]
- Positive margins shown to more than double risk of recurrence[2]
- 25% of women who have breast cancer local recurrence do not survive[3]

1. Tang et al. 2015; 2. Morrow et al. 2016; 3. Clarke et al. 2005

# Potential Negative Consequences from Incomplete Resections and Second Surgeries

Anxiety

Morbidity

Cosmesis

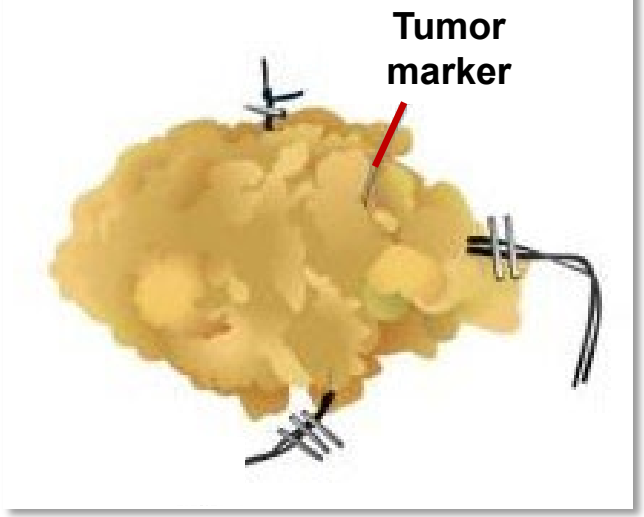
Delay in adjuvant therapy

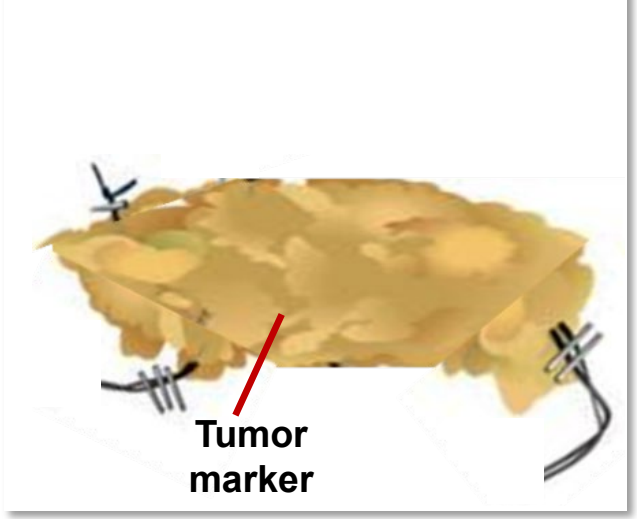
Surgical Complications

Grant et al. 2018

# Limitations of SoC Pathology Margin Assessment

**Lumpectomy Specimen** → **Excision** → **Deformed Sample** → **Pathology** → **Sliced and Inked Sample**



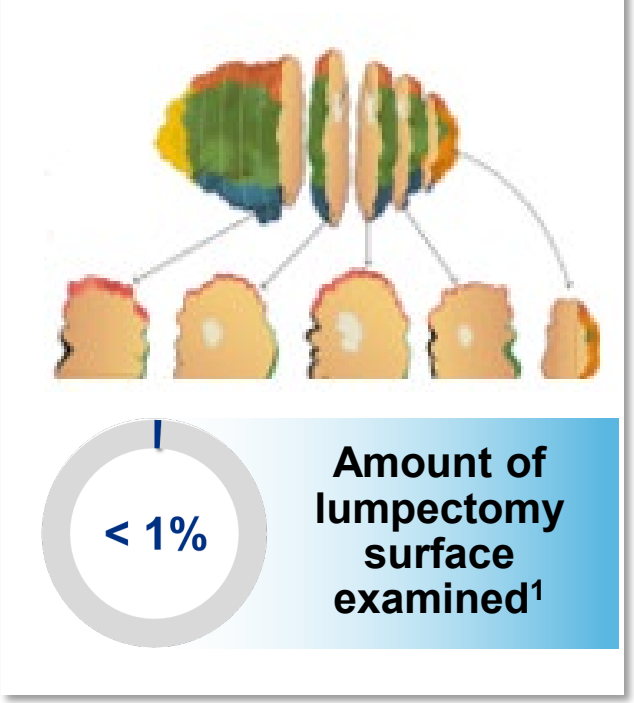
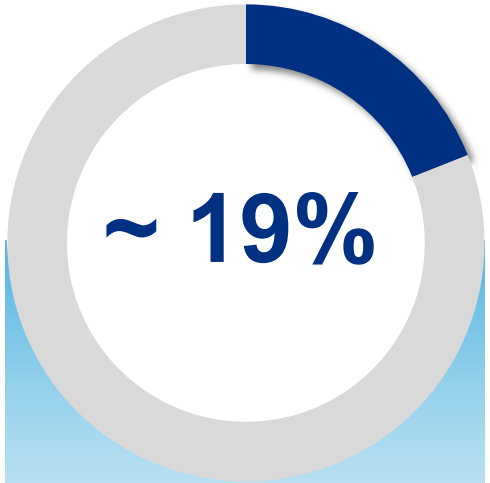
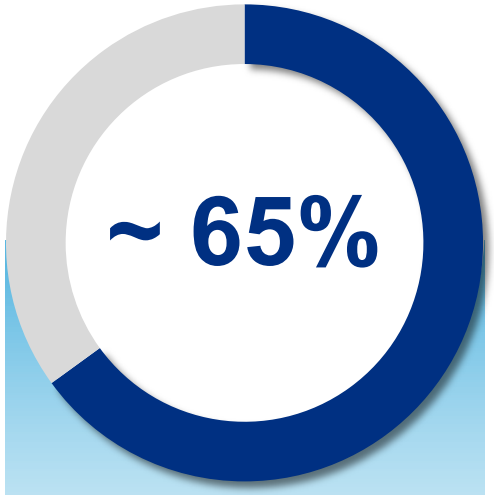




Figure adapted from Royal College of Pathologist, 2016; 1. Carter, 1986

# Pathology Assessment of Excised Tissue Can Lead to False Positives and False Negatives




**of negative margins have residual tumor remaining[1]**




**of positive margins have no actual tumor left behind[1]**


**re-excision rates[2,3]**

1. Tang et al. 2015; 2. Dupont et al. 2021; 3. Bundred et al. 2022

# Summary of Unmet Need

1. Current tools limited and do not identify extent of tumor accurately enough, making it challenging to achieve complete tumor resection

2. Limitations lead to second surgeries

3. Clear unmet need for visualization tool that looks inside breast cavity for residual cancer during surgery to enable more complete resection

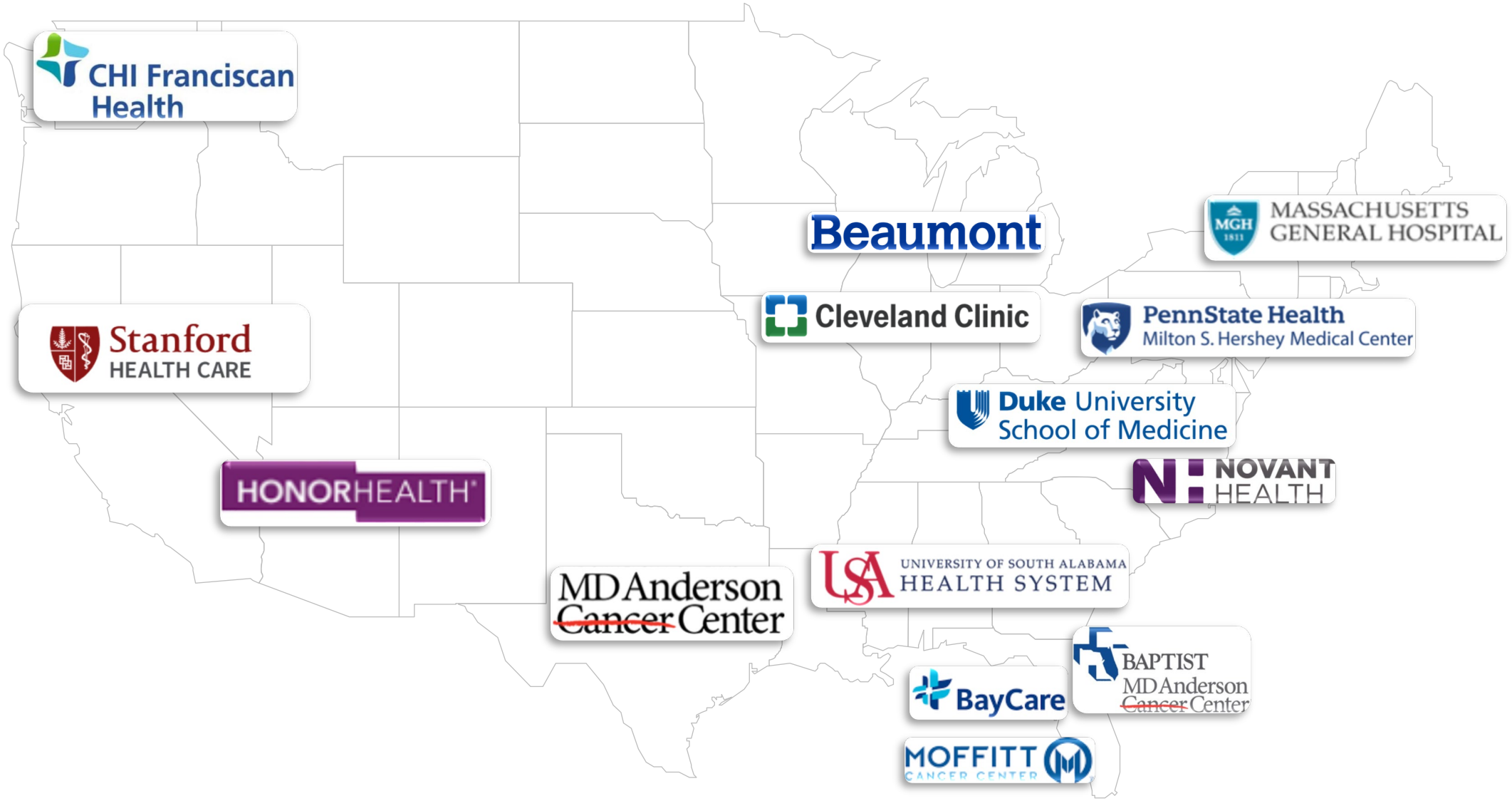
**Adjunctive to SoC, LUM System enables *in vivo* cavity assessment in real-time for more effective resection**

# Pivotal Study CL0007 Efficacy Results

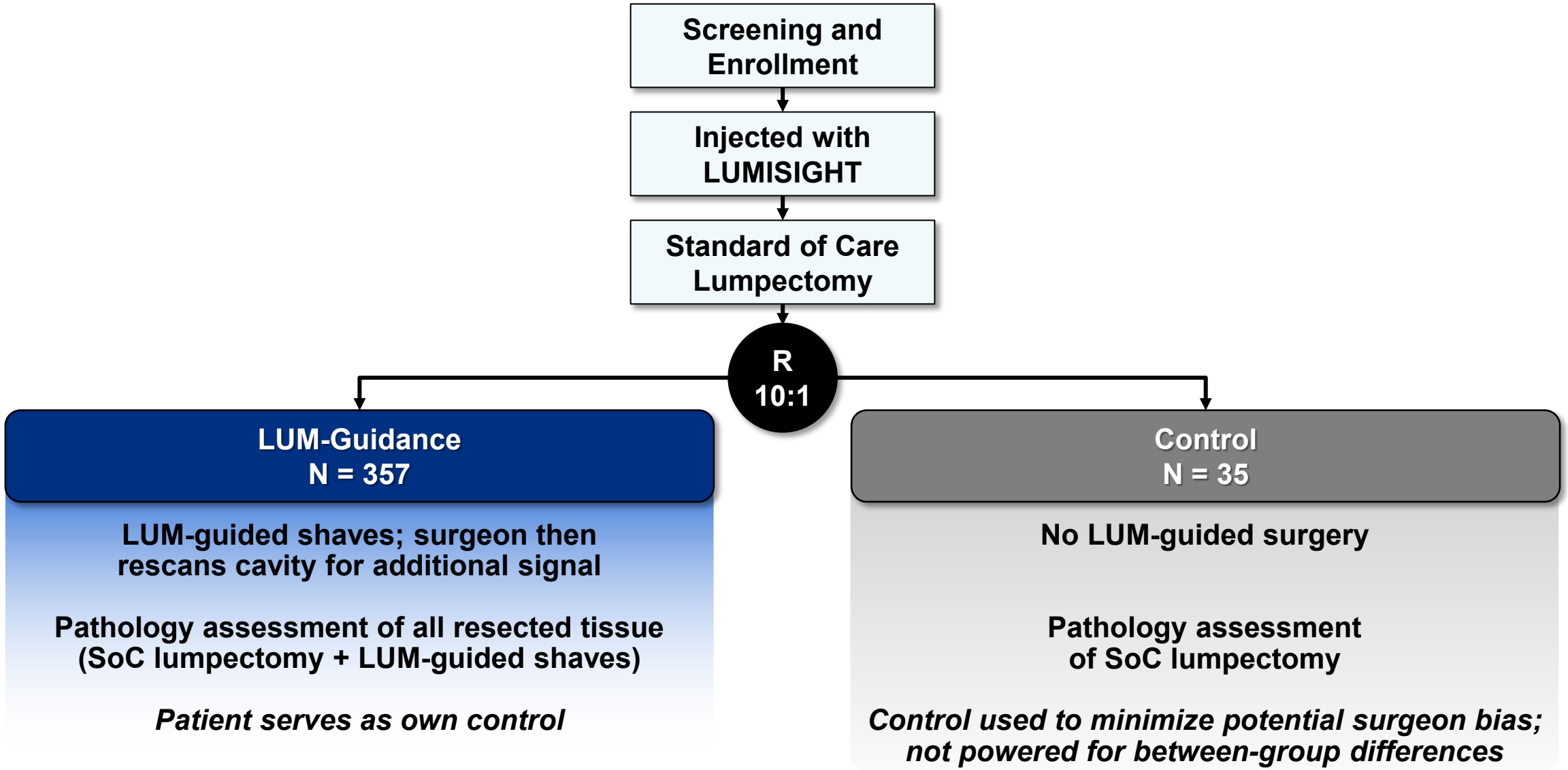
**E. Shelley Hwang, MD, MPH**

Mary and Deryl Hart Distinguished Professor of Surgery
Vice Chair of Research Department of Surgery
Leader, Breast Cancer Disease Group
Duke University and Duke Cancer Institute

# Pivotal Study Included 14 Medical Settings – Academic and Community Hospitals



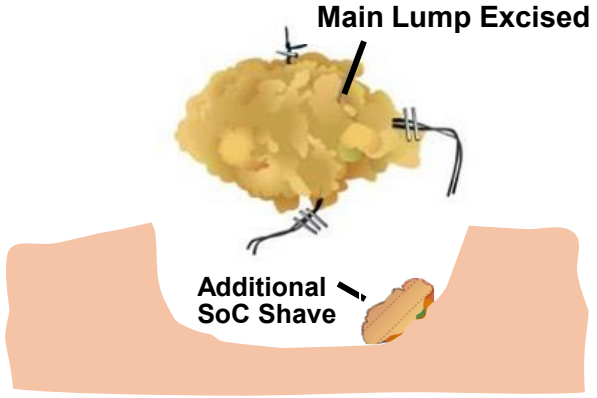
# Study CL0007 Randomized, Blinded Clinical Study



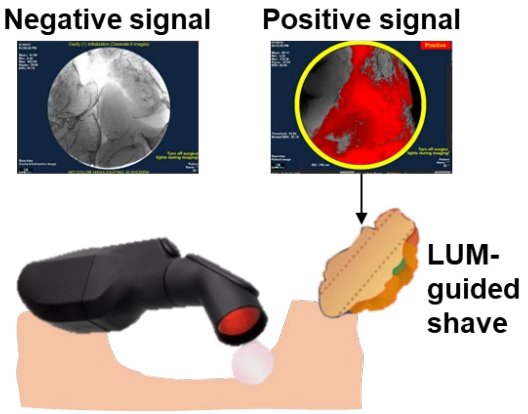
# Study Procedures for Patients Randomized to Treatment Arm

**Initial Lumpectomy**

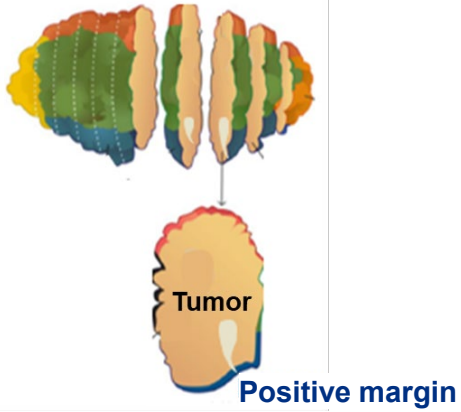
**1 SoC Lumpectomy**




**2 LUM-Guided Shave(s) Taken**

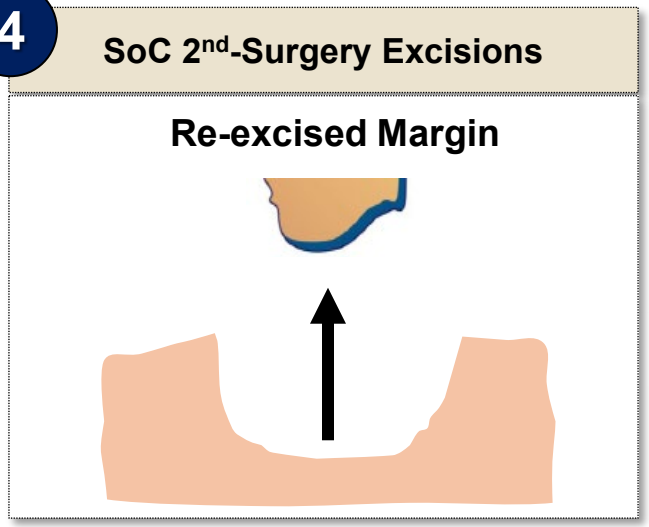



**3 Pathology Assesses SoC Tissue + LUM-Guided Shaves**




**Second Surgery**

**4 SoC 2nd-Surgery Excisions**




**5 Pathology Assesses SoC 2nd-Surgery Tissue**

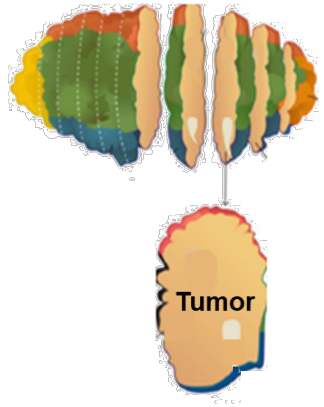
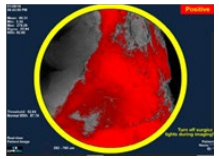


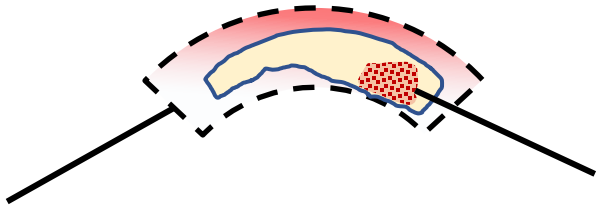

Figure adapted from Royal College of Pathologist, 2016

# LUM-Image Results Compared with Pathology Findings

**True Positive**

Positive LUM-signal

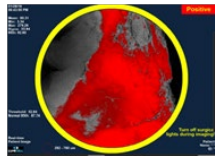


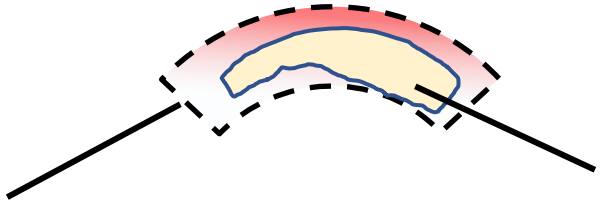


LUM-guided shave **contains tumor**

**False Positive**

Positive LUM-signal



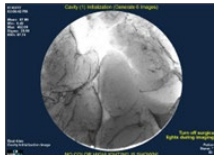


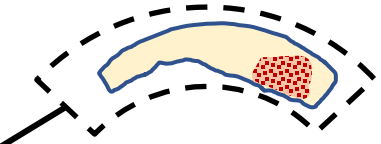
LUM-guided shave does **not contain tumor**

**False Negative**

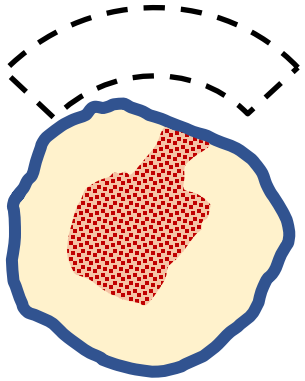
Second surgery **finds tumor**

Negative LUM-signal





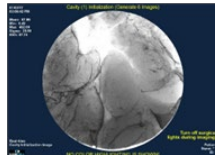
No additional tissue excised

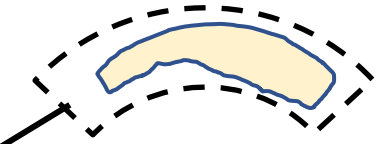


**True Negative**

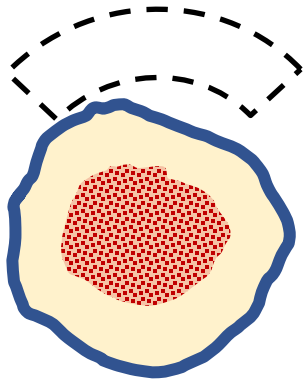
Second surgery **finds no tumor**

Negative LUM-signal





No additional tissue excised



# Pivotal Study Endpoints

| | |
|---|---|
| **Primary Endpoints** | ▪ **Removal of Residual Cancer:** % pts. with residual cancer in LUM-shave<br>▪ **Tissue-level Sensitivity:** true positive rate of LUM-positive signal<br>▪ **Tissue-level Specificity:** true negative rate of LUM-negative signal |
| **Clinically Relevant Secondary Endpoints** | ▪ Patients converted from positive margins after SoC to final negative margins<br>▪ Average volume of LUM-guided shaves; contribution to total excision volume |
| **Exploratory Endpoint** | ▪ Impact of LUM-guided shave volume on patient perceived cosmesis |

# Performance Goals for Co-Primary Endpoints

- **Removal of Residual Cancer: lower bound of CI > 3%**
  - Based on published estimates of 5.3% local recurrence after whole breast radiation[1]

- **Sensitivity: lower bound of CI > 40%**
  - Based on previous study, SoC margin pathology showed 38% sensitivity

- **Specificity: lower bound of CI > 60%**
  - Based on previous study showing ~ 1 LUM-guided shave/patient of 68%

1. Moran et al. 2014

# Key Enrollment Criteria

## Inclusion Criteria

- Female
- Age ≥ 18 years
- Histologically or cytologically confirmed primary invasive breast cancer, DCIS, or primary invasive breast cancer with DCIS component
- ECOG 0 or 1

## Exclusion Criteria

- Bilateral breast cancer and undergoing bilateral resection procedure
- Received neoadjuvant therapies
- Administration of blue dyes for sentinel lymph node mapping prior to LUM imaging
- History of allergic reaction to polyethylene glycol or any oral or IV contrast agent

# Baseline Demographic Characteristics

| Characteristic, % | LUMISIGHT / Lumicell DVS N = 357 |
|---|---|
| **Age, mean** (SD) | **62.4** (9.6) |
| **Race** | |
| **White** | **83%** |
| **Black** | **6%** |
| **Asian** | **6%** |
| **Other, unknown or not reported** | **5%** |
| **Hispanic or Latino** | **3%** |
| **BMI, mean** (SD) | **29.8** (6.7) |
| **Menopausal status** | |
| **Postmenopausal** | **84%** |
| **Pre/perimenopausal** | **16%** |

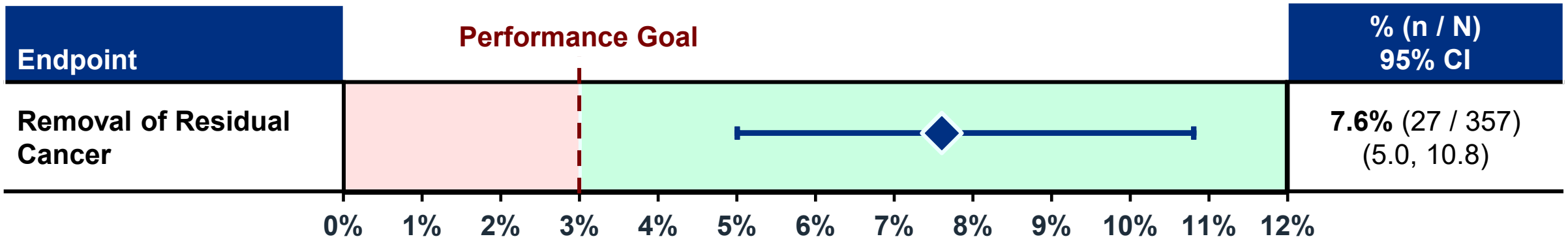
**Efficacy Population**

# Baseline Tumor Histology Characteristics

| Characteristic, % | LUMISIGHT / Lumicell DVS N = 357 |
|---|---|
| **Largest dimension of tumor in main specimen (cm), mean** (SD) | **1.7** (1.3) |
| **Tumor histology (preoperative)** | |
| **DCIS only** | **20%** |
| **IDC** | **70%** |
| **ILC** | **10%** |
| **IDC + ILC** | **1%** |
| **Node positive disease** | **15%** |
| **No lymph node resection** | **19%** |

**DCIS: Ductal carcinoma in situ; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma**
**Efficacy Population**

# Co-Primary Efficacy Endpoint Met:
## LUM-Guided Shaves with Residual Cancer Removed in 7.6% of Patients



# Aggressive and Extensive Residual Cancer Found in LUM-Guided Shaves

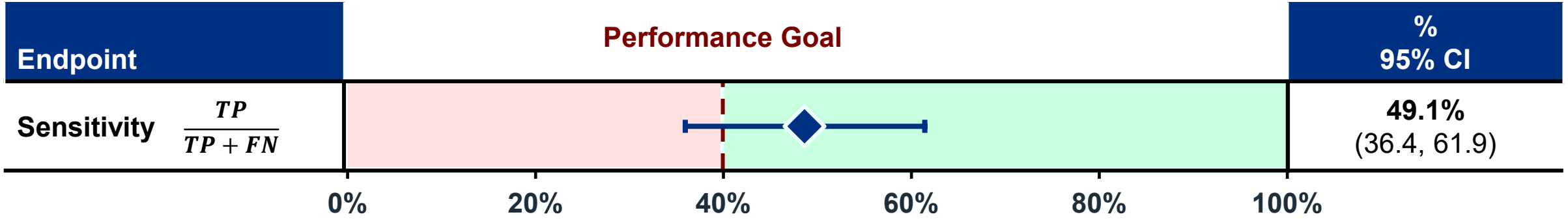
| Characteristic, n (%) | LUM System N = 27 |
|---|---|
| **Tumor grade** | |
| **1** | **2** (7%) |
| **2** | **12** (44%) |
| **3** | **13** (48%) |
| **Residual cancer size 1 – 13mm** | **20** (74%) |
| **Residual cancer removed after negative margin** | **19** (70%) |

**LUM System enabled removal of aggressive, sizable, and undetected cancerous tissue**

# Tissue-Level Sensitivity Not Met

## Missed Lower Bound of PG by 3.6 Percentage Points

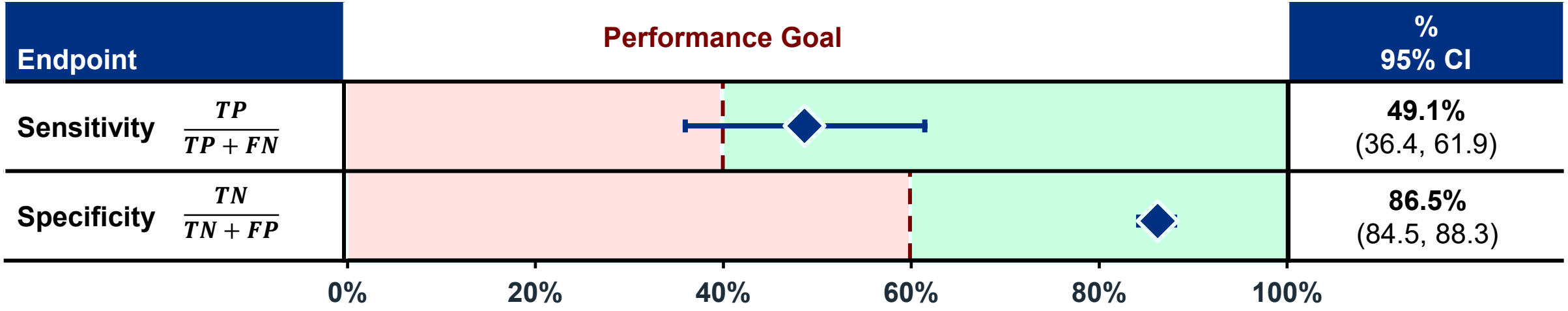
| | | Hierarchy Truth Standard | |
|---|---|---|---|
| | | Positive | Negative |
| LUM Signal | Positive | TP = 34 | FP = 337 |
| | Negative | FN = 35 | TN = 1,940 |




Diagnostic performance CIs calculated using GEE approach; TP = true positives; FN = false negatives; TN = true negatives; FP = false positives

# Tissue-Level Specificity Co-Primary Endpoint Met
## Exceeded Lower Bound of PG

| | | Hierarchy Truth Standard | |
|---|---|---|---|
| | | Positive | Negative |
| LUM Signal | Positive | TP = 34 | FP = 337 |
| | Negative | FN = 35 | TN = 1,940 |




Diagnostic performance CIs calculated using GEE approach; TP = true positives; FN = false negatives; TN = true negatives; FP = false positives

# Diagnostic Accuracy of 84%
## Exceeds 50% Expected for Random Outcome Test

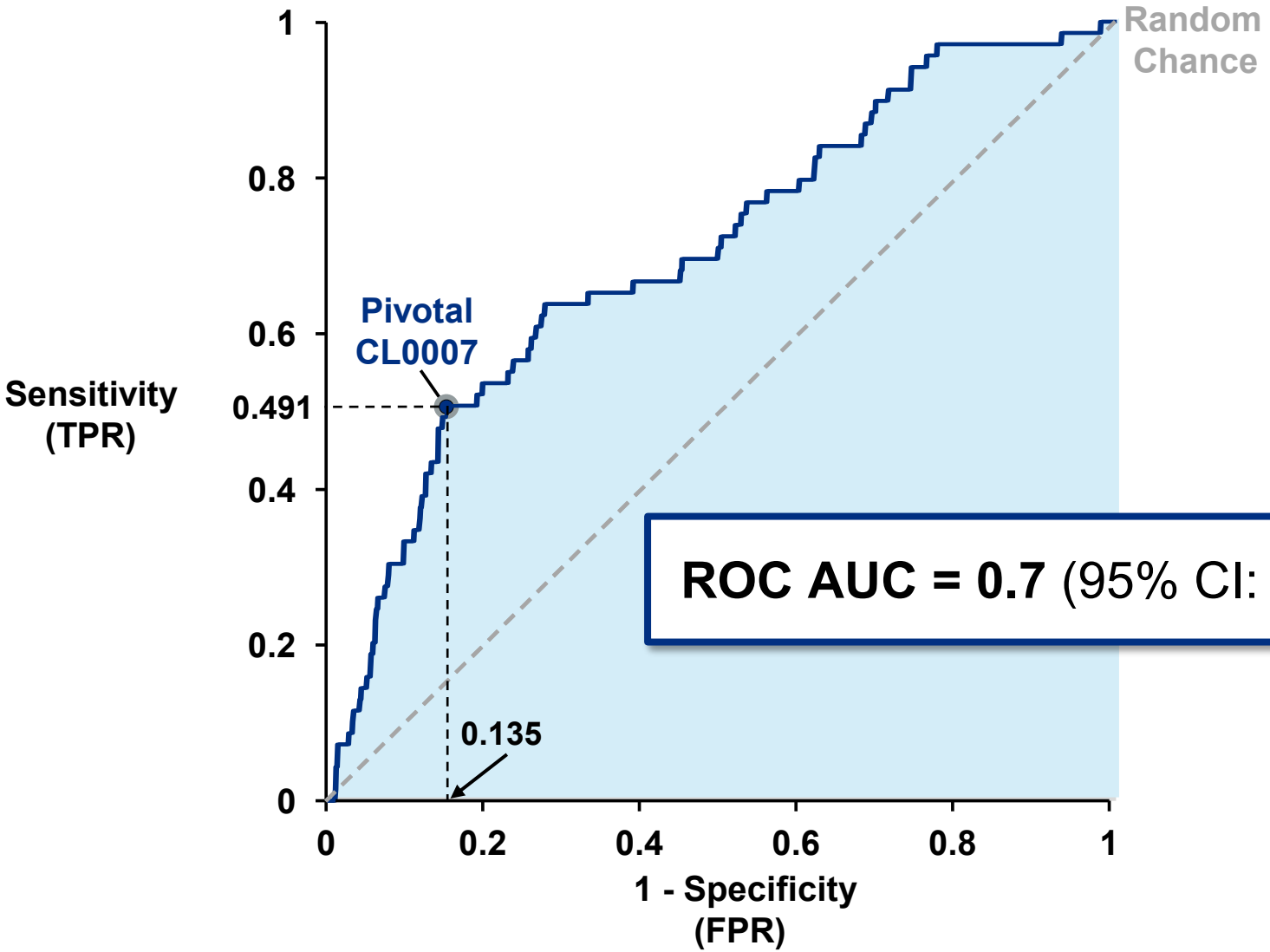
| | | Hierarchy Truth Standard | |
|---|---|---|---|
| | | Positive | Negative |
| LUM Signal | Positive | TP = 34 | FP = 337 |
| | Negative | FN = 35 | TN = 1,940 |

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} = \mathbf{84\%}\ (95\%\ \text{CI: } 82.6, 85.6)$$

Diagnostic performance CIs calculated using GEE approach; TP = true positives; FN = false negatives; TN = true negatives; FP = false positives

# Diagnostic Performance Demonstrates Effectiveness

| | |
|---|---|
| **AUC** | Area under the curve |
| **FPR** | False positive rate |
| **ROC** | Receiver operating characteristics |
| **TPR** | True positive rate (sensitivity) |

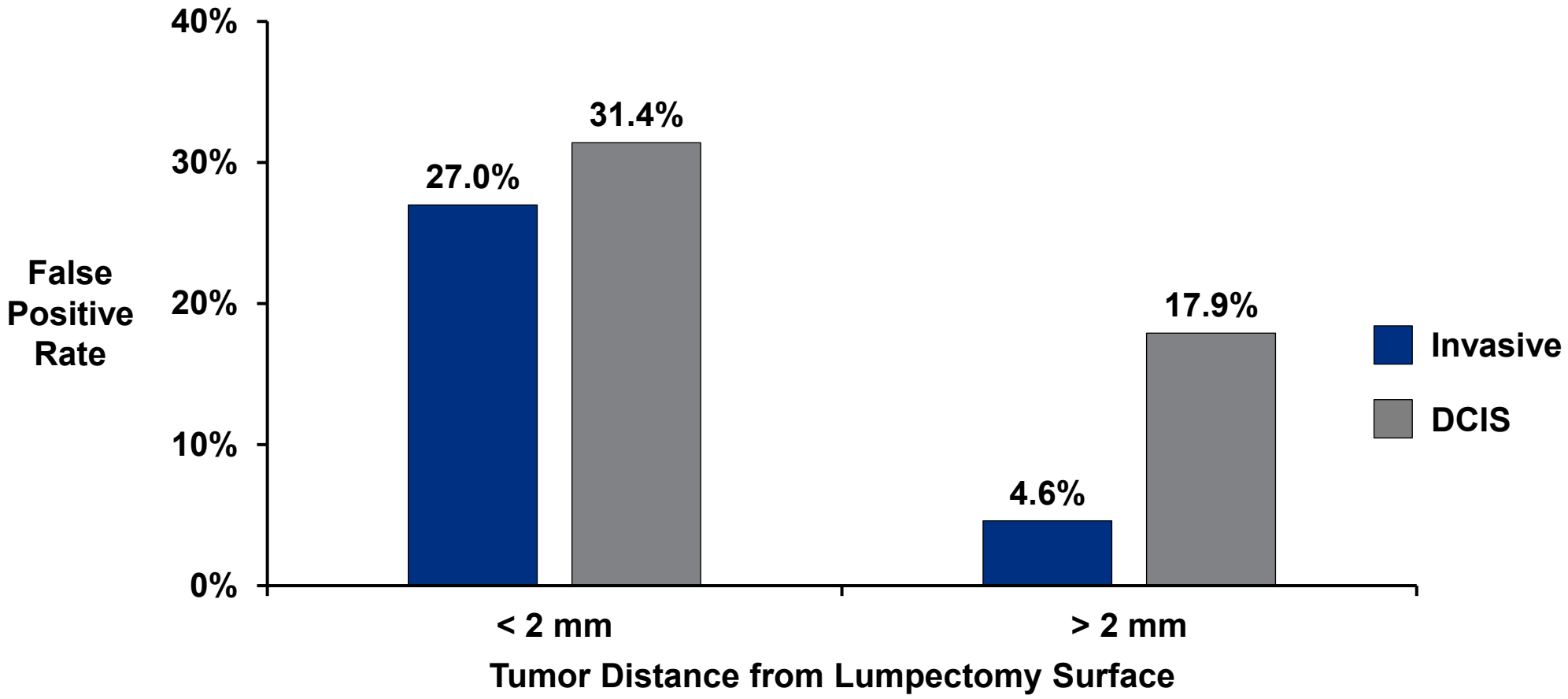



**ROC AUC = 0.7** (95% CI: 0.63, 0.77) **> 0.5** (random chance)

# Secondary Endpoint: LUM-Guided Conversion of Positive Margins to Final Negative Margins

| **Clinically Relevant Pre-Defined Secondary Endpoint, n** (%) (95% CI) | **Efficacy Population N = 357** |
|---|---|
| Patients having positive margins after SoC lumpectomy procedure n (%) | **62** (17%)<br>(13.6, 21.7) |
| Percent of patients converted from positive margins after SoC lumpectomy procedure to final negative margins by excising LUM-guided shaves n/n (%)<br>▪ **8 patients avoided second surgery by removing LUM-guided shaves**<br>▪ **1 patient still underwent second surgery despite final negative margins** | **9/62** (15%)<br>(6.9, 25.8) |
| Of remaining 53 patients with SoC pathology-determined positive margins<br>▪ **45 patients proceeded to second surgery**<br>– **28 patients had no residual cancer found** | **28/45** (62%)<br>(48.1, 76.4) |

# LUMISIGHT Activation in Areas Adjacent to Tumor

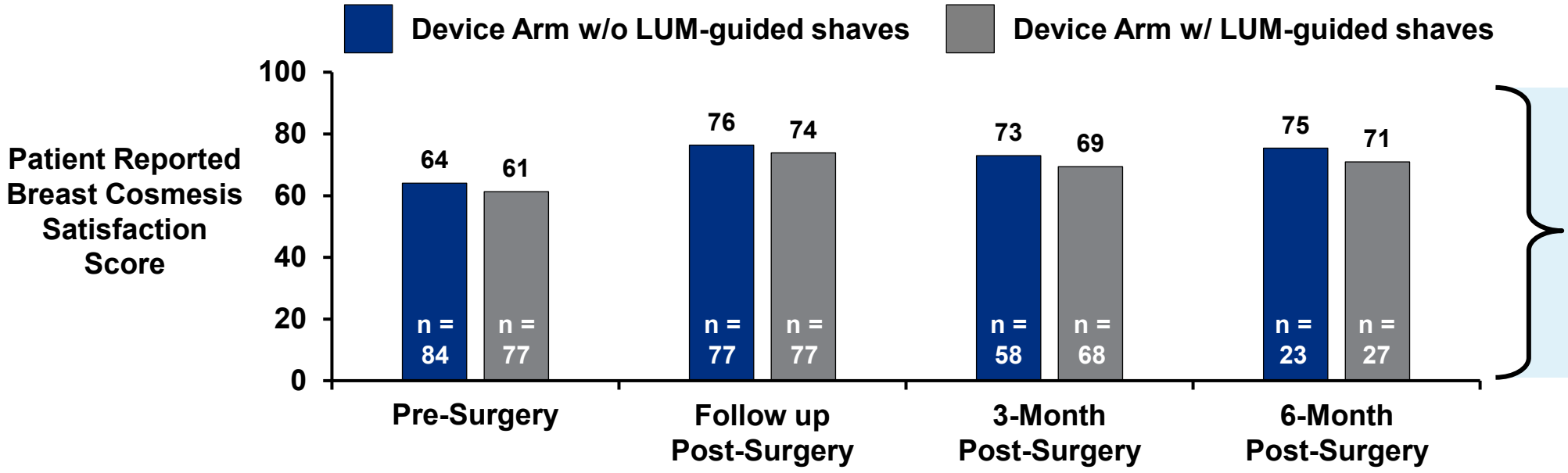



**LUMISIGHT's MoA generates elevated fluorescence adjacent to tumor; reasonable to attribute conversion to negative margins to drug effect**

Lanahan et al. 2021

# Secondary Endpoint: Contribution to Excision Volume and (Exploratory) Its Impact to Patient Perceived Cosmesis

| Clinically Relevant Secondary Endpoint, % (±SD) | N = 166 |
|---|---|
| **Contribution of LUM-guided shaves to total excision volume when ≥ 1 removed** | **20%** (±15%) |




**Results do not suggest that additional LUM-guided shaves worsened cosmetic outcomes**

# 35 Patients Had Improved Surgical Outcomes by Removing LUM-Guided Shaves

| Surgical benefits from LUM-guided shaves, n (%) | Efficacy Population N = 357 |
|---|---|
| **Patients with improved surgical outcomes** | **35*** (9.8%) |
| **Residual cancer removed** | **27** |
| **Converted to final negative margins** | **9** |

*1 patient overlapped

# Summary of Efficacy

1. Removal of residual cancer co-primary endpoint met performance goal; LUM System enabled residual cancer removal in 27 (8%) patients
2. Tissue-level sensitivity endpoint missed; tissue-level specificity endpoint met; 84% diagnostic accuracy
3. Converted 15% of positive margins to negative, sparing 8 patients second surgeries
4. Results do not suggest that additional tissue resection driven by LUMISIGHT worsened cosmetic outcomes
5. Provided real-time, *in vivo* examination of lumpectomy cavity

# Safety

**Peter Blumencranz, MD, FACS**

Medical Director, BayCare Oncology Service Line

Health System

Medical Director, The Comprehensive Breast Care Center of Tampa Bay

# LUMISIGHT Safety Profile Well Characterized from 726 Patients

| Population | Number of Patients |
|---|---|
| Overall safety population | 726 |
| Breast cancer safety population | 703 |
| Other solid tumors | 23 |

**Pivotal Study CL0007 includes > 50% of safety population (N = 406)**

# Administration of LUMISIGHT in Preoperative Area Under Medical Supervision

- Administered 2-6 hours prior to imaging at 1 mg/kg dose by IV injection over 3 minutes
- Performed in preoperative area under medical supervision
- All serious events were managed immediately with standard interventions
- Premedication at discretion of physician

# Adverse Events Were Infrequent and Mostly Unrelated Other Than Chromaturia as Expected

| Preferred Term, n (%) | Overall Safety Population N = 726 |
|---|---|
| **AEs** | 633 **(87%)** |
| **AEs related to LUMISIGHT** | 615 **(85%)** |
| **Chromaturia** (discolored urine) | 613 **(84%)** |
| **Hypersensitivity** (includes 4 SAEs in next slide) | 9 **(1%)** |
| **Extravasation** | 4 **(0.6%)** |
| **Blood creatinine decreased** | 4 **(0.6%)** |
| **AEs not related to LUMISIGHT** | 151 **(21%)** |
| **Seroma** | 31 **(4%)** |
| **Breast Pain** | 22 **(3%)** |
| **Nausea** | 15 **(2%)** |

# Few Patients Experienced Serious Adverse Event

| Preferred Term, n (%) | Overall Safety Population N = 726 |
|---|---|
| **SAEs** | 7 **(1%)** |
| **SAEs related to LUMISIGHT** | 4 **(0.6%)** |
| **Anaphylactic reaction** | 3 **(0.4%)** |
| **Hypersensitivity** | 1 **(0.1%)** |
| **SAEs not related to LUMISIGHT** | 3 **(0.4%)** |
| **Breast cellulitis** | 1 **(0.1%)** |
| **Vascular pseudoaneurysm** | 1 **(0.1%)** |
| **Somnolence** | 1 **(0.1%)** |
| **Acute kidney injury** | 1 **(0.1%)** |
| **Acute respiratory failure** | 1 **(0.1%)** |

# Related AEs Leading to Study Discontinuation Were Infrequent and All Events Resolved

| Preferred Term, n (%) | Overall Safety Population N = 726 |
|---|---|
| **AEs leading to discontinuation** | 8 **(1%)** |
| **AEs related to LUMISIGHT leading to discontinuation** | 8 **(1%)** |
| **Hypersensitivity reaction** | 3 **(0.4%)** |
| **Anaphylactic reaction** | 2 **(0.3%)** |
| **Extravasation event** | 2 **(0.3%)** |
| **Nausea** | 1 **(0.1%)** |
| **Skin discoloration** | 1 **(0.1%)** |

**All events resolved, most on same day**

# No Deaths

| Category, n | Overall Safety Population<br>N = 726 |
|---|---|
| Deaths | 0 |

# Summary of Safety

1. LUMISIGHT safety profile at 1 mg/kg characterized in 726 patients; dose well tolerated

2. All patients with AEs and SAEs recovered and continued to receive SoC lumpectomy procedure

3. Personally enrolled and used LUM System in > 65 patients; comfortable using LUMISIGHT

# Allergic Reactions and Hypersensitivity

**Tanya Laidlaw, MD, FAAAI**

Director of Translational Research, Division of Allergy and Clinical Immunology

Chief, Section of Clinical and Translational Sciences, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital

Associate Professor, Harvard Medical School

# Expert Allergists Involved in Review of Allergic Reaction Events

## Tanya Laidlaw, MD, FAAAAI

Director of Translational Research, Division of Allergy and Clinical Immunology
Chief, Section of Clinical and Translational Sciences, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital
Associate Professor, Harvard Medical School

## Jamie Waldron, MD

Allergist and Immunologist, Massachusetts General Hospital
Instructor of Medicine, Harvard Medical School

## Anna Wolfson, MD, FAAAAI

Chair of Quality and Safety, Allergy and Immunology and Assistant Clinical Director, Allergy and Immunology, Massachusetts General Hospital
Assistant Professor, Harvard Medical School

# Trial Reported SAEs of Anaphylaxis or Hypersensitivity

| Patient | Reported in Trial |
|---|---|
| **Patient #1** | Anaphylaxis<br>Life-threatening |
| **Patient #2** | Hypersensitivity<br>Severe |
| **Patient #3** | Anaphylaxis<br>Severe |
| **Patient #4** | Anaphylaxis<br>Severe |

- Goal of post-hoc analysis was to further characterize allergic reactions and suggest appropriate mitigations
- Anaphylaxis guidelines: CTCAE (used in trial), EAACI, NIAID, WAO, USDAR, Ring and Messmer, Brown and NAP6

# Patient #1 Summary

- Cefazolin IV given 6 minutes prior to LUMISIGHT
- 1.5-2 minutes into LUMISIGHT administration (received 30mg of 104mg): patient reported chest tightness, dyspnea, upper body pain, noted to have a red face
- Administration of LUMISIGHT stopped
- Anesthesiologist reported patient as nauseous, diaphoretic, dyspneic, appearing cyanotic + apneic, having a weak pulse with generalized rash
- Treatment: 10L oxygen, epinephrine, Pepcid, Solumedrol IV, Benadryl IV; transferred to MICU
- Symptoms resolved in < 12 hours; discharged following day; lumpectomy performed 17 days later

## Allergists Post-Hoc Review

- Probably related, life-threatening, anaphylaxis
- Etiology could have been cefazolin or LUMISIGHT; LUMISIGHT more likely given timing
- Patient had history of hives to iodinated contrast media

# Patient #2 Summary

- Nuclear medicine injection and image-guided wire insertion 75 minutes prior to LUMISIGHT
- Tylenol 1000mg and gabapentin 300 mg given 32 minutes prior to LUMISIGHT
- 2 minutes into LUMISIGHT administration (received 27 mg of 61 mg): patient reported nausea, vomiting, headache, and lightheadedness; found to have profuse erythema, heart rate in 50s and BP 60/30 mmHg
- Infusion stopped
- Treatment: reclined; 500mL IV normal saline, Zofran 4 mg IV, Benadryl 25 mg IV
- Symptoms resolved within 13 minutes; lumpectomy occurred next day
- Allergy-related lab work: histamine (52 → 22), tryptase (11.5 → 12.6)

## Allergists Post-Hoc Review

- Probably related, severe, anaphylaxis
- Tylenol and gabapentin near LUMISIGHT administration → uncommon causes of allergic reactions
- Elevated histamine and less-so tryptase suggest mast cell-mediated mechanism of reaction

# Patient #3 Summary

- 1.5 minutes into LUMISIGHT administration (received 22 mg of 91 mg): patient reported dyspnea, tingling in tongue / hands / feet, nausea, swollen lip, eye redness, seeing “black spots”
- Vital signs normal with heart rate 88 and BP 110/89 mmHg
- Treatment: Benadryl 50 mg IV, hydrocortisone 100 mg, Zofran 4 mg, Pepcid 20 mg
- Patient recovered within 20 – 30 minutes; lumpectomy occurred same day
- Allergy-related lab work: histamine (55 → 11), tryptase (3.6 → 4.3)

## Allergists Post-Hoc Review

- Probably related, moderate, possible allergic reaction
- Lab results reassuring after quick improvement
- Patient symptoms mostly subjective; documentation shows absence of tachypnea / hypoxia
- Briefly elevated histamine suggests mast cell-mediated mechanism of reaction

# Patient #4 Summary

- During 3-minute LUMISIGHT administration (full dose at 61 mg completed), patient reported feeling “funny” with itching in hands, feet and lips; BP 125/76 mmHg immediately after injection, 10 minutes later had BP 98/51 mmHg, 5 minutes after that BP 64/38 mmHg
- Treatment: 1L lactated ringers; reverse Trendelenburg
- Blood pressure normalized within 30 minutes; symptoms resolved within 70 minutes
  - Felt well during subsequent needle localization procedure
  - Brought to PACU in wheelchair felt lightheaded: experienced vasovagal event
  - Treated with 10 mg IV ephedrine, symptoms resolved; Lumpectomy occurred same day
- Allergy-related lab work: histamine (< 8 → < 8), tryptase (4.2 → 4.6)

## Allergists Post-Hoc Review

- Possibly related, moderate, vasovagal reaction
- Heart rate remained stable with subsequent vasovagal reaction ~ 3 hours after LUMISIGHT
- Diagnosis of hypersensitivity reaction unlikely due to symptoms resolving with IV fluids alone, and completely normal blood histamine and tryptase levels

# Summary of SAEs of Anaphylaxis or Hypersensitivity

| Patient | Reported in Trial | Allergist Review |
|---|---|---|
| **Patient #1** | Anaphylaxis<br>Life-threatening | Anaphylaxis<br>Life-threatening |
| **Patient #2** | Hypersensitivity<br>Severe | Anaphylaxis<br>Severe |
| **Patient #3** | Anaphylaxis<br>Severe | Possible allergic reaction<br>Moderate |
| **Patient #4** | Anaphylaxis<br>Severe | Vasovagal reaction<br>Moderate |

**All 4 patients had reactions that were well identified, well managed, and did not prevent continuing with SoC lumpectomy**

# Preoperative Settings Well Equipped to Manage Anaphylaxis Risk

- Rate of preoperative mortality due to anaphylaxis expected to be very low
  - Patient is verbal, monitored for reaction, and skin is visible
  - No deaths in any Lumicell clinical trials due to anaphylaxis or any other AEs
- Preoperative and operating rooms already well equipped and well trained to manage anaphylaxis due to commonly used perioperative agents
  - 0.5% of new exposures to cefazolin report an allergic reaction[1]
    (50% of Lumicell population administered cefazolin prior to surgery)
  - ~ 2% of exposures to isosulfan blue report an allergic reaction[2]

**1. Drug allergy: A 2022 practice parameter update 2022; 2. Isosulfan blue prescribing information**

# Summary of Allergic Reactions and Hypersensitivity

1. Events infrequent with rate of 0.6% (4 / 726 patients); study protocol updated after first anaphylactic reaction
2. All events occurred at healthcare setting, treated by trained personnel, fully recovered, and proceeded to SoC lumpectomy
3. Risk of mortality expected to be extremely low in preoperative setting
4. Observed rates of anaphylaxis and hypersensitivity infrequent and acceptable in context of perioperative procedures
5. Mitigations reasonable to manage rate of reactions

# Risk Mitigation Strategies

**Jorge Ferrer, PhD**

Chief Scientific Officer

Lumicell

# Risk Mitigation Strategies – Labeling

- Proposed additional warnings and details in Prescribing Information
  - Clearly indicate risk of "life-threatening anaphylaxis" in Highlights and Warnings and Precautions section
  - Advise healthcare providers that before LUMISIGHT administration, obtain history of allergy and prior hypersensitivity reactions
  - Indicate that patients with history of multiple food or drug allergies or other hypersensitivities may be at increased risk
  - Specify to always administer LUMISIGHT in healthcare settings and have emergency resuscitation drugs, equipment, and trained personnel available
  - Instruct to interrupt injection if hypersensitivity reaction is suspected
  - Monitor patients for 15 minutes after injection

# Risk Mitigation Strategies – Training

**Current**

- Pre-Procedure
- Procedure
- Post-Procedure
- Granted System Login

**Validated In-Service User Training**

**Proposed**

**Warnings and Precautions**
- **Risks/mitigations hypersensitivity**
- **Surgeons to inform staff of Warnings and Precautions**
- **Enhanced pharmacovigilance**

- Pre-Procedure
- Procedure
- Post-Procedure
- Granted System Login

# Risk Mitigation Strategies – Enhanced Pharmacovigilance (PV)

- Partnered with PV vendor with experience in combination products
- Provide clear, accurate, and timely medical information
- Collect, evaluate, and report adverse events
- Implement an Adverse Events of Special Interest (AESI) program
- Train users on Lumicell's PV program
- Standardize collection of additional data to help us learn more about etiology of reactions

# Risk Mitigation Strategies – Postmarket Study

## Design

- Prospective, observational study

## Objectives

- Primary objective: evaluate incidence of anaphylactic reactions after administration of LUMISIGHT
- Secondary objective: evaluate incidence of other hypersensitivity symptoms after administration of LUMISIGHT

## Data collection

- Baseline and post-injection: vital signs; tryptase and histamine
- Complete medical histories regarding allergies
- Details on patient status and concomitant medications preceding LUMISIGHT injection
- Adverse events or symptoms related to hypersensitivity
- Treatment and outcome

# Sponsor-Proposed Risk Mitigation Strategies for LUMISIGHT Administration

- Clear Labeling
- Training Program
- Enhanced Pharmacovigilance
- Postmarket Study

# Clinical Perspective

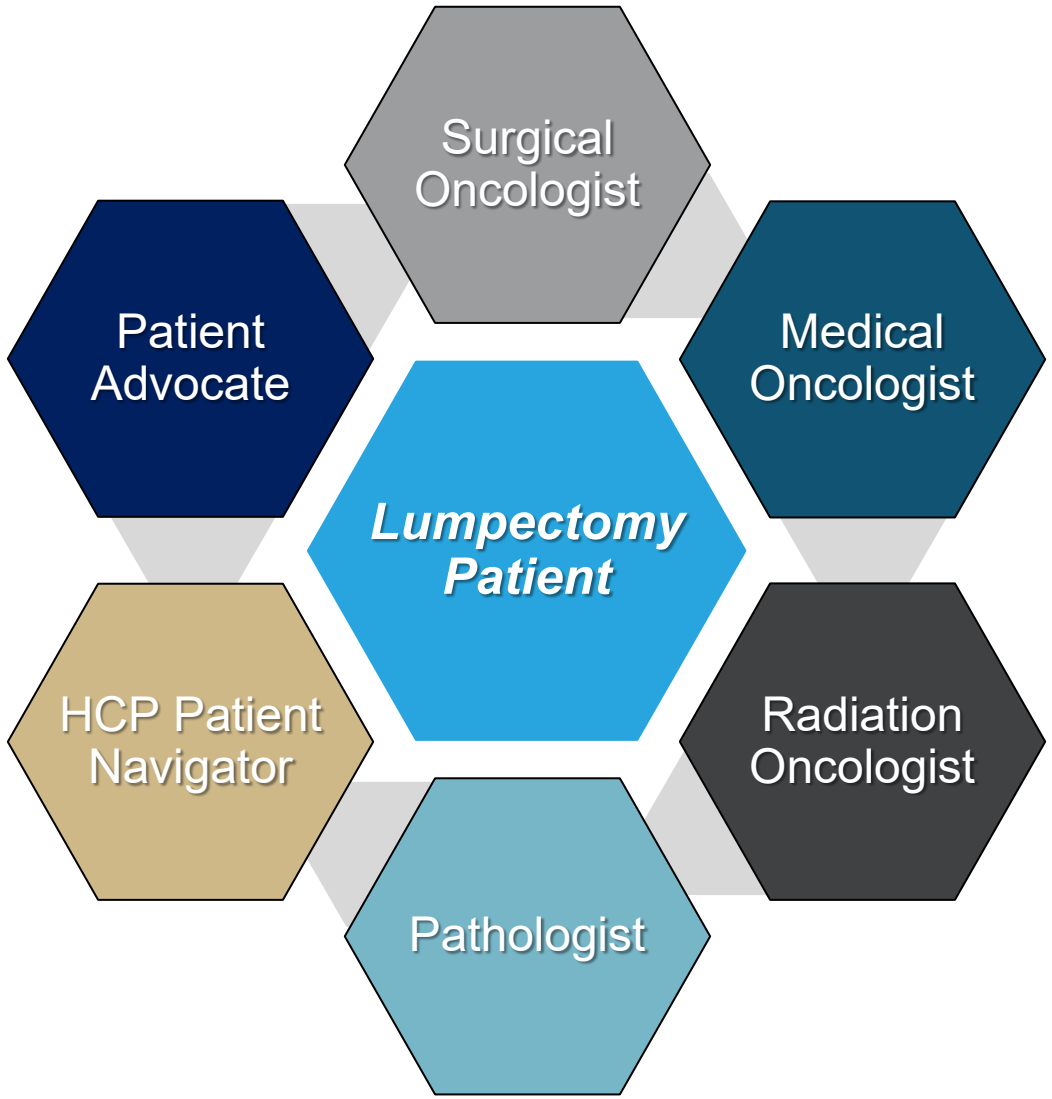
**Barbara Smith, MD, PhD**

Director, Breast Program, Massachusetts General Hospital

Massachusetts General Hospital Trustees Chair in Breast Surgery

Professor of Surgery, Harvard Medical School

# We Believe Change Is Needed Now




# Urgent Need for Improved Tool for More Complete Resection

## Intraoperative Tools

- Limited to *ex vivo* specimen analysis
- Predict specimen margin status
- Do not directly assess cavity

## Pathology Margins

- < 1% of surface[1]
- Examines deformed specimen
- 1 to 2 weeks
- Positive margins require 2nd surgery

## Second Surgeries

- Healing has deformed cavity during 2nd surgeries
- 65% of time no tumor in positive margin patients[2]

1. Carter, 1986; 2. Tang et al. 2015

# Benefits of LUM System Outweigh Risks

## Benefits

- Enables removal of residual cancer missed by SoC surgery and pathology
- Converts positive margins to negative, sparing potential second surgeries
- Does not appear to worsen cosmesis
- Provides real-time *in vivo* imaging to surgeons
- As adjunct to SoC, improves surgical outcomes

## Risks

- False positives can lead to unnecessary tissue removal
- 0.6% serious hypersensitivity or anaphylaxis risk (4 / 726 patients)

**Benefits of removing residual cancer left behind by SoC surgery outweigh any identified risks that can be managed in preoperative setting and with labeling**

# Moderator for Q&A

**Jorge Ferrer, PhD**

Chief Scientific Officer

Lumicell

# LUMISIGHT™ and Lumicell™ Direct Visualization System (DVS) as Adjunct to Standard of Care to Identify Residual Cancer Within the Lumpectomy Cavity

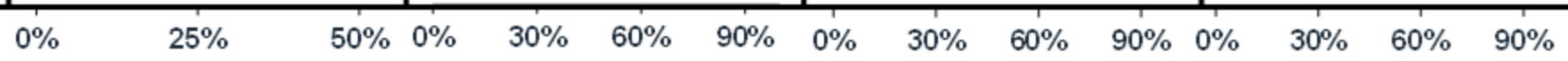
## March 5, 2024

Lumicell

Medical Imaging Drugs Advisory Committee (MIDAC)

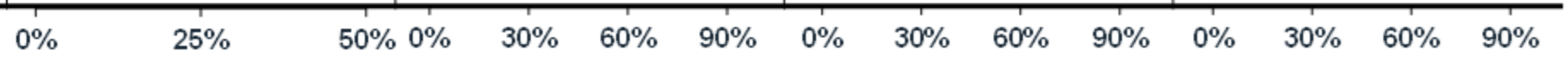
# Performance by Tumor Histology

| Tumor Histology<br>Based on Pre-op Biopsy | Patients | Residual Cancer Removal Rate<br>% (95% CI) | Sensitivity<br>% (95% CI) | Specificity<br>% (95% CI) | Margin Conversion<br>% (95% CI) |
|---|---|---|---|---|---|
| All | 357 | | | | |
| IDC/ILC ± DCIS | 287 | | | | |
| DCIS only | 70 | | | | |



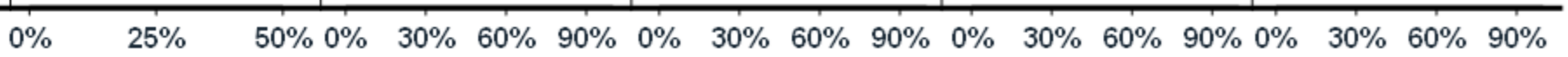
# Performance by Tumor Grade

| Tumor Grade | Patients n | Residual Cancer % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Margin Conversion % (95% CI) |
|---|---|---|---|---|---|
| All | 357 | | | | |
| Grade 1 | 59 | | | | |
| Grade 2 | 182 | | | | |
| Grade 3 | 107 | | | | |



# Performance by SoC Procedure:
## Comprehensive, Selective, and No Shaves

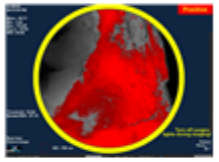
| SoC Procedure | Patients n | Residual Cancer % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Margin Conversion % (95% CI) | Median Volume Added by LUM-Shaves for Patients with ≥ 1 Shave % (95% CI) |
|---|---|---|---|---|---|---|
| All | 357 | | | | | |
| Comprehensive shaves | 71 | | | | | |
| Selective shaves | 165 | | | | | |
| No SoC shaves | 121 | | | | | |

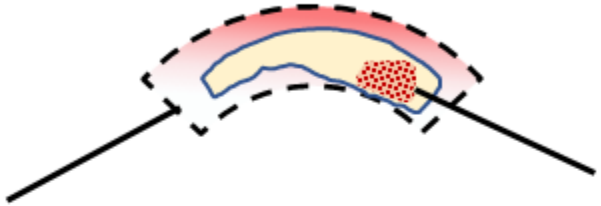


# LUM-Image Results Compared with Pathology Findings

## True Positive

Positive LUM-signal



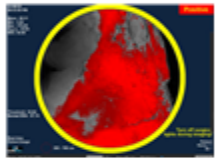


LUM-guided shave **contains** tumor

**n = 34 shaves**

## False Positive

Positive LUM-signal

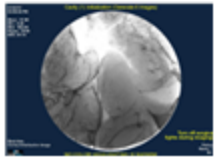


LUM-guided shave does **not** contain tumor

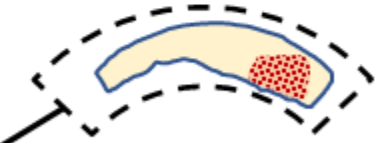
**n = 337 shaves**

## False Negative

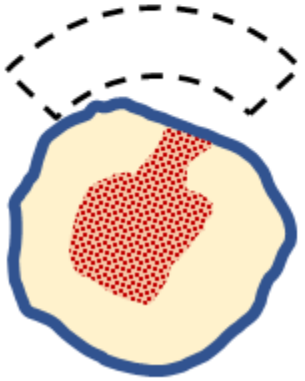
Negative LUM-signal



Second surgery finds tumor



No additional tissue excised

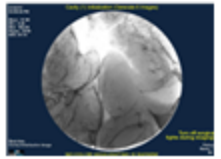


**n = 24 shaves**

**n = 11 shaves**

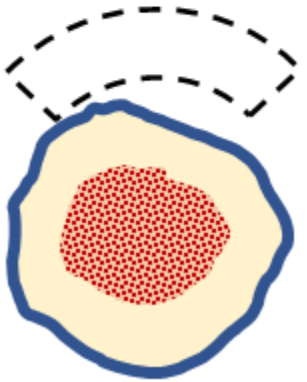
## True Negative

Negative LUM-signal



Second surgery finds **no** tumor

No additional tissue excised



**n = 43 shaves**

**n = 1,897 shaves**