Clinical Trial Results Using Fluorescently-Labeled Antibody to Guide Surgical Resection

Deep South Otolaryngology Meeting
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Dr. Rosenthal’s Lab
Overview

• Background
  ▪ Current Challenge in Head & Neck Surgery
  ▪ Antibody-based Surgical Navigation

• Study Design

• Results
  ▪ Imaging
  ▪ Safety

• Conclusions & Future Directions
Identifying Cancer in the O.R.

• Surgeons rely on **visual** and **tactile** information to distinguish tumor from normal tissue

Can we better visualize cancer at the time of surgery to ensure a complete resection?
Differentiating Cancer from Normal Tissue

- Head & Neck
- Lung
- Colorectal

- Breast

- Colorectal
- Ovarian (Europe)
Antibody-based Fluorescence

Cetuximab-IRDye800

Preclinical Studies
- Mouse
- Macaque Monkey

Phase I Trial Objectives
- Can the dye distinguish tumor from normal tissue?
- Is Cetuximab-IRDye800 safe in humans?
- What is the optimal dose?
**Study Design**

**Key Inclusion/Exclusion Criteria**
- Head and neck squamous cell carcinoma
- Normal ECG (normal QTc)
- Tolerates unlabeled cetuximab

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg/m²</td>
<td>25 mg/m²</td>
<td>62.5 mg/m²</td>
</tr>
</tbody>
</table>

**I.V. Dye Infusion**
- Day 0: Cohort 1
- Day 1: Cohort 2
- Day 3 or 4: Cohort 3

**Surgery**
- Day 15: Cohort 1, Cohort 2, Cohort 3

**Follow-Up**
- Day 30: Cohort 1, Cohort 2, Cohort 3

**Safety**
- ✓ Cohort 1
- ✓ Cohort 2
- ✓ Cohort 3

**Imaging**
- ✓ Cohort 1
- ✓ Cohort 2
- ✓ Cohort 3
Imaging Workflow

REAL-TIME

1 CLINIC

LUNA

2 OPERATING ROOM

POST-RESECTION

3 O.R. BACK TABLE

PEARL

4 SURGICAL PATHOLOGY

ODYSSEY
# Patient Characteristics

<table>
<thead>
<tr>
<th>Cohort 1 (2.5 mg/m²)</th>
<th>#</th>
<th>Age</th>
<th>Sex</th>
<th>Cancer Origin</th>
<th>Tumor Site</th>
<th>Cancer Stage</th>
<th>Prior Chemo</th>
<th>Prior Radiation</th>
<th>Dye Dose (mg)</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>Oral Cavity</td>
<td>Lateral Tongue</td>
<td>T1, N2b</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>5.0</td>
<td>Partial Glossectomy with ND</td>
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<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>Cutaneous</td>
<td>Temple</td>
<td>T2, N1</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>6.1</td>
<td>Wide Local Excision with ND and FF</td>
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<tr>
<td>3</td>
<td>64</td>
<td>F</td>
<td>Oral Cavity</td>
<td>Floor of Mouth</td>
<td>T3, N0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>4.4</td>
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</table>

<table>
<thead>
<tr>
<th>Cohort 2 (25 mg/m²)</th>
<th>#</th>
<th>Age</th>
<th>Sex</th>
<th>Cancer Origin</th>
<th>Tumor Site</th>
<th>Cancer Stage</th>
<th>Prior Chemo</th>
<th>Prior Radiation</th>
<th>Dye Dose (mg)</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>4</td>
<td>77</td>
<td>M</td>
<td>Oral Cavity</td>
<td>Floor of Mouth</td>
<td>T4a, N0</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>44.5</td>
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<tr>
<td>5</td>
<td>40</td>
<td>M</td>
<td>Oral Cavity</td>
<td>Lateral Tongue</td>
<td>T2, N1</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>59.0</td>
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<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>Lip</td>
<td>Neck Metastasis</td>
<td>T0, N3</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>45.5</td>
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<table>
<thead>
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<th>Cohort 3 (62.5 mg/m²)</th>
<th>#</th>
<th>Age</th>
<th>Sex</th>
<th>Cancer Origin</th>
<th>Tumor Site</th>
<th>Cancer Stage</th>
<th>Prior Chemo</th>
<th>Prior Radiation</th>
<th>Dye Dose (mg)</th>
<th>Procedure</th>
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<tr>
<td>7</td>
<td>84</td>
<td>F</td>
<td>Nasal Cavity</td>
<td>Septum</td>
<td>T2, N0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>92.5</td>
<td>Rhinectomy with ND and FF</td>
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<td>8</td>
<td>60</td>
<td>M</td>
<td>Oropharynx</td>
<td>Tonsil</td>
<td>T2, N1</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>151.25</td>
<td>Tonsillectomy with ND</td>
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<tr>
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<td>57</td>
<td>M</td>
<td>Oral Cavity</td>
<td>Floor of Mouth</td>
<td>T3, N2</td>
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<td>N</td>
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<td>147.5</td>
<td>Composite Resection with ND and FF</td>
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ND = Neck Dissection, FF = Free Flap Reconstruction
Intraoperative Imaging

Cohort 1

50 yo M with L temple cutaneous SCC and metastatic L parotid node
69 yo F with hx of oral cavity SCC, now with eroded L neck metastatic lymph node
Intraoperative Imaging

84 yo F with cutaneous SCC of the nasal vestibule

Cohort 3

Day 0

Day 1

Day 4

Post-Resection
Dose Effects on Fluorescence

Cohort 1 (n=3)

Cohort 2 (n=3)

Cohort 3 (n=3)
Tracking the dye from Patient to Histology

Clinic

O.R. Backtable

Surgical Pathology

Positive  Positive  Positive  Positive  Negative  Negative

Negative  Positive  Positive  Positive
Pathologic Confirmation

Fluorescence

H&E
Pathologic Confirmation

Fluorescence

EGFR
Metastatic Disease
Metastatic Lymph Node

Cohort 2

Fluorescent

H&E
Is Cetuximab-IRDye safe?

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>Cohort 3</th>
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<tbody>
<tr>
<td></td>
<td>Probably/Possibly Related</td>
<td>Unrelated</td>
<td>Probably/Possibly Related</td>
<td>Unrelated</td>
<td>Probably/Possibly Related</td>
<td>Unrelated</td>
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<td>Grade 1</td>
<td>4</td>
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<td>4</td>
<td>23</td>
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<tr>
<td>Grade 2</td>
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<td>5</td>
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<td>8</td>
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<td>Grade 3</td>
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<td>5</td>
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<tr>
<td>Grade 4</td>
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<td>Grade 5</td>
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</table>

- Dose escalation does not lead to more AEs
ECG Surveillance

QTc

![Graph showing QTc values across different time points and cohorts](image)

- Pre
- Post 30m
- Post 2H
- Post 30d

Cohort 1
Cohort 2
Cohort 3
Conclusions

- Cetuximab-IRDye800 appears safe & demonstrates tumor-specific fluorescence even at low doses

- Optimal dose is between 25 - 63 mg/m²

- Dye can be tracked from pre-op through surgery and pathologic processing
Future Directions

• Histologic localization of dye
  ▪ Can the dye be used to study therapeutic delivery?

• Intraop characterization of cancer
  ▪ Is there a fluorescence threshold that can determine whether a specimen/margin has cancer or not?

• Guiding surgical margins with fluorescence
  ▪ Can pre-op fluorescence refine surgical margins?

• Many more questions to answer

"The solution of one problem brings us face to face with another problem" - Martin Luther King Jr.
• Study Leaders
  ▪ Eben Rosenthal MD
  ▪ Kurt Zinn DVM, PhD

• Rosenthal Lab
  ▪ Jason Warram PhD
  ▪ Melissa Korb MD
  ▪ Esther deBoer
  ▪ Yolanda Hartman
  ▪ Lisa Clemons RN

• Co-Investigators
  ▪ William Carroll MD (ENT)
  ▪ Cecelia Schmalbach MD (ENT)
  ▪ Margaret Brandwein-Gensler MD (Pathology)
  ▪ Joshua Richman MD PhD (Surgery)
  ▪ Theresa Strong PhD (Vector Facility)
  ▪ Lisle Nabell MD (Oncology)