5-Aminolevulinic Acid Hydrochloride (5-ALA HCl) for Oral Solution

Medical Imaging Drugs Advisory Committee Meeting

May 10, 2017

Introduction

Alan Ezrin, PhD

President & CEO
NX Development Corporation

Proposed Indication

5-ALA is an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery
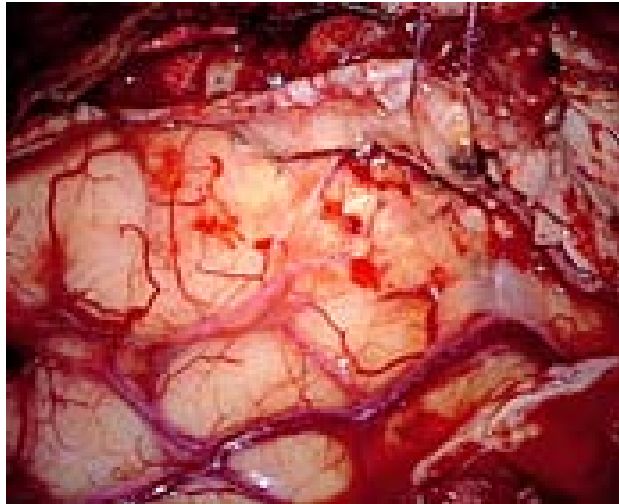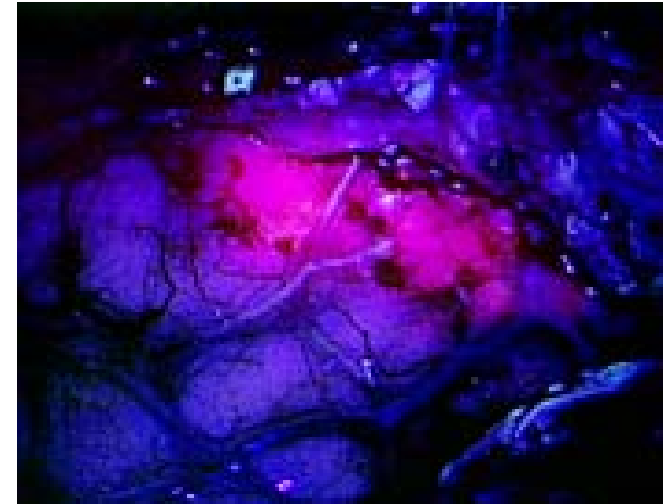
Real-time Tumor Visualization of Glioma

Problem	Current Situation	5-ALA Solution

◆ **Surgeon can only resect tumor that can be seen**

◆ **Visualization of gliomas is difficult under white light**
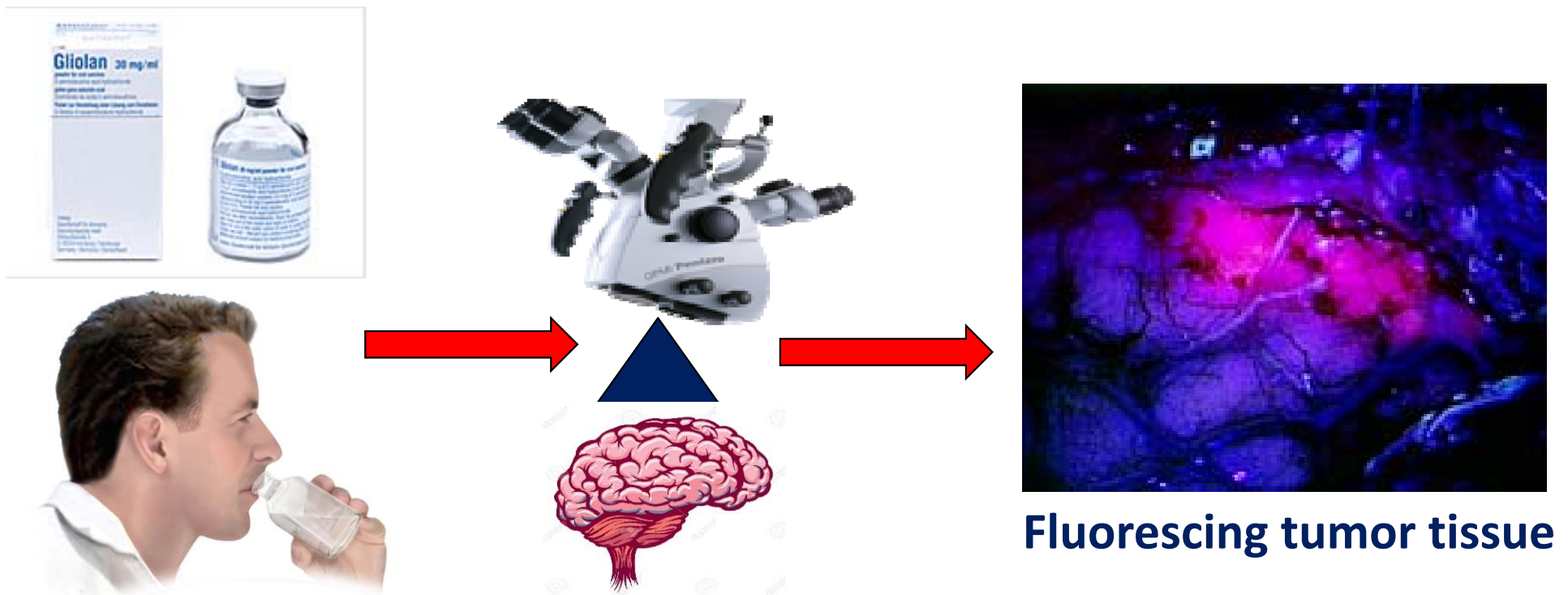
◆ **Real-time visualization of tumor with high predictive accuracy**

5-ALA Features

- ◆ **Orally administered 3 hours prior to surgery**
- ◆ **When illuminated under fluorescent light tumor appears intense red, while normal tissue appears blue**

Fluorescing tumor tissue

Regulatory and Marketing History of 5-ALA for Glioma Visualization

- ◆ **5-ALA developed by photonamic/medac GmbH**

- ◆ **Clinical studies conducted in Germany**

- ◆ **Approved as Gliolan® in the EU (2007)**

- ◆ **Approved in 40 countries**

- ◆ **Over 58,000 patients received 5-ALA**

- ◆ **NX Development Corp holds US license**

- ◆ **NDA submitted in 2016**

Agenda: 5-ALA Visualization of Glioma

Introduction	**Alan Ezrin, PhD** *President & CEO* *NX Development Corporation*
Visualization of Tumor During Glioma Surgery	**Constantinos G. Hadjipanayis, MD, PhD** *Professor and Chair, Dept. of Neurosurgery, Director of Neurosurgical Oncology, Professor of Oncological Sciences, Mount Sinai*
Clinical Efficacy	**Walter Stummer, Prof Dr med** *Department of Neurosurgery, University of Münster*
Safety Results	**Walter Stummer, Prof Dr med**
Benefit / Risk	**Constantinos G. Hadjipanayis, MD, PhD**
Conclusion	**Alan Ezrin, PhD**

Agenda: 5-ALA Visualization of Glioma

Introduction	**Alan Ezrin, PhD** *President & CEO* *NX Development Corporation*
Visualization of Tumor During Glioma Surgery	**Constantinos G. Hadjipanayis, MD, PhD** *Professor and Chair, Dept. of Neurosurgery, Director of Neurosurgical Oncology, Professor of Oncological Sciences, Mount Sinai*
Clinical Efficacy	**Walter Stummer, Prof Dr med** *Department of Neurosurgery, University of Münster*
Safety Results	**Walter Stummer, Prof Dr med**
Benefit / Risk	**Constantinos G. Hadjipanayis, MD, PhD**
Conclusion	**Alan Ezrin, PhD**

Visualization of Tumor During Glioma Surgery

Constantinos G. Hadjipanayis, MD, PhD

Professor and Chairman of Neurosurgery,

Mount Sinai Beth Israel Hospital

Director of Neurosurgical Oncology

Mount Sinai Health System

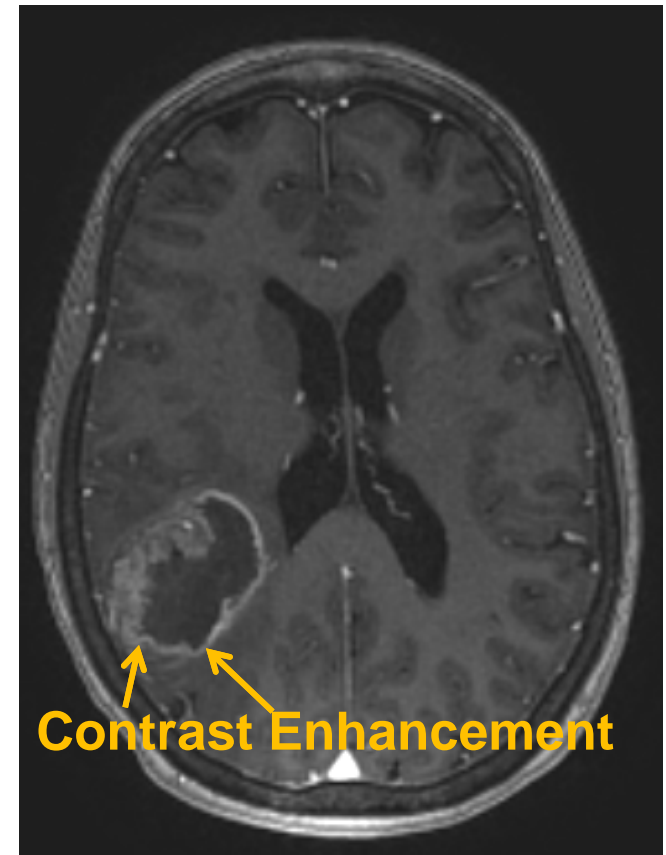*New York, NY*

Glioma Surgery Goals and Needs

◆ **Glioma incidence, prognosis, presentation, and treatment**

◆ **Goal of safe maximal extent of resection (EOR)**

◆ **Limitations of available tools for glioma surgery**

◆ **Current unmet need in glioma surgery**

◆ **5-ALA fluorescence-guided surgery (FGS)**

Gliomas: Background

- **US Incidence: 14,000 – 30,000 gliomas/yr**

- **Majority malignant high grade (WHO grade III, IV)**
  - Glioblastoma (GBM; WHO grade IV) most common

- **Universally lethal**
  - Median survival for malignant gliomas ~15 – 36 months despite all therapies
  - Metastases rare
  - Local recurrence common

- **Most low-grade gliomas (WHO grade II) transform to malignant gliomas**
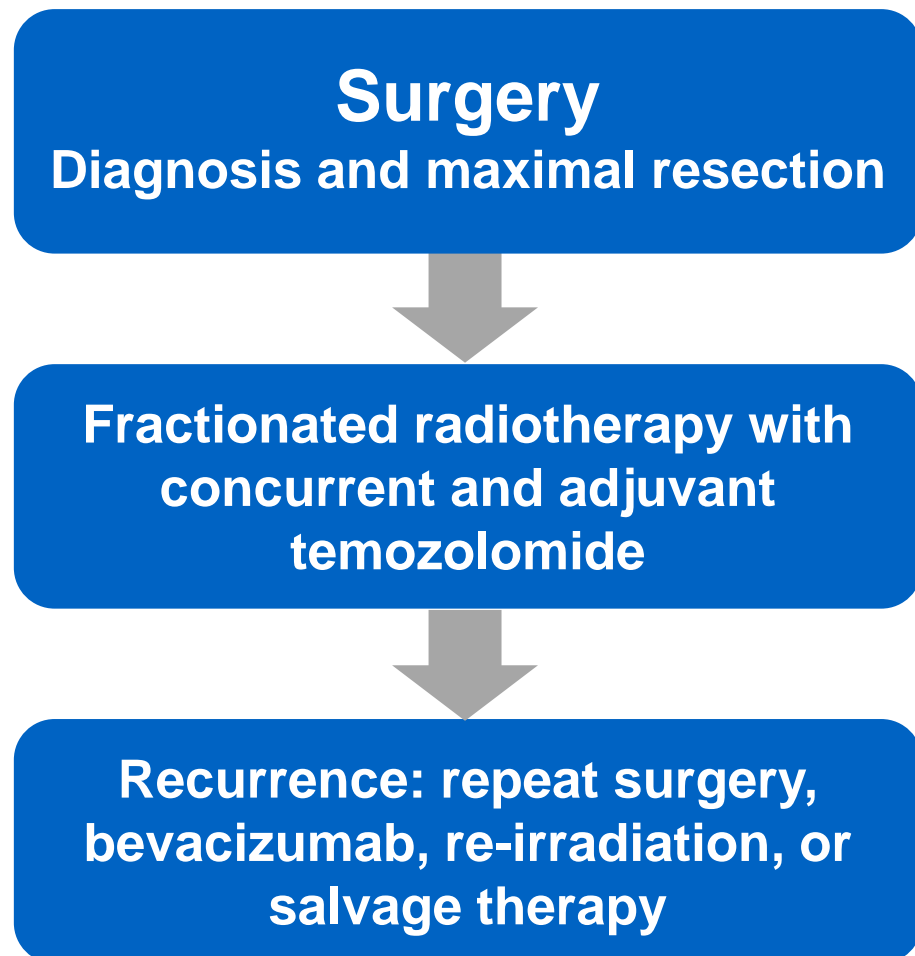
Glioma Patient Presentation

- ◆ **Headaches, new onset seizure**

- ◆ **Motor, speech, or sensory (visual) function may be impaired by tumor location**

- ◆ **Evaluation of patient in ER**
  - – MRI of malignant glioma reveals rim-enhancing lesion causing brain swelling

Contrast Enhancement

Preop MRI T1 w/Gad

Glioma Standard of Care

Malignant Glioma

Surgery
Diagnosis and maximal resection

↓

Fractionated radiotherapy with concurrent and adjuvant temozolomide

↓

Recurrence: repeat surgery, bevacizumab, re-irradiation, or salvage therapy

Low-Grade Glioma

Surgery
Diagnosis and maximal resection

↓

Observation with maximal resection

↓

Frequent recurrence and transformation to malignant glioma
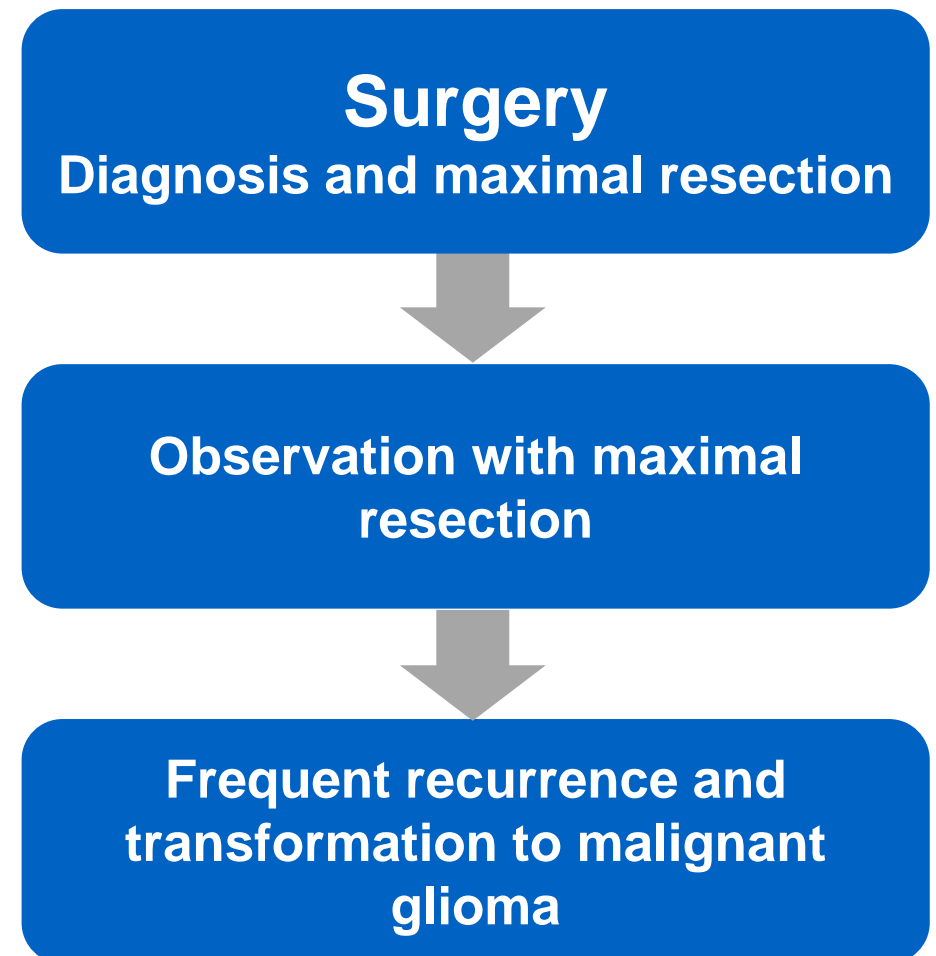
Consensus on Surgery:
# Maximal Safe Glioma Resection is Goal

◆ **Global Standard of Care**

- American Association of Neurological Surgeons (AANS)/ Congress of Neurological Surgeons (CNS) Section on Tumors 2008, 2014, and 2015

- National Institute for Health and Clinical Excellence (NICE) 2007

- National Cancer Institute (NCI), 2017

- European Society Medical Oncology (ESMO) 2014

- National Comprehensive Cancer Network (NCCN) 2016
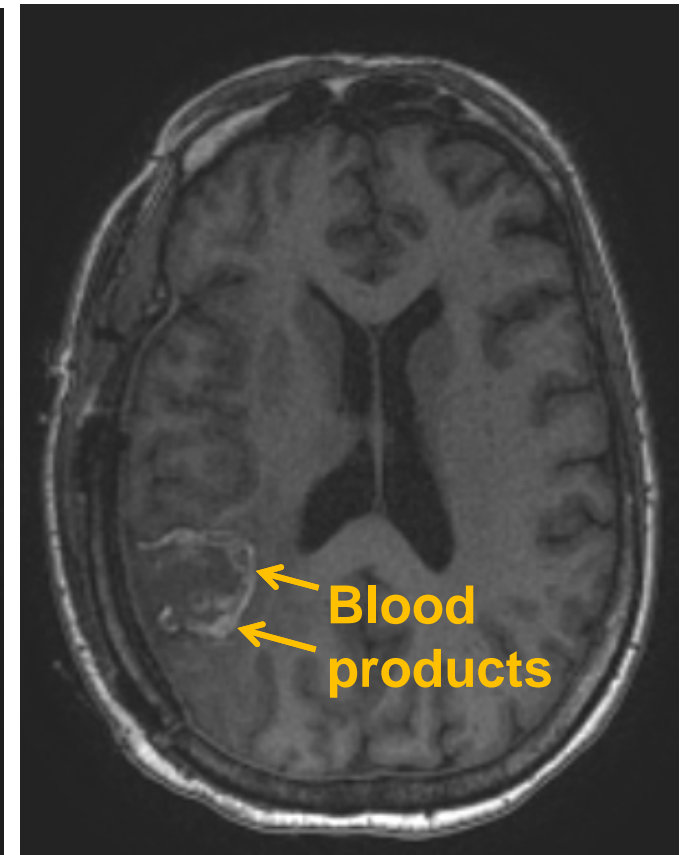
Maximal Extent of Resection (EOR)
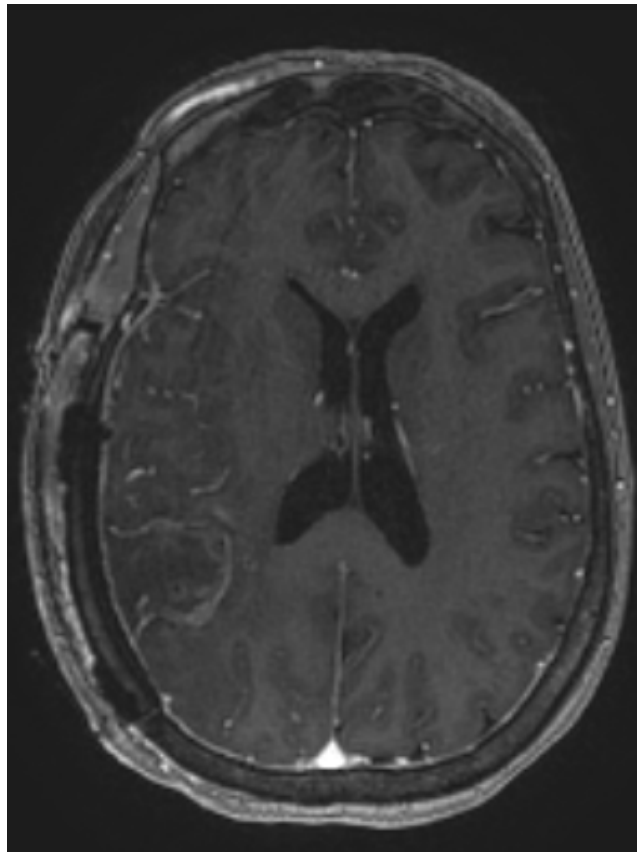
Preop MRI T1 w/Gad   **Postop MRI T1 w/Gad**   **Postop MRI T1 w/out Gad**

Maximal Extent of Resection (EOR)= Complete Resection of the MRI Contrast-Enhancing Portion of a Malignant Glioma

Impossible to Resect All Glioma Tumor Cells

- ◆ **Invasive and infiltrative tumors**

- ◆ **Difficult to visualize tumor and perform maximal EOR**

- ◆ **Residual tumors cells outside of contrast enhancing margin**

- ◆ **Almost all recurrences local**

Invasive Tumor cells

Postop MRI T1 w/Gad

Claes A et al. *Acta Neuropathol* 2007; Kelly PJ et al. *J Neurosurg* 1987.
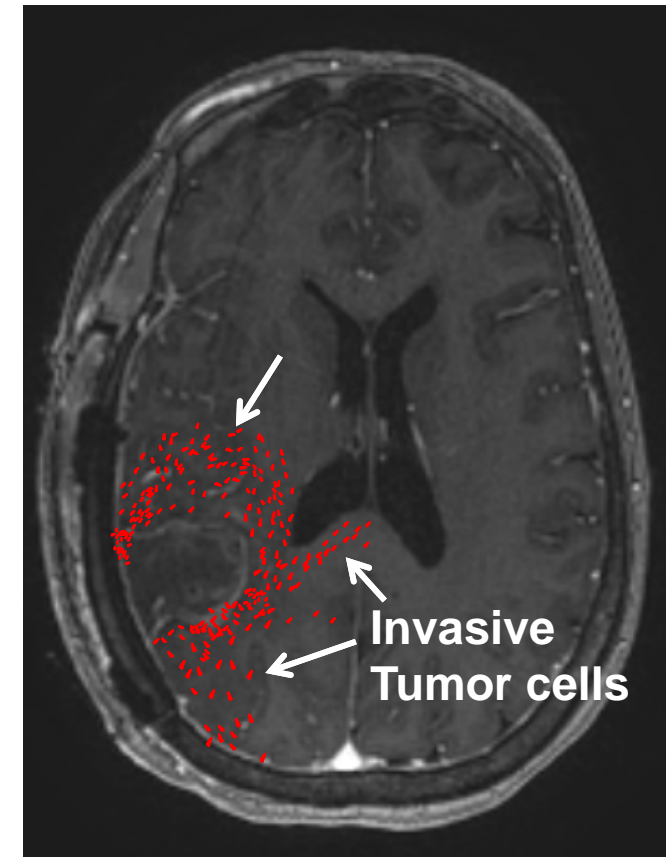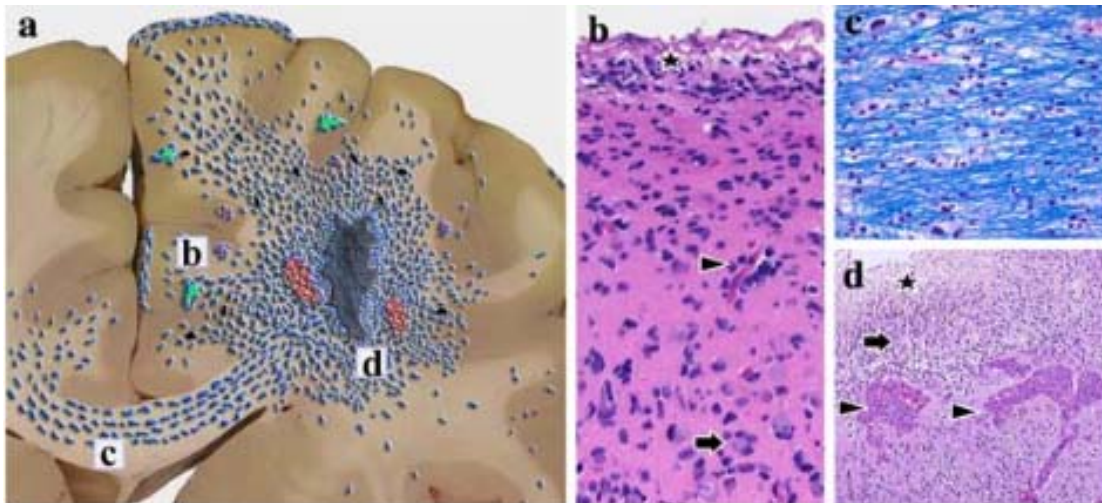
Extent of Resection (EOR) and Patient Benefit

◆ **Greater EOR correlates with overall survival**

◆ **Greater EOR permits better efficacy of chemoradiation**

◆ **Majority of patients DO NOT have maximal EOR**

Vuorinen V et al. *Acta Neurochir* 2003; Brown T. et al. *JAMA Oncology* 2016; Orringer D. et al. *J Neurosurg* 2012; McGirt M et al. *J Neurosurg* 2009; Lacroix M et al. *J Neurosurg* 2001; Sanai N et al. *J Neurosurg* 2011; Li YM et al. *J Neurosurg* 2016; Stummer W et al. *J Neuroonc* 2012.

Need to Localize Tumor and Preserve Neurologic Function

- ◆ **Localization and visualization of tumor important**

- ◆ **Understanding tumor relationship to surrounding critical tracts for speech, motor, sensory function**

- ◆ **Attempt to preserve neurologic function**
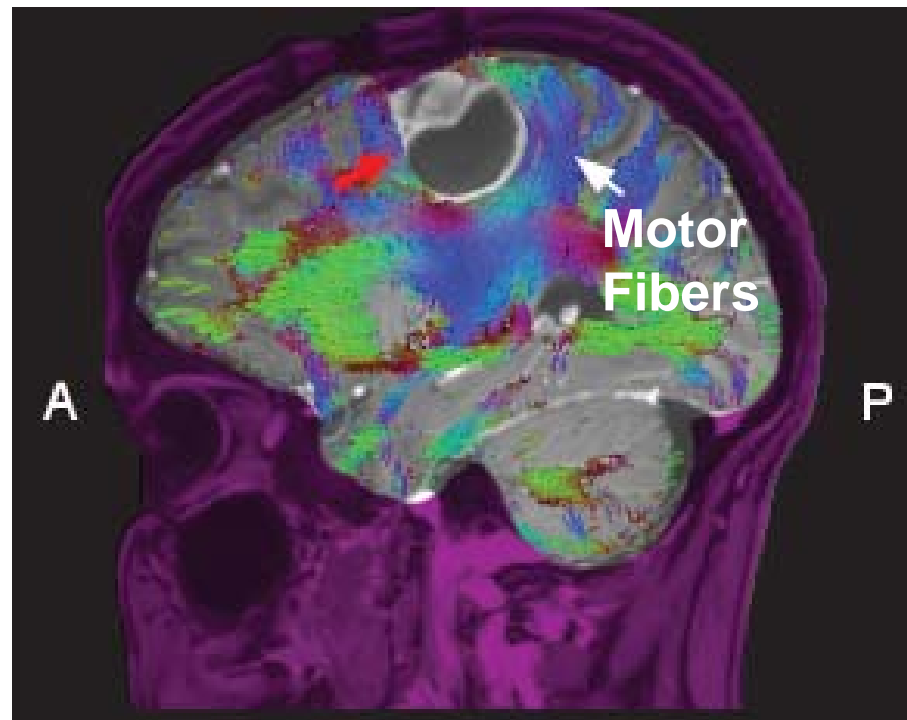
Current Surgical Tools and Challenges

- ◆ **Neuronavigation for localization**
  - – Does not account for brain shift during surgery
- ◆ **Localization of neurologic function during surgery**
  - – Intraoperative electrophysiologic mapping
  - – Awake brain surgery for speech mapping
- ◆ **Intraoperative MRI (iMRI) and ultrasound**

Neuronavigation
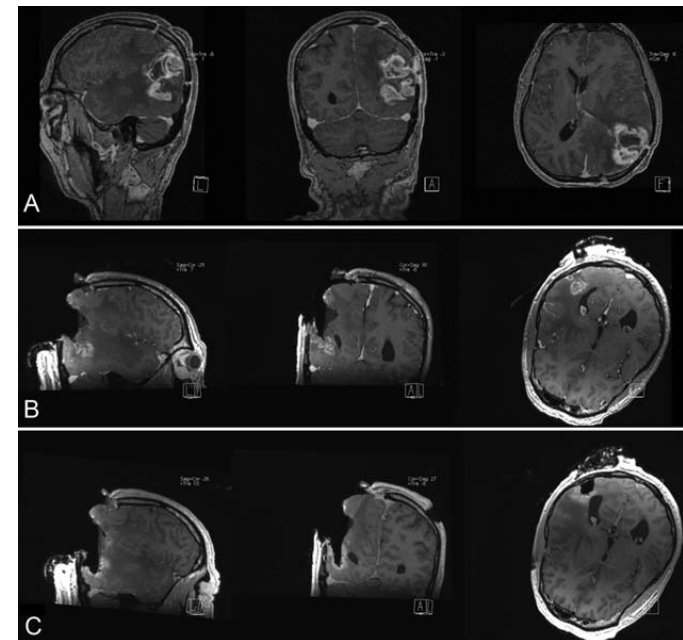
iMRI

Challenges of Glioma Surgical Resection

◆ **Tumors difficult to visualize due to infiltrative biology**

◆ **Often present in or close to critical areas of brain**

◆ **No real-time tumor localization tools for surgery**

◆ **Brain shift renders neuronavigation unreliable**

◆ **Some technology not available at all centers**

Unmet Need: What Surgeons Need for Glioma Resection

- ◆ **Visualize malignant tumor in real-time to guide surgery**

- ◆ **Delineate tumor from normal tissue**

- ◆ **Confidence that what is resected is tumor tissue**

- ◆ **Unambiguous, high resolution intraoperative imaging of tumor**

- ◆ **Solve complication of brain shift**

- ◆ **Achieve safe maximal extent of resection**

Intraoperative Glioma Visualization with Surgical Microscope

◆ **Difficult to delineate infiltrating tumor at margin**

◆ **Maximal extent of resection appears complete**
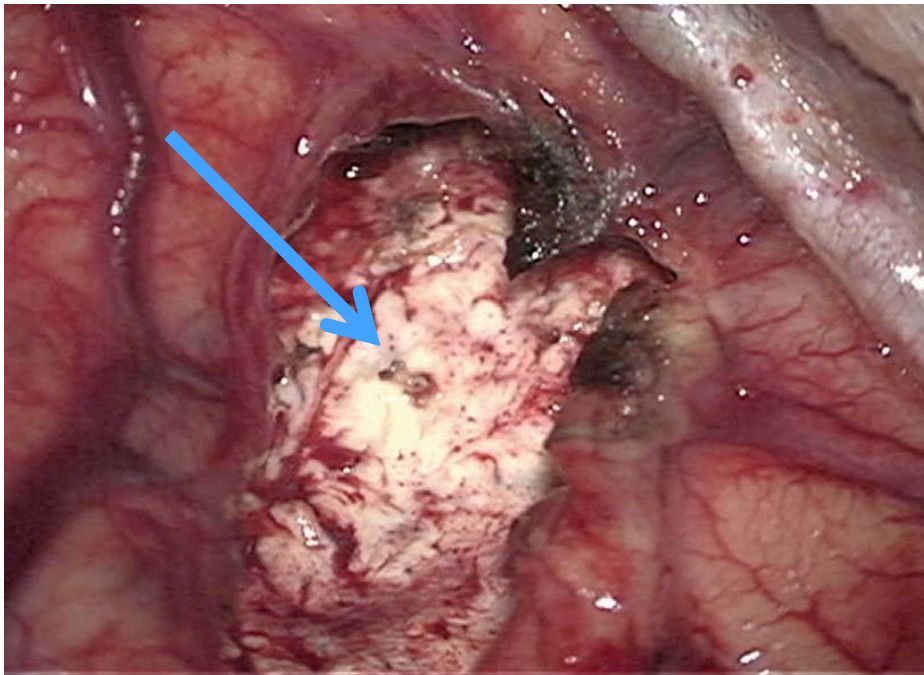
Microscope white light
illumination of glioma
resection cavity
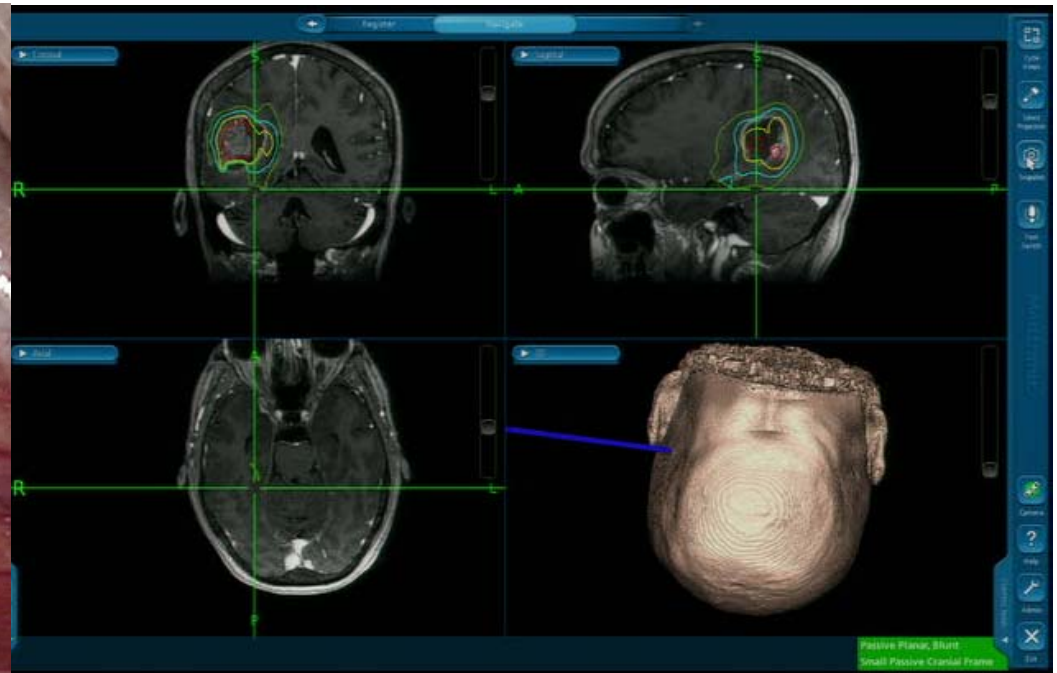
Neuronavigation

5-ALA Fluorescence-Guided Surgery (FGS)

◆ **Fluorescent malignant tumor revealed**
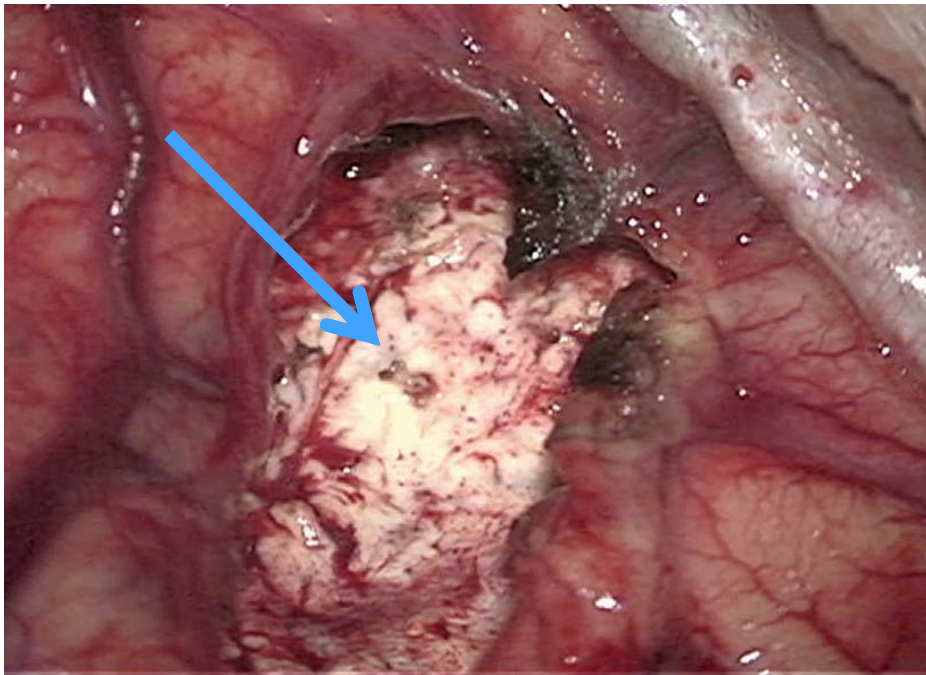
White light illumination
Normal appearing brain
after maximal resection
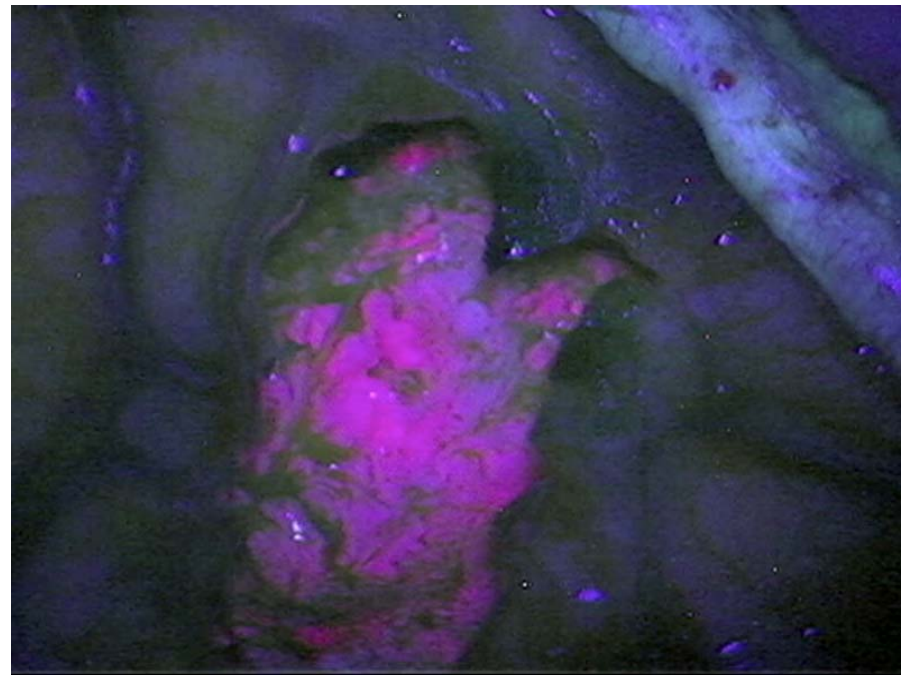
Blue-violet illumination
Tumor fluorescent

Hadjipanayis C. et al. *Neurosurgery* 2015.

5-ALA Oral Dosing

5-ALA $\xrightarrow{\text{Enzymes of heme biosynthesis} \atop \text{Malignant glioma intracellular synthesis}}$ **Protoporphyrin IX (PpIX)**
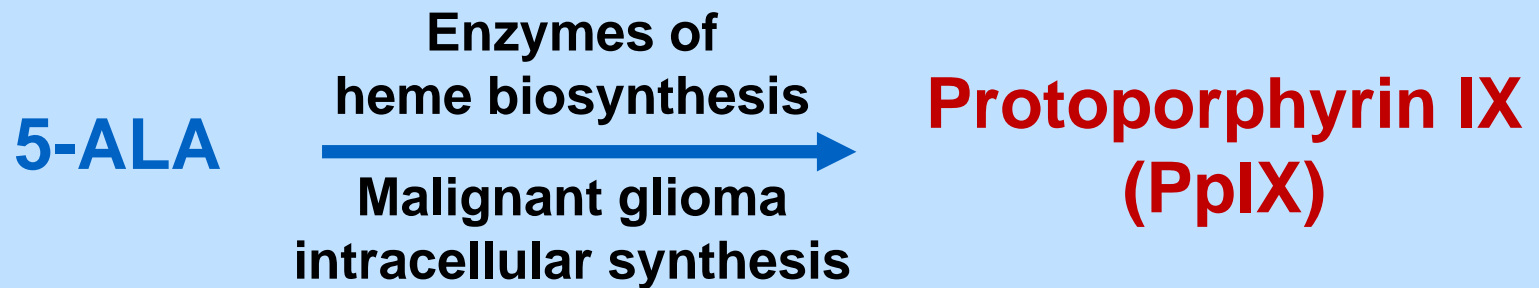
- ◆ Dosing at 20 mg/kg
- ◆ Rapid uptake in the blood
- ◆ Given 3 hours before surgery
- ◆ Tumor tissue fluorescence >8 hours after administration

5-ALA Profile

- **PpIX selectively accumulates in tumor cells**

- **Visualization after excitation by 400- 410 nm blue light**

- **Essentially nontoxic**
  - Skin photosensitivity within 24 hours
  - Liver metabolism (transient LFT elevation)

Conventional microscope

Blue Light 410 nm

PpIX Intraoperative Tumor Fluorescence and Real-Time Image-Guided Surgery
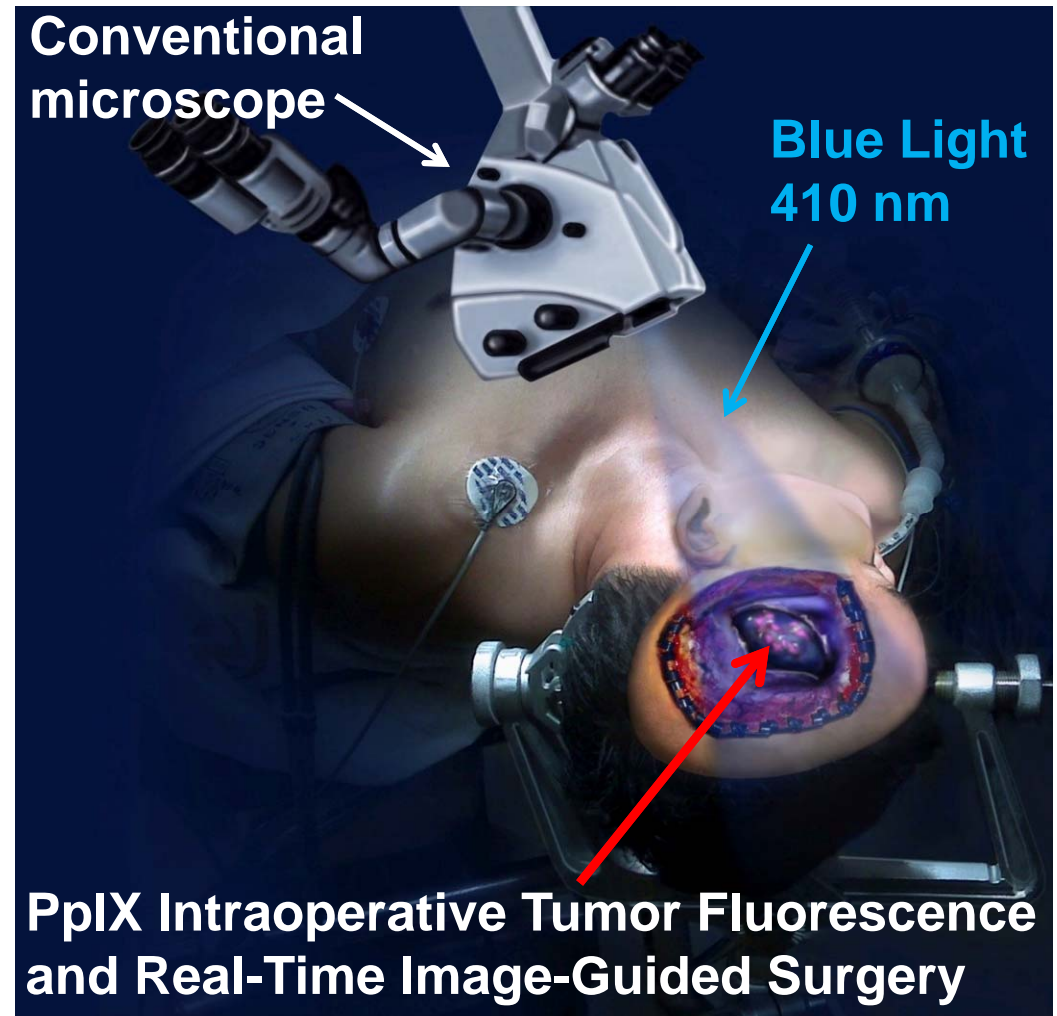
5-ALA FGS Real-Time Image Guidance
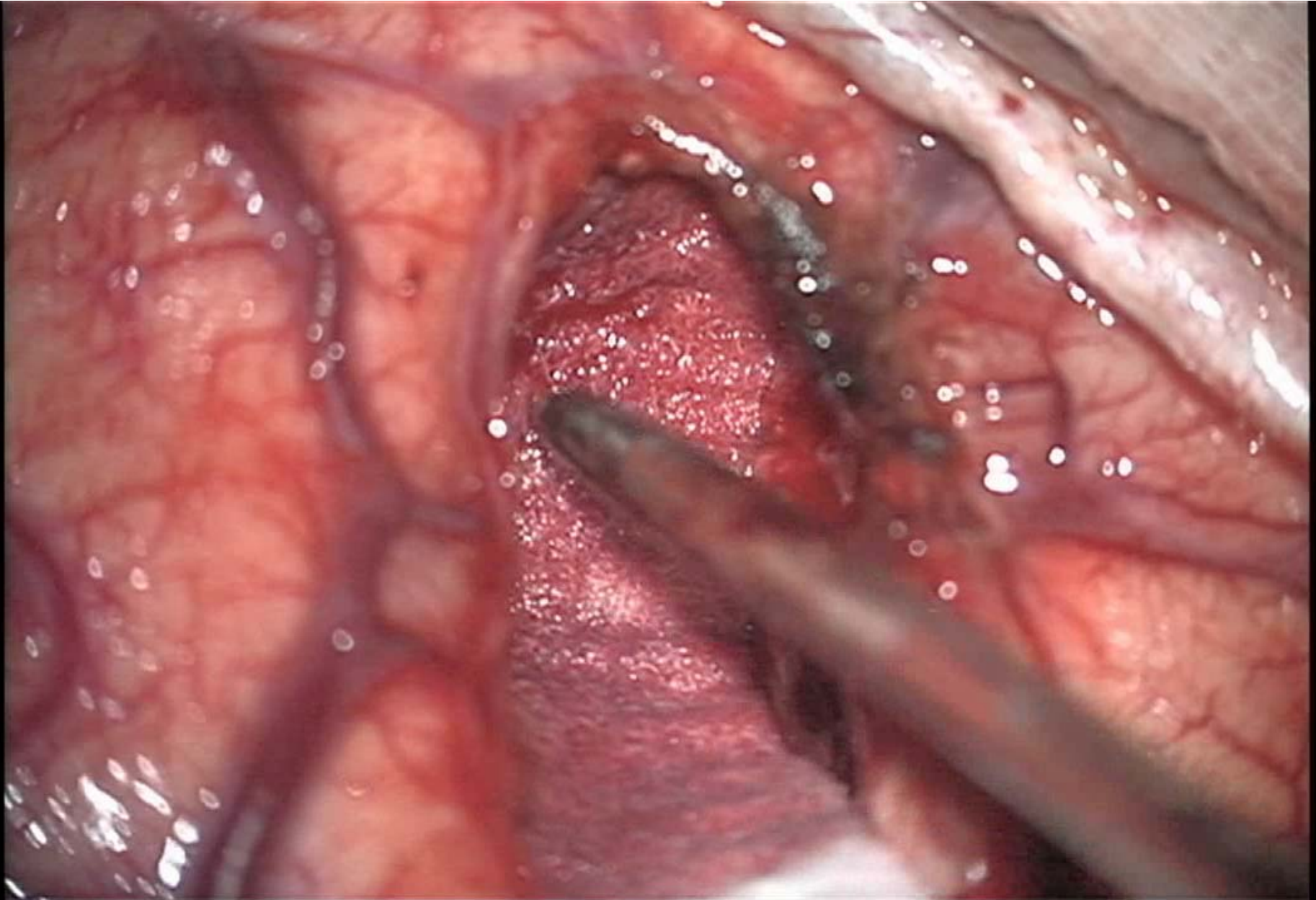
5-ALA in Clinical Practice

◆ **Convenient – administered orally prior to surgery**

◆ **Appropriate for patients with presumed primary or known recurrent gliomas**

◆ **Compatible with existing operating microscopes**

◆ **Adjunct to standard surgery and operative tools**

◆ **Provides real time visualization of malignant tumor tissue previously unseen**

◆ **Flow of surgery not interrupted**

Visualization of Tumor During Glioma Surgery: Summary

◆ **Gliomas are universally lethal**

◆ **Maximal safe extent of resection is surgical goal**

◆ **Localization of tumor and important surrounding neurologic tracts essential**

◆ **Glioma tumor margins difficult to visualize under white light**

◆ **Current tools not continuous real time, may not provide full picture**

◆ **Better visualization allows neurosurgeons to provide better surgical care for patients**

◆ **Improved surgery impacts downstream therapies**

Agenda: 5-ALA Visualization of Glioma

Introduction	**Alan Ezrin, PhD** *President & CEO* *NX Development Corporation*
Visualization of Tumor During Glioma Surgery	**Constantinos G. Hadjipanayis, MD, PhD** *Professor and Chairman of Neurosurgery,* *Mount Sinai Beth Israel Hospital* *Director of Neurosurgical Oncology,* *Mount Sinai Health System, New York, NY*
Clinical Efficacy	**Walter Stummer, MD** *Department of Neurosurgery,* *University of Münster*
Safety Results	**Walter Stummer, MD**
Benefit / Risk	**Constantinos G. Hadjipanayis, MD, PhD**
Conclusion	**Alan Ezrin, PhD**

Clinical Efficacy of 5-ALA HCl

Professor Dr. Walter Stummer

University of Münster

Department of Neurosurgery

Contents of Clinical Presentation

◆ **Presentation of Clinical Studies and Endpoints**

 – Study 3

 – Study 28

 – Study 30

◆ **Summary of Key Clinical Study Finding**

◆ **Summary of Visualization Endpoints**

◆ **Discussion of Imaging Endpoints**

◆ **Utility of Predictive Accuracy and Clinical Usefulness**

◆ **Summary**

Clinical Data: Totality of Evidence

◆ **Clinical trial data**

◆ **Publications**

◆ **Post-marketing experience**

	Numbers of Patients		
	Clinical Trials	**Scientific Literature**	**Global Post-Marketing**
Efficacy	418	377	–
Safety	527	≃2,000	≃58,000

5-ALA Clinical Trial Development Program

Study #	Phase/Type	Population	20 mg/kg 5-ALA		
			N Enrolled	N Efficacy	N Safety
Study 20	Phase 1 Bioavailability	Healthy males	21	--	21
Study 8	Phase 1/2 Safety	1° Malignant Glioma	21	--	7
Study 3	Phase 3 Safety/Efficacy	1° Malignant Glioma	415 207 5-ALA 208 control	176 5-ALA 173 control	201
Study 28	Phase 2 Safety/Efficacy	1° Malignant Glioma	39	33	36
Study 30	Phase 2 Safety/Efficacy	Recurrent Glioma	40	36	40
Study 32	Phase 3 Safety	1° Malignant Glioma	245	--	243

Study 3 Design

◆ **Randomized, group-sequential, rater-blinded, balanced parallel-group, controlled multicenter phase III study of a method for tumor visualization**

Entry Criteria
- **Suspected maligant glioma**
- **Indication for surgery**
- **Age 18-72**
- **KPS ≥70%**

Control Group:
All visible tumor tissue is resected under white light

5-ALA Group:
Tumor resected after 5-ALA administration *alternating* between white and fluorescent light

Primary Endpoints
- **Resection rates (MRI)**
- **PFS 6**

Secondary Endpoints
- **Safety**
- **Residual Tumor volume**
- **OS**

PFS = Progression-free Survival.

Statistical Methods:

- ◆ **415 patients randomized 1:1, stratified by:**
  - – Age
  - – Karnofsky Performance Score (KPS)
  - – Eloquent location
  - – Site

- ◆ **Sample size**
  - – 80% power, experiment-wise type I error rate of 0.05
  - – Primary endpoints tested in an a priori defined hierachical order

- ◆ **Prespecified interim analysis at 270 patients**

- ◆ **Appropriate adjustments for**
  - – Multiple endpoints
  - – Interim analysis

Study 3: Patient Disposition

	5-ALA	Control	Total
Patients enrolled based on imaging	207	208	415
Patients Excluded from FAS	31	35	66
Histopathological diagnosis not met	21	20	41
Radiological diagnosis not met	5	10	15
Withdrawal of consent before surgery	2	3	5
No tumor resection	2	1	3
Other	1	1	2
Patients Discontinued	0	3	3
Lost to follow up	0	1	1
Withdrawal of consent after surgery	0	2	2
Full Analysis Set (pre-specified)	176	173	349

Demographics Study 3: Full Analysis Set (FAS)

Prognostic Variables		5-ALA N=176 n (%)	Control N=173 n (%)
Age	≤55 years	55 (31)	52 (30)
	>55 years	121 (69)	121 (70)
	Median years	61	60
KPS	Low	37 (21)	41 (24)
	High	139 (79)	132 (76)
Eloquent	No	81 (46)	72 (42)
	Yes	95 (54)	101 (58)
Histology	WHO ° III	5 (3)	5 (4)
	WHO ° IV	171 (97)	126 (96)

Study 3: % of Patients w/o Residual Enhancing Tumor (FAS)
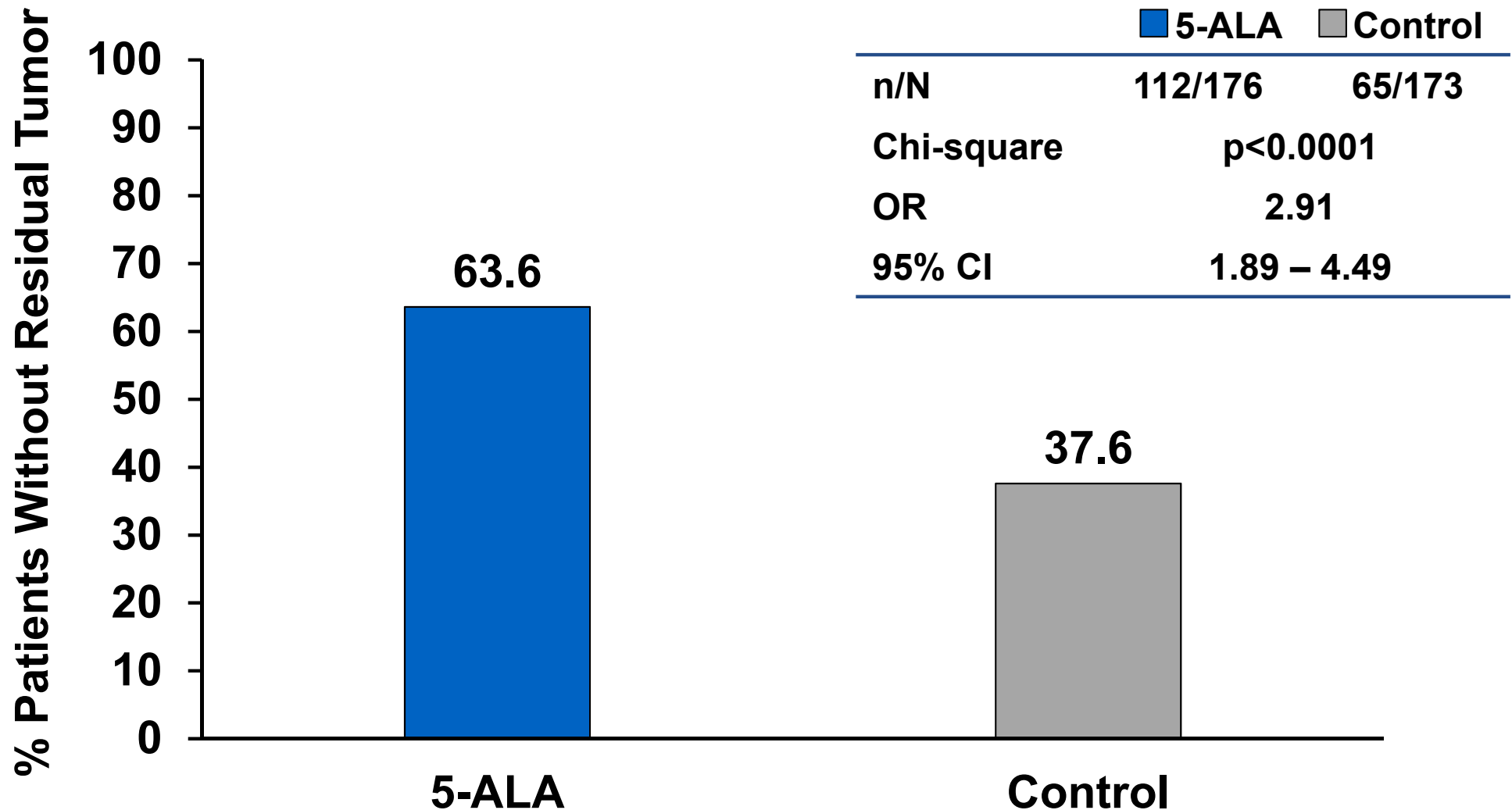
5 patient(s) (2 in 5-ALA and 3 in Control arm) with not evaluable/missing early postoperative MRI data were/was included as patient(s) with residual tumor.

Early Postoperative MRI Resection Status: Valid for All Groups (FAS)

Subgroup	n/N		OR (95% CI)
	5-ALA	Control	
Overall	112/176	65/173	2.91 (1.88, 4.49)
Age (p=0.8472*)			
≤55 yrs	41/55	25/52	3.16 (1.40, 7.14)
>55 yrs	71/121	40/121	2.88 (1.70, 4.86)
Baseline KPS (p=0.7569*)			
≤80%	19/37	12/41	2.55 (1.00, 6.48)
>80%	93/139	53/132	3.01 (1.84, 4.95)
Eloquent (p=0.5665*)			
Yes	56/95	31/101	3.24 (1.80, 5.84)
No	56/81	34/72	2.50 (1.29, 4.85)

Odds Ratio (OR): 0, 5, 10, 15, 20 — Control Better / 5-ALA Better
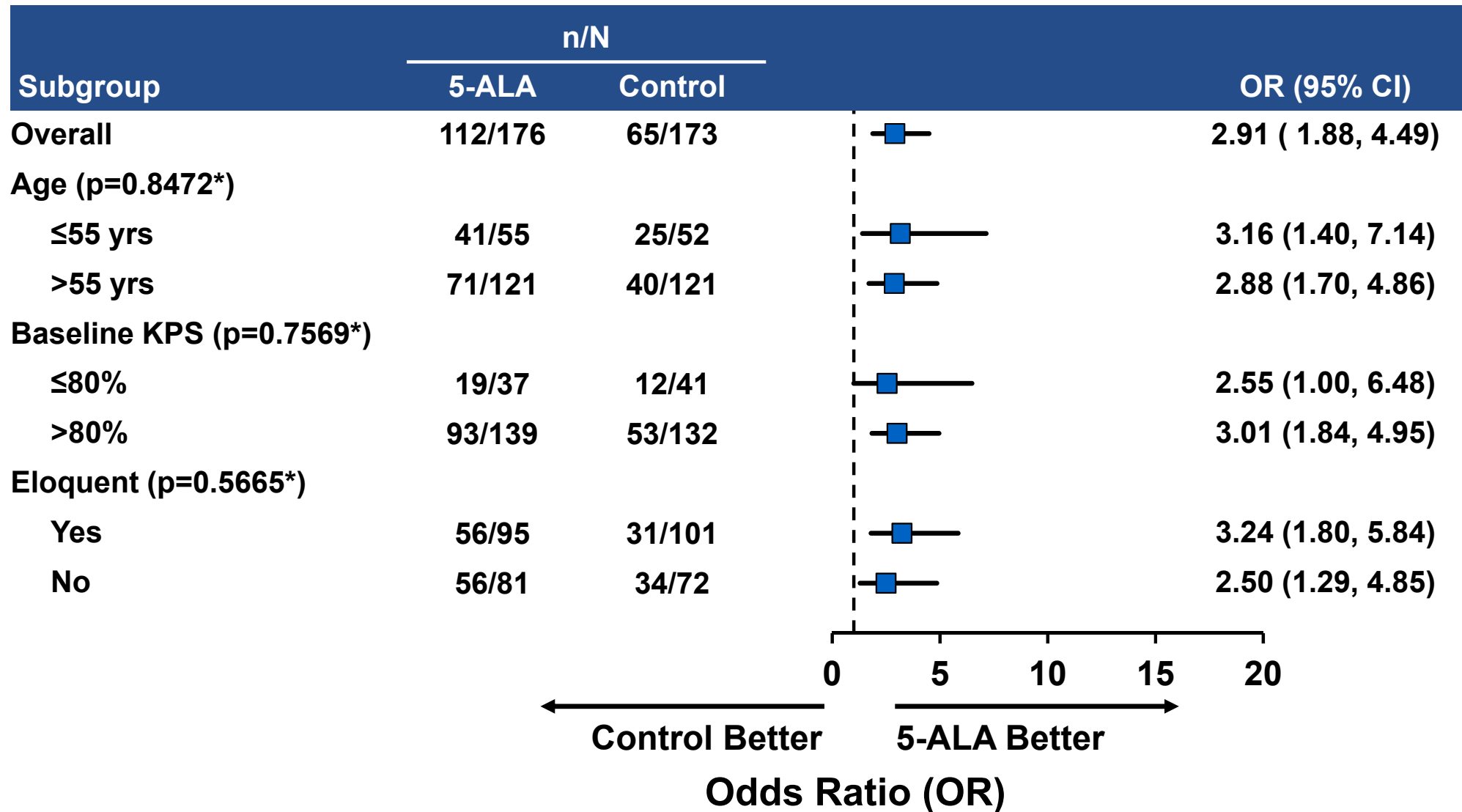
n=number with complete resection on early postoperative MRI; N=number in treatment group.
*p-value for Breslow-Day test for homogeneity of the odds ratio.

Study 3: % of Patients Progression Free at 6 Months (FAS)

	5-ALA	Control
n/N	36/176	19/173
Chi-square	p=0.0152	
OR	2.08	
95% CI	1.12 – 3.88	

% Patients Without Progression or Death

20.5

11.0

5-ALA

Control
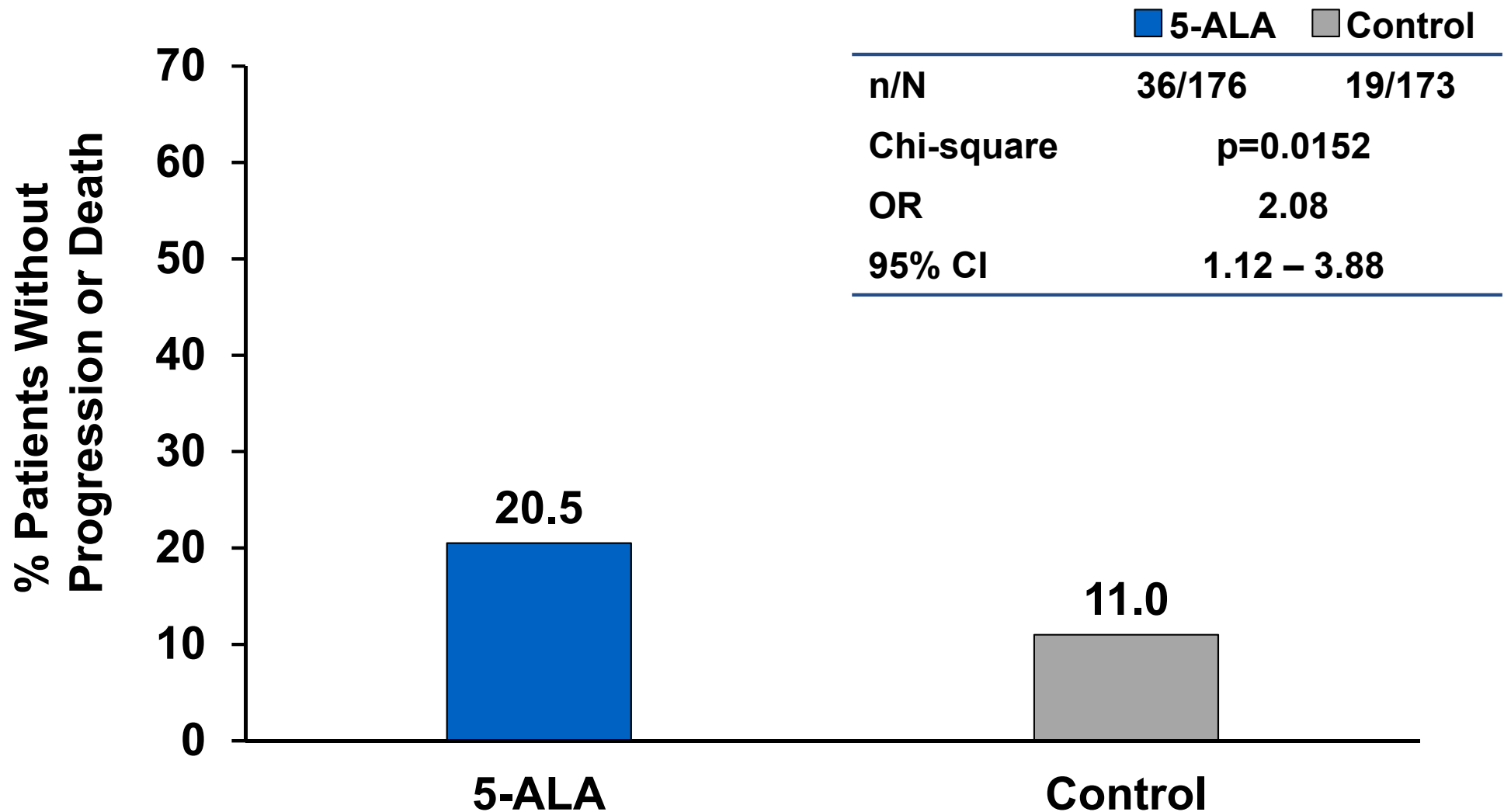
Progression Free Survival at 6 Months: Valid for All Groups (FAS)

Subgroup	n/N		OR (95% CI)
	5-ALA	**Control**	
Overall	36/176	19/173	2.08 (1.14, 3.80)
Age (p=0.8956*)			
≤55 yrs	14/55	7/52	2.20 (0.81, 5.97)
>55 yrs	22/121	12/121	2.02 (0.95, 4.29)
Baseline KPS (p=0.4900*)			
≤80%	6/37	5/41	1.39 (0.39, 5.01)
>80%	30/139	14/132	2.32 (1.17, 4.61)
Eloquent (p=0.1128*)			
Yes	14/95	12/101	1.28 (0.56, 2.93)
No	22/81	7/72	3.46 (1.38, 8.96)

Control Better ← → 5-ALA Better
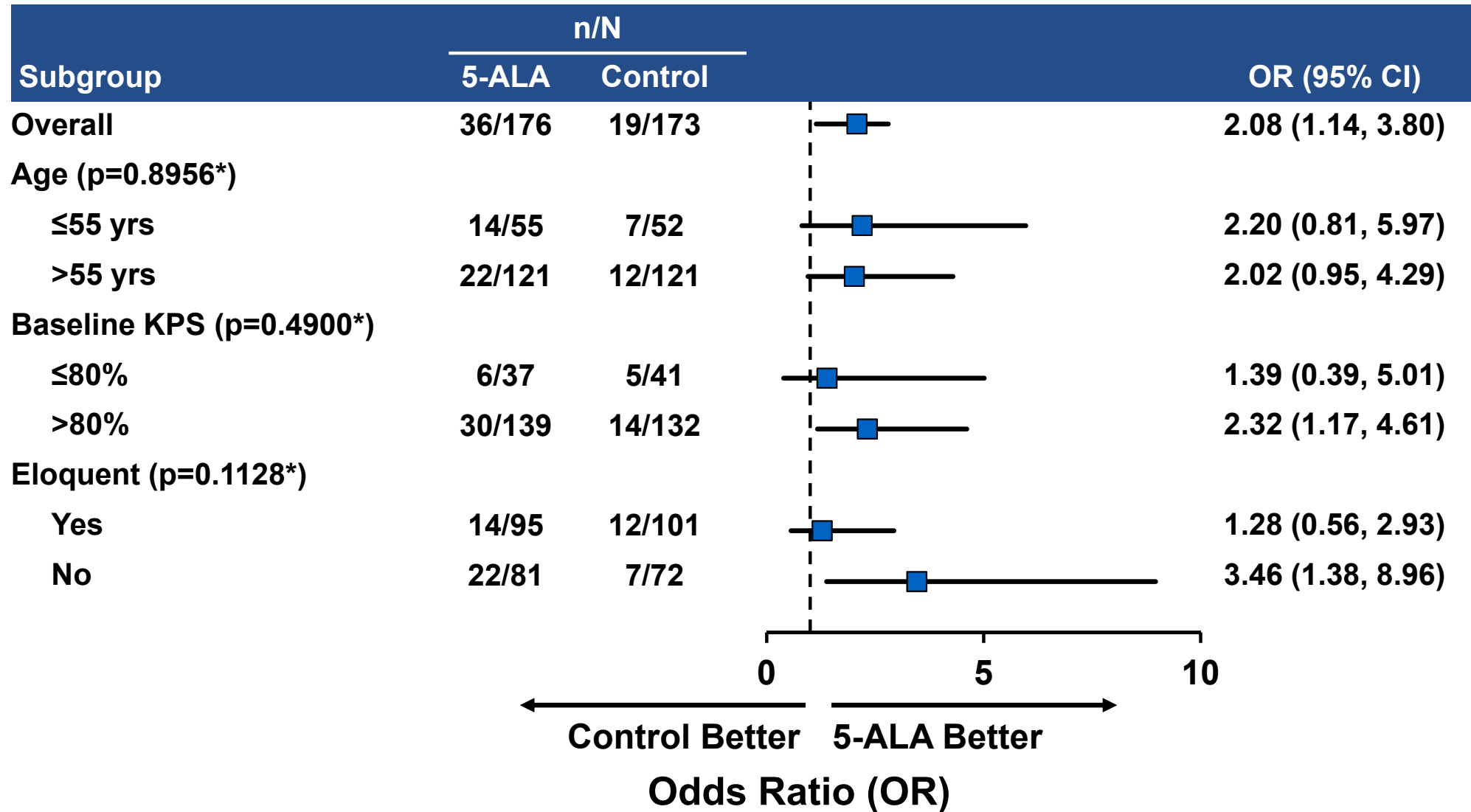
Odds Ratio (OR)

n=numbers alive without progression at 6 months.; N=number in group.
*p-value for Breslow-Day test for homogeneity of the odds ratio.; **Exact confidence interval for odds ratio.

Study 3: Progression Free Survival by Treatment Group (FAS)

Log rank p=0.0215

Treatment Group:
— 5-ALA
- - - Control
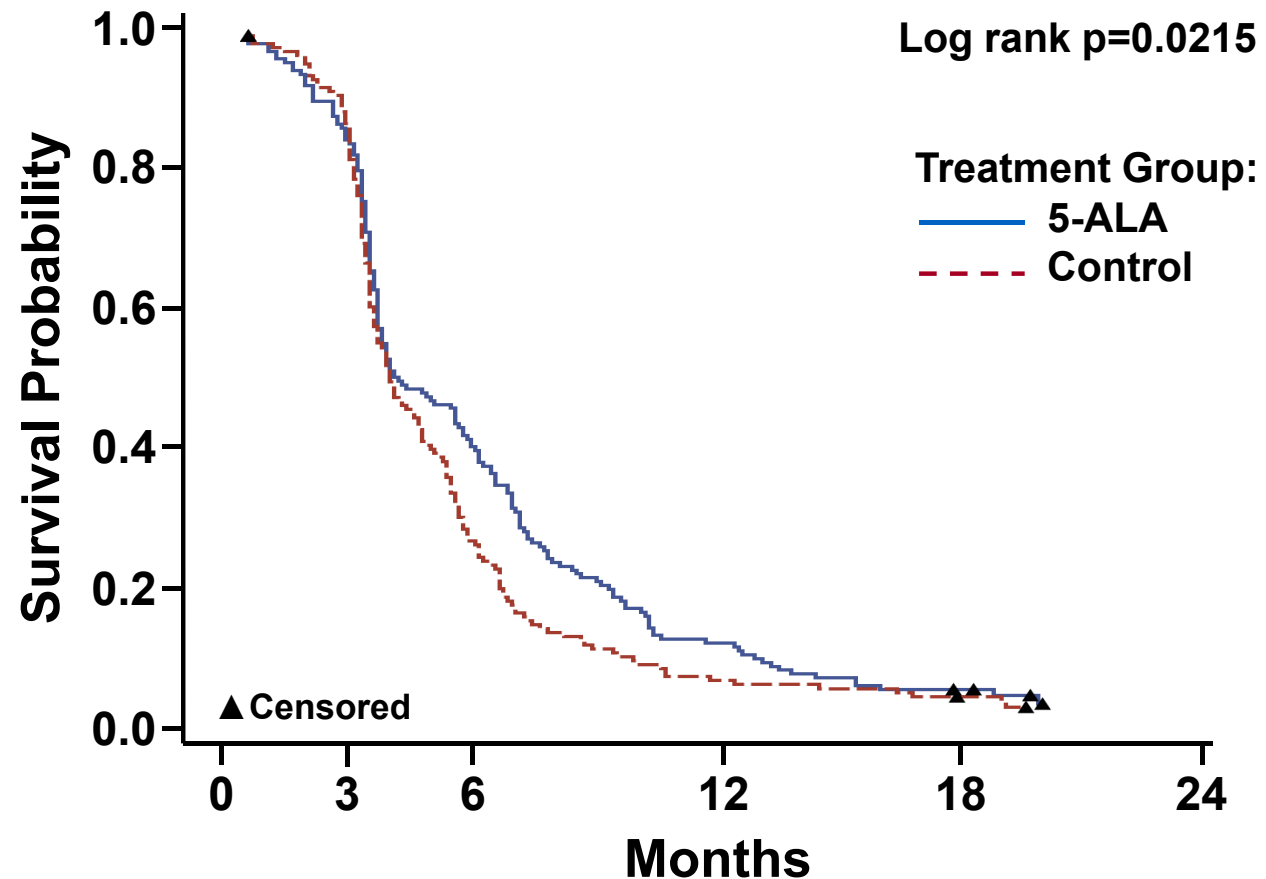
▲Censored

Number at Risk, (Censored)						
5-ALA	176(0)	125(0)	64(0)	18(2)	4(2)	0(0)
Control	173(3)	113(0)	38(0)	8(1)	3(1)	0(0)

Progression free survival (PFS) is time from surgery date to date of first progressive disease or death, patients alive without progressive disease at end of study are censored at last contact date.

Study 3: Progression Free Survival by Completeness of Resection (Pooled Treatment Groups, FAS)

Log rank p<0.0001

Resection Status
(Independent of treatment group):
—— **Complete**
‑ ‑ ‑ **Incomplete**

▲ Censored

Survival Probability (y-axis): 1.0, 0.8, 0.6, 0.4, 0.2, 0.0

Months (x-axis): 0, 3, 6, 9, 12, 18, 24
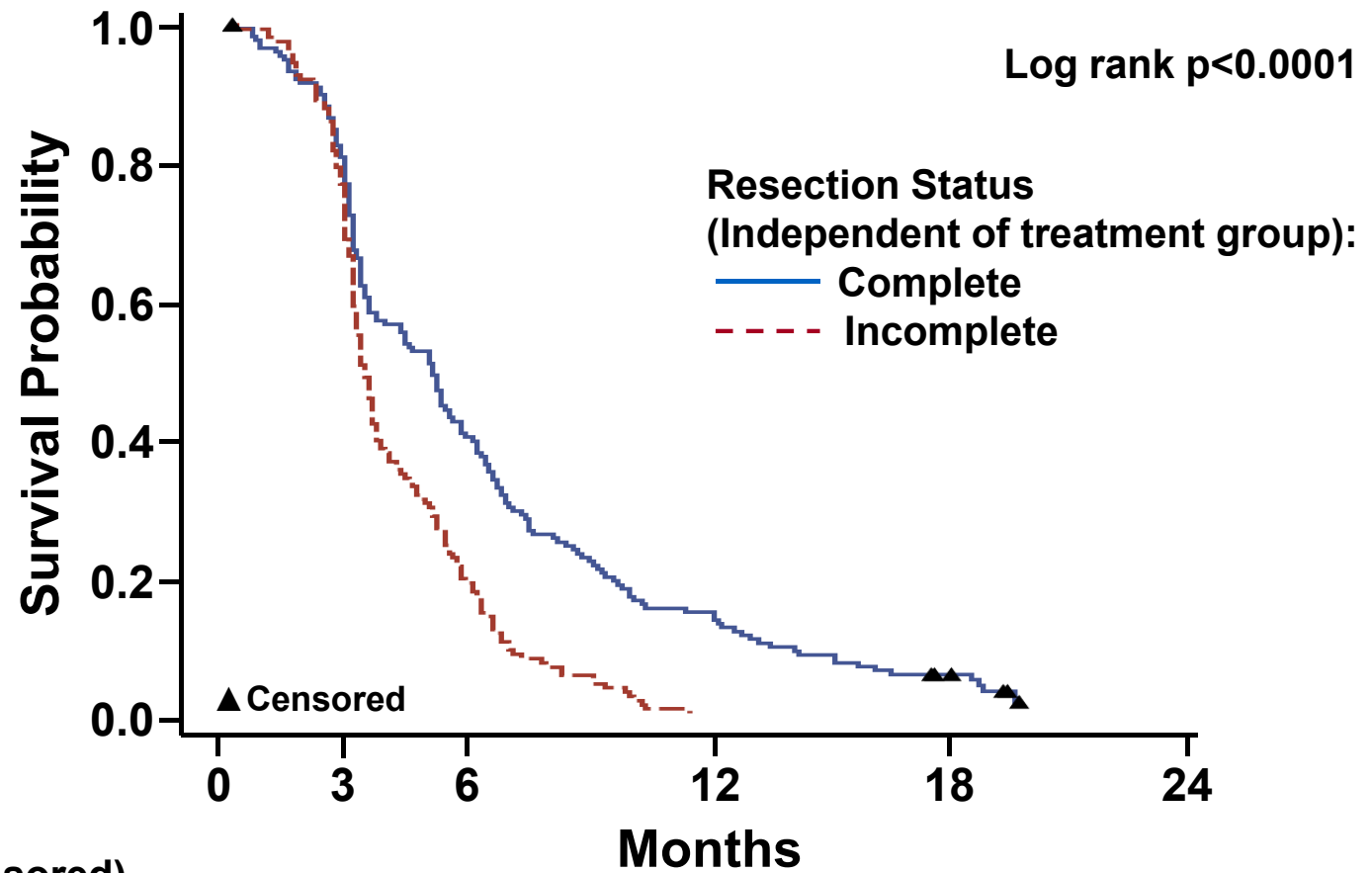
Number at Risk, (Censored)

Complete	177(0)	128(0)	71(0)	26(3)	7(3)	0(0)
Incomplete	167(3)	109(0)	31(0)	0(0)		

Patients with not evaluable/missing early postoperative MRI data are excluded from analysis
Progression free survival (PFS) is time from surgery date to date of first progressive disease or death, patients alive without progressive disease at end of study are censored at last contact date.

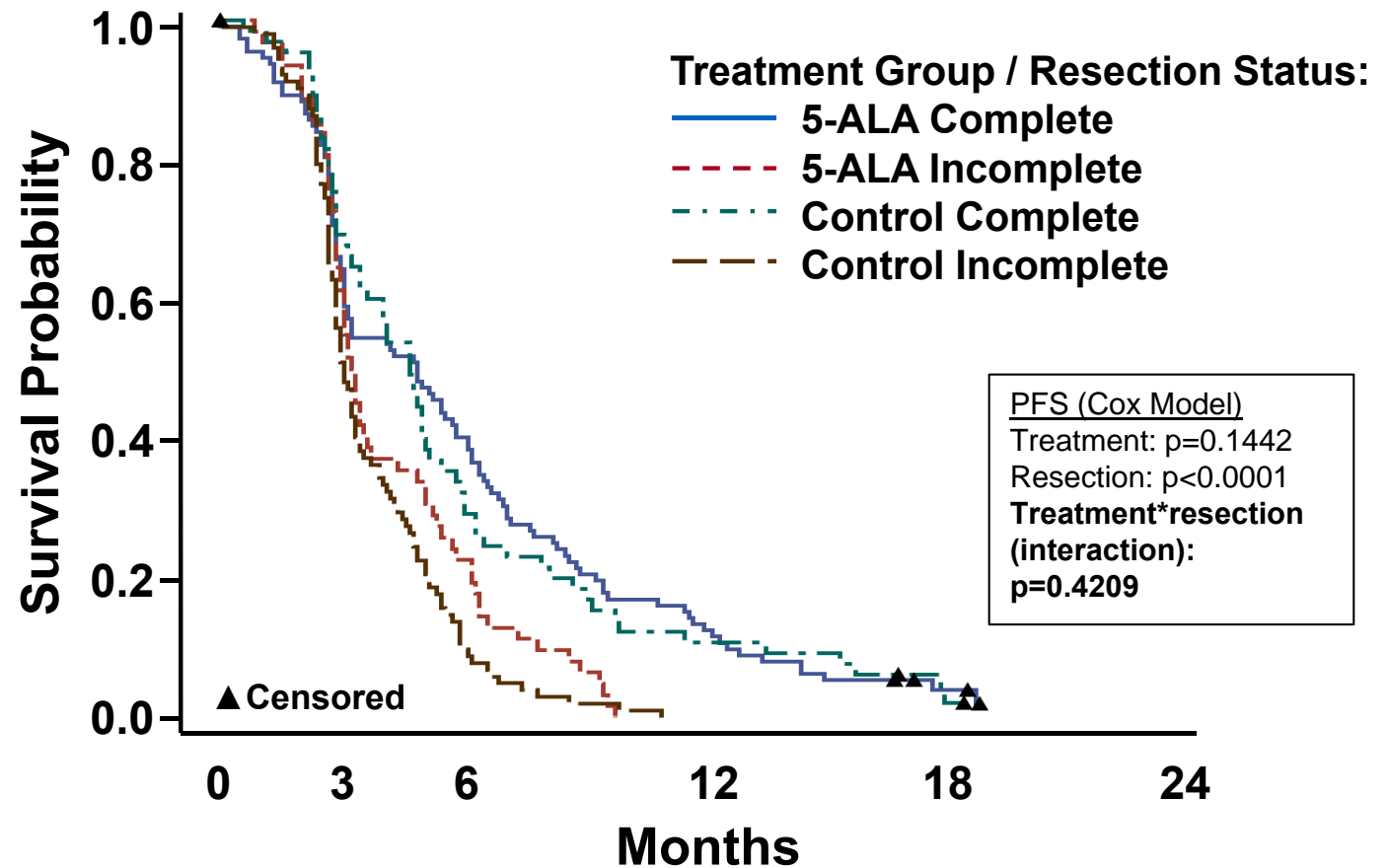# Study 3: Progression Free Survival by Completeness of Resection (FAS)

PFS (Cox Model)
Treatment: p=0.1442
Resection: p<0.0001
Treatment*resection (interaction): p=0.4209

Treatment Group / Resection Status:
— 5-ALA Complete
--- 5-ALA Incomplete
-·-· Control Complete
-- Control Incomplete

▲Censored

Number at Risk, (Censored)

5-ALA Complete	112(0)	79(0)	48(0)	18(2)	4(2)	0(0)
5-ALA Incomplete	62(0)	45(0)	16(0)	0(0)		
Control Complete	65(0)	49(0)	23(0)	8(1)	3(1)	0(0)
Control Incomplete	105(3)	64(0)	15(0)	0(0)		

Study 3: Overall Survival by Treatment Group (FAS)
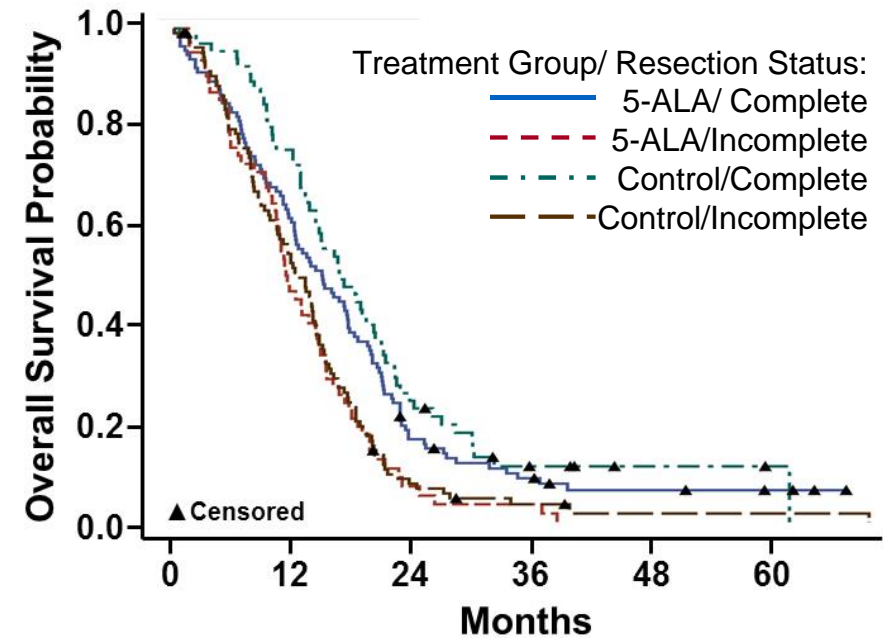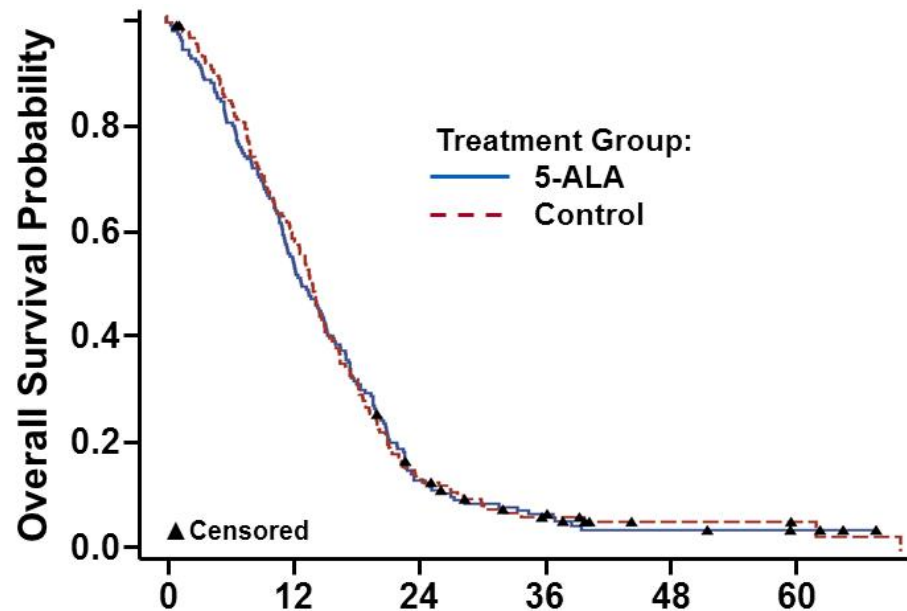
Number at Risk, (Censored)

5-ALA	176(0)	97(2)	22(1)	11(2)	5(2)	3(3)
Control	173(2)	102(0)	24(4)	8(4)	3(1)	2(0)

Number at Risk, (Censored)

5-ALA Complete	112(0)	68(1)	18(1)	9(2)	5(2)	3(3)
5-ALA Incomplete	62(0)	29(1)	4(0)	2(0)	0(0)	
Control Complete	65(0)	49(0)	16(3)	5(3)	2(1)	1(0)
Control Incomplete	105(2)	53(0)	8(1)	3(1)	1(0)	1(0)

Patients with not evaluable/missing early postoperative MRI data are excluded from analysis.

Study 3:
5-ALA Reduces Incidence of Second Surgery (FAS)

Test of Gray: DF=1; p=0.0311

24 months rate 0.30 vs. 0.39

Cumulative Incidence (y-axis: 0.0 to 1.0)

Time [months] (x-axis: 0, 6, 12, 18, 24, 30, 36, 42, 48, 54)

Control

5-ALA
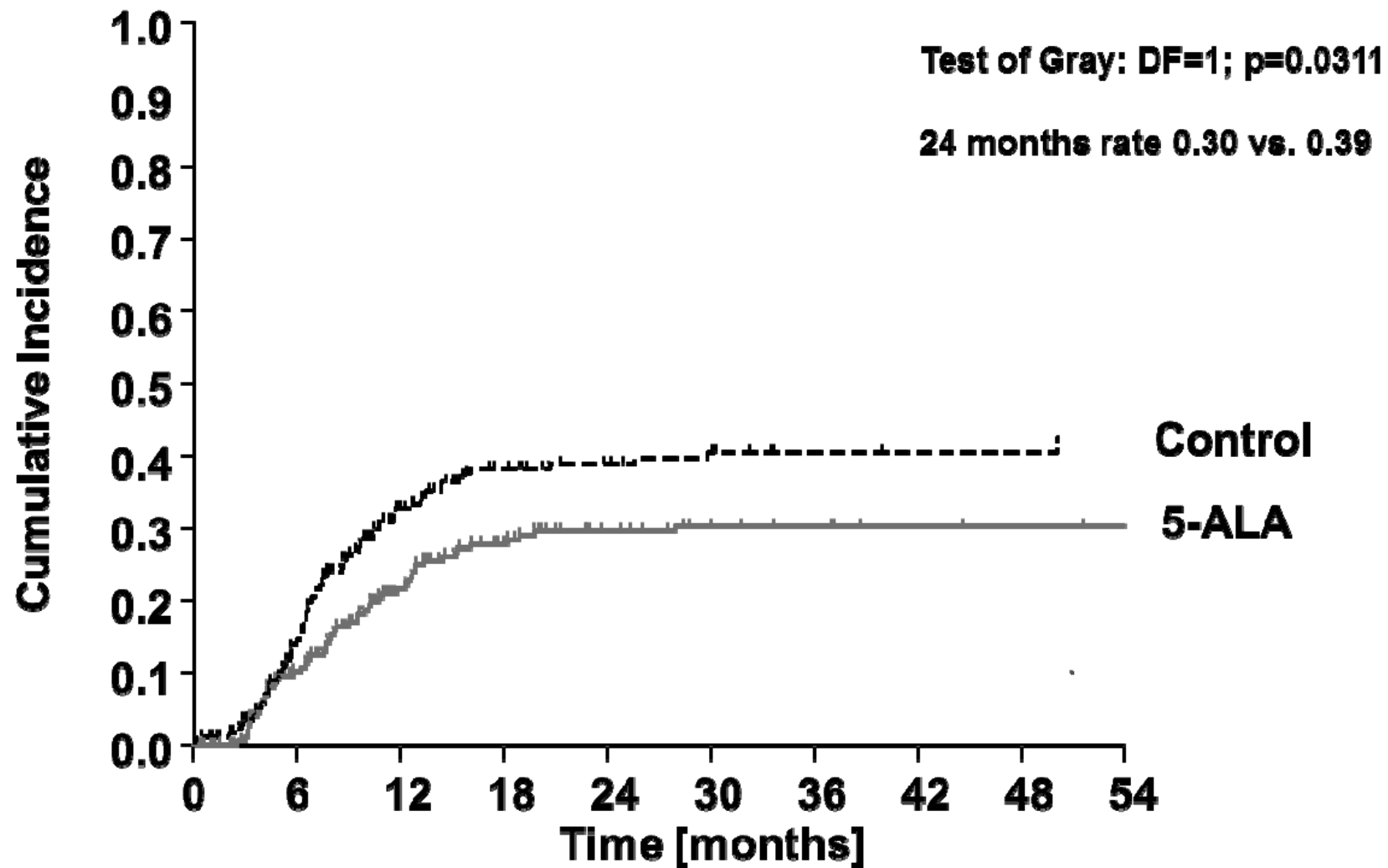
Patients under observation (n, censored):

176	125(20)	69(33)	37(19)	17(14)	10(3)	7(2)	4(3)	3(1)	2
173	122(22)	53(29)	23(19)	11(11)	7(7)	2(4)	1(2)	1(0)	0

# NDA Endpoints for Visualization and Clinical Usefulness

- ◆ **Is tissue highlighted by fluorescence truly tumor?**
  - – PPV
  - – Studies 3, 28, 30
- ◆ **What cell densities can be visualized?**
  - – Study 28
- ◆ **Can the surgeon see more with fluorescence than under white light?**
- ◆ **How does the fluorescence signal relate to MR contrast enhancement?**

Clinical Studies:
Efficacy Endpoints NDA

	Study 3 Randomized 5-ALA vs Control	Study 28 Single-arm; all 5-ALA	Study 30 Single-arm; all 5-ALA
Primary	◆ PPV: Biopsy-based	◆ PPV: Biopsy-based ◆ Clinical usefulness (qualitative)	◆ PPV: Biopsy-based ◆ Clinical usefulness (qualitative)
Methods	◆ Biopsy location, timing not defined	◆ Biopsies correlated with imaging	◆ Biopsies after white light resection
Supportive	◆ PPV: Pt-based ◆ NPV: Biopsy based ◆ NPV: Pt-based	◆ PPV: Pt-based ◆ NPV: Biopsy based ◆ NPV: Pt-based	◆ PPV: Pt-based ◆ NPV: Biopsy based ◆ NPV: Pt-based

Study 3: Biopsy-based PPV

- **One biopsy each from solid tumor, tumor margin, normal tissue**
  - 3 biopsies per patient
- **Both under white light and blue light in the fluorescence arm**
- **Biopsies not supervised nor correlated with location (e.g. by neuronavigation)**
- **No prespecification of whether biopsy sites were identified under fluorescence or under white light**

WL
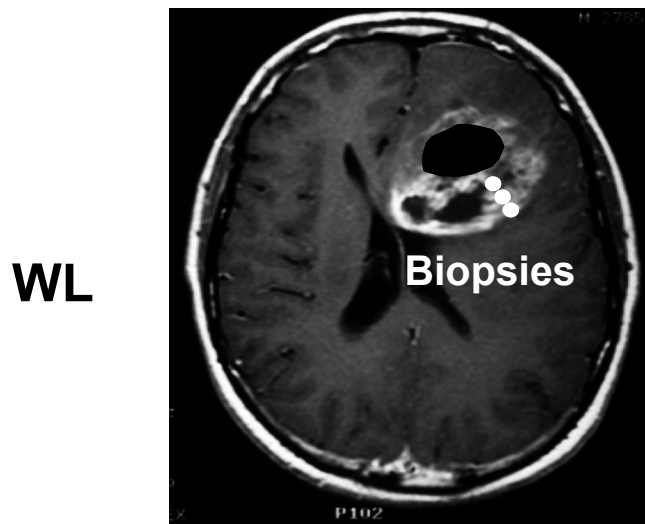
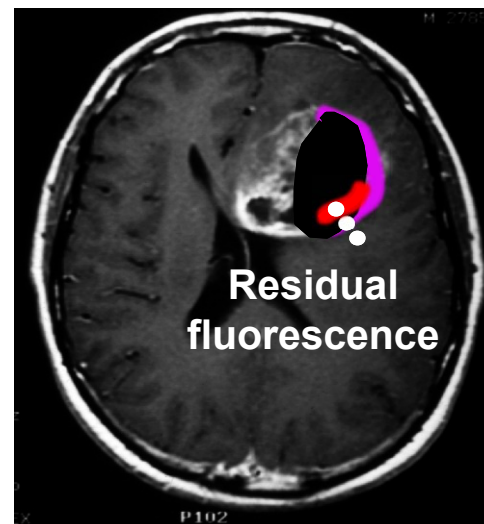

Illustration

5-ALA

Illustration

Study 3: Biopsy-based PPV

- **One biopsy each from solid tumor, tumor margin, normal tissue**
  - 3 biopsies per patient
- **Both under white light and blue light in the fluorescence arm**
- **Biopsies not supervised nor correlated with location (e.g. by neuronavigation)**
- **No prespecification of whether biopsy sites were identified under fluorescence or under white light**

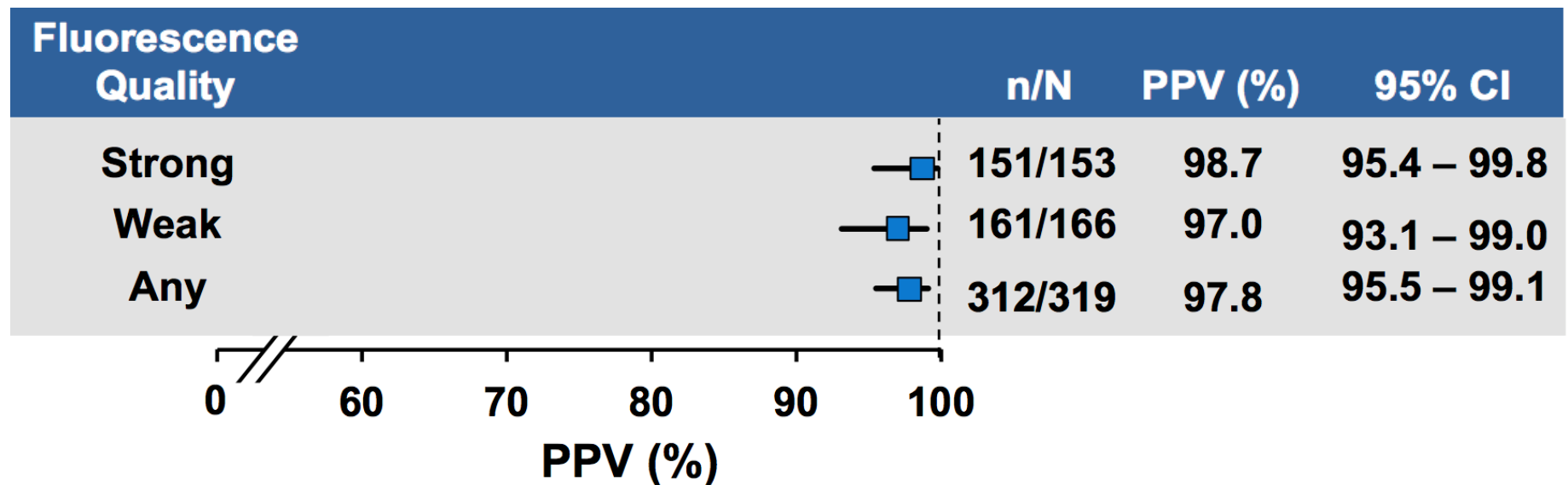| Fluorescence Quality		n/N	PPV (%)	95% CI
Strong		151/153	98.7	95.4 – 99.8
Weak		161/166	97.0	93.1 – 99.0
Any		312/319	97.8	95.5 – 99.1

PPV (%)
0   60   70   80   90   100

Study 28: Methods

◆ **Multicentric, prospective**

- n=33
- Median age 61 (range 21-72)
- Median KPS 90 (range 70-100)
- Histology: 4 AA, 29 GBM

◆ **Designed to**

- Establish the significance of strong and weak fluorescence at margin
- Correlate residual fluorescence with tumor cell density
- Correlate residual fluorescence with post-OP MRI by neuronavigation

Red and pink fluorescence at margin

Residual fluorescence
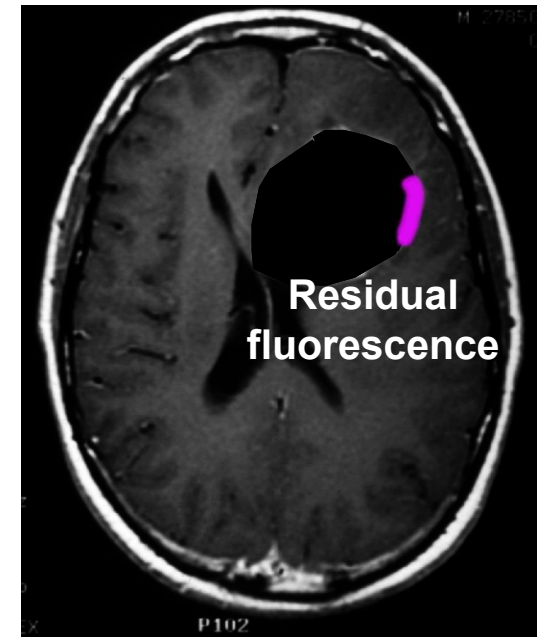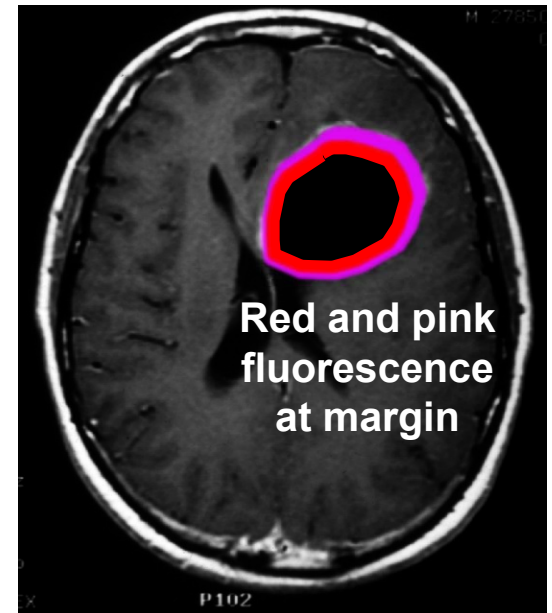
Study 28: Methods

- **Resect** to tumor margins

- **Perform biopsies** in areas with strong and weak fluorescence, from non-fluorescing tissue near and distant to cavity for blinded histology

- **Locate residual fluoresence** using **neuronavigation** for radiological **correlation to post-OP MRI**
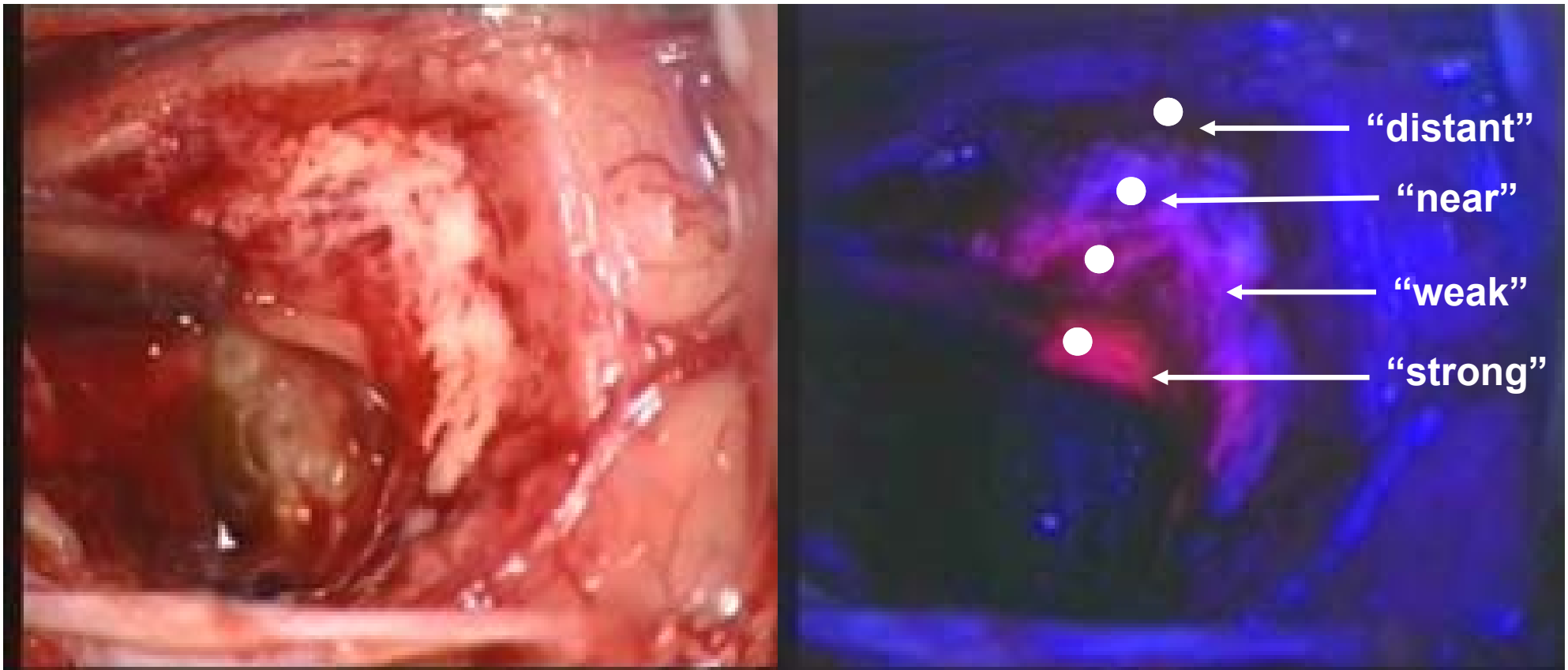
Resolution of Fluorescence
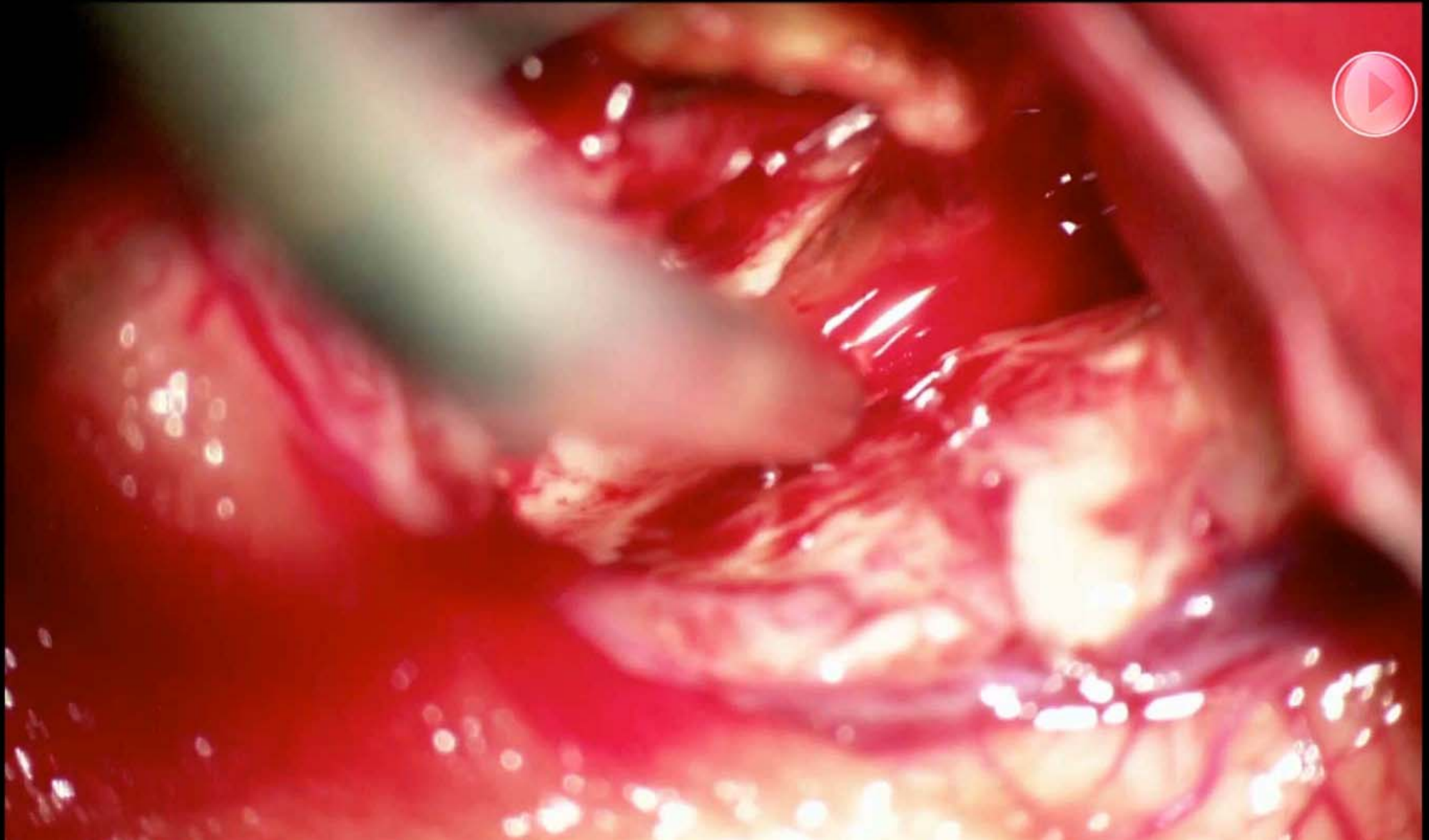
Study 28:
Fluorescence Reflects Cell Density
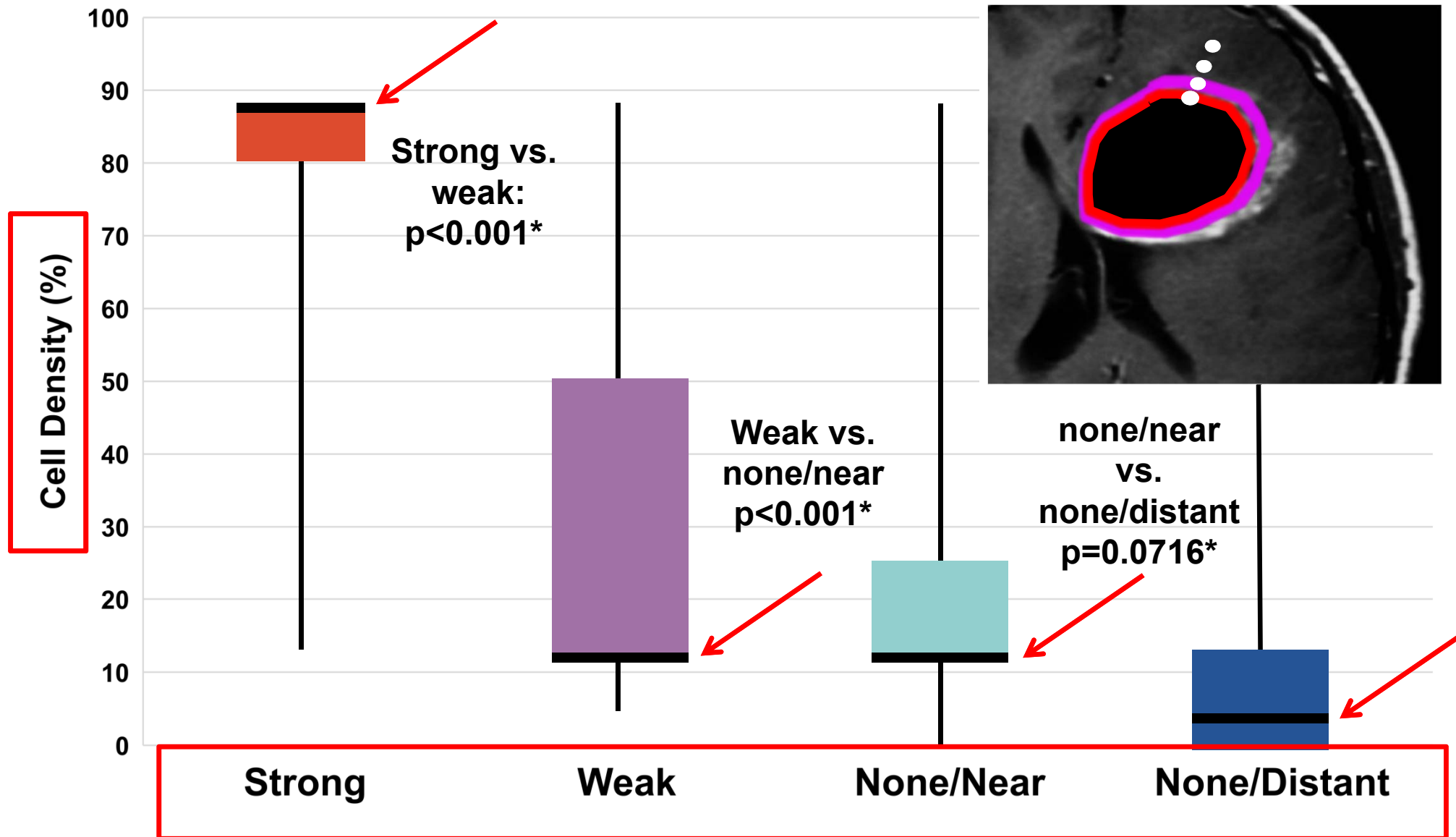
Stummer et al. *Neurosurgery* 2014; Friedman p<0.001, *post hoc ANOVA

Study 28: Results PPV

Fluorescence Quality	n/N	PPV (%)	95% CI
Strong	95/95	100.0	96.2 – 100.0
Weak	83/90	92.2	84.6 – 96.8
Any	178/185	96.2	92.4 – 98.5

PPV (%)
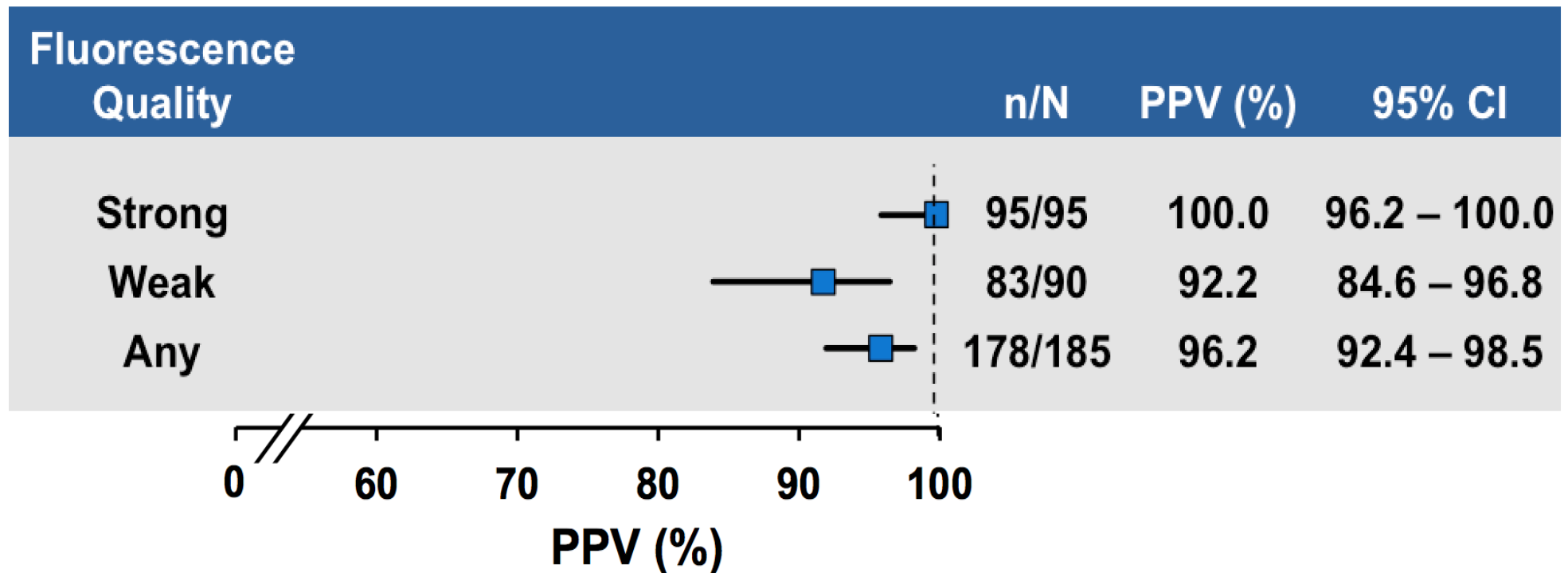
Study 30

◆ **Designed to determine the PPV in recurrent malignant glioma**

◆ **n=40, multicenteric, prospective; <u>recurrent</u> malignant glioma**

◆ **Biopsy regimen:**

1. Tumor resection under white light followed by blue light

2. Biopsies collected from pathological and normal areas (WL impression) if they fluoresced

Resection gross tumor

Illustration
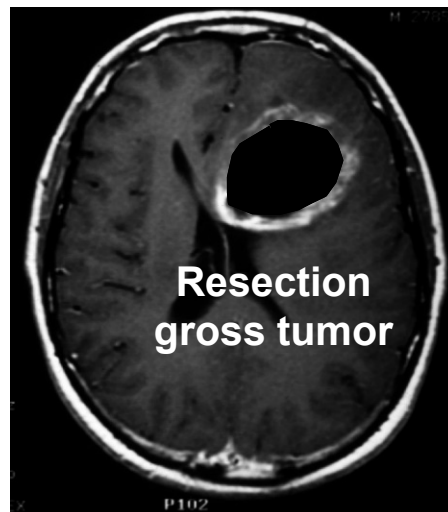
Fluorescence at margin
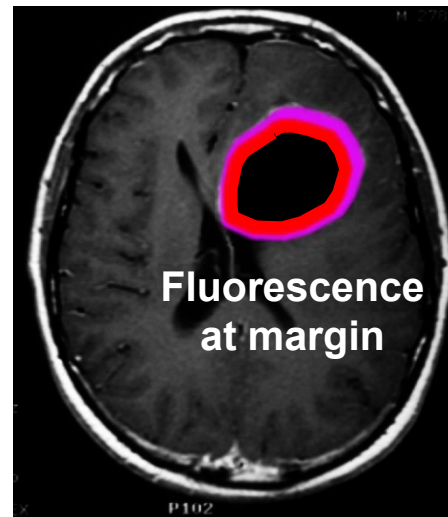
Illustration

Study 30: Results PPV

◆ **PPV in recurrent malignant glioma similar to newly diagnosed malignant glioma**

Fluorescence Quality		n/N	PPV (%)	95% CI
Strong		161/164	98.2	94.7 – 99.6
Weak		181/190	95.3	91.2 – 97.8
Any		342/354	96.6	94.2 – 98.2

PPV (%)

Nabavi et al. *Neurosurgery*, 2009.
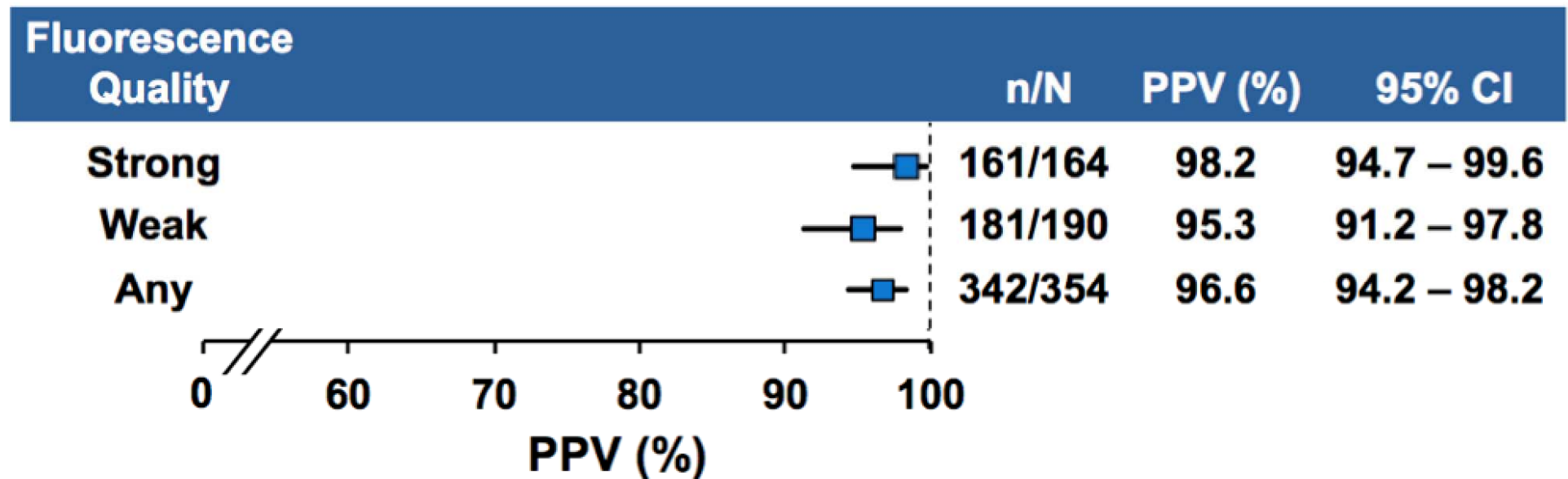
Predictive Accuracy of 5-ALA: Biopsy-based PPV

Study	Fluorescence Quality				n/N	PPV (%)	95% CI
Study 3	Strong				151/153	98.7	95.4 – 99.8
	Weak				161/166	97.0	93.1 – 99.0
	Any				312/319	97.8	95.5 – 99.1
Study 28	Strong				95/95	100.0	96.2 – 100.0
	Weak				83/90	92.2	84.6 – 96.8
	Any				178/185	96.2	92.4 – 98.5
Study 30	Strong				161/164	98.2	94.7 – 99.6
	Weak				181/190	95.3	91.2 – 97.8
	Any				342/354	96.6	94.2 – 98.2

0   60   70   80   90   100

PPV (%)
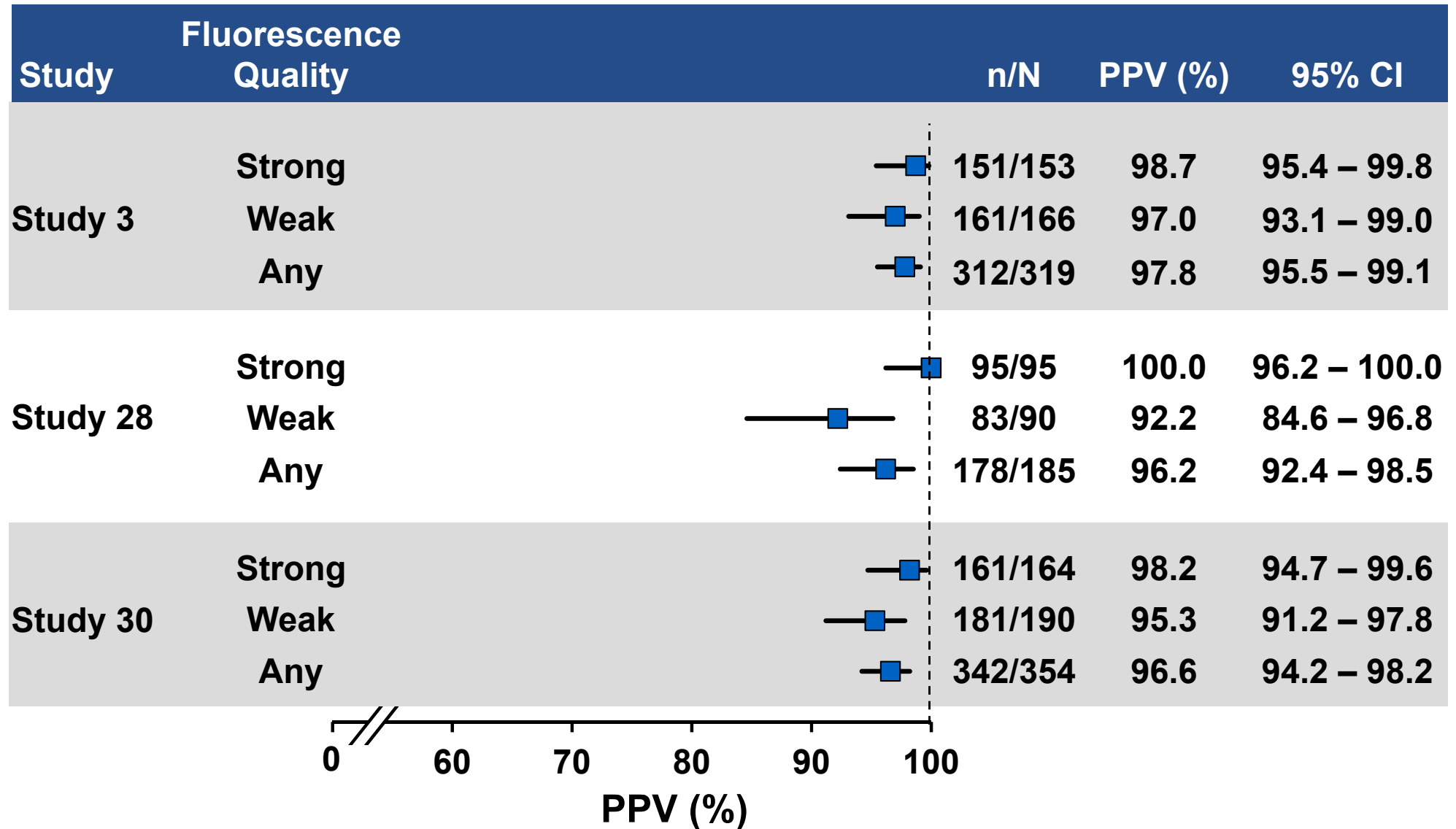
Biopsy-based PPV
from Peer-Reviewed Literature

	n/N
Lau et al. 2016	– /211
Stummer et al. 2000*	211/212
Coburger et al. 2014	95/96
Díez Valle et al. 2011*	142/144
Ewelt et al. 2011*	14/14
Idoate et al. 2011*	119/121
Panciani et al. 2012*	41/46
Hauser et al. 2016	89/93
Roberts et al. 2011	82/86
Stummer et al. 1998a*	53/53
Valdés et al. 2010*	16/16

Biopsy-based PPV (%)
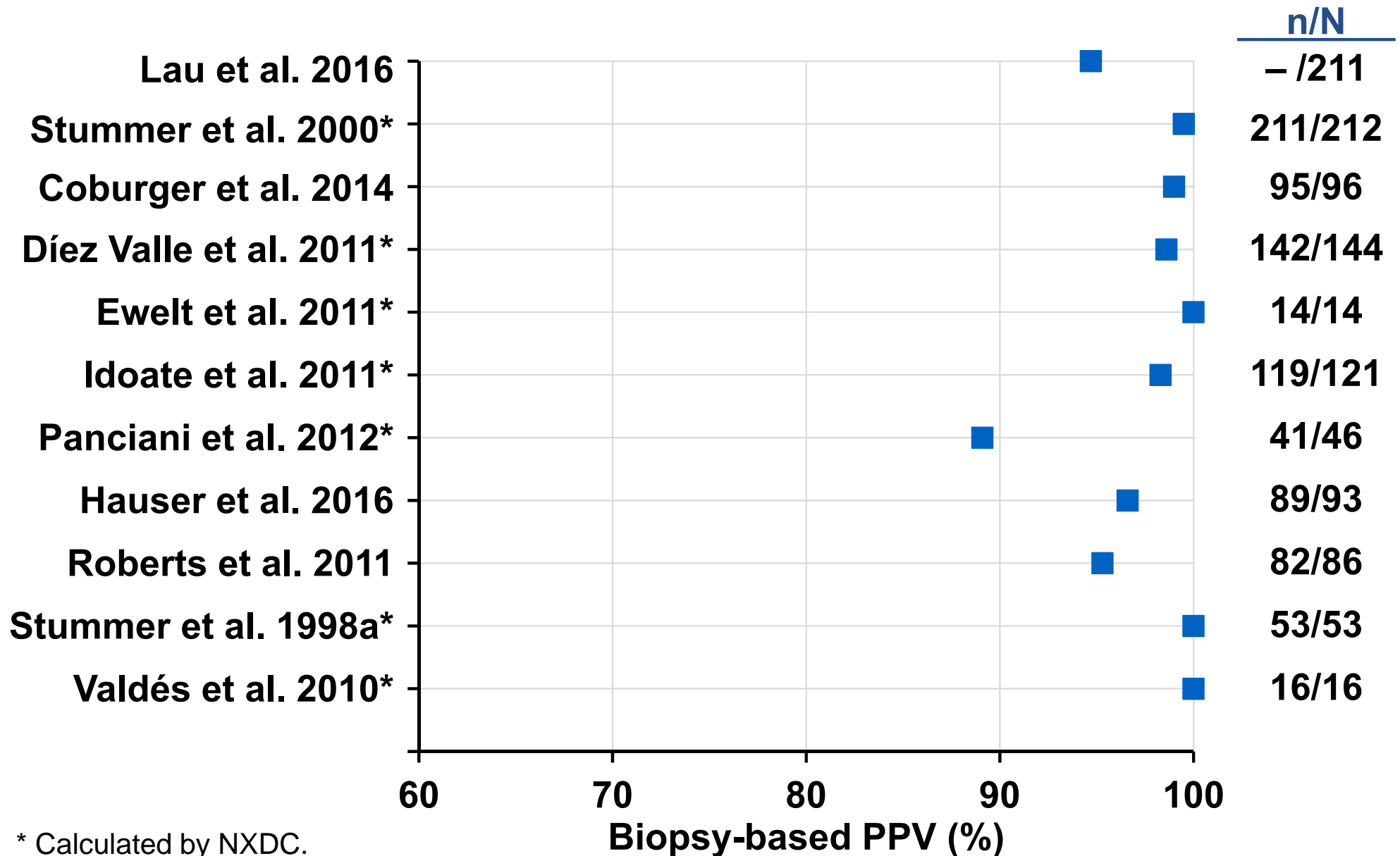
* Calculated by NXDC.

Biopsy-based Estimates of NPV

Study	n/N	NPV (%)	95% CI
Study 3	30/160	18.8	13.0 – 25.7
Study 28	27/121	24.1	16.5 – 33.1
Study 30	3/16	18.8	4.0 – 45.6

0   10   20   30   40   50

NPV (%)
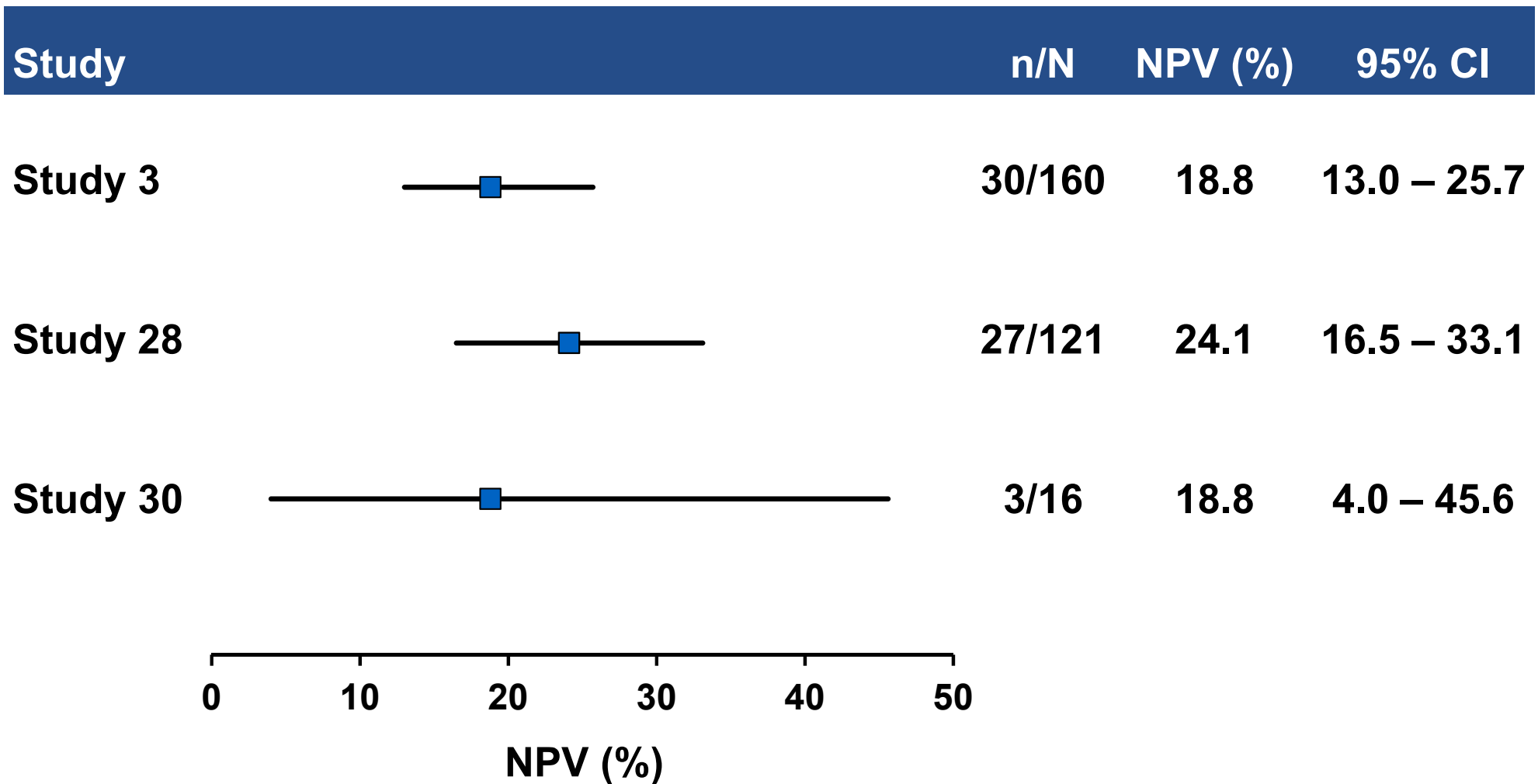
Summary of Biopsy-based NPV from Peer-Reviewed Literature

Citation:	Biopsy-based NPV		n/N
Coburger et al. 2014	43% (solid tumor)		4/18
	22% (tumor & infiltration zone)		
Díez Valle et al. 2011	66%		24/36
Ewelt et al. 2011	NR		NR
Hauser et al. 2016	12.5%		3/24
Idoate et al. 2011	67%		30/45
Lau et al. 2016	37.7%		NPV=37.7[a]
Panciani et al. 2012*	91.3%		42/46
Roberts et al. 2011	26%		10/38
Stummer et al. 1998a*	75.0		10/36
Stummer et al. 2000*	50.0%		26/52
Valdés et al. 2010	20%		NPV=20[a]

Biopsy-based NPV (%)
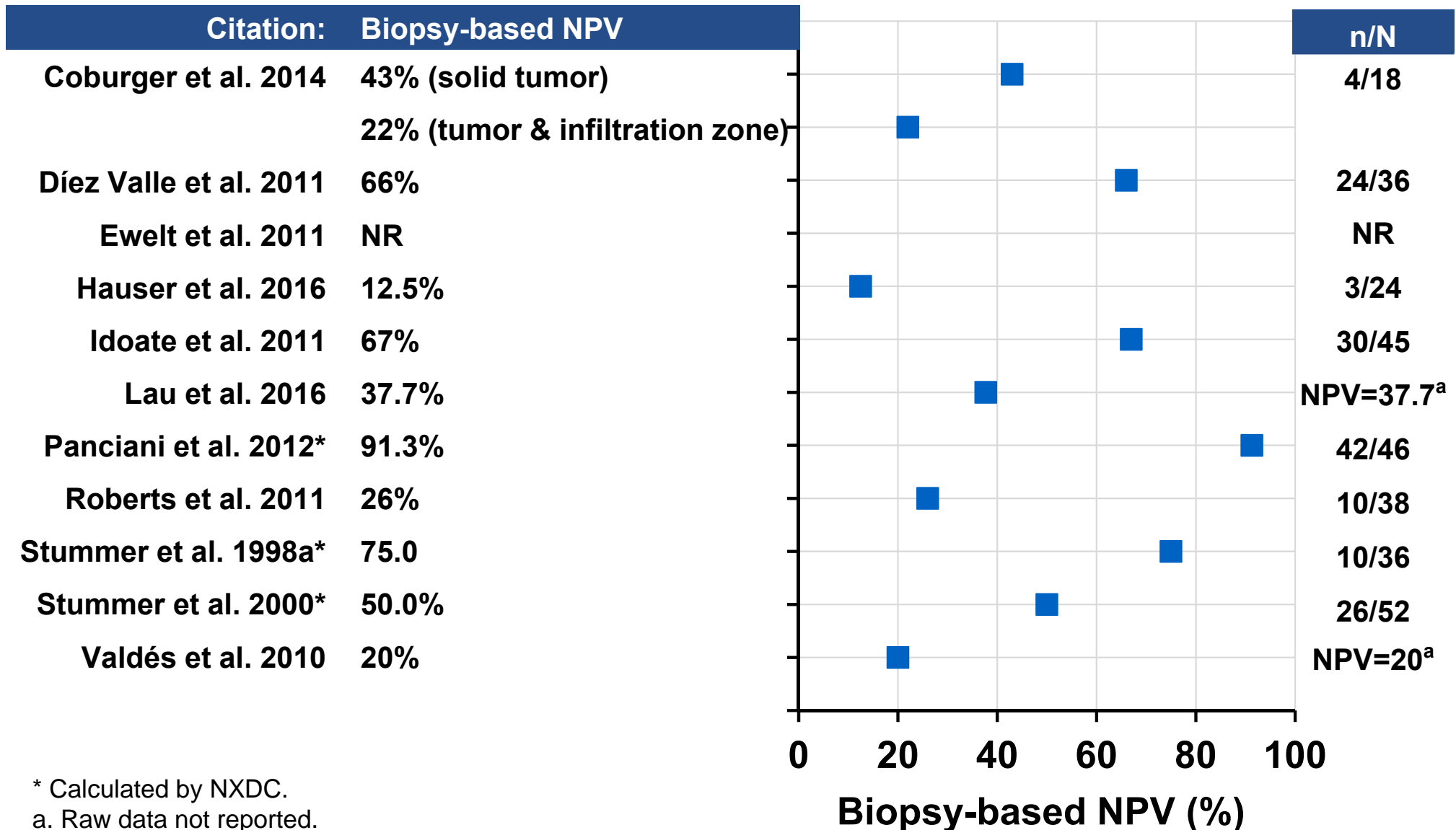
* Calculated by NXDC.
a. Raw data not reported.

NPV and Distance from Tumor
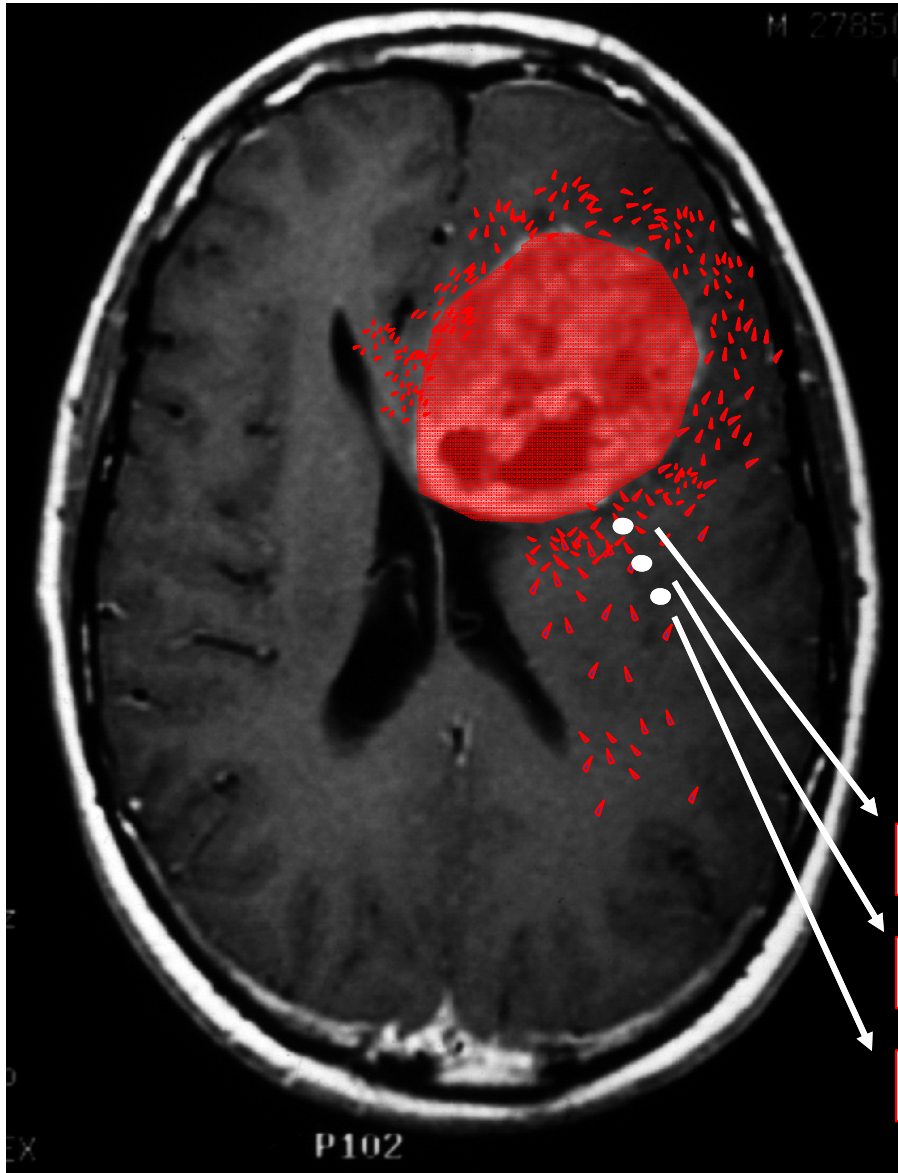
- Tumor cells spread diffusely to brain outside the enhancing tumor
- NPV is based on any histologically detectable tumor cells
- Residual infiltrating cells will lead to non-fluorescing biopsies with positive histology (false negative)
- The likelihood for false negatives depends on distance, affecting NPV, sensitivity and specificity

False negative fluorescence common, NPV low

False negatives fluorescence less likely, NPV medium

False negative fluorescence rare, NPV high

Pivotal Studies:
Biopsy-Based Diagnostic Measures

Measure	Study 3 (Primary)	Study 28 (Primary)	Study 30 (Recurrent)
PPV	97.8	96.2	96.6
NPV	18.8	24.1	18.8
Sensitivity	70.6	67.7	96.3
Specificity	81.1	79.4	20.0

Literature Visualization Performance Parameters (FDA Briefing Document)

| Study	No. Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Stummer et al (2000)	52	89	96	99	50
Roberts et al (2011)	11	75	71	95	26
Panciani et al (2012)	41	91	89	89	91
Coburger et al (2014)	34	91	80	99	22
Yamada et al (2015)	97	95	53	92	69
Hauser et al (2016)	12	81	43	96	12.5
Stummer et al	9	85	100		
Diez Valle et al (2011)	36	91	89	100 (S) 97 (W)	66
Hefti et al (2008)	57	100 (S) 76 (W)	98(S) 85(W)		
Zhao et al (2015)	Meta-analysis	87	89		

S=strongly fluorescent; W=weakly florescent

Clinical Usefulness

◆ **Demonstrated use of 5-ALA for enhancing delineation of tumor: PPV**

◆ **Ability to aid surgeons in identification of malignant tumor under fluorescent light that may otherwise be overlooked during conventional microsurgical resection?**

Study 28: 5-ALA Fluorescence Identifies Tumor Beyond MRI Contrast Enhancement

- ◆ **After maximal safe resection areas with residual fluorescence were mapped using neuronavigation**
- ◆ **Unresectable Residual Tumor Adjacent to Eloquent Structures**
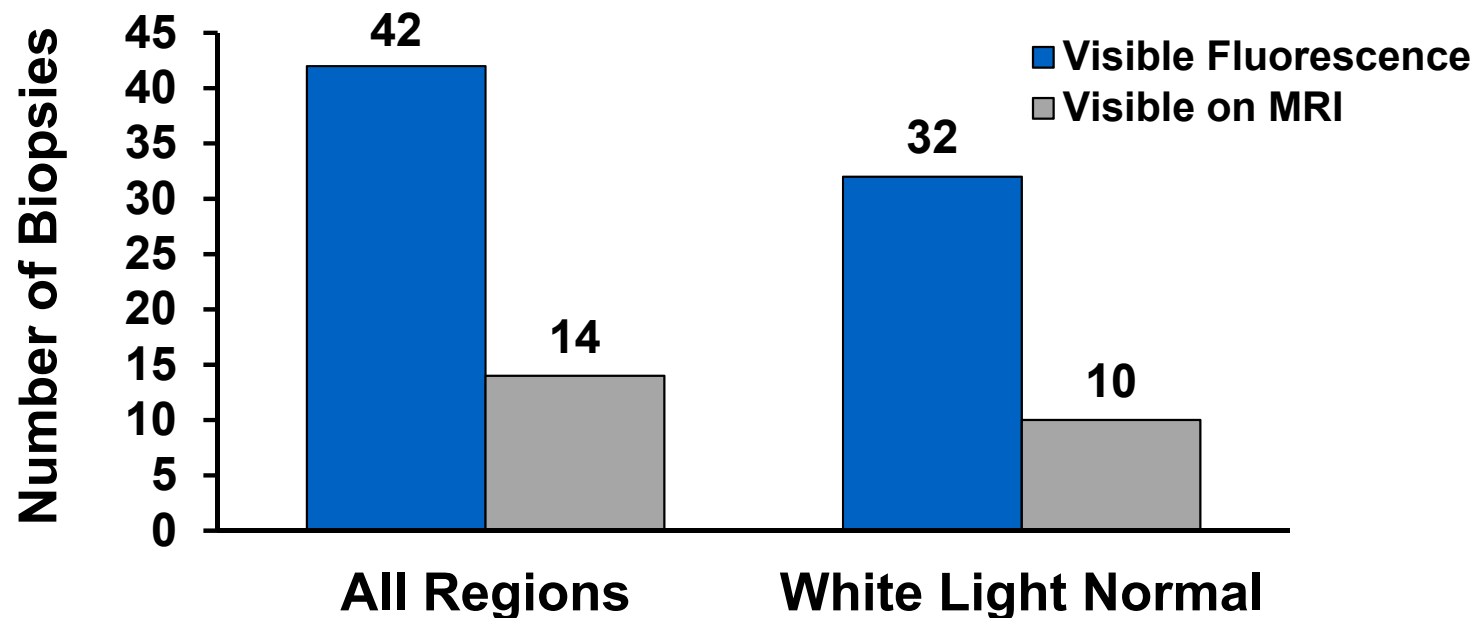
Comparison to post-OP MRI by blinded raters.
Stummer et al. *Neurosurgery* 2014.

Study 30: 5-ALA Identifies Tumor in Normal-looking Brain Tissue

1. **White light resection of gross tumor**

2. **White light resection to "normal tissue" at tumor margin**

3. **Switch to blue light**

4. **Biopsies from regions with different fluorescence qualities**

5. **Rater blinded assessment**

Resection gross tumor — Illustration

Fluorescence at margin — Illustration

Nabavi et al. *Neurosurgery* 2009.
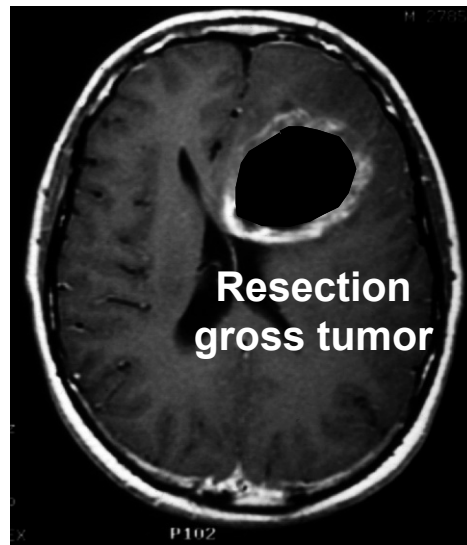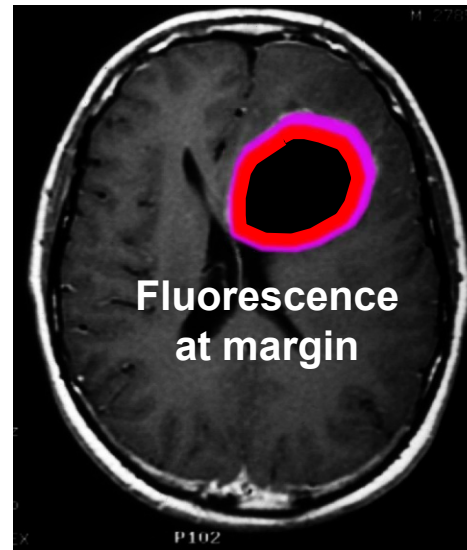
Study 30: 5-ALA Identifies Tumor in Normal-looking Brain Tissue

1. White light resection of gross tumor

2. White light resection to "normal tissue" at tumor margin

3. Switch to blue light

4. Biopsies from regions with different fluorescence qualities

5. Rater blinded assessment

White Light Appearance and Fluorescence Quality	Biopsies N	True-Positive Biopsies N	Predictive Value %	95% CI
"Normal tissue"				
Strong	64	62	96.9	89.2 – 99.6
Weak	93	84	90.3	82.4 – 95.5
Any	157	146	93.0	87.8 – 96.5

Nabavi et al. *Neurosurgery* 2009.

Summary of Efficacy

- **Predictive accuracy**
  - Fluorescence highly predictive of malignant tumor (PPV ~95%)
- **Clinical usefulness**
  - Additional malignant tumor visualized with 5-ALA FGS
- **Clinical significance**
  - Significantly more patients with maximal EOR (63.6 vs 37.6%)
  - Significant improvement in PFS 6 months (imaging and MacDonalds)
  - Post hoc analysis suggests reduced need for subsequent surgeries
- **Data from literature consistent with pivotal studies**

Safety Results

Walter Stummer, Prof Dr med

Safety

- ◆ **Clinical Study Safety Data**

- ◆ **Supportive Literature**

- ◆ **Post-marketing Surveillance Data**

- ◆ **Safety Summary**

Safety Considerations for FGS with 5-ALA

Related to:

◆ **5-ALA**

◆ **Surgery**

– Patient factors

– Individual surgical technique and experience

◆ **Extending resections based on information from additional visualization**

– Structural information (Navigation, MRI, fluorescence) only one aspect

– Knowledge of anatomy/function paramount

Safety Population
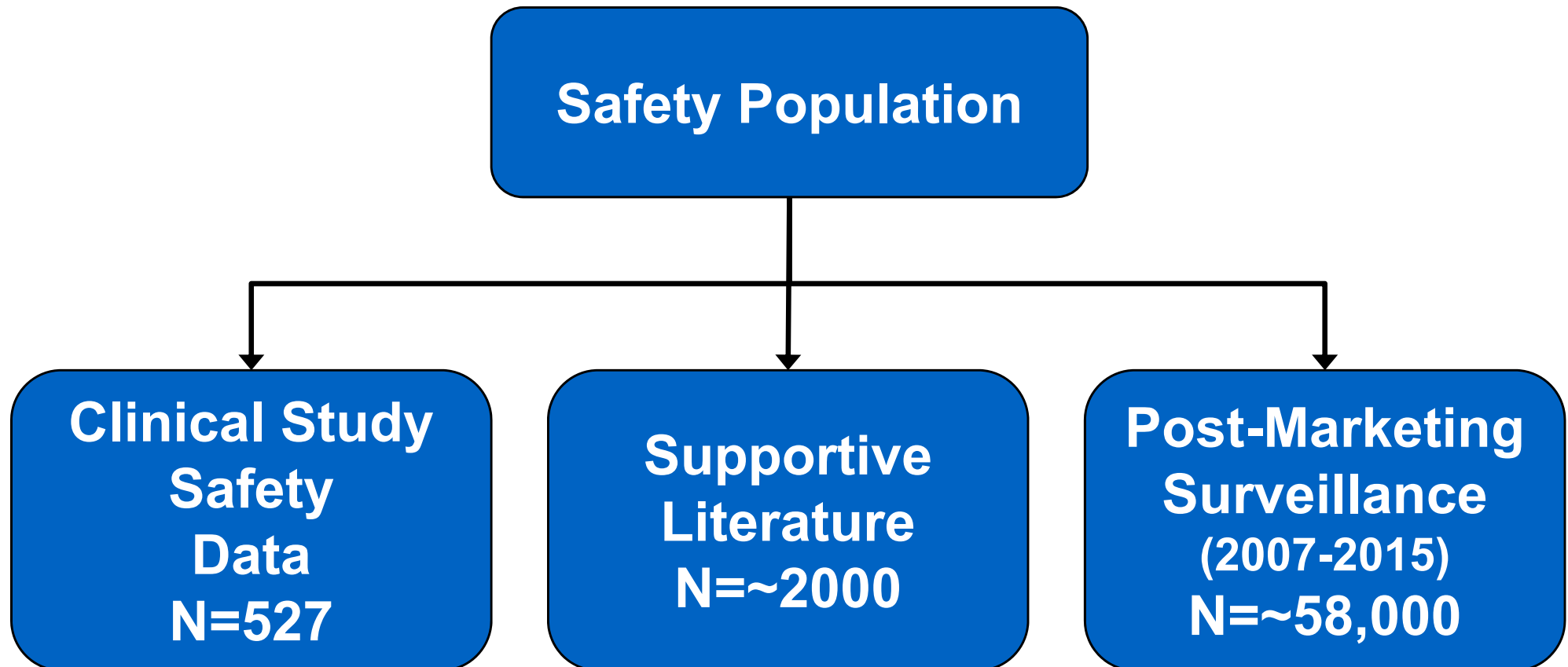
Clinical Study Safety Data

Study Number	Phase	Patients, n 20 mg/kg bw
Full Safety Population		527
Study 8	1/2	7
Study 28	2	36
Study 30	2	40
Study 3	3	201
Study 32	3	243

Definition and Collection of Adverse Events

◆ **TEAEs = AEs that start or worsen during or after 5-ALA administration**

- Reported as mild, moderate, severe, life-threatening, or fatal

- Categorized as:
    - Short term = within 1 week of surgery
    - Mid term = >1 week but within 6 weeks of surgery
    - Long term = >6 weeks after surgery

◆ **Any event with a relationship of certain, probable, or possible were considered drug related**

- An unknown relationship to 5-ALA was reported as drug related

Underlying Disease/Resection Surgery

- **Glioma patients are a seriously ill population**
  - Include a number of underlying comorbidities
  - Death is an outcome due to underlying disease
- **Surgery itself is associated with risks and AEs**
- **AEs collected during mid and long term might be influenced by tumor progression or side effects of surgery/therapy**

Summary of AEs

- **Of the 527 patients:**
  - 317 patients (60.2%) experienced a total of 802 TEAEs
    - 23 TEAEs were drug-related
  - 130 patients (24.7%) experienced an SAE
  - 25 patients (4.7%) experienced TEAEs that resulted in death
- **TEAE rates for 5-ALA comparable to those in Study 3 control group**

Most Frequently Reported TEAEs

- **Nervous System Disorders**
  - Reported in 29.4% of patients
  - Most within 1 week of surgery

- **Neurological events within 1-6 weeks of surgery indistinguishable from Study 3 control group**

- **Neurological TEAEs likely due to disease and/or surgery**

Most Frequently Reported Nervous System Disorder TEAEs

System Organ Class Preferred Term	N (%) N=527
Nervous system disorders	155 (29.4)
Aphasia	42 (8.0)
Hemiparesis	41 (7.8)
Hemianopia	17 (3.2)
Headache	14 (2.7)
Seizure	10 (1.9)
Hemiplegia	10 (1.9)
Monoparesis	7 (1.3)
Hypoaesthesia	6 (1.1)

Low Incidence of Drug Related TEAEs
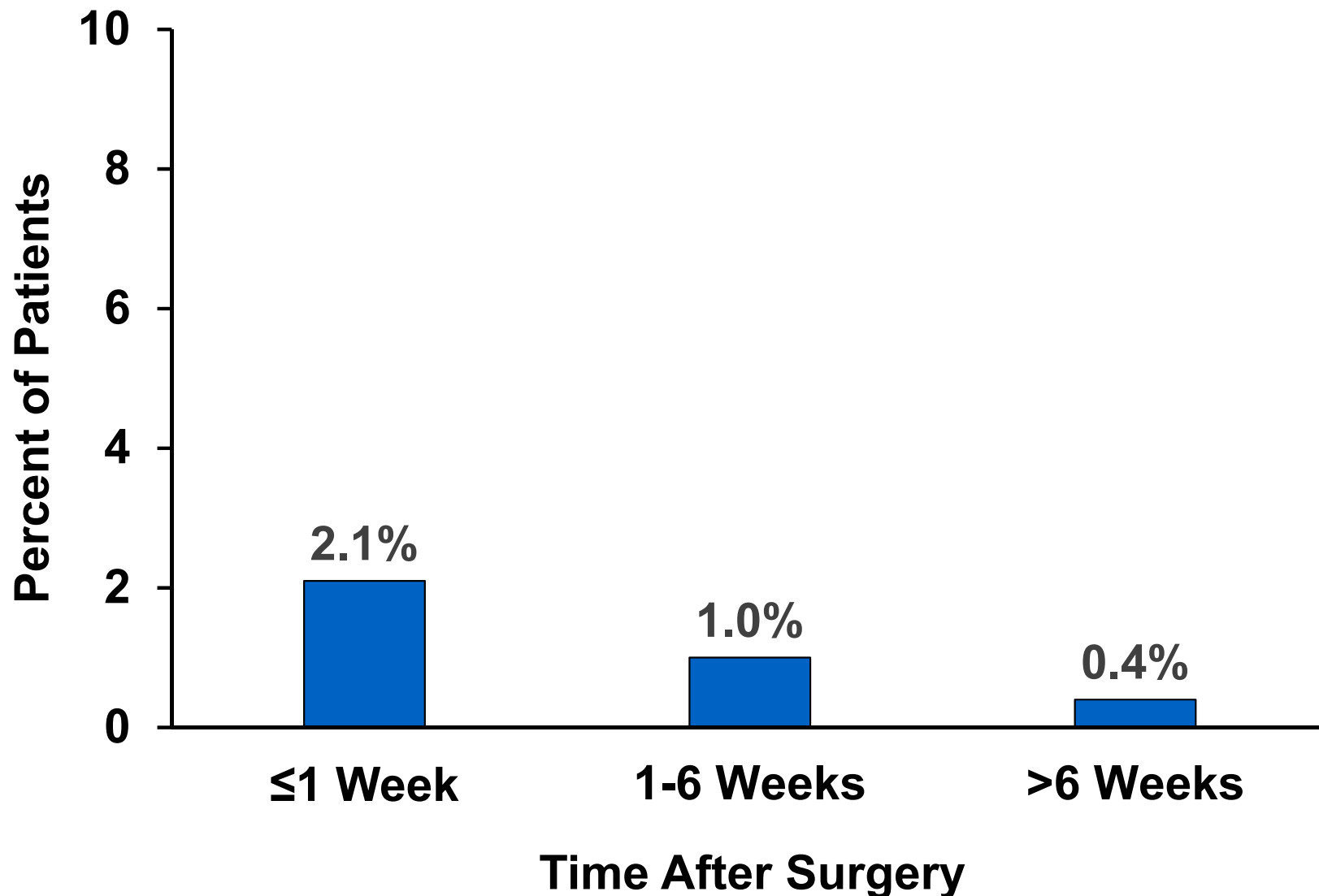
Pooled Safety Set, N=527

Drug-related TEAEs Within First 6 Weeks After Surgery

Preferred Term	N=527 n (%)
Brain edema	1 (0.2)
Hemianopia	1 (0.2)
Hypoaesthesia	1 (0.2)
Pyrexia	2 (0.4)
Chills	1 (0.2)
Photosensitivity reaction	2 (0.4)
Solar dermatitis	1 (0.2)
Hypotension	1 (0.2)
Abnormal LFT	1 (0.2)
Diarrhea	1 (0.2)
Venous thrombosis	1 (0.2)

Serious Adverse Events

◆ **SAEs occurred in 130 patients (24.7%)**
- – 13.1% within 1 week after surgery
- – Most common: Nervous System Disorders (9.3%)
- – 10.0% >1 week but within 6 weeks of surgery
- – 7.3% > 6 weeks after surgery

Safety population, N=527.

SAEs within 1 Week of Surgery

System Organ Class Preferred Term	Pooled Studies N=527 n (%)
Nervous system disorders	49 (9.3)
Hemiparesis	23 (4.4)
Seizure	5 (0.9)
Aphasia	10 (1.9)
Hemiplegia	7 (1.3)
Cerebral infarction	4 (0.8)
Partial seizures	2 (0.4)
Monoparesis	2 (0.4)

Study 3: Neurological AEs

Parameter	Patients, %	
	5-ALA	Control
All Non-serious Neurological AEs*	42.8	44.5
CTCAE Grade III/IV*	7.0	5.2
All neurological SAEs	12.4	11.6

*Excluding SAEs.

Risks of 5-ALA Use: NIH-SS Increased by ≥1 Point

Parameter	5-ALA	Control	p-value	Absolute Risk
NIH-SS deteriorated				
48 hours after surgery	26.2%	14.5%	0.02	11.7%
7 days after surgery	20.5%	10.7%	0.09	9.8%
6 weeks after surgery	17.1%	11.3%	0.29	5.8%
3 months after surgery	19.6%	18.6%	0.77	1.0%

Risks of 5-ALA Use: KPS

Parameter	5-ALA	Control	p-value	Absolute Risk
KPS deteriorated				
6 weeks after surgery	32.9%	28.8%	1.0	4.1%
3 months after surgery	36.2%	37.9%	0.94	-1.7%
6 months after surgery	35.7%	49.1%	0.12	-13.4%

Mortality

- **284 deaths occurred over 18 months**

- **25 patients died as a result of a TEAE**

- **No deaths considered related to 5-ALA**

N=527

Other Safety Parameters

- ◆ **No clinically significant patterns of change in laboratory parameters that could be associated with the study treatment**

- ◆ **Predominantly mild/moderate and transient increase in transaminases and gamma-GT**

- ◆ **No QT prolongation or arrhythmogenic effect**

Liver Function Tests

		5-ALA, n (%) N=201 CTCAE Grade III/IV	Control, n (%) N=173 CTCAE Grade III/IV
AST/GOT	Baseline	0	0
	24 hours	3 (1.5)	0
	7 days	1 (0.5)	1 (0.6)
ALT/GPT	Baseline	2 (1.0)	1 (0.6)
	24 hours	7 (3.5)	4 (2.3)
	7 days	15 (7.5)	9 (5.3)
GGT	Baseline	1 (0.5)	0
	24 hours	4 (2.0)	2 (1.2)
	7 days	21 (10.6)	10 (5.8)

Clinical Studies Summary

◆ **Few TEAEs considered drug related**

◆ **Most frequent TEAEs and SAEs nervous system disorders**

– Likely due to disease and/or surgery

◆ **Few TEAEs led to death**

◆ **No clinically significant patterns of change in laboratory values or QT measures**

Supportive Literature

- **NXDC conducted systematic literature review**
  - January 1, 1995 to June 9, 2016
- **29 studies identified**
- **~2,000 patients**
- **No new AE patterns revealed vs clinical trials**

Post-Marketing Surveillance Data

- **European Union PSUR**
  - 2007-2015
  - ~58,000 patients
- **Safety profile seen post-marketing consistent with clinical trials**

Safety Summary: 5-ALA Well Tolerated

- **Extensive safety database**
  - Clinical studies (N=527)
  - Literature (N=~2000)
  - Post-marketing experience (N=~58,000)
- **Well established safety profile**
  - AEs predominantly result of procedure, underlying disease
  - Neurological AEs consistent with and correlate to surgical procedure

Agenda: 5-ALA Visualization of Glioma

Introduction	**Alan Ezrin, PhD** *President & CEO* *NX Development Corporation*
Visualization of Tumor During Glioma Surgery	**Constantinos G. Hadjipanayis, MD, PhD** *Professor and Chair, Dept. of Neurosurgery, Director of Neurosurgical Oncology, Professor of Oncological Sciences, Mount Sinai*
Clinical Efficacy	**Walter Stummer, Prof Dr med** *Department of Neurosurgery, University of Münster*
Safety Results	**Walter Stummer, Prof Dr med**
Benefit / Risk	**Constantinos G. Hadjipanayis, MD, PhD**
Conclusion	**Alan Ezrin, PhD**

Benefit/Risk of 5-ALA for the Visualization of Glioma During Resection Surgery

Constantinos G. Hadjipanayis, MD, PhD

Professor and Chairman of Neurosurgery,

Mount Sinai Beth Israel Hospital

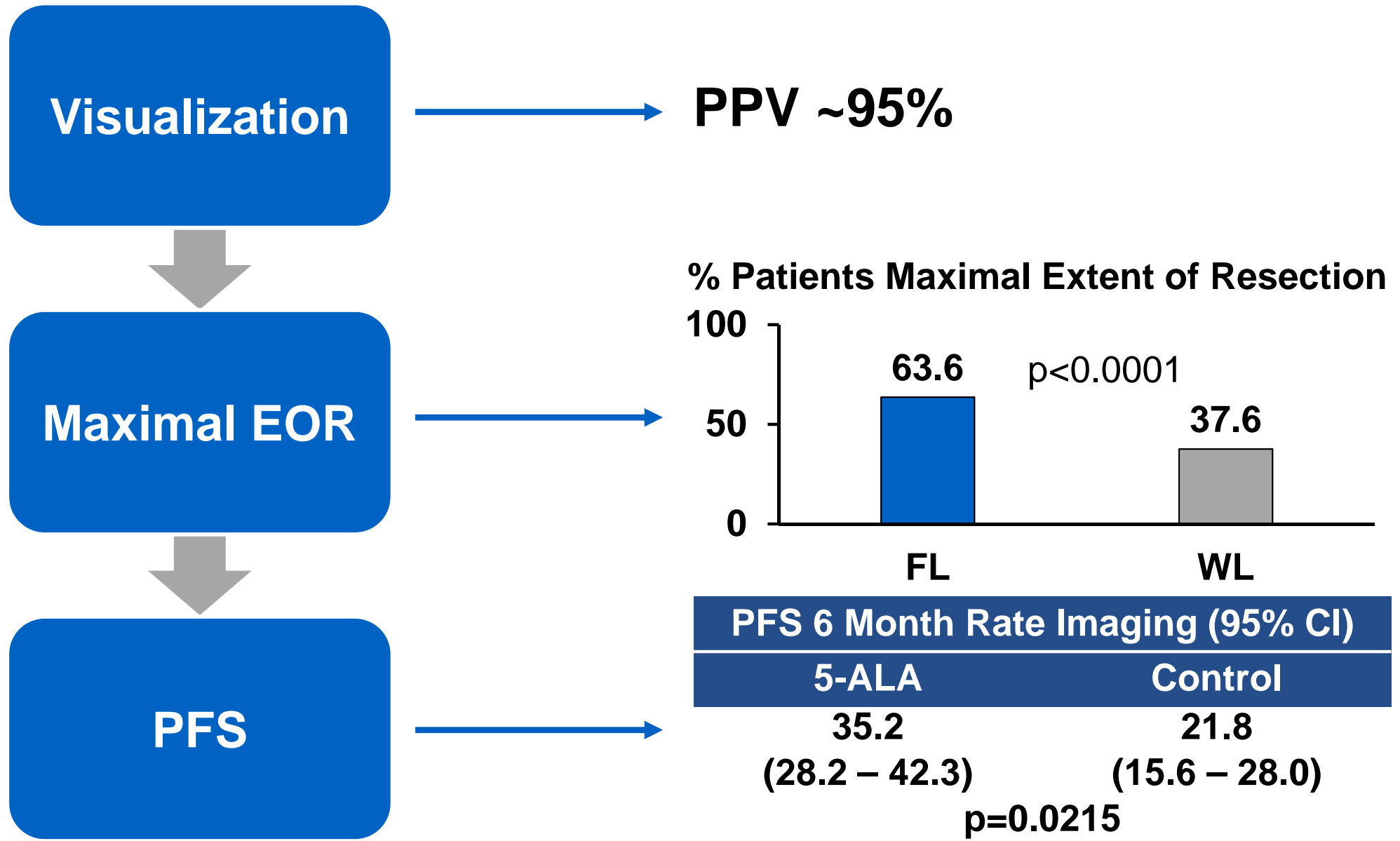*Director of Neurosurgical Oncology*

Mount Sinai Health System

New York, NY

Need for Better Visualization of Malignant Tumor Tissue

◆ **Goal of surgery is safe maximal extent of resection**

◆ **Maximal resection is associated with better patient outcomes**

◆ **Gliomas are difficult to identify at the margin and infiltrate the normal brain**

◆ **Accurate tumor delineation not in real time**

Visualization to Clinical Benefit From Phase 3 Study

Visualization ⟶ **PPV ~95%**

Maximal EOR ⟶

% Patients Maximal Extent of Resection

PFS ⟶

PFS 6 Month Rate Imaging (95% CI)	
5-ALA	**Control**
35.2	**21.8**
(28.2 – 42.3)	**(15.6 – 28.0)**
p=0.0215	

Benefits of 5-ALA

◆ **Well tolerated and safe**

◆ **High resolution intraoperative visualization tool**

◆ **Unambiguous delineation**

◆ **Compatible with standard surgical microscope**

◆ **Oral administration**

◆ **Does not disrupt flow of surgery**

◆ **Accuracy not affected by brain shift**

◆ **5-ALA provides greater maximal EOR, PFS-6, and fewer repeat surgeries**

Risks

- **Visualization and resection of additional malignant tumor not seen with white light**
  - Neurosurgeon still decides if tumor tissue can be safely resected
  - Transient neurologic deficits
- **Temporary skin photosensitivity**
- **Transient LFT elevation**

5-ALA Medicines Management Program

◆ **Program will**

1. Instruct surgeons in 5-ALA FGS and proper use

2. Limit use to neurosurgeons certified (and recertified every two years) after instruction

3. Ensure 5-ALA dispensed from hospital pharmacies only to surgeons certified

5-ALA Benefit/Risk Summary

- ◆ **Improved visualization of malignant glioma tissue during surgical resection**

- ◆ **Real time visualization of malignant tumor tissue guiding surgery**

- ◆ **Structural delineation of tumor from normal brain**

- ◆ **Confidence that what is removed is tumor tissue**

- ◆ **Patient benefit with better PFS, maximal EOR, and fewer repeat surgeries**

- ◆ **Well understood safety profile**

Agenda: 5-ALA Visualization of Glioma

Introduction	**Alan Ezrin, PhD** *President & CEO* *NX Development Corporation*
Visualization of Tumor During Glioma Surgery	**Constantinos G. Hadjipanayis, MD, PhD** *Professor and Chairman of Neurosurgery, Mount Sinai Beth Israel Hospital* *Director of Neurosurgical Oncology, Mount Sinai Health System, New York, NY*
Clinical Efficacy	**Walter Stummer, MD** *Department of Neurosurgery, University of Münster*
Safety Results	**Walter Stummer, MD**
Benefit / Risk	**Constantinos G. Hadjipanayis, MD, PhD**
Conclusion	**Alan Ezrin, PhD**

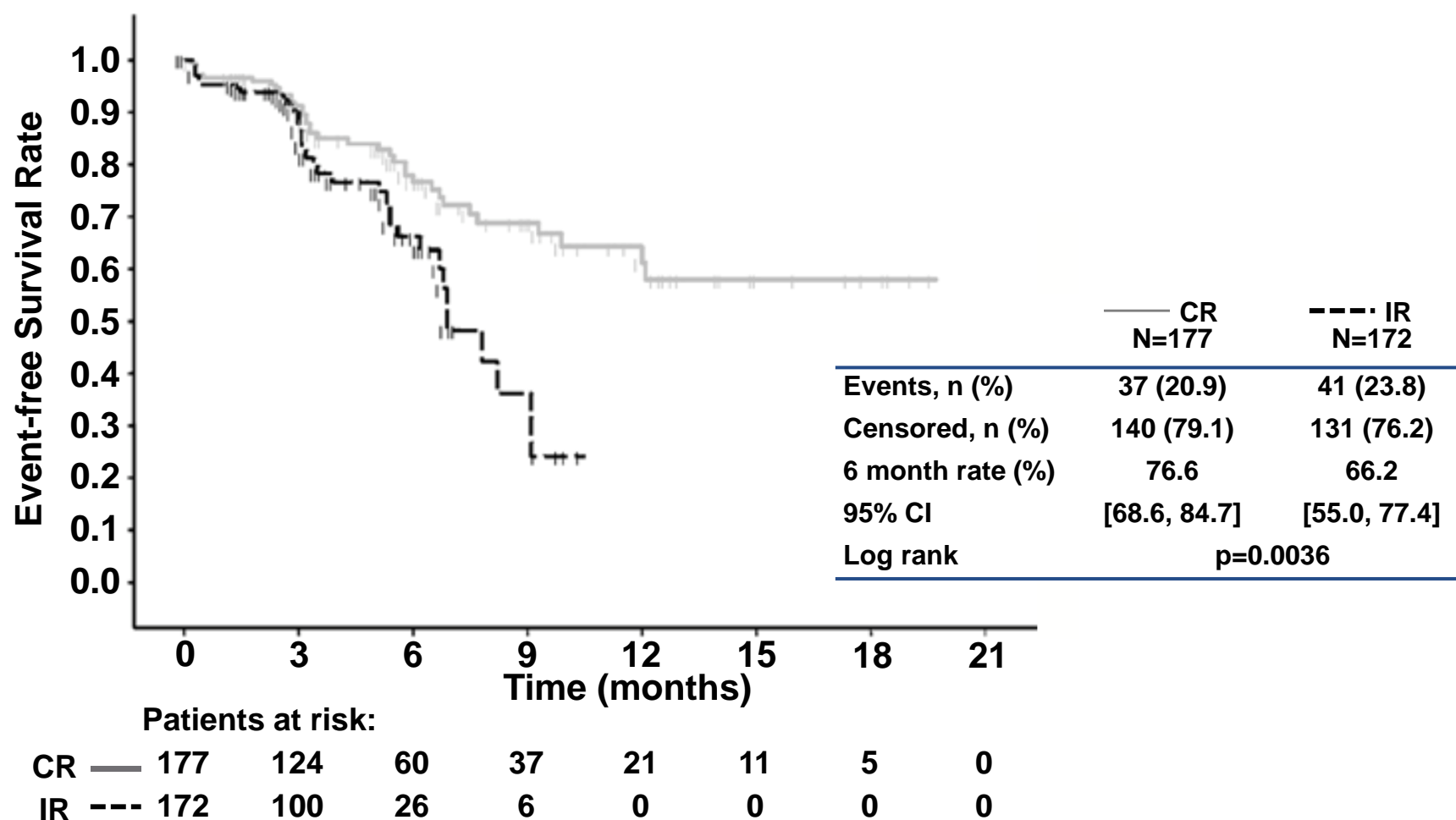# Conclusion

Alan Ezrin, PhD

President & CEO
NX Development Corporation

Proposed Indication

5-ALA is an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery

Supporting Slides

Extent of Resection and Event Free Survival

	CR N=177	IR N=172
Events, n (%)	37 (20.9)	41 (23.8)
Censored, n (%)	140 (79.1)	131 (76.2)
6 month rate (%)	76.6	66.2
95% CI	[68.6, 84.7]	[55.0, 77.4]
Log rank	p=0.0036	

Patients at risk:

CR	177	124	60	37	21	11	5	0
IR	172	100	26	6	0	0	0	0

Time from randomization to NIH-SS deterioration (≥ 1 point) with stable/increased use of steroids − event-free survival − Kaplan-Meier estimates (death/radiological progression censored). CR=complete resection; IR=incomplete resection.

Stummer et al. Journal of *Neurosurgery*, 2008

Study 3: Summary of NIHSS
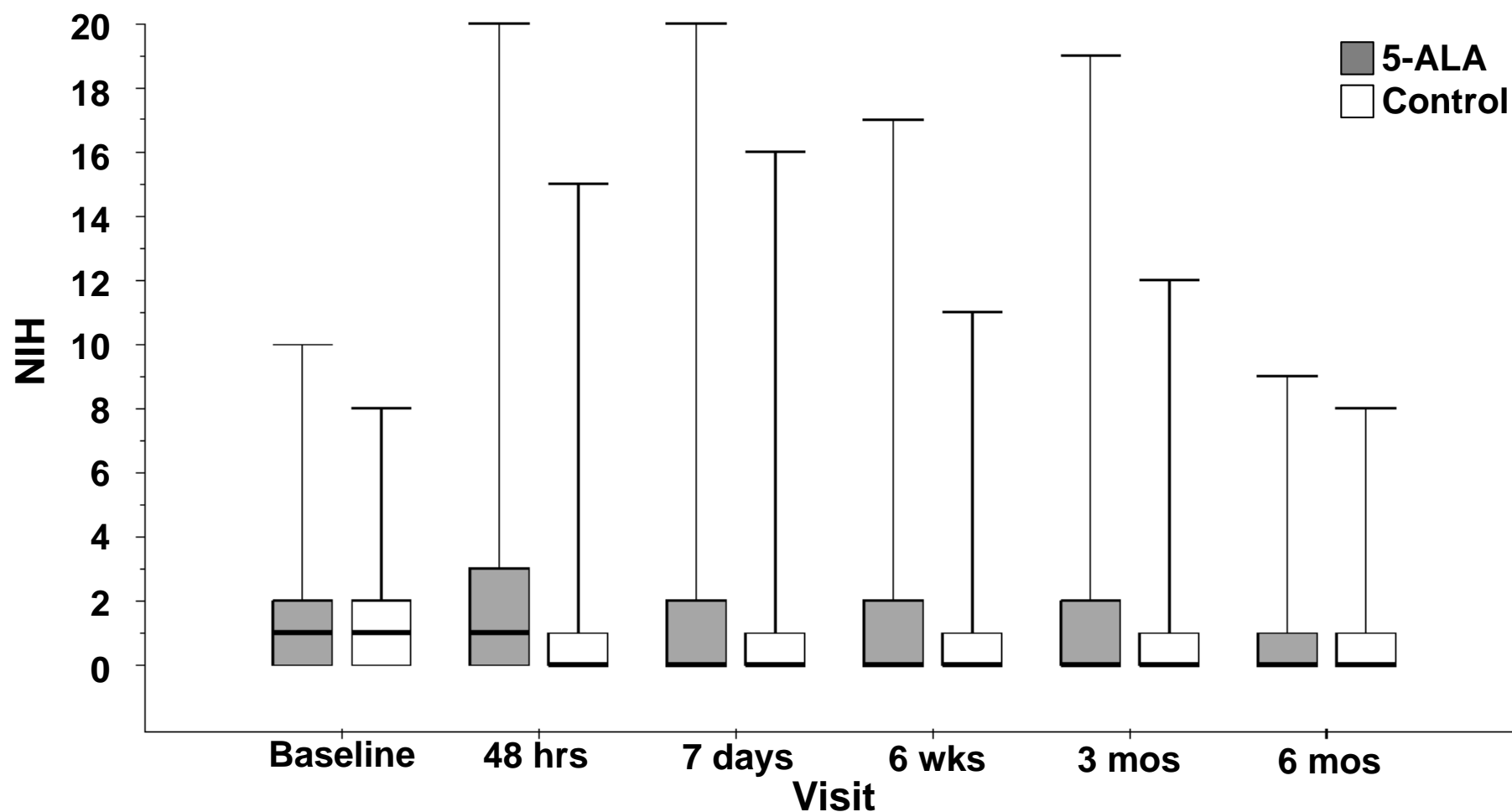
	Baseline	48 hrs	7 days	6 wks	3 mos	6 mos
5-ALA, n=	160	157	156	138	127	65
Control, n=	166	166	164	147	135	54

Study 3:
Deterioration from Baseline in NIHSS by ≥1 Point Stratified by Baseline NIHSS (Full Analysis Set)

| Time | Baseline NIH-SS | Deteriorated | n (%) | | P value* |
			5-ALA N=172	Control N=172	
48 hours	Total	No	127 (73.8)	147 (85.5)	0.0106
		Yes	45 (26.2)	25 (14.5)	
	0	No	51 (79.7)	56 (81.2)	1.000
		Yes	13 (20.3)	13 (18.8)	
	>0	No	76 (70.4)	91 (88.3)	0.0020
		Yes	32 (29.6)	12 (11.7)	

* P value based on Fisher's exact test.

5-ALA Metabolism

Mitochondrion

Glycine – Succinyl CoA

Negative feedback

Hemoglobin

5-Aminolevulinic acid

Protoporphyrin IX

Protoporphyrinogen IX

Porphobiligen

Cograporphyrinogen III

Cytoplasm

Uroporphyrinogen III

Hadjipanayis C et al. *Semin Oncol* 2011.