

**Ethylol<sup>®</sup> (amifostine) NDA#20-221/S012**  
**Oncologic Drugs Advisory**  
**Committee**

Presentation by  
U.S. Bioscience, Inc.



June 8, 1999

**Introduction**

Wolfgang Oster, MD  
Executive Vice President  
Clinical Research  
U.S. Bioscience, Inc.

## **Amifostine**

- ◆ Amifostine is indicated for reduction of cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer.
- ◆ Amifostine has been approved in similar or extended indications in 50 countries.
- ◆ EU approval for reduction of radiation-induced xerostomia (April 1999)
- ◆ Amifostine has been administered in 250,000 treatment cycles in 83,000 patients.

## **Amifostine SNDA**

- ◆ Indication: Amifostine reduces the incidence of moderate to severe radiation-induced xerostomia
- ◆ Orphan Drug designation
- ◆ Application submitted December 1998
- ◆ Priority Review Status February 1999

## **Unmet Medical Need**

- ◆ **Reduction of severe xerostomia is of significant benefit to patients undergoing radiation therapy for head and neck cancer**

## **Xerostomia**

- ◆ **Salivary glands are sensitive to radiation.**
- ◆ **Radiation is a fundamental treatment modality for head and neck cancer.**
- ◆ **Xerostomia is a frequent complication of radiotherapy.**
- ◆ **Xerostomia is often permanent.**

- ◆ The data presented today will show:  
Amifostine has demonstrated a clinically meaningful effect on an irreversible morbidity (xerostomia)
  - Large multi-center study (WR-38)
  - Multiple independent but logically-linked endpoints
  - Statistically very persuasive findings
- Supportive studies show consistent efficacy

### **Scientific Team**

- ◆ David Grdina, PhD
- ◆ David Brizel, MD
- ◆ John Mackowiak, PhD
- ◆ Gary Koch, PhD
- ◆ Lesley Russell, MD
- ◆ Walter Curran, MD
- ◆ Todd Wasserman, MD
- ◆ Robert Capizzi, MD
- ◆ Francis Le Veque, DDS
- ◆ Kenneth Kent, DDS
- ◆ Irving Hwang, PhD
- ◆ Kenneth Tew, PhD
- ◆ Thomas Pajak, PhD

## Amifostine: Mechanism of Action

David Grdina, PhD  
Professor of Radiation and  
Cellular Oncology  
University of Chicago  
Chicago, Illinois

### Amifostine (WR-2721)



+

Alkaline phosphatase

 $\Downarrow$ 

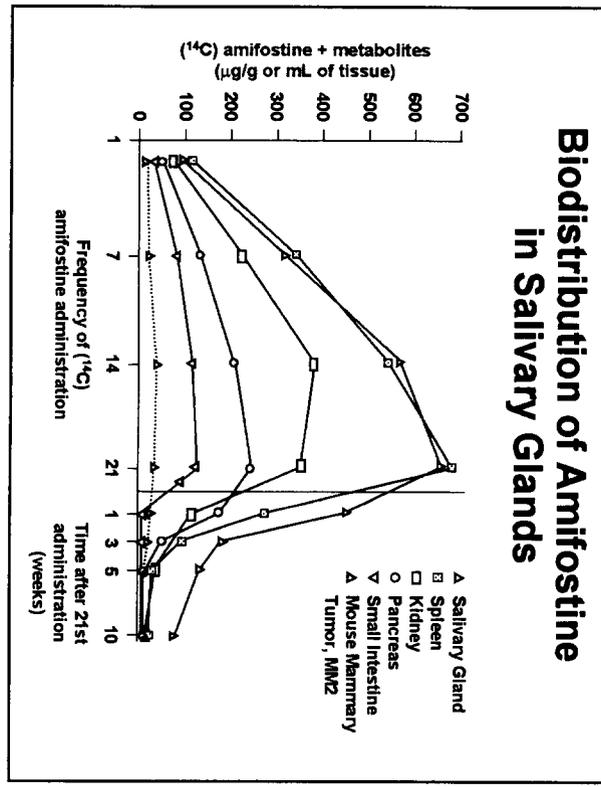
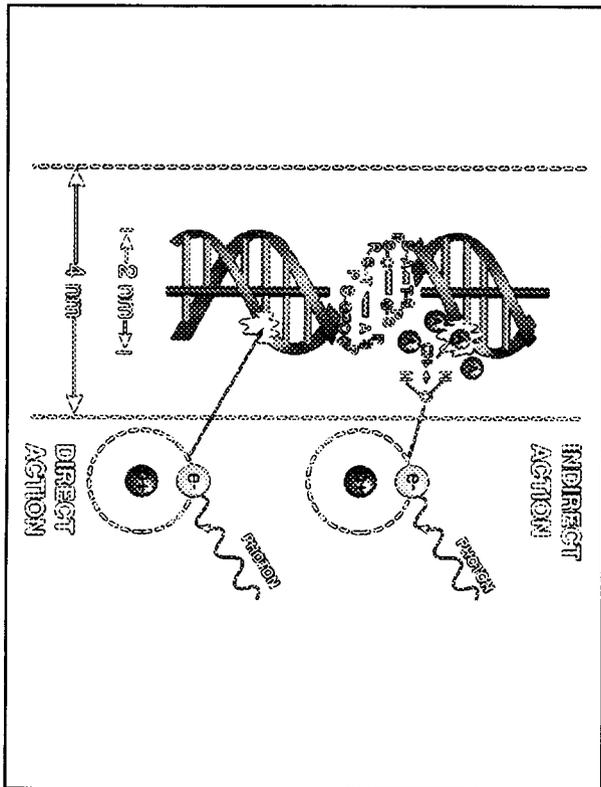
WR-1065



Reduction  $\Uparrow$  Oxidation  $\Downarrow$

WR-33278





## **Selective Protection**

### **Normal Tissue**

- ◆ **Activation of pro-drug**
- ◆ **Drug delivery**
- ◆ **Drug tissue concentrations**
- ◆ **Timing of treatment**

## **Summary**

- ◆ **Designed for, and acts as, a potent radioprotector**
  - **Binds to and shields DNA**
  - **Scavenges RT-induced free radicals**
- ◆ **High concentrations in salivary glands**
- ◆ **High protection factor in salivary glands**
- ◆ **Protective effects are concentration-dependent and selective for normal tissues**

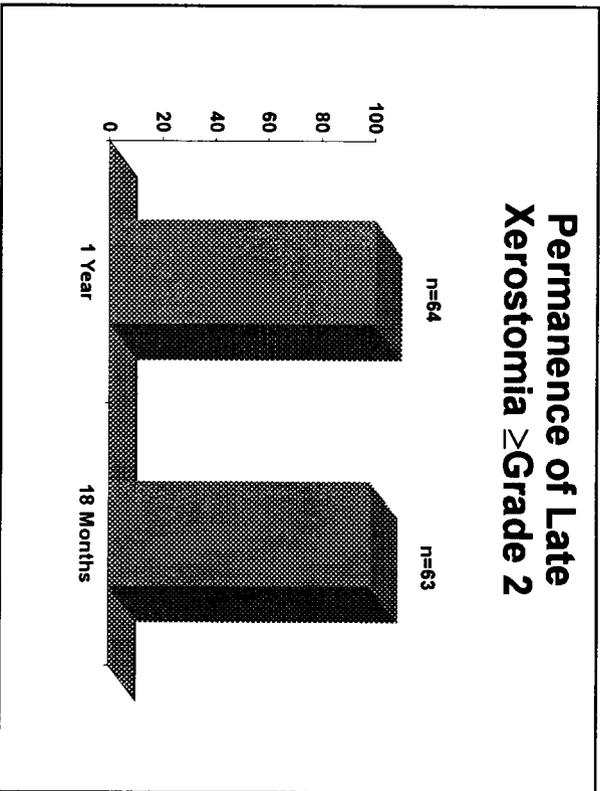
**Phase III Trial of Radiation  
Therapy ± Amifostine in  
Patients with Head and Neck  
Cancer (WR-38)**

**David M. Brizel, MD**  
Associate Professor of Radiation Oncology  
Duke University Medical Center  
Durham, North Carolina

*Principal Investigator*

**Xerostomia**





- ### Primary Endpoints
- ◆ Incidence of  $\geq$  Grade 2 acute xerostomia (RTOG criteria)
  - ◆ Incidence of  $\geq$  Grade 2 late xerostomia (RTOG criteria)
  - ◆ Incidence of  $\geq$  Grade 3 acute mucositis (RTOG criteria)
  - ◆ Preservation of anti-tumor efficacy
    - Local-regional control rates at 12 months

## **Secondary Endpoints**

- ◆ Time to occurrence of  $\geq$  Grade 2 xerostomia
- ◆ Whole saliva production
- ◆ Patient Benefit Questionnaire
- ◆ Disease-free survival
- ◆ Overall survival

## **RTOG Grading Scale Acute Xerostomia**

- ◆ Grade 1
  - Mild mouth dryness
- ◆ Grade 2
  - Moderate to complete dryness
- ◆ No Grade 3
- ◆ Grade 4
  - Salivary gland necrosis

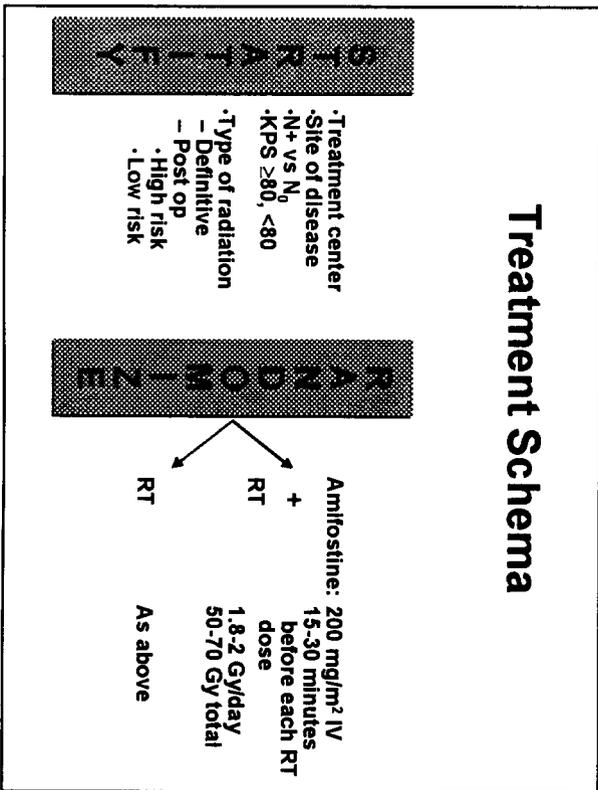
### **Patient Eligibility Criteria**

- ◆ Newly diagnosed squamous cell head and neck cancer
- ◆ Inclusion of at least 75% of both parotid glands within RT fields
- ◆ Age  $\geq$ 18 years; KPS  $\geq$ 60
- ◆ Neutrophils  $\geq$ 2,000/mm<sup>3</sup>, platelets  $\geq$ 100,000/mm<sup>3</sup>
- ◆ Prophylactic use of pilocarpine prohibited

### **Patients and Follow-up**

- ◆ 315 patients randomized
- ◆ 303 patients treated
  - 150 in amifostine + RT arm
  - 153 in RT alone arm
- ◆ Median follow-up: 26 months

## Treatment Schema



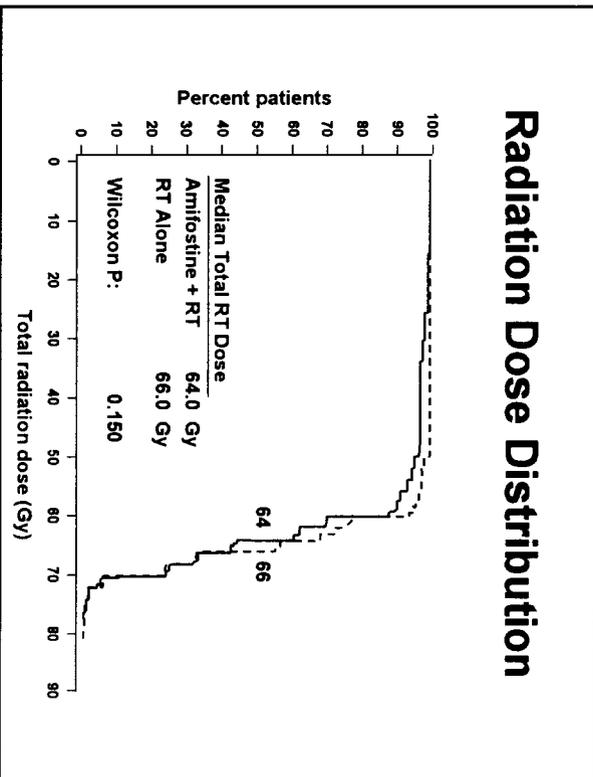
## Patient Demographics

- ◆ Well-balanced pre-treatment for:
  - Age
  - Gender
  - Tumor site
  - Tumor stage
  - Nodal status
  - RT type
  - RT dose

### Radiation Treatment WR-38

Duration of Treatment	Amifostine + RT (N=150)	RT Alone (N=153)	p-Value
Median (Range)	48 days (11-84)	49 days (36-66)	0.432
<b>RT Treatments</b>			
Median (per patient) (Range)	32 (8-40)	33 (25-42)	0.136

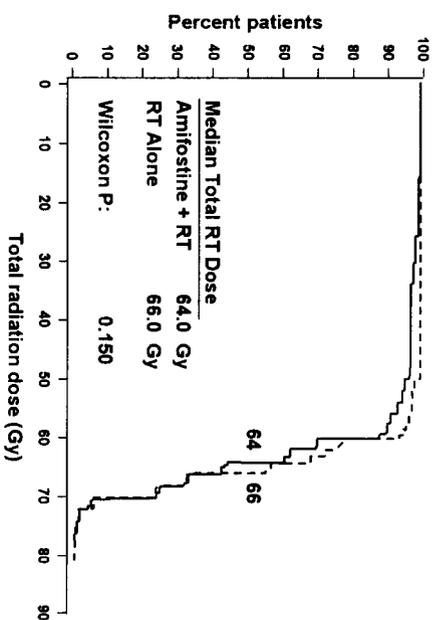
### Radiation Dose Distribution



## Acute Xerostomia $\geq$ Grade 2

	Amifostine + RT (N=150)	RT (N=153)	<i>p</i> -Value (2-sided)
Incidence	51%	78%	<0.0001
Cumulative RT dose (50% incidence)	60 Gy	42 Gy	0.0001

## Radiation Dose Distribution



### Acute Grade 2 Xerostomia by Total RT Dose

Total Dose (Gy)	Amifostine + RT		RT Alone		p-Value
	n	%	n	%	
40-49	1/1	—	—	—	—
50-59	6/12	50%	8/9	89%	—
≥60	67/131	51%	112/144	78%	<0.0001
Overall	75/144	51%	120/153	78%	<0.0001

### Late Xerostomia at 1 Year Patients with Available Data

RTOG Grade	Amifostine + RT (n=97)		RT Alone (n=106)		p-Value (2-sided)
	n	%	n	%	
0	16	16%	12	11%	0.0019
1	48	49%	34	32%	
≥2	33	34%	60	57%	

## Robustness of Late Xerostomia ≥ Grade 2

Completion of Therapy	Amifostine + RT		RT Alone		p-Value
	%	(n)	%	(n)	
≥3 months	45%	132	64%	141	0.0024
≥5 months	43%	122	65%	130	0.0006
≥7 months	38%	112	61%	119	0.0010
≥9 months	36%	104	60%	112	0.0004
≥11 months	33%	97	58%	105	0.0004

## Late Xerostomia ≥ Grade 2 at 1 Year All Patients\*

RTOG Grade	Amifostine + RT		RT Alone		p-Value (2-sided)
	(n=150)	%	(n=153)	%	
≥2	33	22%	60	39%	0.0012

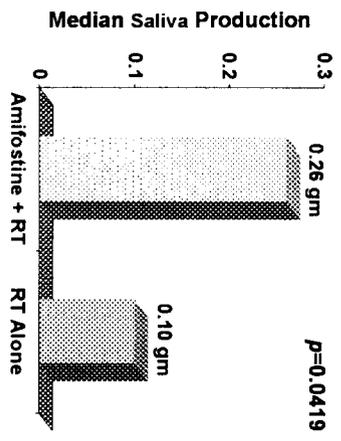
### Late Xerostomia $\geq$ Grade 2 at 1 Year by RT Dose

Total Dose (Gy)	Amifostine + RT		RT Alone		P-Value
	n	%	n	%	
40-49	1/1	—	—	—	
50-59	2/8	—	4/7	—	
$\geq$ 60	30/88	34%	56/99	56%	0.0032

### Saliva Production Analysis

- ◆ Whole saliva volume determines patient symptoms and well-being
  - Protocol defined endpoint
- ◆ Whole saliva volume at 1 year
  - Independent measure of late xerostomia

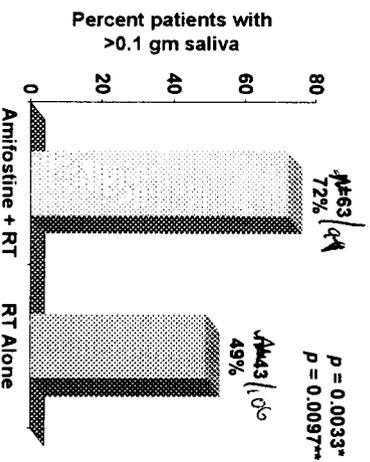
### Unstimulated Median Saliva Production at 1 Year WR-38



### Saliva Threshold

- ◆ 0.1 gm defined prior to analysis (pilocarpine precedent)
- ◆ FDA Dental Review
- ◆ *“0.1 gm/5 min would be an acceptable indicator of clinical efficacy.”*

### Unstimulated Saliva Production At 1 Year (>0.1 gm)



\* Fisher's Exact Tests  
\*\* Adjusted for multiple time points

### Analysis on Change from Baseline

- ◆ Results are driven by variability in pre-treatment volumes
- ◆ Does not reflect end of treatment volume
- ◆ Examples from WR-38:
  - Patient 1301 - Largest change from baseline
 

Baseline	Month 11	Change from baseline
6.51 gm	1,007 gm	- 5.503 gm
  - Patient 2827 - Poorest clinical outcome
 

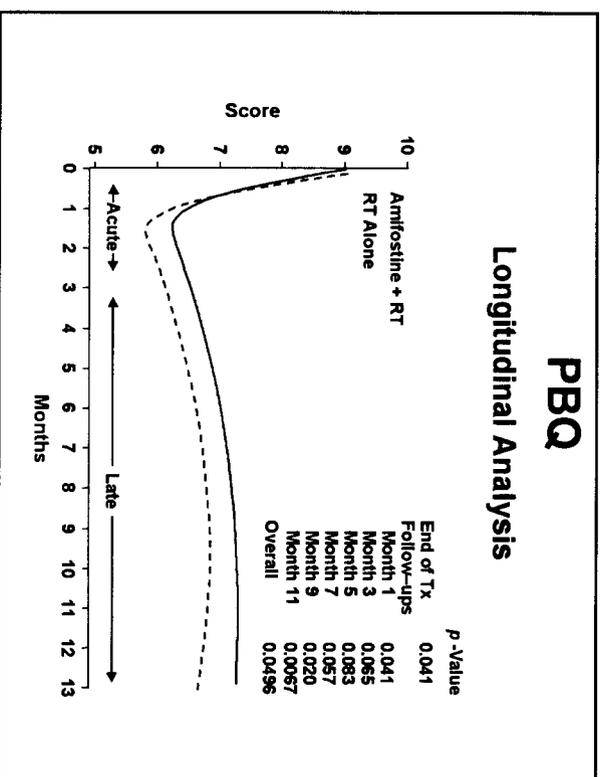
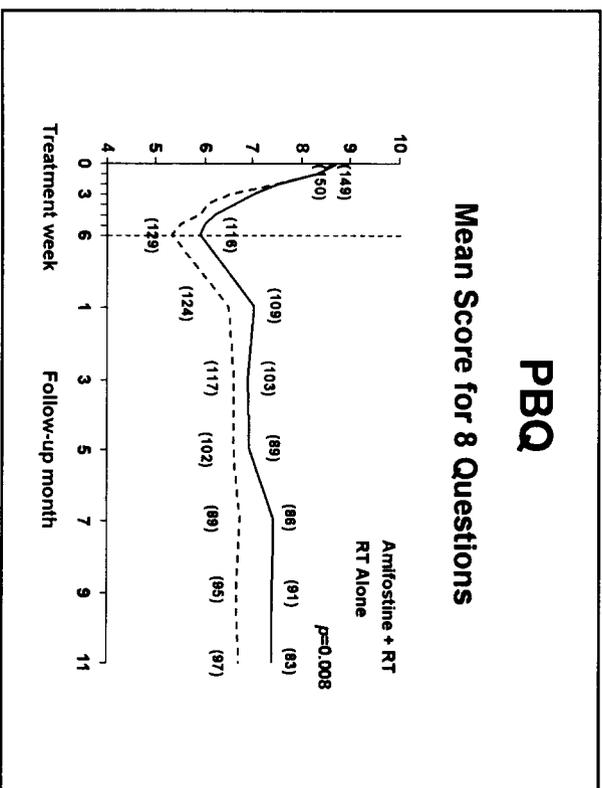
Baseline	Month 11	Change from baseline
2.10 gm	0,00 gm	- 2.10 gm

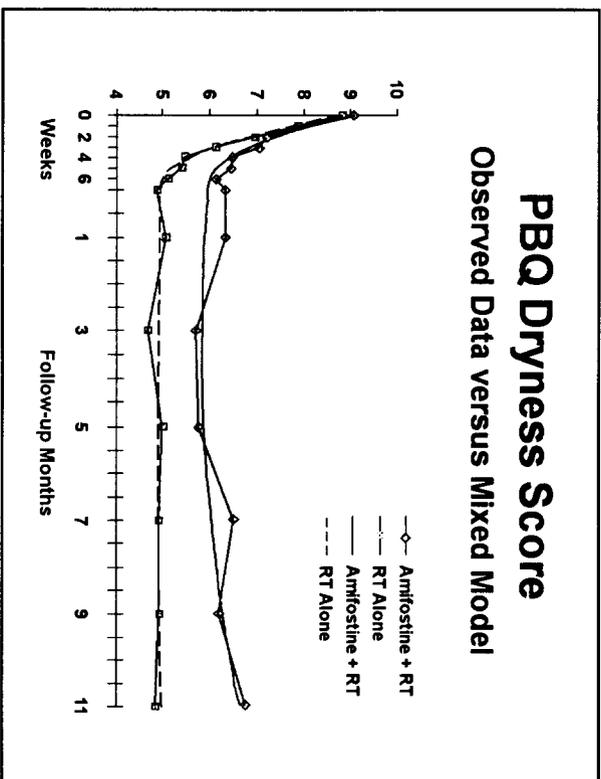
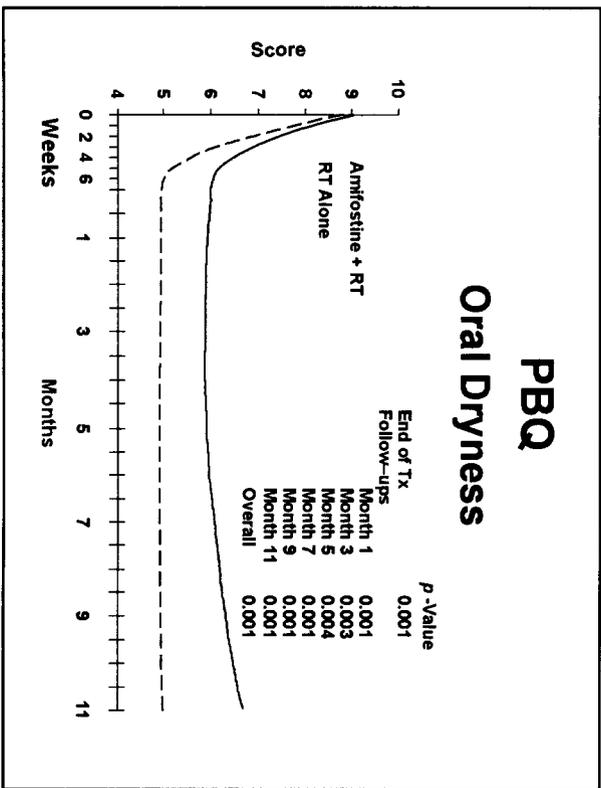
## **Patient Benefit Questionnaire**

**John Mackowiak, RPh, PhD  
Center for Outcomes Research  
Chapel Hill, North Carolina**

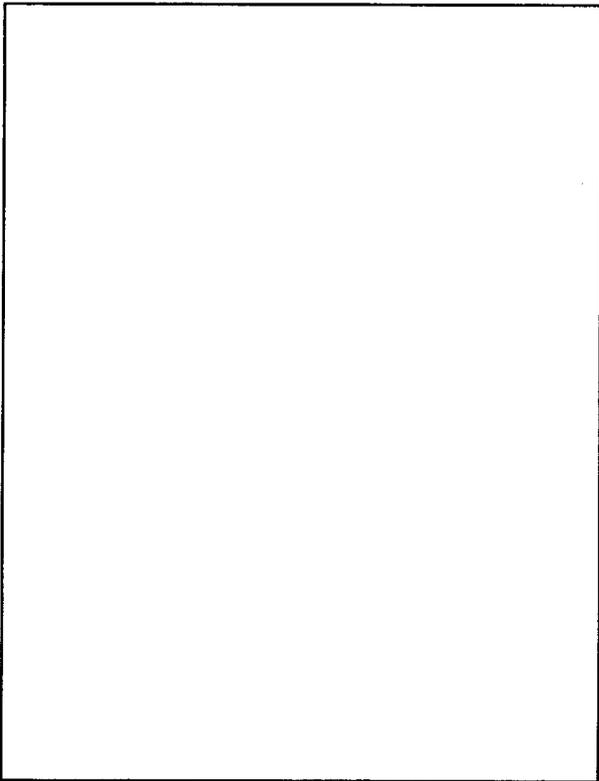
## **Patient Benefit Questionnaire PBQ**

- ◆ 8-item, 10-point scale, clinical benefit questionnaire
  - Symptoms
  - ADL issues (speaking, eating, sleeping)
  - Fluid intake
- ◆ Validated using Medical Outcomes Trust Guidelines
- ◆ Administered at:
  - Baseline
  - Weekly during RT
  - At months 1, 3, 5, 7, 9, and 11 following treatment





<b>PBQ</b>		
<b>Relevant Clinical Results</b>		
<u>RTOG Toxicity Grade Change</u>	<u>PBQ Change</u>	<u>p -Value</u>
One grade level worse	↓ 0.96	<0.0001
One grade level better	↑ 1.17	0.0001



### **≥Grade 2 Xerostomia Correlation of Endpoints**

**$p=0.0001$  for each of these correlations  
Correlation coefficients: 0.304 - 0.529**

- ◆ Late xerostomia with saliva production
- ◆ Late xerostomia with PBQ score
- ◆ Late xerostomia with oral dryness  
(Question 1 PBQ)
- ◆ PBQ score with saliva production
- ◆ Oral dryness with saliva production  
- (Question 1 PBQ)

### **Preservation of Anti-tumor Efficacy**

## Local-Regional Control Ratio 12 Months\*

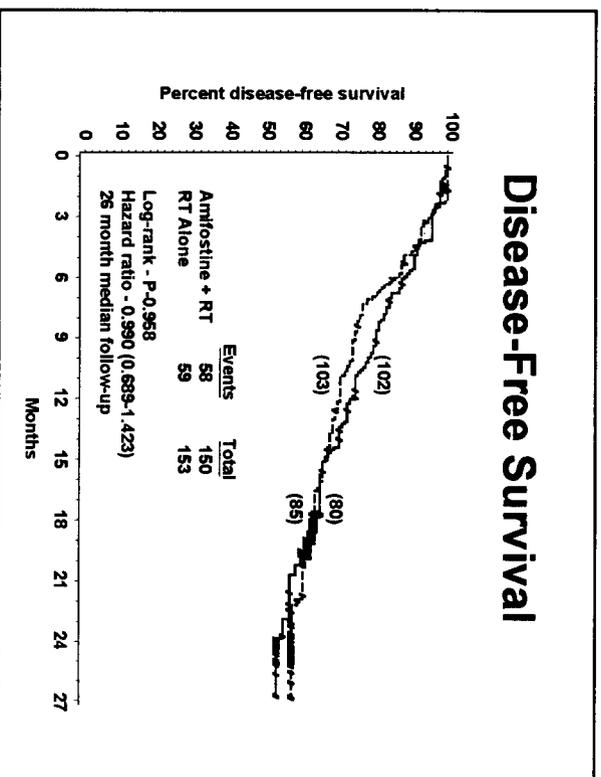
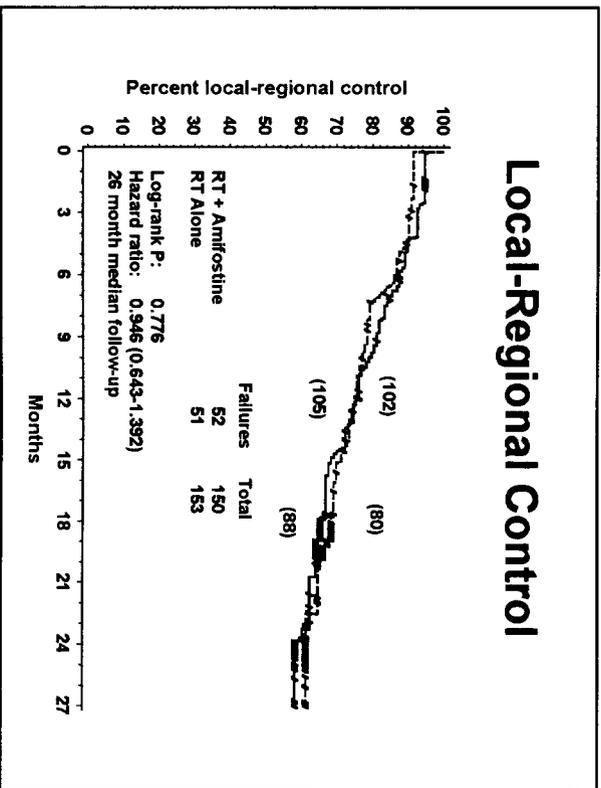
Local/Regional Control	Amifostine + RT	RT Alone	p-Value**
Local/regional control rate	72%	71%	1.000
Local/regional control ratio***	1.008		
Lower limit of 95% one-sided confidence interval	(0.886)		
95% confidence interval (2-sided)	(0.864, 1.175)		

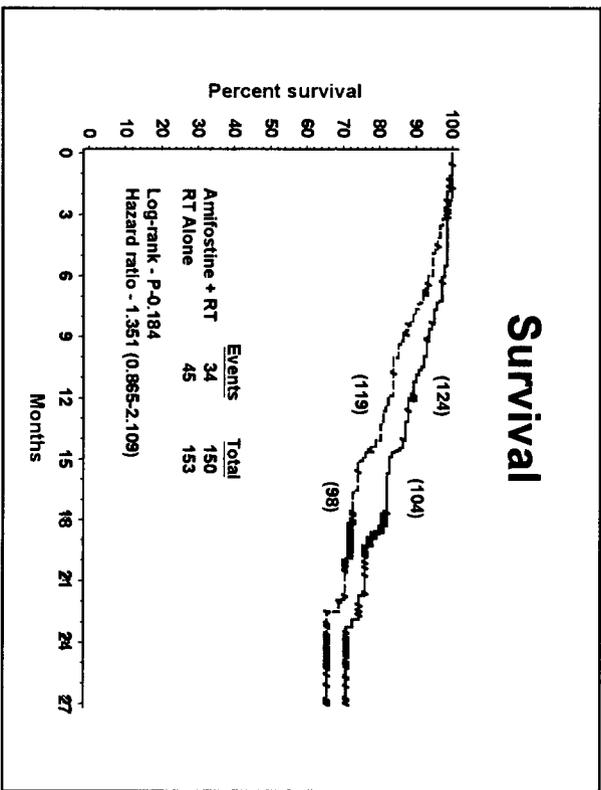
\* 12 month rates calculated using product-limit method  
 \*\* p-Value based on Fisher's Exact Test  
 \*\*\*Odds ratio >1.0 favors amifostine + RT arm

## Local-Regional Control Ratio 18 Months\*

Local/Regional Control**	Amifostine + RT	RT Alone	p-Value**
Local/regional control rate	61%	64%	0.700
Local/regional control ratio***	0.956		
Lower limit of 95% one-sided confidence interval	(0.816)		
95% confidence interval (2-sided)	(0.792, 1.155)		

\* 18 month rates calculated using product-limit method  
 \*\* p-Value based on Fisher's Exact Test  
 \*\*\*Odds ratio >1.0 favors amifostine + RT arm





- ### Safety
- #### Nausea/Vomiting and Anti-emetic Use
- ◆ Nausea/Vomiting
    - Mild to moderate severity
    - Grade 3 incidence
      - 8% of patients
      - <1% of infusions
  - ◆ Anti-emetics
    - Oral 5HT3 antagonists were most commonly used anti-emetics

# Weight Loss During Treatment

Percent Weight Loss*	Amitostine + RT (N=150)	RT Alone (N=153)	p-Value
None	24%	14%	0.0437
<5%	29%	31%	
5%-10%	30%	35%	
>10%	17%	21%	

\*Normalized to pre-treatment baseline

# Hypotension

- ◆ PO/IV hydration 30 minutes prior to administration
- ◆ Overall incidence
  - 15% of patients
  - 1% of infusions
- ◆ Moderate
  - 3% of patients (transient)
  - <1% of infusions
- ◆ No sequelae

### Safety

**Other Grade 3/4 Adverse Events >1%**

	Amifostine + RT (N=150) Patients (%)	Infusion %	RT Alone (N=153) Patients (%)
Allergic-type/skin	3%	<1%	0%
Fever	2%	<1%	0%

### Reasons for Discontinuation of Amifostine

	Number of Patients (n = 29)
Nausea/vomiting	15
Allergy/rash	4
Hypotension	3
Fever	2
Patient request (unspecified)	2
Drowsiness	1
Cachexia	1
Other	1

## Hospitalizations

	Amifostine + RT (N=150)	RT Alone (N=153)
Patients	42	23
Hospitalizations	50	31
Amifostine-related	6	n/a

## Safety

### Conclusions

- ◆ Amifostine generally well tolerated
- ◆ No new or cumulative toxicities
- ◆ Nausea, vomiting, and hypotension most frequent adverse events

## **Overall Conclusions**

- ◆ Amifostine reduces the incidence of  $\geq$ Grade 2
  - Acute xerostomia (RTOG)
  - Late xerostomia (RTOG)
- ◆ Amifostine preserves greater saliva flow
- ◆ Amifostine provides clinical benefit to patients (PBQ)
- ◆ Amifostine does not reduce anti-tumor efficacy (LRC, DFS, and OS)
- ◆ Amifostine is safe at the recommended dose

## **Statistical Evidence of Effectiveness and Preservation of Anti-tumor Efficacy**

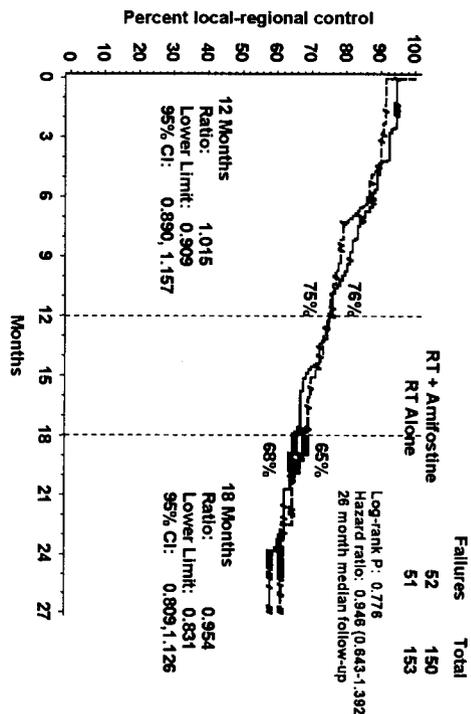
Gary Koch, PhD  
Chapel Hill, NC

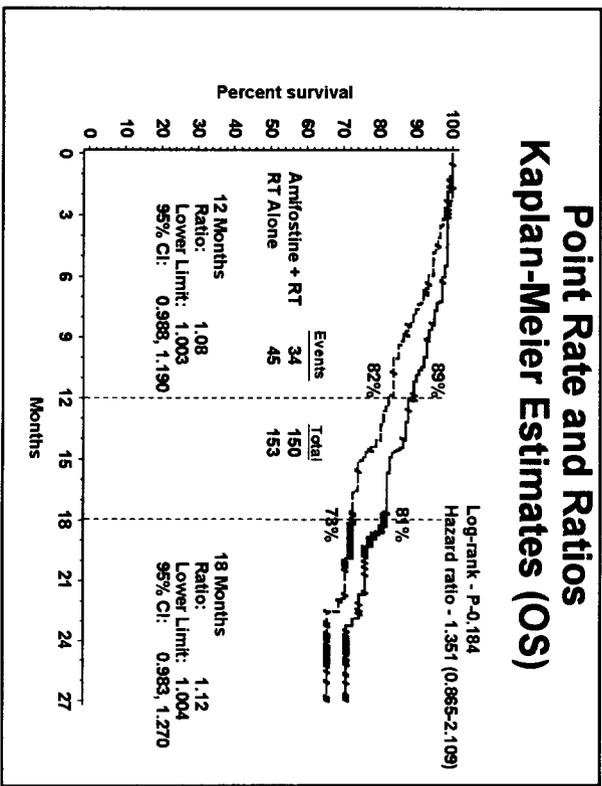
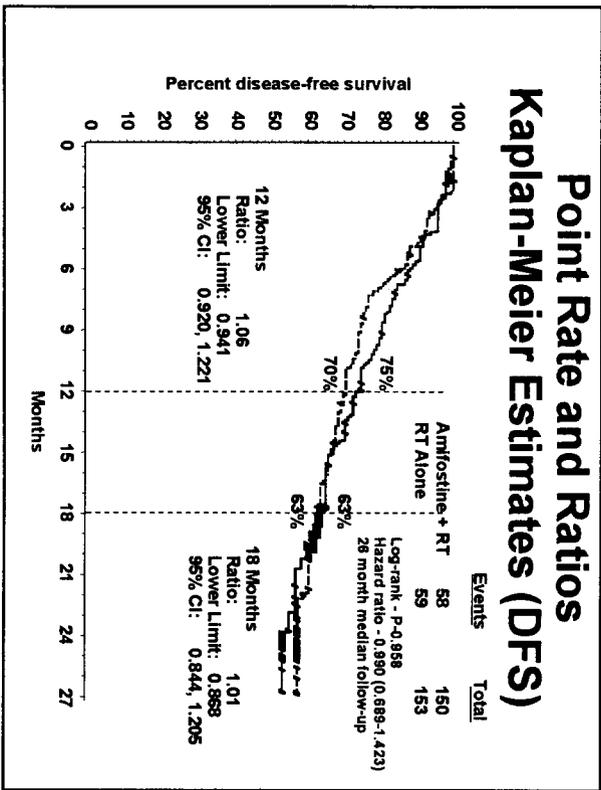
## Preservation of Anti-tumor Efficacy (LRC)

	12 Months	18 Months
<b>Local/regional control rate</b>		
Amifostine + RT	91/127 (72%)	77/126 (61%)
RT Alone	96/135 (71%)	85/133 (64%)
<b>p-Value*</b>	1.000	0.700
<b>Local/regional control ratio**</b>	1.008	0.956
<b>Lower limit of 95% one-sided confidence interval</b>	(0.886)	(0.816)
<b>95% confidence interval (2 sided)</b>	(0.864, 1.175)	(0.792, 1.155)

\*p-Value based on Fisher's Exact test  
 \*\*Local/regional control ratio > 1.0 favors Amifostine + RT

## Point Rate and Ratios Kaplan-Meier Estimates (LRC)





### Preservation of Anti-tumor Efficacy Difference in LRC Rates-Crude Data Analysis

	12 Months	18 Months
Local/regional control rate*		
Amifostine + RT	0.7165	0.6111
RT Alone	0.7111	0.6391
Difference between rates	0.0054	-0.0280
95% confidence interval (2-sided)	-0.104, 0.115	-0.146, 0.090

\*Crude rate calculation

### Preservation of Anti-tumor Efficacy Difference in LRC Rates - Kaplan Meier Estimates

	12 Months	18 Months
Local/regional control rate		
Amifostine + RT	0.7613	0.6533
RT Alone	0.7501	0.6846
Difference between rates	0.0112	-0.0313
95% confidence interval (2-sided)	-0.088, 0.110	-0.142, 0.079

**Preservation of Anti-tumor Efficacy  
Difference in DFS Rates - Kaplan Meier  
Estimates**

	12 Months	18 Months
<b>Disease-Free survival rate</b>		
Amifostine + RT	0.7464	0.6332
RT Alone	0.7045	0.6279
<b>Difference between rates</b>	0.0419	0.0053
<b>95% confidence interval (2-sided)</b>	-0.061, 0.145	-0.107, 0.118

**Preservation of Anti-tumor Efficacy  
Difference in Survival Rates - Kaplan  
Meier Estimates**

	12 Months	18 Months
<b>Overall survival rate</b>		
Amifostine + RT	0.8943	0.8127
RT Alone	0.8249	0.7273
<b>Difference between rates</b>	0.0694	0.0854
<b>95% confidence interval (2-sided)</b>	-0.010, 0.149	-0.012, 0.183

**Conclusions**  
**Preservation of Anti-tumor Efficacy**

**Lower limits of one- and two-sided 95%  
confidence intervals are sufficiently  
high to assure non-inferiority of  
amifostine group**

**Supportive Studies**

**Lesley Russell, MD  
Senior Director, Clinical Research  
U.S. Bioscience**

## Amifostine Efficacy (Xerostomia) in Radiation Therapy

Study	Design	Patients (N)
Britzel (WR-38)	Phase III, Open label, parallel group	303
Antonadou	Phase II, Open label, parallel group	45
Bohuslavizki	Phase II, Double-blind, placebo controlled	50
Takahashi	Phase I, Single-arm, historical control	105
McDonald	Phase III, Single-arm, historical control	12
Büntzel	Phase II, Open label	39
<b>TOTAL PATIENTS TREATED</b>		<b>554</b>

### Treatment Schedule

Antonadou

**R A N D O M I Z E**

- Radiation 2 Gy/day, total dose 60-74 Gy  
 Carboplatin 90 mg/m<sup>2</sup>/week  
 Amifostine 300 mg/m<sup>2</sup>/day  
 n=22
- Radiation 2 Gy/day, total dose 60-74 Gy  
 Carboplatin 90 mg/m<sup>2</sup>/week  
 n=23

## Patient Demographics

◆ Well-balanced pre-treatment for:

- Age
- Gender
- Tumor site
- Tumor stage
- Nodal status

## Xerostomia Results \*

Radiation Toxicity/ RTOG Grade	Amifostine + RCT		RCT		p-Value
	N=22	%	N=23	%	
Late-Effect Xerostomia					0.0001
Grade 0	4	18%	0	0	
Grade 1	12	55%	4	17%	
Grade 2	6	27%	17	74%	
Grade 3	0	----	2	9%	
Total ≥Grade 2	6	27%	19	83%	0.0001

\*3 months post treatment

## Xerostomia Results\*

### Updated Information

Radiation Toxicity/ RTOG Grade	Amifostine + RCT N=24		RCT N=25		P-Value
		%		%	
9 Months					
Grade 2	2	8.3%	15	60%	
Grade 3	2	8.3%	3	12%	
Total ≥Grade 2	4	16.6%	18	72%	0.0001
12 Months					
Grade 2	2	8.3%	13	52%	
Grade 3	0	—	1	4%	
Total ≥Grade 2	2	8.3%	14	56%	0.0006

\*9 and 12 months post treatment

## Anti-tumor Efficacy Results

	Amifostine + RCT (N=22)	RCT (N=23)	P-Value
Tumor response (complete and partial)	100%	100%	
Complete response	20/22 pts	18/23 pts	0.4140
Partial response	2/22 pts	5/23 pts	
Local-regional control (18 months)	83%	76%	

## **Safety**

**Amifostine + RT**

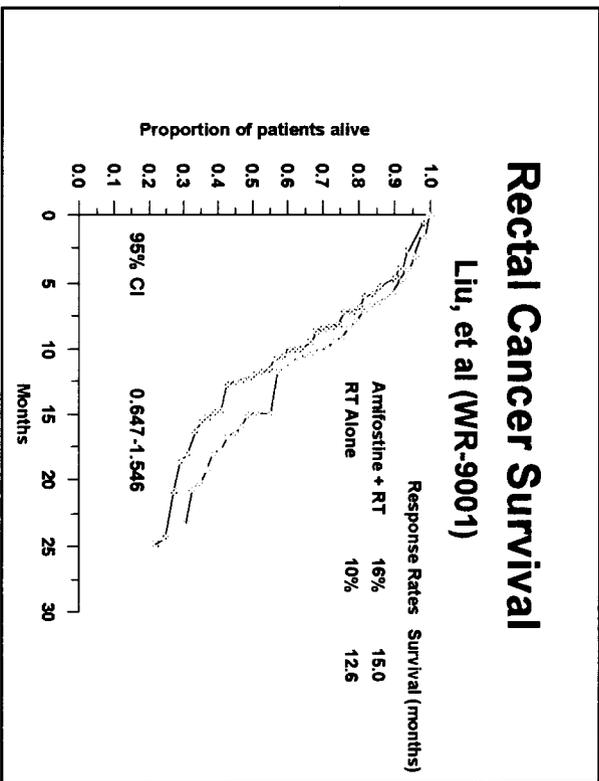
- ◆ Nausea/vomiting 1%
- ◆ Transient hypotension 3%

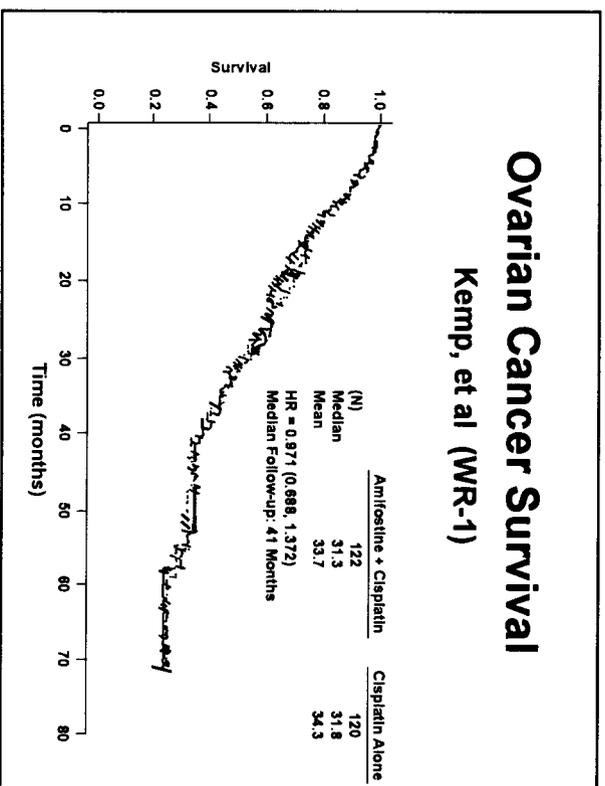
## **Conclusions**

- ◆ Significant reduction in  $\geq$ Grade 2 late xerostomia
- ◆ Preservation of anti-tumor efficacy
- ◆ Amifostine well tolerated

# Supportive Studies

## Preservation of Anti-tumor Activity





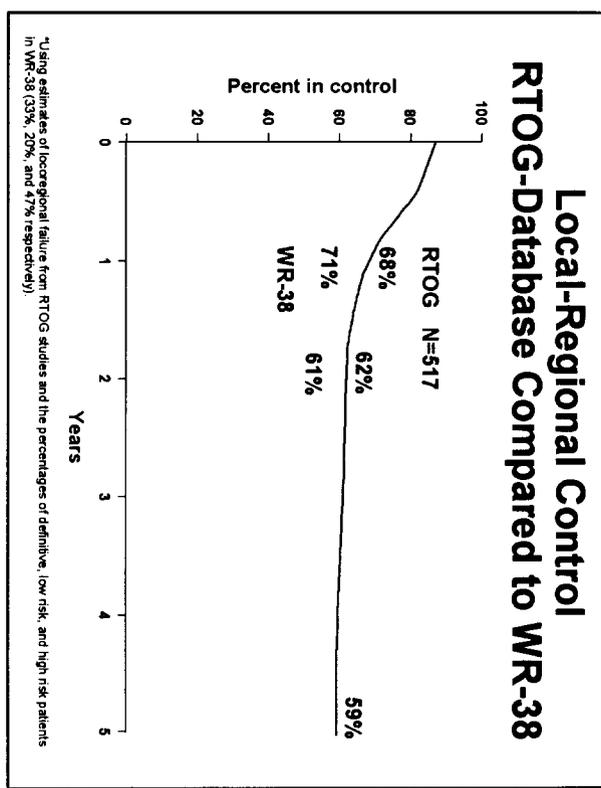
### Conclusions

#### Anti-tumor Efficacy

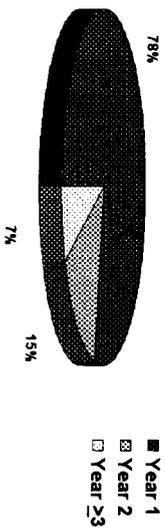
- ◆ Three randomized, well-controlled Phase III studies demonstrate that amifostine does not compromise anti-tumor efficacy

**Benefits/Risks of Amifostine  
in Radiation Therapy for  
Head and Neck Cancer**

**Walter Curran, MD**  
**Professor and Chairman, Radiation Oncology**  
**Kimmel Cancer Center**  
**Jefferson Medical College**  
**Chairman, Radiation Therapy Oncology Group**  
**Philadelphia, Pennsylvania**



### Local/Regional Failure Estimated Rates Using Matched Controls from RTOG Database



### Conclusions

Wolfgang Oster, MD  
U.S. Bioscience, Inc.

## Substantial Evidence

- ◆ New indication for drug already approved in cancer treatment
- ◆ Reduction of irreversible morbidity—xerostomia
- ◆ WR-38 plus supportive studies confirm efficacy in xerostomia
- ◆ All studies consistently report positive xerostomia results

## WR-38

- ◆ Different, but logically linked, endpoints
  - All statistically very persuasive
  - $\geq$  Grade 2 acute xerostomia  $p < 0.0001$
  - $\geq$  Grade 2 late xerostomia  $p = 0.0019$
  - Saliva production  $> 0.1$  gm  $p = 0.0033$
  - PBQ longitudinal at month 11  $p = 0.0067$
  - PBQ oral dryness at month 11  $p = 0.001$
- ◆ Statistically significant correlation of endpoints
- ◆ Clinically meaningful
- ◆ Patients experienced significant clinical benefit

**Amifostine SNDA  
Conclusions**

- ◆ **Reassuring evidence for safety**
- ◆ **Demonstration that amifostine preserves anti-tumor efficacy**

**Amifostine SNDA  
Conclusions**

- ◆ **Amifostine is safe and effective for the indication:  
*To reduce the incidence of moderate to severe radiation-induced xerostomia***