

Head and Neck Cancers Update

Sarah L. Scarpace, PharmD, BCOP

Assistant Professor

Albany College of Pharmacy

Albany, New York

BCOP
Recertification

Disclosures

- Advisory Board for Bristol-Myers-Squibb
- Speakers Bureau for Pfizer

Goals

- Provide an overview of the various treatment approaches to head and neck cancers
 - Limited to oro-, hypo-, naso-, -pharyngeal and -laryngeal cancers
- Discuss supportive care issues of the head and neck cancer patient

Objectives

At the conclusion of this program, participants will be able to:

- Explain the advantages and disadvantages of the use of chemoradiation for organ preservation in the treatment of head and neck cancers
- Compare and contrast the efficacy and toxicity of carboplatin- versus cisplatin-based chemotherapy regimens for head and neck cancers

Objectives - continued

- Differentiate the various clinical settings and associated efficacy and toxicity of different cetuximab regimens used in the treatment of head and neck cancers
- Outline a pharmacist's approach to the management of selected supportive care issues of the head and neck cancer patient

Overview

- Chemoradiation for Organ Preservation
- Cisplatin vs. Carboplatin
- Role of Cetuximab
- Supportive Care Issues

Chemoradiation for Organ Preservation Preview

- Preferred over surgery for locoregionally advanced HN cancers
- Improves organ preservation vs. radiation alone
- Induction chemotherapy in this setting controversial
- Cisplatin-based chemo-rads generally preferred

Chemo-rads vs. Surgery or XRT alone

- VA Laryngeal Cancer Study Group
 - Induction chemo → XRT vs. laryngectomy → adjuvant XRT
 - Equivalent survival (68% 2-year survival; 55% 3-yr survival)
- RTOG 91-11
 - Chemo-rads vs. induction chemo → XRT vs. XRT alone
 - Better laryngeal preservation and locoregional control w/ chemo-rads
 - Overall survival comparable across treatment groups
 - More grade 3/4 toxicities in chemo arms vs. XRT alone

Chemo-rads vs. XRT alone

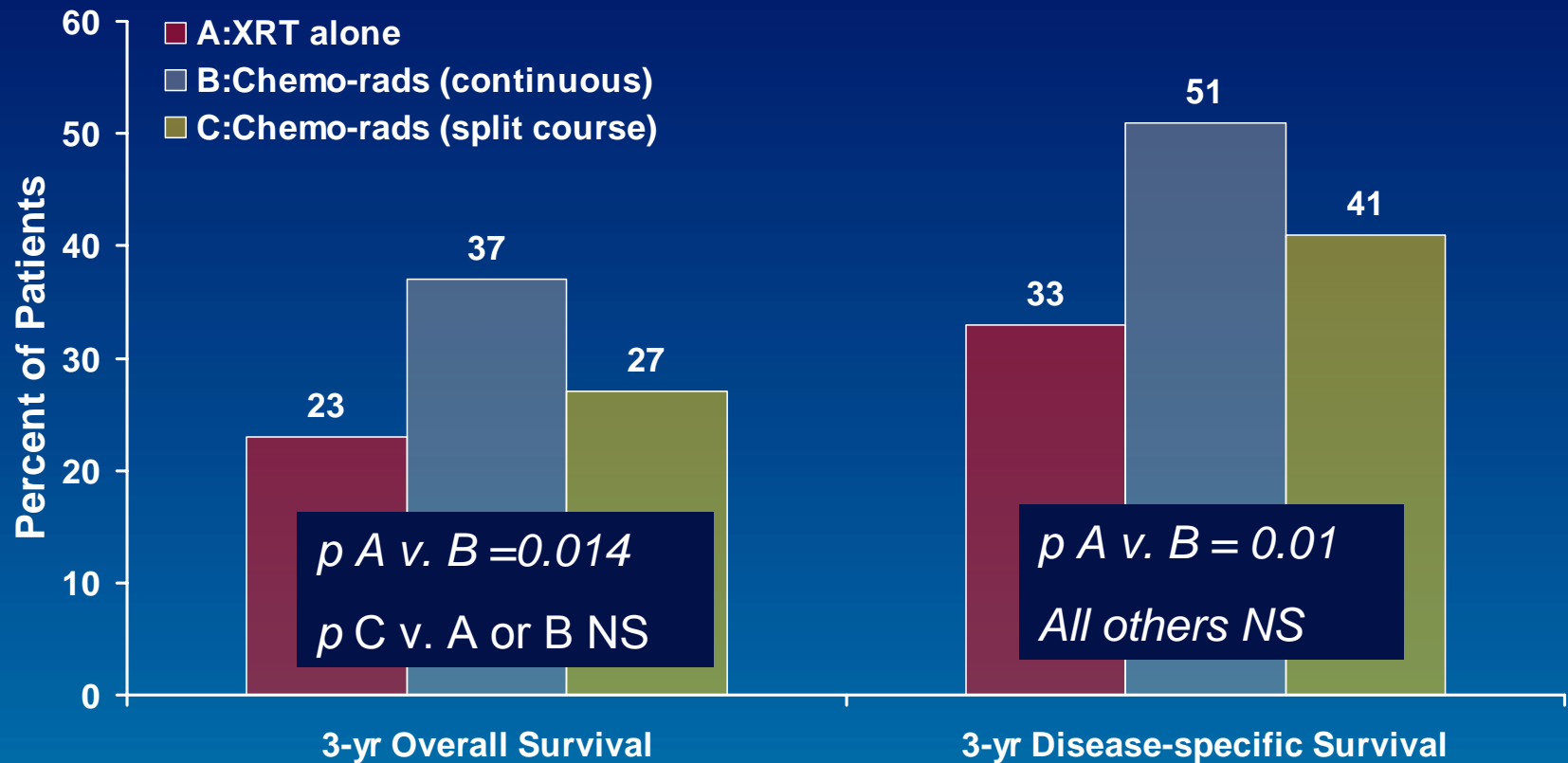
- Phase 3 randomized Intergroup trial, n = 295
- Stage 3 or 4 unresectable non-metastatic squamous HN cancer

Radiation Regimens

	Arm A	Arm B	Arm C
XRT	Continuous	Continuous	Split Course
Cisplatin	None	100 mg/m ² d 1, 22, 43	75 mg/m ² d1 Q4 weeks
5FU	None	None	1000 mg/m ² /d x4 days x 3

Chemo-rads vs. XRT (Intergroup trial)

Survival



QOL: Surgery + XRT vs. Chemo-XRT for Organ Preservation

- Retrospective, single-center (Italy) trial of 67 laryngeal patients
 - Surgical patients had less dry mouth and sticky saliva
 - Chemorads had better:
 - Physical, social, and role-functioning
 - Sleeping, breathing, pain, speech
 - Global QOL
- Retrospective, single center (US) trial of 35 oropharyngeal patients
 - No differences in:
 - Pain, appearance, swallowing, chewing, speech, saliva, mood
 - Trend that chemo-XRT patients had worse taste outcomes ($P = 0.07$)

Chemo-XRT for Organ Preservation

NCCN Category 1 Recommendations

- Oropharynx: \geq T3 or any N+
 - Glottic larynx: most T3, any N
 - Supraglottic larynx:
 - Requiring laryngectomy
 - T3-T4a, any N if no cartilage destruction and minimal base of tongue involvement
 - Not requiring laryngectomy:
 - T1-T2 and N+,
 - select T3 – T4a
- *Cisplatin-based regimens preferred in all cases

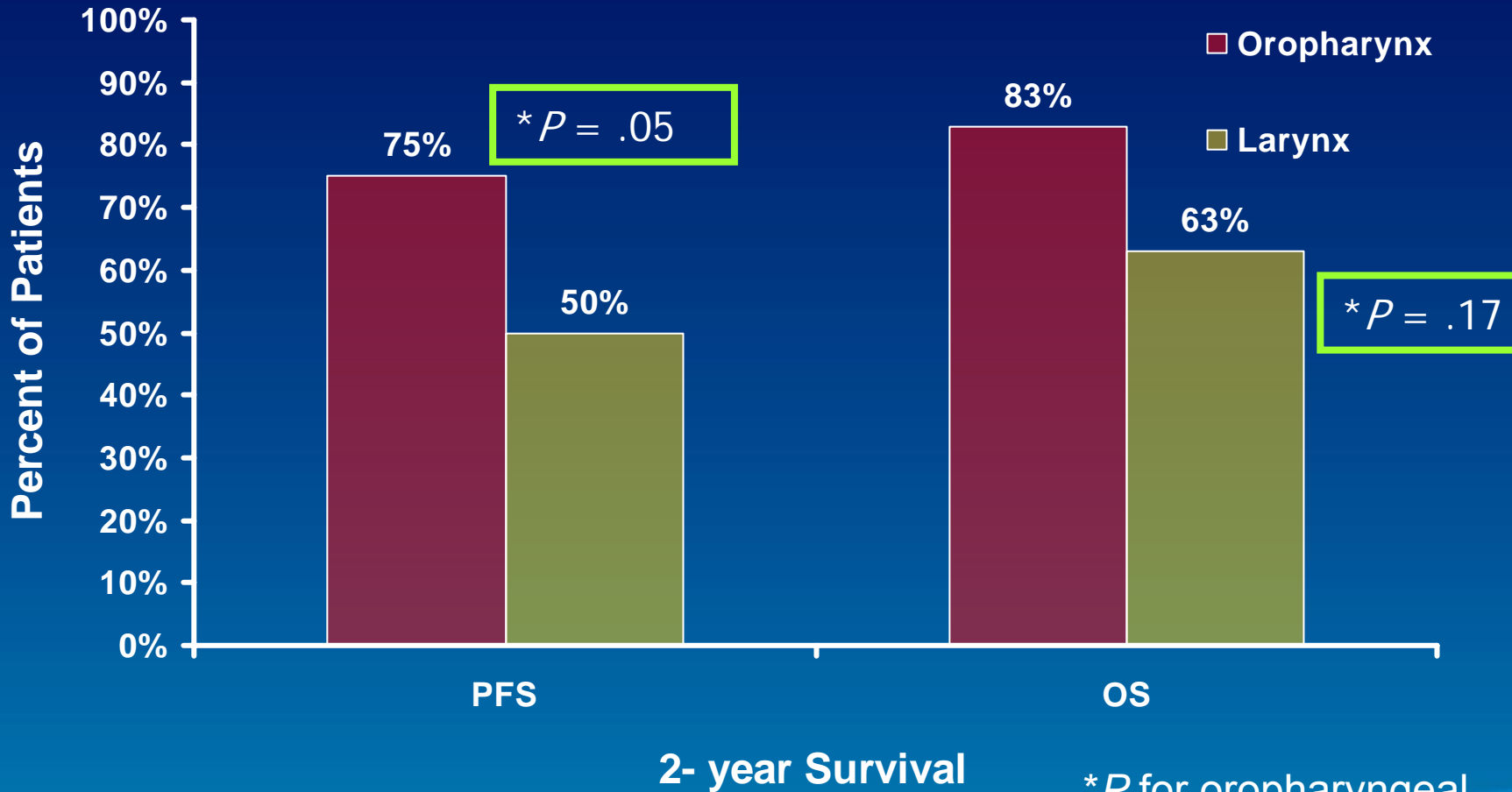
Role of Induction Chemotherapy

- Controversial for most tumors
 - Decreases distant mets but more toxic
 - Oropharyngeal may respond better than laryngeal
 - Taxane-based regimens have been shown to improve OS and PFS when compared to either chemo-radiation or radiation alone
 - Variability in defining standard chemotherapy regimen
- Exception is some hypopharyngeal cancers

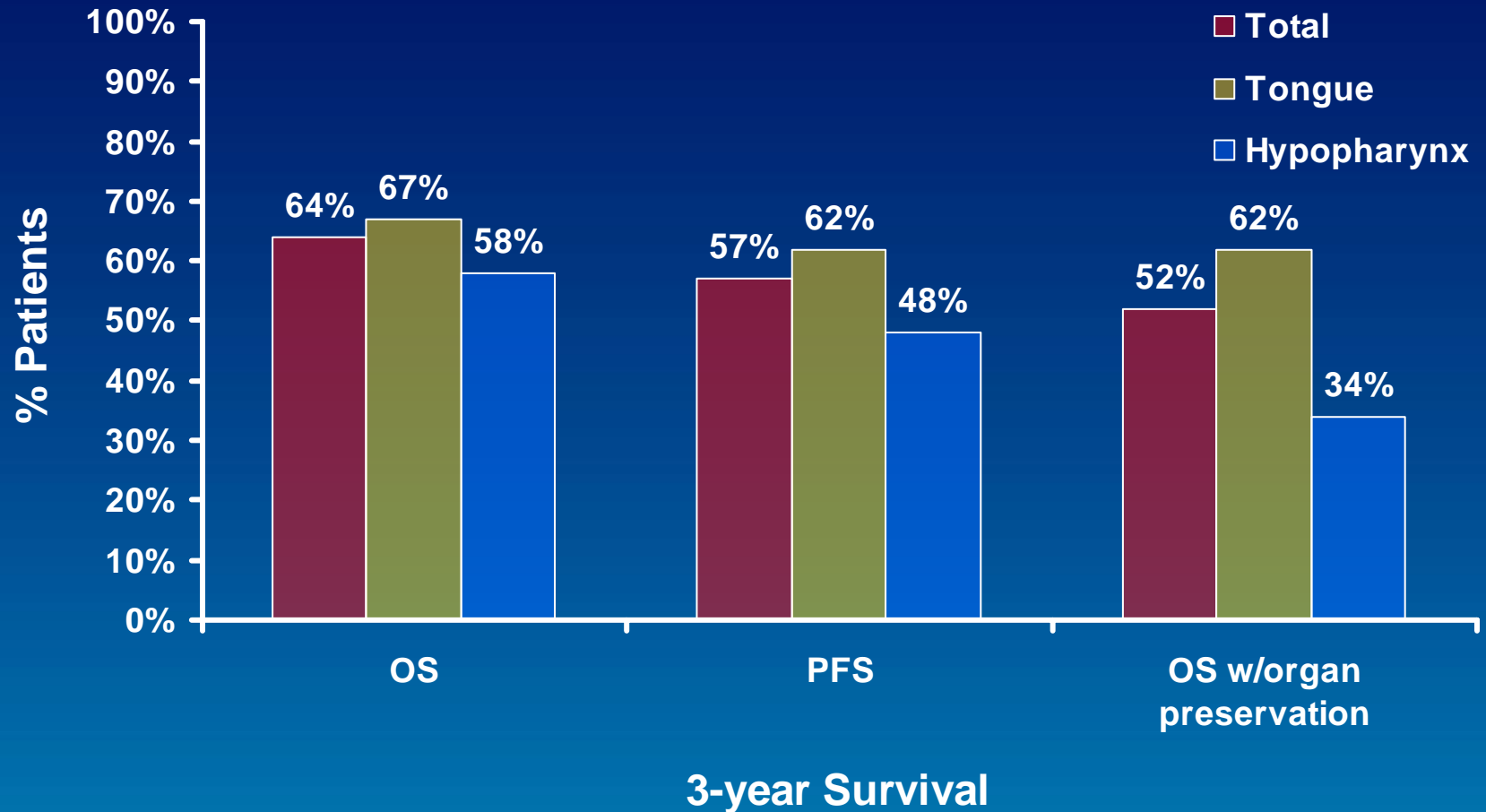
Induction Chemotherapy Trials

- ECOG E2399 (phase 2)
 - Induction carbo-paclitaxel q 21 days x 2 cycles
 - Concurrent chemo-rads with weekly paclitaxel
- SWOG 9451 (phase 2)
 - Induction cisplatin + 5FU q21 days x 2 cycles
 - Concurrent chemo-rads with high-dose cisplatin
- TAX324 (phase 3)
 - Induction cisplatin + 5FU +/- docetaxel x 3 cycles
 - Concurrent chemo-rads with weekly carboplatin
- TAX323 (phase 3)
 - Induction cisplatin + 5FU +/- docetaxel x 3 cycles
 - Radiation alone

ECOG E2399 Results: Survival



SWOG 9451: Survival

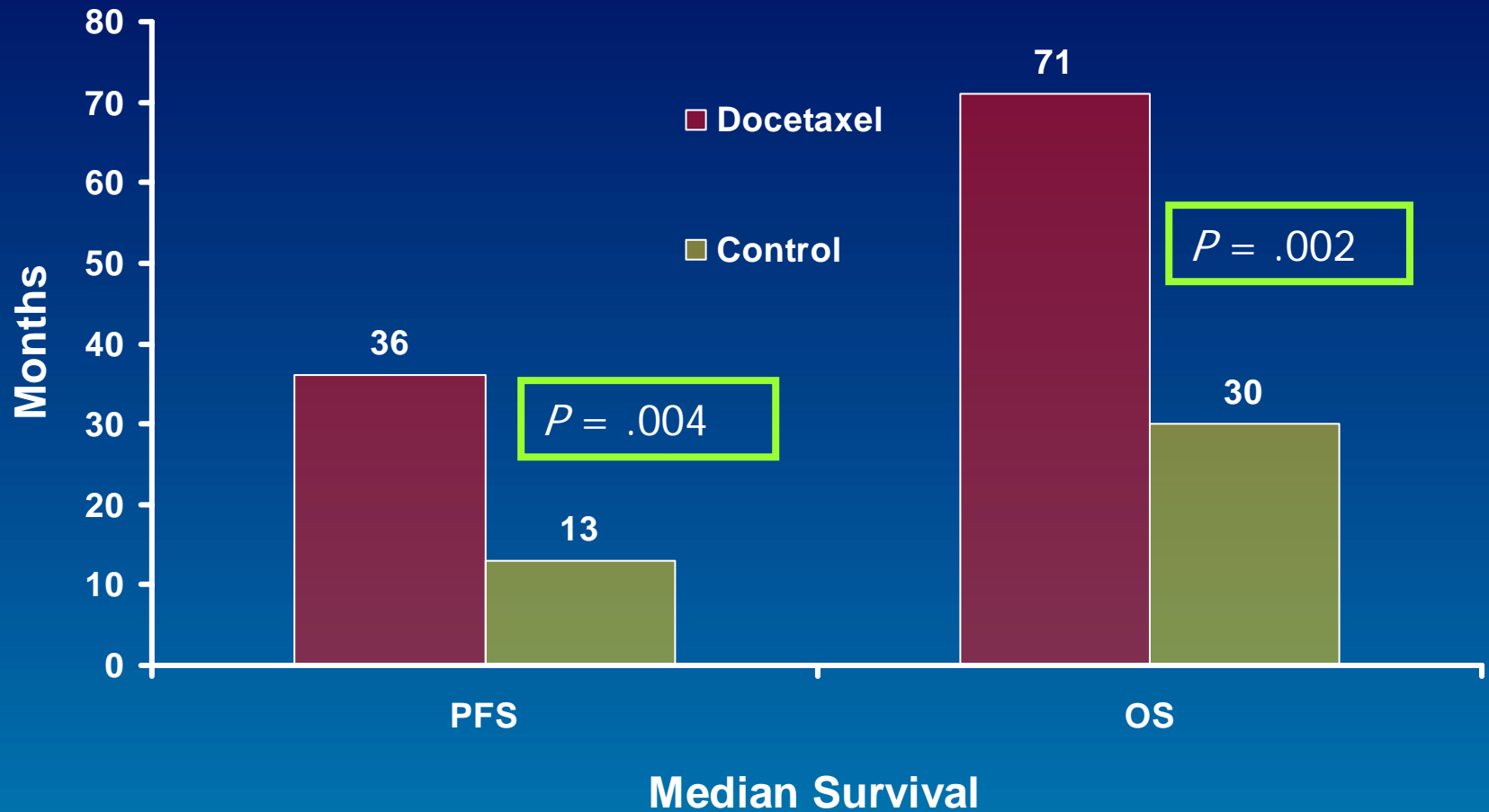


SWOG 9451: Toxicities

Grade 3/4 Toxicities

Toxicity	Induction (N=59)	Chemo-XRT (N=42)
Neutropenia	25	8
Leukopenia	14	9
Anemia	2	11
Stomatitis/mucositis	15	4
Any	34	33

TAX 324: Survival



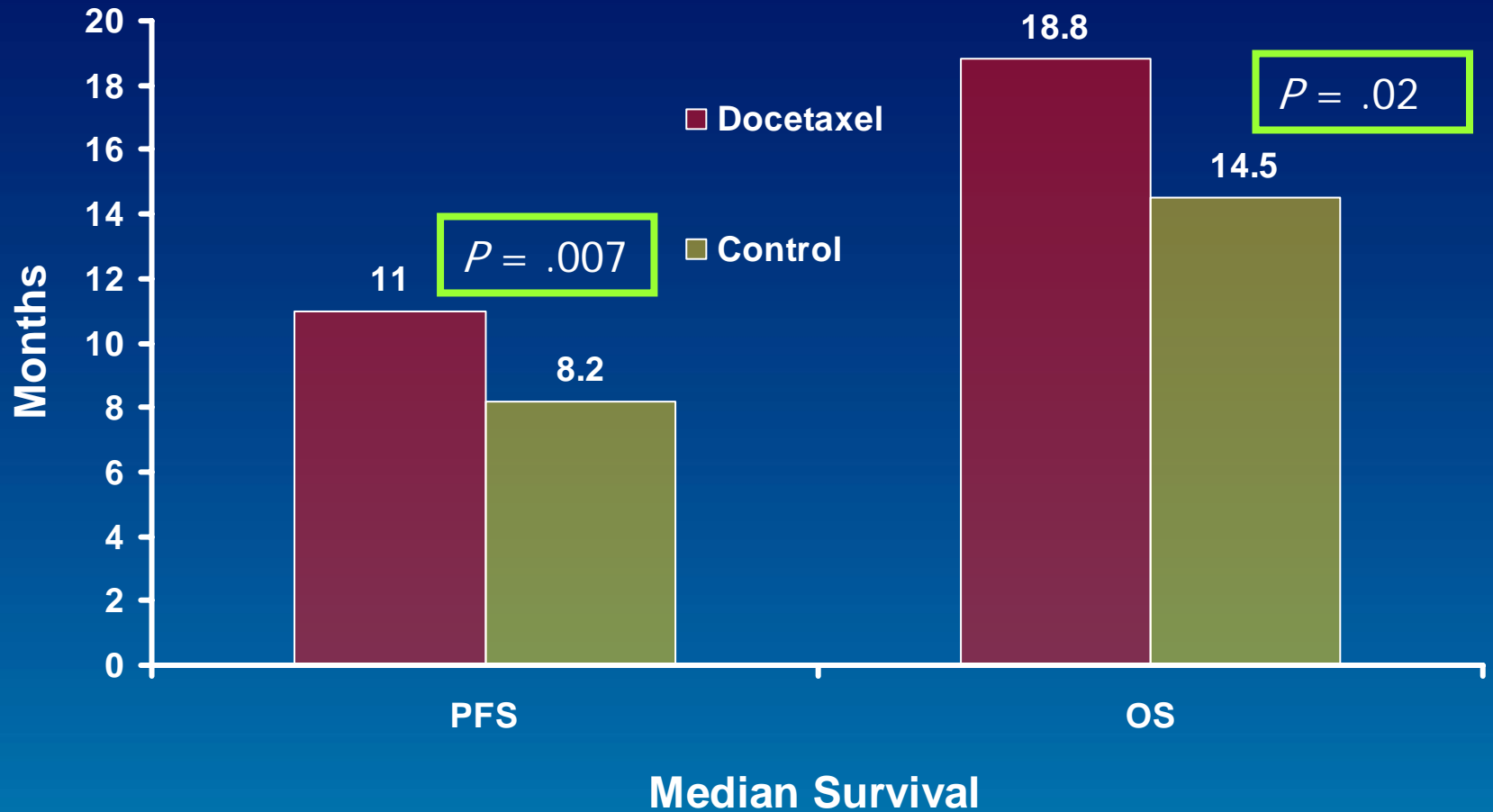
TAX 324 Toxicities

Toxicities Different Between Arms

Event	Docetaxel (N=251)	Control (N=243)	P-value
Grade 3/4 PLT	4%	11%	0.005
Grade 3/4 WBC	83%	56%	<0.001
Febrile neutr.	12%	7%	0.04
Lethargy	5%	10%	0.03
Delay in Tx	29%	65%	<0.001

No differences in grade 3/4 non-hematological toxicities

TAX 323: Survival



TAX 323 Toxicities

Select Grade 3/4 Toxicities

Event	Control (N=251)	Docetaxel (N=243)
Neutropenia	52.5%	76.9%
Febrile neutropenia	2.8%	5.2%
Thrombocytopenia	17.9%	5.2%
Alopecia	0%	11.6%
Nausea	6.7%	0.6%
Vomiting	4.5%	0.6%
Hearing loss	2.8%	0%

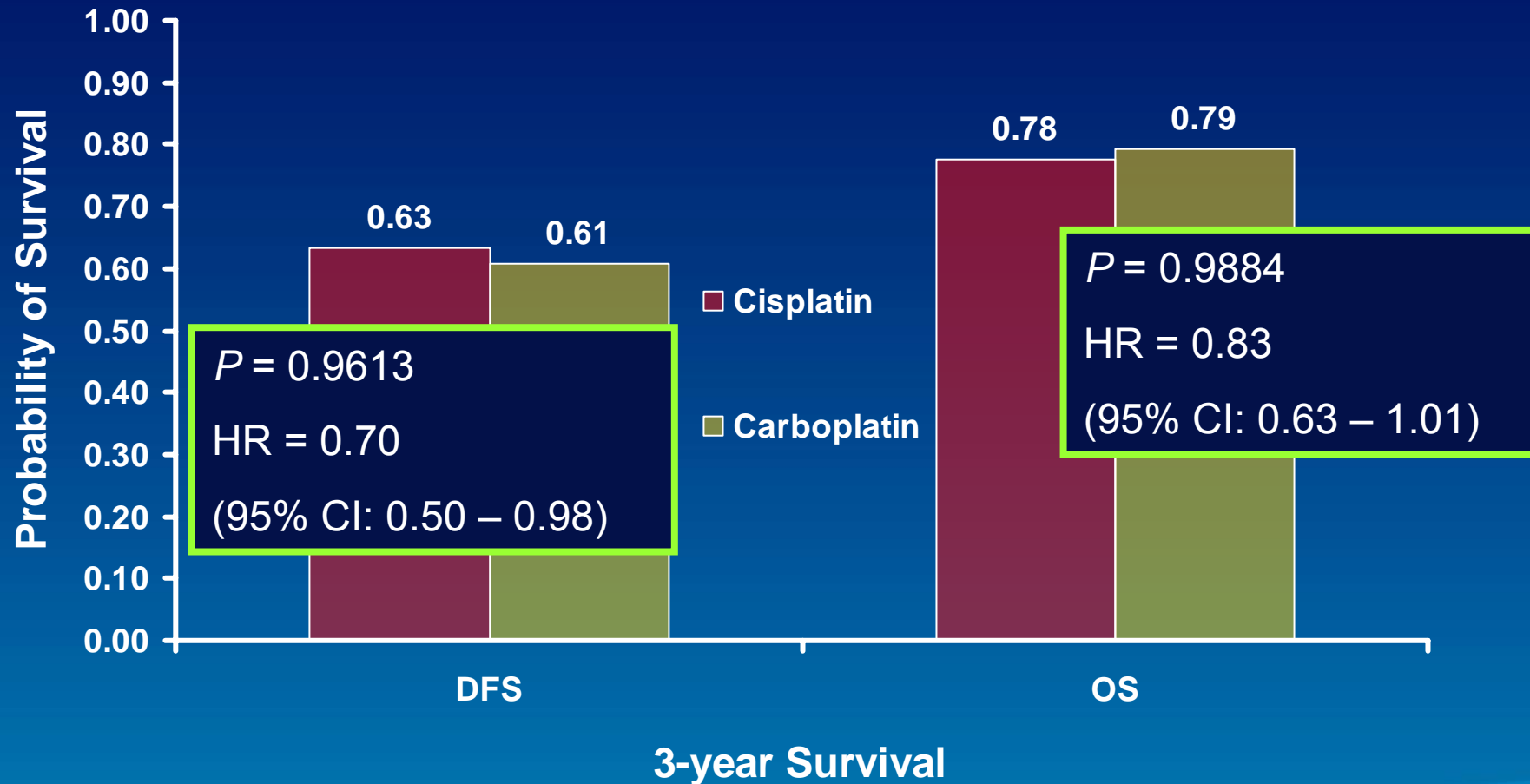
Cisplatin vs. Carboplatin: Preview

- Cisplatin and carboplatin appear interchangeable in chemoradiation regimens
 - Equivalent efficacy in several trials
 - Carboplatin may be better tolerated
- Cisplatin-based regimens are preferred by NCCN for locoregionally advanced HN
- No preference for cisplatin or carboplatin by NCCN for unresectable/recurrent HN

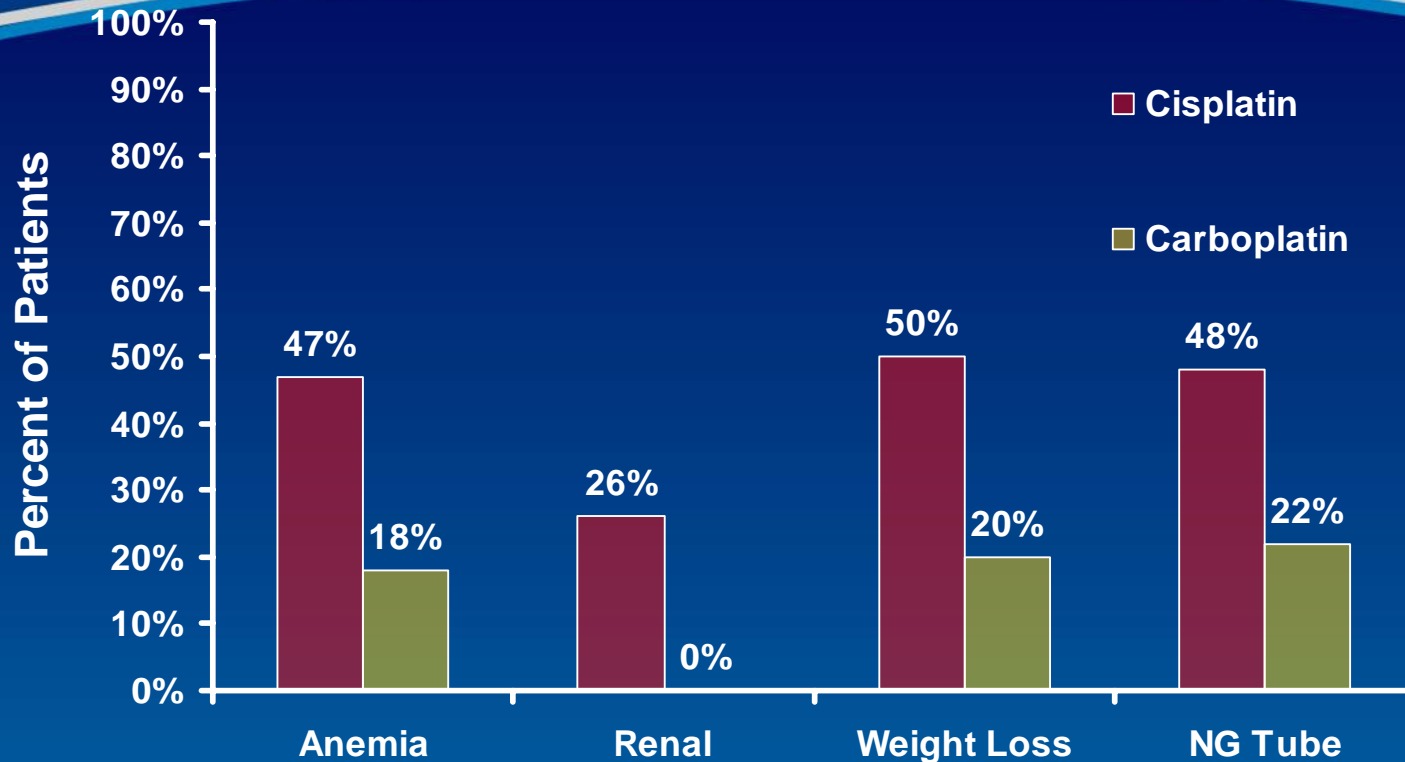
Cisplatin vs. Carboplatin Trials

- Locally advanced nasopharyngeal
 - XRT PLUS either cisplatin or carbo
- Recurrent/metastatic HN
 - Cisplatin/5FU or carbo/5FU or methotrexate
 - Cetuximab/5FU + cisplatin or carbo q 3 weeks
- Recurrent/metastatic platinum-refractory HN
 - Cetuximab added to cisplatin or carbo regimen

Cisplatin vs. Carboplatin in Nasopharyngeal



Cisplatin vs. Carboplatin in Nasopharyngeal



Toxicities different between arms - All grades

- Grade 3/4 more likely with cisplatin – though #s small
- No difference: WBC, PLT, n/v, mucous membrane, skin

Cisplatin/5FU or Carbo/5FU or Methotrexate in Recurrent/metastatic Disease

Efficacy

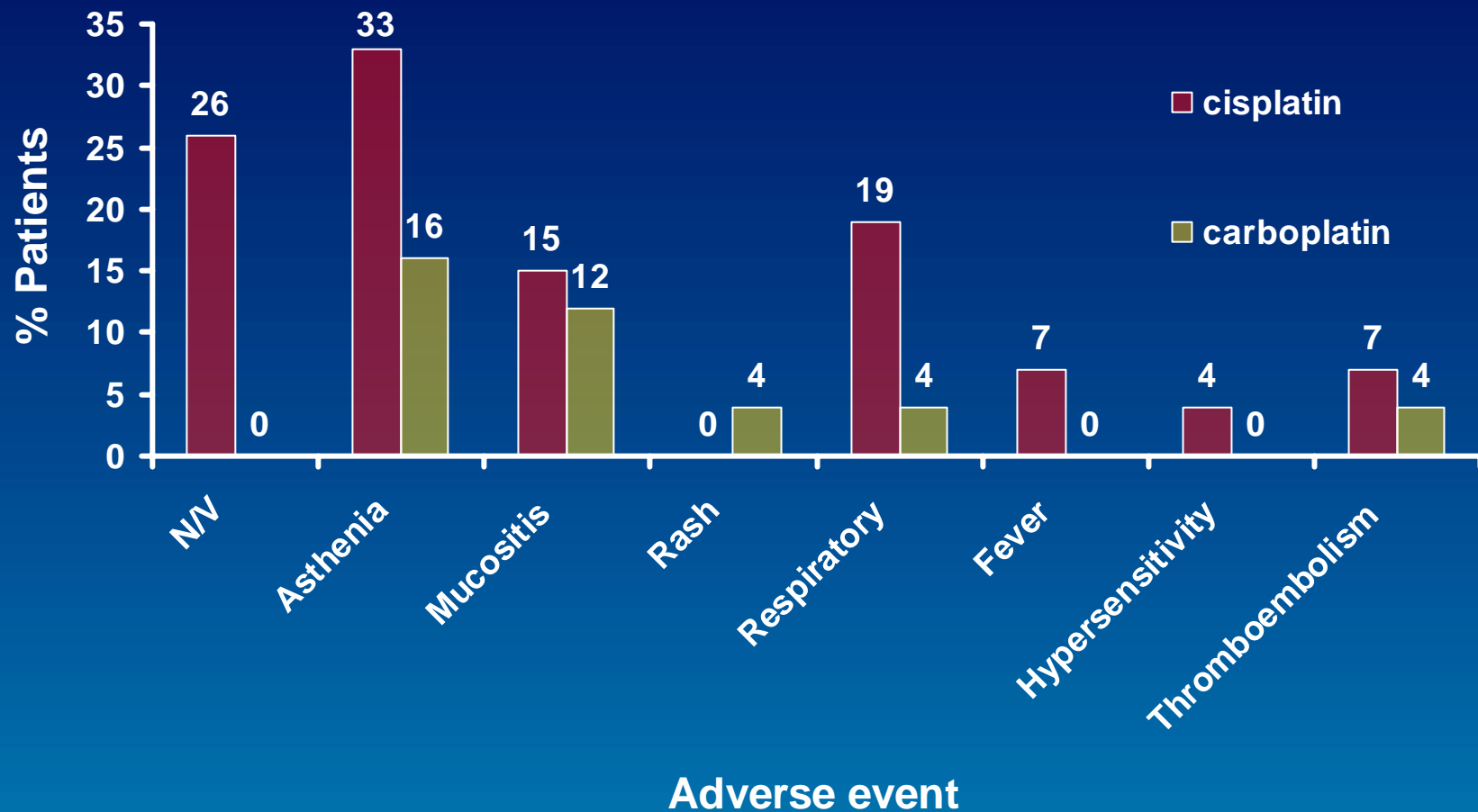
	Response Rates (RR)*
Cisplatin/5FU	32%
Carboplatin/5FU	21%
Methotrexate	10%

*P significant only for comparisons to methotrexate

Median survival similar across treatment groups

Toxicity: cisplatin >>carboplatin > methotrexate

Cetuximab/5FU + Cisplatin or Carboplatin: Grade 3/4 Toxicities



Cetuximab + Cisplatin or Carboplatin in Recurrent/metastatic Disease

Efficacy

	Cisplatin (N = 58)	Carboplatin (N = 34)
Response rate	12%	9%
Median TTP	85 days	76 days
Median OS	184 days	185 days

Cetuximab: Preview

- Cetuximab improves PFS and OS when added to radiation in the treatment of locoregional HN
- Single agent cetuximab yields similar response rates to cisplatin alone with few grade 3/4 toxicities
- Cetuximab added to cisplatin in the palliative setting does not improve PFS or OS unless rash is experienced
- Cetuximab should not be added to cisplatin-based chemoradiation outside of a clinical trial

Cetuximab + XRT

- XRT (one of 3 regimens) plus cetuximab vs
- XRT alone (one of 3 regimens)

Radiation Regimens

	Total Dose (Gy)	# Fractions
Once daily	70.0	35
Twice daily	72.0 – 76.8	60-64
Concomitant boost	72.0	42

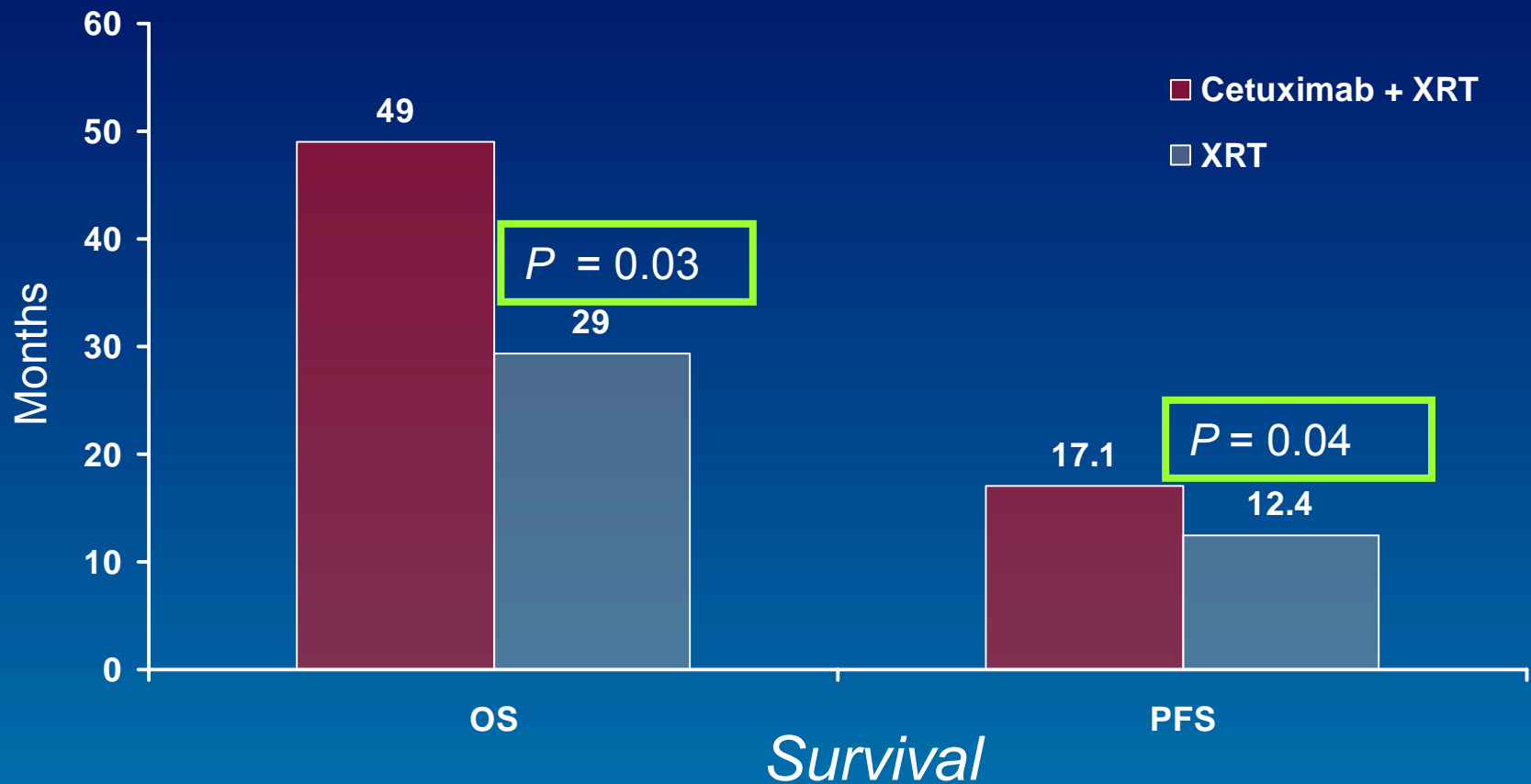
Cetuximab + XRT: LRC & RR

Locoregional Control & Response Rates

	Cetux + XRT	XRT	P (95% CI)
LR Control	24.4 months	14.9 months	.005* (.52-.89)
ORR	74%	64%	.02 (.36-.90)

*HR = 0.68

Cetuximab + XRT: Survival



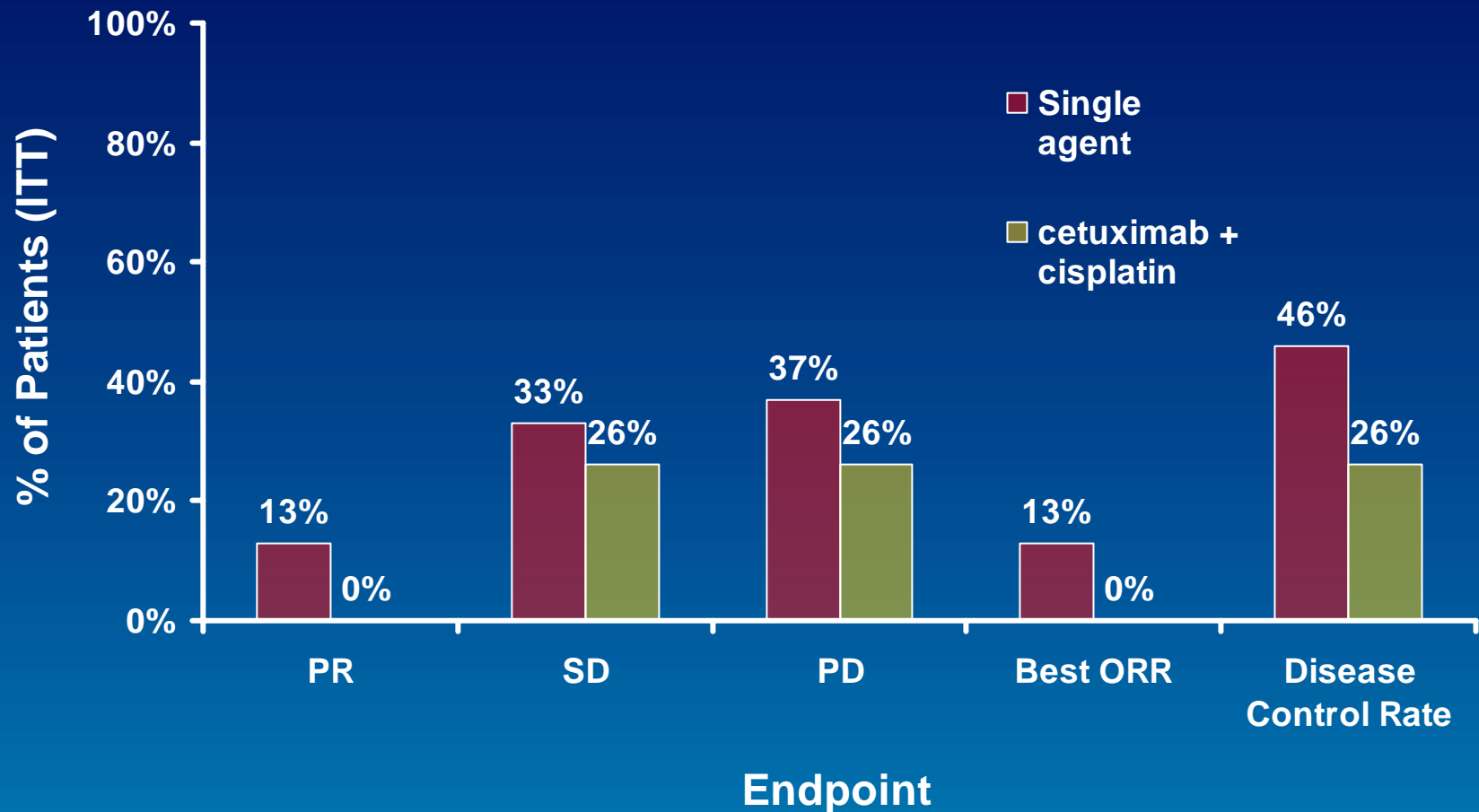
Cetuximab + XRT – Safety/AE

- RTOG Grade 3-5 acneiform rash and infusion-related events statistically more common with cetuximab arm
- RTOG all grades of acneiform rash, weight loss, nausea, headache, pruritus, infusion reactions, and chills more common with cetuximab arm
- No exacerbations of XRT-related AE
- Good compliance with each type of XRT regimen

Cetuximab for Palliation

- Recurrent/metastatic squamous H/N
- Cisplatin failures
- Cetuximab 400 mg/m² week 1, 250 mg/m² weekly for at least 6 weeks
- At week 6:
 - If response or SD, tx continued until progression
 - If PD, salvage cetuximab + cisplatin offered
- Primary endpoint: best overall response

Cetuximab for Palliation: Response



Cetuximab Single-agent: Toxicities

■ Any grade:

- Rash (49%)
- Acne (26%)
- Asthenia (24%)
- Nail disorder (16%)
- Dry skin (14%)
- Fever (14%)
- Nausea (13%)
- Vomiting (11%)
- Dyspnea (5%)
- Infusion reactions (6%)

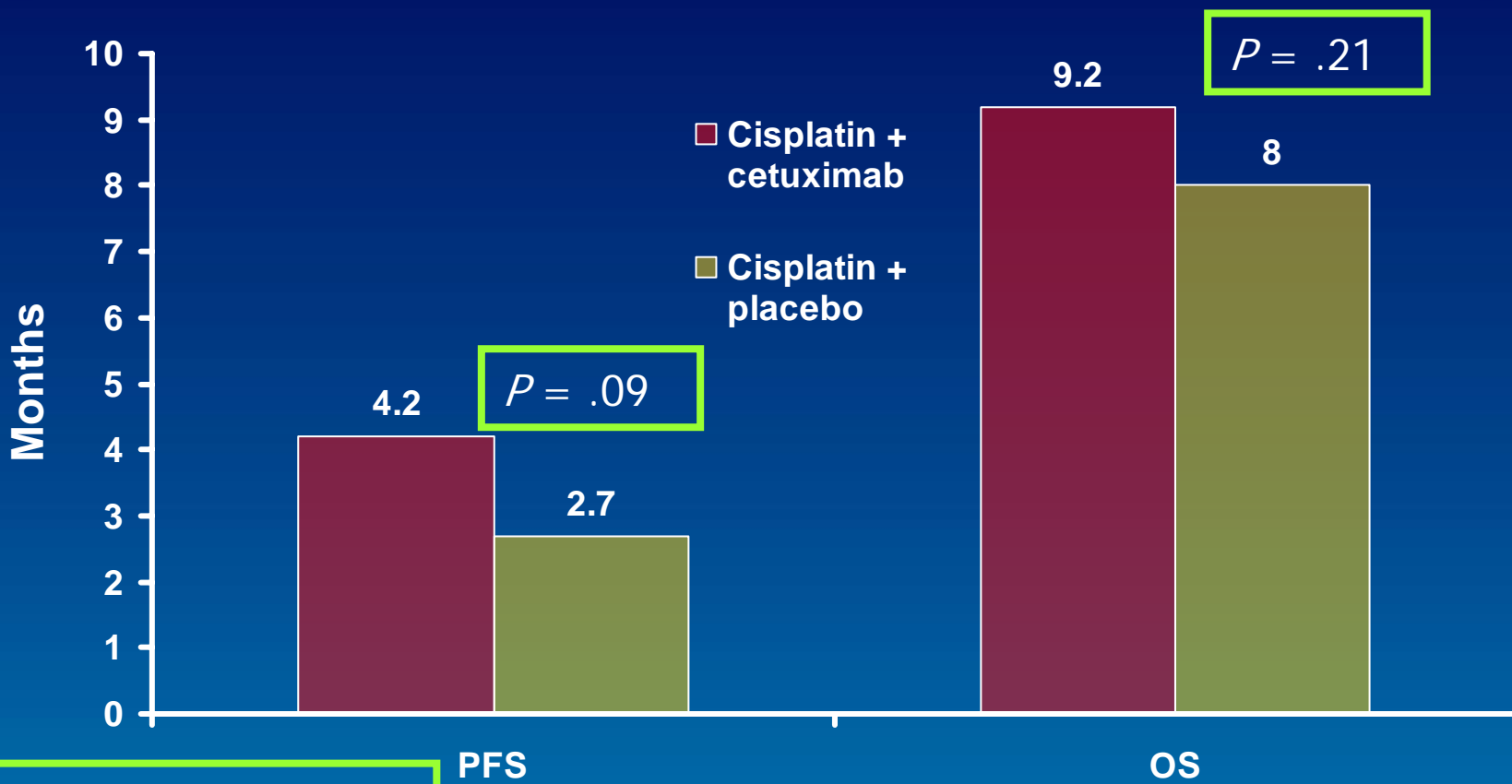
■ Grade 3/4 :

- Rash (1%)
- Asthenia (4%)
- Fever (1%)
- Nausea (1%)
- Vomiting (2%)
- Dyspnea (4%)
- Infusion reactions (1%)

Cisplatin + Cetuximab vs. Cisplatin + Placebo for Recurrent/Metastatic

- Phase 3, R, MC, n = 117
- First-line treatment of recurrent/metastatic disease
- Primary endpoint: PFS
- Cisplatin + cetuximab vs.
 - Cisplatin 100 mg/m² q28 days
 - Cetuximab 400 mg/m² week 1250 mg/m² q week
- Cisplatin + placebo - as above

Cisplatin/cetuximab vs. Cisplatin/placebo Survival



HR for PFS by rash = 0.74 ($P = .37$)

HR for OS by rash = 0.42 (95% CI 0.21-0.86)

Cisplatin/cetuximab vs. Cisplatin/placebo Toxicities

Toxicities Different Between Arms

Event	Cetuximab (N=58)	Placebo (N=58)	P-value
Any grade 3/4	90%	73%	0.02
Neutropenia	30%	14%	0.04
Hypomagnesemia	14%	0%	0.006
Overall heme	36%	18%	0.04
Any skin	77%	24%	<0.001

Cisplatin + Cetuximab + XRT

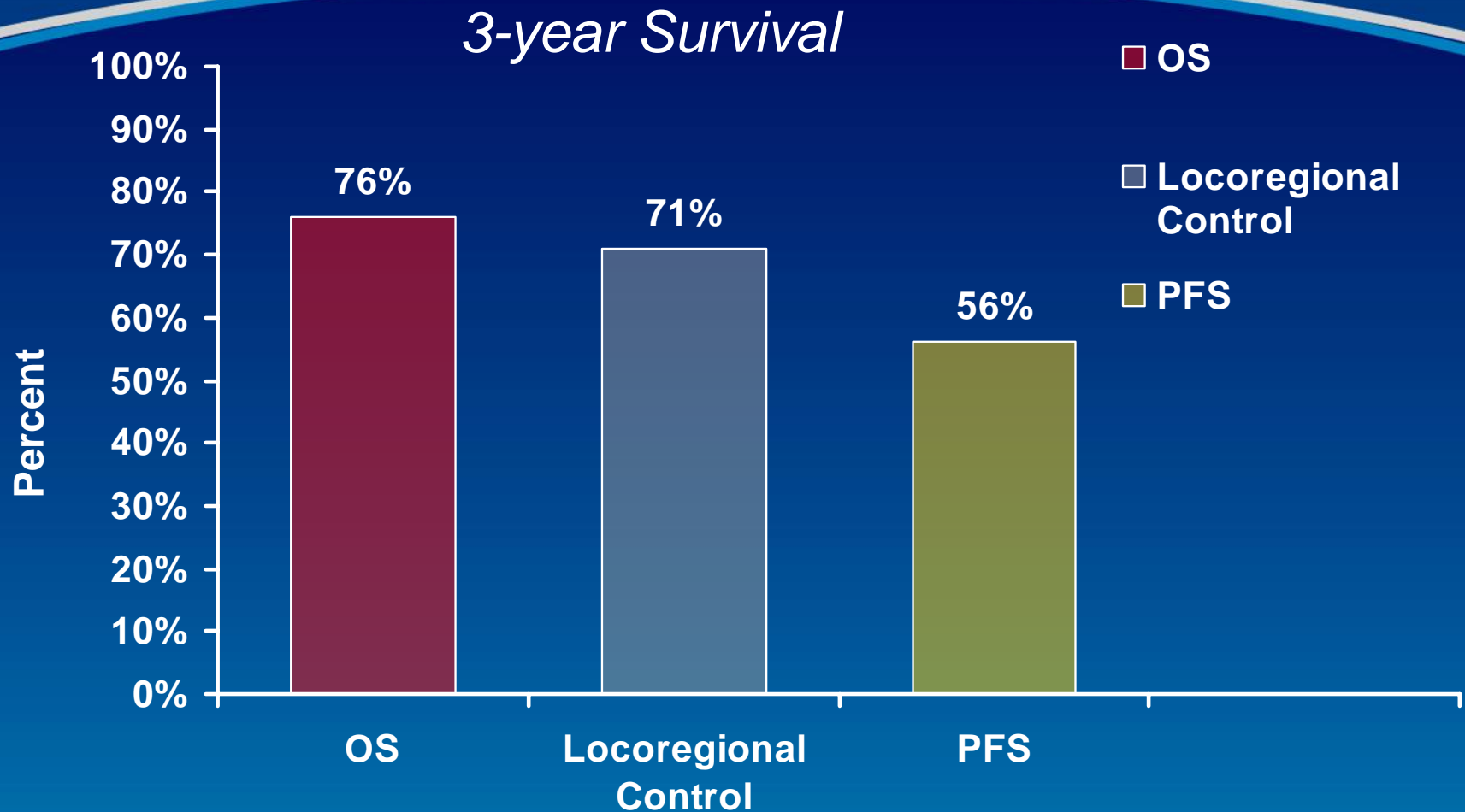
- Phase 2, Stage 3-4 nonmetastatic squamous HN
- Any site except nasopharyngeal
- XRT x 6 weeks as concomitant boost fractionation
- Cisplatin 100 mg/m² Q 3 weeks x 2 cycles
- Cetuximab weekly x 10 weeks
 - 400 mg/m² IV first week w/ 20 mg test dose
 - 250 mg/m² IV subsequent weeks

Cisplatin + Cetuximab + XRT – Toxicity

- Trial closed early due to 5 significant adverse events
 - 2 deaths (pneumonia and one unknown)
 - 3 other serious AE (non-fatal MI, bacteremia, afib)

	Grade I/II	Grade III/IV	Overall
Mucous membrane	62%	38%	100%
Derm	71%	24%	95%
Metabolic	38%	52%	91%
Constipation	57%	14%	71%

Cisplatin + Cetuximab + XRT - Survival



Supportive Care: Preview

- Xerostomia prevention with amifostine is controversial
- Pilocarpine and cevimeline have shown mixed results for treatment of xerostomia
- New guidelines are available to manage radiation dermatitis & co-existing EGFR rash
- ODT formulations, fosaprepitant, and use of drugs that can be crushed/split/changed to liquids can assist patients with swallowing difficulties

Xerostomia

- Most prominent complication of XRT
- 50-60% reduction in salivary flow during first week
- 80% reduction by week 7
- Complications: speech, chewing, and swallowing difficulties; dental cavities or infections; oral pain; anorexia
- 64% of patients may still experience moderate - severe xerostomia 3 years after treatment

Amifostine for Xerostomia Prevention

- Hydrolyzed to active form by alkaline phosphatases in blood vessel endothelium; Free radical scavenger
- SE: mild n/v, transient hypotension
- 200 mg/m² IV before each radiation dose
 - Reduced both acute and chronic xerostomia in phase 3 R, n= 303
 - No difference in survival
- Use is controversial
 - No study has been powered to find small differences in survival
 - No improvements in xerostomia when used with chemoradiation

Xerostomia Treatment

- Oral hygiene
 - Fluoride agents
 - Chlorhexidine and hexitidine rinses
- Saliva substitutes
- Pilocarpine
- Cevimeline

Pilocarpine

- RTOG 97-09: R, DB, PC, phase 3, n = 245 HN who received at least 50 Gy XRT
- Unstimulated salivary flow was improved
- No differences in parotid-stimulated flow, mucositis, QOL related to xerostomia or mucositis

Pilocarpine

- Prospective, R, DB, PC, n = 170 HN patients
- Primary endpoint: Parotid flow rate complication probability
- Secondary: LENT-SOMA and patient-rated xerostomia scores
- Measured 6 weeks, and 6 & 12 months post-XRT
- Pilocarpine vs. placebo during XRT
- No difference between arms

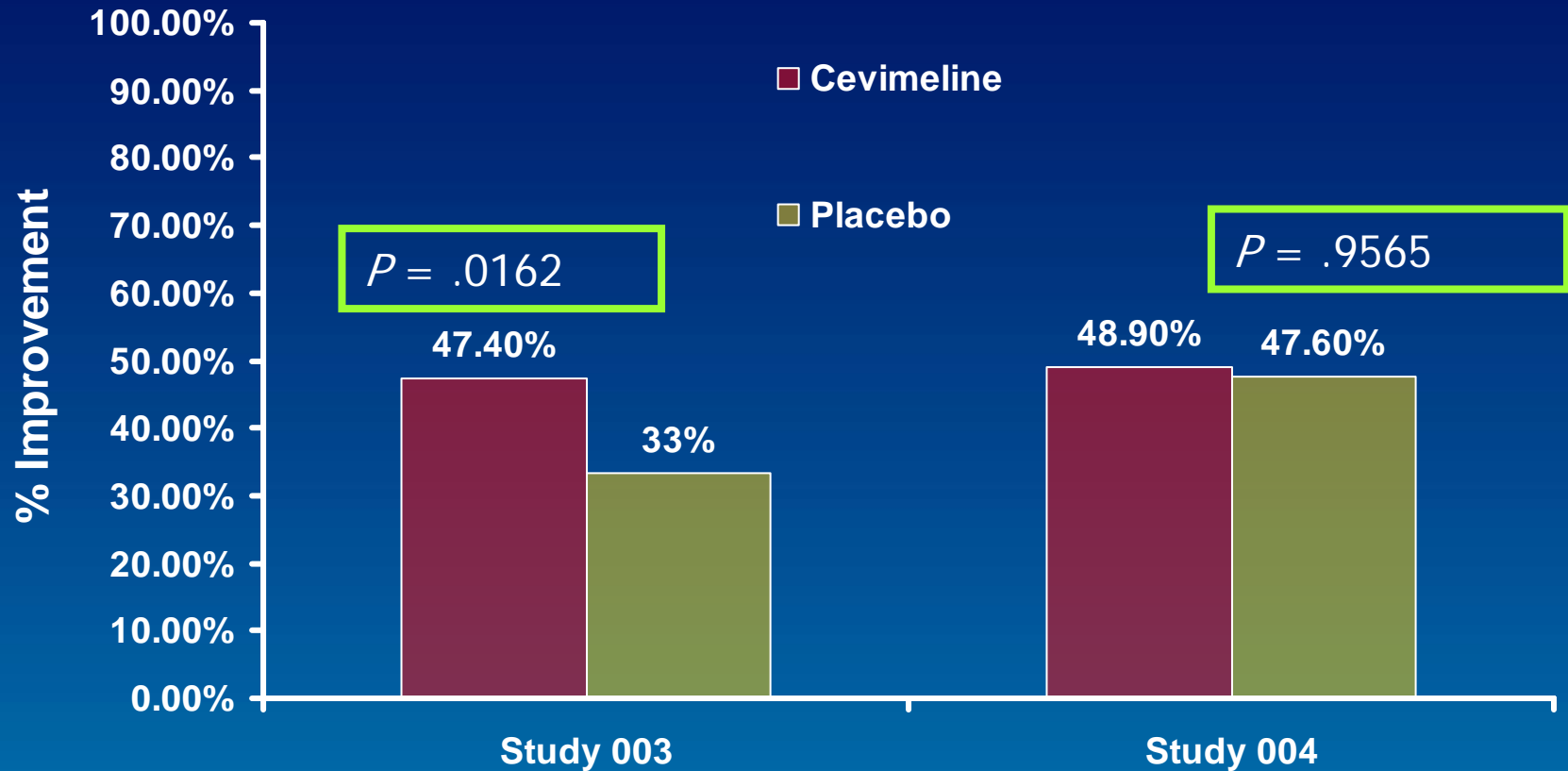
Pilocarpine

- Prospective, R, DB, PC, n = 207 HN who had received at least 40 Gy XRT
- Pilocarpine 5 mg or 10 mg PO TID vs. placebo
- Significant improvement in oral dryness, overall improvements, improved mouth/tongue comfort, and speaking ability with 5 mg vs. placebo
- Similar effects in 10 mg dose
- Sweating and other cholinergic AE

Cevimeline (Evoxac[®])

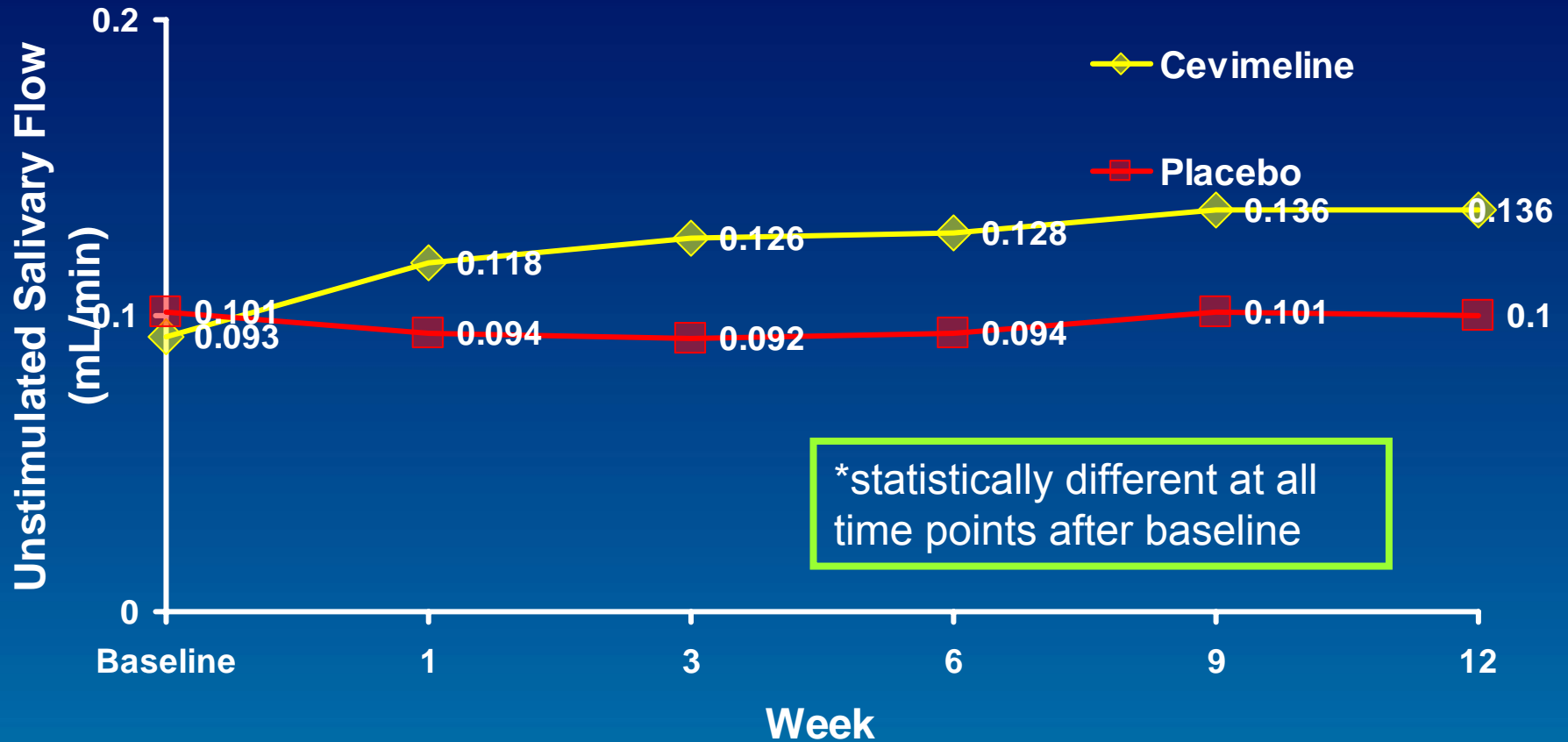
- Approved 1/00 for dry mouth d/t Sjögren's
- 12/05: post-marketing reports of cholecystitis
- 2 R, DB, MC, placebo-controlled trials, n = 547
- 30 mg cevimeline PO TID vs. matched placebo x 12 weeks
- Primary endpoint: final global evaluation of xerostomia

Cevimeline Efficacy

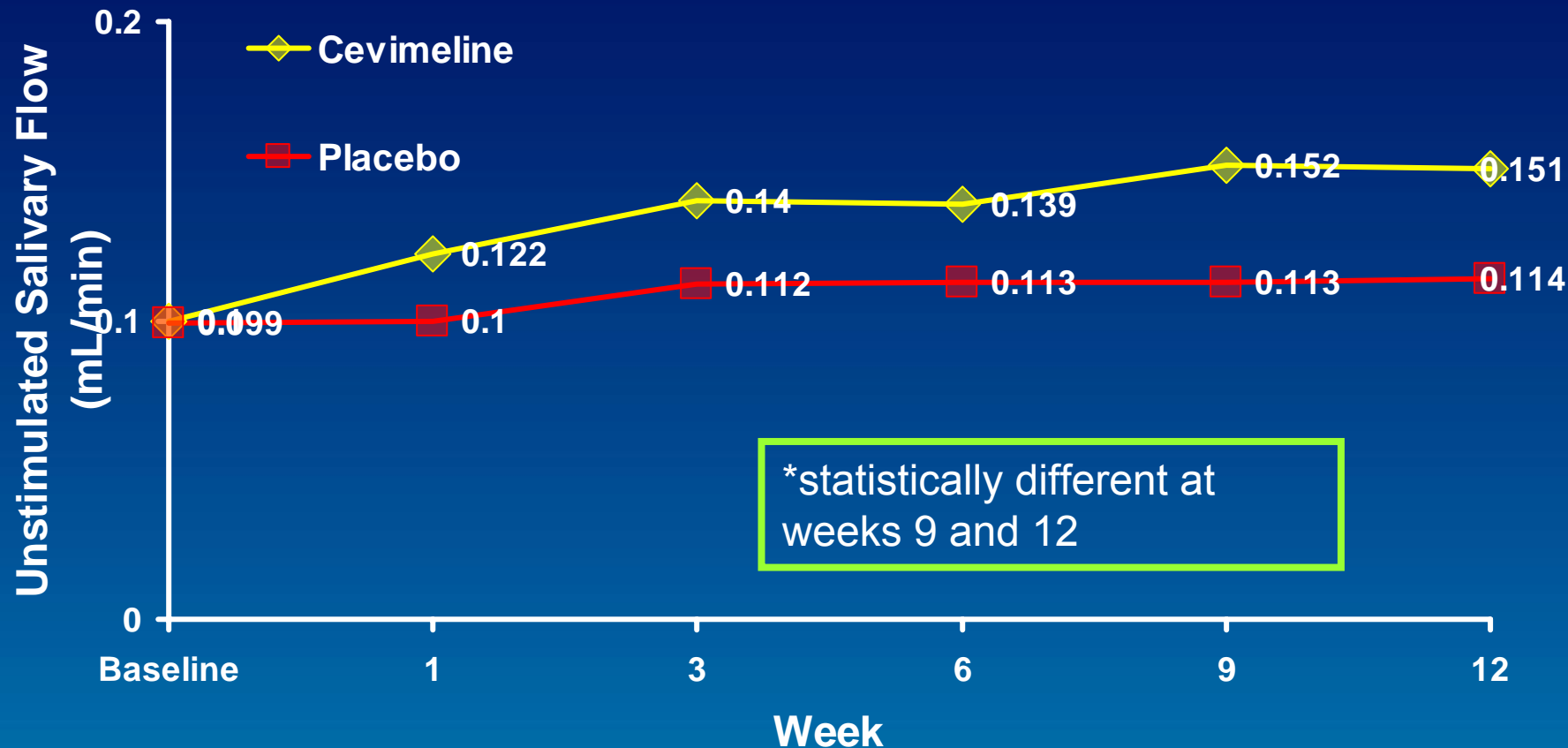


Global Evaluation of Improvement

Unstimulated Salivary Flow: Study 003



Unstimulated Salivary Flow: Study 004



Cevimeline Toxicities

- Events statistically different from placebo, either study:
 - General systemic (~30%)
 - Fatigue (~7%)
 - Increased sweating (~19%)
 - General GI (~35%)
 - Dyspepsia (~7%)

Dermatitis & Coexisting EGFR Rash

- Consensus guideline for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck
- 11 European and US medical and radiation oncologists, dermatologists

Radiation Dermatitis

- Incidence: 47-94% overall, usually mild
- 20-25% have severe reactions
- Higher with conventional vs. alternative fractionation schemes
- Increases with addition of chemotherapy
- Begins within first few weeks of treatment
- Dose, dose/fraction, overall treatment duration, beam type/energy, exposed surface area all influence incidence

Radiation Dermatitis: NCI CTC v.3 Grading

- Grade 1: faint erythema/dry desquamation
- Grade 2: moderate-brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
- Grade 3: moist desquamation beyond skin folds; bleeding induced by minor trauma/abrasion
- Grade 4: skin necrosis or ulceration; spontaneous bleeding from involved site
- Grade 5: death

Radiation Dermatitis & Cetuximab

- Radiation appears to delay onset of EGFR-rash
- No relationship between severity of EGFR-rash outside radiation fields and severity of radiation dermatitis
- No statistically significantly increased incidence/severity of radiation dermatitis with cetuximab vs. radiation alone

General Management

- Proper XRT planning and delivery
- Rule out other causes
- Keep area clean – gentle cleansers, soft towels, pH neutral synthetic detergent preferred over soap
- Drying pastes within skin folds
- Gels for seborrheic areas
- Creams for outside skin folds/seborrheic areas
- Hydrophilic dressings for moist areas
- Avoid greasy topical products
- Limit use of corticosteroids
- Pain relief
- Avoid sun exposure, skin irritants (perfumes, etc), scratching

Management by Grade

- Grade 1: no specific treatment; non-perfumed moisturizer; limited topical antibacterial moisturizers
- Grades 2 & 3:
 - Drying gels
 - Hydrophilic dressings
 - Anti-inflammatory emulsion
 - Zinc oxide paste
 - Silver sulfadiazine (after radiotherapy at HS)
 - Topical antibiotics (NOT prophylactically)
- Grade 4: specialized wound care

Co-morbid XRT Dermatitis & EGFR Rash

- Grade 0 or 1: follow guidelines for EGFR-inhibitor rash outside irradiated fields
 - Prevention: bath/shower oil (not soap), tepid water, emollient creams, avoid sun
 - Grade 1: topical anti-acne/anti-rosacea agents; avoid topical/systemic steroids and retinoids
 - Grade 2: grade 1 treatments + topical menthol cream or oral antihistamine and oral tetracycline; avoid isotretinoin
 - Grade 3: delay EGFR therapy; add compresses w/ anti-inflammatory solutions; high-dose tetracyclines
 - Grade 4: treat in burn unit; d/c EGFR agents
- Grade 2 or greater: follow radiation dermatitis guideline

Oral Medication Administration

- ODT vs. standard formulations
- Aprepitant, fosaprepitant
- Meds that can be split/crushed

ODT vs. Standard Formulations in Dysphagic Adults

Results

Parameter	ODT (N = 36)	Standard (N = 36)	P-value
# swallows	2 (1-19)	3 (1-20)	0.002
Total time (s)	49.8 (1.92-323)	56.7 (5.23-323)	<0.001
Use of liquid	6	14	0.02
Muscular effort (sEMG)	55.8 (25.7)	62.1 (26.1)	<0.001

Fosaprepitant (Emend for Injection)

- R, open-label, incomplete crossover, bioequivalence study of 138 subjects
- → same PK as 125 mg PO aprepitant
- → same approval as PO aprepitant
- 115 mg IV over 15 minutes pre-chemo
 - Replaces day 1 of 125 mg PO aprepitant
 - Still give aprepitant 80 mg PO days 2 and 3

Key Points

- Chemoradiation is preferred over surgical interventions for early-stage HN cancers
- Cisplatin and carboplatin appear interchangeable in chemoradiation regimens – equal efficacy but carboplatin may be better tolerated
- Cetuximab improves PFS and OS when added to radiation in the treatment of locoregional HN
- Docetaxel improves PFS and OS when added to either chemoradiation or radiation only as induction therapy
- Xerostomia, treatment-related skin toxicities, and oral medication administration present opportunities for pharmacist-managed supportive care of HN patients