

TUMOREN IM HNO-BEREICH



Therapie der lokal fortgeschrittenen Kopf-Hals-Tumoren

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“State of the Art” in Hämatologie und Onkologie
Hannover-Meeting
22.-23.01.2010
MARITIM AIRPORT HOTEL

Treatment of Locally Advanced Head and Neck Cancer

Definitive Chemoradiation (CRT) for Organ Preservation:

- What are the evidences for CRT in oro- and hypopharyngeal head and neck cancer?
- Are there evidences for competitive (different) regimes, e.g. neoadjuvant chemoradiation and targeted therapies?

Chemoradiation is More Effective than Dose Escalation in Locally Advanced H&N-Cancer

10-Years Results of a German Multicenter Randomized Trial (ARO 95-06)

supported by Deutsche Krebshilfe, Grant 70-3103

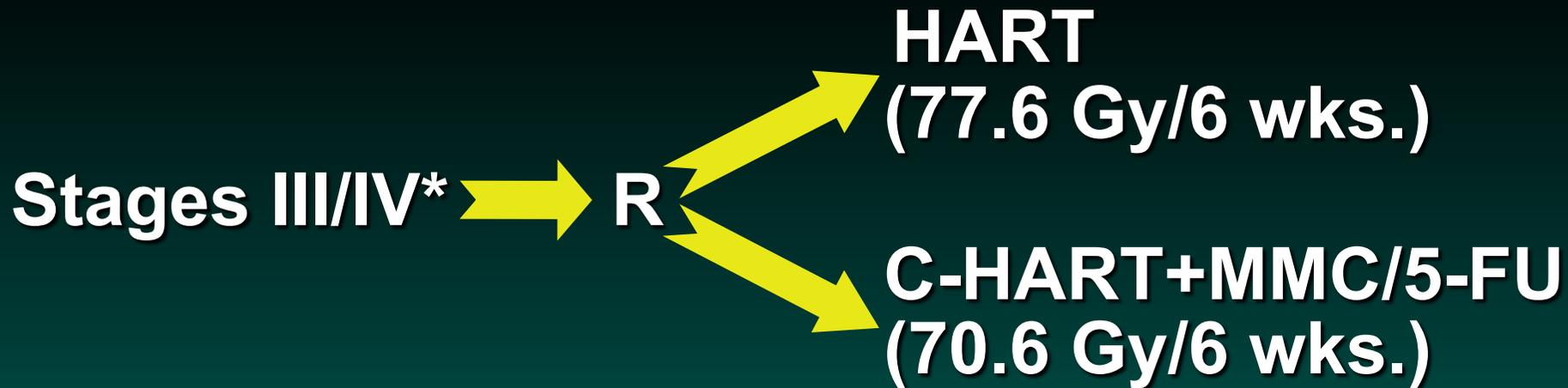


Charité

Volker Budach, M.D.¹, Martin Stuschke, M.D.³, Wilfried Budach, M.D.⁵, Michael Baumann, M.D.⁶, Dirk Geismar, M.D.¹, Gerhard Grabenbauer, M.D.⁷, Christoph Matthias, M.D.², Klaus Jahnke, M.D.⁴, Georg Stueben, M.D.³, Thomas Herrmann, M.D.⁶, Michael Bamberg, M.D.⁵, Peter Wust, M.D.⁸, Wolfgang Hinkelbein, M.D.⁹, Klaus-Dieter Wernecke, Ph.D.¹⁰

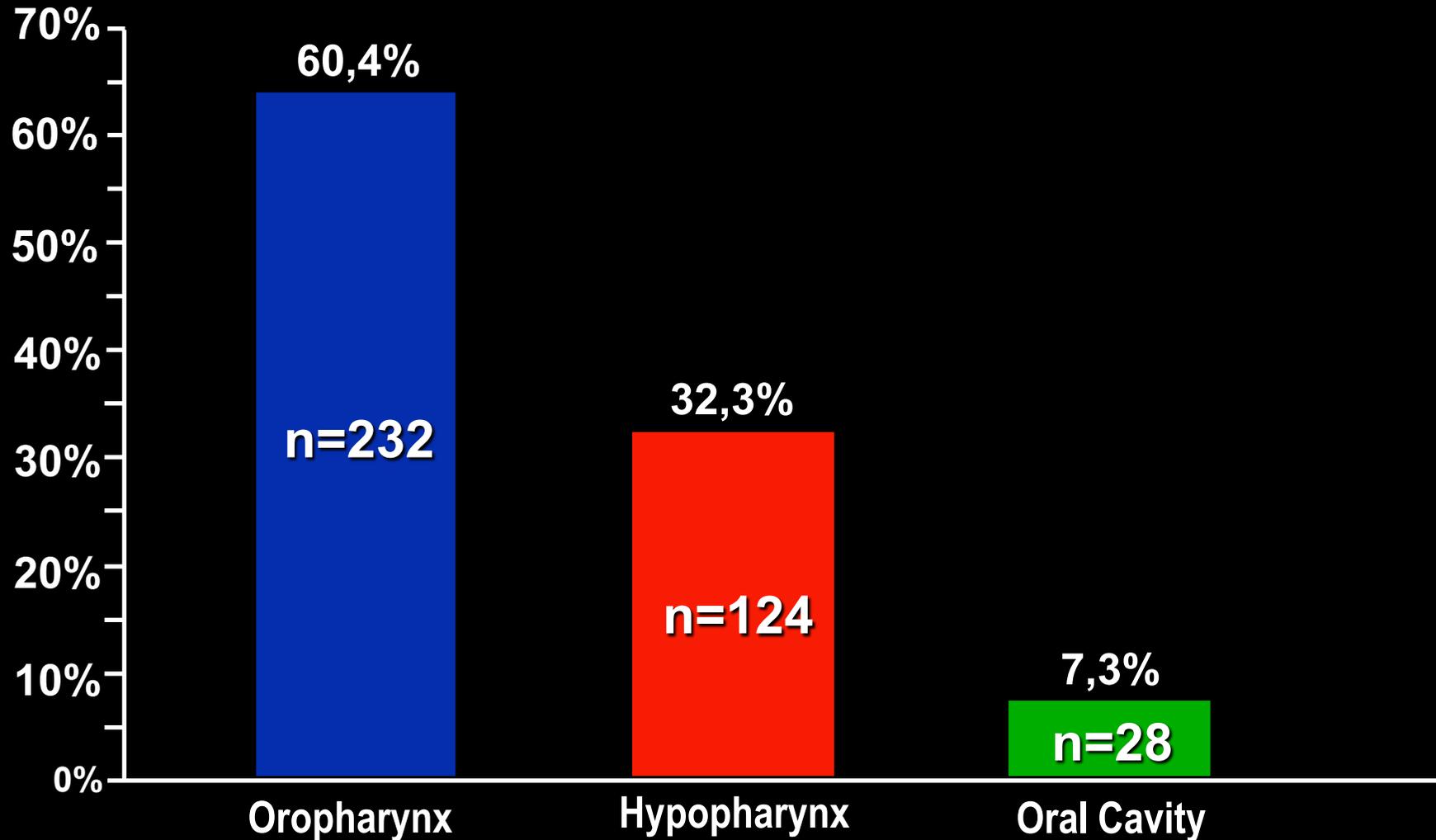
From the Departments of Radiation Oncology, Campus Mitte¹ and Wedding⁸, Head and Neck Surgery², University Hospitals Charité, Berlin; Radiation Oncology³ and Head and Neck Surgery⁴, University Hospitals of Essen; Radiation Oncology⁵, University Hospitals of Tuebingen, Radiation Oncology⁶, University Hospitals of Dresden, Radiation Oncology⁷, University Hospitals of Erlangen, Radiation Oncology⁹, University Hospitals Benjamin-Franklin, Berlin; Institute for Medical Biometry¹⁰, University Hospitals Charité, Berlin

Design of the ARO 95-6 Study



**Locally advanced H&N-cancer of the oral cavity, oro- and hypopharynx stratified according to centres, tumor sites, N-stage and grading*

Tumour Site



Multicentric Phase-III Trial "Accelerated Hyperfractionation 5-Fluorouracil / Mitomycin C
for locally advanced head & neck cancer

TNM-Matrix

	N0	N1	N2	N3	Total
T1			3	3	6
T2		1	21	5	27
T3	5	15	46	3	69
T4	14	17	207	44	282
Total	19	33	277	55	384

Stage III: 5.5% (n=21)

Stage IV: 94.5% (n=363)

Multicentric Phase-III Trial "Accelerated Hyperfractionation 5-Fluorouracil / Mitomycin C
for locally advanced head & neck cancer (ARO 95-6)

Acute Toxicity (EORTC / RTOG)

(n = 348)

	Erythema	Moist Desquamation	Pigmentation	Mucositis	Dysphagia	Xerostomia	Dysgeusia
Brunner*	p=0.30**	p=0.24***	p=0.30	p=0.65	p=0.82	p=0.60	p=0.98

*non-parametric analysis of variance for repeated measures

**isolated significance at 5th and 6th time points (Mann-Whitney-U-test)

***isolated significance at 6th time point (Mann-Whitney-U-test)

Late Morbidity (EORTC/RTOG)

(n=331)

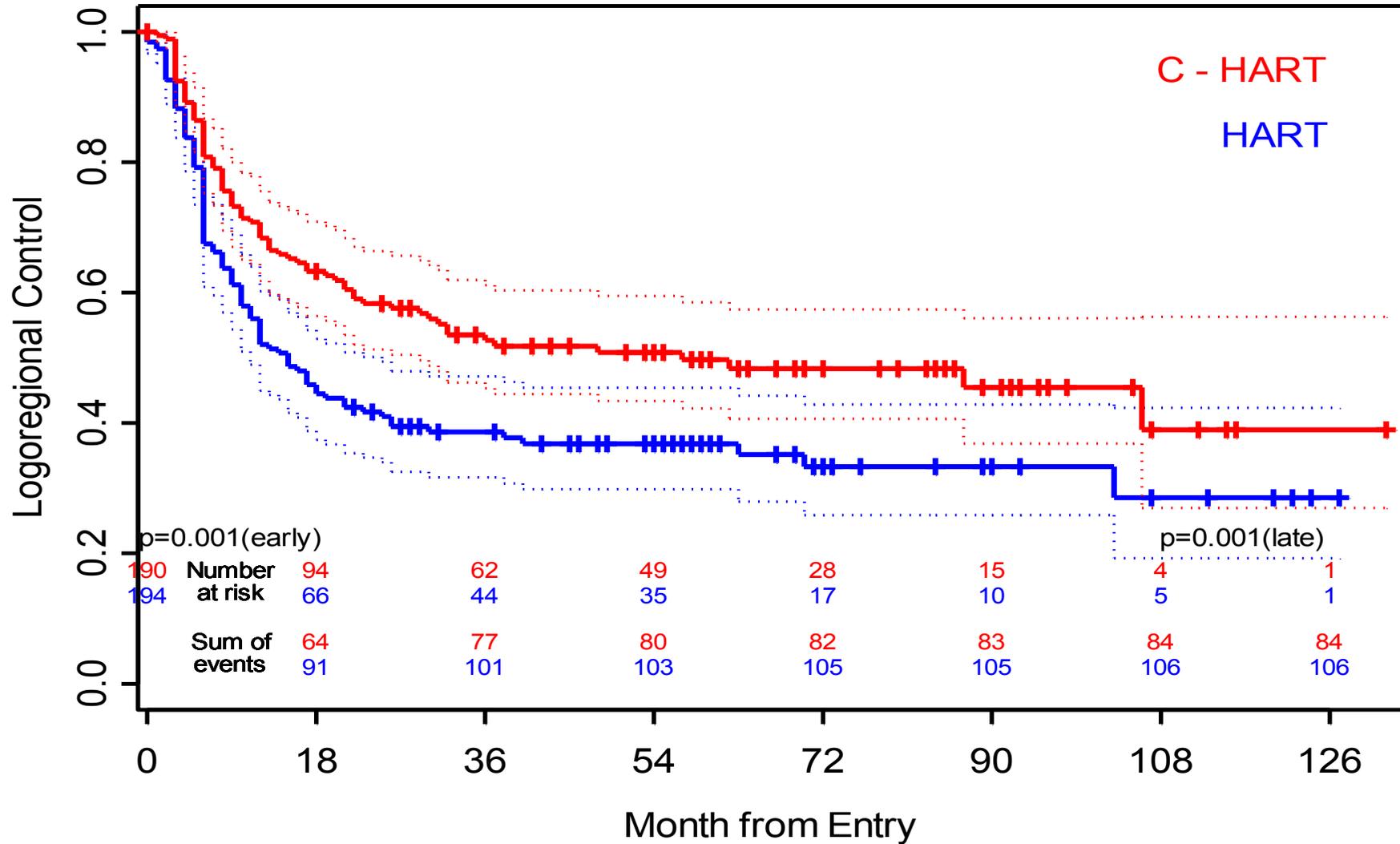
Brunner* analysis	Xero-** stomia	Dys- geusia	Dys-*** phagia	Tele- angiect.	Fibrosis	Trismus	Plexo- pathy	Osteorad. necrosis	Pigmen- tation	Lymph- edema	Mucosal necrosis	Neurol. sympt.
@ 5 yrs.	p=0.58	p=0.79	p=0.24	p=0.43	p=0.95	p=0.82	p=0.29	p=0.96	p=0.74	p=0.75	p=0.26	p=0.93

**isolated significance at 11th observation (Mann-Whitney-U-test)

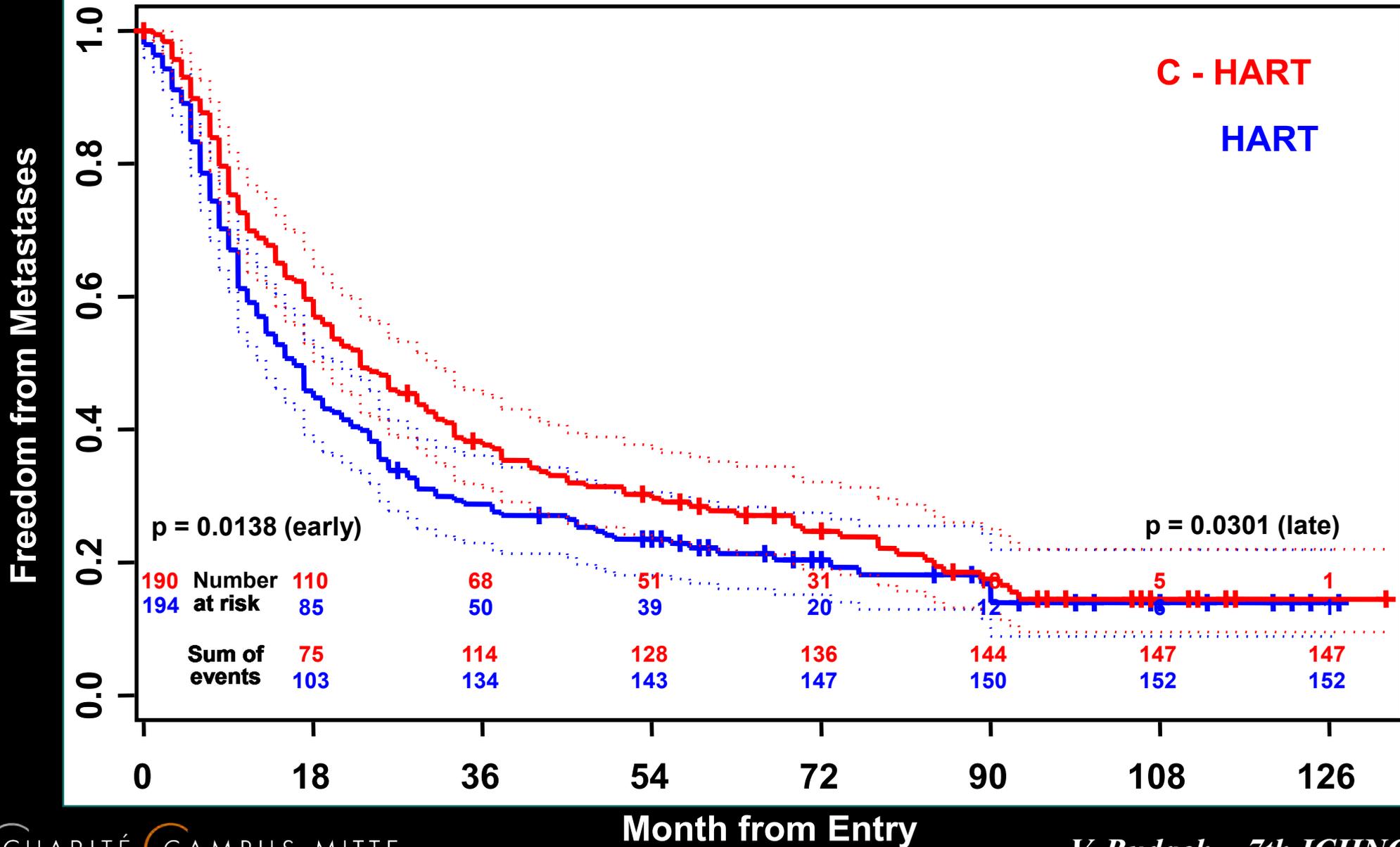
***isolated significance at 2nd, 3th, 5th and 9th observation (Mann-Whitney-U-test)

Locoregional Control

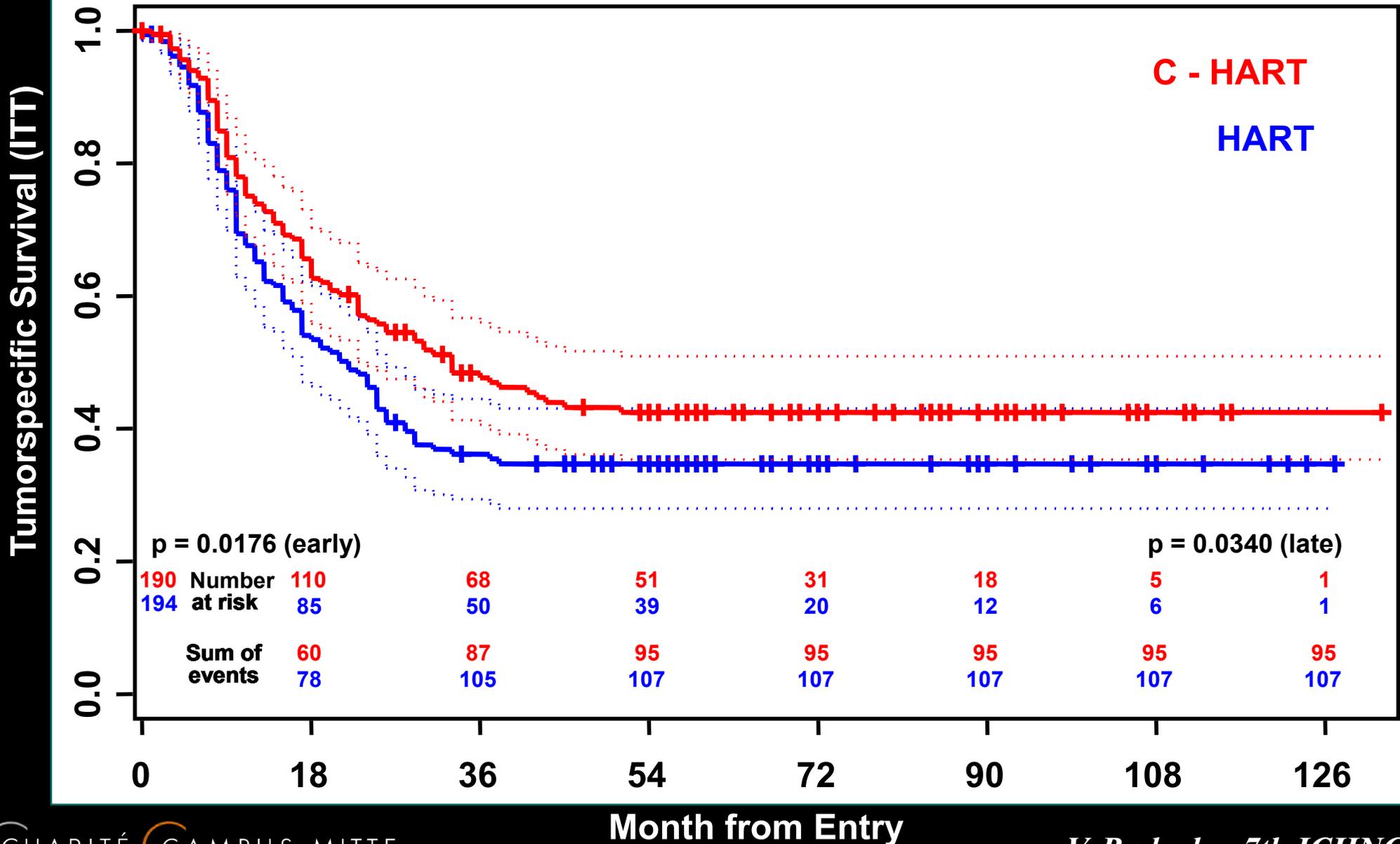
Locoregional Control



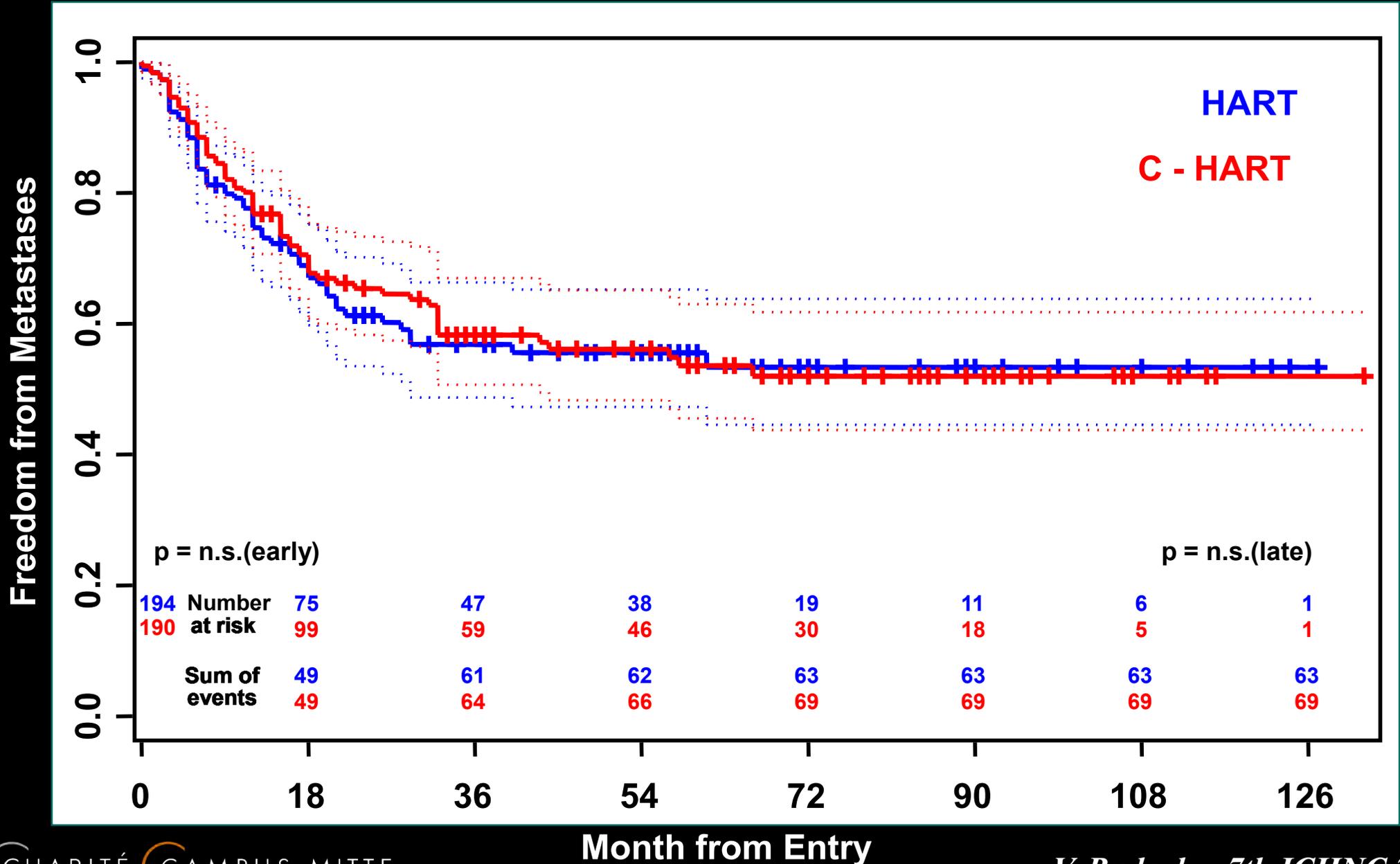
Overall Survival



Tumorspecific Survival



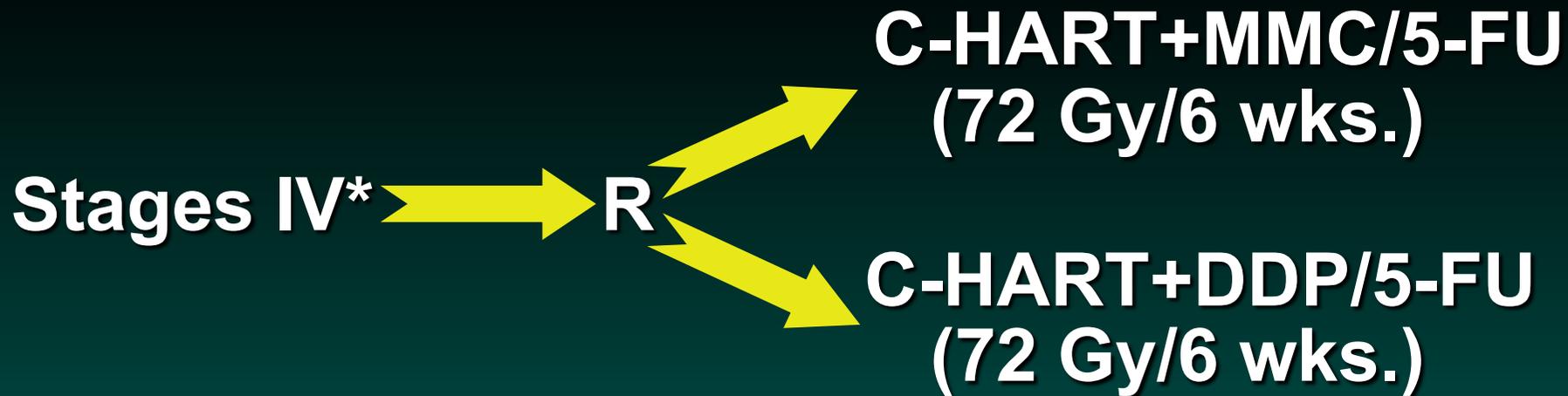
Metastases-free Survival



Conclusions

- **Chemotherapy + Hyperfraction. Accelerated RadioTherapy ("C-HART") with 70.6 Gy + MMC/ 5-FU is outperforming a dose-escalated HART with 77.6 Gy alone at isoeffective levels of acute and late radiation damage ➡ Therapeutic Radio↑!**
- **Increased long-term and *not* tumor-specific mortality after treatment with C-HART equals overall survival rates after 7 years of follow-up.**
- **The rates of distant metastases were not reduced after chemoradiation!**

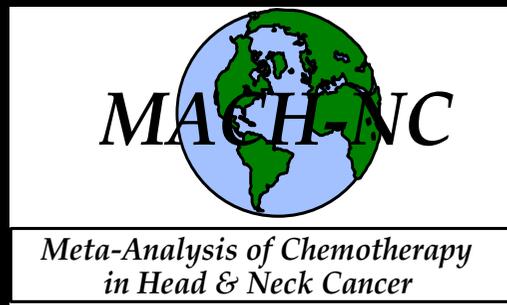
Design of the ARO 04-01 Study



**Locally advanced H&N-cancer of the oro- and hypopharynx stratified according to centres, tumor sites, N-stage, grading and Hb-level \leq vs. $>$ 14g%*

“High-lights” of the ARO 06-01 Trial

- Currently world-wide the only multicenter trial, which compares **MMC/5-FU with a DDP/5-FU regimen**
- The only multicenter trial, which uses a **once weekly Cisplatin regimen** with 30mg/m² x 6 cycles
- **Stage IV tumors exclusively stratified for oropharyngeal and hypopharyngeal sites**
- **High cost-efficiency** since all drugs are available out of license (5-FU, MMC und DDP)
- **Stratification for pretherapeutic hemoglobin level**

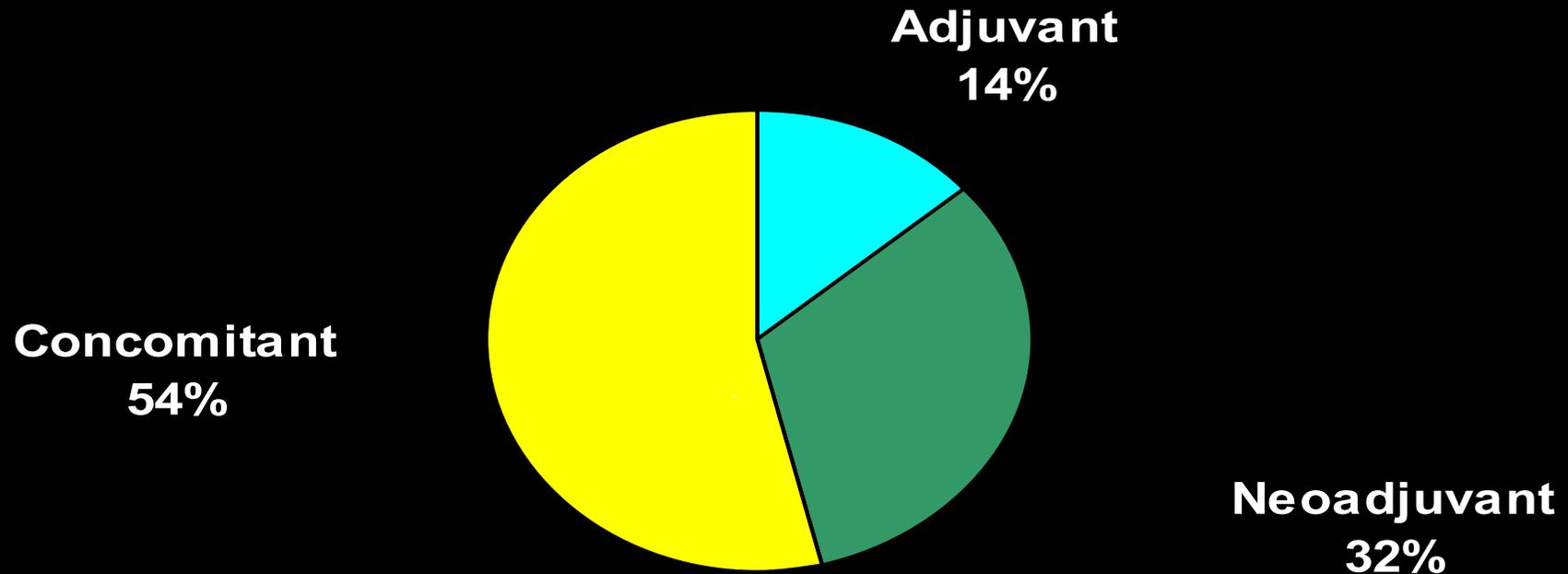


***Update of the MACH-NC database
focusing on concomitant chemo-radiotherapy.***

J Bourhis, C Amand, JP Pignon

*on behalf of the
Meta-Analysis of Chemotherapy in Head and Neck Cancer
(MACH-NC) Collaborative Group*

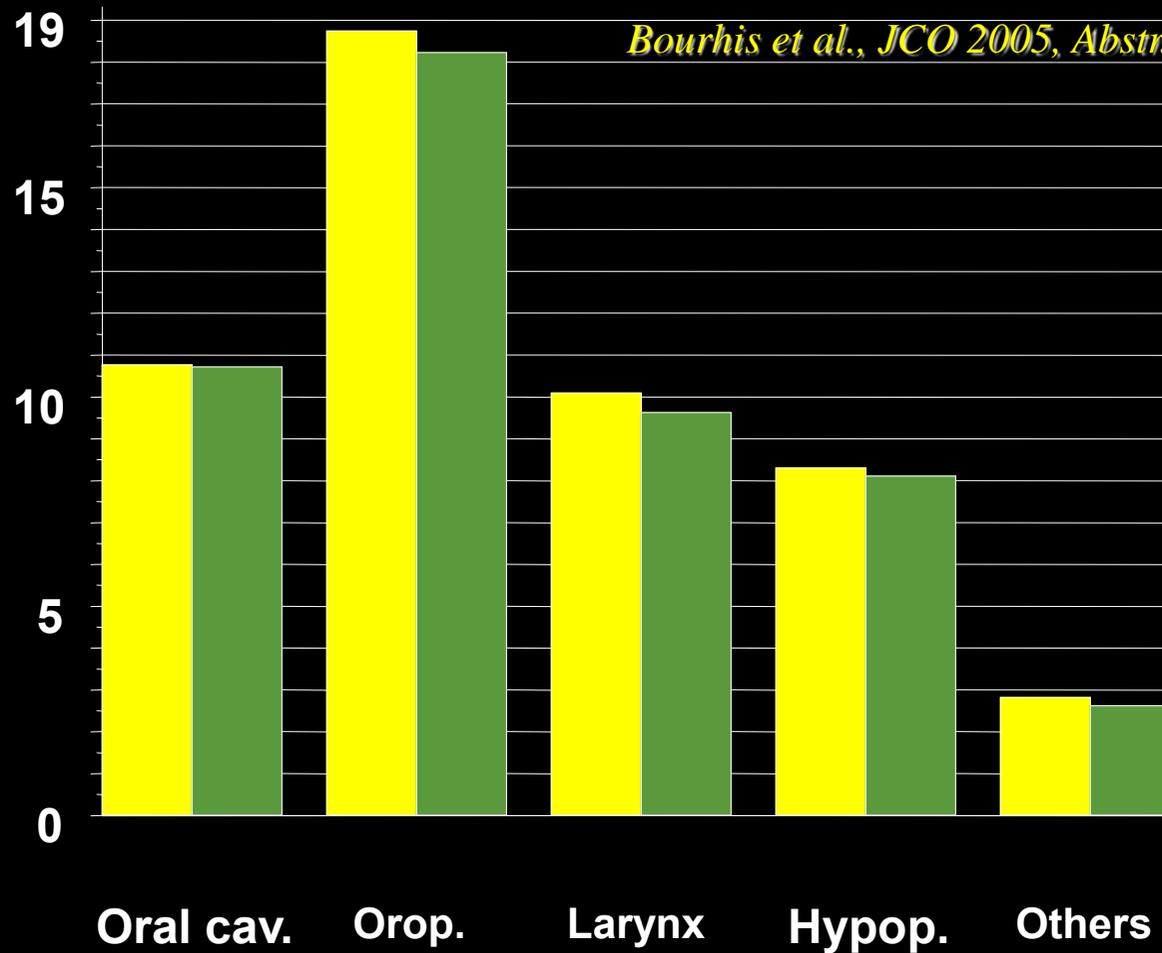
Chemotherapy timing (n= 17 858)



Bourhis et al., JCO 2005, Abstr.

Site of the primary (n= 17 858)

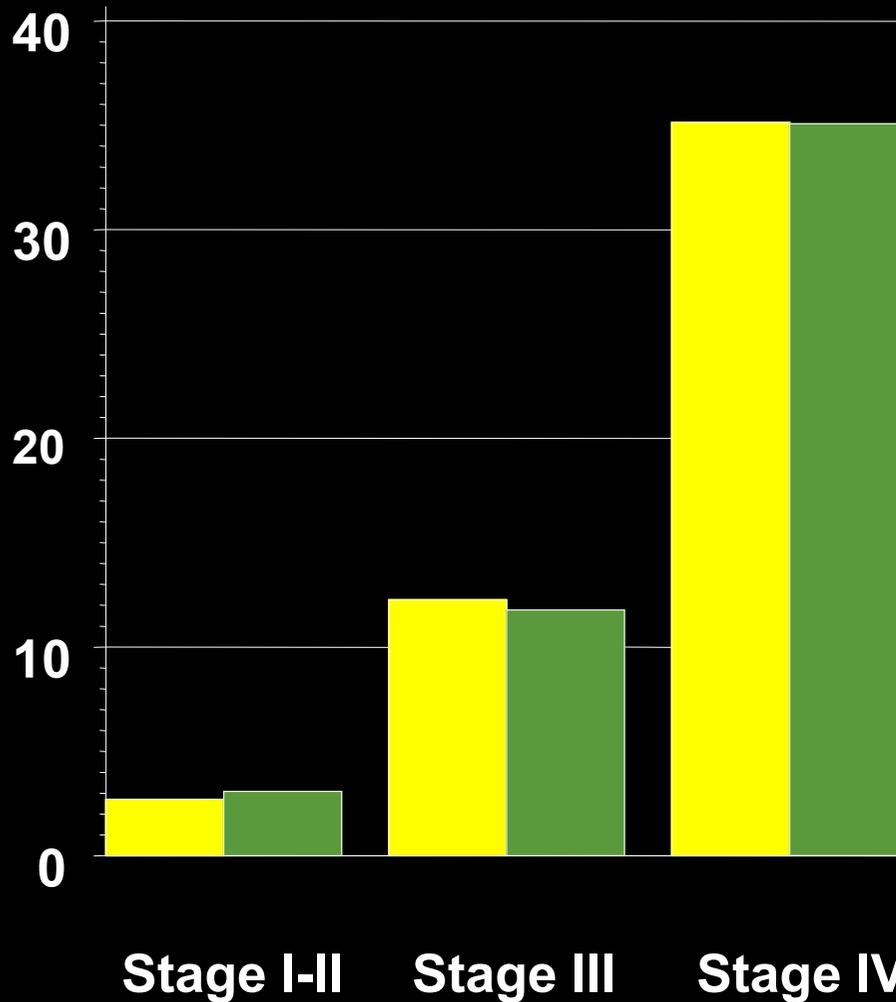
PERCENT



Treatment: ■ Chemotherapy ■ No Chemotherapy

Stage (UICC 1997) (n= 17 858)

PERCENT



Bourhis et al., JCO 2005, Abstr.

Treatment:

■ Chemotherapy

■ No Chemotherapy

Results : Overall survival

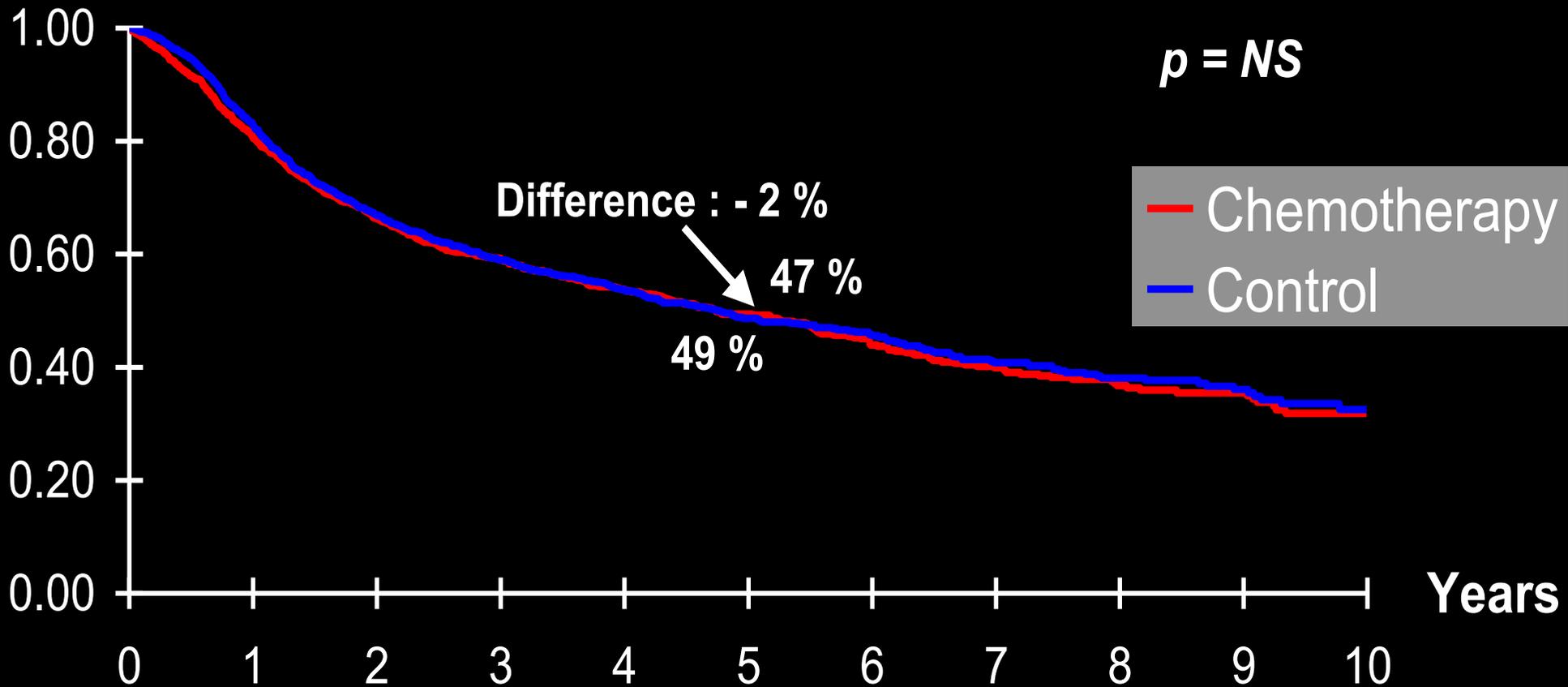
<i>Chemotherapy timing</i>	<i>Risk reduction</i>	<i>p-value</i>	<i>Absolute benefit at 5 years *</i>
Adjuvant	-6 %	NS	- 2 %
Neoadjuvant	4 %	NS	2 %
Concomitant	19 %	< 0.0001	8 %
Total	12 %	< 0.0001	5 %

* 5-year survival rate in control group : 30%

Bourhis et al., JCO 2005, Abstr.

Overall Survival

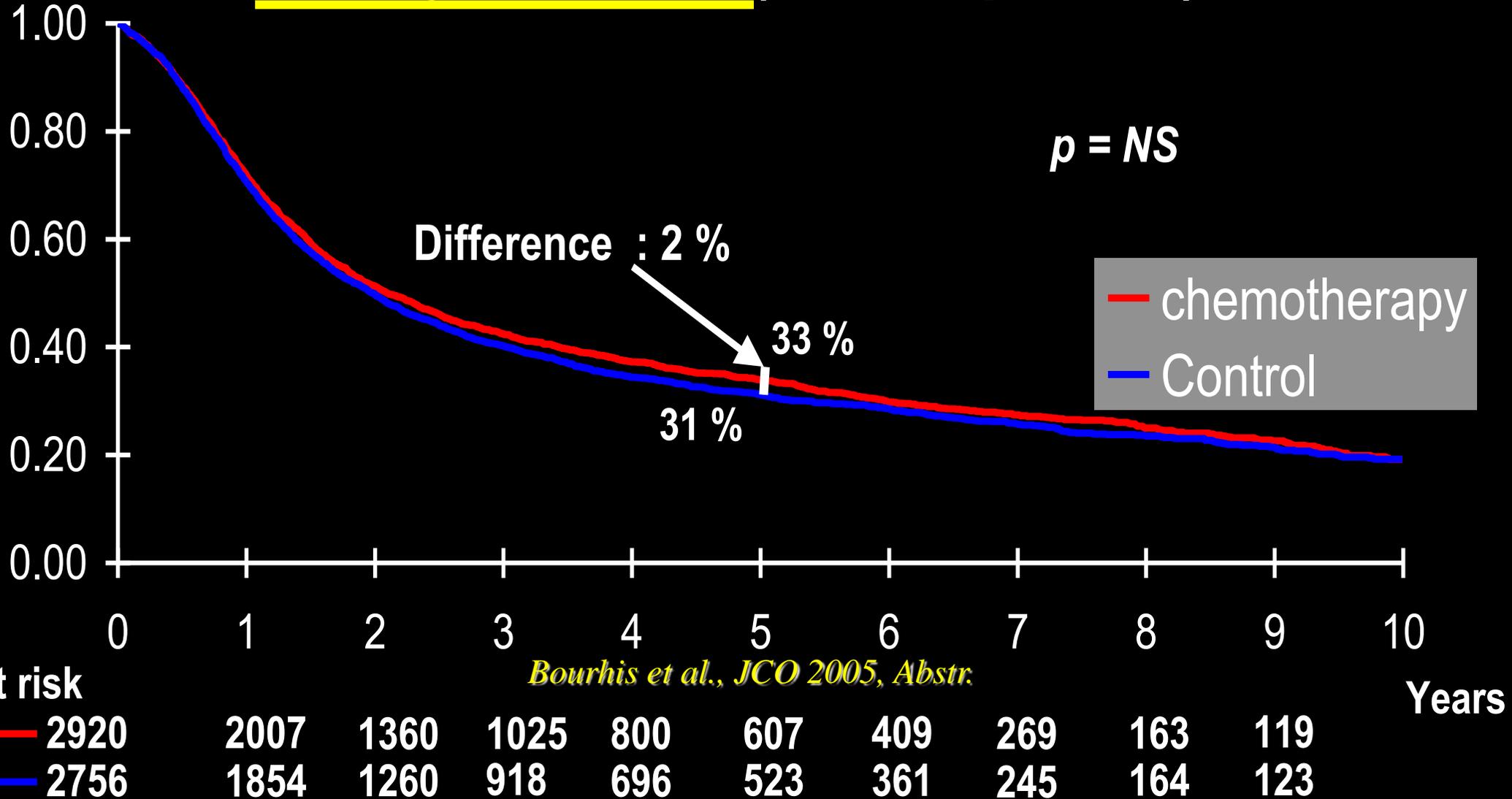
Adjuvant Trials (N=2567 patients)



At risk

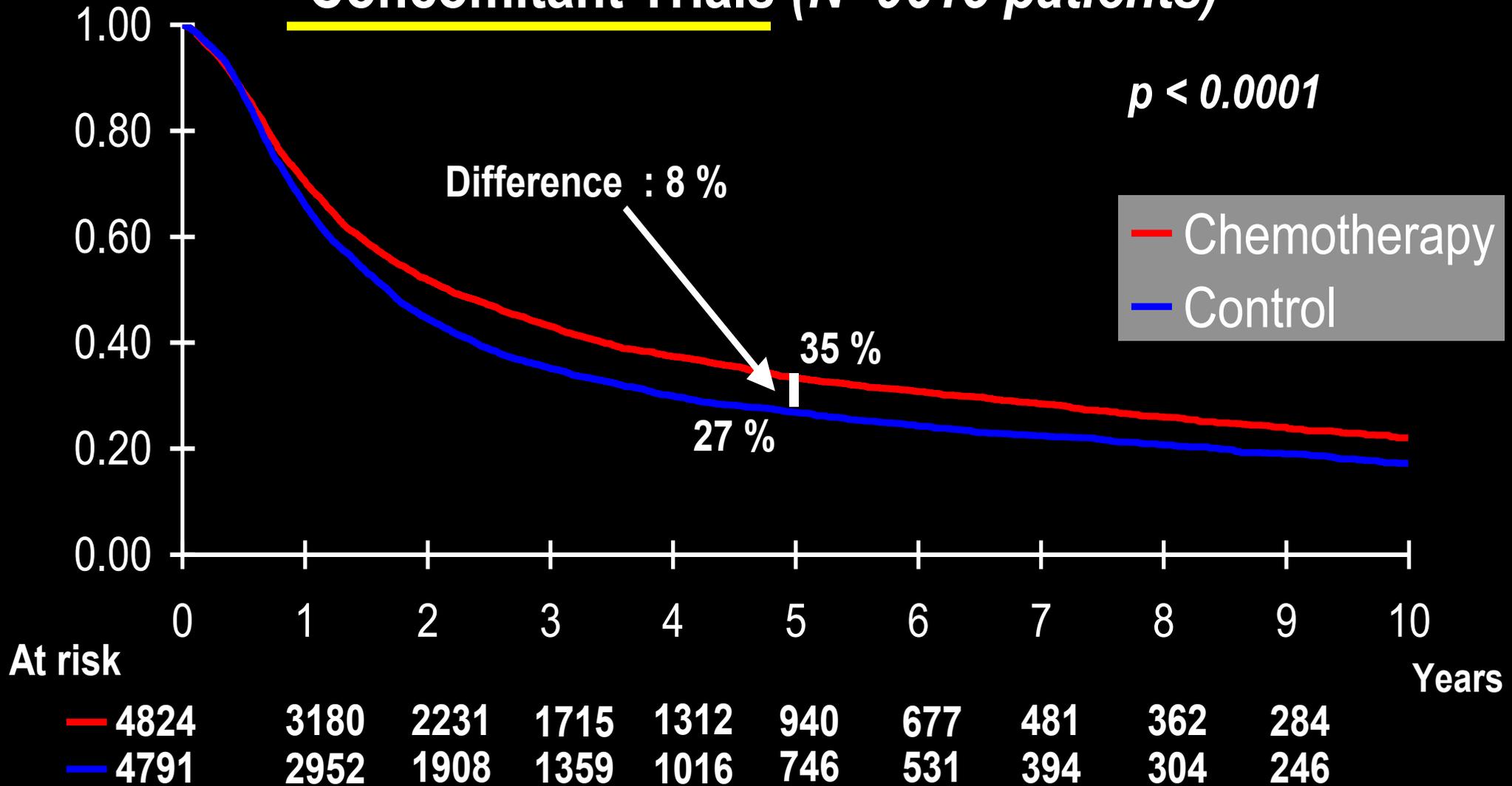
—	1244	971	743	602	424	290	202	149	98	66
—	1323	1049	799	640	454	301	212	155	104	62

Overall Survival Neoadjuvant Trials (N= 5676 patients)



Overall Survival

Concomitant Trials (N=9615 patients)

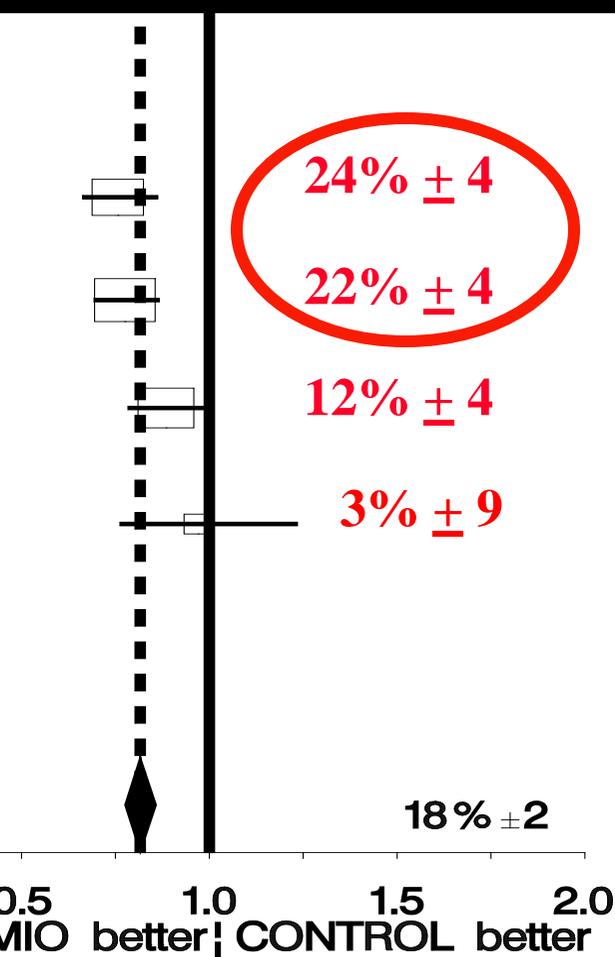


Bourhis et al., JCO 2005, Abstr.

Survival, concomitant trials by age

Category	No. Events/ CHIMIO	No. Entered CONTROL	O – E	Variance	Relative Risk Redn. (CHIMIO:CONTROL)(±SD)
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Age < 50	803/1296	860/1288	-108	386.6
Age 51 – 60	1069/1645	1198/1661	-137.3	539.3
Age 61 – 70	972/1368	988/1330	-56.2	457.8
Age 71 +	266/347	255/331	-3.5	114.7
Total	3110/4656	3301/4610	-304.9	1498.5



Test for trends: $p=0.003$

Test for interaction: $X^2_3 = 10.06$ 2P = 0.02

0.0 0.5 1.0 1.5 2.0
CHIMIO better | CONTROL better
CHIMIO effect 2P < 0.0001

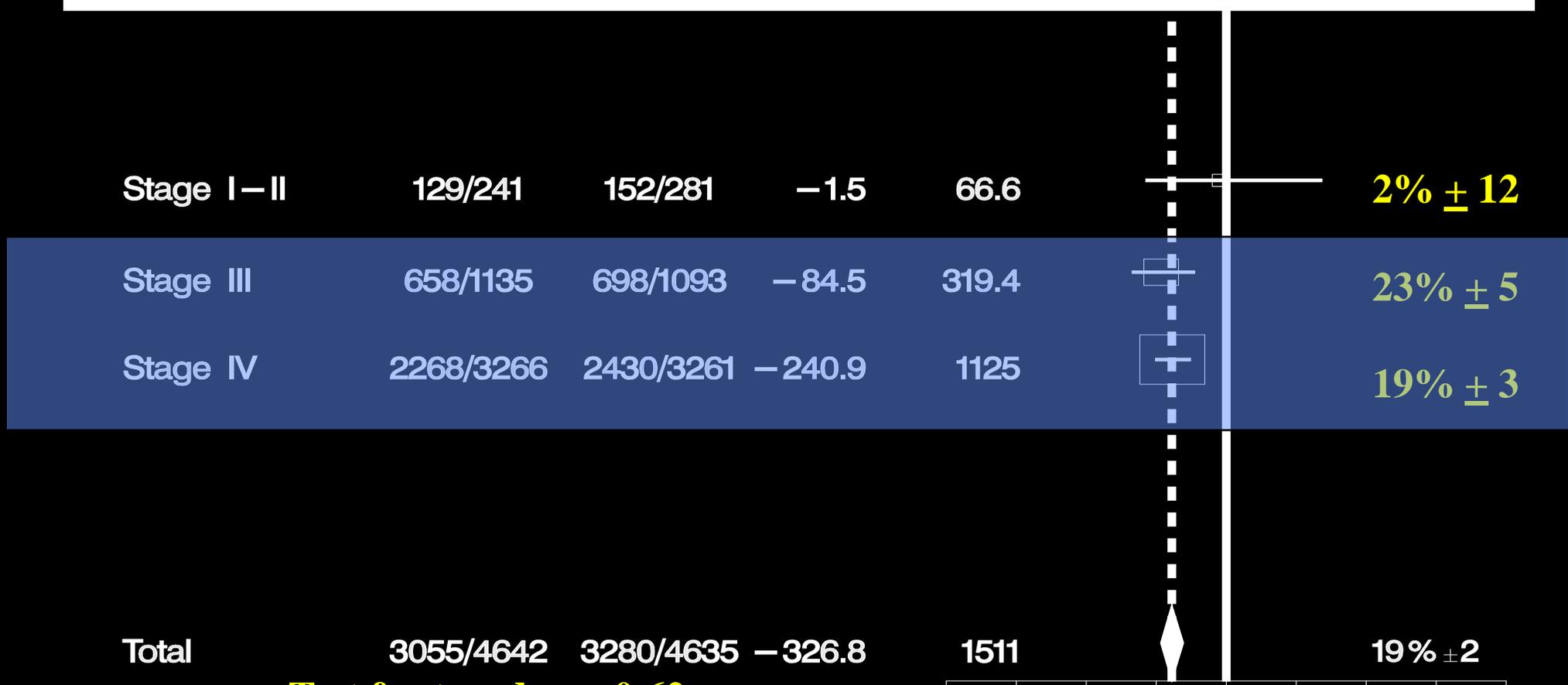
Bourhis et al., JCO 2005, Abstr.

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< 50
↓
> 70

Survival, concomitant trials by Stage

No. Events/ No. Entered
CHIMIO CONTROL O-E Variance
Relative Risk Risk Redn.
(CHIMIO:CONTROL)(\pm SD)



Test for trends: $p=0.62$

Test for interaction: $X^2_2 = 3.26$ 2P = 0.2

0.0 0.5 1.0 1.5 2.0
CHIMIO better | CONTROL better

CHIMIO effect 2P < 0.0001

Bourhis et al., JCO 2005, Abstr.

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Concomitant trials : effect by type of CT

Meta-Analysis of Chemotherapy
in Head & Neck Cancer

Category	No. Events/ CHIMIO	No. Entered CONTROL	O – E	Variance	Relative Risk (CHIMIO:CONTROL) (±SD)
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Platin + 5 – FU

679/1122

774/1116

– 93.7

356.2

23% ± 5

Platin w/o 5 – FU

741/1194

777/1103

– 107.2

358.2

26% ± 5

5FU w/o Platin

684/903

729/929

– 70.5

344.2

19% ± 5

CT w/o Platin or 5FU

1067/1605

1109/1643

– 56.7

528.4

10% ± 4

Total

3171/4824

3389/4791

– 328.1

1587

19% ± 2

test for interaction: $X^2_3 = 9.44$ 2P = 0.02



Conclusion

- ➔ Small benefit of chemotherapy on survival = **confirmed (5%)**
- ➔ Evidence of a **higher survival benefit with concurrent** = confirmed
- ➔ Absolute benefit in concomitant = **8% at 5 years** (11% with Cisplatin alone)
- ➔ Benefit of chemotherapy observed **in post-op, and with definitive RT** (conventional or hyperfractionated)

Bourhis et al., JCO 2005, Abstr.

Chemo-Enhanced RTX in SCC of the Head & Neck

Altered Fractionation Regimen:

- What are the evidences for unconventional (altered) fractionation schedules in the definitive radiotherapy of head and neck cancer?

Accelerated or Hyperfractionated Radiotherapy vs. Standard Fractionated Radiotherapy

publication	trial #	control arm		experimental arm		fractionation	Stage 4 [%]	N3 [%]
		dose [Gy]	RT time [days]	dose [Gy]	RT time [days]			
group 2		conventional fract.		acceleration				
Dische [16]	20	66	45.5	54	12	CHART	72	6
Dobrowsky [37]	21	70	49.0	55.3	17	CHART		12
Olmi [41]	22	68	47.3	65.6	42.7	AF split	70	7
Fu [42]	23	70	49.0	67.2	43.4	AF split	68	13
v. den Bogaert [43]	24	72.5	56.0	69.6	44.8	AF split	65	47
Horiot [23]	25	70	51.7	72	35	AF split	0	0
Fu [42]	26	70	49.0	72	42	concomittant boost		
Overgaard [44]	27	66–68	39.0	66–68	46.0	weekend	25	
Skladowsky [13]	28	70.6	54	70.75	40	weekend	17	0
group 3		conventional fract.		hyperfractionation				
Sanchiz [18]	29	60	42.0	70.4	44.8	HFX		30
Pinto [45]	30	66	46.2	70.4	44.8	HFX	54	25
Horiot [46]	31	70	51.1	80.5	49	HFX		15
Fu [42]	32	70	49.0	81.6	47.6	HFX	68	13

W. Budach et al., BMC Cancer 6/28, 2006

Accelerated Radiotherapy vs. Standard Fractionated Radiotherapy

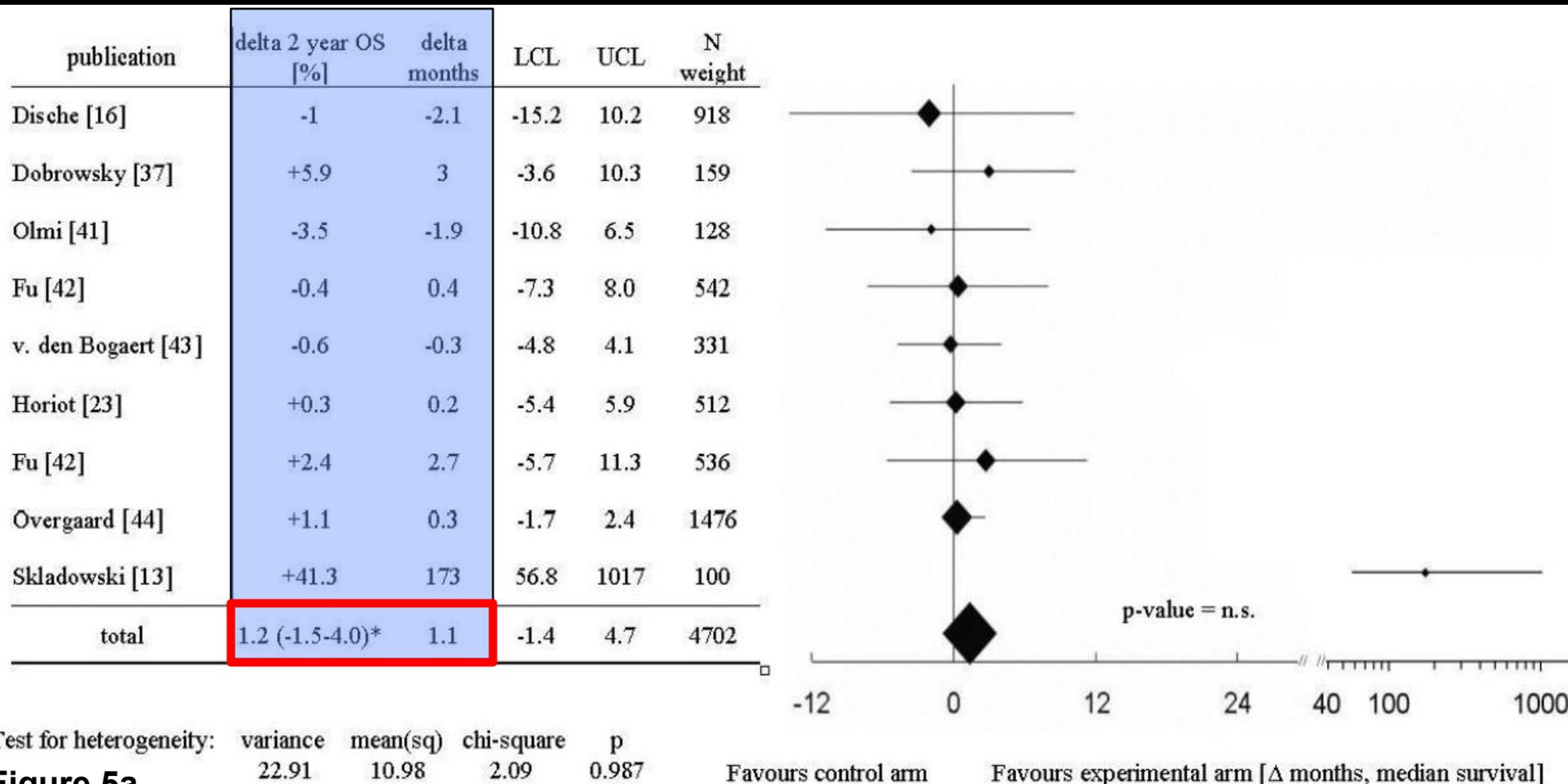
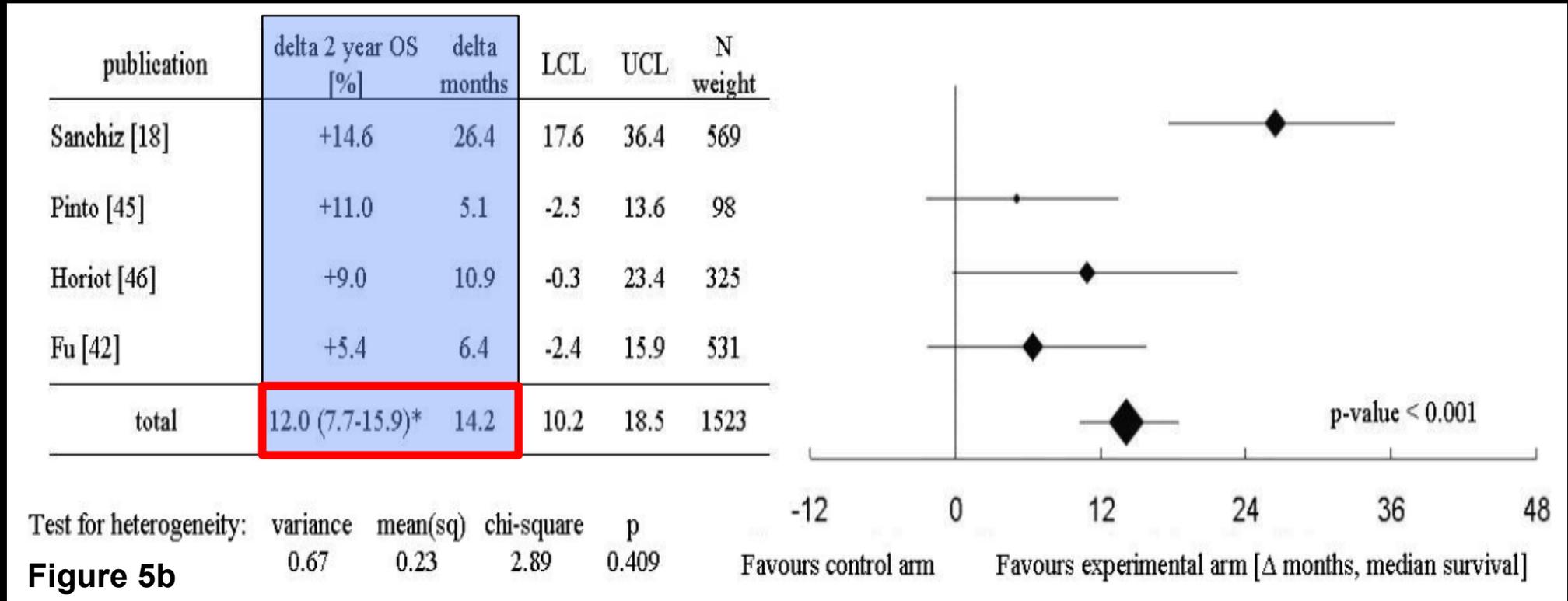


Figure 5a

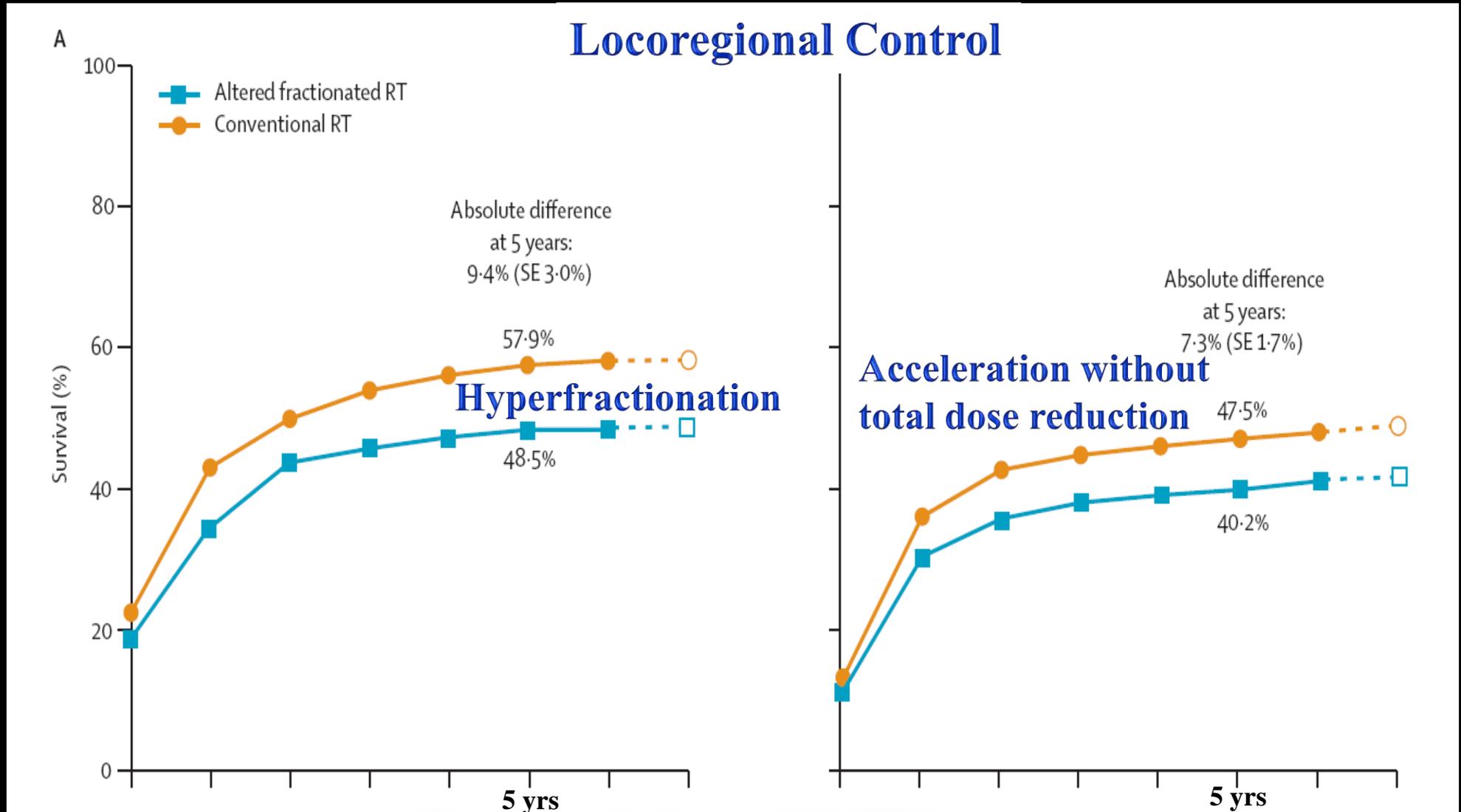
W. Budach et al., BMC Cancer 6/28, 2006

Hyperfractionated Radiotherapy vs. Standard Fractionated Radiotherapy



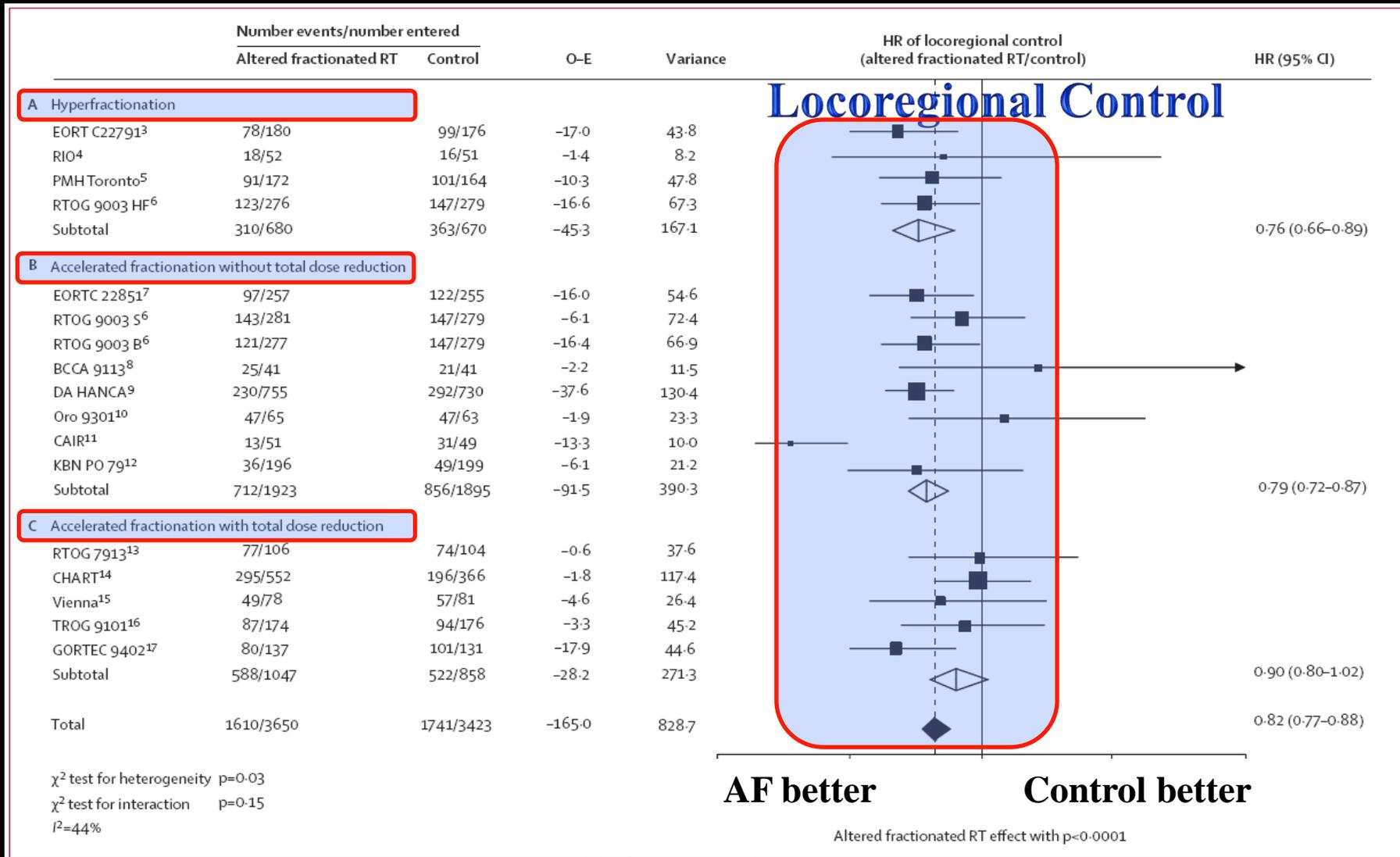
W. Budach et al., BMC Cancer 6/28, 2006

MARCH Meta-Analysis of Hyperfractionated or Accelerated Radiotherapy in H&N Cancer



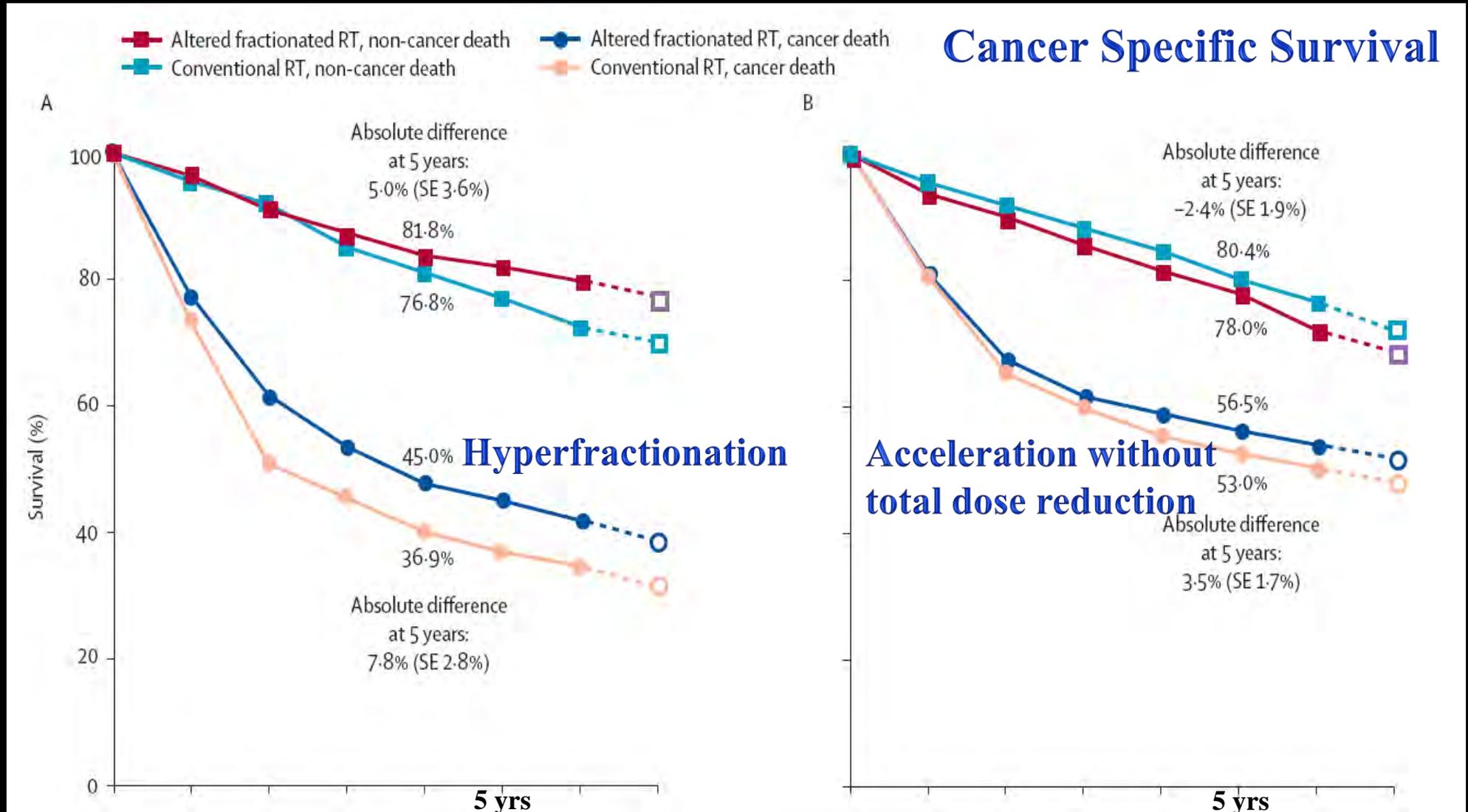
Bourhis et al., Lancet 368, 2006

MARCH Meta-Analysis of Hyperfractionated or Accelerated Radiotherapy in H&N Cancer



Bourhis et al., Lancet 368, 2006

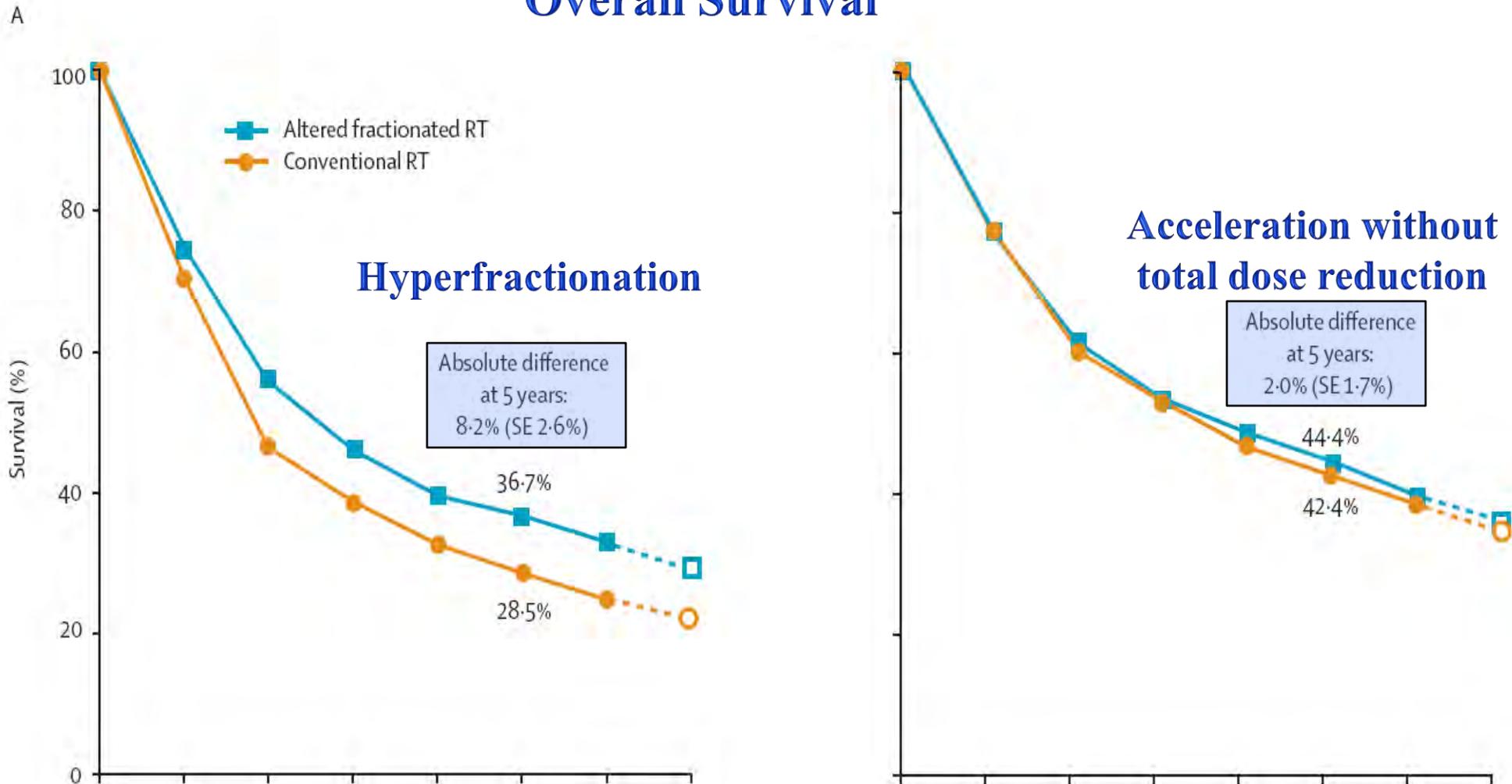
MARCH Meta-Analysis of Hyperfractionated or Accelerated Radiotherapy in H&N Cancer



Bourhis et al., Lancet 368, 2006

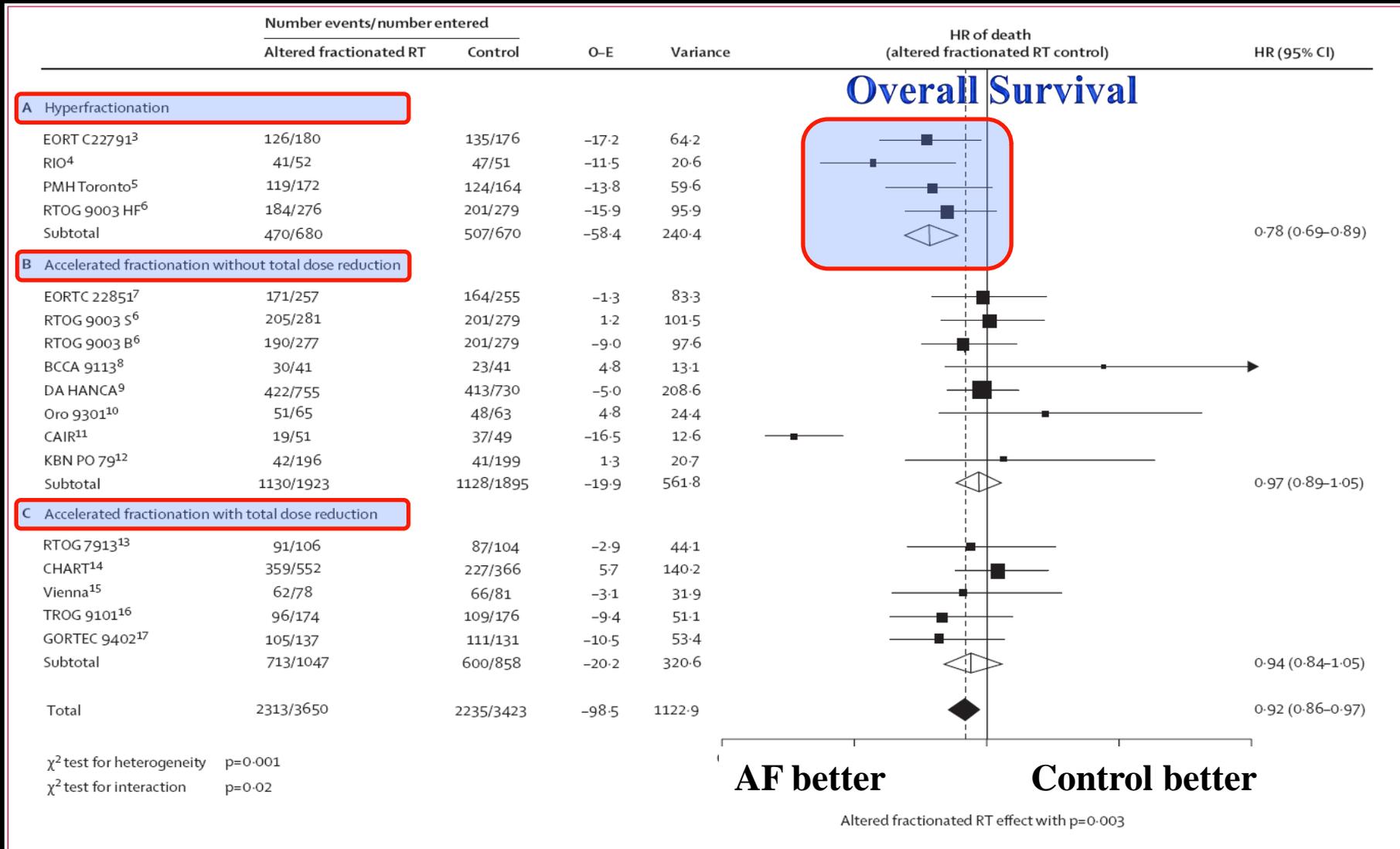
MARCH Meta-Analysis of Hyperfractionated or Accelerated Radiotherapy in H&N Cancer

Overall Survival



Bourhis et al., Lancet 368, 2006

MARCH Meta-Analysis of Hyperfractionated or Accelerated Radiotherapy in H&N Cancer



Bourhis et al., Lancet 368, 2006

The Use of Altered Fractionation in H&N Cancer

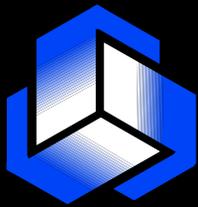
- Take Home Message -

- The Meta-Analyses shown here provide strong evidence that altered fractionated radiotherapy can improve survival in head and neck cancer.
- The survival benefit was mainly seen in the group with increased total dose and unchanged OTT (i.e. HF!), and corresponded to an absolute benefit of 8% at 5 years in this group.
- This benefit is of the same magnitude as the effect of concurrent chemoradiotherapy in head and neck cancer (MACH-NC Meta-Analysis).

Treatment of Locally Advanced Head and Neck Cancer

Neoadjuvant CTX in LAD:

- What are the evidences for neoadjuvant CTX followed by RTX/CRT?
- Are there evidences for competitive (different) regimes, e.g. targeted therapies?

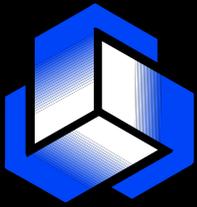


EORTC 24971 / TAX 323

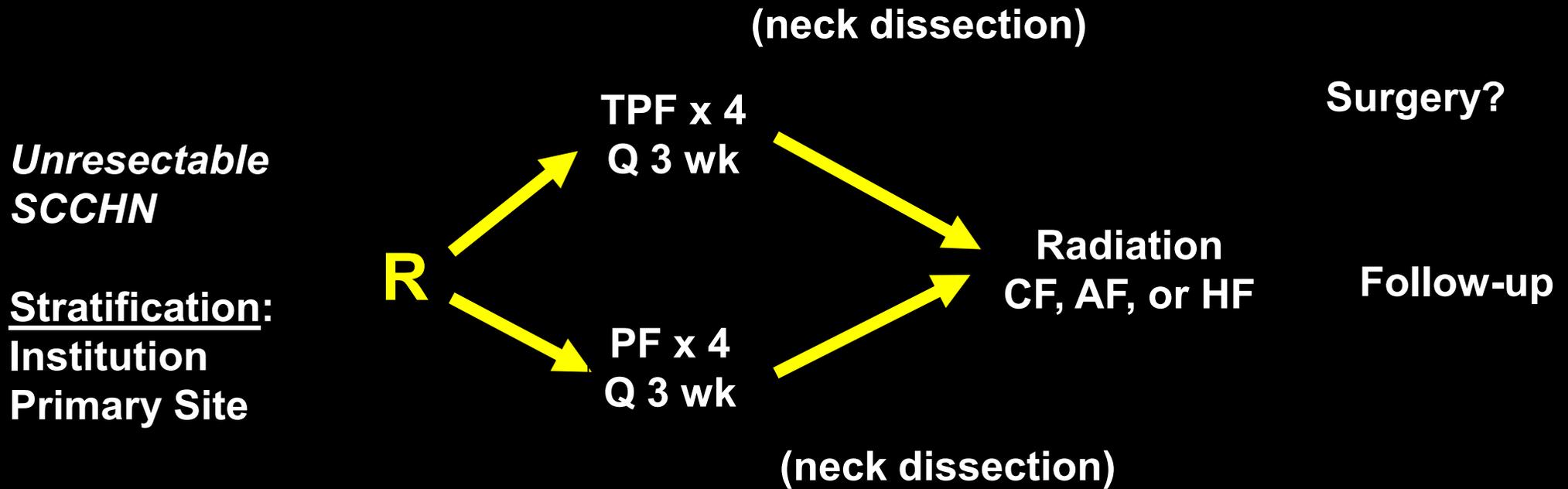
A randomized phase III multicenter trial of neoadjuvant Docetaxel (Taxotere®) plus Cisplatin plus 5-Fluorouracil versus neoadjuvant Cisplatin plus 5-Fluorouracil in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN)

J. B. Vermorken, E. Remenar, C. Van Herpen,
J. Germa Lluch, S. Stewart, T. Gorlia,
M. Degardin, K. Schollen, J. Bernier
for the EORTC Head and Neck Cancer Group

J Vermorken et al, NEJM 357, 2007



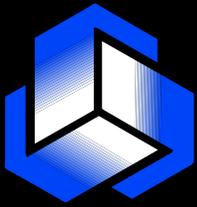
Study Design



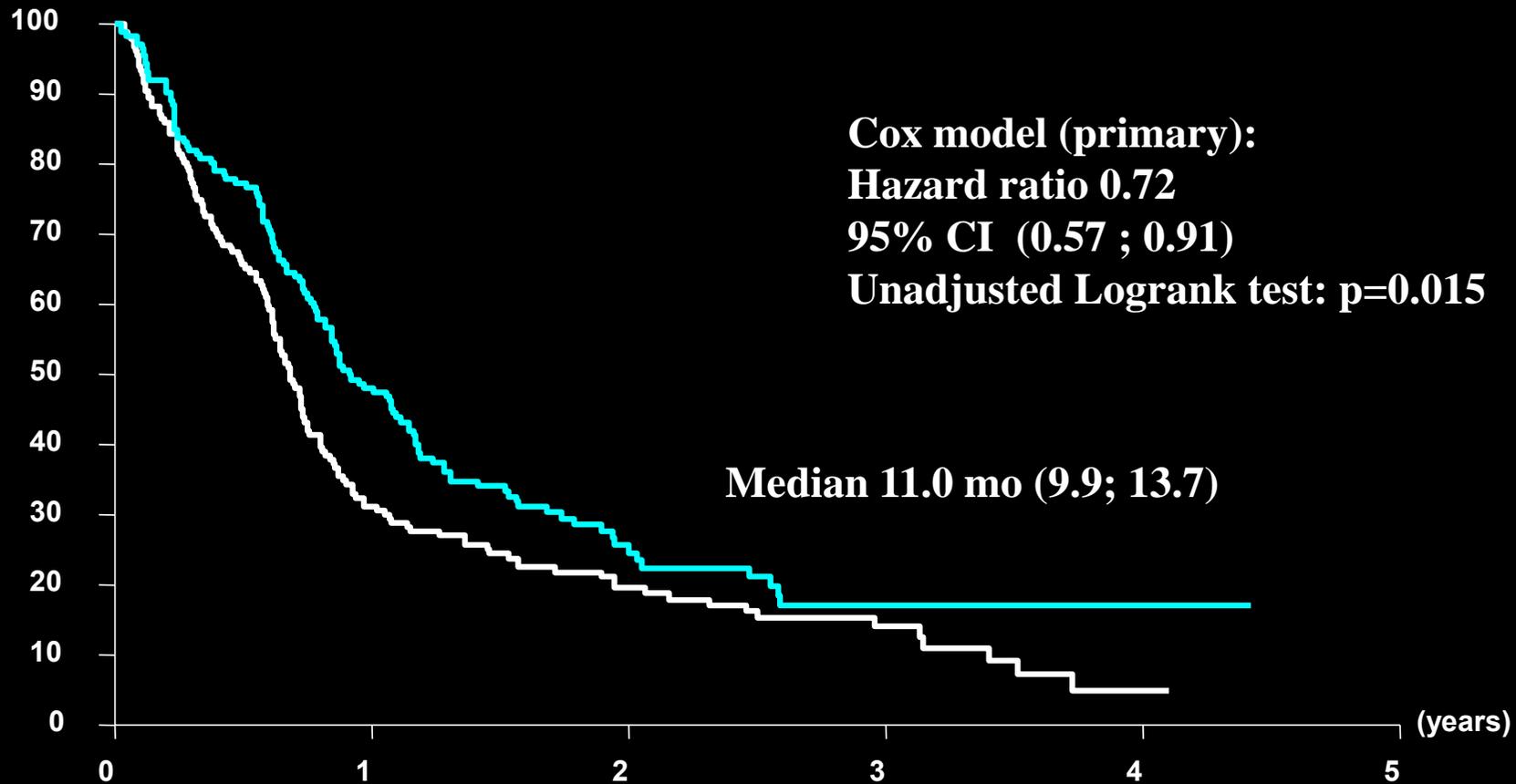
Planned Sample Size: 348 pts

Number of events: 260 progression events needed to show 50% increase in PFS (10 to 15 months; Hazard ratio 0.67)

J Vermorken et al, NEJM 357, 2007



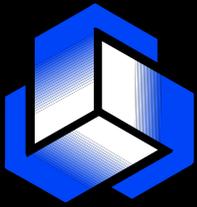
Progression Free Survival



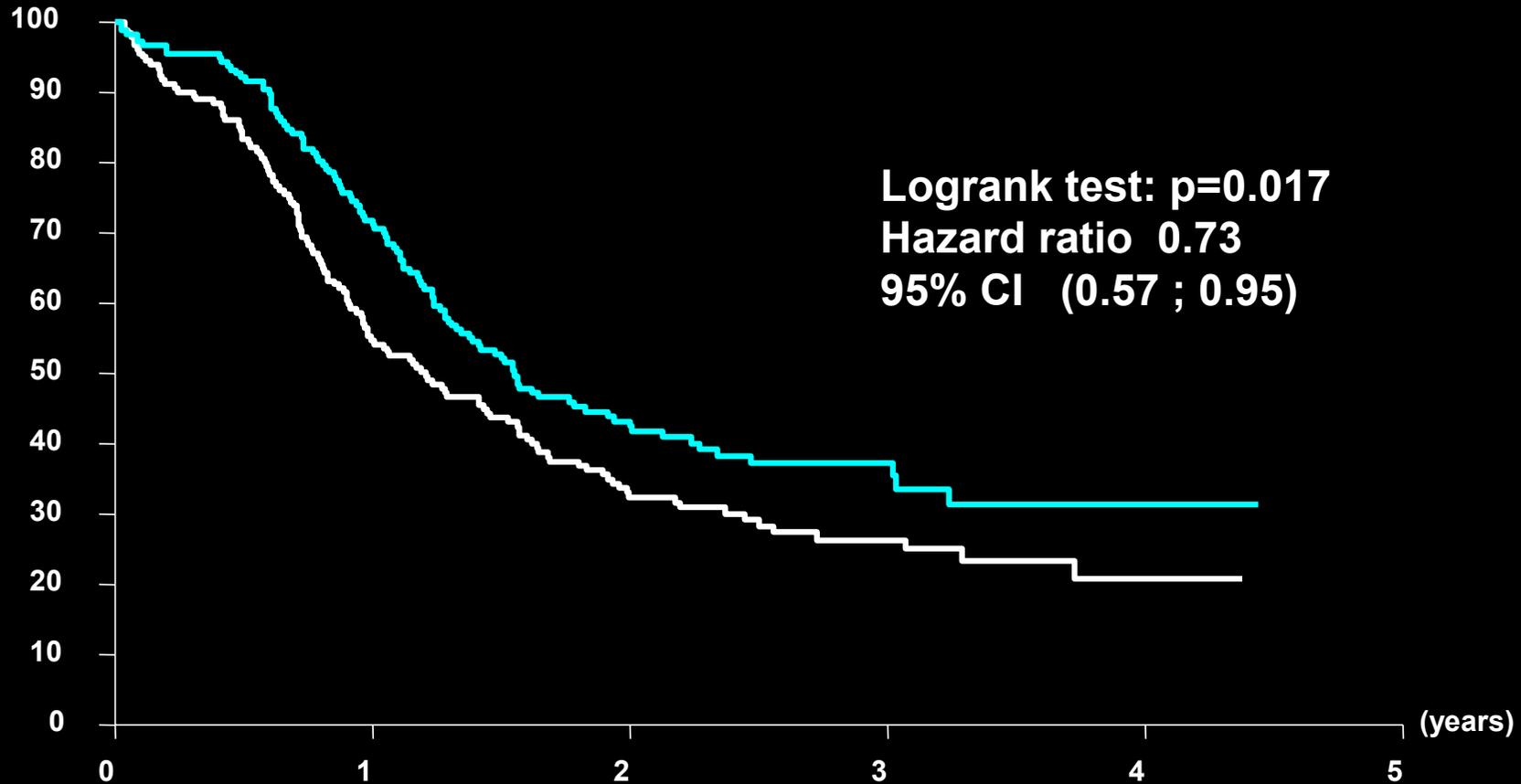
O	N	Number of patients at risk :				Randomized Treatment	
147	181	52	25	11	1	— PF	
126	177	79	23	5	1	— TPF	

J Vermorken et al, NEJM 357, 2007

V. Budach – 7th ICHNC 2008



Overall Survival



O	N	Number of patients at risk :				Randomized Treatment	
128	181	97	49	20	4	—	PF
108	177	127	57	21	1	—	TPF

J Vermorken et al, NEJM 357, 2007

V. Budach – 7th ICHNC 2008



Conclusion

- TPF (→ RT) is superior to PF (→ RT) in terms of response rate, progression free survival (primary endpoint) and overall survival and is better tolerated
- The survival data with TPF in this randomised phase III trial are similar to those seen in the phase I-II feasibility study
- The outcome of this study suggests that the role of neoadjuvant chemotherapy in head and neck cancer should be revisited

Treatment of Locally Advanced Head and Neck Cancer

TAX 324: A Phase III Trial of TPF vs PF Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced SCCHN

MR Posner, D Hershock, L Le Lann,
PM Devlin, RI Haddad
for the TAX 324 Study Group

M Posner et al, NEJM 357, 2007

Treatment of Locally Advanced Head and Neck Cancer

TAX 324: Sequential Combined Modality Therapy TPF vs PF Followed by Chemoradiotherapy



TPF: Docetaxel 75_{D1} + Cisplatin 100_{D1} + 5-FU 1000_{CI-D14} Q 3 weeks x3

PF: Cisplatin 100_{D1} + 5-FU 1000_{CI-D15} Q 3 weeks x3

M Posner et al, NEJM 357, 2007

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Treatment of Locally Advanced Head and Neck Cancer

TAX324: Analysis Populations

	TPF	PF	ALL
All Randomized	280	259	539
INTENT TO TREAT Population*	255	246	501
Treated With Chemotherapy	251 (98%)	243 (99%)	494 (98.6%)

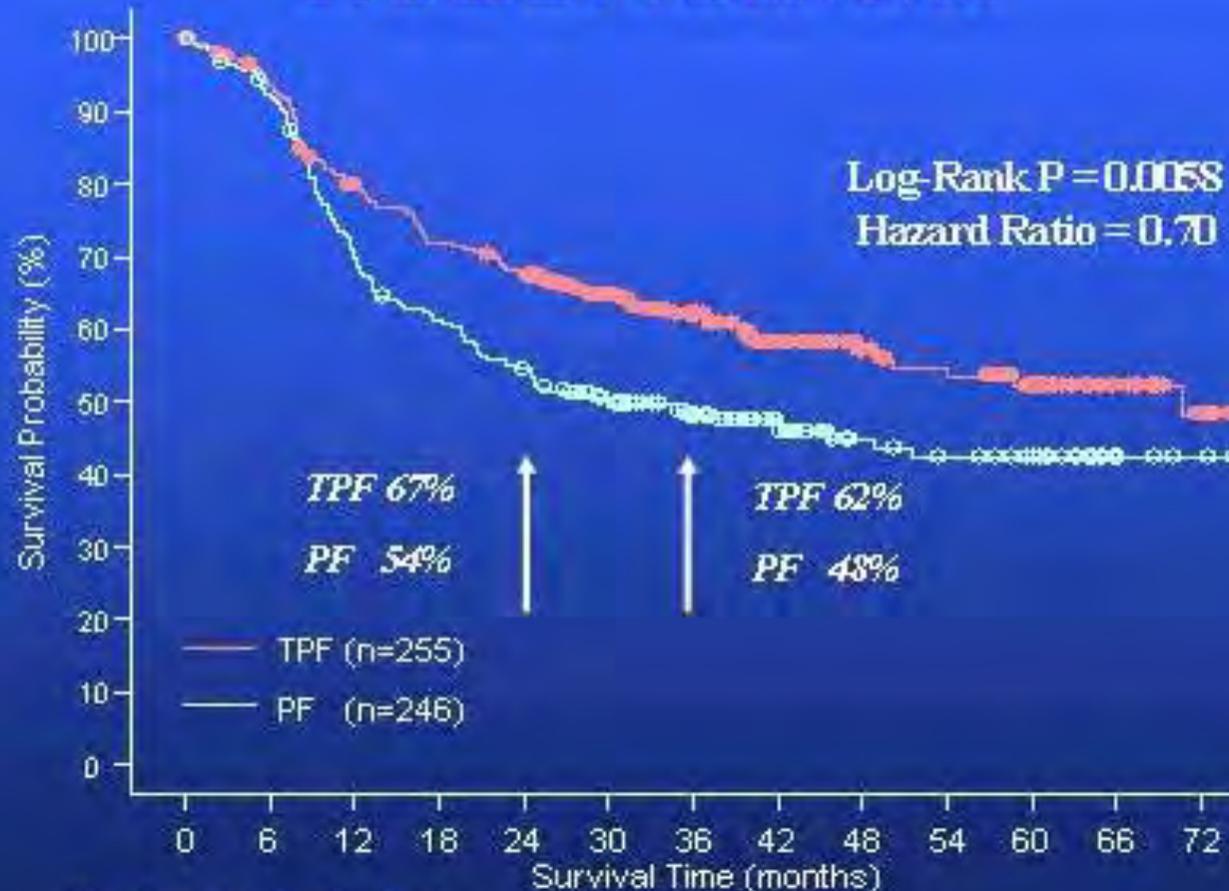
	TPF (N=251)	PF (N=243)	ALL (N=494)
SAFETY Population			
Chemotherapy Treated	251 (100%)	243 (100%)	494 (100%)
Receiving Chemoradiotherapy per Protocol	202 (81%)	184 (76%)	386 (78%)
Not Receiving Chemoradiotherapy per Protocol	49 (19%)	59 (24%)	108 (22%)

* ITT excludes 37 patients were erroneously randomized and 1 patient with GCP compliance issue

M Posner et al, NEJM 357, 2007

Treatment of Locally Advanced Head and Neck Cancer

TAX324 : Survival



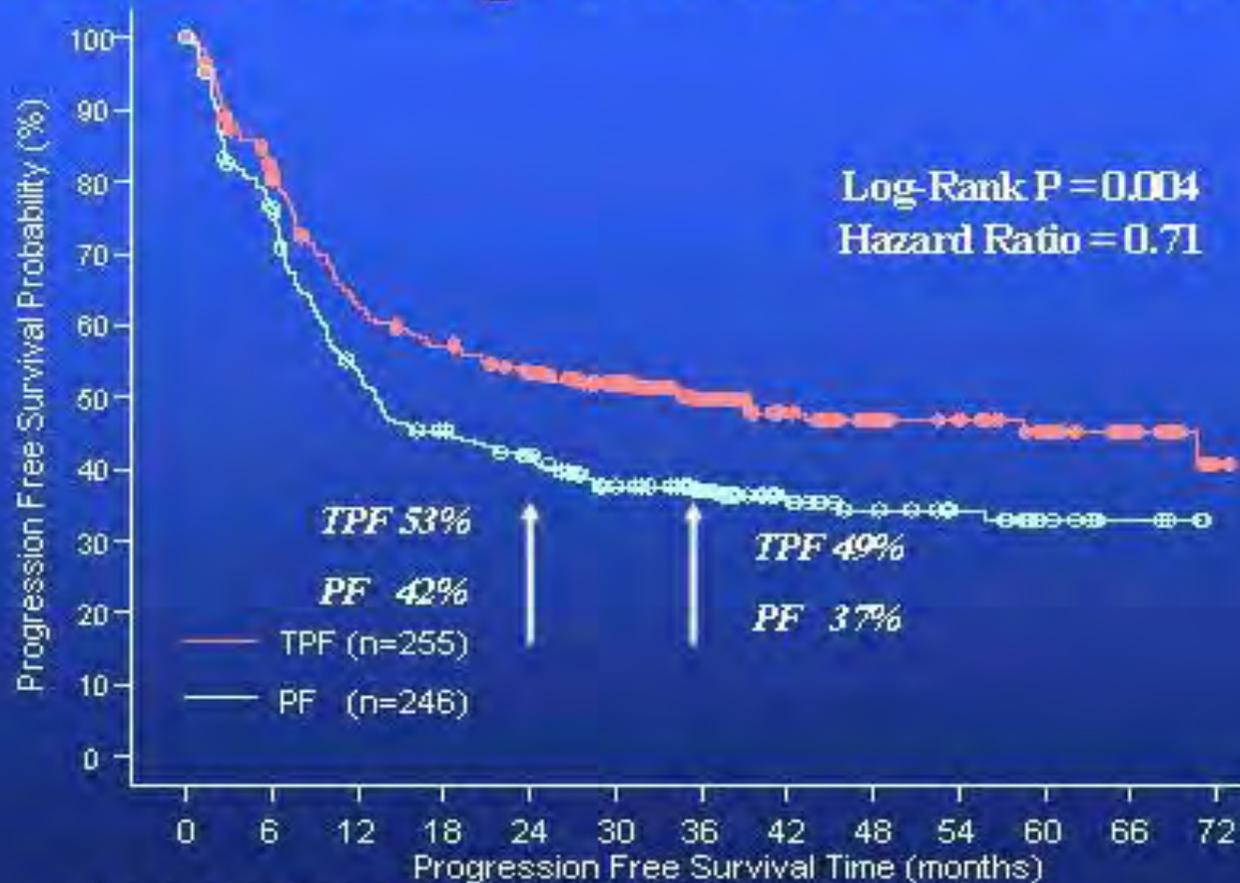
Number of patients at risk

TPF: 255	234	196	176	163	136	105	72	52	45	37	20	11
PF: 246	223	169	146	130	107	85	57	36	32	28	10	7

M Posner et al, NEJM 357, 2007

Treatment of Locally Advanced Head and Neck Cancer

TAX324 : Progression Free Survival



Number of patients at risk													
	0	6	12	18	24	30	36	42	48	54	60	66	72
TPF: 255	198	150	135	121	100	73	50	39	35	26	16	5	
PF: 246	183	125	104	92	72	57	38	30	25	14	8	2	

M Posner et al, NEJM 357, 2007

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Treatment of Locally Advanced Head and Neck Cancer

TAX 324: Conclusions

- TPF Significantly Improves Survival Compared To PF
 - There is a 14% Absolute Improvement in 3-Year Survival and a 30% Reduction in Mortality ($P=0.0058$) for TPF
 - 62% of TPF Patients are Alive at 3-Years
- Sequential Therapy With TPF is Tolerable and Safe
 - The Toxicity of TPF is Arguably Less Than That of PF
- Sequential Therapy with TPF Followed by Carboplatinum-Based Chemoradiotherapy Represents a New, Acceptable Standard of Care for Locally Advanced SCCHN
 - Sequential Therapy Makes Biological Sense and is Effective
 - Ongoing Phase III Trials Will Determine How TPF-Based Sequential Therapy Compares to Chemoradiotherapy

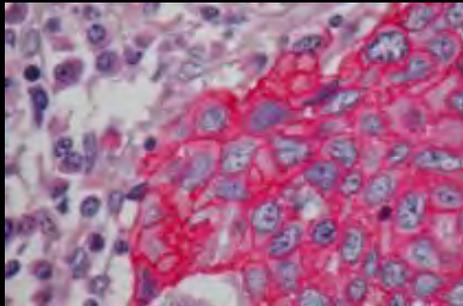
M Posner et al, NEJM 357, 2007

Treatment of Locally Advanced Head and Neck Cancer

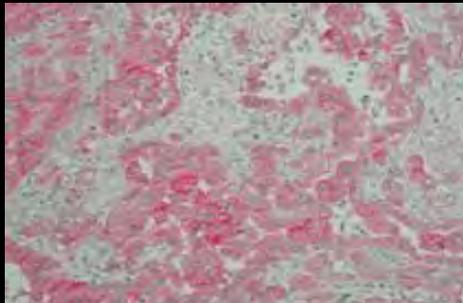
Questions:

- What are the evidences for targeted therapies in head and neck cancer?

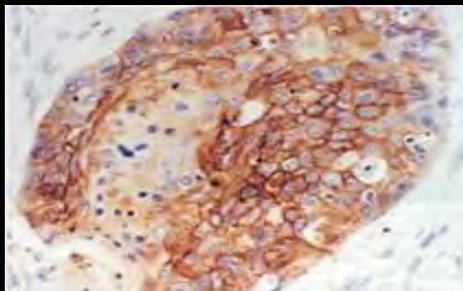
EGFR expression in human tumors



Head and neck



**Lung
(NSCLC)**



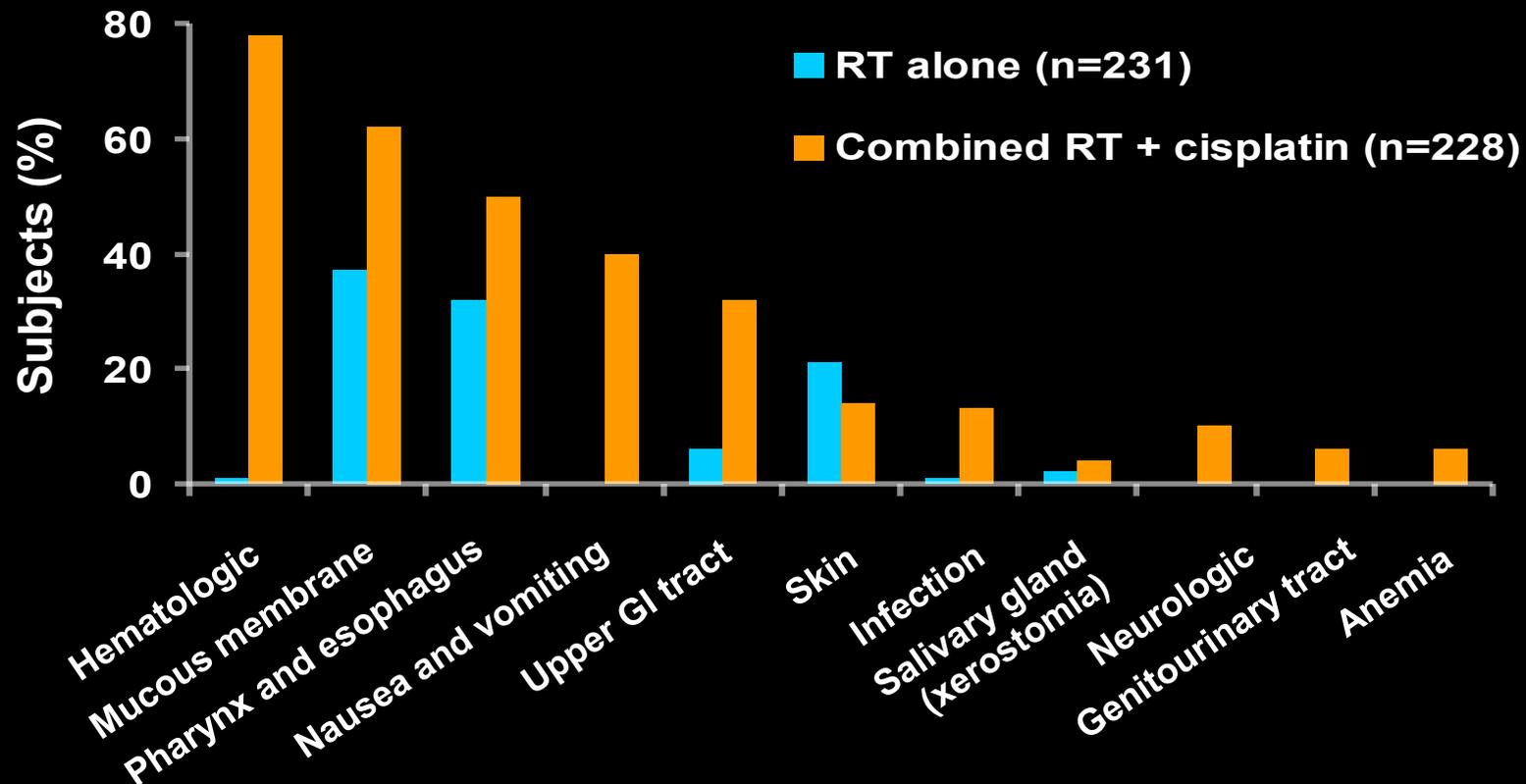
Colorectal

Type of tumor	Tumors with EGFR expression
Head and neck	90–100%
Colon	75–89%
Pancreas	Up to 95%
Breast	Up to 91%
Renal	Up to 90%
NSCLC	Up to 80%
Ovary	Up to 77%
Bladder	Up to 72%
Glioma	Up to 63%

Combined RT + CT results in significant increases in acute toxicity

Acute adverse effects: grade 3 or higher

77% with combined RT + CT vs 34% with RT alone (p<0.001)



Post-operative setting

Cooper JS, et al. *N Engl J Med* 2004;350:1937–1944

Study design

Stratify by:

- Karnofsky score:
90–100 vs 60–80
- Regional nodes:
negative vs positive
- Tumor stage:
AJCC T1–3 vs T4
- RT fractionation:
Concomitant boost
Once daily
Twice daily

R
A
N
D
O
M
I
Z
E

Arm 1 (RT)

Radiation therapy

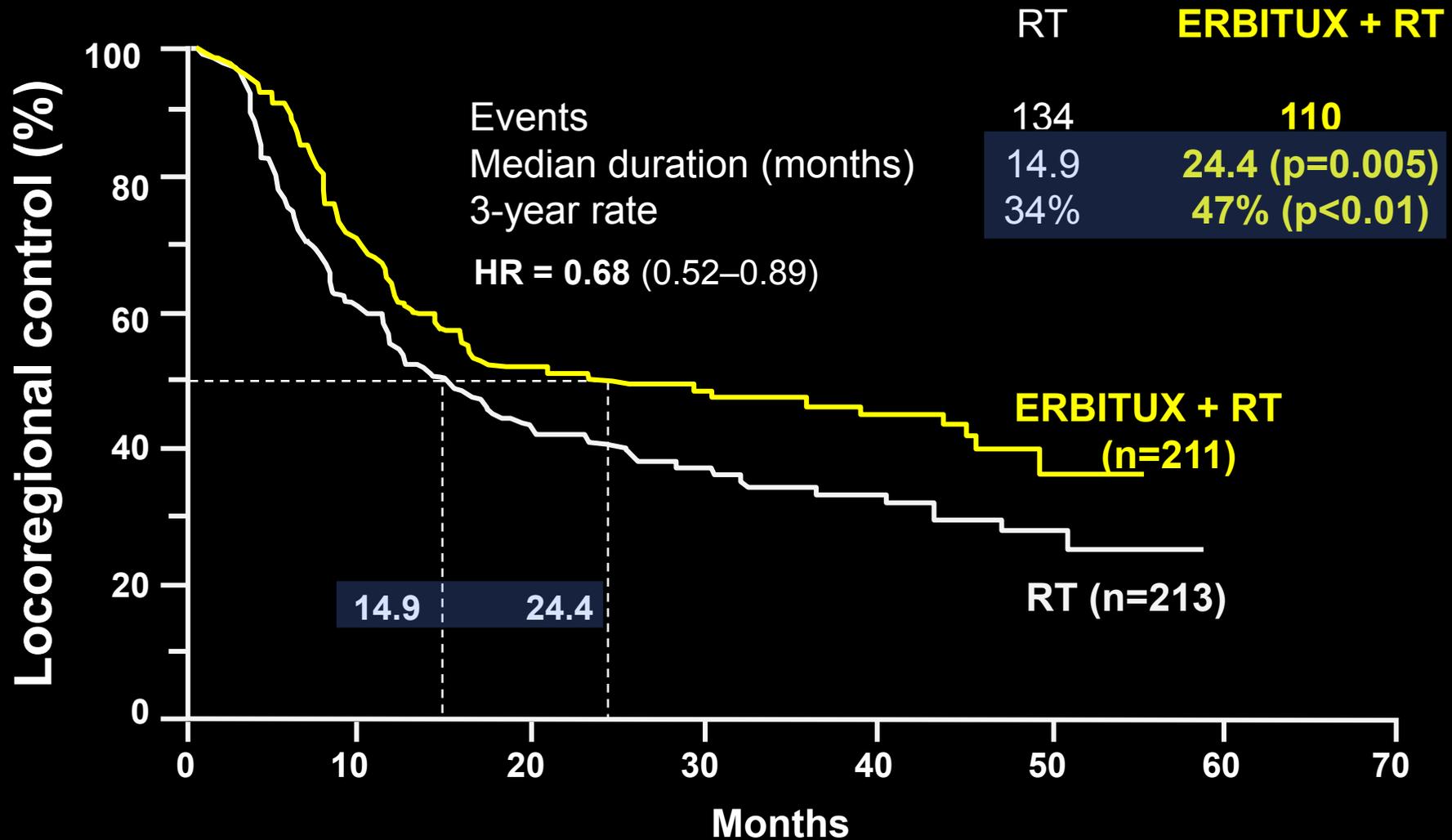
424 patients randomized

Arm 2 (ERBITUX + RT)

Radiation therapy +
ERBITUX, weekly

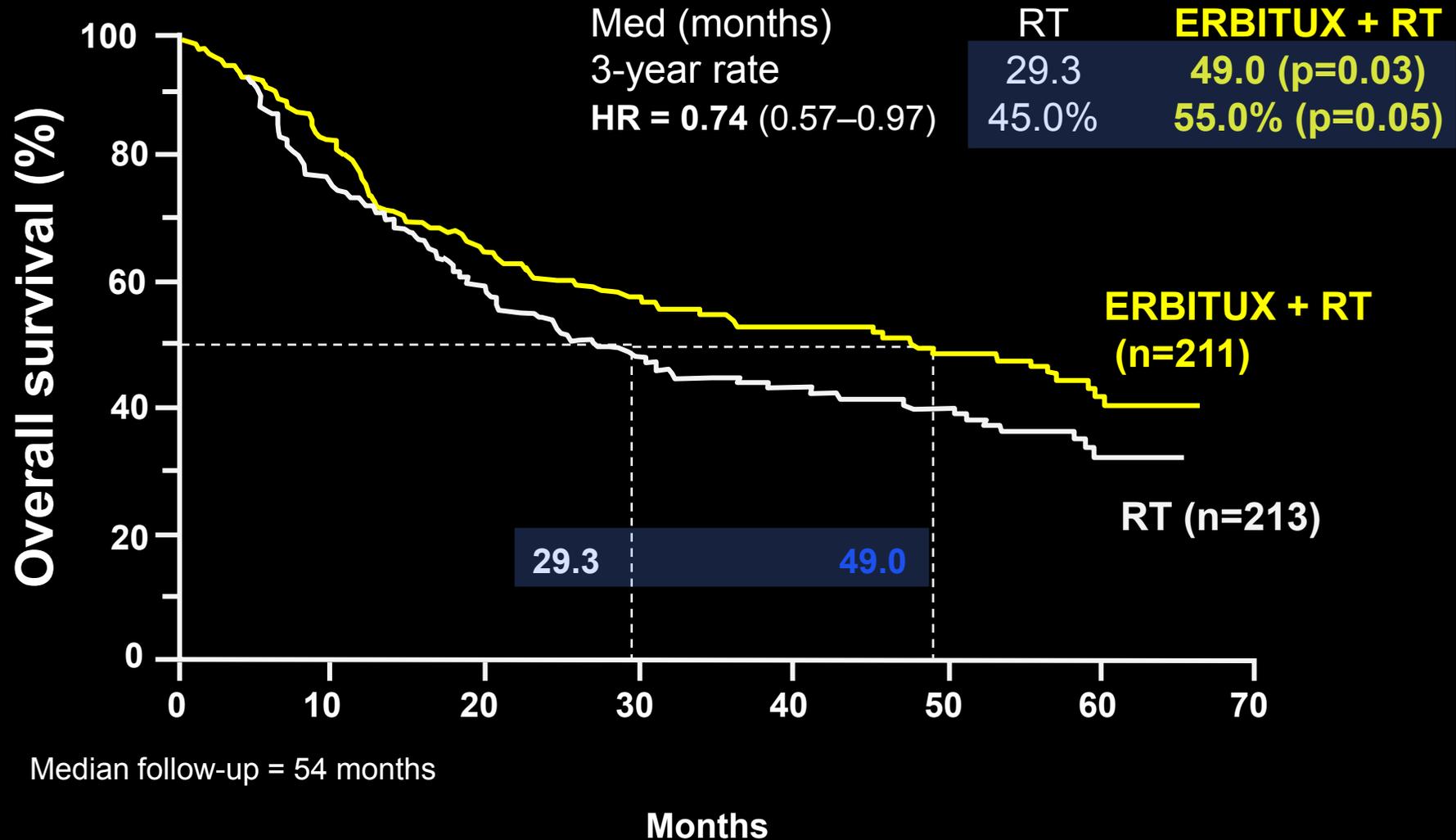
Bonner J, Harari P, Giralt J, et al. N Engl J Med 2006;354:567–578

Locoregional control (primary endpoint)



Bonner J, Harari P, Giralt J, et al. *N Engl J Med* 2006;354:567-578

Overall survival



Bonner J, Harari P, Giralt J, et al. *N Engl J Med* 2006;354:567–578

ERBITUX + RT study conclusions

The addition of ERBITUX to high-dose radiation in locoregionally advanced SCCHN resulted in:

Statistically significant improvement in

- **Locoregional control**
- **Overall survival**

Minimal additive skin toxicity, with no additional effect on mucositis and delay in radiotherapy

Bonner J, Harari P, Giralt J, et al. N Engl J Med 2006;354:567–578

Treatment of Locally Advanced Head and Neck Cancer

Take Home Message - 1

Cisplatinum-based concurrent CRT leading to a survival benefit of about 8% (11% DDP) @5 years is considered the „Standard of Care“ for inoperable LAD of the Oro- and Hypopharynx!

➤ **LOE: Ia and Ib/IIa, STANDARD of CARE!**

Treatment of Locally Advanced Head and Neck Cancer

Take Home Message - 2

For comorbid patients not fit for a DDP-based CRTX,
altered fractionated radiotherapy (AFX/HFX)
offering a survival benefit of 8% @ 5 yrs., Cetuximab-
RTX or concurrent RTX + MMC/5-FU is advised in
inoperable LAD of the Oro- and Hypopharynx!

➤ **LOE: Ia and Ib, STANDARD of CARE!**

Treatment of Locally Advanced Head and Neck Cancer

Take Home Message - 3

Recent phase III trials and subgroup meta-analyses indicate neoadjuvant TPF followed by RTX or CRTX also to be an valid option within clinical controlled trials or on individual patient's decision!

➤ **LOE: Ib and IIa, NOT STANDARD of CARE!**