Estado da arte no tratamento do cancro de cabeça e pescoço

Update

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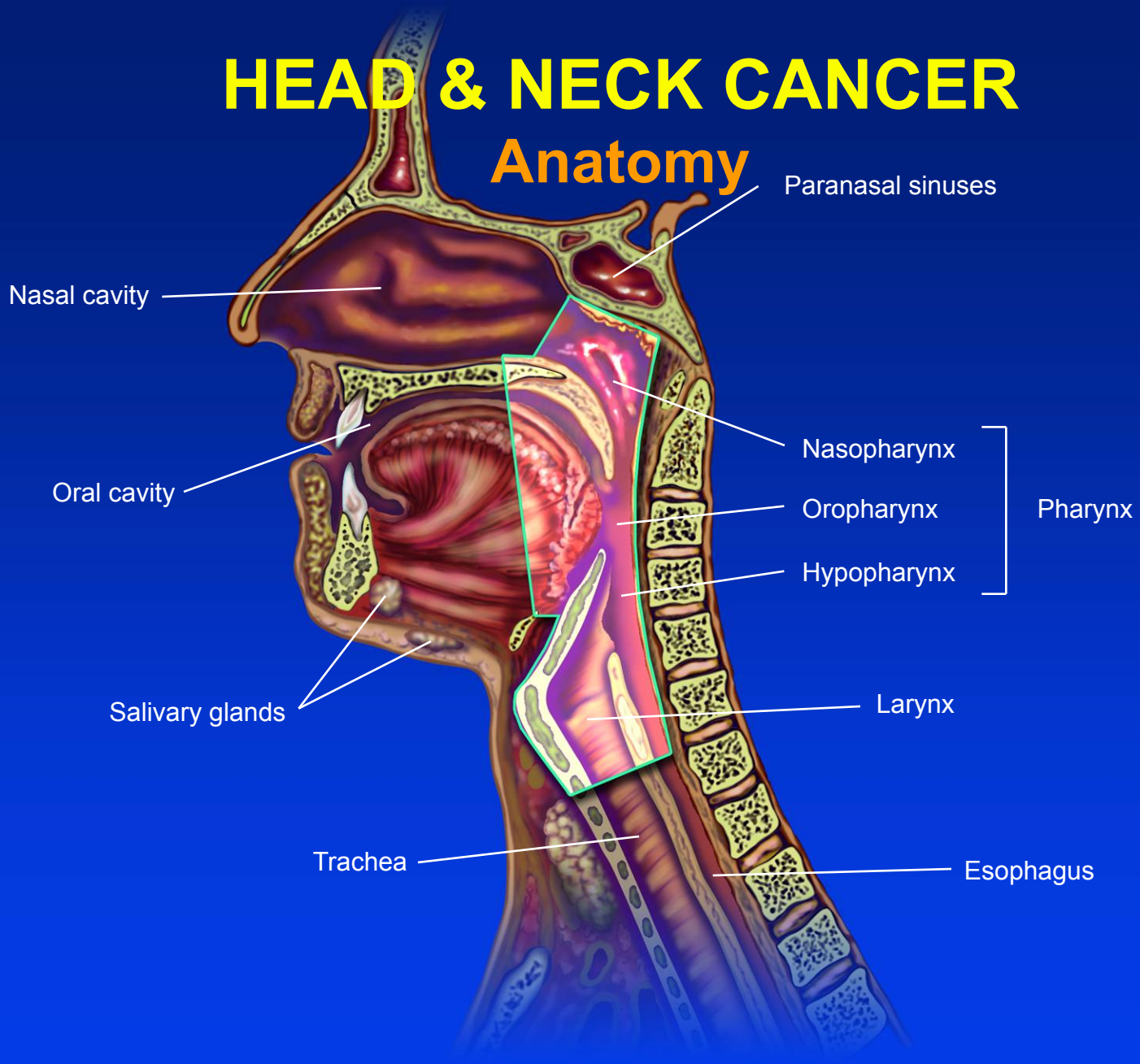
Agradecimento

Professor Doutor Jan Vermorken pela cedência dos slides

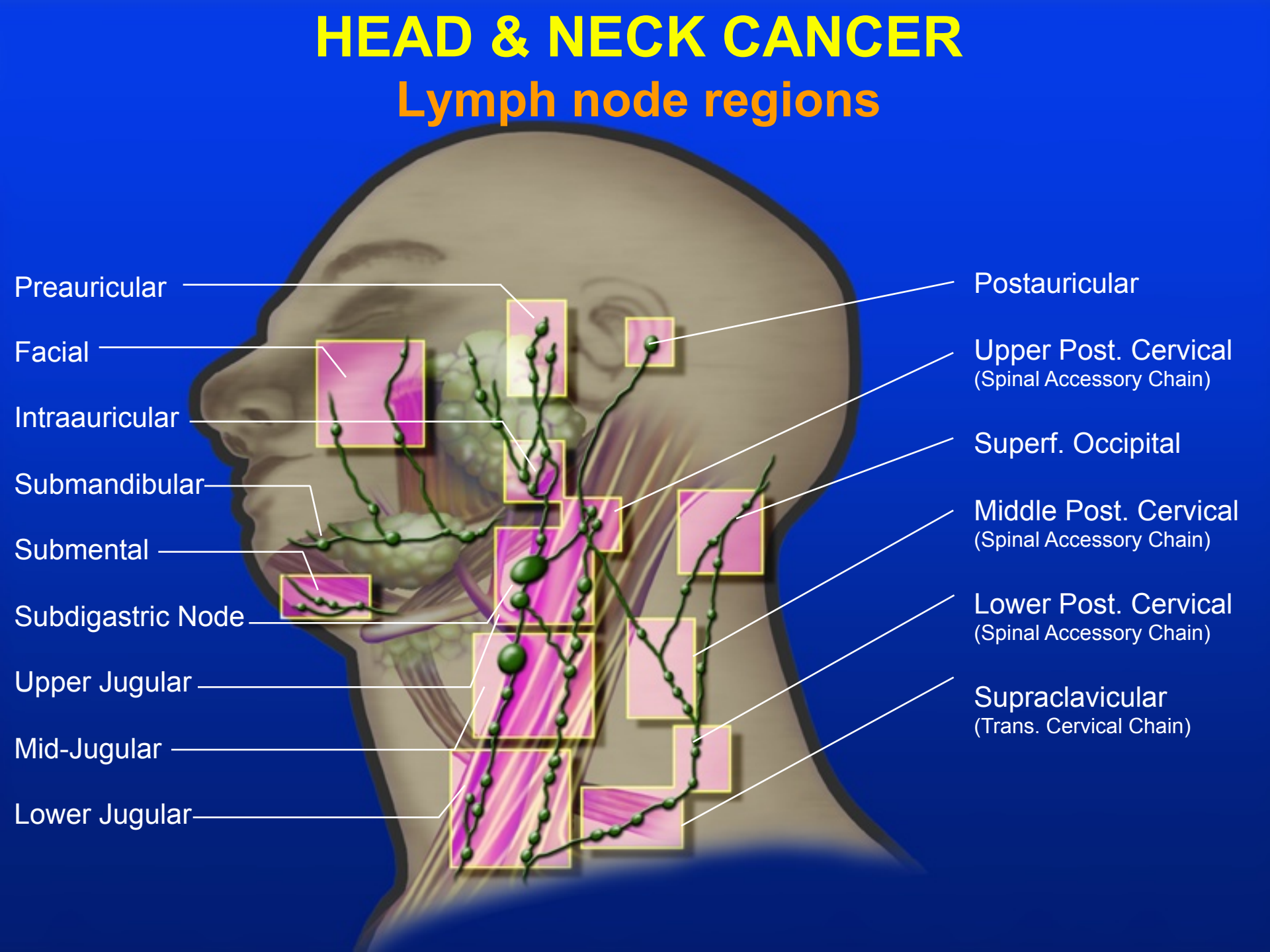
HEAD & NECK CANCER

Anatomy



HEAD & NECK CANCER

Lymph node regions



Head and Neck Cancer (HNC)
Malignant Tumors

Squamous cell carcinoma (SCC)

- Most common primary cancer (> 90%)
- Differentiation (well-moderate-poor) based on keratinization

Other carcinomas

- Adenocarcinoma
- Mucoepidermoid carcinoma
- Lymphoepithelioma

Lymphomas

- Non-Hodgkin's
- Hodgkin

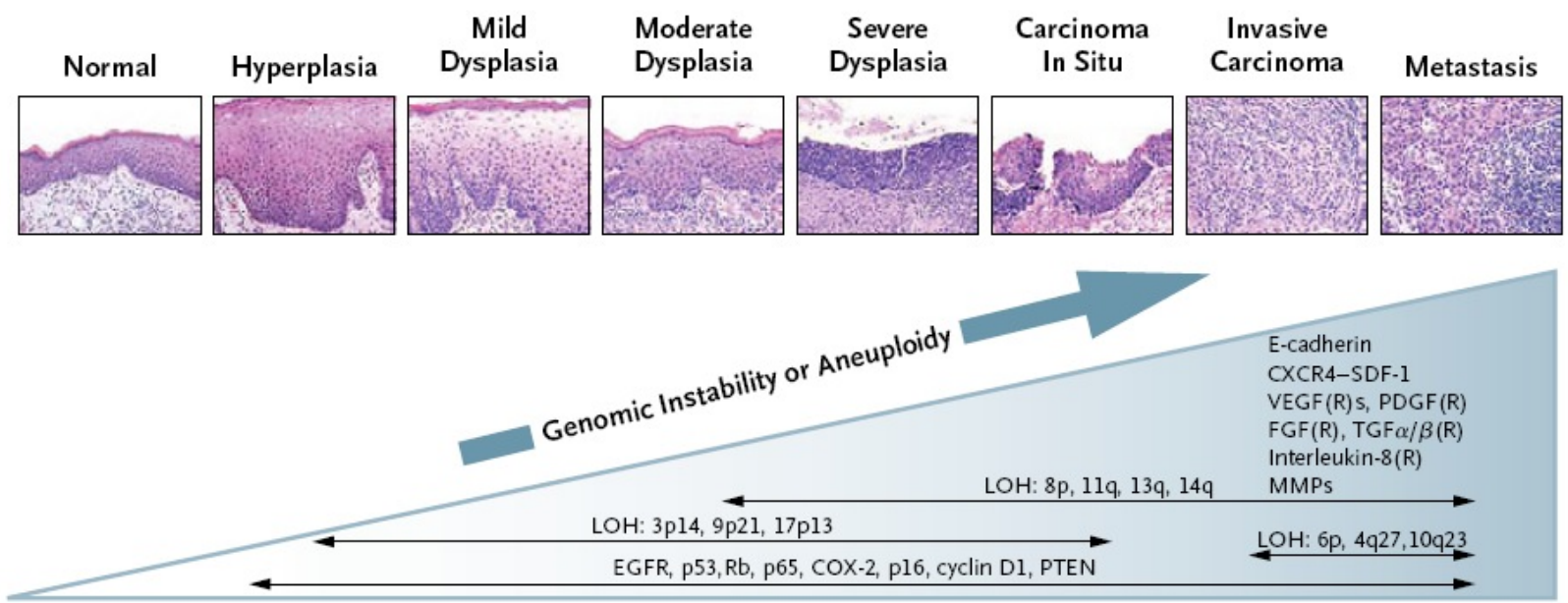
Sarcomas

Metastatic cancers

- Lung
- GI tract
- Breast

Head and Neck Cancer

Models of Genetic Instability and Progression in Head and Neck Cancer



From Haddad RI, Shin DM. N Engl J Med 2008; 359: 1143-54

Head and Neck Cancer
Epidemiology and clinical presentation

- 5-6% of all cancers (about 650.000 new cases/year)
- > 90% squamous cell origin (Western world)
- Risk factors:
  - tobacco smoking
  - alcohol use
  - betel chewing
  - HPV
  - poor oral health
  - mechanical irritation
  - occupational exposure
  - malnutrition
- Localized disease 40%, regional mets 50% distant mets 10%
- 2/3 locally/regionally advanced
- Major threat: local recurrence, SPT, SFT

Head and Neck Cancer
Typical symptoms by site

Site of origin	Early Symptoms
Nasopharynx	Hearing loss, tinnitus, epistaxis nasal obstruction, single lymph node (LN)
Oral cavity	Superficial mucosal pain, denture malposition, mouth bleeding
Glottic larynx	Hoarseness (glottic)
Supraglottis/oropharynx Hypopharynx	Dysphagia or otalgia (supraglottic)

O'Sullivan et al, 1999

Work-up in SCCHN

- Physical examination
- Endoscopical evaluation (EUA)*
- Biopsy of the primary lesion
- FNA in case of a suspected lymph node
- Imaging techniques (CT, MRI, PET)
- Careful dental evaluation recommended

NB. Open biopsies of neck masses are reserved if all clinical and radiological studies cannot reveal the primary tumor

EUA= examination under anesthesia

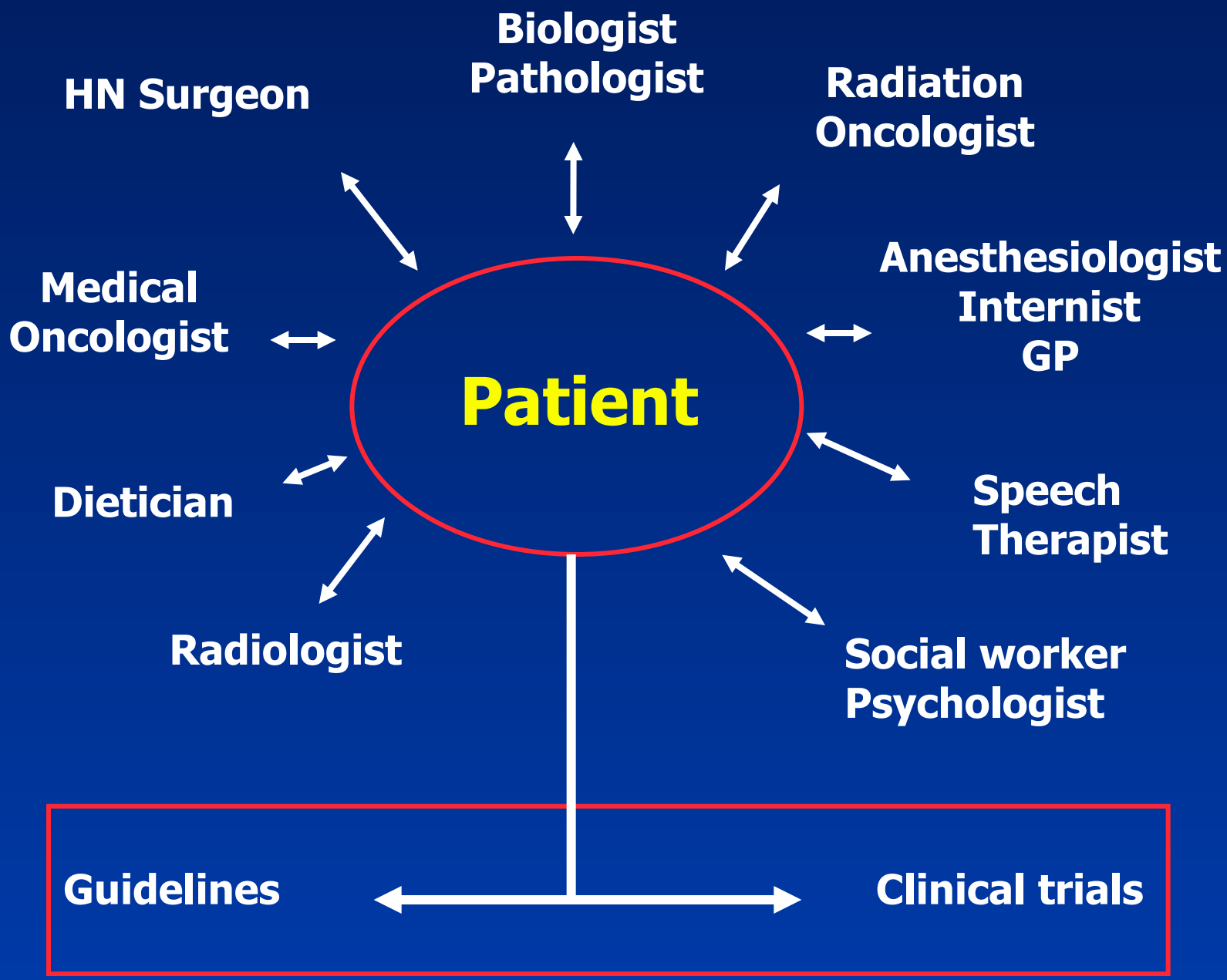
TNM Staging

<table>
<tr><th></th><th>N0</th><th>N1</th><th>N2</th><th>N3</th></tr>
<tr><td>T1</td><td>I</td><td rowspan="3">III</td><td colspan="2" rowspan="3">IVa[3], b[4], c[5]</td></tr>
<tr><td>T2</td><td>II</td></tr>
<tr><td>T3</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>T4a[1]
T4b[2]</td><td colspan="3"></td></tr>
</table>

[1] resectable; [2] unresectable; [3] advanced resectable; [4] advanced unresectable; [5] distant metastatic

Diagnosis and Staging Procedures
Conclusions

- Being aware of risk factors (e.g. tobacco, alcohol, HPV) and early signs a/o symptoms of crucial importance for early diagnosis
- Clinical and endoscopical evaluations play the most important role in the diagnostic work-up of SCCHN
- Imaging techniques very useful in refining the extent of the disease
- Accurate staging very important for decision making
- Open biopsies of neck masses only when all clinical and radiological studies cannot reveal the primary tumor.
-

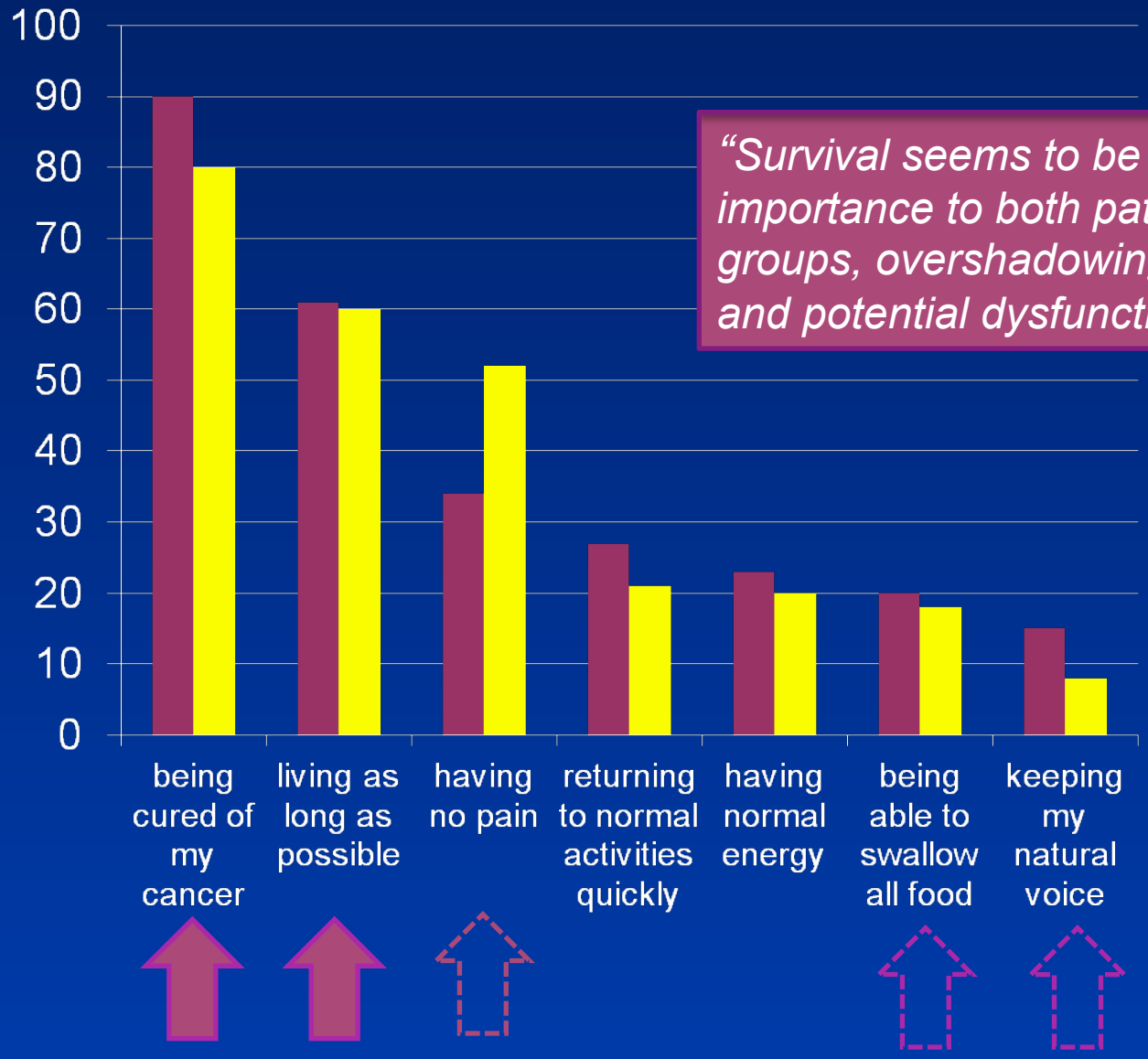

Biologist
Pathologist
HN Surgeon
Radiation
Oncologist
Medical
Oncologist
Anesthesiologist
Internist
GP
Patient
Dietician
Speech
Therapist
Radiologist
Social worker
Psychologist
Guidelines
Clinical trials

Considerations in Decision Making

- Disease factors (e.g. site, stage, biology [HPV, EGFR], specific risk factors for locoregional or distant relapse)
- Patient factors (e.g. age, sex, performance status, lifestyle habits, socio-economic status)
- Treatment factors (radiotherapy, chemotherapy, targeted therapy, surgery)[1]
- What do patients want?

[1]*Schantz SP et al. Cancer: Principles & Practice of Oncology, 6th ed. 2001; 797-860*

What do Patients Look For? Prioritizing Treatment Outcomes



"Survival seems to be of paramount importance to both patient and non patient groups, overshadowing associated toxicities and potential dysfunction"

List MA er al. Head Neck 2004;26:163-170

Treatment Modalities in SCCHN 2014

- Surgery
- Radiotherapy (RT)

} as single modality* or in combination

- Chemotherapy (CT)**
  - combined modality treatment (CMT):

    Induction CT (ICT); concomitant CT and RT (CCRT); sequential therapy (ICT → CCRT); adjuvant CT (ACT); postoperative CCRT
  - Palliative therapy

- **Targeted therapy (TT)****
  - **Alone or combined with RT, CMT or palliative CT**

** In early disease; ** in locoregionally advanced and recurrent/metastatic disease*

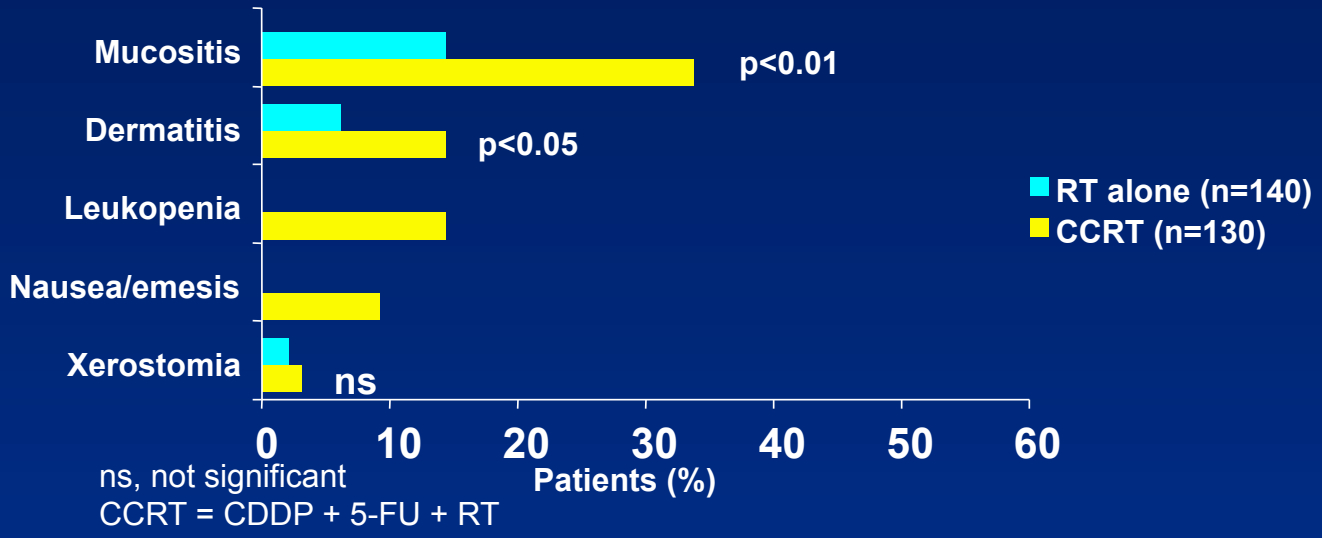
EHNS-ESMO-ESTRO Clinical Practice Guidelines 2010
Locoregionally advanced disease

	Level of evidence	Grade of recommendation
Surgery → RT or CCRT	**I**	**A**
Concomitant CT and RT*	**I**	**A**
Cetuximab plus RT	II	B
ICT → RT and CCRT for organ preservation	II	A
ICT → CCRT	investigational	

**in case of mutilating surgery and in nonresectable disease*

Gregoire V et al, Ann Oncol 2010: 21 (suppl 5): VI84-VI86

Acute adverse effects: Grade ≥3

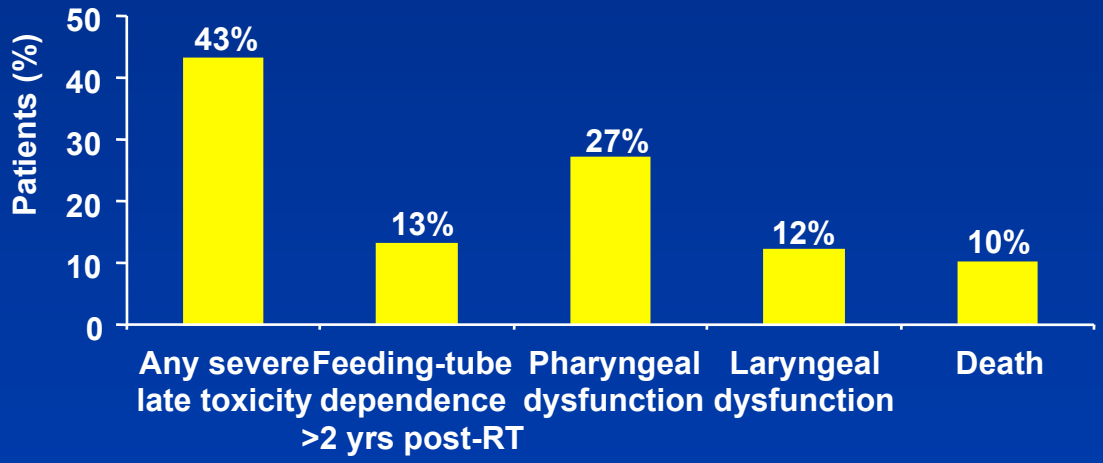


ns, not significant
CCRT = CDDP + 5-FU + RT

Wendt TG, et al. J Clin Oncol 1998;16:1318–1324

Late Toxicity

Analysis of 230 patients receiving CCRT in 3 studies (RTOG 91-11, 97-03, 99-14)



Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589

Methods to Reduce the Toxicity of Cisplatin-based CCRT in SCHN

Better ballistics

- CT – MRI – (PET)
- IGRT

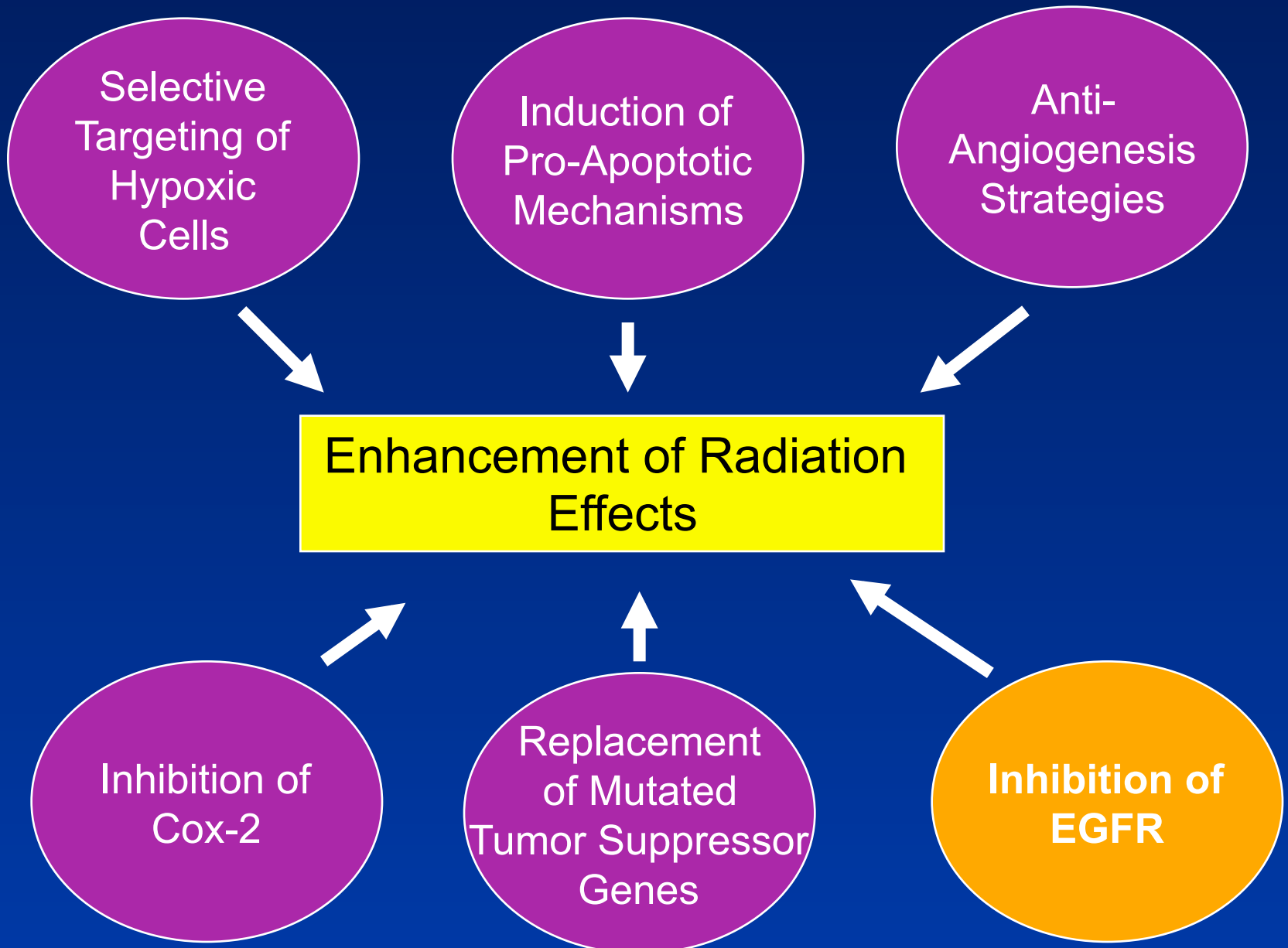
New radiotherapy techniques

- IMRT and SW-IMRT
- Stereotactic radiotherapy
- IMPT

RT sensitization with cytotoxics other than CDDP

RT sensitization with biological agents

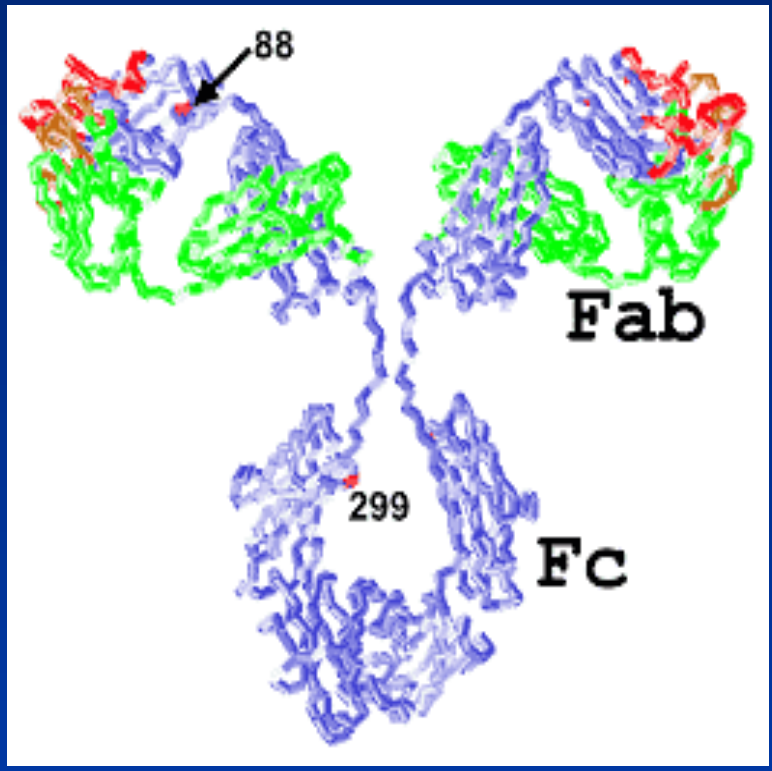
CT= computed tomography; MRI= magnetic resonance imaging; IGRT= image-guided RT; IMPT intensity-modulated particle therapy; IMRT= intensity-modulated RT; PET= positron emission tomography; RT= radiotherapy



Several biological mechanisms that have potential to alter sensitization strategies (Choy and MacRae, 2003)

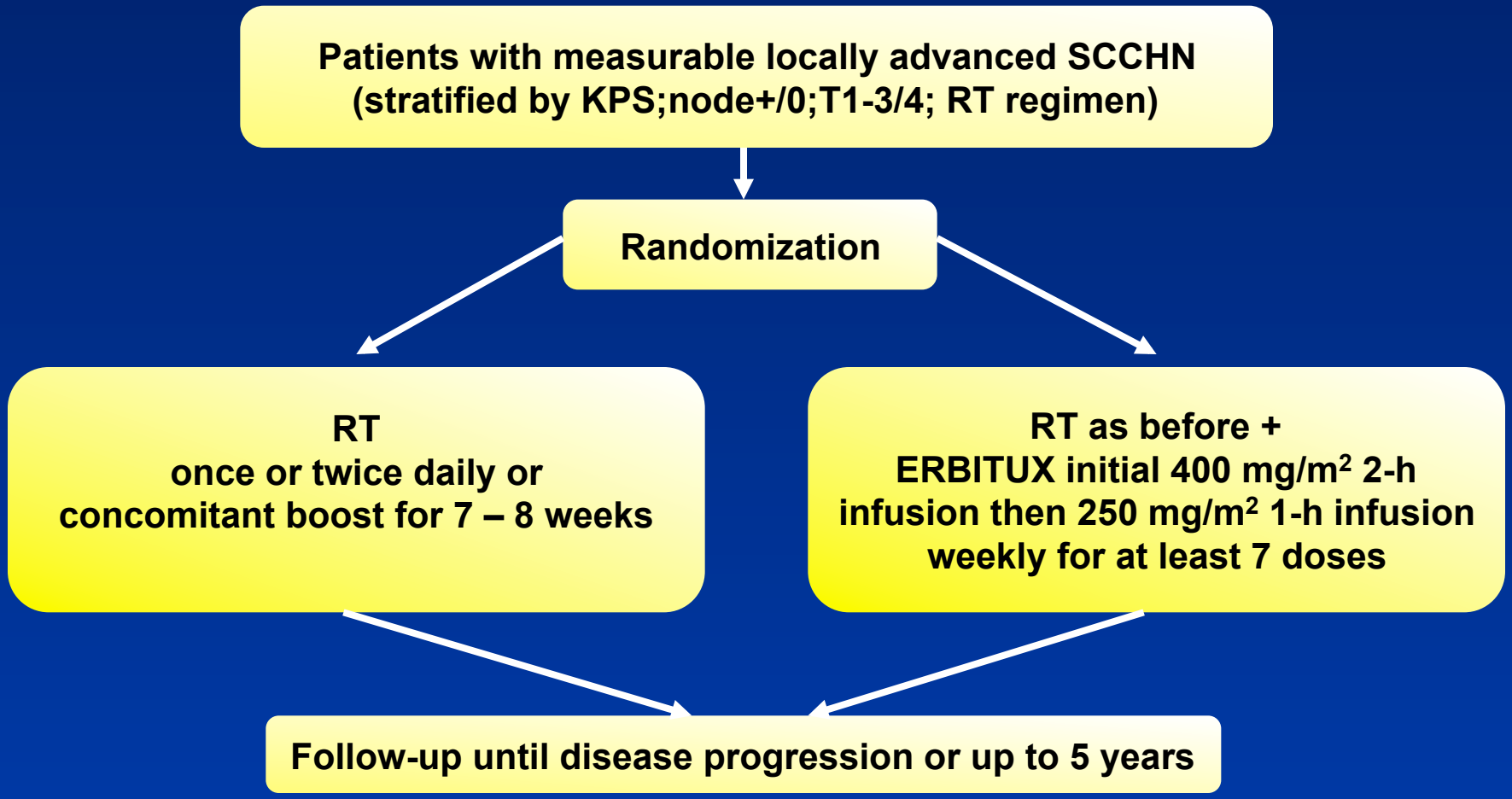
Cetuximab: Properties and Mechanism of Action

- IgG**1** monoclonal antibody
- Specifically binds to the EGFR with higher affinity than its natural ligands (TGFα, EGF), thus competitively inhibiting their binding
- High affinity: Kd = 0.39 nM
- Induces apoptosis and ADCC1
- Preclinical synergistic activity in combination with chemotherapy and radiotherapy



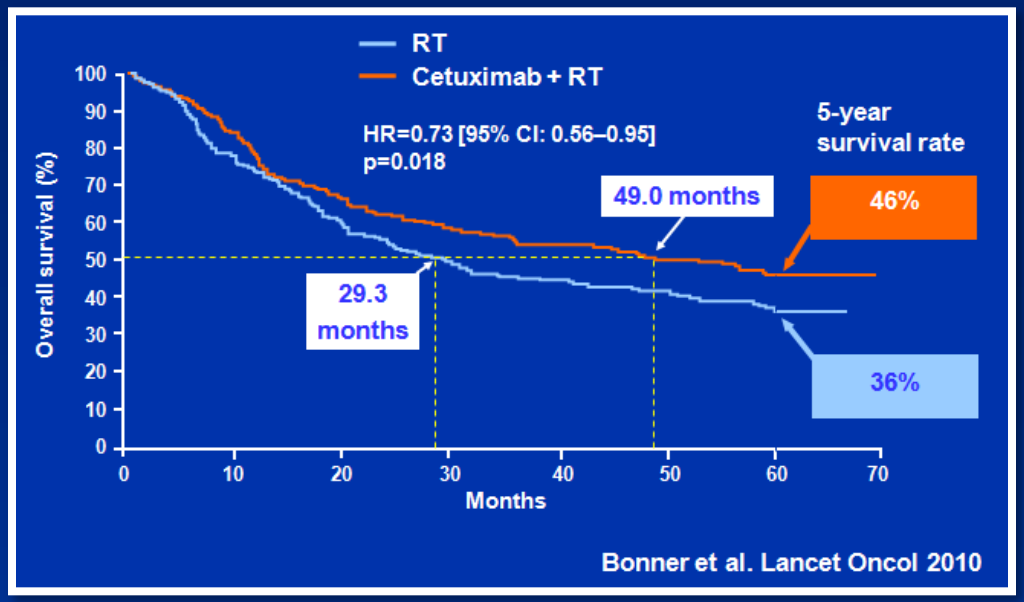
ADCC = antibody-dependent cellular cytotoxicity

Cetuximab + RT in locally advanced SCCHN: Study design



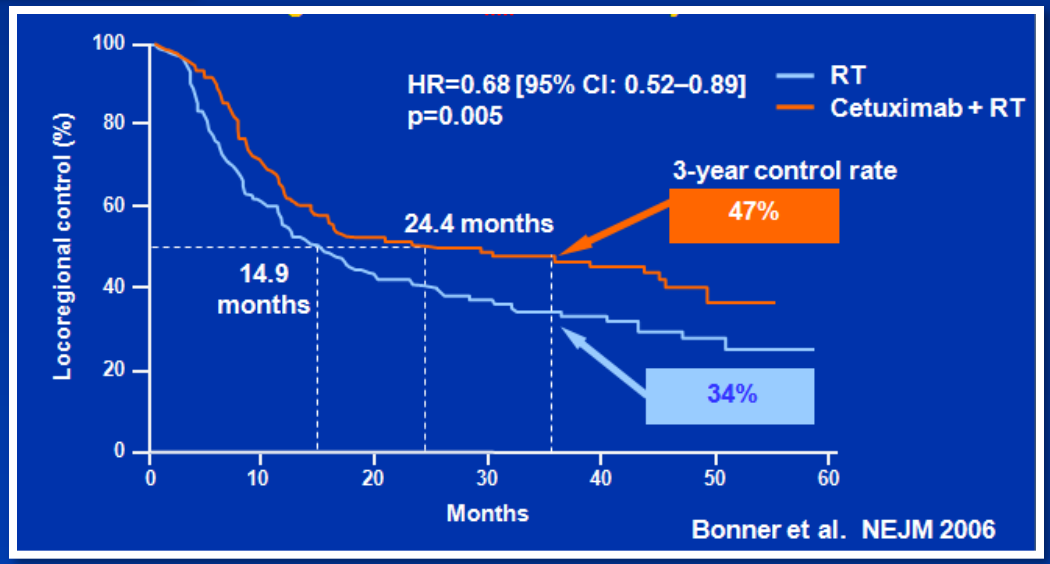
Bonner et al. N Engl J Med 2006; 354: 567-578

Cetuximab in Locally Advanced SCCHN



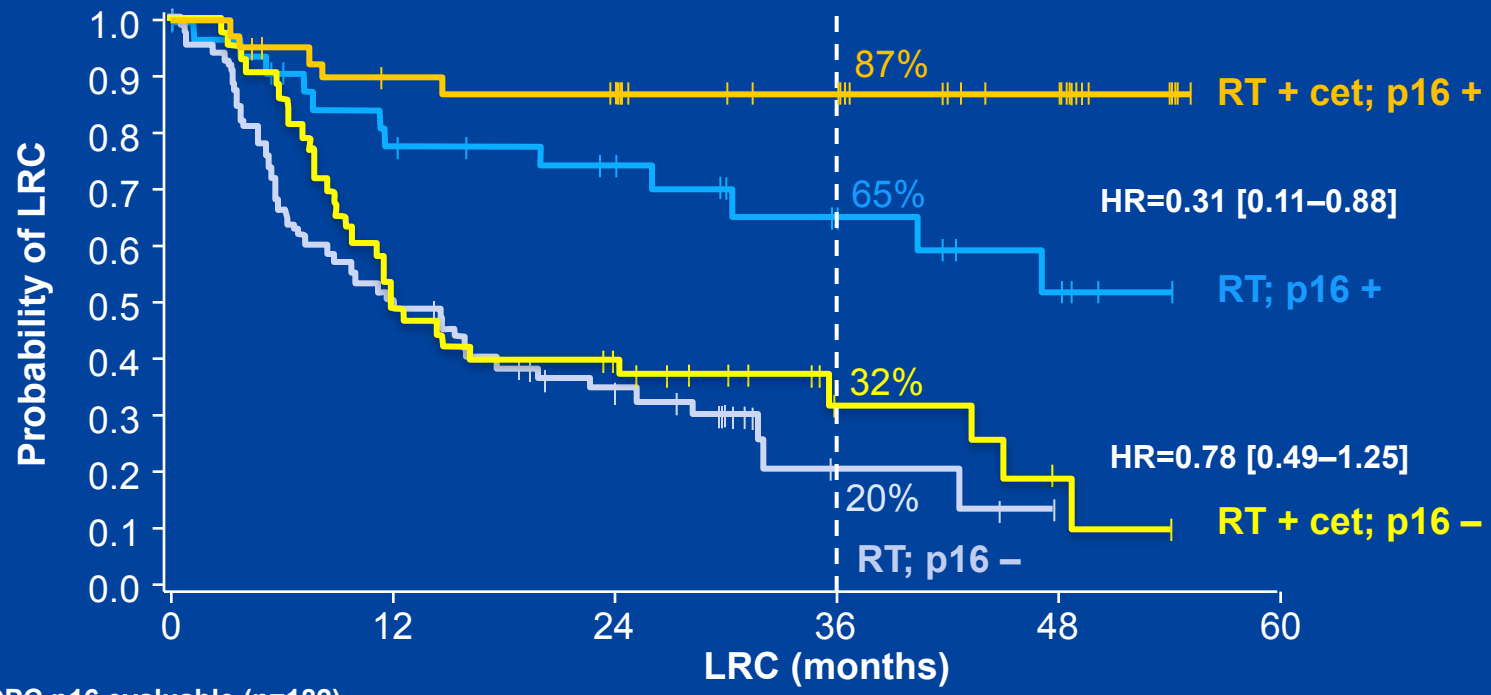
Cetuximab + RT
5-year survival update

Cetuximab + RT significantly increases median duration of locoregional control vs RT alone by 10 months



LRC in OPC Subpopulation According to p16 Status and Treatment Effect of RT + Cetuximab vs RT Alone

LRC interaction test p=NS



No. at risk OPC p16 evaluable (n=182)

RT p16 negative	64	31	17	3	0	0
RT p16 positive	34	24	20	12	6	0
RT + cet p16 negative	43	21	16	6	2	0
RT + cet p16 positive	41	33	30	21	12	0

Rosenthal et al. ASCO 2014 (Abstract #6001)

Chemoradiation and Bioradiation

50 trials, 9615 pts (MA)*	1 trial, 424 patients
HR of death 0.74 (0.67-0.82)+	HR of death 0.74 (0.57-0.97)**
Main effect on local failure Modest effect on DM	Only effect on local failure No effect on DM
Efficacy irrespective of site and of fractionation schedule	Effect may be site and RT schedule specific
Significant acute toxicity which may inflict on late toxicity, in particular swallowing dysfunction	Grade 3-4 mucositis and radiation dermatitis not significantly increased. Late toxicity does not seem increased. High compliance.

No direct comparison in phase III reported

** Pignon et al, Radioth Oncol 2009: 92; 4-14 (level I evidence); **Bonner et al. N Engl J Med 2006; 354: 567-578 (level II evidence); +with mono Platin therapy*

RTOG 0522: Study Objective & Design

Test hypothesis that adding cetuximab to the radiation-cisplatin platform for frontline therapy of stage III-IV HNSCC improves progression-free survival (PFS)

Stage III & IV* SCC of:

- Oropharynx
- Larynx
- Hypopharynx

Stratify :

- Lx vs Non-Lx
- N0 vs N1-2b vs N2c-3
- Zubrod PS
- 3-D vs IMRT
- PET (yes vs no)

RANDOMIZE

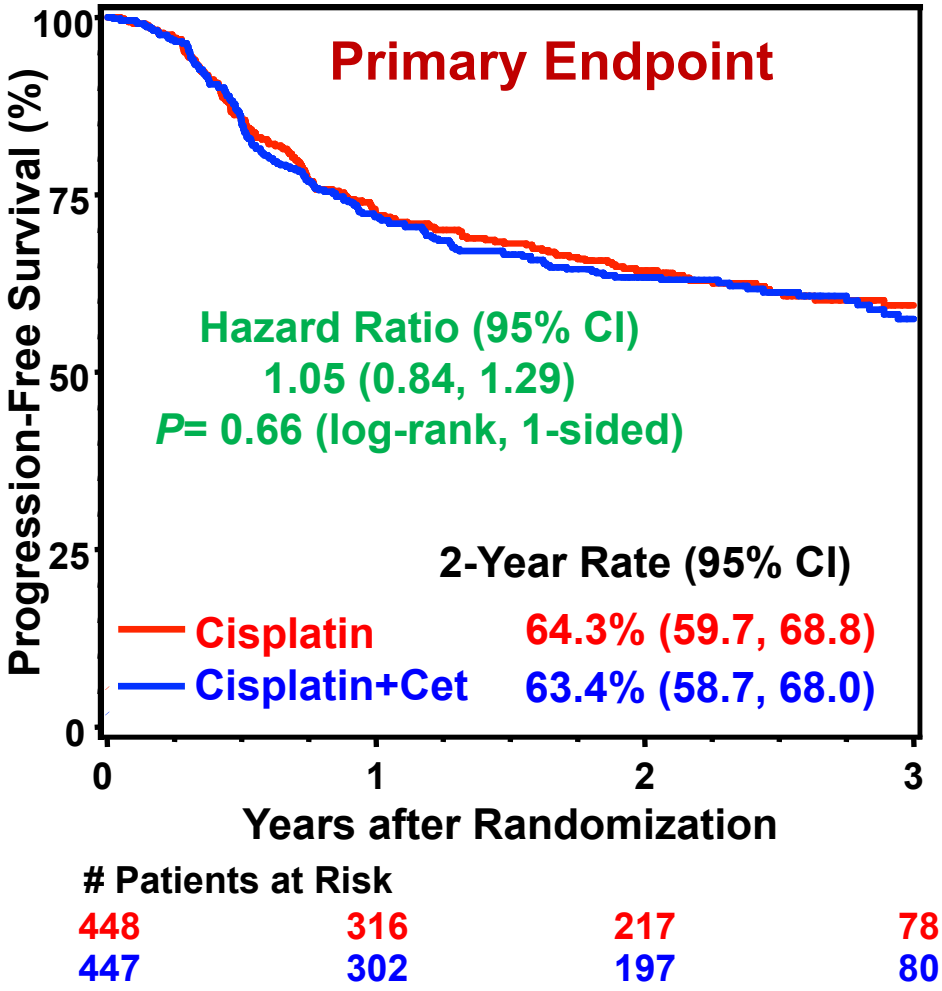
1. AFX-CB: 72 Gy/42 F/6 W + Cisplatin: 100 mg/m^2, q3W x 2

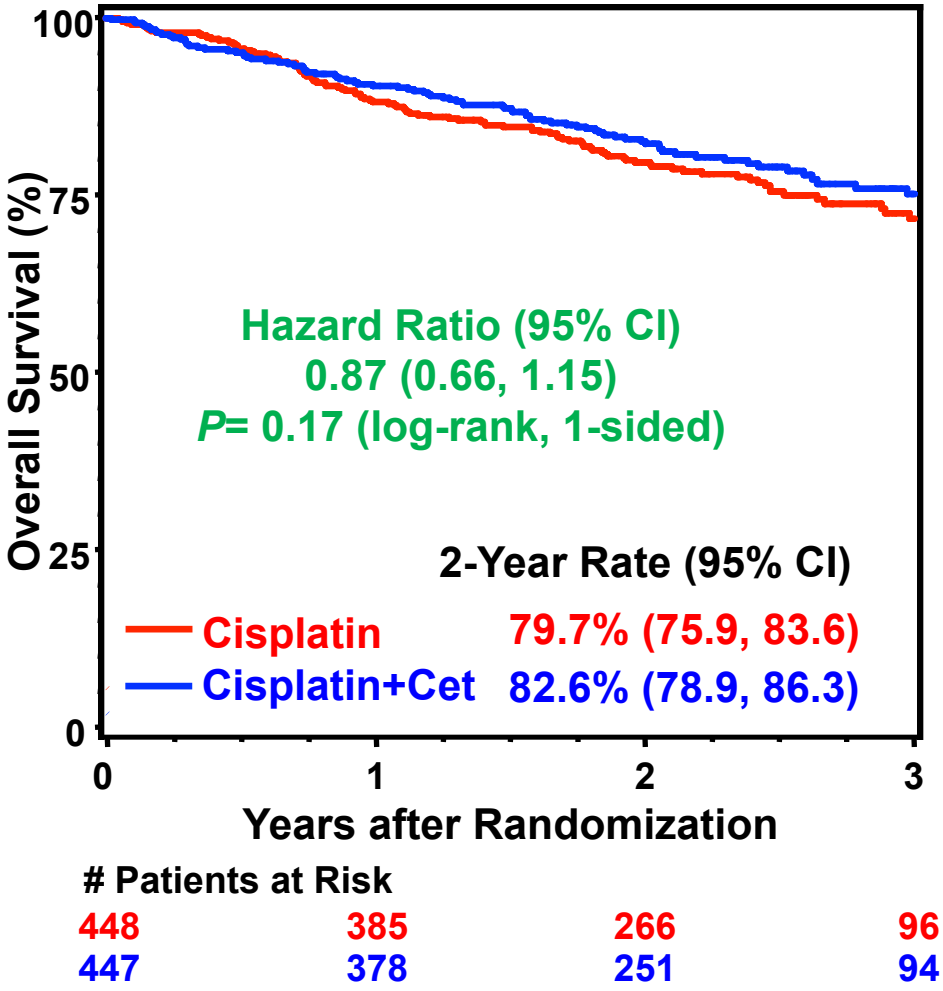
2. AFX-CB: 72 Gy/42 F/6 W + Cisplatin: 100 mg/m^2, q3w x 2 Cetuximab: 400 mg/m^2 x1, then 250 mg/m^2/w

Excluded T1N+, T2N1

Ang KK et al, ASCO 2011 (abstract #5500)

RTOG 0522
Progression-Free Survival & Overall Survival





Ang KK et al, ASCO 2011 (abstract #5500)

Randomized Trials of Sequential Therapy versus Concurrent Chemoradiation Only

Group	Regimen	Survival benefit
TTCC (Sp)[1]	TPF (or PF) x 3 → CCRT (P)	No
	CCRT (cisplatin)	
Boston (US)[2]	TPF x 3 → CCRT (C or TAX)	No
	CCRT (cisplatin)	
Chicago (US)[3]	TPF x 2 → CCRT (THFX)	No
	CCRT (THFX)	
GCTCC (It)[4]	CCRT (PF) w/wo foregoing TPF	Yes
	BRT (Cetuximab) w/wo foregoing TPF	

[1]Hitt et al, Ann Oncol 2013, Nov 19 Epub [ahead of print]; [2]Haddad et al, Lancet Oncol 2013; 14: 257-296
[3]Cohen et al, ASCO 2012 (abstr. #5501); [4]Ghi et al, ASCO 2013 (abstr. #6003) and ASCO 2014 (abstr. #6004)

Locoregionally Advanced SCCHN
Conclusions

Stages III/IV(M_0) patient categories: resectable, unresectable and those treated for organ preservation

Treatment strategies:

1. Surgery → adjuvant RT or concurrent CRT (CCRT)
2. Definitive CCRT , with surgery as an optional salvage or completion treatment
3. Definitive RT + cetuximab (bioradiation; BRT), with surgery as an optional salvage or completion therapy
4. Induction CT → definitive local therapy (RT, CCRT, BRT)

CRT= chemoradiation with cisplatin; BRT= bioradiation

Failure Rate after Primary Therapy for SCCHN

SCCHN is largely a locoregional problem, with distribution of most recurrences after primary, curative-intent RT regimens occuring within the treatment field[1].

MACH-NC analysis (50 trials of CCRT vs RT alone) at 5 years:

- Local and/or regional recurrences:
  - CCRT arm: 50.8%
  - Control (RT alone) arm: 60.1%
- Distant recurrences below 20%[2]

[1]*Strojan et al. Head & Neck-DOI 10.1002/hed.23542*
[2]*Pignon et al. Radiother Oncol 2009; 92: 4-14*

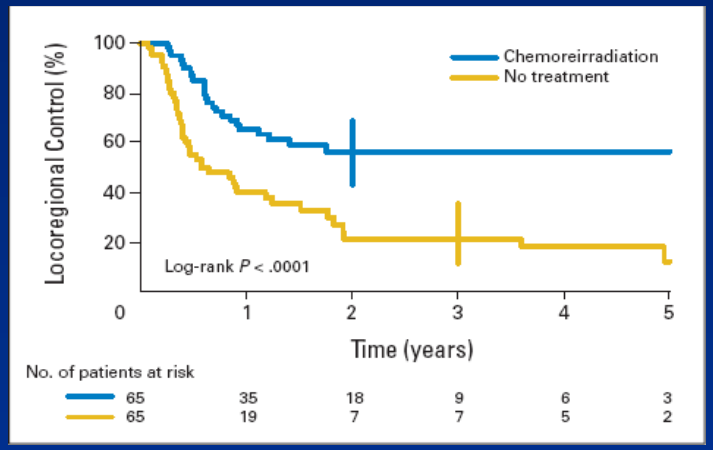
Factors to be Considered when Choosing Treatment Options in R/M-Disease

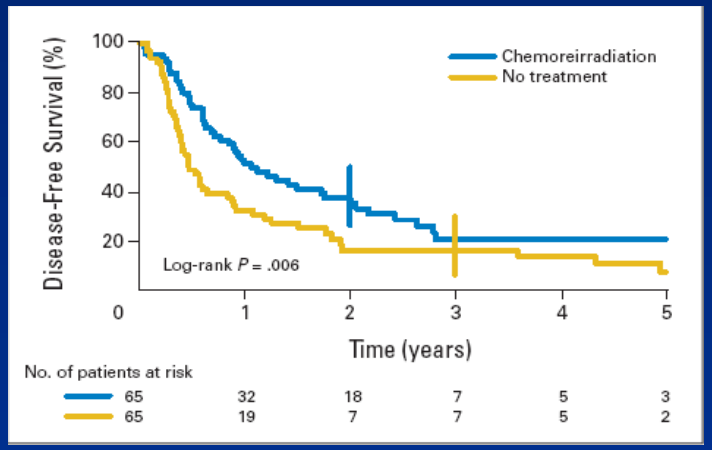
- Type of relapse and time interval “primary TRT-Relapse”
- Type of treatment received in the curative setting
- Performance status
- Comorbidities
- Patient preference
- Logistics

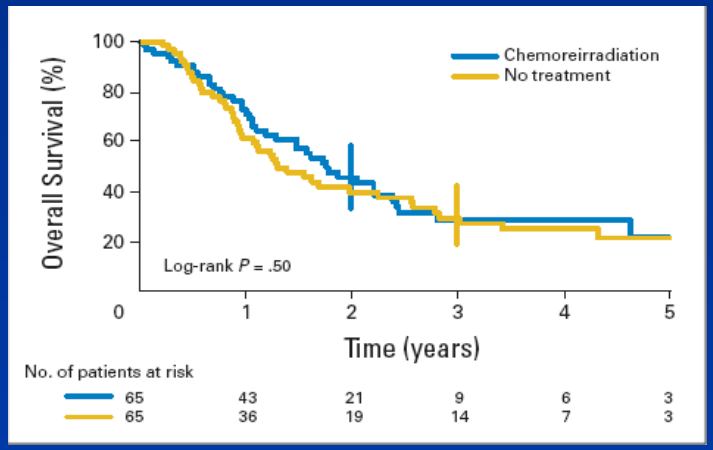
Recurrent/Metastatic SCCHN Treatment Options

- **Surgery**
  - The treatment of choice for non-metastatic second primary or recurrent SCCHN in patients with sufficient good health
  - Best chance for cure: patients with early-stage recurrent tumors and recurrent cancer of the larynx
- **Re-irradiation** (± radiosensitizing agents)
  - Following salvage surgery
  - For unresectable disease
- **Systemic treatment**
- **Best supportive care only**

Randomized Trial of Postoperative CRT after Salvage Surgery versus Salvage Surgery alone in SCCHN







Observations with CRT:

- ↓ Locoregional failure (21 vs 34 patients)
- ↑ Tumor-related death (5 vs 0 patients)
- ↑ Distant metastasis (6 vs 3 patients)
- ↑ Second primary tumor (4 vs 1 patients)
- ↑ Late severe toxicity (40% vs 10%)

Janot F, et al. J Clin Oncol 2008;26:5518–5523

Salvage Surgery and Adjuvant Re-irradiation[1]

Series	No. of pts	RT dose (Gy)	CT	% late ≥ G3 tox	Outcome at 2 years
Emami 1987	48	NS	no	NS	OS 46%
Bechalal 1997	14	60	no	50%	LC 27%, OS 36%
De Crevoisier 2001	25	60	HU+5FU	NS	OS 48%
Machtay 2004	16	60	P+5FU	38%	LRC 100%, OS 81%
Kasperts 2006	39	60-66%	No	NS	LRC 74%, OS 67%
Salama 2006	49	60-74	HU+5FU	NS	LRC 68%, OS 39%[2]
Suh 2008	12	50.5	Yes, 42%	33%	OS 52%
Janssen 2010	20	46	yes, 35%	NS	LRC 21%, OS 24%

[1]Conventional techniques; [2]3-years data (modified from Strojan et al, 2013)

Re-irradiation in Unresectable SCCHN (conventional techniques)

Series	N	Targets + margins (cm)	Median re-irradiation dose (Gy)	± Chemo-therapy	Late grade ≥3 toxicity (%)	2-year OS (%)
De Crevoisier, 1998[1]	169	GTV + (1.5–2)	65	(+)	50	21
Schaefer, 2000	32	GTV + 2	40–50	+	15	10
Hehr, 2005	27	GTV + 1	40	+	N/A	18*
Kramer, 2005	38	GTV + 2	50–60	+	38	35
Salama, 2006[2]	114	GTV + 1 + LN	64	+	18	22*
Langer, 2007	99	GTV + 2 + LN	65	+	38	25
Spencer, 2008	79	GTV + 2	60	+	23	15

**3 year data*

[1]RTOG Multicenter study, many cases without CT-based planning (CF–RT ± chemotherapy): median survival 10–11 months

[2]University of Chicago experience: RT dose, surgery, cisplatin, paclitaxel, and gemcitabine were prognostic

GTV, gross tumor volume; LN, lymph node; RT, radiotherapy (modified from Strojan et al, 2013)

Independent Prognostic Factors

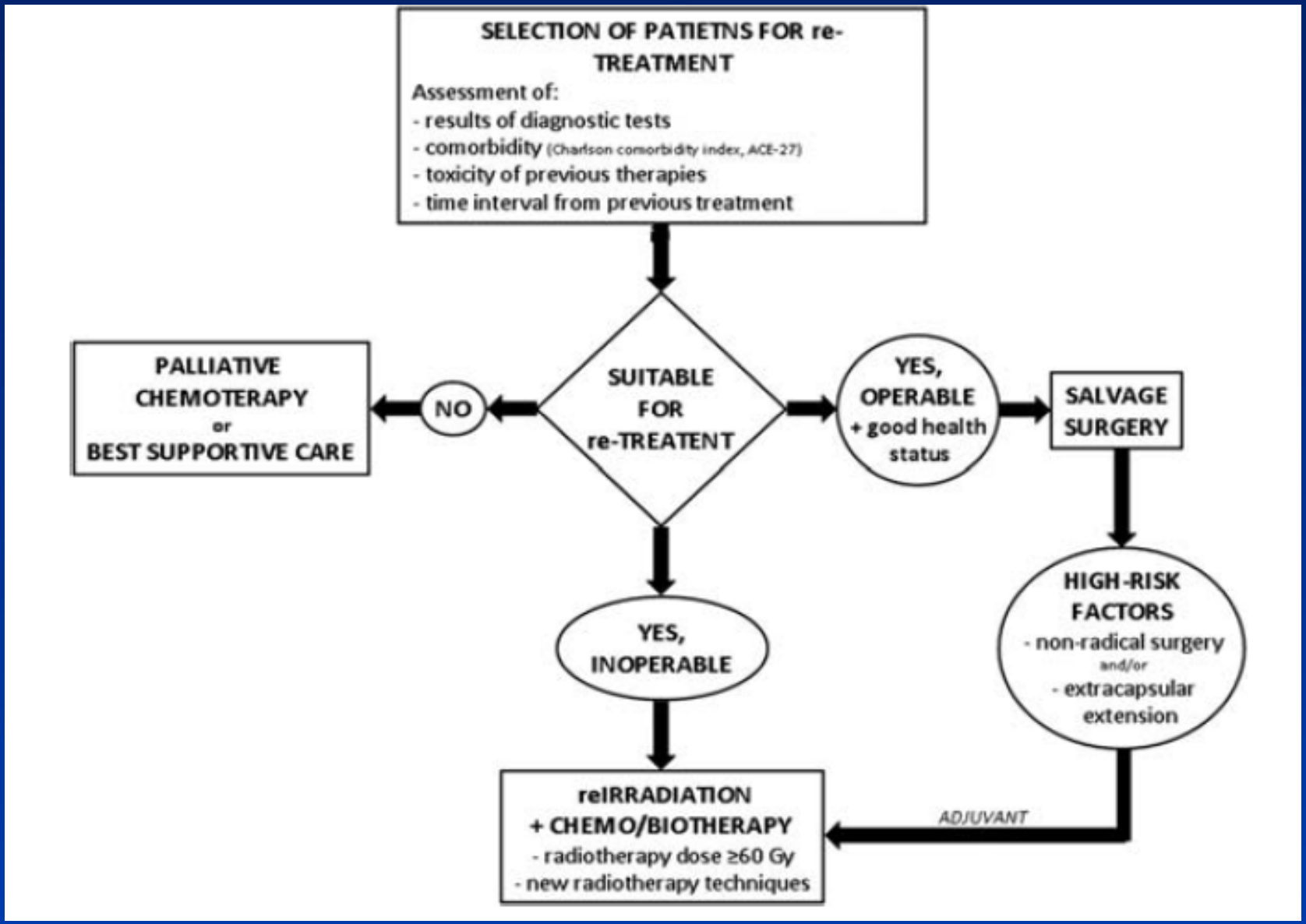
- Interval since last radiation
- Organ dysfunction[1]
- Charlson comorbidity index[2] (per index increase)
- ACE-27 comorbidity grade[3] (per grade increase)
- Recurrent T-stage (T0-T4)
- Tumor bulk after salvage surgery (per cm increase)
- Reirradiation dose (≤ 50 Gy or > 50 Gy)

[1]feeding tube dependency, functioning tracheostomy, soft tissue defect including uncovered open wound of skin or mucosa, fistula, osteonecrosis

[2]weighted index of 19 clinical conditions; [3]severity of comorbidity based on 26 disease systems

Tanvetyanon et al. J Clin Oncol 2009; 27: 1983-1991

Locoregional Recurrences: Conclusions
Algorithm for reirradiation



Strojan et al. Head & Neck- DOI 10.1002/hed.23542

Recurrent/Metastatic SCCHN
Medical Treatment

- Supportive care only
- Single agent chemotherapy
- Multiagent chemotherapy
- Targeted therapy (single agent or combined)
- Targeted agents combined with cytotoxics
- Immunotherapy
- Other approaches (BNCT, HT, ECT, PDT)

BNCT= boron neutron capture therapy; HT= hyperthermia; ECT= electrochemotherapy; PDT= photodynamic therapy

Single Agents with Activity[+] in R/M-SCCHN*

Conventional drug	% RR	Newer agents	%RR
Cyclofosfamide	36	Edetrexate	6-21
Methotrexate	31	Pemetrexed	26
Vinblastine	29	Vinorelbine	6-22
Cisplatin	28	Irinotecan	21
Ifosfamide	26	Capecitabine	8-22
Carboplatin	25	S-1	27
Doxorubicin	24	Orzel	21
Bleomycin	21	Paclitaxel	20-43
5-Fluorouracil	15	Docetaxel	20-42

•Pooled data in advanced disease (from Vermorken JB; In Bernier J (ed.) Head and Neck Cancer: Multimodality Management, Springer Science+Business Media, LLC 2011; [+]Activity defined as ≥15% responses

Randomized Single Agent Trials in R/M-SCCHN

Author (year)	No. of pts	Drugs randomized	RR %	OAS (mo) median
Schornagel (1995)	264	MTX	16	6.0
		EDX	21	6.0
Grose (1985)	100	MTX	16	4.6
		DDP	8	4.1
Hong (1983)	38	MTX	23	6.1
		DDP	29	6.3
Vermorken (1999)	95	MTX	16	6.8
		PACL	11 (-23)	6.5
Guardiola (2004)	57	MTX	15	3.9
		DOCE	27	3.7

MTX= methotrexate; EDX=edetrexate, DDP= cisplatin; PACL=paclitaxel; DOCE= docetaxel

Platinum Combinations vs Single Agents
Randomized trials in R/M disease

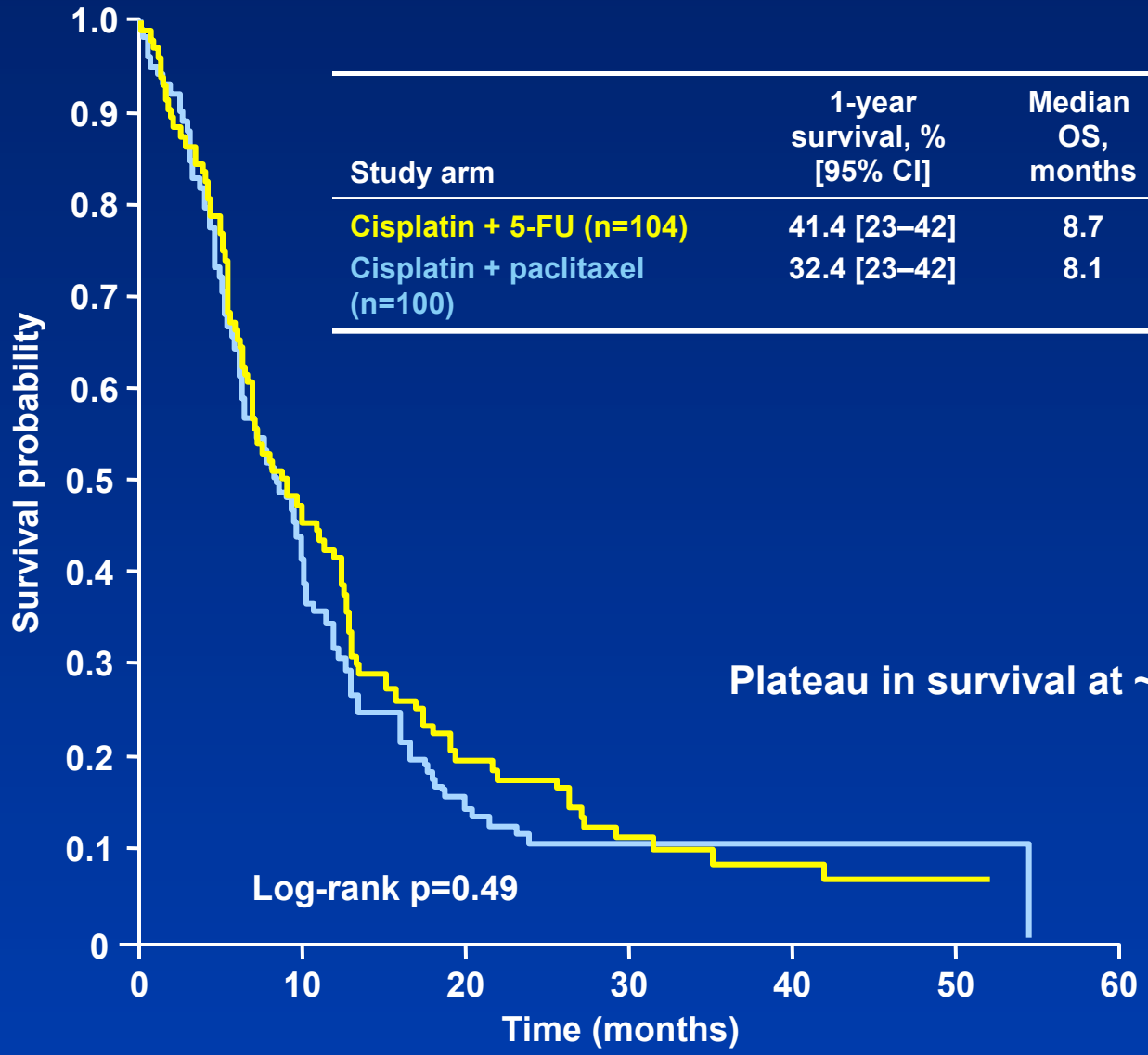
Investigator	N	Regimen	ORR (%)	Median OS (months)	Significant OS benefit
Jacobs et al 1992	249	Cisplatin + 5-FU	32*	5.5	No
		Cisplatin	17	5.0	
		5-FU	13	6.1	
Forastiere et al 1992	277	Cisplatin + 5-FU	32*	6.6	No
		Carboplatin + 5-FU	21	5.0	
		Methotrexate	10	5.6	
Clavel et al 1994	382	CABO	34*	7.3	No
		Cisplatin + 5-FU	31*	7.3	
		Cisplatin	15	7.3	
Urba et al 2012	795	Cisplatin/Pemetrexed	12	7.3	No
		Cisplatin/placebo	8	6.3	

**Statistically significant*

Jacobs et al, J Clin Oncol 1992; Forastiere et al. J Clin Oncol 1992; Clavel et al. Ann Oncol 1994 ; Urba et al, Cancer 2012

E1395: No significant difference in survival between PF and TP

Study arm	1-year survival, % [95% CI]	Median OS, months	OR, %	Grade 3/4 toxicity
Cisplatin + 5-FU (n=104)	41.4 [23–42]	8.7	30%	Reduced for cisplatin + paclitaxel
Cisplatin + paclitaxel (n=100)	32.4 [23–42]	8.1	26%	



Gibson MK, et al. J Clin Oncol 2005;23:3562–3567

E1395: Efficacy and Safety

	PF (n=104)	TP (n=100)
CR + PR, %	29.8	26
CR, %	6.7	7
Median survival, months	8.7	8.1
1-year survival, %	41	32
Grade 3–5 toxicity, %		
ANC	67	55
PLT	23	4
Hb	33	13
Infection	21	13
Diarrhea	6	1
Stomatitis	31	0

Gibson MK, et al. J Clin Oncol 2005;23:3562–3567

Unfavorable Predictors of Outcome in HNC
R/M disease

Based on data from E 1393 and E 1395 (n=399)

Median FUP: 4.75 years

Median OS: 7.8 months	1 yr	2 yr	3 yr	5 yr
Survival	32%	12%	7%	3.6%

Predictors for RR: weight loss, PS, RD, site other than OP, history of RT, WD/MD tumors

Factors for OS: weight loss, PS, PD (favorable), OC/HP history of RT

Factors for TTP: PD (favorable), OC/HP, history of RT

≤ 2 adverse PF → Median survival 1 year

3-5 adverse PF → Median survival 0.5 year

Argiris et al, 2004

Treatment of Platinum-Refractory R/M-SCCHN
Retrospective data

- Best supportive care (BSC)
  Chemotherapy (CT)
  Radiation therapy (RT)
  Other local therapies

- In a retrospective analysis of 151 patients with platinum-refractory disease 45% received BSC, and 55% any form of treatment (Leon et al, Clin Oncol 2005; 17: 418-424)

- Overall response rate was 2.6%, the clinical benefit rate 15.2%, and survival 103 days.
  (for patients receiving BSC 56.5 days, CT 107 days)

Second-Line Treatment in R/M-SCCHN
Phase II/III data

Reference	Drug	Prior CT for R/ M-SCCHN	Median PFS (months)	Median OS (months)
Pivot[1]	MTX	62%	1.5	3.7
Stewart[2]	MTX	unclear	NA	6.7
Machiels[3]	BSC+MTX78%	45%(55%<6mo)	1.9	5.2
Numico[4]	docetaxel	61%	4.0 (TTP)	6.0
Zenda[5]	docetaxel	unclear	1.7	4.6
Specenier[6]	docetaxel	77%	1.7	4.1
Argiris[7]	docetaxel	unclear	2.1(TTP)	6.0

[1] Ann Oncol 2001; [2] J Clin Oncol 2009; [3] Lancet Oncol 2011; [4] Ann Oncol 2002
[5] Jpn J Clin Oncol 2007; [6] Am J Clin Oncol 2011; [7] J Clin Oncol 2013

Cytotoxic Chemotherapy in R/M-SCCHN
Conclusions

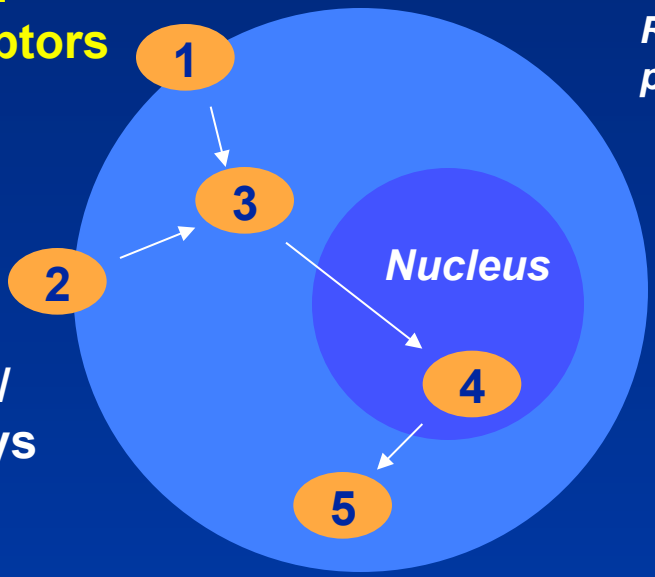
- Single agent methotrexate is still a standard of care
- Platinum-based combinations are superior in terms of response rate (but at the cost of more toxicity), no survival benefit
- In first-line setting, median survival is 6-9 months and 1-year survival rates vary between 20% and 40%
- Once platinum-resistance occur, outlook is very poor
- R/M SCCHN patients are candidates for phase I and phase II trials of experimental therapeutics

Targets for Next-generation Therapy

Tumor cell

1. **Growth factors and growth-factor receptors**
   HER family, c-kit/SCFR

3. **Signal transduction pathways**
   Ras, raf, MAPK, MEK, ERK, AKT protein kinase C, PI3K



2. **Extracellular matrix/ angiogenic pathways**
   VEGFR, integrins, MMPs

4. **Cell-survival pathways**
   Cyclin-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2

5. **Protein production**
   Proteasome

EGFR-targeting Agents under Clinical Investigation in SCCHN

Monoclonal antibodies				Toxicity
Cetuximab	IMC225	chimeric human/murine	IgG1	skin
Matuzumab	EMD72000	humanized mouse	IgG1	skin
Nimotuzumab	h-R3	humanized mouse	IgG1	systemic/hemodynamic
Zalutumumab	2F8	human	IgG1	skin
Panitumumab	ABX-EGF	human	IgG2	skin
Tyrosine kinase inhibitors				
Gefitinib	ZD1839	reversible	EGFR	skin/gastrointestinal (GI)
Erlotinib	OSI-774	reversible	EGFR	skin/GI
Lapatinib	GW-572016	reversible	EGFR/erbB2	skin/GI/systemic
Afatinib	BIBW-2992	irreversible	Pan Her*	skin/GI/systemic
Dacomitinib	PF-00299804	irreversible	Pan Her*	skin/oral/GI/systemic

** EGFR/Her2/Her4*

Cetuximab in Platinum Pretreated Patients with R/M-SCCHN

Author	Phase	N	Regimen	ORR (%)	Median PFS (months)	Median OS (months)
Vermorken 2007	II	103	cetuximab	13	2.3 (TTP)	5.9
Baselga 2005	II	96	cetuximab + Platinum	10	2.8 (TTP)	6.1
Herbst 2005	II	79	cetuximab + Cisplatin	10	2.2 (TTP)	5.2
Knoedler 2013	II	84	cetuximab + Docetaxel	11	3.1	6.7

Baselga et al. JCO 2005; Herbst et al. JCO 2005; Knoedler et al. Oncology 2013; Vermorken et al. JCO 2007

Anti-EGFR TKIs in R/M-SCCHN

Drug	Phase/ prior CT	Reference	Resp. Rate,%
Erlotinib	II 0-1 lines	Soulieres, JCO, 2004	4
Gefitinib	II 0-1 lines	Cohen, JCO, 2003	11
	II 0-5 lines	Cohen, CCR, 2005	2
	II 0-1 lines	Kirby, BJC, 2006	9
	III Pt+ / Pt-	Stewart, JCO, 2009	3-8
Lapatinib	II unclear	Abidoye, ASCO 2006	0
Afatinib	II R prior Pt	Seiwert, Ann Oncol 2014	16/8*
Dacomitinib	II no prior Pt	Siu, JCO 2011	**13**

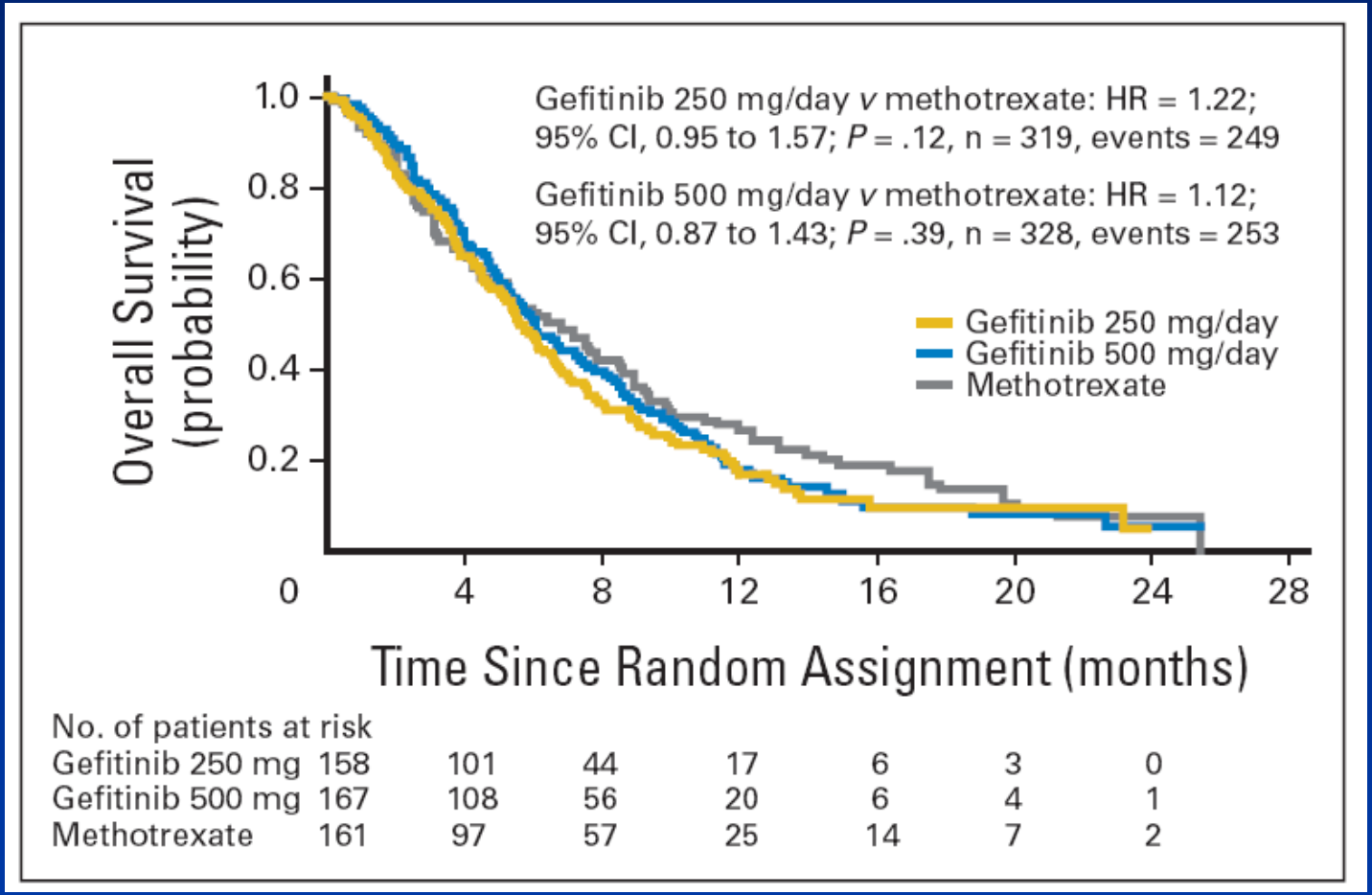
Prior CT= for recurrent/metastatic disease (by IR/ICR)*

Second-line Treatment with Anti-EGFR Drugs
Randomized trials in R/M-SCCHN

Study/Reference	N	Regimen	RR (%)	PFS	OS (mo)
IMEX Stewart et al, J Clin Oncol 2009	486	Gefitinib (250 mg) Gefitinib (500 mg) Methotrexate	2.7 7.6 3.9	ND ND ND	5.6 6.0 6.7
ECOG 1302 Argiris et al, J Clin Oncol 2013	270	D + Gefitinib D + placebo	12 6	3.5 (TTP) 2.1 (TTP)	7.3 6.0
ZALUTE Machiels et al, Lancet Oncol 2010	286	Z + BSC (-MTX) BSC (optional MTX)	6 1	2.3* 1.9*	6.7° 5.2°

BSC = best supportive care; Z = zalutumumab; MTX = methotrexate; ND = no data; TTP= time to progression
**HR (95% CI): 0.62 (0.47-0.83), p=0,0010; °HR (95% CI): 0.77 (0.57-1.05), p=0.0648*

Phase III Study of Gefitinib vs Methotrexate
Second-line treatment in R/M SCCHN



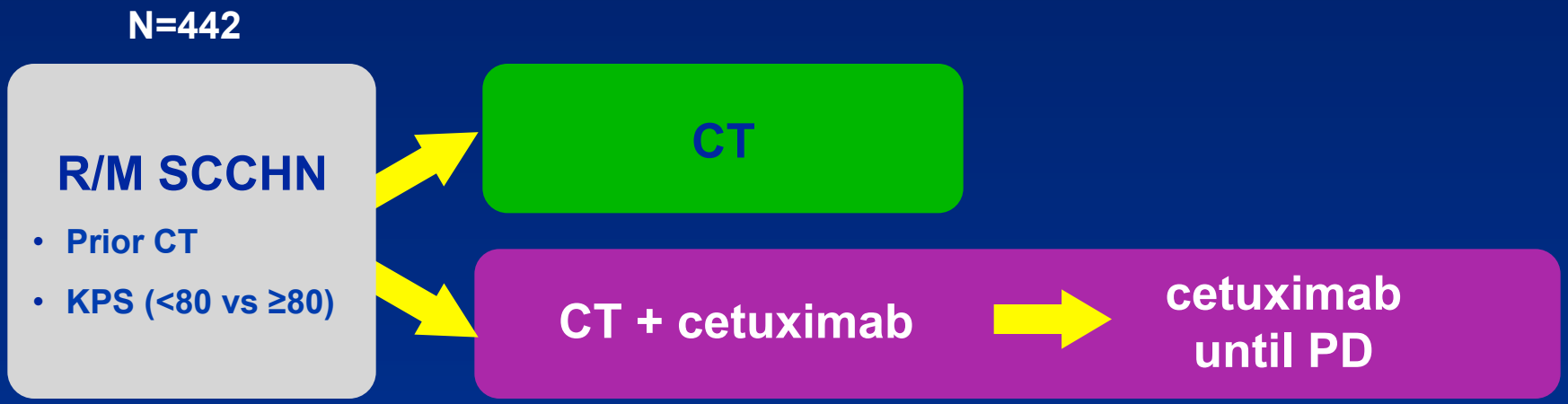
Stewart et al, J Clin Oncol 2009; 11: 1864-1871

First-line Treatment with Anti-EGFR MoAbs
Randomized trials in R/M-SCCHN

Study/Reference	N	Regimen	RR (%)	PFS (mo)	OS (mo)
ECOG 5397/ Burtness et al J Clin Oncol 2005	117	Cisplatin + cetuximab Cisplatin + placebo	26[a] 10	4.2 2.7	9.2 8.0
EXTREME/ Vermorken et al N Engl J Med 2008	442	PF^1 + cetuximab PF^1	36[a] 20	5.6[b] 3.3	10.1[c] 7.4
SPECTRUM/ Vermorken et al Lancet Oncol 2013	657	PF^2 + panitumumab PF^2	36[a] 25	5.8[b] 4.6	11.1 9.0

PF^1 = cisplatin or carboplatin plus 5-FU; PF^2 = cisplatin plus 5-FU
[a, b, c]: significant differences

EXTREME: Phase III Study Design



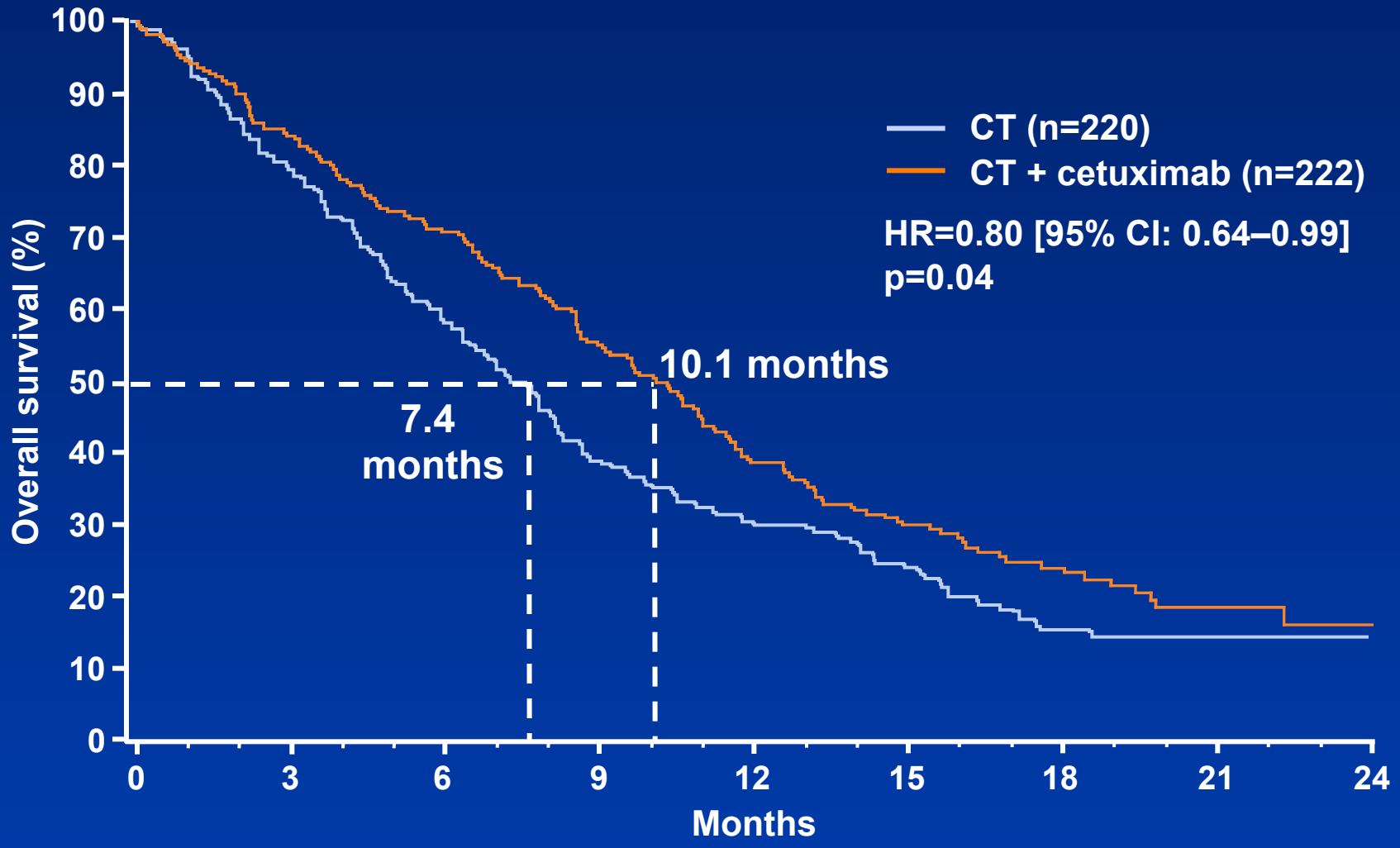
CT
Cisplatin (100 mg/m^2 IV, day 1) or
Carboplatin (AUC 5, day 1) +
5-FU (1000 mg/m^2 IV, days 1–4)
Every 3 weeks, up to 6 cycles

cetuximab
Initial dose 400 mg/m^2
then 250 mg/m^2 weekly
until progressive disease (PD)

Primary endpoint: OS
Secondary endpoints: PFS, RR, safety

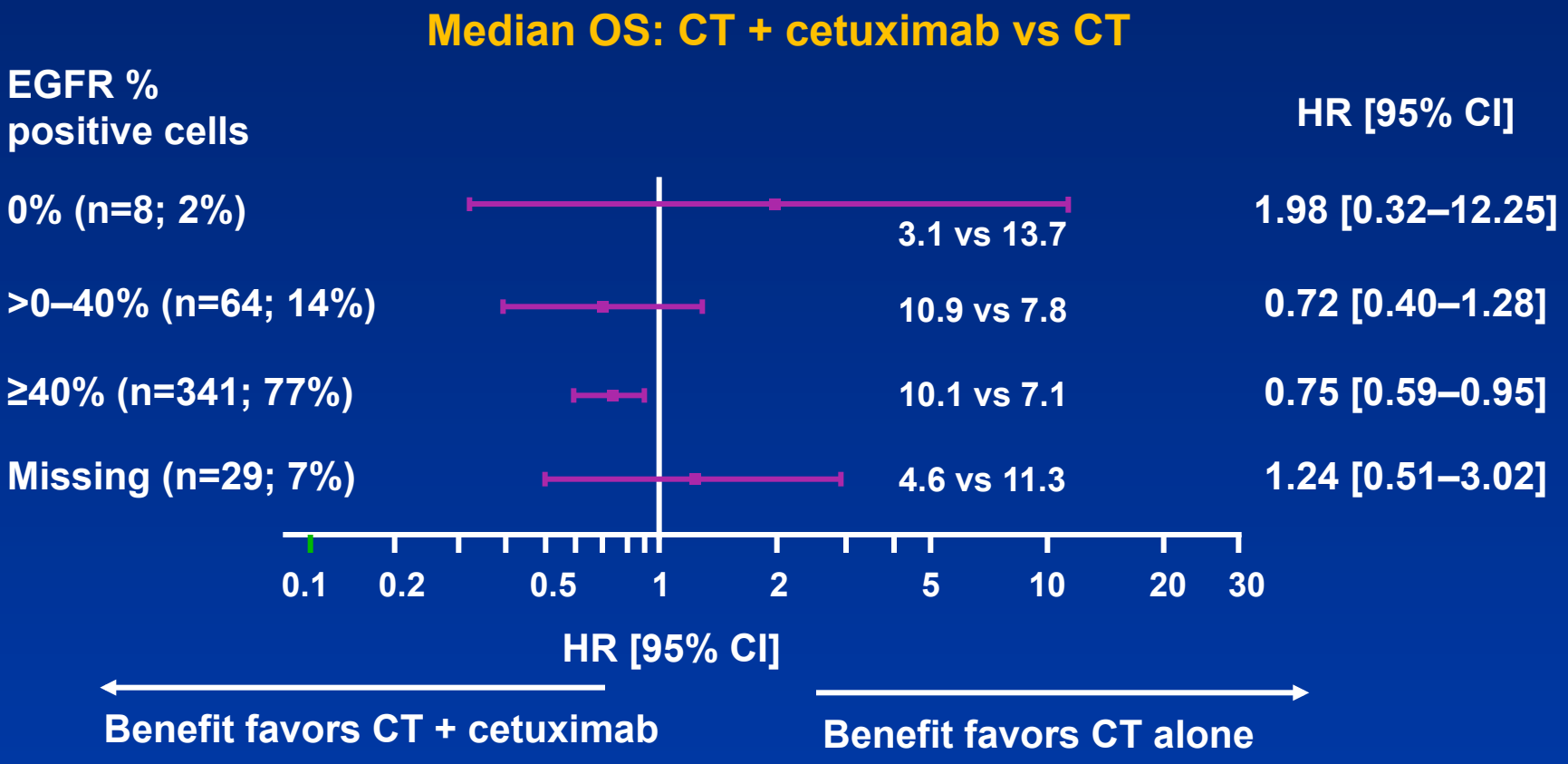
Vermorken et al. NEJM 2008

EXTREME: Overall Survival



Vermorken et al. NEJM 2008

EXTREME: Relationship between EGFR Expression and Survival



Modified from Vermorken et al. NEJM 2008

EXTREME: Retrospective Analysis of EGFR Gene Copy Number

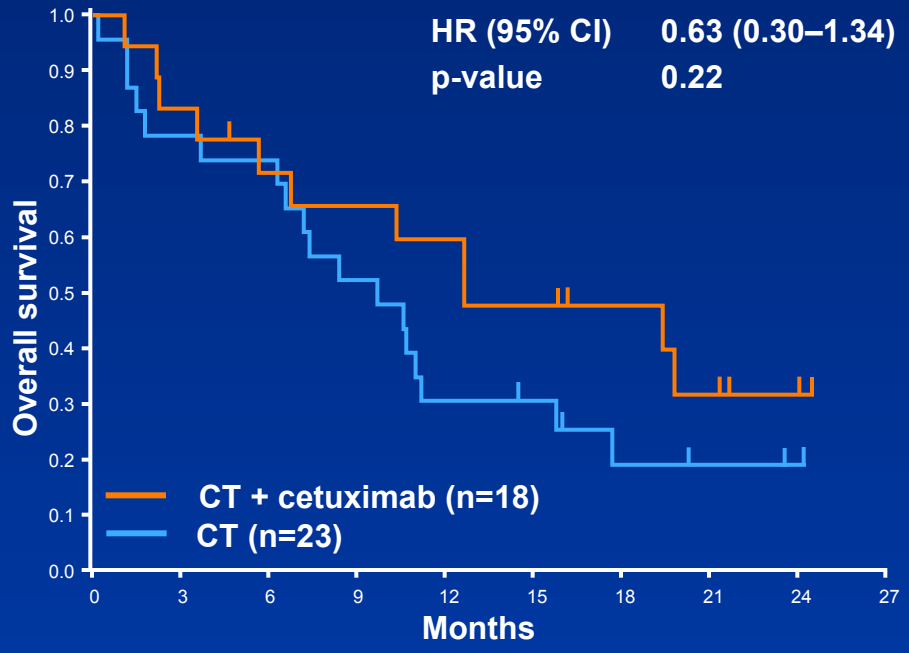
	OS		PFS		RR	
	CT	CT + cetuximab	CT	CT + cetuximab	CT	CT + cetuximab
FISH+	7.2 mo	10.5 mo	3.1 mo	6.2 mo	11.8%	36.0%
FISH-	7.8 mo	10.6 mo	4.1 mo	5.7 mo	22.3%	34.3%
FISH+ vs FISH-	HR 1.04	HR 1.02	HR 1.05	HR 0.86	OR 0.46	OR 1.08
95% CI	[0.71–1.51]	[0.69–1.51]	[0.71–1.54]	[0.58–1.27]	[0.18–1.22]	[0.54–2.18]

cetuximab + CT patients: 50 FISH+, 108 FISH-; CT patients: 51 FISH+, 103 FISH-
HR: Hazard ratio
OR: Odds ratio

Licitra et al. Ann Oncol 2010

Overall Survival in EXTREME by p16 Status

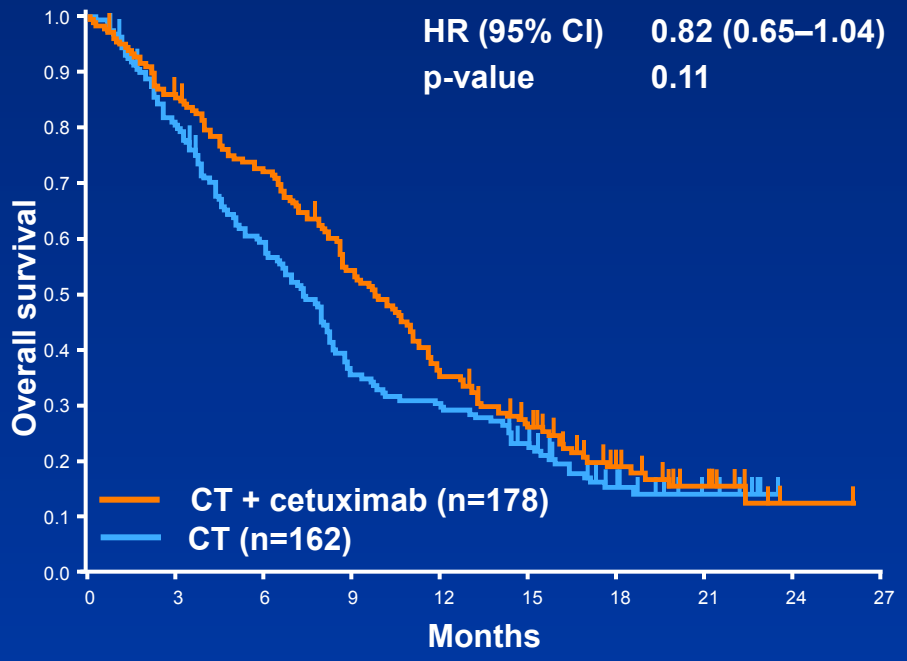
p16+ patients



Number of patients at risk

18	15	12	11	10	8	6	4	1	0
23	18	17	12	7	6	3	2	1	0

p16− patients



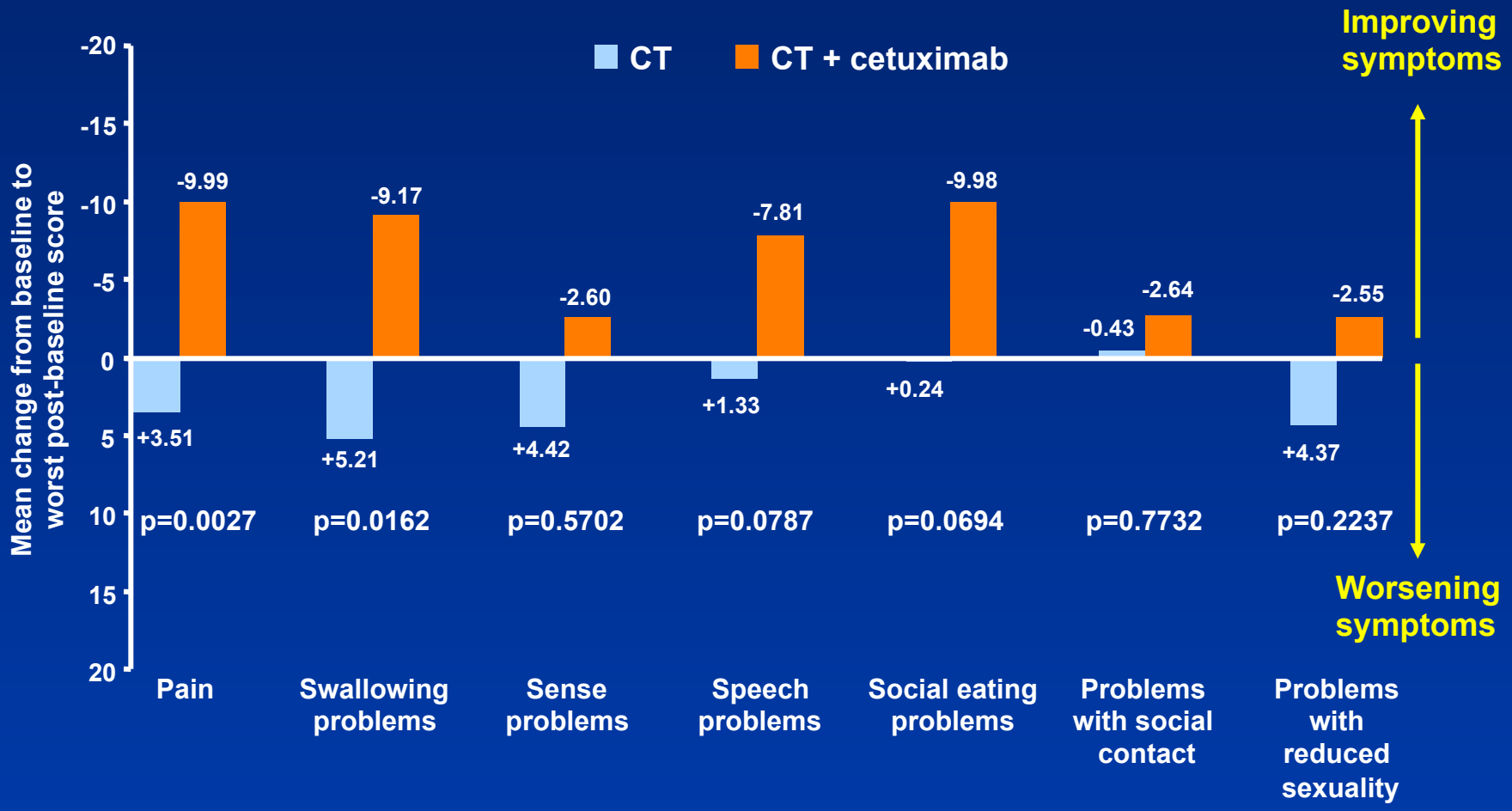
Number of patients at risk

178	150	126	93	61	40	19	10	1	0
162	128	92	56	47	33	15	6	0	0

Vermorken et al, Ann Oncol 2014

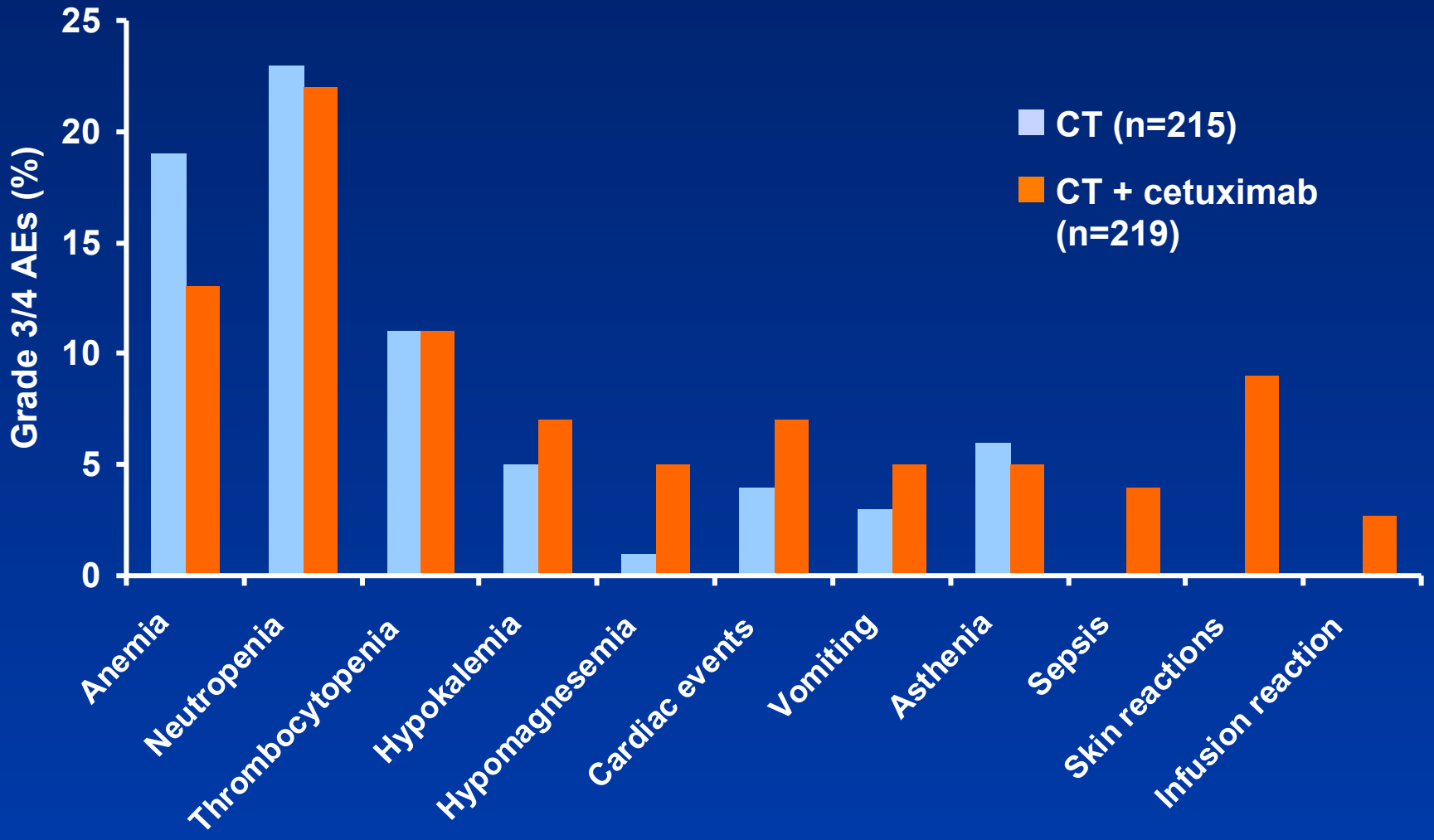
HRs are CT + cetuximab vs CT; CI, confidence interval; HR, hazard ratio

EXTREME: Symptom Control



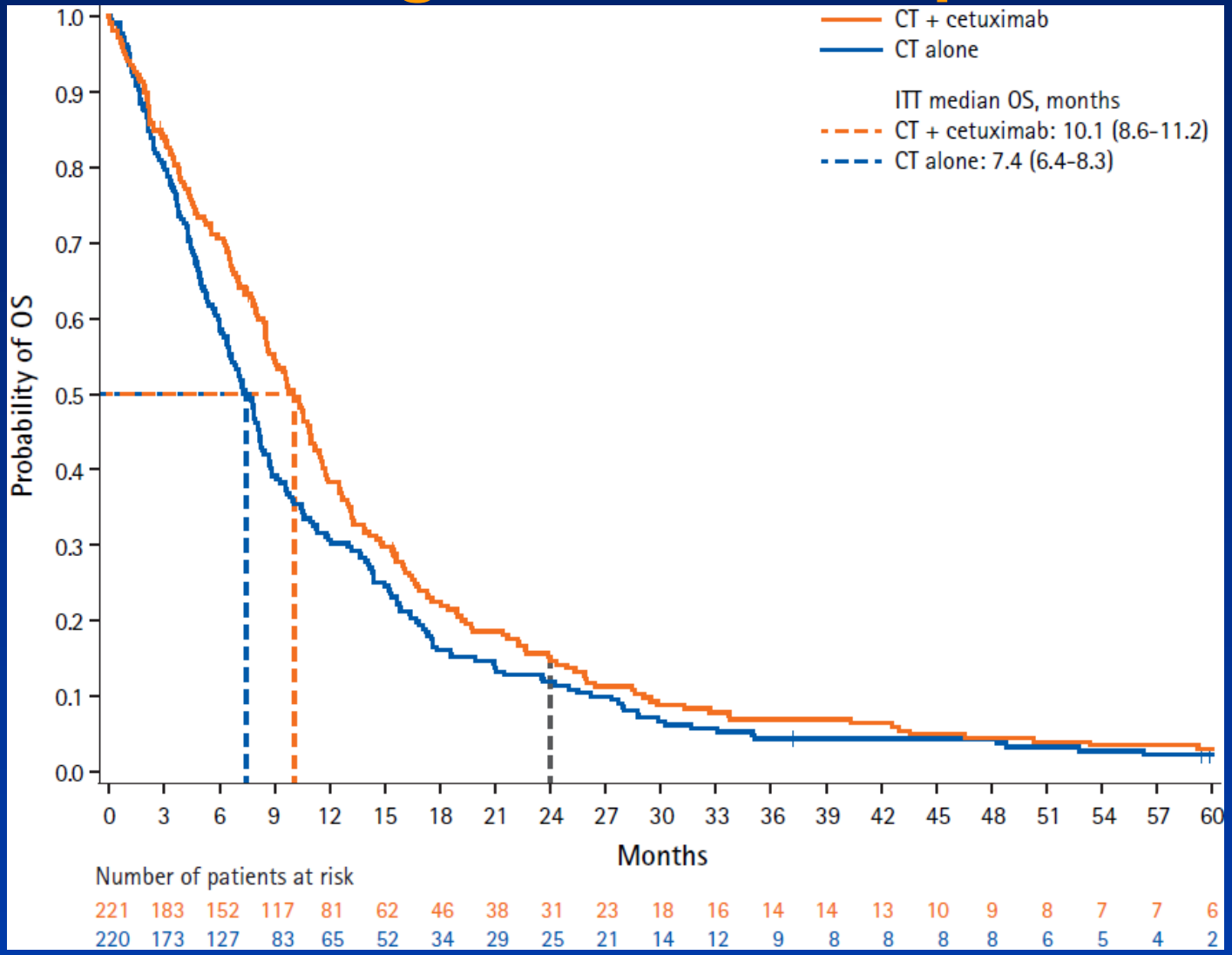
QLQ-H&N35 module
Modified from Mesía et al. Ann Oncol 2010

EXTREME: Safety Profile



Vermorken et al. NEJM 2008

EXTREME – Overall Survival
Long-term follow-up



Vermorken et al. ASCO 2014 (abstr. #6021)

Cetuximab and Beyond
Conclusions

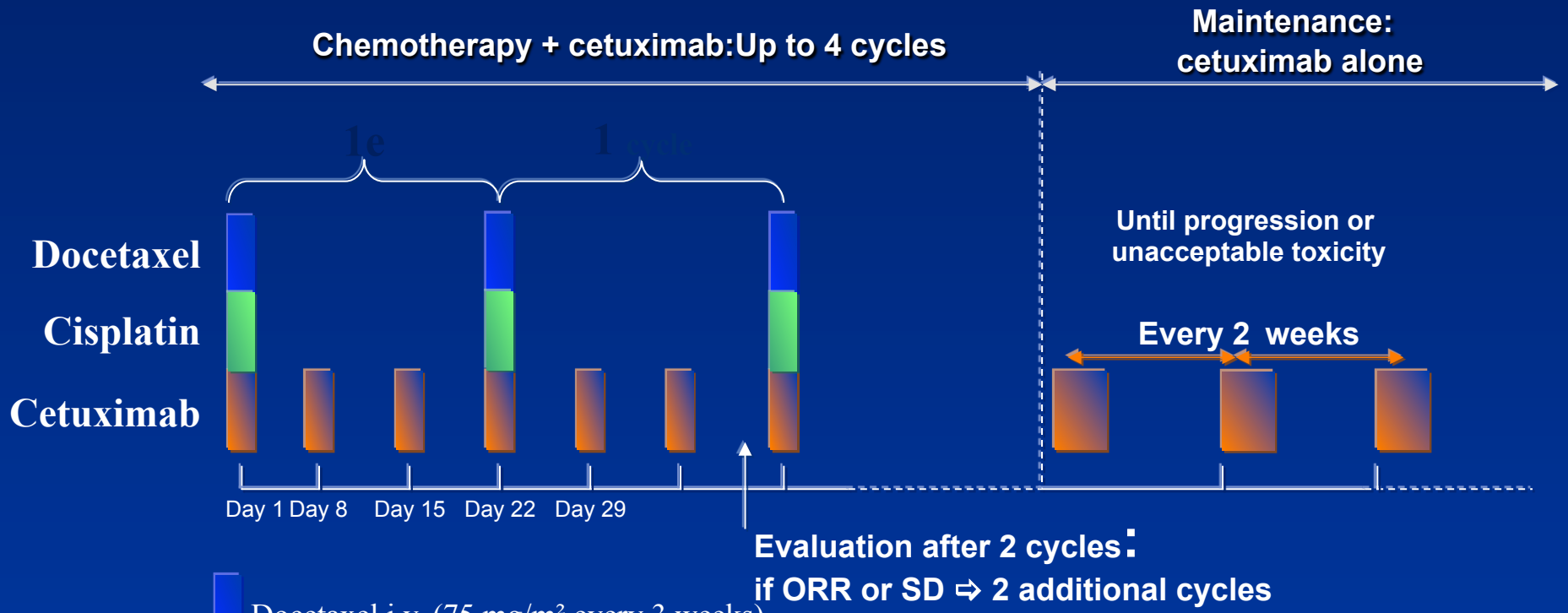
- Cetuximab has palliative value comparable to methotrexate and taxanes in second therapy and can be used as a control arm to test other targeted agents.
- PF + cetuximab is a new standard regimen in 1st-line SCCHN for good-risk patients with benefit regardless of known biomarkers
- However, long-term survival with this regimen still disappointing
- Therefore, studies combining cetuximab with other cytotoxic agents, with other anti-EGFR compounds, with dual compounds or pan-HER inhibitors, and other noval targeted agents or combinations are ongoing
- Confirmatory studies on the prognostic/predictive value of p16/HPV in R/M-SSCHN are needed.

CT plus Cetuximab in First-Line SCCHN
Taxane regimens promising

Author	Phase	N	Regimen	ORR (%)	Median PFS (months)	Median OS (months)
Vermorken 2008	III	442	PF PF + cetuximab	20 36*	3.3 5.6*	7.4 10.1*
Burtness 2005	III	117	Cis + Placebo Cis + cetuximab	10 26*	2.7 4.2	8.0 9.2
Buentzel 2007	II	23	Pacli/Carbo + cetuximab	56	5.0**	8.0
Hitt 2011	II	46	Pacli + cetuximab	54	4.2	8.1
Guigay 2012	II	54	Doce/Cis /cetuximab	54	7.1	15.3

**Significant; **TTP*
Vermorken et al. NEJM 2008; Burtness et al. JCO 2005;
Hitt et al. Ann Oncol 2011; Buentzel et al. ASCO 2007; Guigay et al. ASCO 2012

Treatment schedule



Guigay et al (ASCO 2012; abstract 5505)

Docetaxel / Cisplatin plus Cetuximab (TPE)
Safety*

Toxicity	Grade 3 (%)	Grade 4 (%)
Skin rash	15	-
HSR	6	-
Febrile neutropenia	6	-
Non-febrile neutropenia	6	11
Diarrhea	3.7	-

*Grade 3-4 toxicities occurring>5%
Guigay et al (ASCO 2012; abstract 5505)

TPExtreme TRIAL - GORTEC 2014-01

PI: J Guigay

Phase II
(R 1:1)
Minimization on :
PS
Metastatic status,
Previous cetuximab
Country

R

SCCHN
R/M 1st line
(N = 416)

- ✓ **Age < 71 y**
- ✓ **PS < 2**
- ✓ **Previous:**
  cddp < 300mg/m²
  anti-EGFR > 1y

N = 270

Control arm (EXTREME)

(6 cycles every 3 weeks)

Cisplatin: 100 mg/m2 iv

5FU: 4000 mg/m2 during 96h in continuous infusion

Cetuximab: 400 mg/m2 iv (loading dose), then 250 mg/m2 iv

- **Cetuximab weekly until progression or unacceptable toxicity**

N = 270

Experimental arm (TPEx)

(4 cycles every 3 weeks)

Cisplatine: 75 mg/m2 iv

Docetaxel: 75 mg/m2 iv

Cetuximab: 400 mg/m2 iv (loading dose), then 250 mg/m2 iv

+ G CSF after each cycle

- **Cetuximab every 2 weeks until progression or unacceptable toxicity**

- ✓ **Primary objective: OS**
- ✓ **Ancillary studies:** QOL, cost-effectiveness, p16 / HPV tumor status

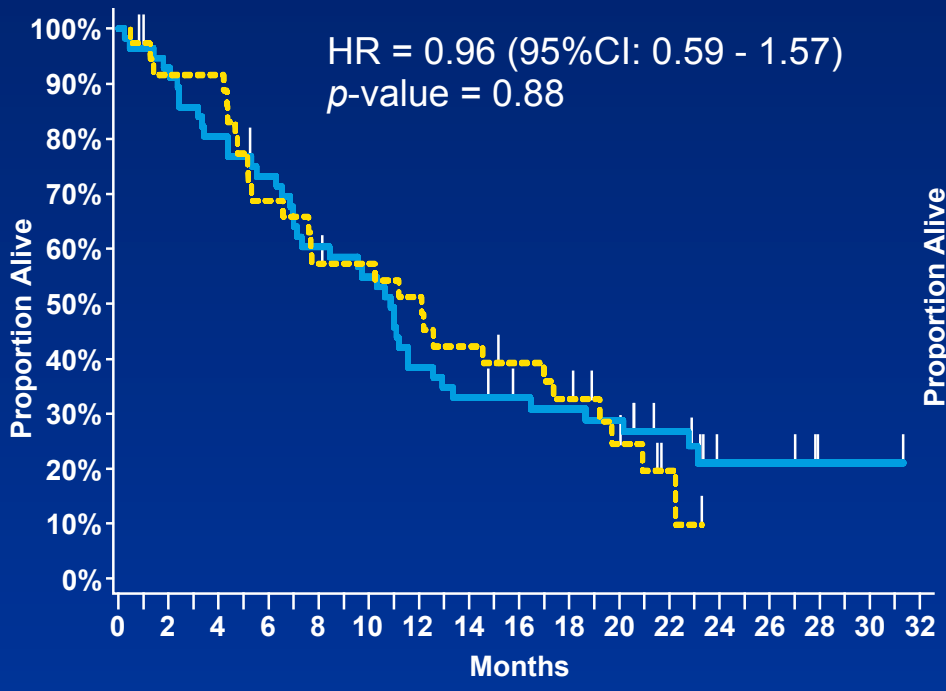
Completed Randomized Trials in First-Line Recurrent/Metastatic SCCHN

Study/Reference	N	Regimen	RR (%)	PFS (mo)	OS (mo)
ECOG 5397/ Burtness et al J Clin Oncol 2005	117	Cisplatin + cetuximab Cisplatin + placebo	26[a] 10	4.2 2.7	9.2 8.0
EXTREME/ Vermorken et al N Engl J Med 2008	442	PF^1 + cetuximab PF^1	36[a] 20	5.6[b] 3.3	10.1[c] 7.4
SPECTRUM/ Vermorken et al Lancet Oncol 2013	657	PF^2 + panitumumab PF^2	36[a] 25	5.8[b] 4.6	11.1 9.0

PF^1 = cisplatin or carboplatin plus 5-FU; PF^2 = cisplatin plus 5-FU
[a, b, c]: significant differences

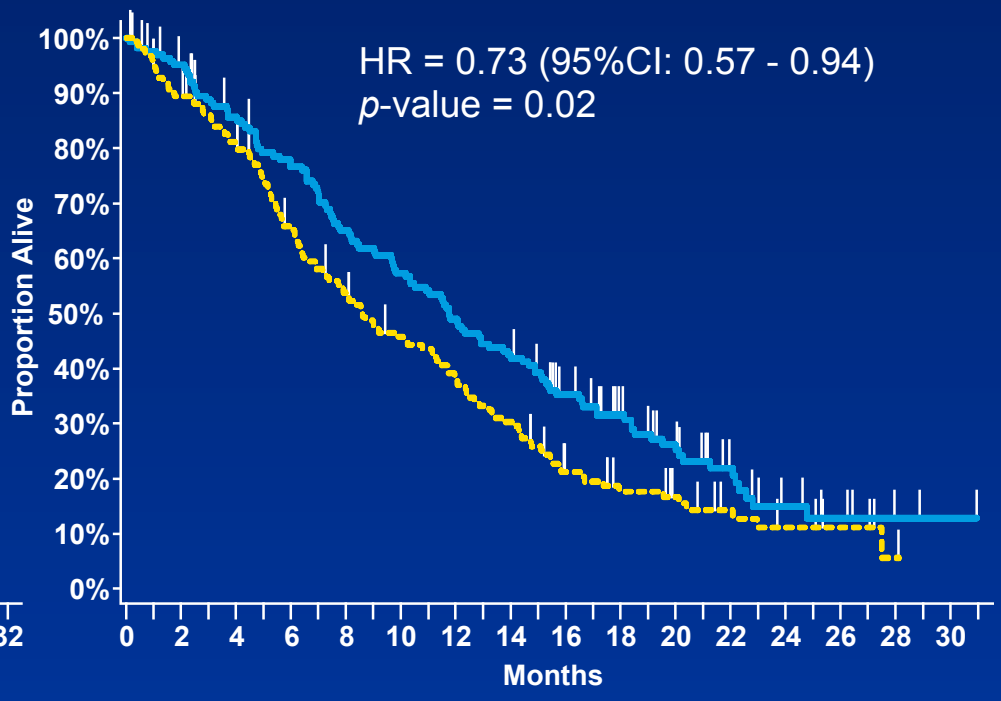
SPECTRUM: Overall Survival by p16 Status

P16+ patients



	Median OS (95% CI) months
Pmab + CT (n = 56)	10.9 (7.1 - 12.6)
CT alone (n = 37)	12.1 (7.6 - 17.4)

P16- patients



	Median OS (95% CI) months
Pmab + CT (n = 165)	11.8 (9.8 - 14.0)
CT alone (n = 153)	8.6 (6.9 - 11.3)

Quantitative interaction test p-value = 0.332

Relationship p16/HPV Status and Outcomes in R/M-SCCHN

Drugs	Type of Study	Study Group	Disease Site	Prognostic / predictive
- PF ± Cetuximab[1]	Phase III	EXTREME	All*	Yes/no
- PF ± Panitumumab[2]	Phase III	SPECTRUM	All*	Yes/Yes
- PF vs PT[3]	Phase III	ECOG 1395	All*	Yes/ NR
- CPT-11 + docetaxel[3]	Phase II	ECOG 3301	All*	Yes/NR

[1]Vermorken et al, Ann Oncol 2014; [2]Vermorken et al, Lancet Oncol 2013; [3]Mehra et al, ASCO 2013, abstract 6006

** Hypopharynx, oral cavity, larynx and oropharynx (OPC)*

The Problem of Resistance

- EGFR is a validated therapeutic target in SCCHN
- Discordance between EGFR expression and response

Possible mechanisms of resistance

- EGFR mutations
- Increased EGFR internalization
- Parallel signaling pathways, such as
  - IGF-1R, MET, erbB2
  - PI3K/AKT mutations
  - Cycline D1 amplification

Examples of Strategies to Overcome Resistance to Anti-EGFR Drugs

- Blockage of multiple HER receptors
  - *Lapatinib*: oral reversible dual TKI of EGFR and HER2
  - *Afatinib* and *dacomitinib*: irreversible pan-HER inhibitors

- Dual targeting mAbs or mixture of mAbs
  - *MEHD7945A* (DAF): –Randomized phase II vs cetuximab in patients progressing on/after Pt-CT (*NCT01577173*)
  - *Catumaxomab* (anti-EpCAM^{x}anti-CD3), cytotoxicity assay[1]
  - *Ertumaxomab* (anti-HER2/neu^{x}anti-CD3), cytotoxicity assay[1]
  - *Sym004* (mixture of 2 mAbs targeting non-overlapping epitopes on EGFR)

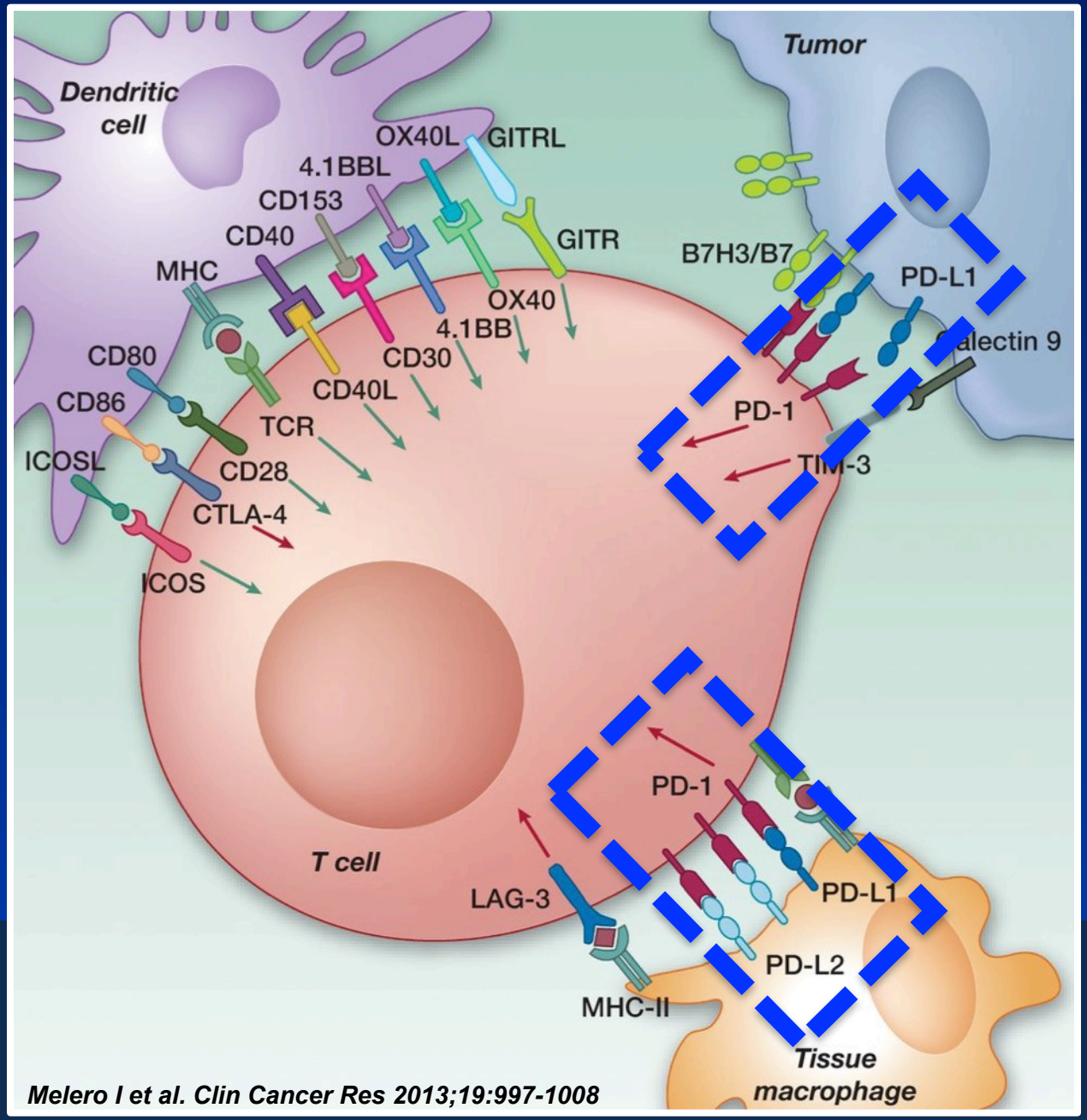
Other Novel Targeted Agents in SCCHN

- Anti-angiogenesis
  - VEGF
  - VEGFR
- Integrin inhibitors
- Histone deacetylase inhibitors
- PI3K/Akt/mTOR pathway inhibitors
- Proteasome inhibitors
- IGFR inhibitors
- SRC inhibitors

No phase III

Data available

Basis for Immune therapy – Immune Escape



Melero I et al. Clin Cancer Res 2013;19:997-1008

- Expression of PD-L1 on
  a) tumor cells &
  b) macrophages
  can suppress immune surveillance.
- In mouse models antibodies ***blocking PD-1 / PD-L1 interaction*** lead to tumor rejection
- **Clinical prognosis** correlates with presence of **TILs** and **PD-L1** expression in

A Phase Ib Study of *Pembrolizumab (MK-3475)* in Patients with HPV-*negative* and HPV-*positive* Head & Neck Cancer

Tanguy Seiwert, Barbara Burtness, Jared Weiss, Iris Gluck, J. Paul Eder, Sara I. Pai, Marisa Dolled-Filhart, Kenneth Emancipator, Kumudu Pathiraja, Christine Gause, Robert Iannone, Holly Brown, Jennifer Houp, Jonathan Cheng, Laura Q. Chow

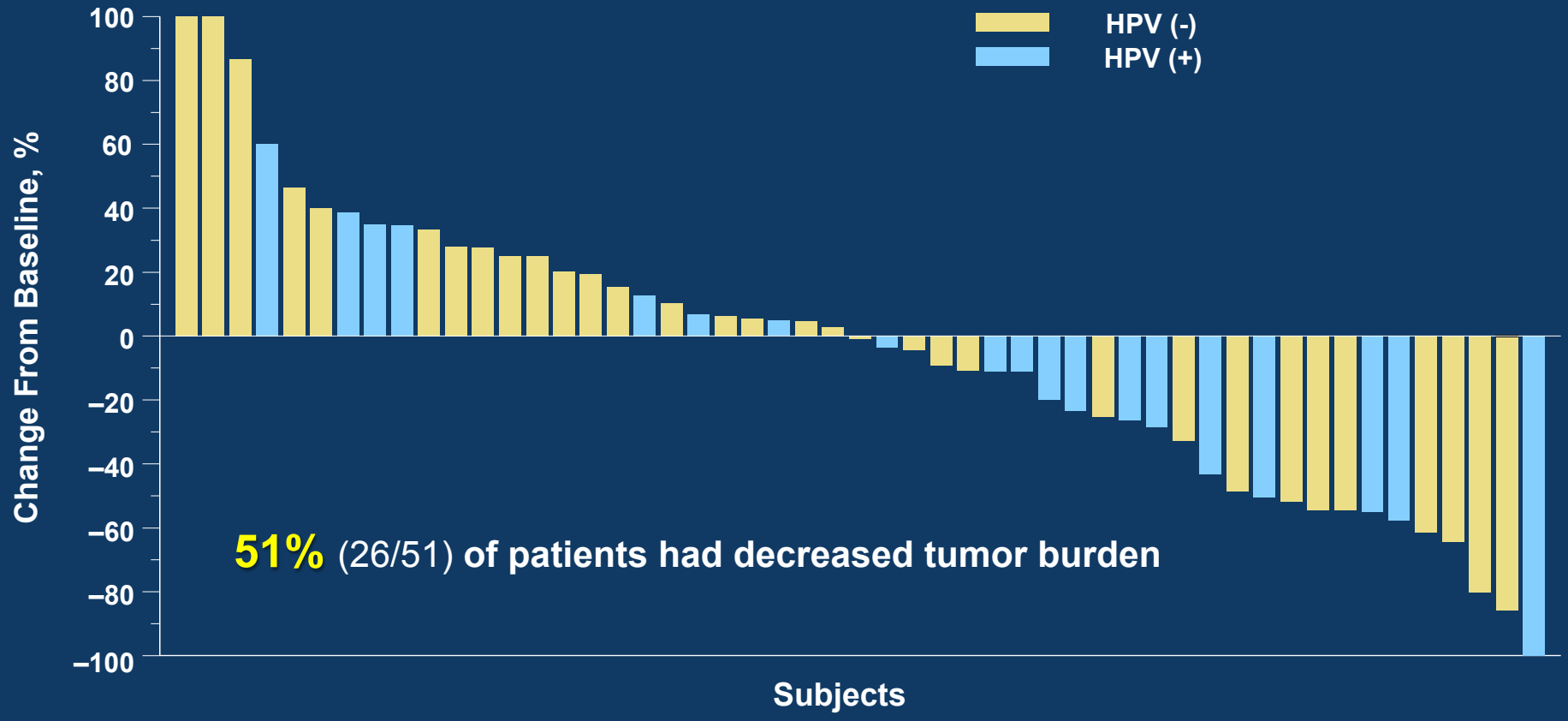
Presented at **ASCO 2014** by:

Tanguy Seiwert, MD

Assistant Professor of Medicine
Associate Director Head and Neck Cancer Program
Fellow, Institute for Genomics and Systems Biology

The University of Chicago

Efficacy: Waterfall Plot*



→ Best percent change from baseline in target lesions (site assessment) delineated by HPV status

*as of May 23, 2014; Includes only patients with RECIST measurable lesions at baseline and at least 1 follow-up scan (n=51)

Presented by: Tanguy Seiwert (ASCO 2014; abstr. 6011)

Best Overall Response*

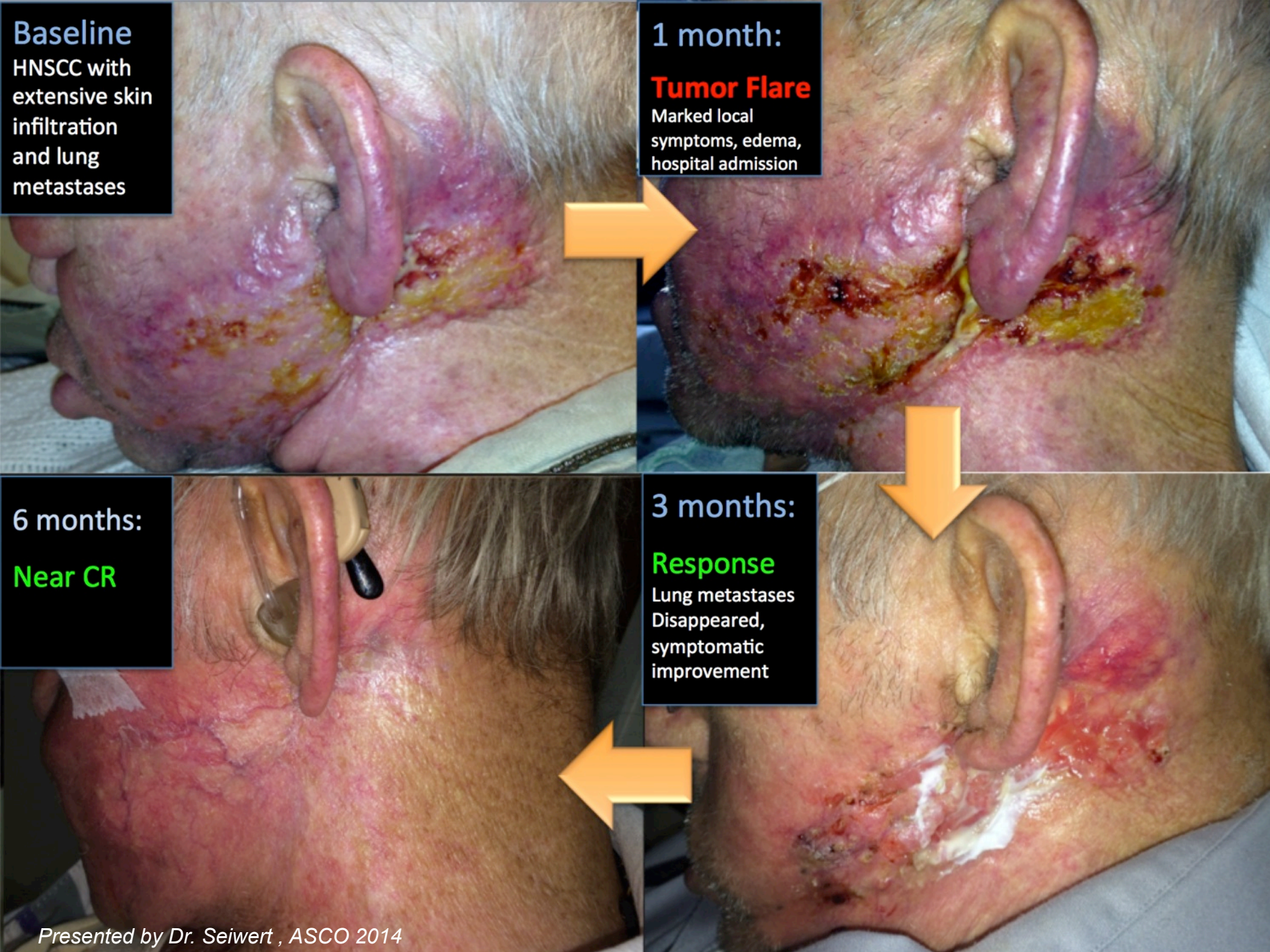
56 pts evaluable for Response	Total Head/neck N=56†		HPV (+) N=20		HPV (-) N=36§	
Response Evaluation	**n (%)**	**95% CI†**	**n (%)**	**95% CI†**	**n (%)**	**95% CI†**
Complete Response	1 (1.8)	(0.0, 9.6)	1 (5.0)	(0.1, 24.9)	0 (0.0)	(0.0, 9.7)
Partial Response	10 (17.9)	(8.9, 30.4)	3 (15.0)	(3.2, 37.9)	7 (19.4)	(8.2, 36.0)
Best Overall Response (Complete + Partial)‡	**11 (19.6)**	**(10.2, 32.4)**	**4 (20.0)**	**(5.7, 43.7)**	**7 (19.4)**	**(8.2, 36.0)**
Stable Disease	16 (28.6)	(17.3, 42.2)	8 (40.0)	(19.1, 63.9)	8 (22.2)	(10.1, 39.2)
Progressive Disease	25 (44.6)	(31.3, 58.5)	7 (35.0)	(15.4, 59.2)	18 (50.0)	(32.9, 67.1)
No Assessment	4 (7.1)	(2.0, 17.3)	1 (5.0)	(0.1, 24.9)	3 (8.3)	(1.8, 22.5)

Based on RECIST 1.1 Per site assessment; includes confirmed and unconfirmed responses
†61 patients eligible for treatment; 60 patients dosed; 56 patients eligible for pre-defined full analysis set.
‡A single patient with PD followed by PR on treatment was classified as PR.
§Includes 2 patients for whom HPV data unavailable.
† Based on binomial exact confidence interval method.

- PD-L1 expression correlates with Response
- Using a Youden-Index derived, preliminary PD-L1 cut point:
  - Above cutpoint: **45.5% (5/11) RR**
  - Below cutpoint: **11.4% (5/44) RR**

*as of May 23, 2014

Presented by: Tanguy Seiwert (ASCO 2014; abstr. 6011)


Baseline
HNSCC with extensive skin infiltration and lung metastases
1 month:
Tumor Flare
Marked local symptoms, edema, hospital admission
3 months:
Response
Lung metastases Disappeared, symptomatic improvement
6 months:
Near CR
Presented by Dr. Seiwert , ASCO 2014

Take-Home Messages

- Better understanding of the biology of SCCHN has led to change in treatment approaches
- Concurrent CRT is standard of care for locoregionally advanced SCCHN
- Bioradiation (cetuximab) an alternative option for patients with contra-indications for or intolerance of concurrent CRT
- Addition of cetuximab to platinum/5-fluorouracil in patients with R/M-SCCHN → benefit in median survival; long-term survival remains disappointing
- A plethora of new targeted therapies are in various stages of preclinical and clinical development
- Reactivation of immune surveillance by blocking PD1 interaction with its ligands possibly a promising approach for HNC