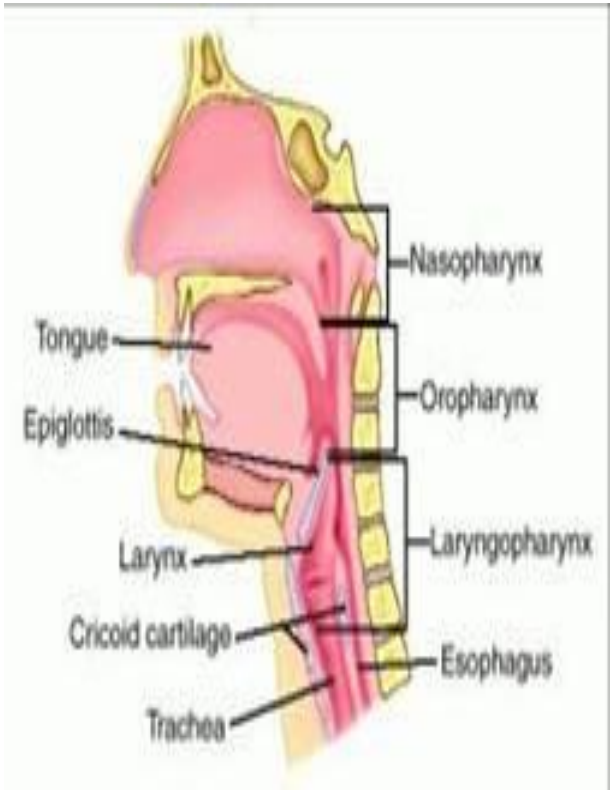
Topics

- **Introduction of head and neck cancer.**
- **The role of chemotherapy in head and neck cancer.**
- **Recent advances of chemotherapy in head and neck cancer.**

頭頸癌

- 鼻咽癌
- 口腔癌 : 唇，舌， 頰， 牙齦，硬顎.. 等等
- 口咽癌 : 扁頭腺，舌根，軟顎 .. 等等
- 下咽癌
- 喉癌
- 其他 : 鼻腔癌， 唾液腺癌，副鼻竇癌... 等等



臺灣地區癌症十大死因, 2009

癌症類	死亡人數	死亡率 (/10^5)	百分比
總死亡數	39917	173.0	100.0
1.肺癌	7951	34.5	19.9
2.肝癌	7759	33.6	19.4
3.大腸直腸癌	4531	19.6	11.4
4.女性乳癌	1588	13.9	4.0
5.胃癌	2282	9.9	5.8
6.口腔口咽下咽癌	2249	9.7	5.6
7.攝護腺癌	936	8.0	2.3
8.食道癌	1489	6.5	3.7
9.胰臟癌	1480	6.4	3.7
10.子宮頸癌	657	5.7	1.6
15.鼻咽癌	674	2.9	1.7

男女性十大癌症發生率, 民國94年

(7159人)肝

(5566人)肺

(5497人)結腸及直腸

(4310人)口腔

(2704人)攝護腺

(2288人)胃

(1403人)食道

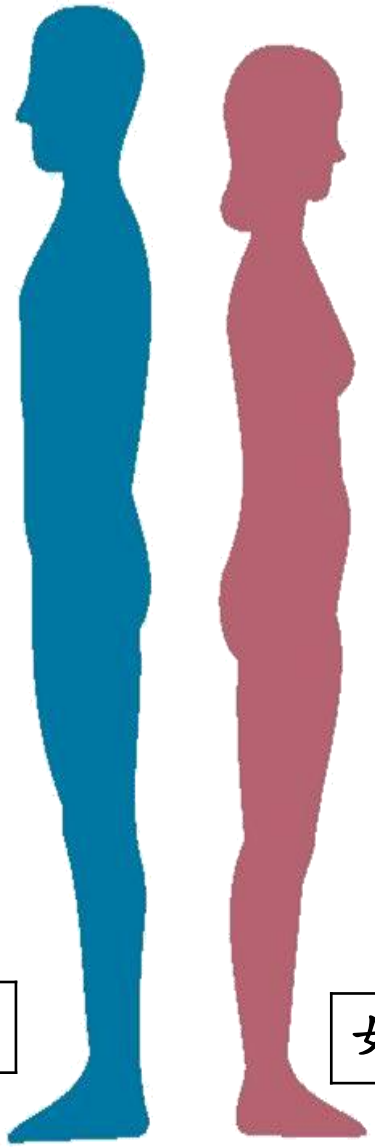
(1363人)膀胱

(1138人)皮膚

(1123人)鼻咽

(6879人)其他癌症

男性共39430人



乳房(6594人)

結腸及直腸(4107人)

肝(2757人)

肺(2746人)

子宮頸 (1977人)

胃(1292人)

甲狀腺(1146人)

皮膚(1039人)

子宮體(987人)

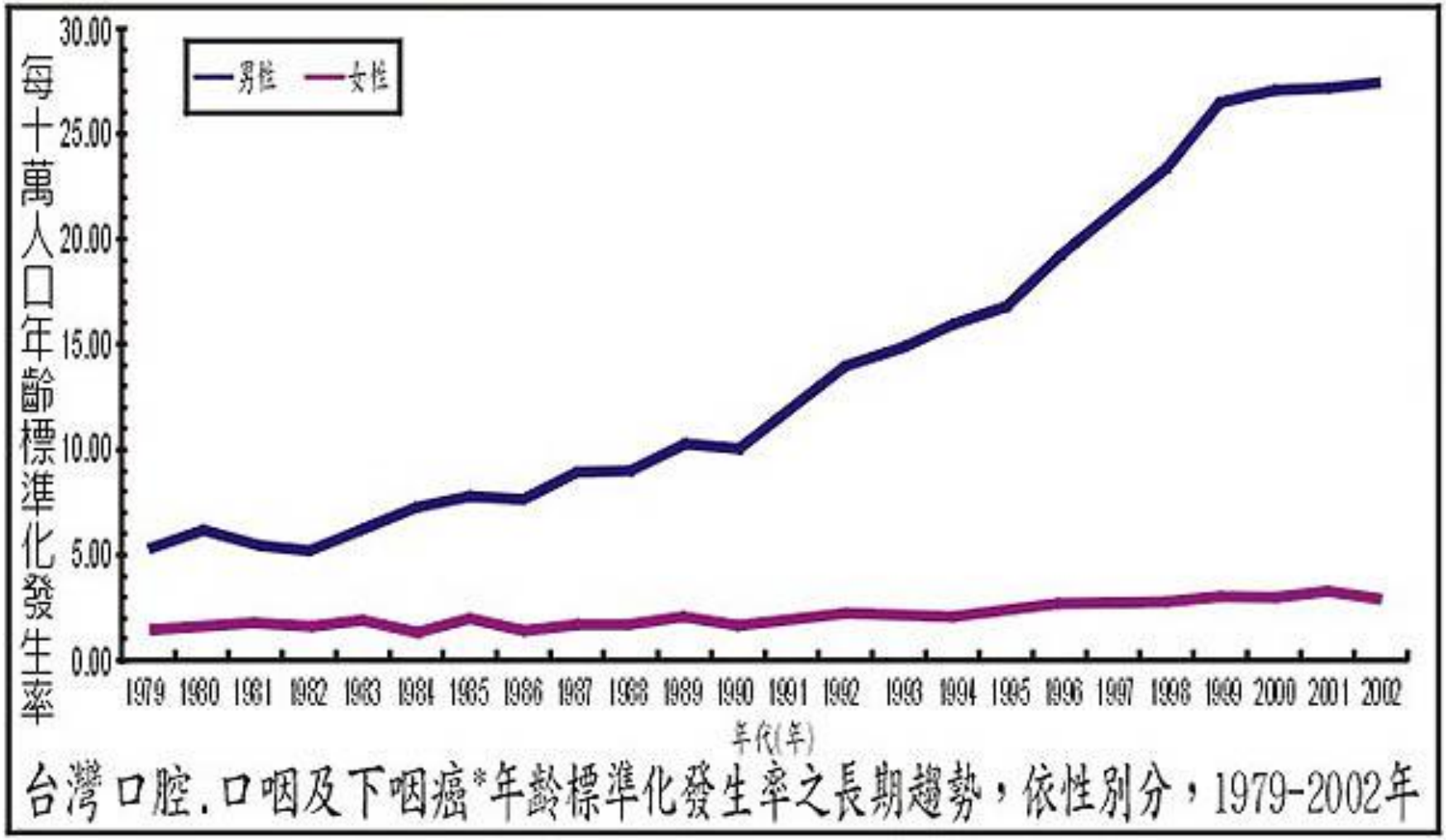
卵巢(894人)

其他癌症(5938人)

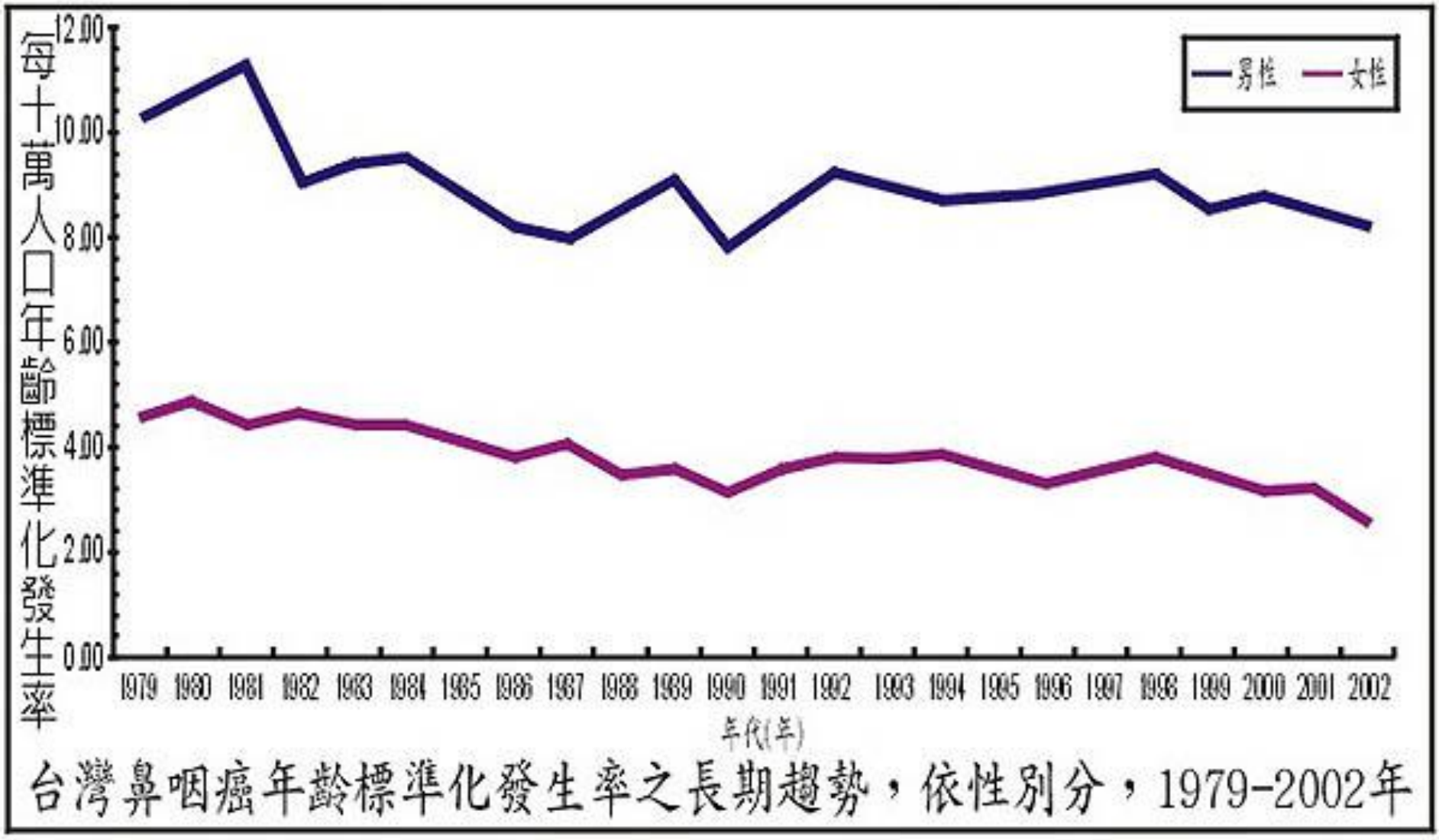
女性共29477人

臺灣地區男性癌症十大死因, 2009

癌症類	死亡人數	死亡率 (/10^5)	百分比
總死亡數	25284	217.4	100.0
1.肝癌	5467	47.0	21.6
2.肺癌	5336	45.9	21.1
3.大腸直腸癌	2562	22.0	10.1
4.口腔口咽下咽癌	2103	18.1	8.3
5.胃癌	1457	12.5	5.8
6.食道癌	1369	11.8	5.4
7.攝護腺癌	936	8.0	3.7
8.胰臟癌	871	7.5	3.4
9.白血病	571	4.9	2.3
10.非何杰金淋巴癌	542	4.7	2.1
11.鼻咽癌	526	4.2	2.1



台灣口腔.口咽及下咽癌*年齡標準化發生率之長期趨勢，依性別分，1979-2002年



台灣鼻咽癌年齡標準化發生率之長期趨勢，依性別分，1979-2002年

圖表資料來自國健局

95-97年台東縣十大惡性腫瘤排名一覽表

排名	95 年	96 年	97 年
1	肺癌	肺癌	氣管、支氣管和肺癌
2	肝癌	肝癌	肝和肝內膽管癌
3	口腔癌	口腔癌	口腔癌
4	食道癌	結腸直腸癌	胃癌
5	結腸直腸癌	胃癌	結腸、直腸和肛門癌
6	胃癌	食道癌	子宮頸及部位未明示子宮癌
7	攝護腺癌	攝護腺癌	前列腺(攝護腺)癌
8	子宮頸癌	子宮頸癌	食道癌
9	女性乳癌	女性乳癌	女性乳房癌
10	鼻咽癌	胰臟癌	胰臟癌
惡性腫瘤死亡人數	494	567	496
每十萬人口死亡率	208.0	241.50	213.1

資料來源：行政院衛生署

97年台東縣與鄰近縣市之十大惡性腫瘤排名比較表

縣市 / 排名	高雄縣	屏東縣	花蓮縣	台東縣
1	肝和肝內膽管癌	肝和肝內膽管癌	氣管、支氣管和肺癌	氣管、支氣管和肺癌
2	氣管、支氣管和肺癌	氣管、支氣管和肺癌	肝和肝內膽管癌	肝和肝內膽管癌
3	結腸、直腸和肛門癌	結腸、直腸和肛門癌	結腸、直腸和肛門癌	口腔癌
4	口腔癌	口腔癌	口腔癌	胃癌
5	女性乳房癌	女性乳房癌	胃癌	結腸、直腸和肛門癌
6	食道癌	食道癌	前列腺(攝護腺)癌	子宮頸及部位未明示子宮癌
7	胃癌	胃癌	食道癌	前列腺(攝護腺)癌
8	子宮頸及部位未明示子宮癌	子宮頸及部位未明示子宮癌	女性乳房癌	食道癌
9	前列腺(攝護腺)癌	前列腺(攝護腺)癌	子宮頸及部位未明示子宮癌	女性乳房癌

頭頸部癌症

- 台灣地區每10名新癌症病患中，就有1位是頭頸癌患者 。
- 好發機率依序為口腔癌、鼻咽癌、喉癌、下咽癌。
- 但台灣一半以上的口腔癌病人發現時，都已第三期、第四期。

頭頸部癌症發生原因

抽菸 :18倍

酒 : 10倍

檳榔 : 28倍

煙+酒+檳榔 : 123 倍

頭頸部癌症發生原因

- 病毒 ： EBV病毒 => 鼻咽癌

  人類乳突狀病毒 => 口咽癌
- 遺傳 ： 一等親內如果有人罹患鼻咽癌，此人發生鼻咽癌的機率唯一般人的16.3倍。
- 食物 ： 鹽醃製品
- 環境汙染物 :含硫酸的強無機酸霧 => 喉癌

頭頸癌是台灣男性重要健康問題

- 94年有4,310人罹病及96年有2,152人死亡，人數持續增加。
- 是發生率和死亡率增加最快的癌症，5年內各增加30%及25%。
- 為青壯年（25-44歲）男性最易罹患的癌症。
- 平均死亡年齡55歲，較其它癌症年輕10歲以上。

Topics

- **Introduction of head and neck cancer.**
- **The role of chemotherapy in head and neck cancer.**
- **Recent advances of chemotherapy in head and neck cancer.**

化學治療於頭頸癌的運用

- 前導性化療 (Neoadjuvant chemotherapy) : 在局部性治療(手術及放射線治療)以前所做的化療就是前導性化療。目的為減少局部腫瘤體積，使開刀較容易，減少遠處轉移以及評估腫瘤對化學治療的反應。

- 併行性放射線化學治療 (Concurrent chemoradiation) : 同時進行放射線治療及化學治療。目的在增強放射線效果同時有細胞毒殺的功用。

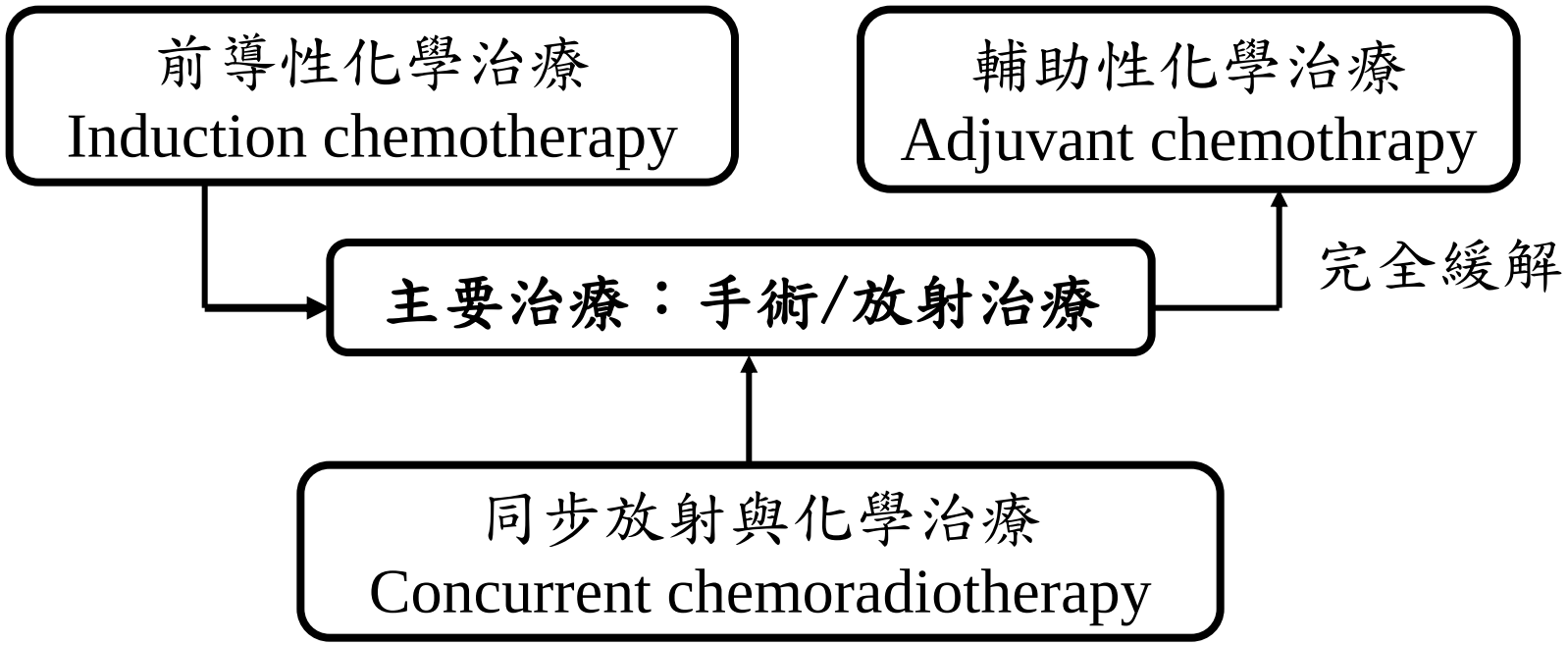
- 輔助性化療 (Adjuvant chemotherapy) :施行於外科手術或放射線治療後，用以殺死肉眼看不見之殘餘癌細胞。目的在減少局部復發及減少遠處轉移的機率。

- 救援性化療 (Salvage chemotherapy) :當第一線治療失敗時，所進行之第二線治療。目的仍以腫瘤為治療目標, 積極地朝治癒方向進行。

- 緩和性化療 (Palliative chemotherapy) :針對轉移性疾病，保守地不以治癒為目標，使用化療藥物減輕癌症引起的症狀，提高病人的生活品質，即使無法延長生命。

固態腫瘤(solid tumor) 的化學治療

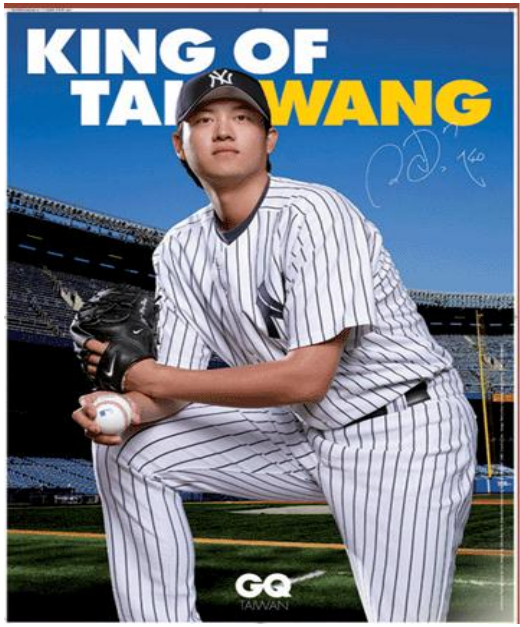
1. 治癒性



2. 姑息性：姑息性化學治療(Palliative chemotherapy)
：復發或遠處轉移病患

化學治療在頭頸癌治療

- 過去化學治療在頭頸癌多半是擔任「症狀緩解治療」的角色，對於復發、轉移之病患以化療減輕症狀，延長生命



- 現在化學治療在頭頸癌的地位，已由過去「救援投手」的角色升任為第一線「先發投手」：

(-) EORTC, RTOG 9111 ：化學治療提升局部晚期頭頸部癌症的器官的保存率

(二) RTOG 9501, EORTC 22931 :化學放射同步治療可提升頭頸癌治癒率

頭頸癌治療原則

- **鼻咽癌**：放射線治療
  化學治療
  標靶治療 (自費)

- **口腔癌**：手術切除
  +/- 放射線治療 / 化學治療 / 標靶治療 (自費)

- **咽喉癌**：

=> 全喉切除 +/- 放射線治療/ 化學治療

=>放射線治療 + 化學治療或標靶治療，若效果不佳再作全喉切除

Milestones in chemotherapy-radiotherapy for SCCHN

ASCO 1982	cisplatin + 5FU, chemo ⇔ radiosensitivity
NEJM 1991	VA trial on larynx preservation
JNCI 1996	EORTC trial on larynx preservation
Lancet 2000	Concurrent CT-RT > sequential CT-RT
NEJM 2003	RTOG 91-11 trial on larynx preservation
NEJM 2004	RTOG 9501 & EORTC 22931 on post-OP adjuvant CCRT
ASCO 2004	→ Taxotere based Induction (TCF) > induction CF → RT + concurrent cisplatin → Erbitux + RT
ASCO 2006	→ Sequential - concurrent CT-RT → Taxotere based Induction (TCF) as a new standard → Molecular targeted therapies

Topics

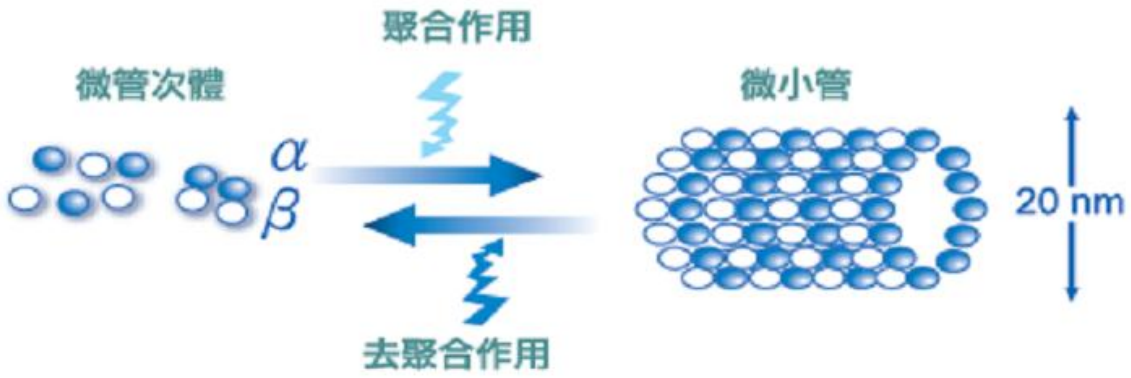
- **Introduction of head and neck cancer.**
- **The role of chemotherapy in head and neck cancer.**
- **Recent advances of chemotherapy in head and neck cancer.**

化學治療在頭頸癌治療

- 傳統以使用順鉑 (Cisplatin) 與 5-FU 兩種藥物為主
- 新一代的化學治療藥物 : Taxotere
- 標靶藥物 : Erbitux

Taxane的作用方式

- Taxane類藥物會促進Tubulin的polymerization作用並抑制Microtubule的depolymerization而形成穩定但無功能之微小管束，在細胞分裂期間，妨礙兩套染色體被分離至2個子細胞中，細胞因此停滯於細胞分裂期，由於不正常的有絲分裂及細胞漿移動(cytokinesis)而死亡。
- 簡單的說, 就是停止細胞內微小管的活動, 進而使癌細胞停止分裂進而死亡.



（圖4. Docetaxel在微小管層次的作用機轉。）

ORIGINAL ARTICLE

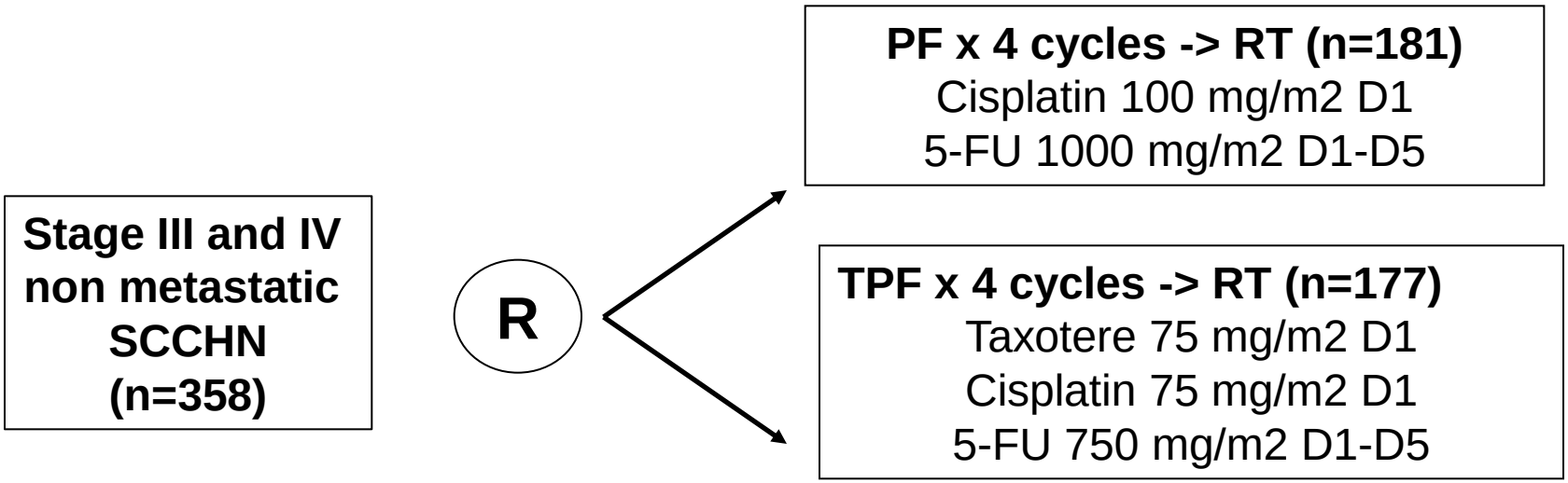
Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Eva Remenar, M.D., Carla van Herpen, M.D., Ph.D., Thierry Gorlia, M.Sc., Ricard Mesia, M.D., Marian Degardin, M.D., John S. Stewart, M.D., Svetislav Jelic, M.D., Jan Betka, M.D., Joachim H. Preiss, M.D., Ph.D., Danielle van den Weyngaert, M.D., Ahmad Awada, M.D., Ph.D., Didier Cupissol, M.D., Heinz R. Kienzer, M.D., Augustin Rey, M.D., Isabelle Desaunois, M.Sc., Jacques Bernier, M.D., Ph.D., and Jean-Louis Lefebvre, M.D., for the EORTC 24971/TAX 323 Study Group*

N Engl J Med 2007;357:1695-704.

TPF in locally advanced SCCHN: phase III study design

Patients : unresectable SCC of the HN cancer.



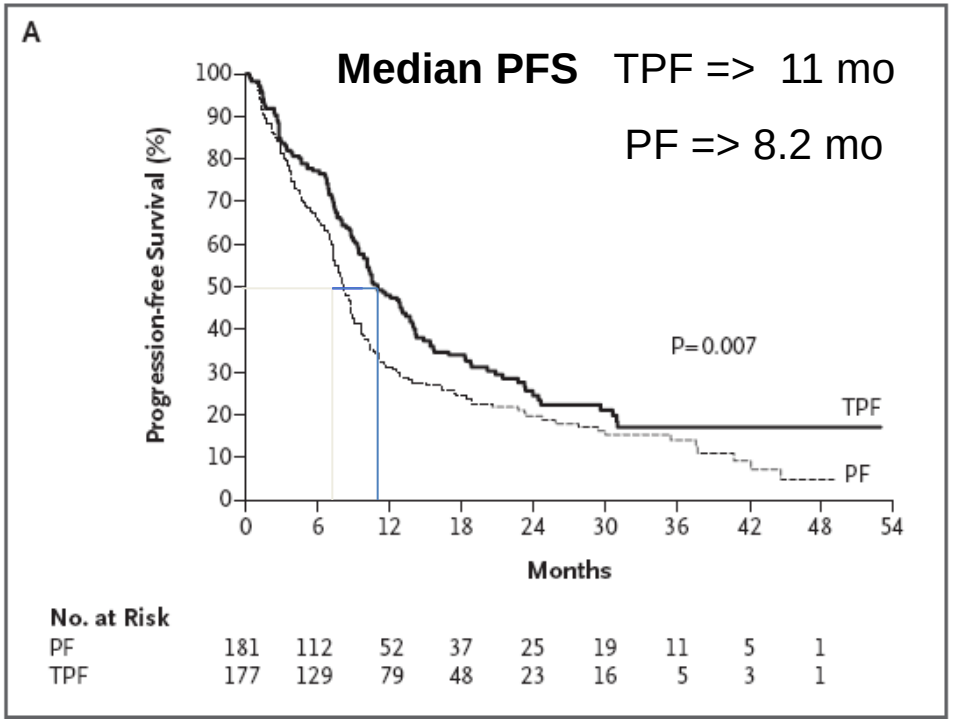
Primary endpoint: progression – free survival

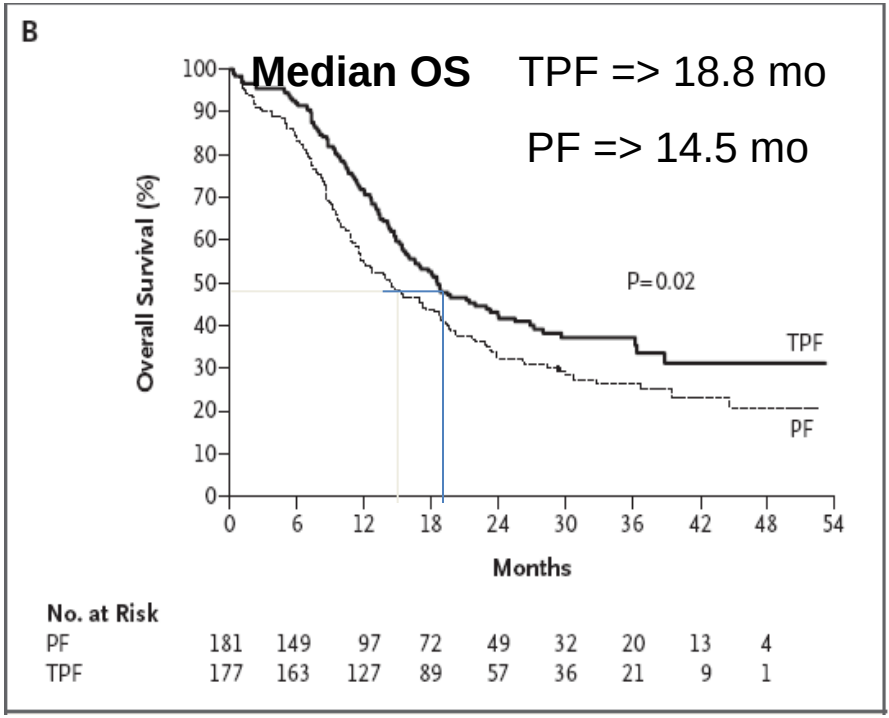
Secondary endpoints: OS, TTF, duration of response, and safety

N Engl J Med 2007;357:1695-704.

Outcome

- Median F/U : 32.5 mo





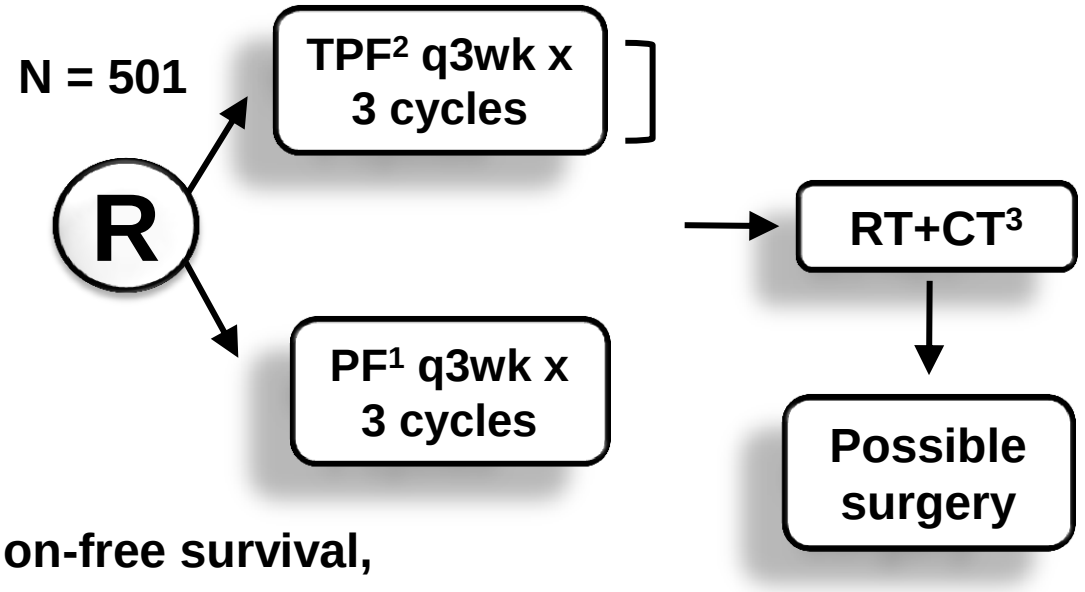
TPF reduces 28% in the risk of disease progression or death compared with PF

TAX 324 Phase III Trial of Induction Docetaxel-Cisplatin-5FU (TPF) vs PF in Unresectable HNC: Study Design

Patient Population
- Stage III or IV
- Inoperable SCCHN

Stratification
- Center
- N status
- Primary site

Endpoints
- Primary: OS
- Secondary: progression-free survival, response rates after induction, toxicity



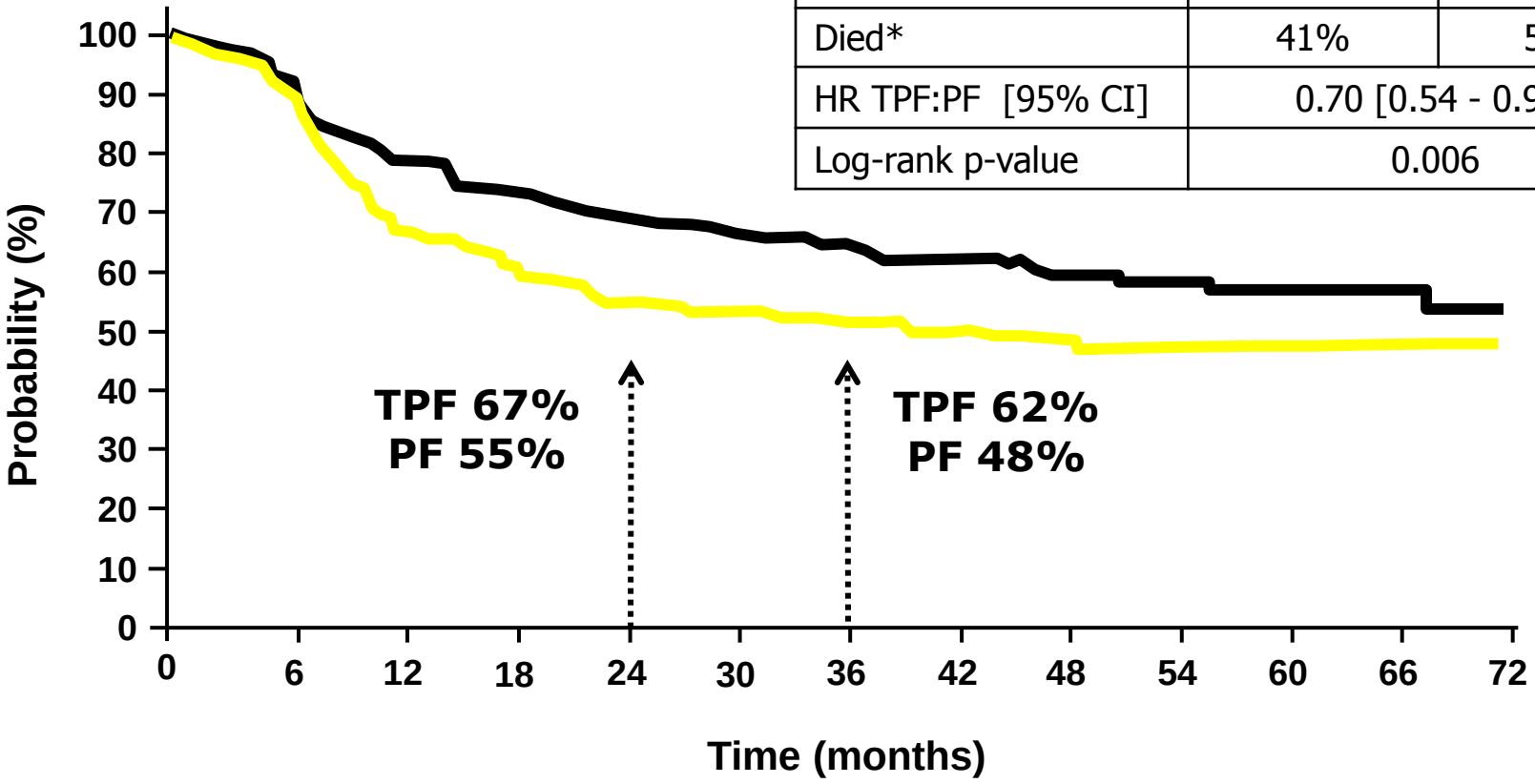
[1] Cisplatin: 100 mg/m² D1 – 5FU: 1000 mg/m² D1 - D5
[2] Docetaxel: 75 mg/m² D1 - CDDP: 100 mg/m² D1 – 5FU: 1000 mg/m² D1 - D4
[3] Weekly Carboplatin (AUC 1.5) x 7 - Conventional radiotherapy = 70 Gy

Posner et al. N Engl J Med. 2007;357:1705-17115.

TAX 324: Overall Survival

Median Follow-up: 42 Months

Parameter	TPF (n=255)	PF (n=246)
Median OS, mo (95% CI)	71 49 - NR	30 21 - 52
Died*	41%	53%
HR TPF:PF [95% CI]	0.70 [0.54 - 0.90]	
Log-rank p-value	0.006	



Posner et al. N Engl J Med. 2007;357:1705-17115.

TAX 324: Toxicity During Induction Chemotherapy

Number of patients	TPF (n=251)	PF (n=243)
NCIC-CTC Classification	Grade 3/4	Grade 3/4
Anemia	12%	9%
Thrombocytopenia	4%	11%*
Neutropenia	83%	56%*
Febrile neutropenia	12%	7%*
Nausea	14%	14%
Alopecia	4%	1%
Stomatitis	21%	27%
Lethargy	5%	10%*
Vomiting	8%	10%
Diarrhea	7%	3%
Anorexia	12%	12%

***Statistically significant (P < .05)**

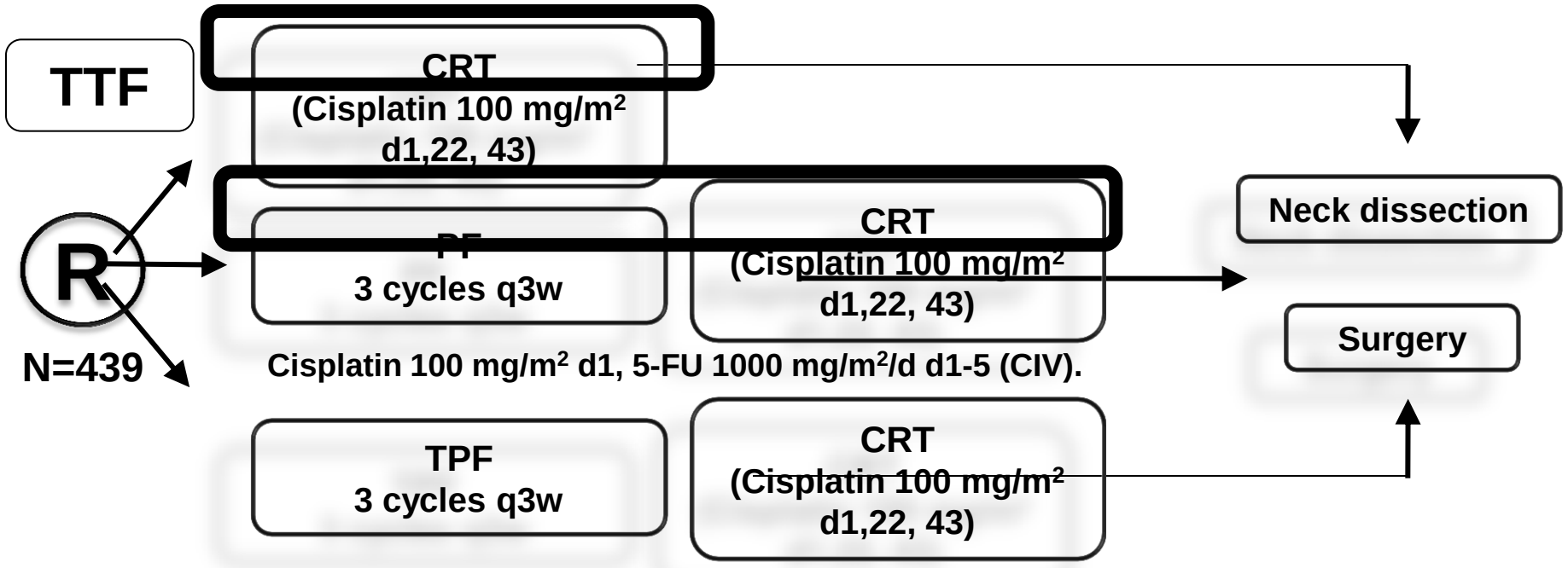
Posner et al. N Engl J Med. 2007;357:1705-17115.

TAX 324 Phase III Trial of Induction TPF: Key Points

- TPF significantly improves survival versus PF
  - 14% absolute improvement in 3-y survival
  - 10% absolute improvement in 5-y survival
  - 26% reduction in mortality (P = 0.014)
- Sequential therapy with TPF is tolerable and safe
  - Toxicity of TPF arguably less than that of PF
  - No significant difference in long-term toxicities (enteral feeding tube and tracheostomy)
- Sequential therapy with TPF followed by carboplatin-based chemoradiotherapy represents an acceptable standard of care for locally-advanced SCCHN

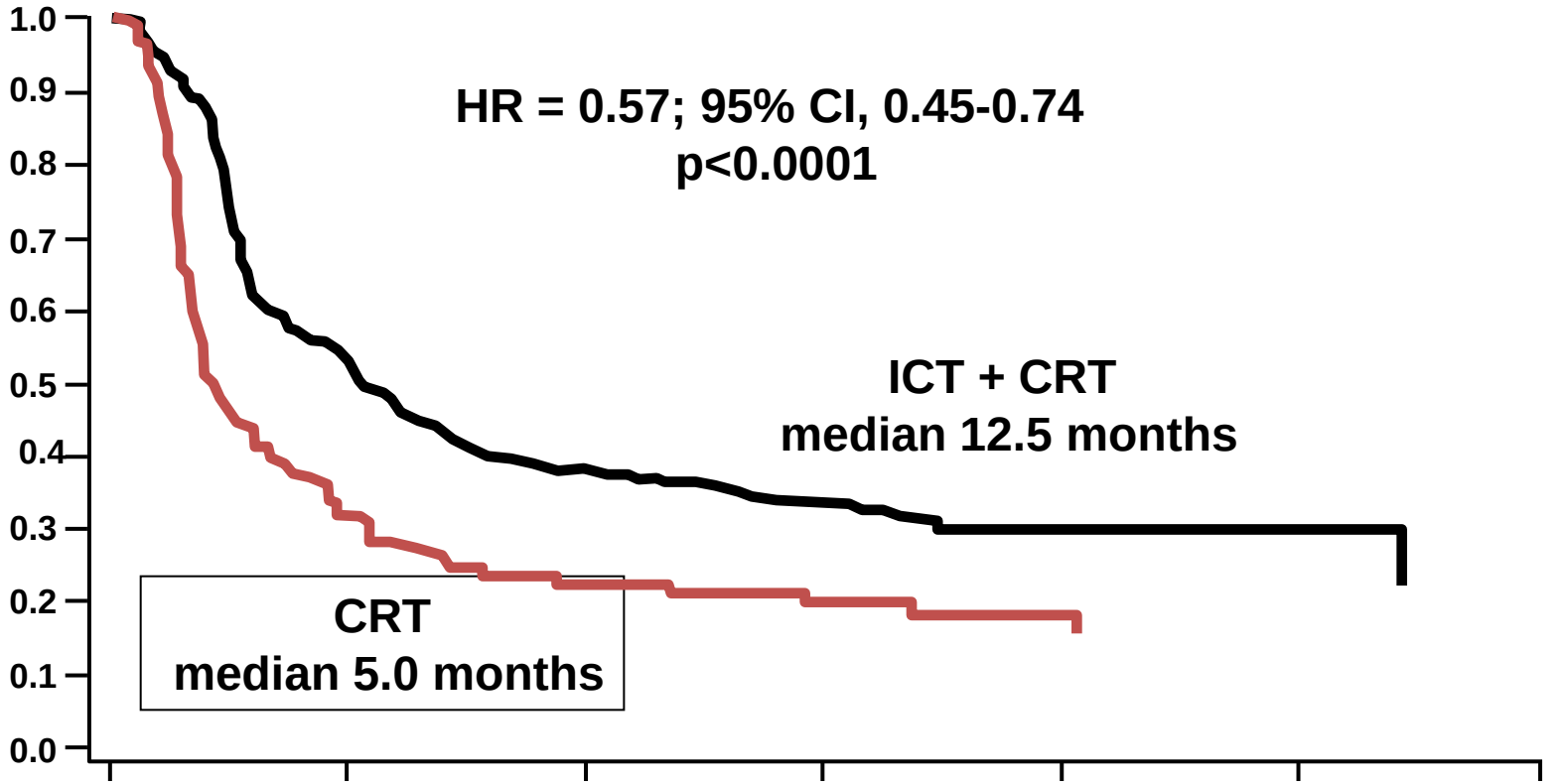
Phase III Trial of Induction (T)PF → CT-RT vs CT-RT Alone in Unresectable Locally Advanced HNC: Study Design

- Primary endpoint: TTF in evaluable population (Time from randomization to progression, recurrence, surgery, death, withdrawal due to adverse events or no locoregional control)
- Secondary endpoints: locoregional control, TTP, OS, safety



Hitt *et al.* ASCO 2009. Abstract 6009.

Phase III Trial of Induction (T)PF → CT-RT vs CT-RT: TTF (evaluable)



Phase III Trial of Induction (T)PF → CT-RT vs CT-RT: Key Points

- Induction chemotherapy (ICT) prior to chemoradiotherapy
  - is achievable, with manageable safety
  - resulted in a doubling of time to treatment failure and significant benefit in locoregional control

- The outcomes suggest that ICT prior to CRT should now be considered as standard in patients with unresectable LAHNC

Taxane in the treatment of HNC

NCCN National Comprehensive Cancer

NCCN Guidelines Version 1.2012
Head and Neck Cancers

NCCN Guidelines Index
Head and Neck Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

The choice of chemotherapy should be individualized based on patient characteristics (performance status, goals of therapy).

- The standard therapy for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy.
- Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (ie, sequential chemoRT). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state of the art concurrent chemoRT (cisplatin preferred, category 1) has not been established. Randomized phase III studies comparing sequential chemotherapy/RT to concurrent chemotherapy/RT alone are ongoing.
- Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is not recommended due to toxicity concerns.[1,2]
- After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus cetuximab or weekly carboplatin are among the options.

Squamous Cell Cancers

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- Primary systemic therapy + concurrent RT
  - Cisplatin alone[3,4] (preferred) (category 1)
  - Cetuximab[5] (category 1)
  - Carboplatin/infusional 5-FU (category 1)[6,7]
  - 5-FU/hydroxyurea[8]
  - Cisplatin/paclitaxel[8]
  - Cisplatin/infusional 5-FU[9]
  - Carboplatin/paclitaxel[10] (category 2B)
- Postoperative chemoradiation
  - Cisplatin alone[11-14] (category 1 for high risk)

Nasopharynx:

- Chemoradiation followed by adjuvant chemotherapy
  - Cisplatin + RT followed by cisplatin/5-FU[15,16] (category 1)

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- Induction*/Sequential chemotherapy
  - Docetaxel/cisplatin/5-FU[17-19] (category 1 if induction is chosen)
  - Paclitaxel/cisplatin/infusional 5-FU[20]
  - Following induction, agents to be used with concurrent chemoradiation typically include weekly carboplatin or cetuximab.[21]

Nasopharynx:

- Induction*/Sequential chemotherapy
  - Docetaxel/cisplatin/5-FU[22]
  - Cisplatin/5-FU[18]
  - Cisplatin/epirubicin/paclitaxel
  - Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[16] or carboplatin.[21]

Non-NPC head and neck cancer

For neo-adjuvant/induction regimen

Cisplatin 100 (75) mg/m2 D1 (or D6)
5-FU 1000 (750) mg/m2 D1~D5

5-FU 2600mg/m2 D1
Cisplatin 75mg/m2 D2

Taxotere 50-75mg/m2 D1
Cisplatin 50-75mg/m2 D1
5FU 500-750mg/m2 D1-D5

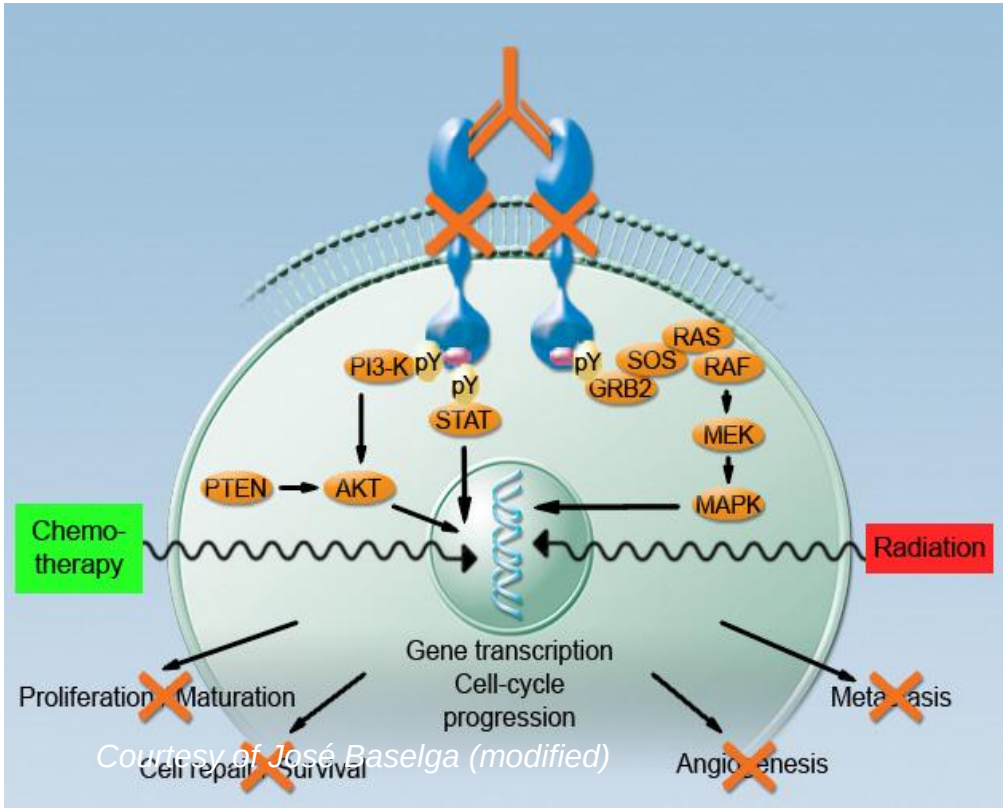
For adjuvant regimen

Cisplatin 100 (75) mg/m2 D1 (or D6)
5-FU 1000 (750) mg/m2 D1~D5

5-FU 2600mg/m2 D1
Cisplatin 75mg/m2 D2

Taxotere 50-75mg/m2 D1
Cisplatin 50-75mg/m2 D1
5FU 500-750mg/m2 D1-D5

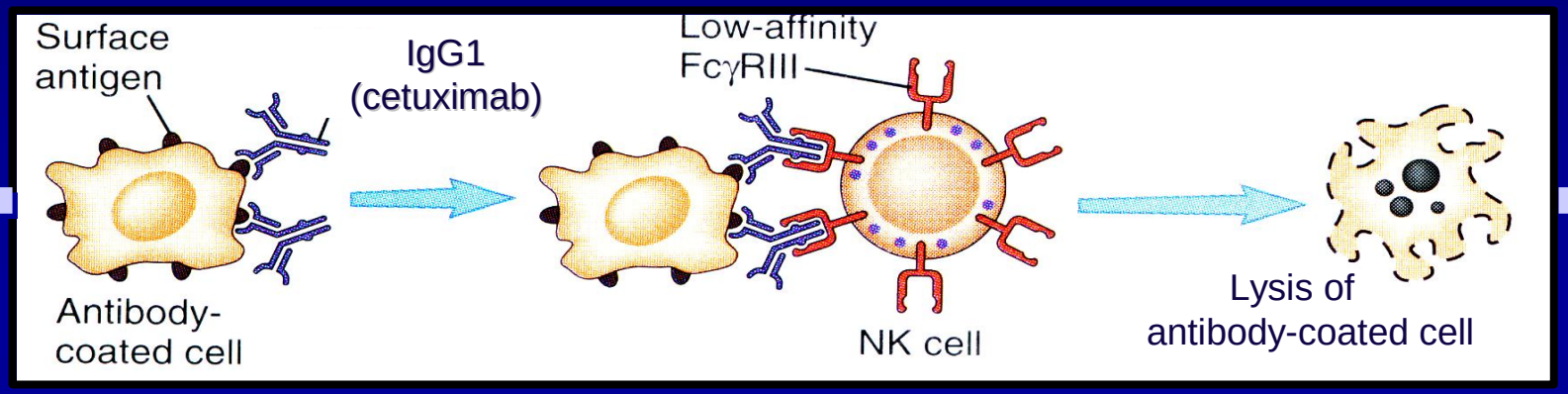
Target Therapy - **Cetuximab**
Mechanisms of action
- Erbitux® (Cetuximab) -



Courtesy of José Baselga (modified)

- **Erbitux is an IgG1 MAb targeting the EGFR**
- **Binding blocks EGFR signaling and inhibits proliferation, angio-genesis and metastasis, and stimulates apoptosis and differentiation**
- **Fc region may induce antibody-dependent cell-mediated cytotoxicity (ADCC) (immune response)**

Cetuximab: IgG1-Induced Antibody-Dependent Cell Cytotoxicity (ADCC)



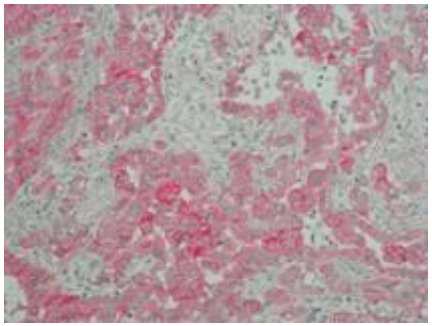
EGFR MEDIATED Anti-tumour Activity

IgG1 MEDIATED ADCC

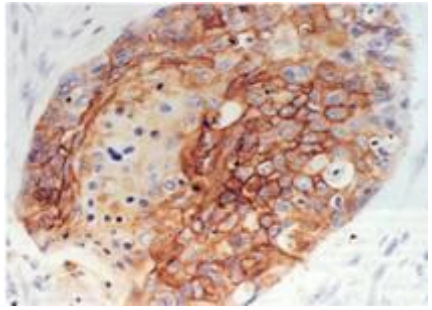
MAXIMIZE ANTI-TUMOUR ACTIVITY

Fan Z, et al. *Cancer Res*.1993;53:4322-8

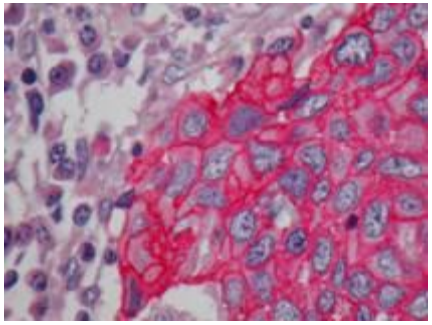
EGFR expression in selected human tumors



Colorectal



Lung (NSCLC)



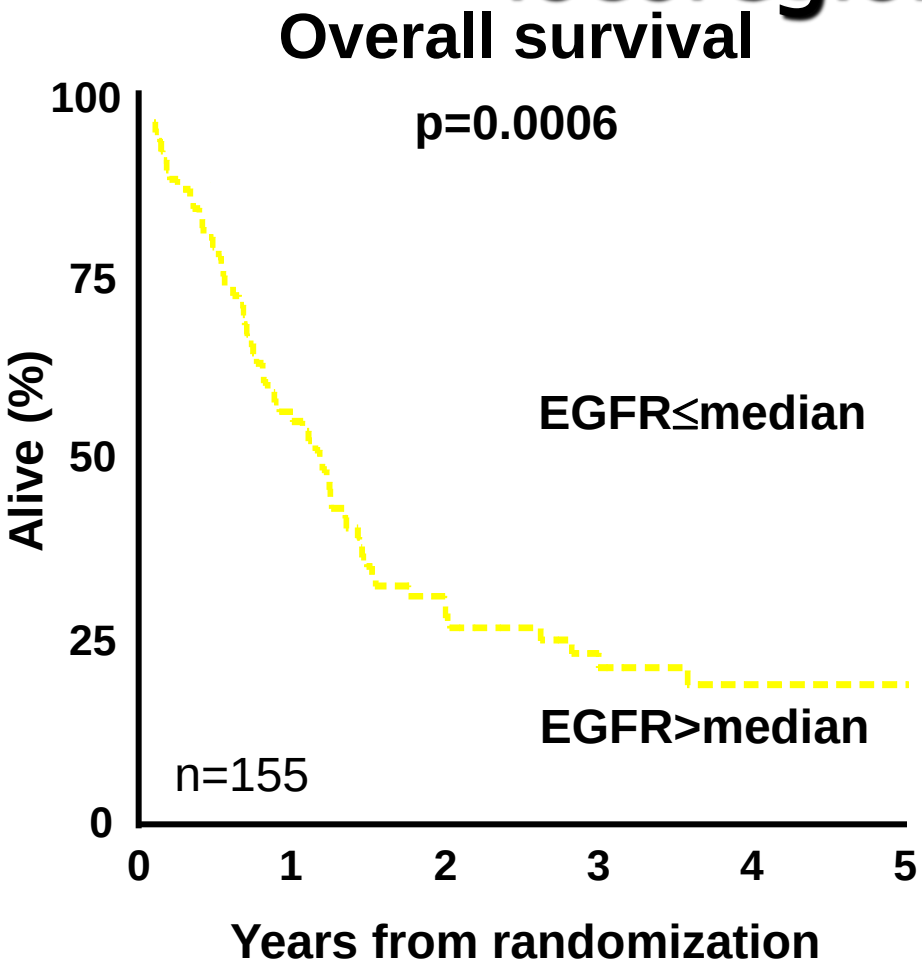
Head & Neck (SCC)

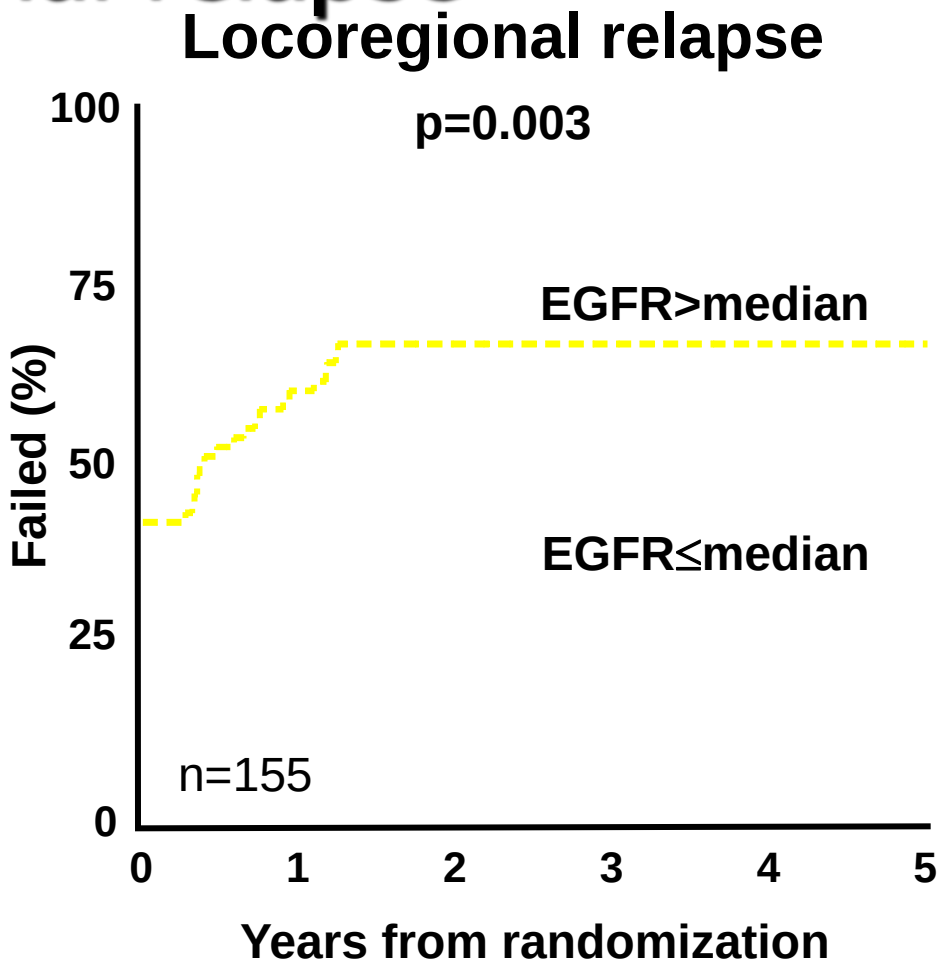
EGFR is expressed in a variety of solid tumors

Head & neck cancer	90 – 100%
Lung cancer (NSCLC)	40 – 91%
Colorectal cancer	72 – 84%
Breast cancer	14 – 91%
Ovarian cancer	35 – 70%
Renal cell cancer	50 – 90%

Cunningham et al. *N Engl J Med* 2004;351:337–345; Grandis et al. *Cancer* 1996;78:1284–1292; Salomon et al. *Crit Rev Oncol Hematol* 1995;19:183–232; Walker & Dearing. *Breast Cancer Res Treat* 1999;53:167–176; Folprecht et al. ASCO 2004 (Abstract #283).

High EGFR expression in SCCHN is linked to lower survival and increased risk of locoregional relapse



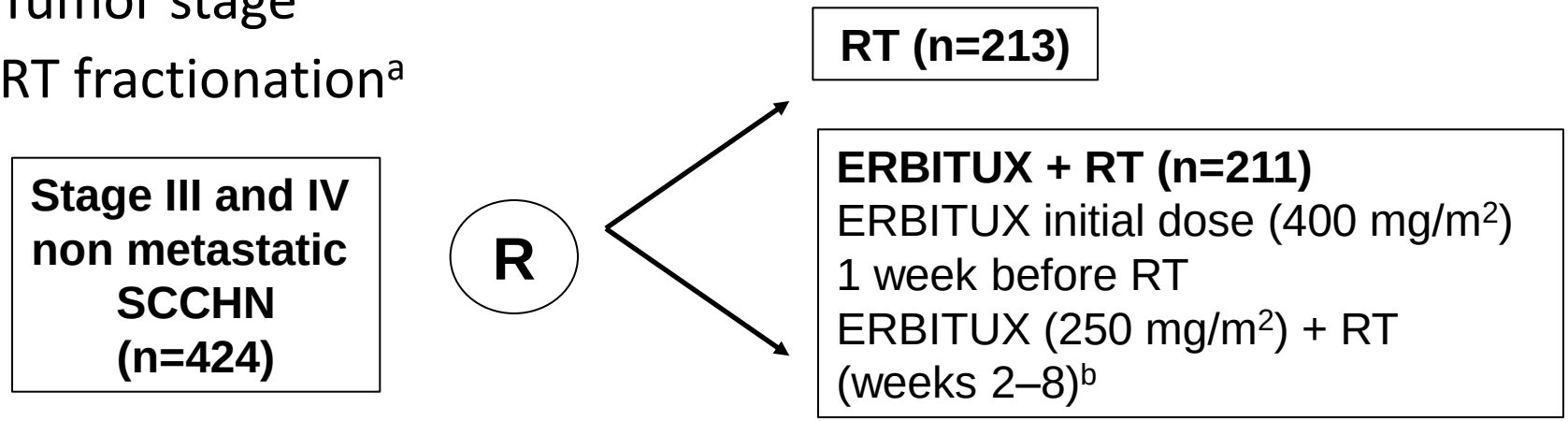


Ang K, et al. Cancer Res 2002;62:7350–7356

ERBITUX + RT in locally advanced SCCHN: phase III study design

Stratified by

- KPS
- Nodal involvement
- Tumor stage
- RT fractionation[a]

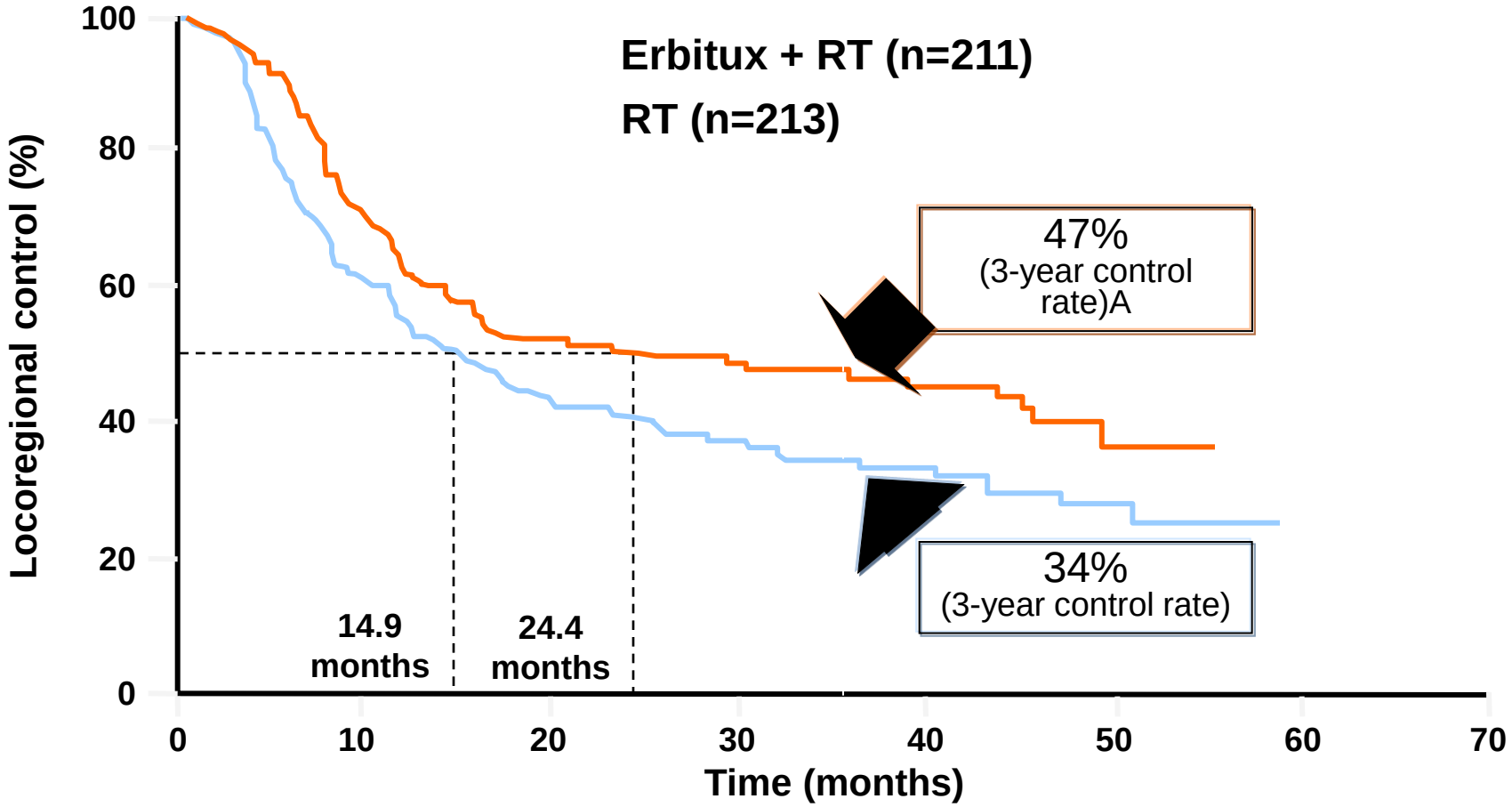


Primary endpoint: duration of locoregional control

Secondary endpoints: OS, PFS, RR, and safety

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

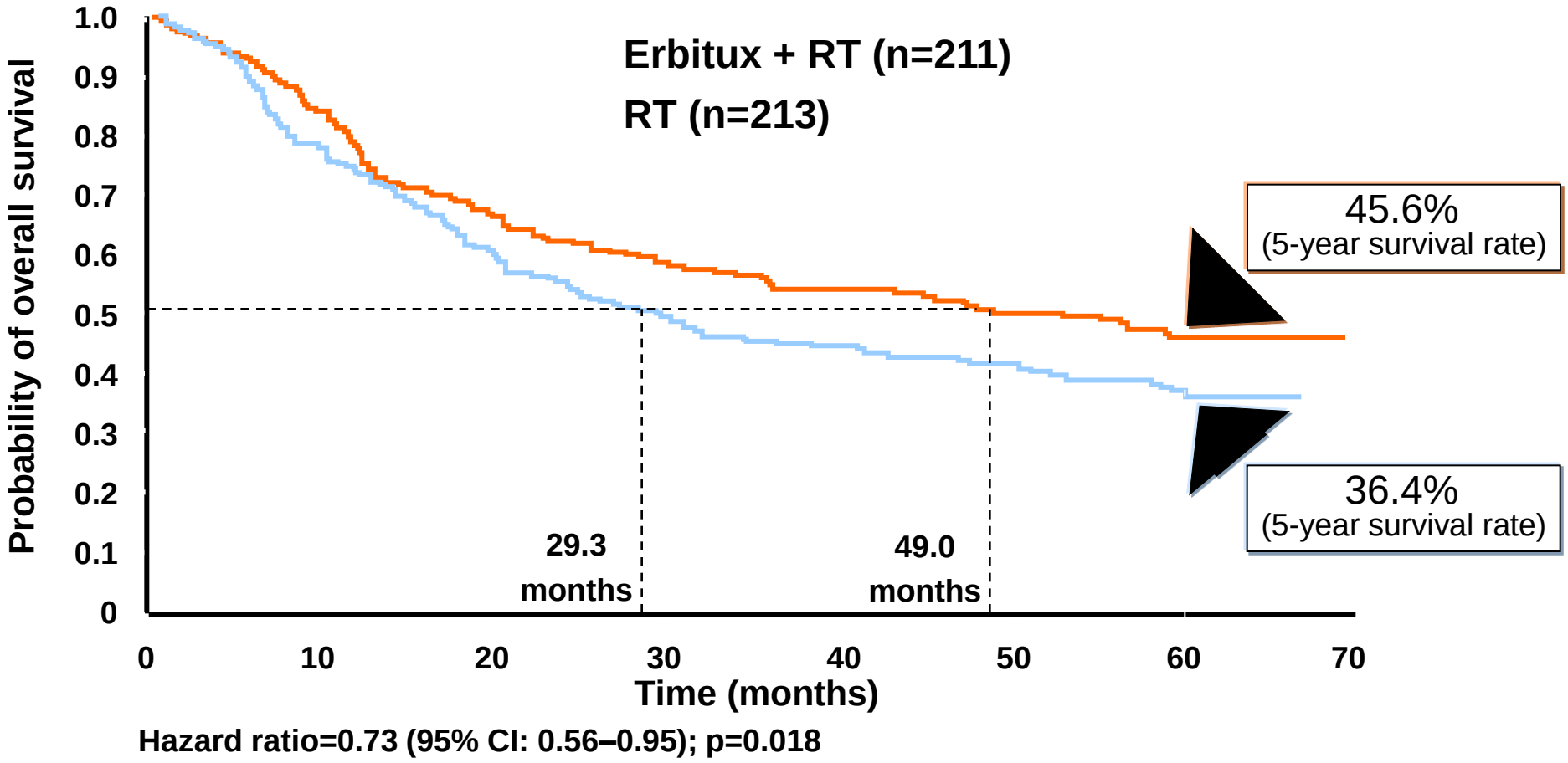
Erbitux + RT: Locoregional control



Hazard ratio=0.68 (95% CI: 0.52–0.89); p=0.005

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

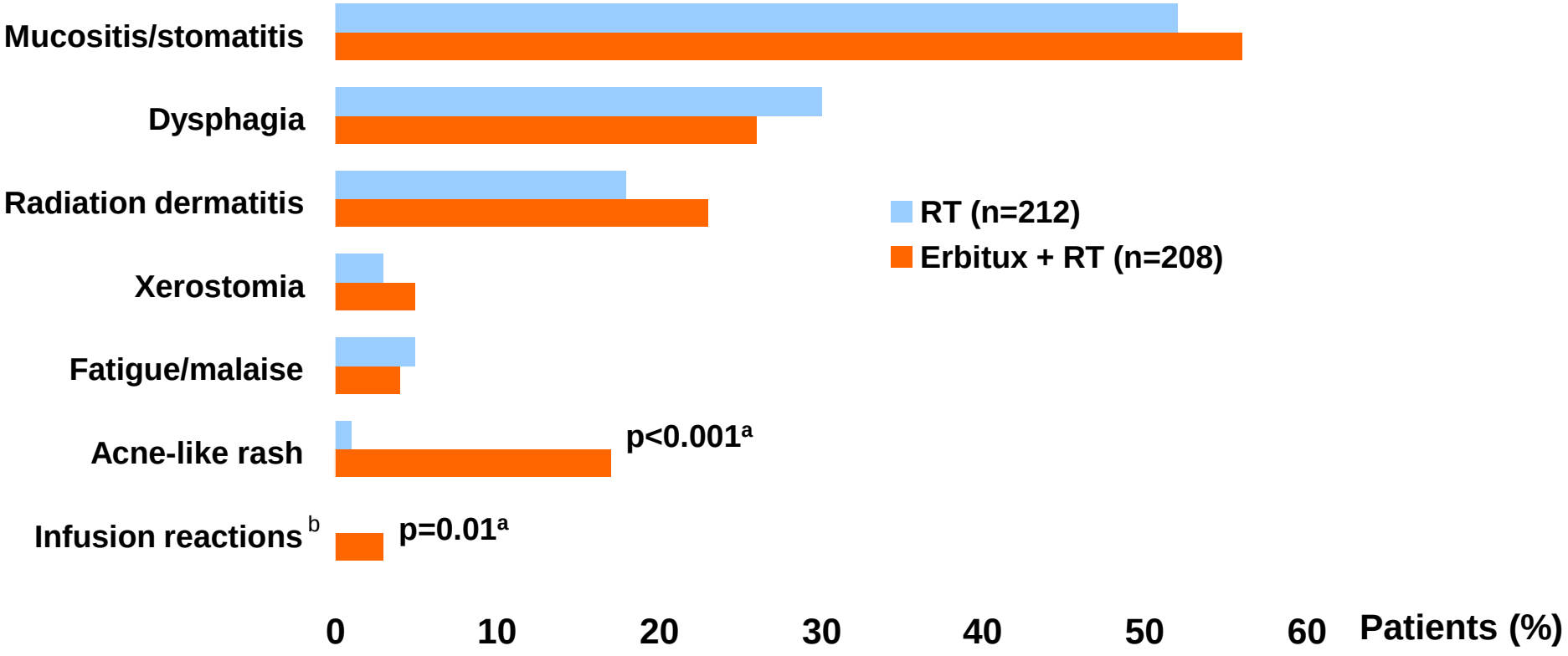
Erbitux + RT: Overall survival
5-year update



Hazard ratio=0.73 (95% CI: 0.56–0.95); p=0.018

Bonner J et al. Lancet Oncology published online Nov 2009

Erbitux + RT: Relevant grade 3–5 adverse events



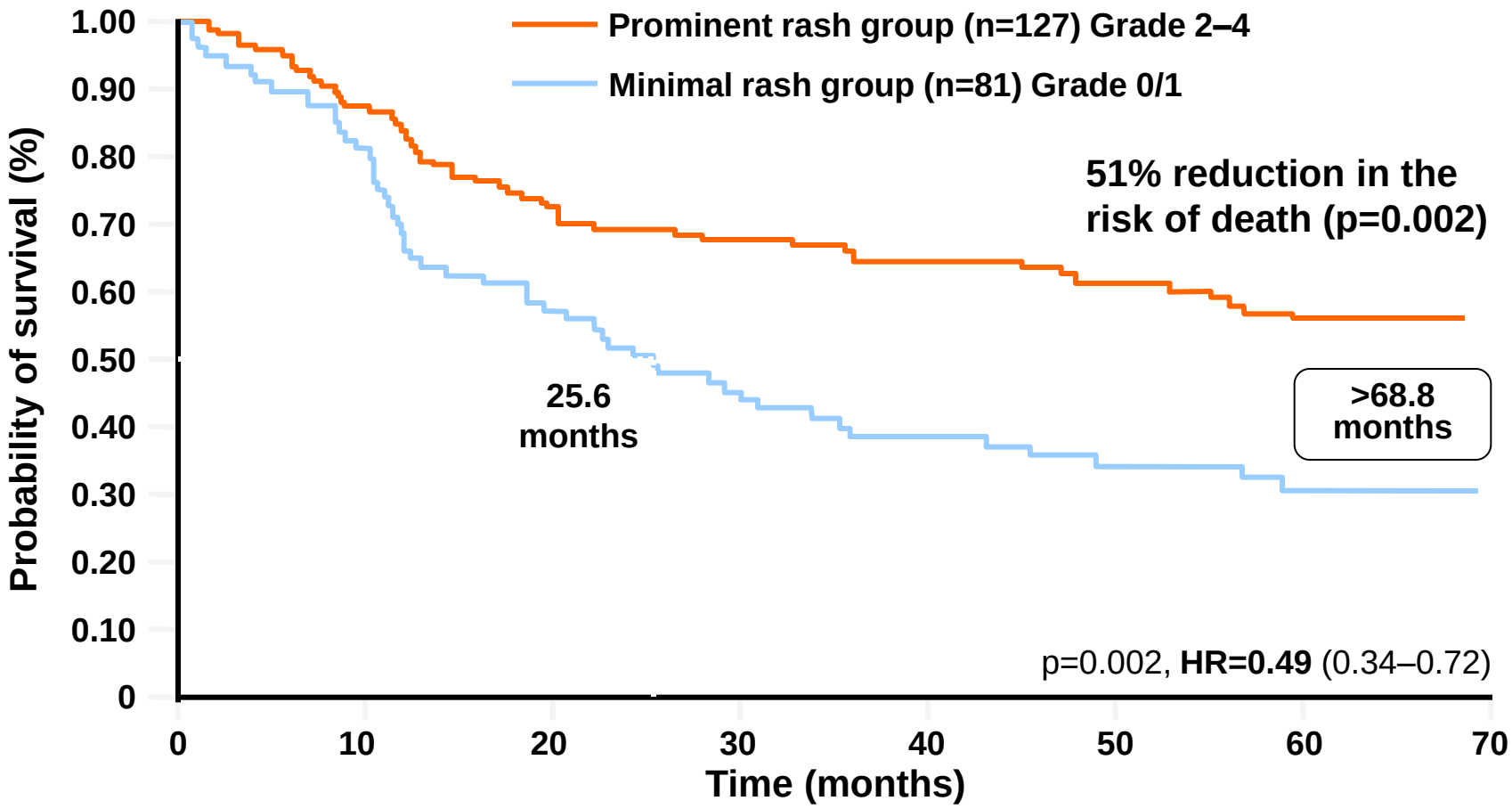
- **Median duration of any mucositis or dysphagia in the overall population was 12–13 weeks and similar in both treatment groups**

[a]Fisher's exact test
[b]Listed for its relationship to Erbitux

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

Erbitux + RT: Impact of skin rash grade on survival

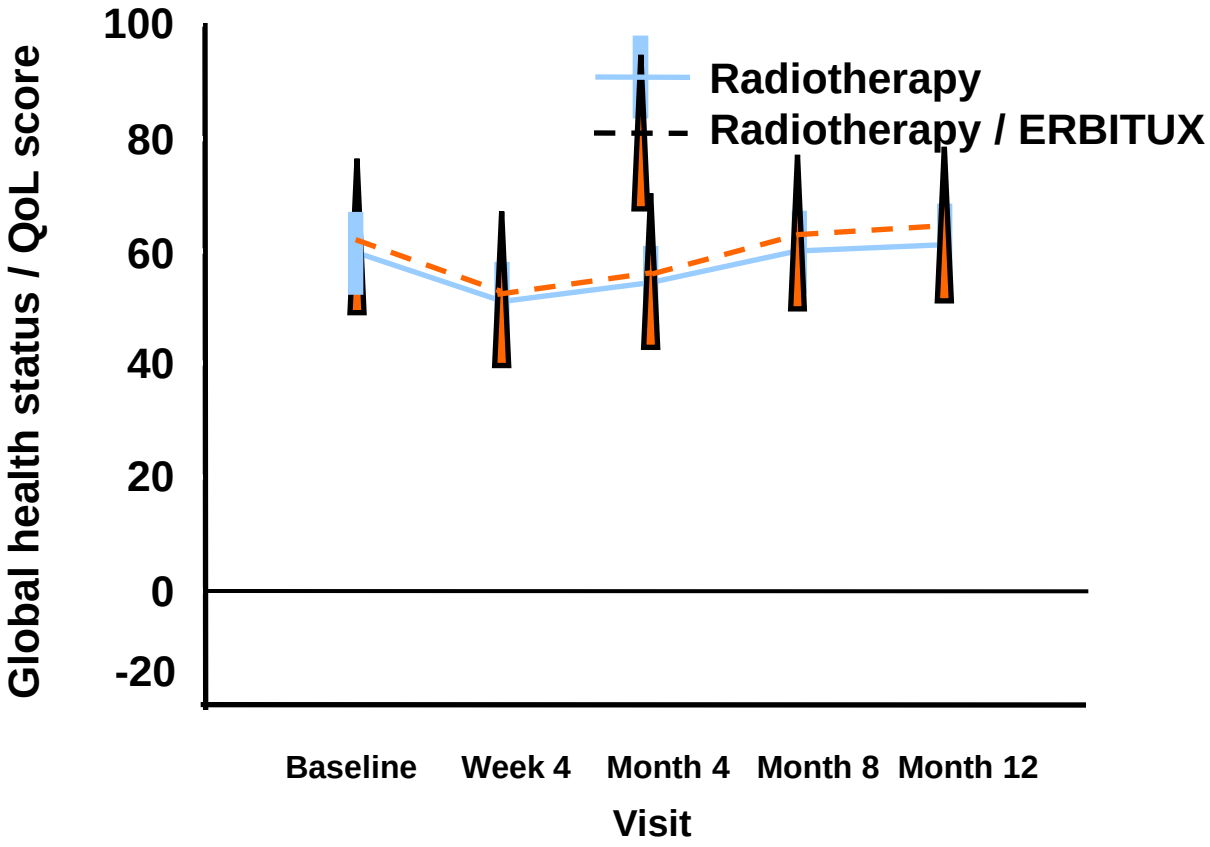
Development of skin rash is a strong predictive factor for prolonged survival



Bonner J et al. Int J Radiat Oncol Biol Phys 2008;72(Suppl):Abstract LB3

Phase III study: change of QoL* as a function of time

- ERBITUX + RT significantly improves locoregional control and overall survival **without** adversely affecting QoL

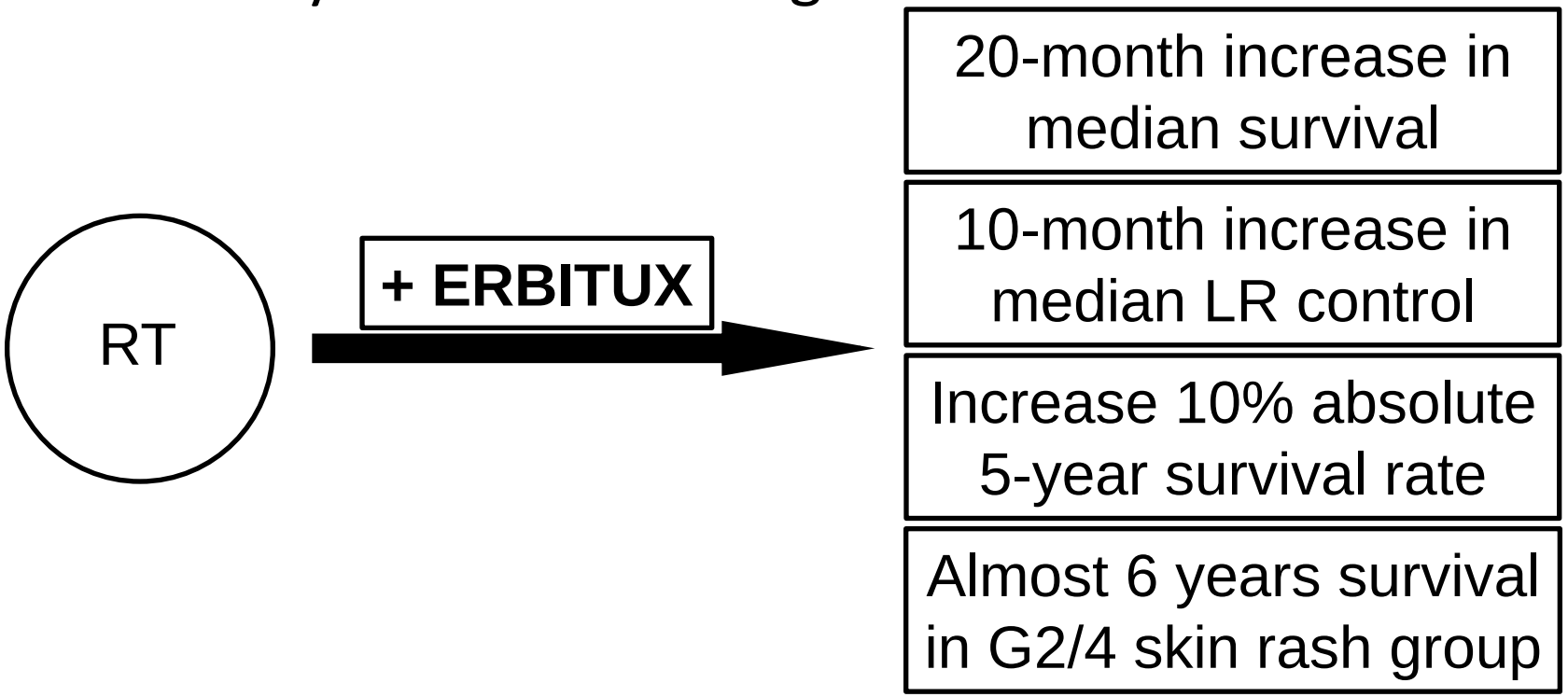


*Postbaseline scores for the QLQ-C30

Curran D, et al. J Clin Oncol 2007;25:2191–2197

ERBITUX in locoregionally advanced SCCHN: efficacy summary

ERBITUX + high-dose RT demonstrated significant efficacy benefits over high-dose RT alone



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

ERBITUX in locoregionally advanced SCCHN: safety summary

- ERBITUX did not significantly increase acute RT-related side effects

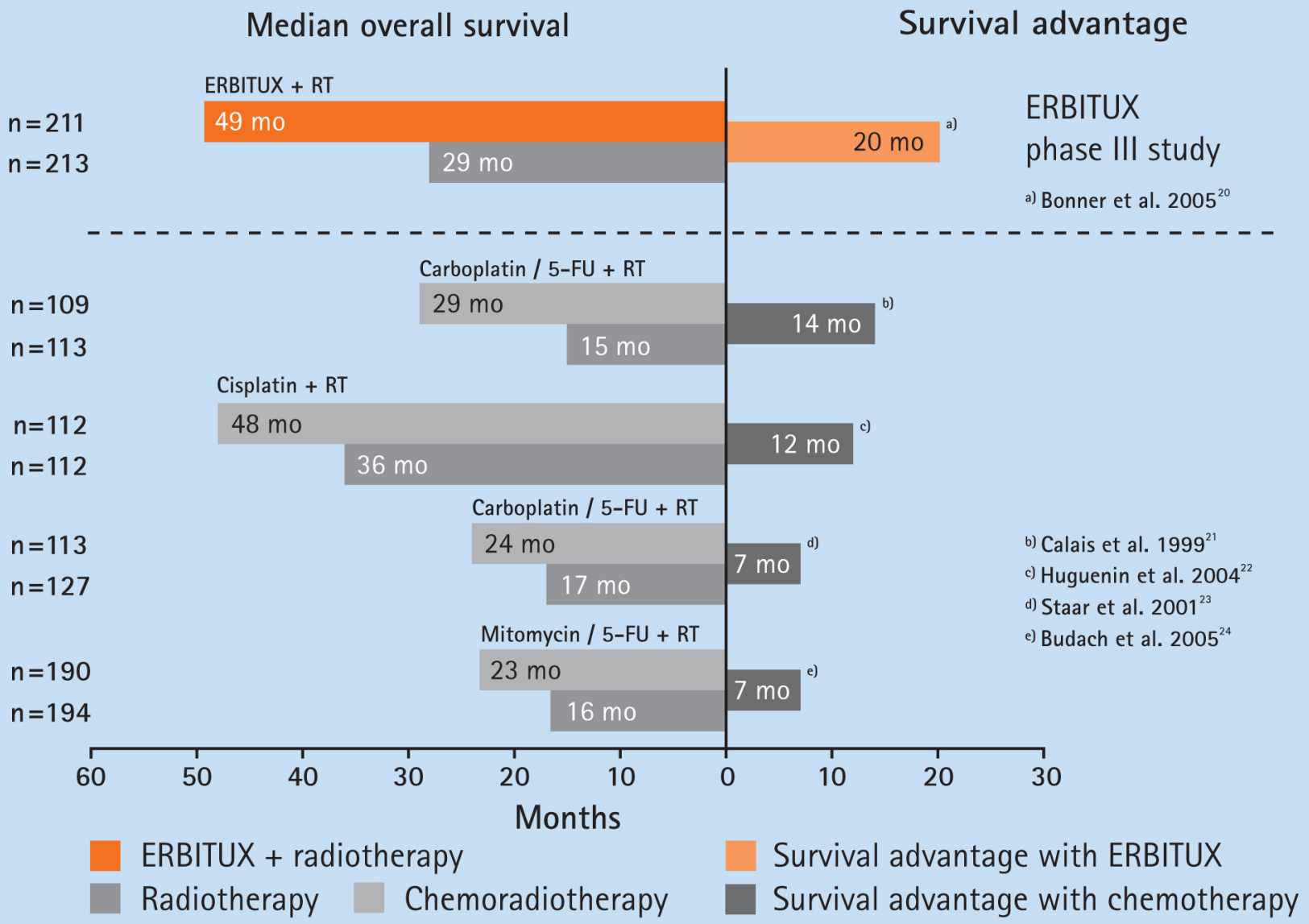
90% of all patients received the planned dose of ERBITUX

ERBITUX did not affect RT-related QoL scores

Main ERBITUX associated side effect was acne-like rash

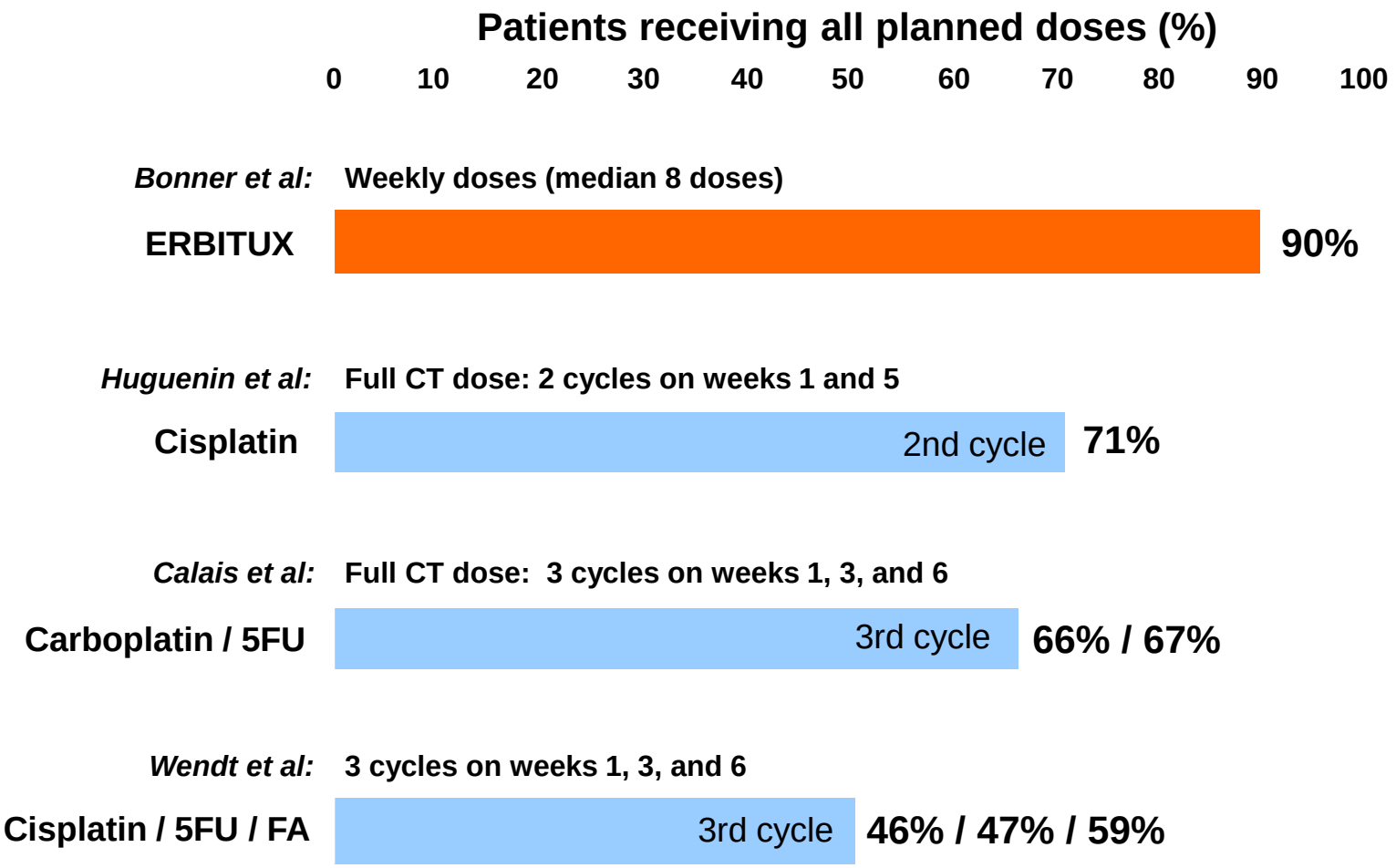
Bonner J, et al. N Engl J Med 2006;354:567–578; Curran D, et al. J Clin Oncol 2007;25:2191–2197

Survival of ERBITUX + radiotherapy compared to large randomized trials of chemoradiotherapy vs radiotherapy



Compliance with ERBITUX or chemotherapy when administered with RT

- **CRT arms of studies comparing CRT vs RT alone**



Bonner J, et al. N Engl J Med 2006;354:567–578; Huguenin P, et al. J Clin Oncol 2004;22:4665–4673
Calais G, et al. J Natl Cancer Inst 1999;91:2081–2086; Wendt TG, et al. J Clin Oncol 1998;16:1318–1324

Taxane in the treatment of HNC

NCCN National Comprehensive Cancer

NCCN Guidelines Version 1.2012
Head and Neck Cancers

NCCN Guidelines Index
Head and Neck Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

The choice of chemotherapy should be individualized based on patient characteristics (performance status, goals of therapy).

- The standard therapy for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy.
- Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (ie, sequential chemoRT). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state of the art concurrent chemoRT (cisplatin preferred, category 1) has not been established. Randomized phase III studies comparing sequential chemotherapy/RT to concurrent chemotherapy/RT alone are ongoing.
- Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is not recommended due to toxicity concerns.[1,2]
- After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus cetuximab or weekly carboplatin are among the options.

Squamous Cell Cancers

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- Primary systemic therapy + concurrent RT
  - Cisplatin alone[3,4] (preferred) (category 1)
  - Cetuximab[5] (category 1)
  - Carboplatin/infusional 5-FU (category 1)[6,7]
  - 5-FU/hydroxyurea[8]
  - Cisplatin/paclitaxel[8]
  - Cisplatin/infusional 5-FU[9]
  - Carboplatin/paclitaxel[10] (category 2B)
- Postoperative chemoradiation
  - Cisplatin alone[11-14] (category 1 for high risk)

Nasopharynx:

- Chemoradiation followed by adjuvant chemotherapy
  - Cisplatin + RT followed by cisplatin/5-FU[15,16] (category 1)

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- Induction*/Sequential chemotherapy
  - Docetaxel/cisplatin/5-FU[17-19] (category 1 if induction is chosen)
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  - Following induction, agents to be used with concurrent chemoradiation typically include weekly carboplatin or cetuximab.[21]

Nasopharynx:

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  - Docetaxel/cisplatin/5-FU[22]
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  - Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[16] or carboplatin.[21]

Erbitux in Treatment of Recur / Meta SCCHN (EXTREME Study)

The NEW ENGLAND JOURNAL of MEDICINE

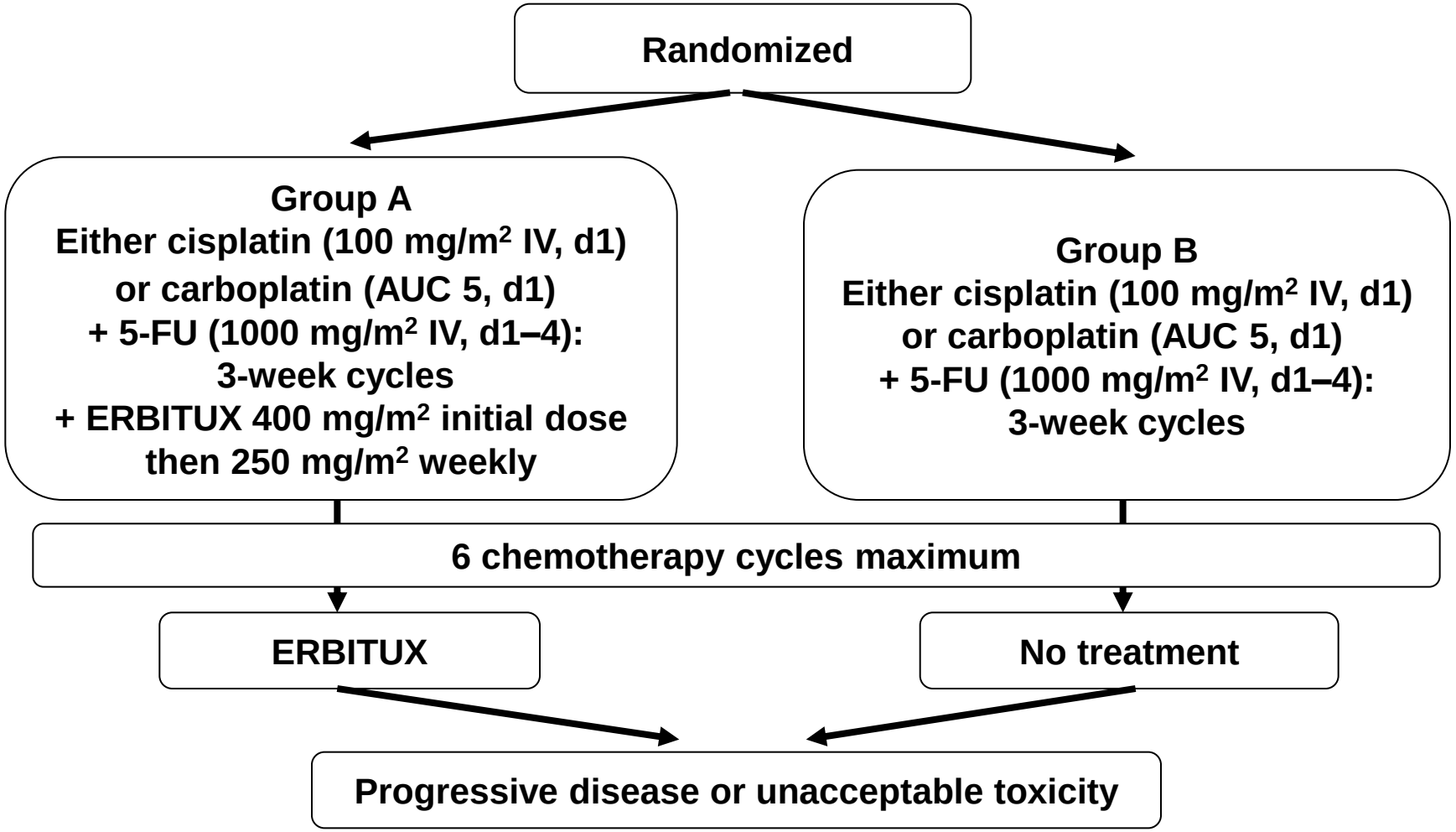
ORIGINAL ARTICLE

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Benasso, M.D., Ihor Vynnychenko, M.D., Ph.D., Dominique De Raucourt, M.D., Carsten Bokemeyer, M.D., Armin Schueler, M.S., Nadia Amellal, M.D., and Ricardo Hitt, M.D., Ph.D.

N ENGL J MED 359;11 WWW.NEJM.ORG SEPTEMBER 11, 2008

EXTREME: Study design



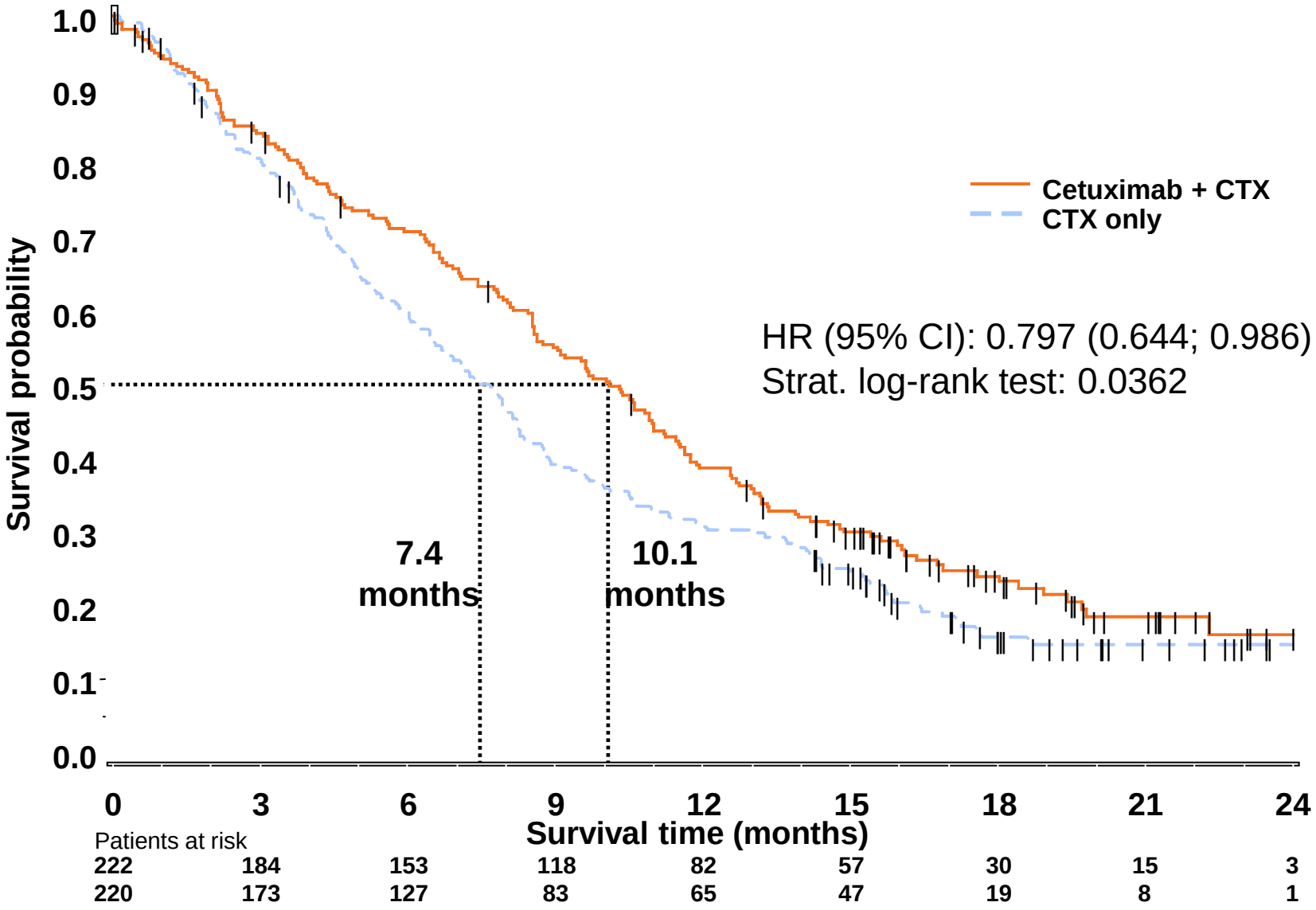
Vermorken JB et al. N Engl J Med 2008;359:1116–1127

EXTREME study

	Cetuximab + platinum / 5-FU (n=222)	Platinum / 5-FU (n=220)
Median age (range)	56 years (37–80)	57 years (33–78)
Men / women	89% / 11%	92% / 8%
Recurrence/metastasis		
Locoregional recurrence	54%	54%
Metastasis[a]	46%	46%
Primary metastatic disease	8%	7%

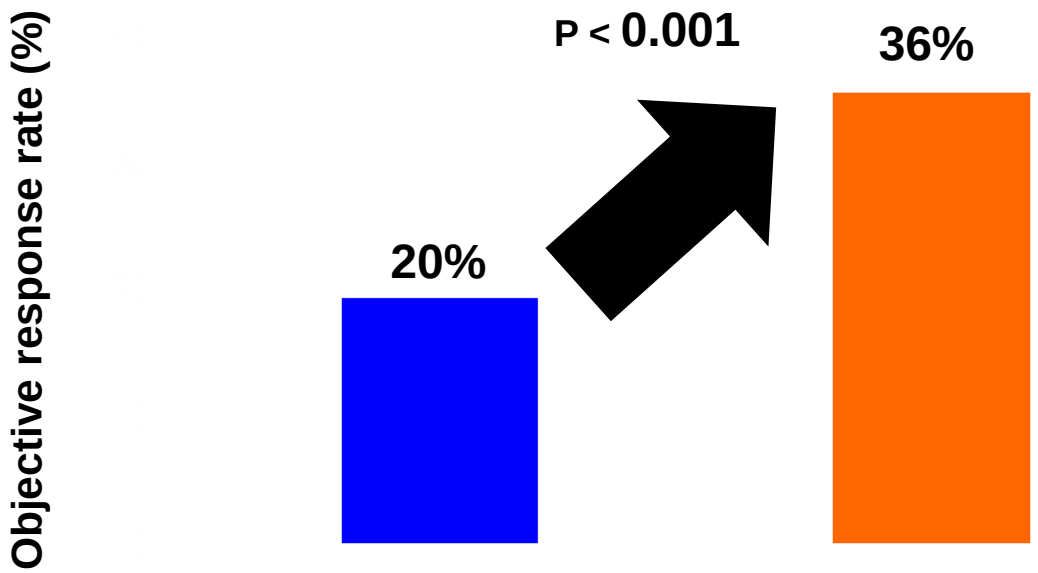
Vermorken JB, et al. N Engl J Med Sep 11;359(11):1116-27

EXTREME: overall survival



Vermorken JB, et al. N Engl J Med Sep 11;359(11):1116-27.

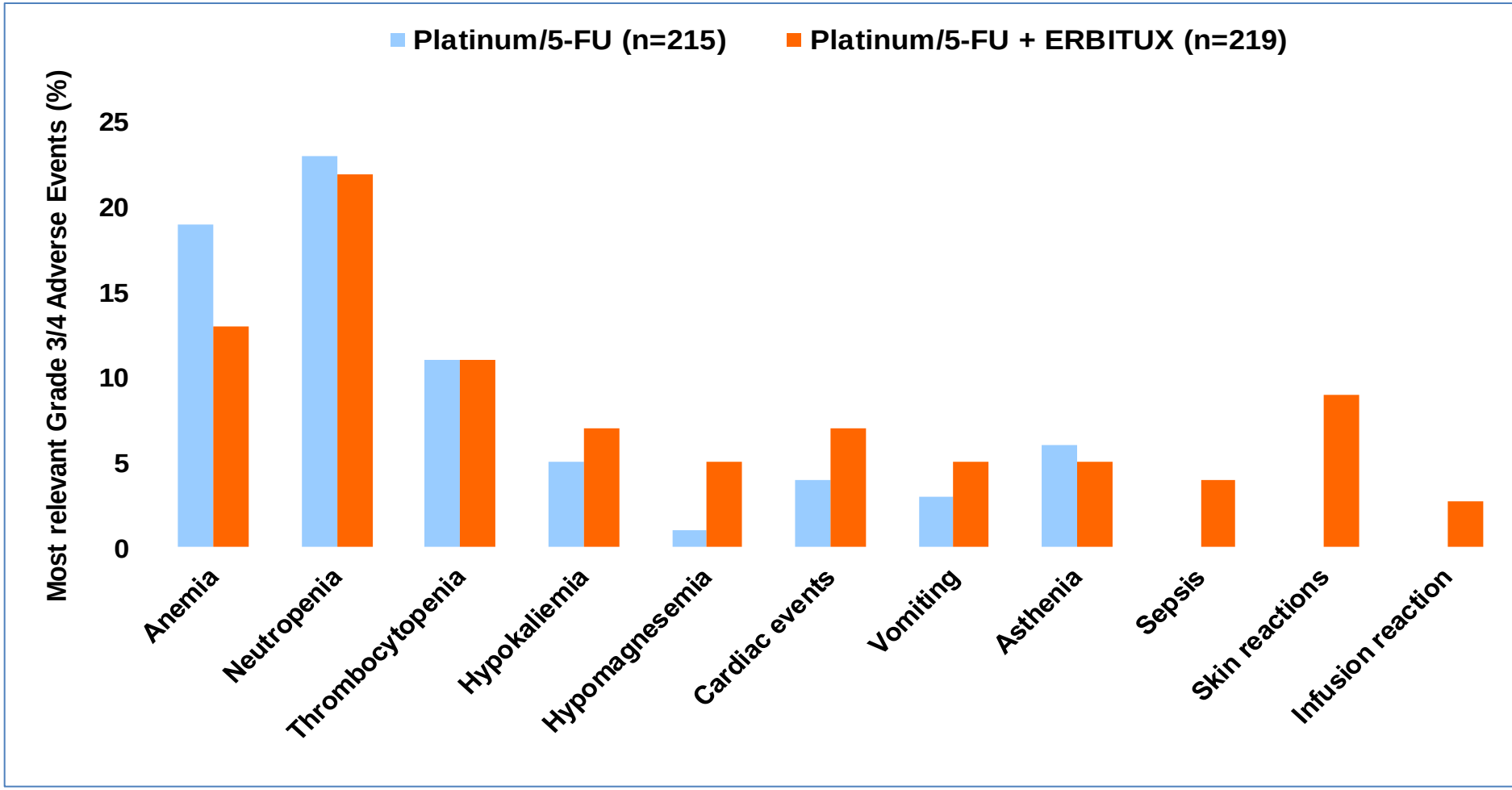
EXTREME: Objective Response Rates[a]



[a]Objective response rate (CR+PR)

Vermorken JB, et al. N Engl J Med 2008;359:1116–27

EXTREME:
Most Relevant Grade 3/4 Adverse Events



Modified from Vermorken JB, et al. N Engl J Med 2008;359:1116–27

Erbitux in the treatment of **Recur / Meta** HNC

NCCN National Comprehensive Cancer

NCCN Guidelines Version 1.2012
Head and Neck Cancers

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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

The choice of chemotherapy should be individualized based on patient characteristics (performance status, goals of therapy).

Recurrent, Unresectable, or Metastatic (incurable)

- Combination therapy
  - Cisplatin or carboplatin + 5-FU + cetuximab (non-nasopharyngeal)[23] (category 1)
  - Cisplatin or carboplatin + docetaxel[24] or paclitaxel[25]
  - Cisplatin/cetuximab (non-nasopharyngeal)[26]
  - Cisplatin + 5-FU[25,27]

- Single agents
  - Cisplatin
  - Carboplatin
  - Paclitaxel
  - Docetaxel
  - 5-FU
  - Methotrexate
  - Ifosfamide
  - Bleomycin
  - Gemcitabine[28] (nasopharyngeal)
  - Cetuximab (non-nasopharyngeal)[29]

Erbitux 爾必得舒於 HNSCC 的使用時機

- 健保局
  - 限與放射線療法合併使用於局部晚期之口咽癌、下咽癌及喉癌患者，且符合下列條件之一：
    1. 年齡 ≧ 70歲；
    2. Ccr ＜50ml/min；
    3. 聽力障礙者(聽力障礙定義為500Hz、1000Hz、2000Hz平均聽力損失大於25分貝)；
    4. 無法耐受 platinum-based 化學治療。

馬偕醫院頭頸癌化學治療準則

For neo-adjuvant/induction regimen
Cisplatin 100 (75) mg/m2 D1 (or D6)
5-FU 1000 (750) mg/m2 D1~D5

5-FU 2600mg/m2 D1
Cisplatin 75mg/m2 D2

Taxotere 50-75mg/m2 D1
Cisplatin 50-75mg/m2 D1
5FU 500-750mg/m2 D1-D5

馬偕醫院頭頸癌化學治療準則

For CCRT

Cisplatin 75-100mg/m2	q3-4 wks
Cisplatin 20~30mg/m2 weekly	
Cisplatin 12/15mg/m2 D1~D5 5-FU 600/750mg/m2 D1~D5	q3~4wks
Cisplatin 12/15mg/m2 weekly 5-FU 600/750mg/m2 weekly	
Taxotere 20mg/m2 weekly Cisplatin 20mg/m2 weekly	

馬偕醫院頭頸癌化學治療準則

For adjuvant regimen
Cisplatin 100 (75) mg/m2 D1 (or D6)
5-FU 1000 (750) mg/m2 D1~D5

5-FU 2600mg/m2 D1
Cisplatin 75mg/m2 D2

Taxotere 50-75mg/m2 D1
Cisplatin 50-75mg/m2 D1
5FU 500-750mg/m2 D1-D5