Molecular and targeted therapy in HN Cancer

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- **Selective versus nonselective therapies**

Depend on tumor biology

- Targeting the tumor microenvironment or vasculature
- Leaving normal cells unaffected
- Focusing on specific protein or signal transduction pathways.

Targeting the Targets: the EGFR

- The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including *cell proliferation, apoptosis, angiogenesis, and metastatic spread*.

- The critical role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signalling pathway.

EGFR HISTORY HIGHLIGHTS[1]

1962

Epidermal growth factor (EGF) is discovered by Stanley Cohen

1978

Epidermal growth factor receptor (EGFR) is identified

1983

EGFR is first targeted with mouse monoclonal antibodies to inhibit proliferation in human cancer cell lines

2004

First chimeric anti-EGFR monoclonal antibody for colorectal cancer is approved by the FDA

2006

First entirely human anti-EGFR monoclonal antibody for metastatic colorectal cancer is approved by the FDA

EGFR Expression in Human Tumors

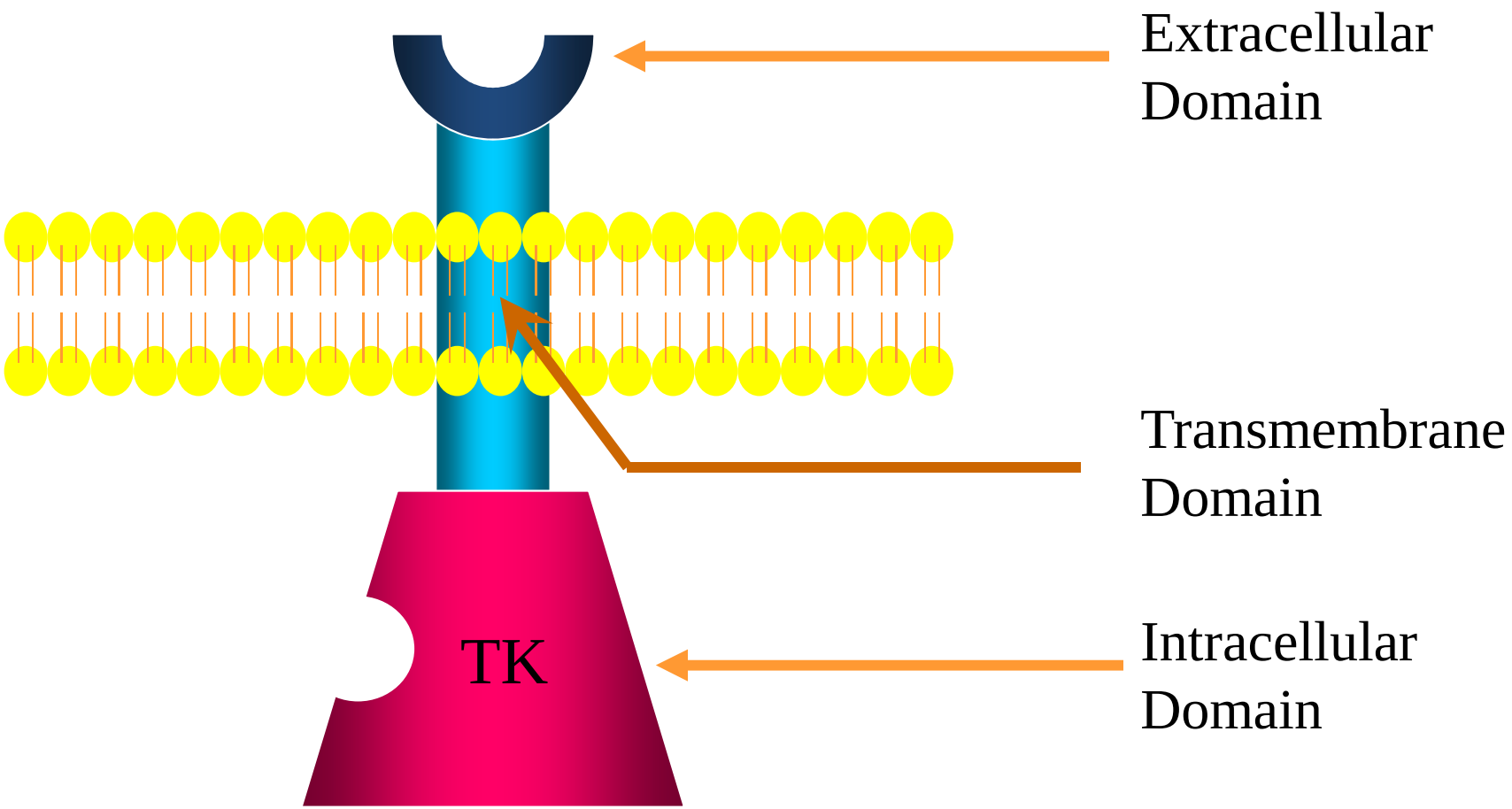
EGFR expression

• NSCLC	40-80%
• Prostate	40-80%
• Head & Neck	88-100%
• Gastric	33-74%
• Breast	14-91%
• Colorectal	75-89%
• Pancreatic	30-95%
• Ovarian	35-77%
• Bladder	31-72%
• Glioma	40-63%

High expression generally associated with

- Invasion
- Metastasis
- Late-stage disease
- Chemotherapy resistance
- Poor outcome

EGFR Structure



Normal cells and cancer cells rely on epidermal growth factor receptor (EGFR) signals, but the signal is not correctly regulated in cancer cells

Rationale and Strategies for Targeting HER/EGFR

- The epidermal growth factor axis is involved in the regulation of normal cell proliferation.
- Up-regulated in > 90% HNSCCs.
- an independent predictor
- several mechanisms-

✓ receptor overexpression,

✓ ligand overproduction,

✓ the presence of constitutively active receptor mutants, and

✓ cross-talk with other amplified receptors and signaling systems

Therapeutic molecular targeting strategies

- EGFR has many naturally occurring ligands -epidermal growth factor (EGF) and TGF-α.
- Multiple ligands have been developed to bind to the receptor.
- These ligands can be conjugated with toxin to produce antitumor responses.

- Azemar et al- antitumor effects against HNSCC cell lines using bacterially derived toxins (eg, diphtheria, *Pseudomonas*),
- These therapies proved to be extremely hepatotoxic.

Therapeutic molecular targeting strategies

- MAbs have also been developed to target EGFR and act by binding the receptor.
- Blockade of EGFR signaling,
- Recruit Fc receptor–expressing immune effector cells(antibody-dependent cellular cytotoxicity and tumor lysis).

Therapeutic molecular targeting strategies

- **TKI-**

✓ Developed to inhibit the tyrosine kinase activity of EGFR.

✓ Adenosine triphosphate (ATP) analogs that compete with native ATP for binding.

- **Nucleic acid–based molecules** –

✓ Interfere with translation of EGFR protein.

✓ Include antisense oligodeoxynucleotides and small interfering mRNA.

✓ Promise increasing sensitivity to various chemotherapeutic agents in both in vitro and in vivo models.

✓ Still in early stages of investigation

Extracellular versus intracellular blockade

Extracellular versus intracellular blockade…….

- Predicting which of these 2 strategies will be more effective - Not possible.

- A molecule that has dual action would be ideal.

Extracellular versus intracellular blockade…….

- Target either

✓The extracellular ligand-binding region of the EGFR -MAbs, immunotoxins and ligand-binding cytotoxic agents)

✓The intracellular tyrosine kinase region (including various small-molecule inhibitors).

Extracellular versus intracellular blockade…….

- The strong points of humanized EGFR MAbs (extracellular blockade) are as follows:-

✓ Prolonged half-life
✓ Some cytolytic actions by immune mediated pathways
✓ Can induce receptor down-regulation
✓ No gastrointestinal toxicity

Extracellular versus intracellular blockade…….

- The strong points of EGFR tyrosine kinase inhibitors (intracellular blockade) :-

✓ Long-term therapy with oral administration

✓ Can inhibit EGFR-homologous kinases such as HER-2

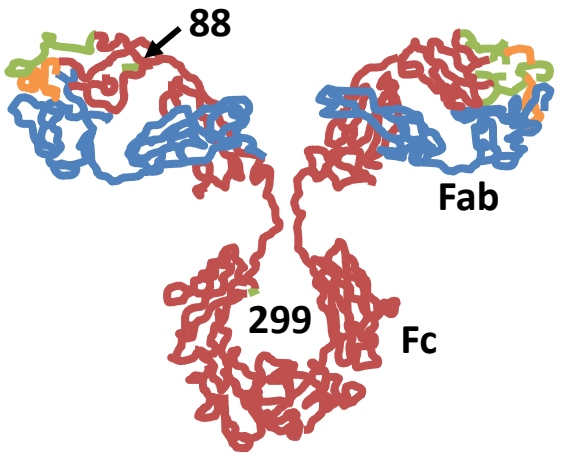
✓ Can directly inhibit HER-2

✓ Less potential for anaphylaxis or allergic reactions

✓ Can inhibit mutant EGFRvIII kinase found in some tumors

Cetuximab (IMC-C225): Properties

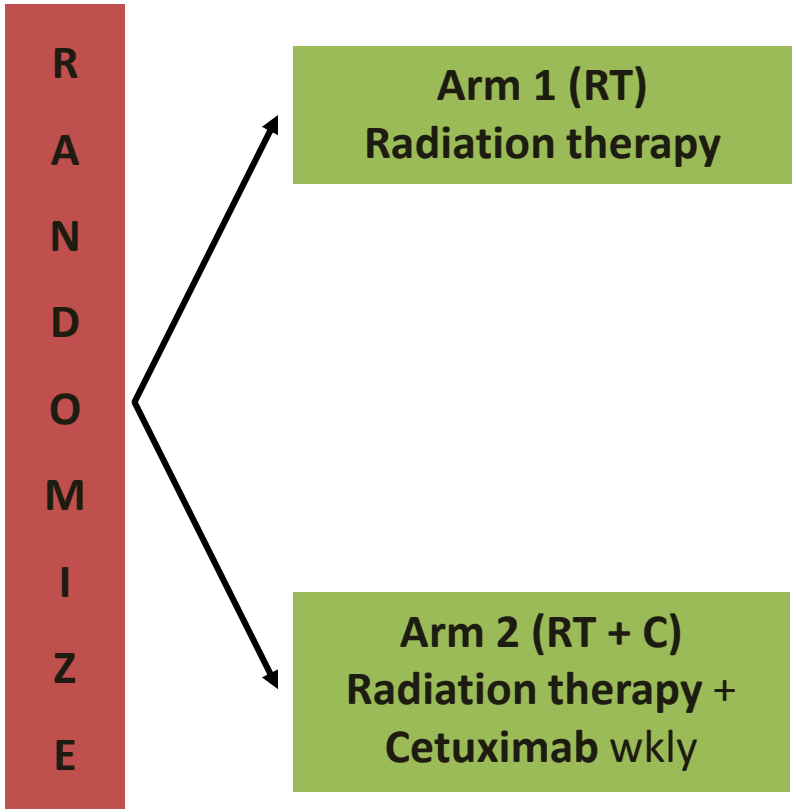
- IgG1 (chimerized antibody)
- Exclusive for EGFR and its heterodimers
- Prevents repair and survival of tumor cells damaged by the effects of chemotherapy and radiotherapy
  - Potentiates apoptosis
  - Inhibits cell cycle progression
  - Decreases production of angiogenic factors
  - Inhibits invasion/metastasis



Phase III Study Design

Stratified by

- Karnofsky score: 90-100 vs 60-80
- Regional nodes: negative vs positive
- Tumor stage: AJCC T1-3 vs T4
- RT fractionation: concomitant boost vs once daily vs twice daily



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

Locoregional Control

Locoregional Control, %	RT (n = 213)	RT + C (n = 211)
1 yr* 2 yrs*	59 48	69 56
Log rank *P* value	0.02	
Distant/second primary control ❖1 yr* ❖2 yrs*	 71 56	 77 62

*Kaplan-Meier estimates.

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

Overall Survival

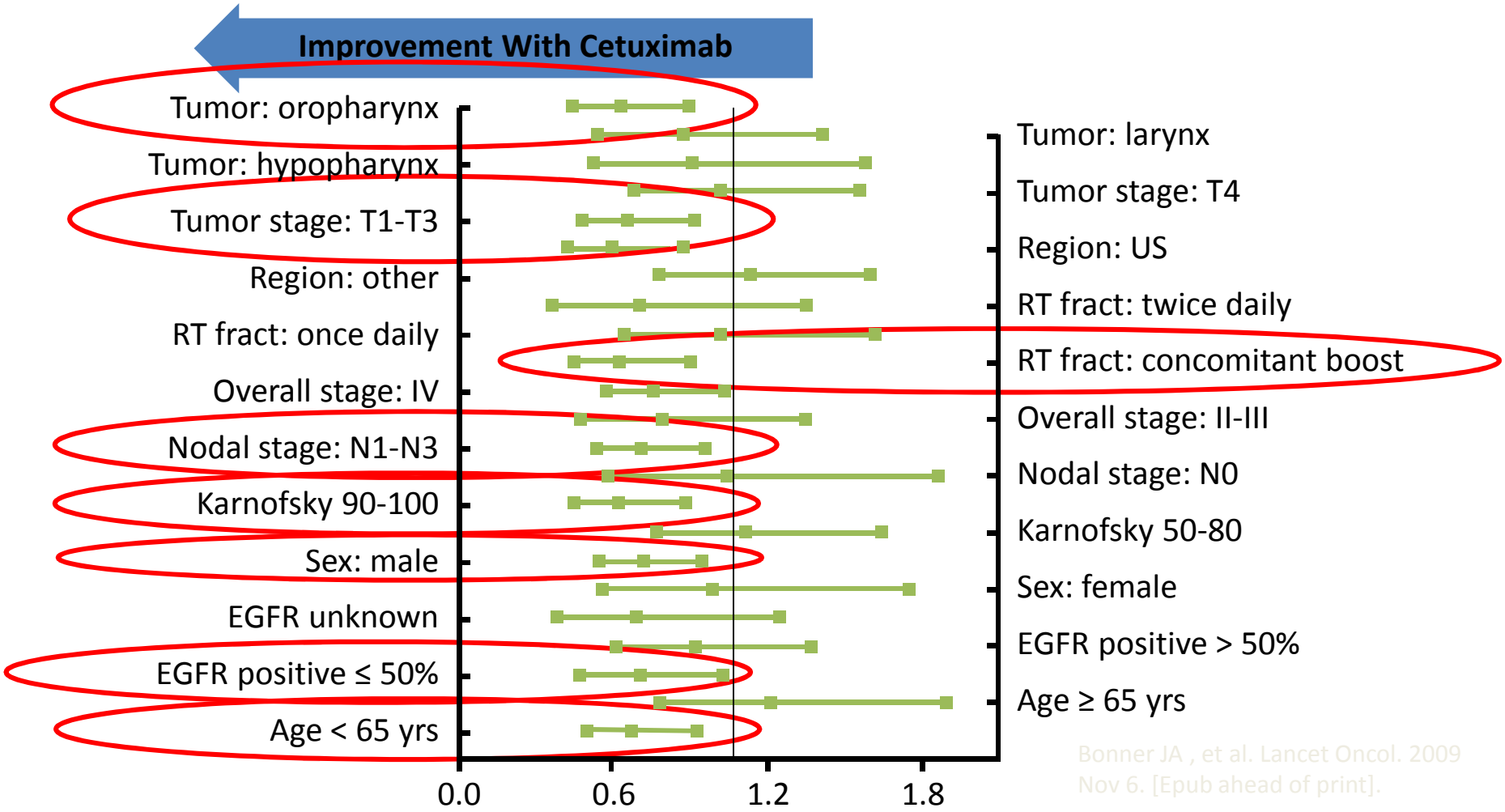
	RT (n = 213)	RT + C (N=211)
Median survival,* mos	29.3	49
❖95% confidence limits	21-38	36-58+
2 yrs, %	55	62
3 yrs, %	44	57
5 yrs, %	36.4	45.6
Log rank *P* value	.018	
HR (95% CI)	0.71 (0.54-0.95)	

Bonner JA , et al. Lancet Oncol. 2009 Nov 6;[Epub ahead of print].

- All patient subgroups demonstrated an improvement with the addition of cetuximab.
- This improvement was pronounced in patients with oropharyngeal carcinoma, T1-T3 disease as opposed to T4, those who received concomitant boost radiation as opposed to once-daily radiation, those with nodal involvement N1-N3, those with better performance status, male patients, those with EGFR expression ≤ 50%, suggesting some potential saturation phenomenon.
- Conclusion:

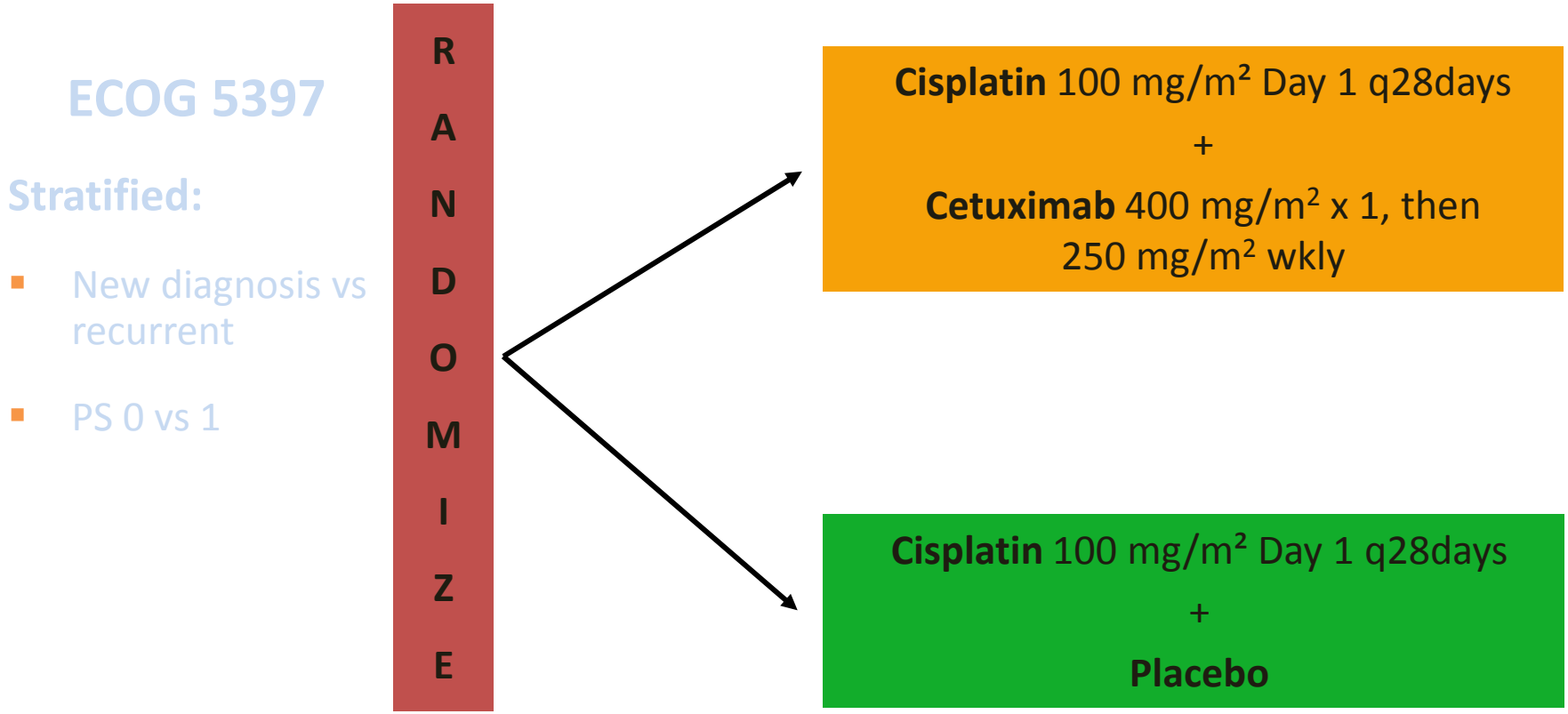
  Treatment of locoregionally advanced HNSCC with concomitant high dose RT plus cetuximab improves locoregional control and reduces mortality without increasing toxicity.

Forest Plot of the HRs by Pretreatment Characteristics: 5-Yr Median Follow-up



Bonner JA , et al. Lancet Oncol. 2009 Nov 6. [Epub ahead of print].

Cisplatin + Placebo vs Cisplatin + Cetuximab: Design



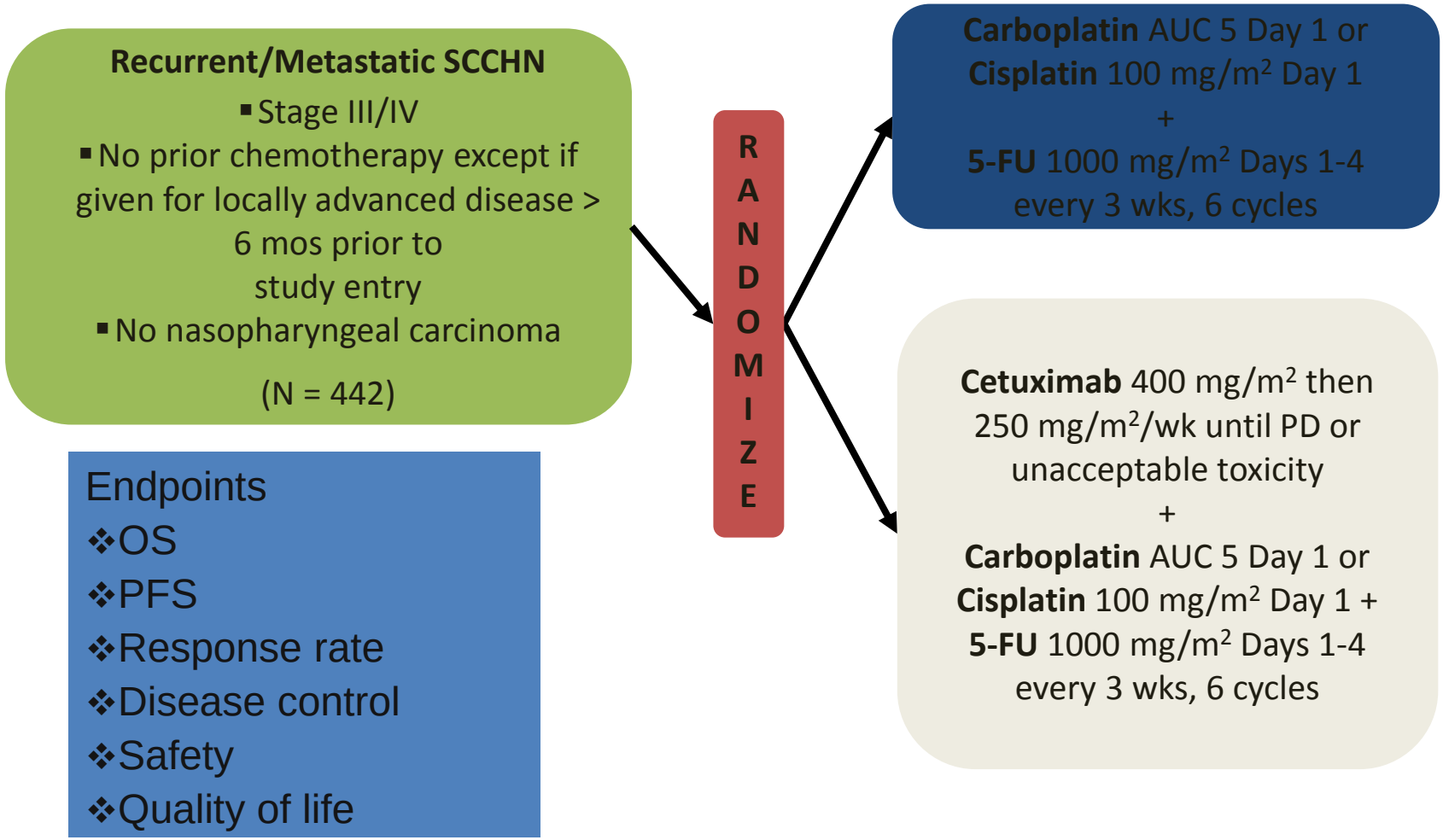
Burtness B, et al. J Clin Oncol. 2005;23:8646-8654.

Cisplatin + Placebo vs Cisplatin + Cetuximab: Results

Parameter	CDDP + Cetuximab (n = 63)	CDDP + Placebo (n = 60)	*P* Value
ORR, % ❖Low-mod EGFR, % ❖High EGFR, %	26.3 40.0 11.8	9.8 11.5 5.9	.029
Median PFS, mos	4.2	2.7	.09
Median OS, mos ❖2-yr OS, %	9.3 15.6	8.0 9.2	.21 NS

- Data suggest that patients with rash may fare somewhat better

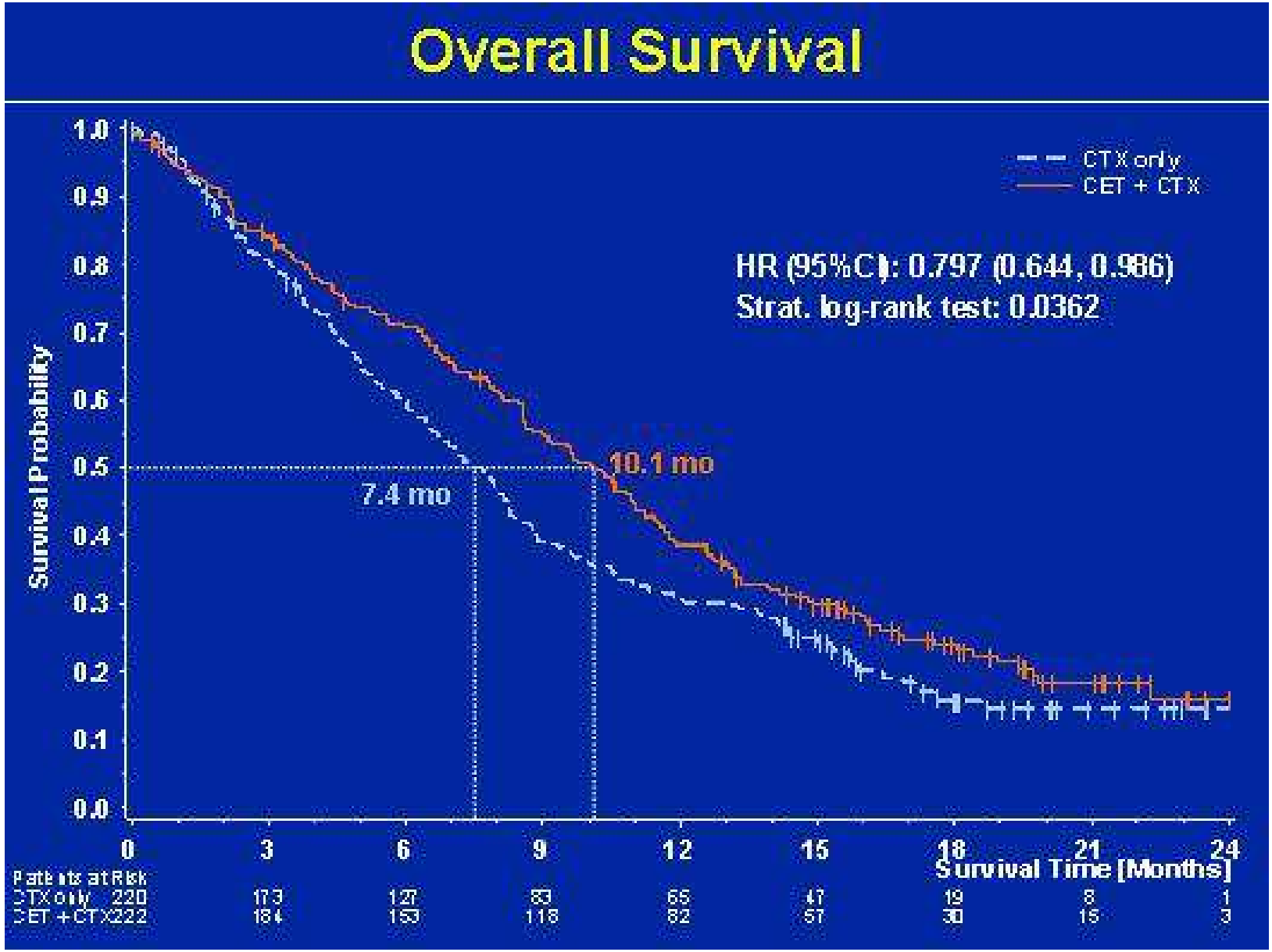
EXTREME: Platinum/5-FU With or Without Cetuximab in Recurrent/Metastatic SCCHN



Vermorken JB, et al. N Engl J Med. 2008;350:1116-1127.

Table 2. Responses to Treatment and Survival.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Survival — mo†				
Overall	10.1 (8.6–11.2)	7.4 (6.4–8.3)	Hazard ratio, 0.80 (0.64–0.99)	0.04‡
Progression-free	5.6 (5.0–6.0)	3.3 (2.9–4.3)	Hazard ratio, 0.54 (0.43–0.67)	<0.001‡
Best response to therapy — %				
Overall	36 (29–42)	20 (15–25)	Odds ratio, 2.33 (1.50–3.60)	<0.001§
Disease control¶	81 (75–86)	60.0 (53–67)	Odds ratio, 2.88 (1.87–4.44)	<0.001§
Time to treatment failure — mo†	4.8 (4.0–5.6)	3.0 (2.8–3.4)	Hazard ratio, 0.59 (0.48–0.73)	<0.001‡
Duration of response — mo‖	5.6 (4.7–6.0)	4.7 (3.6–5.9)	Hazard ratio, 0.76 (0.50–1.17)	0.21‡



Vermorken, ASCO Virtual Meeting 2007: LBA 6091

EXTREME Conclusions

- Addition of Cetuximab to first-line therapy therapy resulted in significantly prolonged OS with a median of 2.7 months compared to chemotherapy alone
  - An increase of 35% in survival
  - Randomized trials of PF alone demonstrated response rates of 30-35% with median OS of 8-9 months
- First randomized phase III trial to demonstrate a survival benefit over platinum-based therapy in this setting!

Cetuximab in recurrent/metastatic SCCHN refractory to first-line platinum-based therapies (ASCO abstract, 2007)

- Multicenter, phase II study for 6 weeks
- 103 Pts with refractory metastatic/recurrent SCCHN
- initial dose of 400 mg/m², followed by 250 mg/m² weekly until disease progression
- The primary endpoint was the response rate to cetuximab monotherapy
- ***Results:***
- 5 CR, 12 PR,
- 38 SD, 47 PD,
- with a response rate of 16.5%,and disease control rate was 53.4%.
- Median time to progression and median survival were 2.3 and 5.9 months, respectively.
- ***Conclusions:*** Cetuximab as single agent can produce major objective responses in pts with platinum-refractory recurrent/metastatic SCCHN, with acceptable toxicity.

Comparison of Cetuximab-Based Therapy and Other Various Second-Line Therapies

Treatment	N	ORR (CR + PR), %	Disease Control (CP + PR + SD), %	Median OS, Mos	Median TTP, Mos
Cetuximab monotherapy	103	13	46	5.9	2.3
Cetuximab + cisplatin or carbo	96	10	53	6.1	2.8
Cetuximab + cisplatin	79	10	56	5.2	2.2
Retrospective ▪ All patients ▪ Pts with CT alone	 151 43	 3 0	 15 9	 3.4 3.6	 N/A N/A

Cetuximab approved in platinum-refractory setting

Vermorken JB, et al. J Clin Oncol. 2007;25:2171-2177.

original article

Annals of Oncology 21: 342–347, 2010
doi:10.1093/annonc/mdp477
Published online 5 November 2009

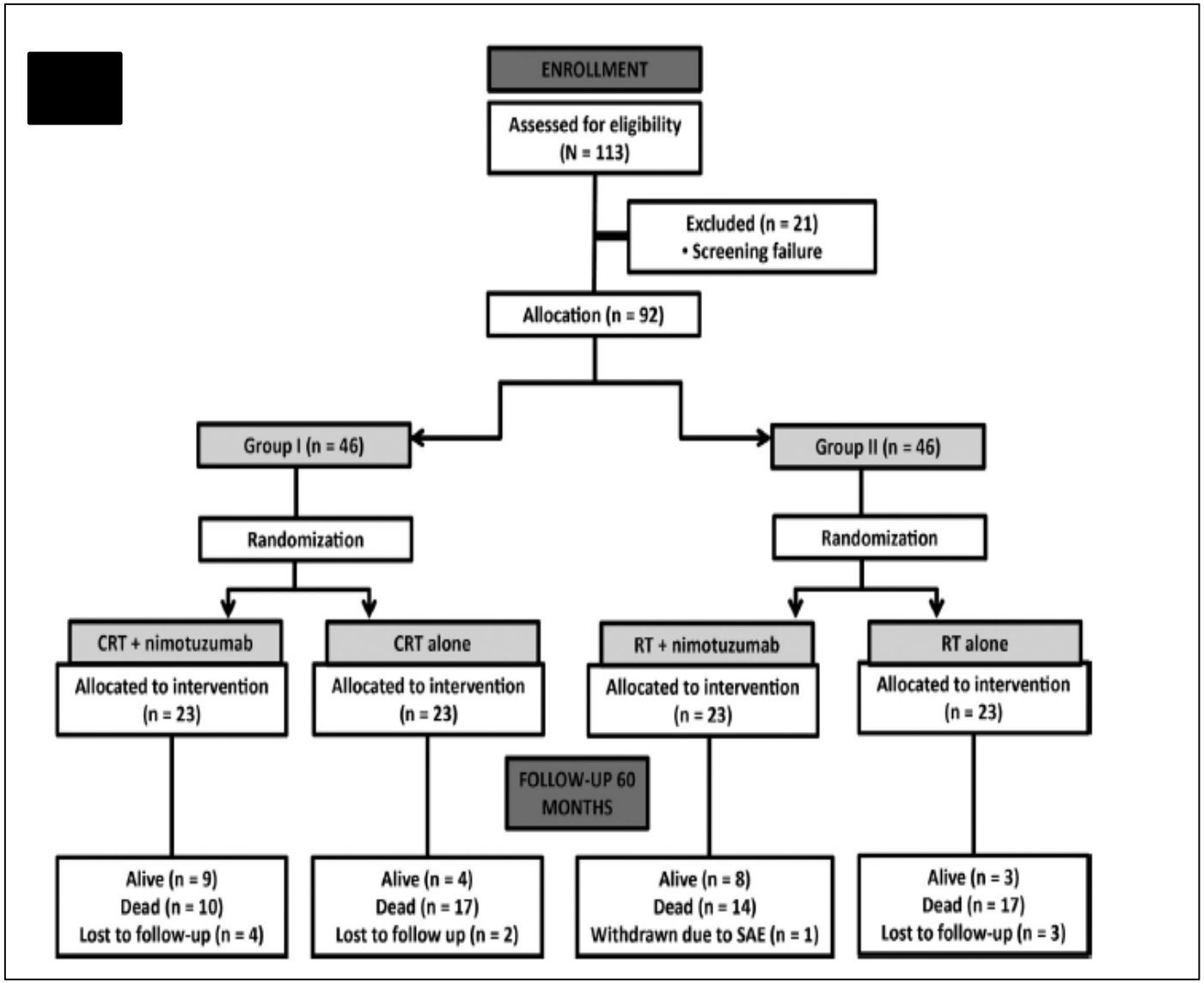
Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck

L. J. Wirth[1*†], A. M. Allen[2†], M. R. Posner[3], R. I. Haddad[3], Y. Li[4], J. R. Clark[1], P. M. Busse[5], A. W. Chan[5], L. A. Goguen[6], C. M. Norris[6], D. J. Annino[6] & R. B. Tishler[2]

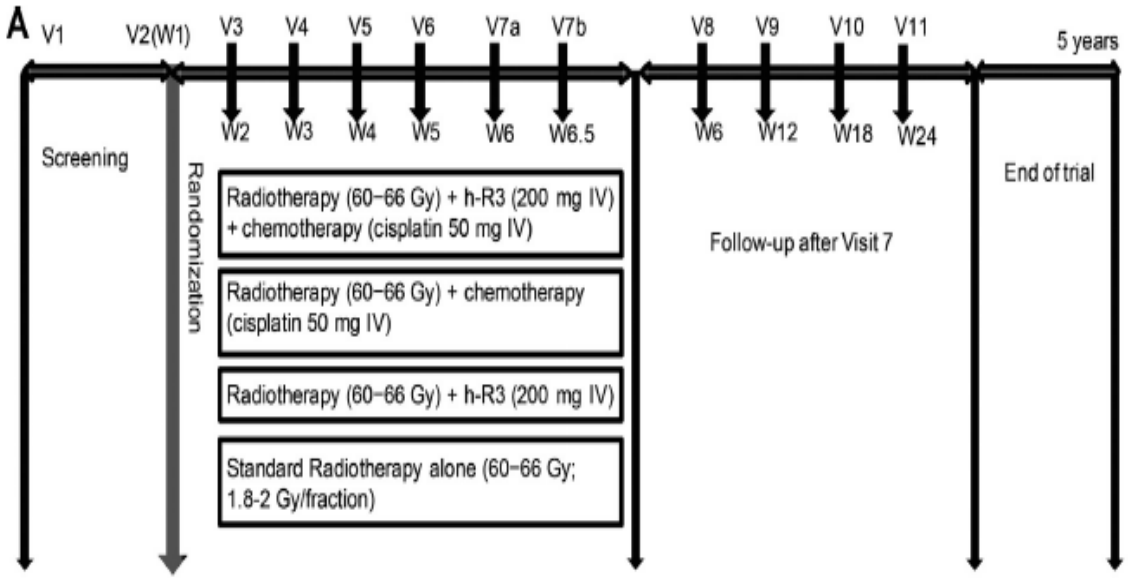
- Panitumumab – FDA approved for Colon Ca
  - fully human IgG2 mAb targeting EGFR
  - Less immunogenic than chimeric mAb
  - Longer half-life and higher affinity for EGFR than other mAbs

Nimotuzumab: The only molecule providing better data compared to CT+Rt and can be given with CT+Rt

Nimotuzumab trial design



Nimotuzumab treatment plan

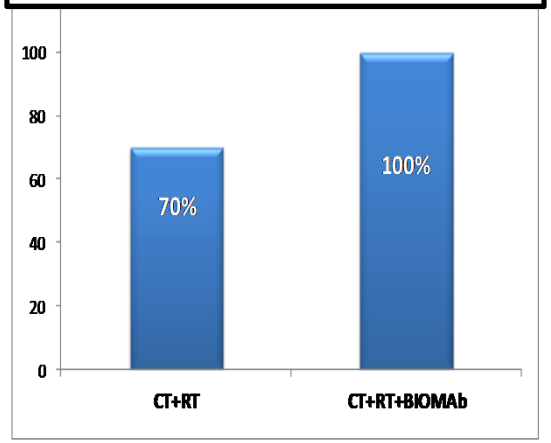


Primary endpoints: response rates for outcomes (CR, PR, SD, PD)

Secondary endpoints: progression-free survival (PFS) and overall survival (OS)

Nimotuzumab not only improved the response rate...

BIOMAb + CTRT v. CTRT alone



BIOMAb + RT v. RT alone

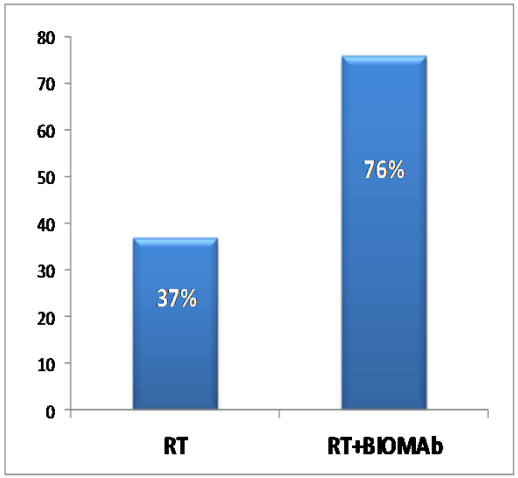


Table 2
Assessment at 6 months post-treatment: response evaluation.

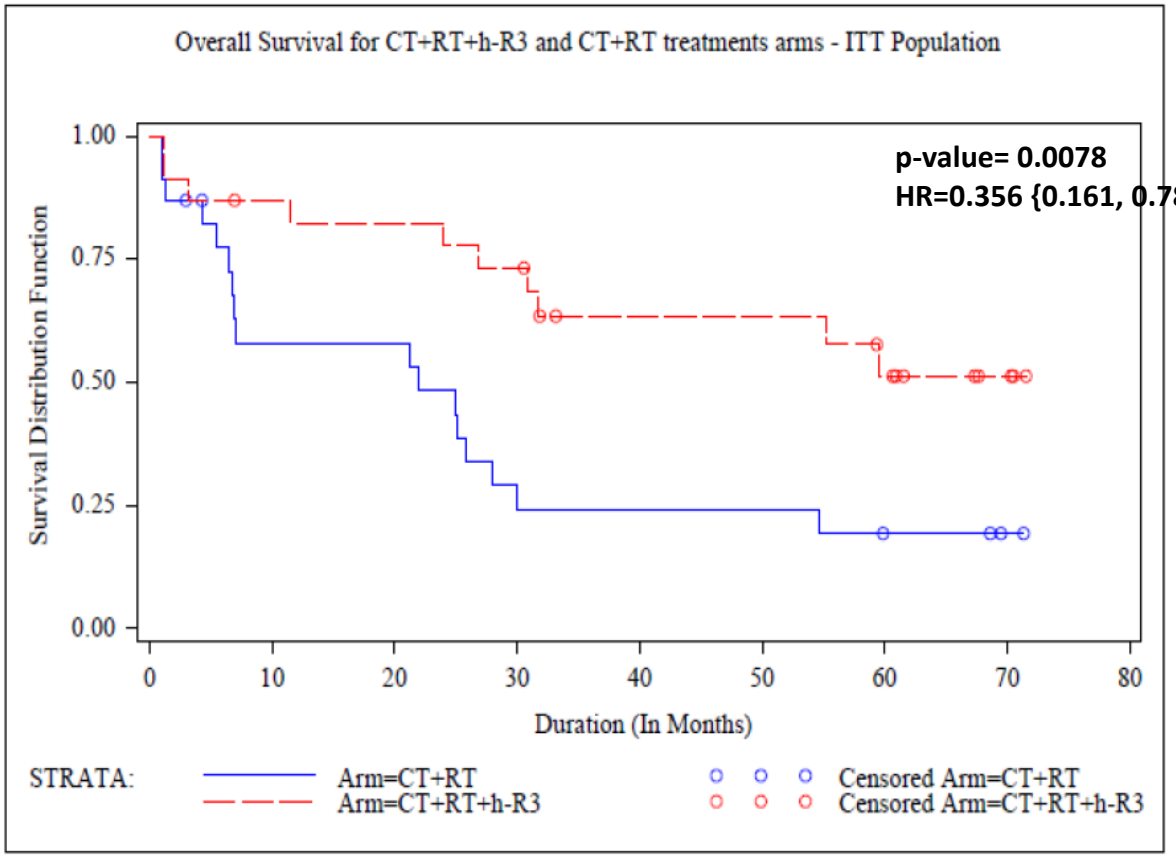
Response, *n* (%)	Chemoradiation group		Radiation group	
	CRT + nimotuzumab (*n* = 20)	CRT (*n* = 20)	RT + nimotuzumab (*n* = 17)	RT (*n* = 19)
CR	18 (90)	14 (70)	12 (70.59)	6 (31.01)
PR	2 (10)	0	1 (5.88)	1 (5.26)
ORR	20 (100)	14 (70)	13 (76.47)	7 (36.84)
PD	0	6 (30)	4 (23.53)	11 (57.89)
SD	0	0	0	1 (5.26)

Abbreviations: CRT, chemoradiotherapy; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

100% disease control rate when Nimotuzumab added to CTRT

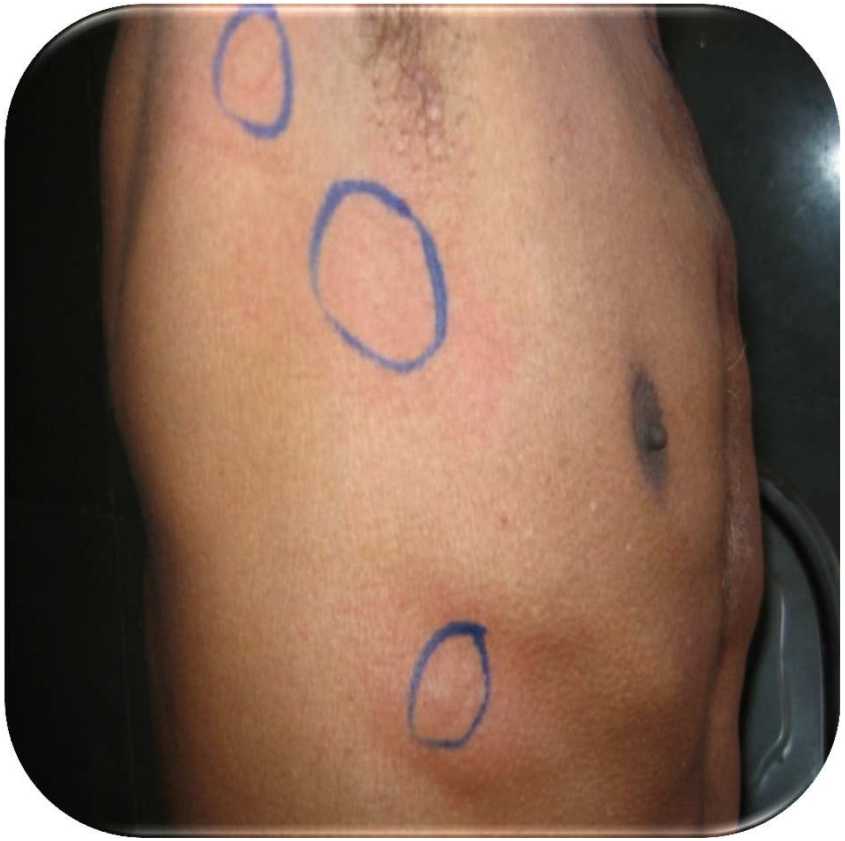
But also improved overall survival – mOS > 60 months

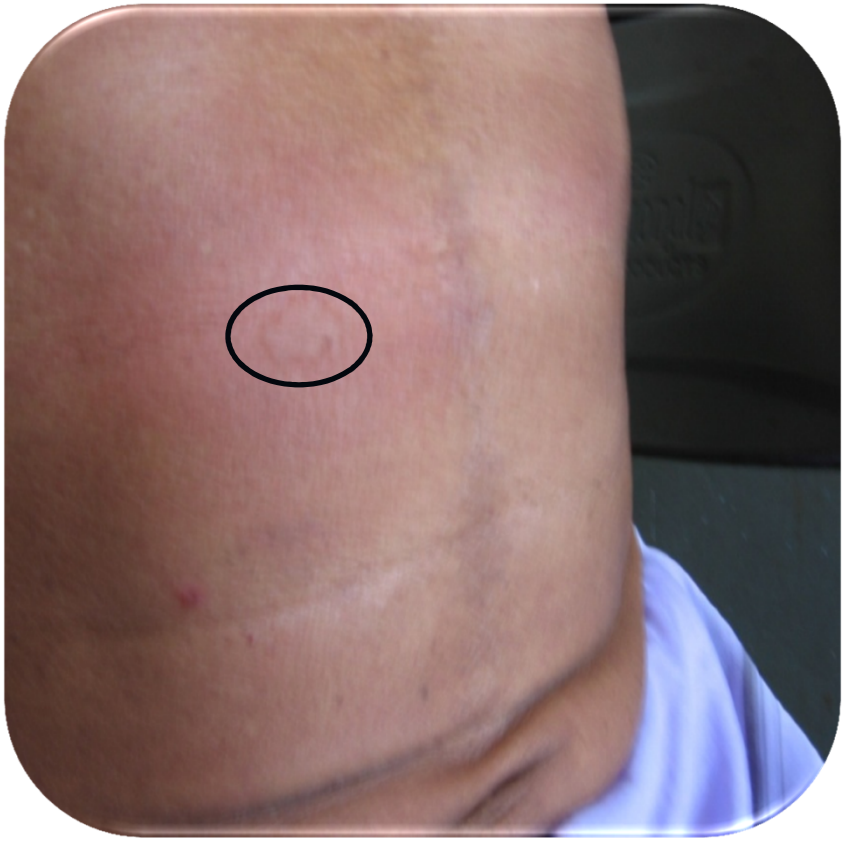
Kaplan-Meier Curve for Overall Survival ['Nimotuzumab+CT+RT' Vs 'CT+RT']



The risk of death was found to be 64% lesser in Nimotuzumab+CT+RT arm, compared to CT+RT arm

Additionally, Nimotuzumab is very safe with negligible toxicity





Negligible Skin Rash was observed in 2 patients

The reason why Nimotuzumab is safer and efficacious compared to Cetuximab?

Comparative binding pattern of anti EGFR Mabs

Tikhomirov et al, Abstract 36, TAT 2010

Nimotuzumab	Cetuximab
Attaches with bivalent bonding	Attaches with Monovalent bonding
Hence, does not bind with EGFR on normal cells with less EGFR density	Hence, binds with EGFR on all cells, normal as well as Tumor Cells
Thus, Nimotuzmab binds selectively with tumor cells	Cetuximab action is blanket

Prescribing Information of Erbitux: Screenshot

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of

Gefitinib, Erlotinib

- When gefitinib monotherapy is given to patients with incurable (metastatic, recurrent) HNSCC, the results are strikingly similar to those obtained in the same setting with as cetuximab
- The development of rash correlated with favorable response, progression, and survival.
- The observation that response appeared to be independent of prior chemotherapy exposure suggested that anti-EGFR agents may be non-crossresistant with agents such as *cis*- and carboplatin
- Erlotinib – Phase II trial of 115 patients showed a 4% partial response rate.

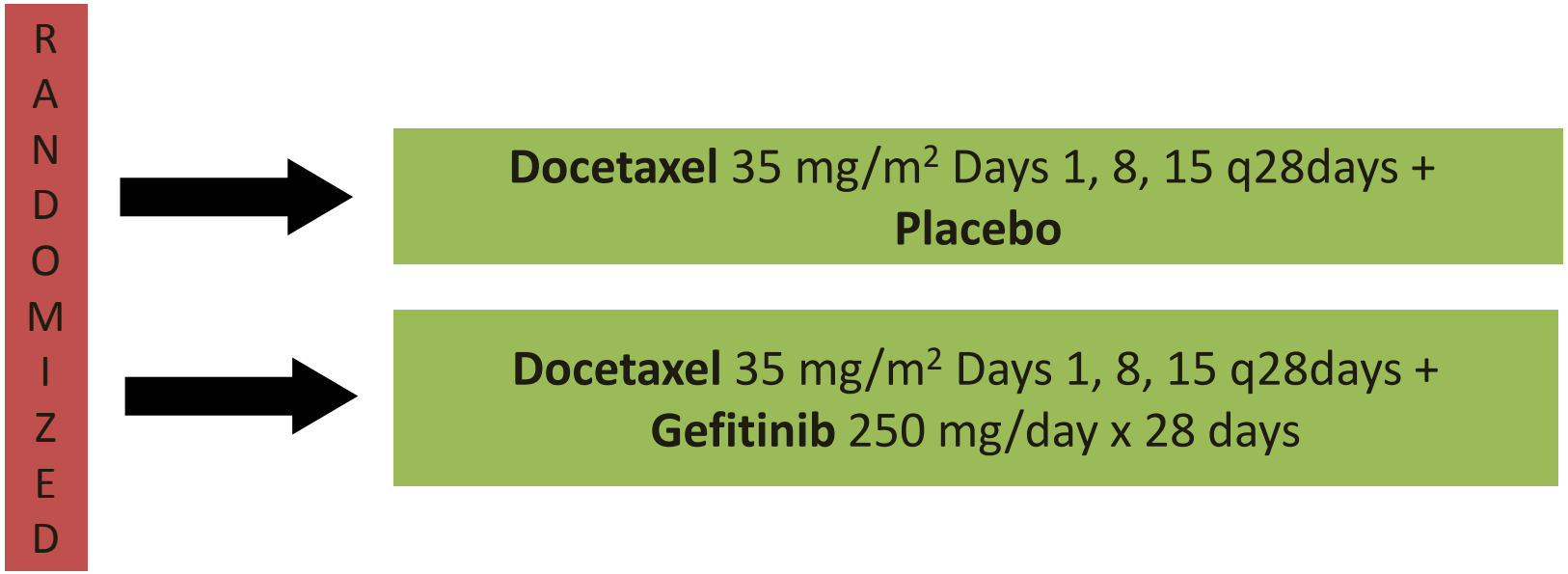
Gefitinib in SCCHN: Response Data

Response	n (%)*
CR	1 (2)
PR	4 (9)
SD	21 (45)
PD	22 (47)

- Gefitinib 500 mg QD PO
- N = 47 eligible patients
- Half received previous palliative treatments
- ORR: 11% (95% CI: 3.5-23.1)
- Disease control (CR + PR + SD): 53%
- Median survival of 8.1 mos
- 13% had disease control ≥ 6 mos
- Skin toxicity strong predictor of survival

Cohen EE, et al. J Clin Oncol. 2003;21:1980-1987.

Docetaxel in PS 2 or Previously Treated Pts With Recurrent or Metastatic SCCHN



- Accrual: N = 271
- 60% PS 2; 72% prior chemotherapy

Argiris A, et al. ASCO 2009. Abstract 6011.

E1302: Phase III Trial of Docetaxel + Placebo vs Docetaxel + Gefitinib

Arm	Docetaxel	Docetaxel + Gefitinib	*P* Value
Patients, n	136	134	
Grade 3/4 fatigue, n/%	12/3	11/0	
Diarrhea, n/%	2/0	11/1	
Grade 5 AEs, %	3	7	
OR, %	6	12	.21
MTTP, mos	2.1	3.5	.047
PFS, mos	2.2	3.3	.18
OS, mos	6	6.8	.97

Argiris A, et al. ASCO 2009. Abstract 6011. Graphic reproduced with permission.

conclusion

- data suggests that use of gefitinib in patients of recurrent/metastatic HNSCC is associated with good response, better survival and longer PFS, and can be used in patients with poor PS

Erlotinib in Recurrent or Metastatic SCCHN: Results

- N = 115 with recurrent/metastatic SCCHN
- 99% received previous chemotherapy
- 5 PR (RR: 4.3%)
- 44 SD (38%) for median 16 wks
  - Range to 90+ wks
- Median survival: 6 mos
- Improved survival in patients with grade ≥ 2 skin rash
  - Skin rash vs no skin rash (7.4 vs 4.0 mos; *P* = .045)
  - No difference on the basis of EGFR expression
- Adverse events (mostly mild) included acneiform rash (79%), diarrhea (37%)

Soulieres D, et al. J Clin Oncol. 2004;22:77-85.

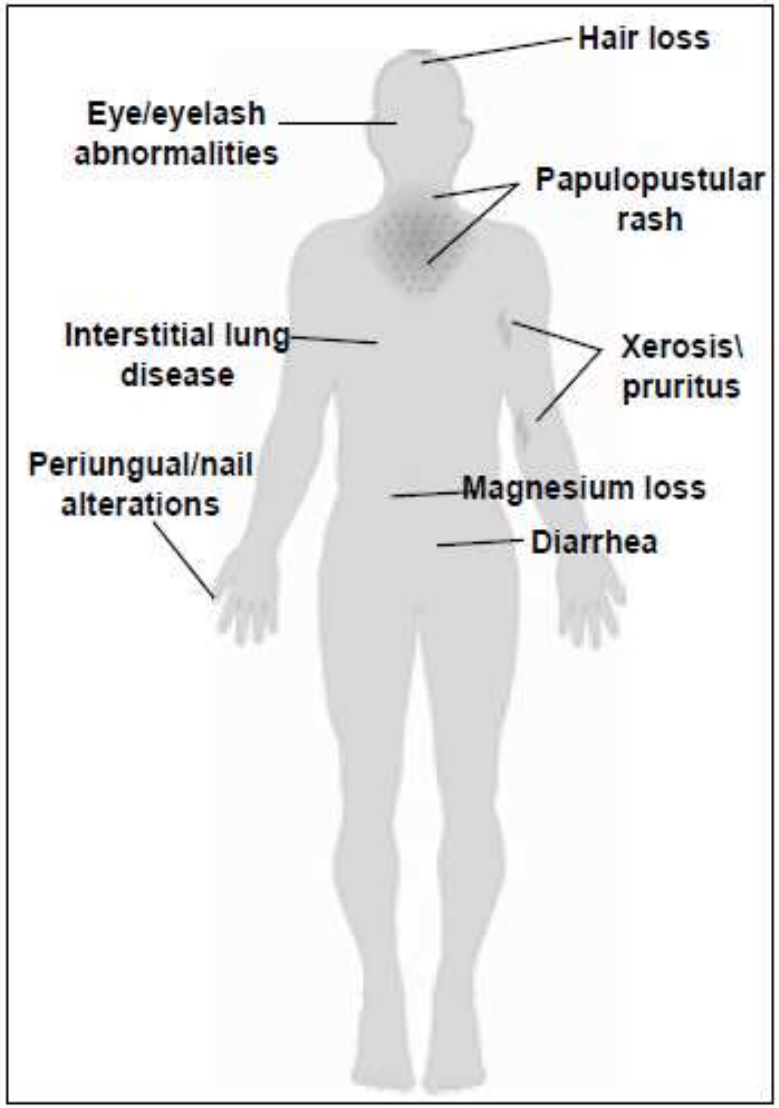
Phase II Study of Lapatinib in SCCHN

- EGFR-HER2 kinase inhibitor
- Arm A: no previous EGFR exposure (n = 27)
- Arm B: previous EGFR exposure (n = 15)
- 42 patients enrolled
- Diarrhea (40%)
- RR: 37% (arm A) and 20% (arm B)
- PFS: 1.6 mos (arm A) and 1.7 mos (arm B)

Abidoye OO, et al. ASCO 2006. Abstract 5568.

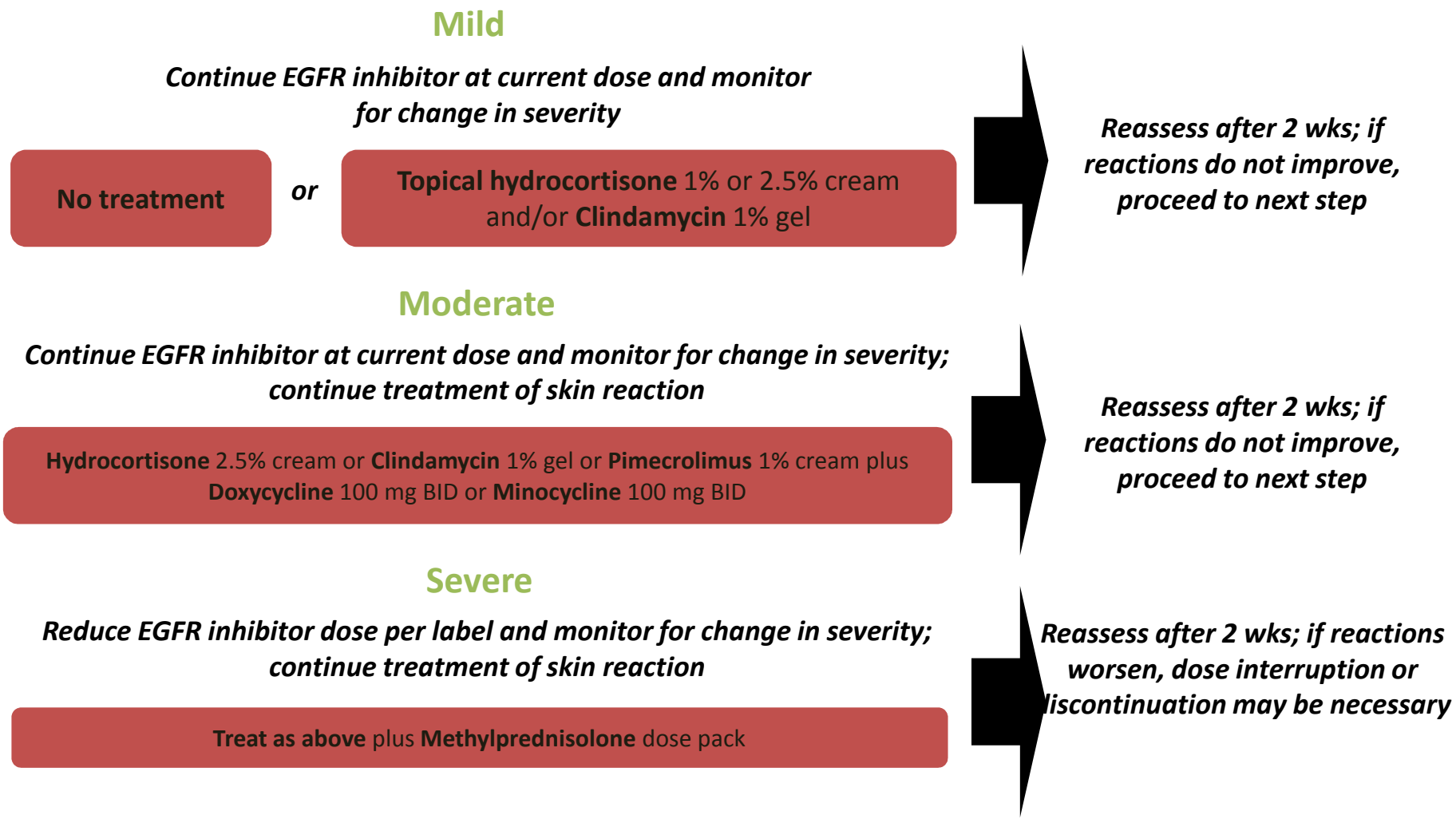
EGFR Inhibitor Side Effects

- Skin effects
  - Papulopustular rash, paronychia, fissures
  - Xerosis or dry skin, itching
  - Hair abnormalities (alopecia, trichomegaly)
  - Eye (conjunctivitis, blepharitis, trichomegaly, corneal erosion, dry eye, ectropion)
- Diarrhea
- ILD
- MoAbs only
  - HSRs
  - Hypomagnesemia



Lacouture and Lai. *Br J Dermatol.* 2006;155:852-854.

A Sample Skin Reaction Algorithm



Lynch TJ Jr, et al. Oncologist. 2007;12:610-621.

Cetuximab Side Effect Profile

- **Hypersensitivity reaction (HSR)**:
  - 2%-5% grade 3/4 (severe); 90% of severe HSRs occur during first infusion
  - 15%-21% grade 1/2
- **Skin rash**: all grades 90% (grade 3/4, 8%)
  - Nail disorder 16% (< 1%)
  - Pruritus 11% (< 1%)
  - Conjunctivitis 7% (< 1%)
  - Skin disorder 4% (0)
  - Alopecia 4% (0)
  - Increased risk of severe rash when combined with RT
- **Hypomagnesemia** (55%, grade 3/4 6%-17%)
- **Diarrhea** (39%), **headache** (33%), **infection** (13%-35%, sepsis 1%-4%)
- **Interstitial lung disease** (ILD): rare (0.5%)
- 2% **cardiopulmonary/sudden death** in patients receiving RT plus cetuximab
- Potentially **fetotoxi**c; effective birth control for 6 months after stopping drug
- *No safety data for the combination of cetuximab, RT, and cisplatin*

Geftinib,Erlotinib Side Effect Profile

- Skin toxicity
  - Rash 75% all grades (grade 3/4, 8%), onset 10 days
  - Pruritus 13%
  - Dry skin 12% (grade 3/4, 0)
- GI toxicity
  - Diarrhea: incidence 54% (grade 3, 6%), onset 15 days
  - Nausea/vomiting 33%/23%
  - Stomatitis 17%
- Eye toxicity
  - Conjunctivitis 12%
  - Keratoconjunctivitis 12%
- ILD (risk increased with gemcitabine)
- Potentially fetotoxic, avoid pregnancy
- Pancreatic cancer
  - Vascular: MI/ischemia (2.3% vs 1.3% placebo arm); DVT (3.9% vs 1.2%), CVA (2.3% vs 0%), rare hemolytic anemia
- Hepatotoxicity (BR, ALT, AST)

Conclusion…

- EGFR over-expression is found in approximately 90% of HNSCC, and This is associated with aggressive tumor behavior and poor clinical outcome .
- EGFR inhibitors- a definite role in treatment of cancer
- Combination chemotherapy – Further studies needed
- Improves QOL with minimal adverse effects
- Can be administered at optimal biological dose
- Potential for use in multiple tumors

Conclusion…

- Role in early stage of cancer needs to be assertained
- Survival not significantly prolonged
- Cetuximab approved with radiation and in metastatic/recurrent setting (2nd line)
- Treatment for metastatic/recurrent SCCHN is still poor, but cetuximab appears to augment the efficacy of standard platinum-based therapy
- Other targeted agents are undergoing further investigation

Techniques for Targeted Molecular Therapy

- Gene therapy,
- Monoclonal antibodies (MAbs),
- Antibody toxin conjugates,
- Small-molecule inhibitors,
- Antisense molecules, and
- Tumor vaccines.

Thanks