

Recurrent SCCHN WHAT TO DO?



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Recurrent Disease
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Department of Thoracic/Head & Neck
Medical Oncology

Recurrent SCCHN

Second primary tumors

Locoregional $\left\{ \begin{array}{l} \text{Potential salvage with S/RT} \\ \text{Infiltrating ds in a radiated field} \end{array} \right.$

Stage IV (M+)/DM

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Recurrent SCCHN ... Novel Approaches

- Antiangiogenesis
- EGFR blockers
- Targeting ras
- p53 modulation

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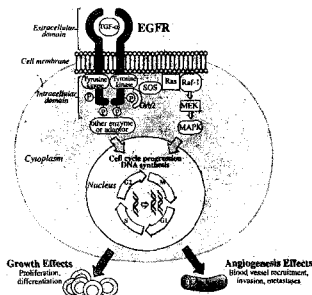
EGFR

- 170 kD transmembrane glycoprotein receptor tyrosine kinase
- Overexpression associated with malignant transformation
- Ligands commonly upregulated (e.g. TGF α)
- Autocrine stimulation key to pathogenesis
- EGFR as therapeutic target validated in xenograft models

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C225 Blockade

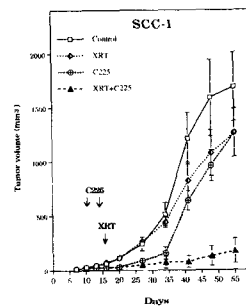
- Receptor internalization
- Inhibits TK phosphorylation
- G1 arrest
- Promotes apoptosis
- Retards angiogenesis
- Decreases MMP-9
- Increases ADCC
- Potentiates CT/RT



Harari

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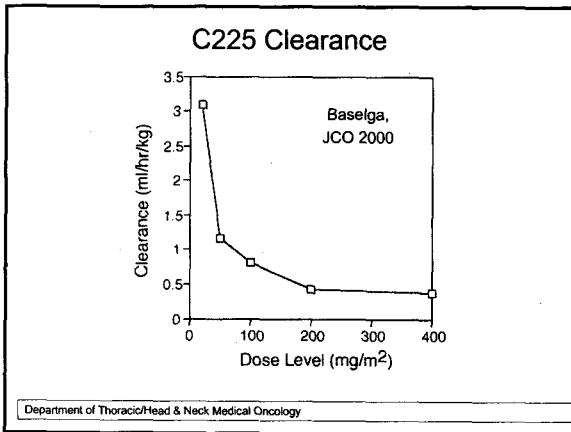
C225 and RT in SCC Xenografts



Huang & Harari,

CCR 2000

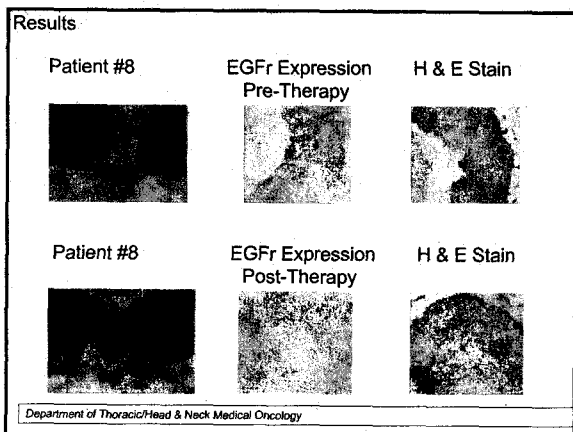
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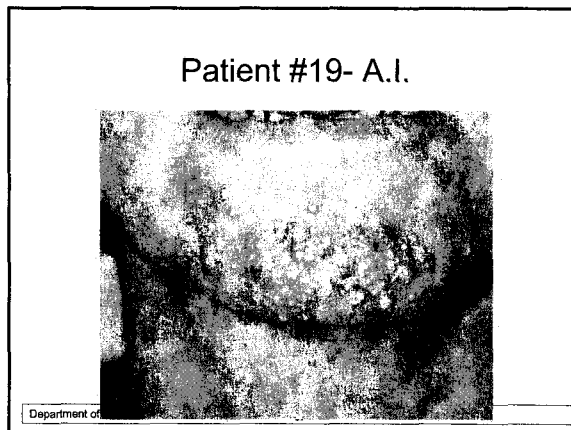
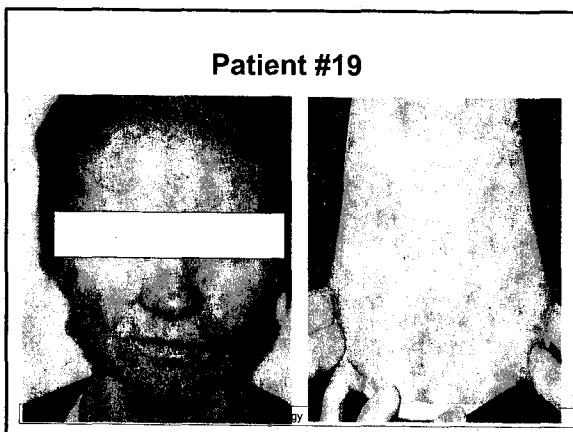
- ### C225 and RT in SCCHN
- Phase I dose escalation format in 15 tmt-naïve pts (stage IV 91%; NØ81%)
 - All responded, 13 CR. Six locoregional recurrences with 2-yr dfs 65%
 - Toxicity: in field mucocutaneous gr 2/3 in all; gr 1/2 acneiform rash in 13; 1 gr 4 allergic reaction; no demonstrated immune response
 - Recommended phase II/III loading dose 400-500 mg/m² with wkly maintenance 250 mg/m²
- Robert,
JCO 2001
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- ### Phase Ib Study of C225 and Cisplatin in Recurrent HNSCC - Objectives
- determine an optimal biological dose
 - establish a safety profile of C225 in combination with cisplatin
- Shin CCR, 2001
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- ### Design
- Cisplatin 100 mg/m² q 3 wks and C225 in loading / wkly doses (mg/m²)
 - 100 / 100 n = 5 pts
 - 500 / 250 n = 4
 - 400 / 250 n = 3
 - Response assessment q 6 wks
 - EGFR saturation studies
 - > tumor specimens
 - > IHC / image analysis
 - > tyrosine kinase activity
 - > EGFR / C225 complexes
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- ### Clinical Responses
- 9/12 "evaluable"
 - Major responses in 6 pts: 2 CR and 4 PR. Of these, 3 pts had previously had progressive ds during cisplatin therapy and 4 responses were in previously radiated areas
 - Response duration?
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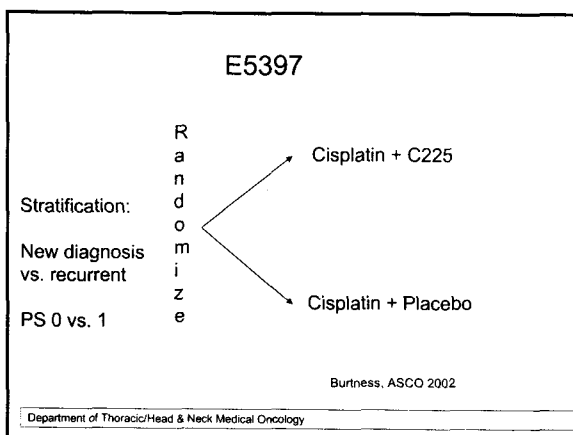


EGFR Targeted Therapy

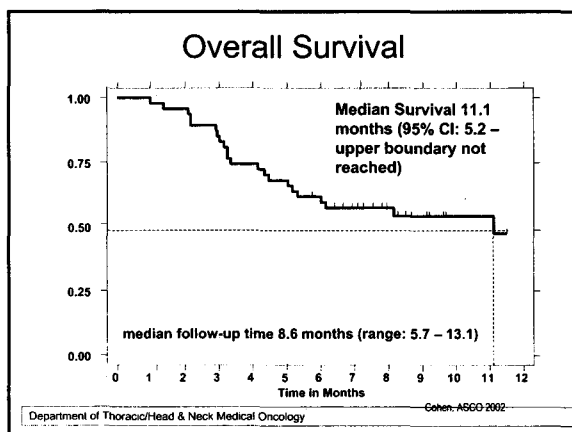
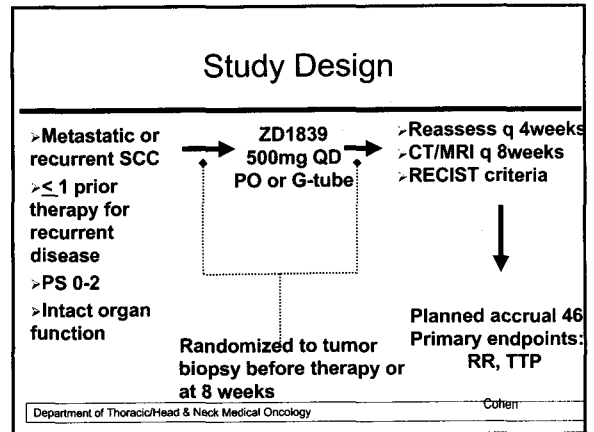
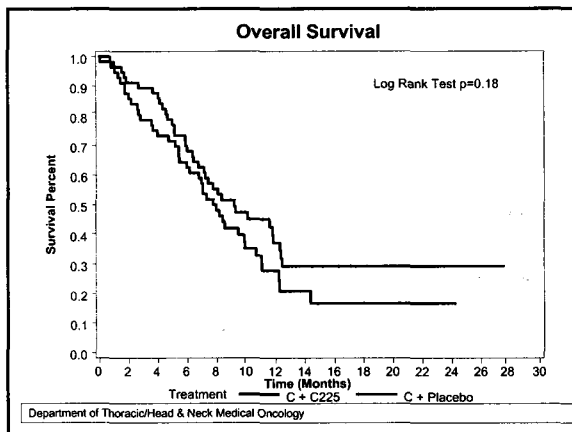
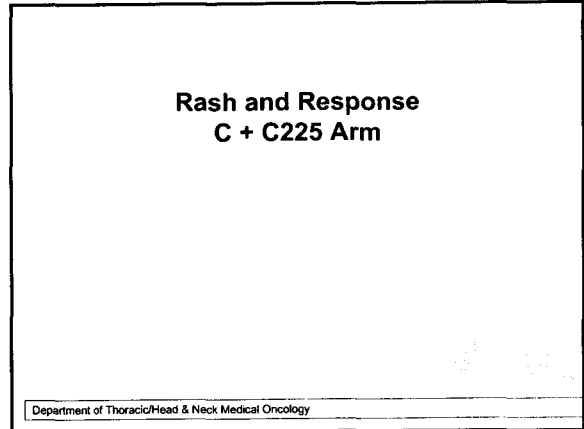
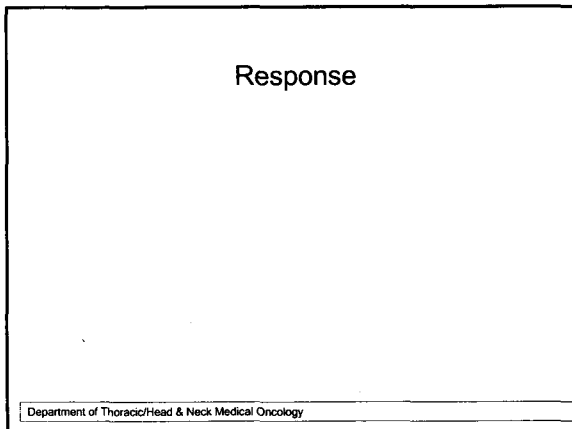
Investigators	Experimental regimen	Trial design	Eligibility
Barcelona	CDDP-C225	II	recurrent/ refractory ds
MDA	CDDP-C225	II	recurrent/ refractory
ECOG	CDDP-C225	III	recurrent
Chicago	ZD-1839	II	recurrent

Phase II trials in patients with refractory SCCHN

	n	responses	allergic
MDA	79	12%	4%
Barcelona	96	14%	? 3%



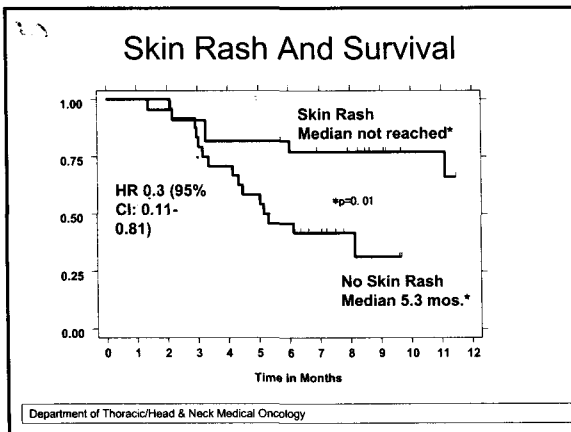
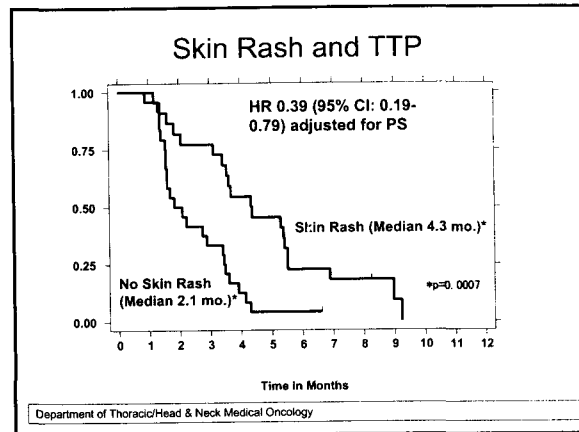
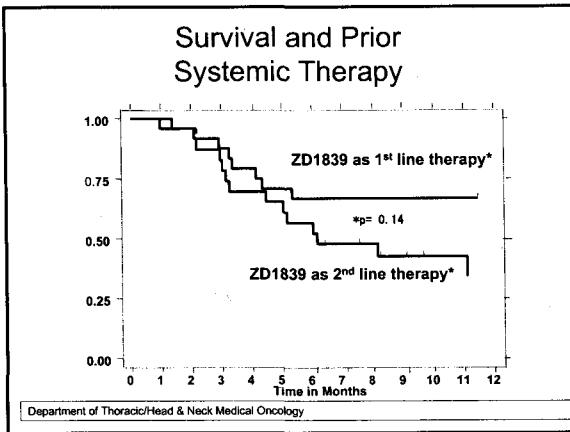
Grade 3/4 Toxicity



Factors Related to TTP and Survival

Characteristic	p-value*
Disease Site (metastatic vs. local)	NS
Prior Systemic Regimen for Rec/Met	NS
Any Chemotherapy	NS
Performance Status	< 0.001
Disease Control	< 0.001
Acneiform Skin Rash	< 0.001

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Early Impressions:

	C225	ZD 1839
single agent	?	active
administration	iv	po/pt
toxicity	rash hypersensitivity	rash diarrhea
association of rash-response	+	+
use in combination	+	?
effects on survival	?	?

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- ### C225 in SCCHN
- single agent activity is not determined
 - administration is iv (vs. po/pt for small molecule TK inhibitors)
 - toxicity is manageable – rash / hypersensitivity
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- ### C225 in SCCHN
- rash is associated with response
 - use in combination with CT/RT is feasible
 - ? effects on tumor control and survival
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Current Projects

- single agent trials in recurrent ds
- phase II induction chemotherapy trial, with cbdca and paclitaxel in HN
- phase III randomized studies of chemotherapy ± C225 and radiotherapy ± C225
- translational projects evaluating the significance of EGFR - and downstream signal transduction effects of C225 therapy

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