Treatment Options for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

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Recurrent and/or metastatic SCCHN: Introduction

- Over 50% of newly diagnosed cases are not cured and will relapse locally or at distant sites
- 10% of newly diagnosed cases present with distant metastases
- Treatment options:
  - Chemotherapy (CT)
  - Re-irradiation
  - Salvage surgery
  - Best supportive care (BSC)

  (Re-irradiation, Salvage surgery: 10-15% of localized recurrences)
- Cisplatin-based CT:
  - Response rate: 30%
  - Overall survival: 6–9 months

Factors Considered When Choosing Treatment

- What did patient receive in the curative setting?
- Interval between curative intent treatment and recurrence
- Performance status
- Co-morbidities
- Patient preference
- Logistics

Recurrent / Metastatic H&N Cancer
Good prognosis patients

- Good performance status
- Minimal disease
- Local recurrence only
- No bony erosion
- Good response to induction chemotherapy
- Good response to previous radiotherapy
- Long disease free interval
- Good organ(s) function
- Complete response to chemotherapy

Modified from Al-Sarraf, 1988

Conventional Agent Activity in R/M-SCCHN*

Drug	Pts	% Response
Methotrexate	1038	42
Bleomycin	435	26
Cisplatin	310	21
Ifosfamide	225	32
5-Fluorouracil	146	27
Cyclofosfamide	77	36
Vinblastine	59	27
Doxorubicin	34	23

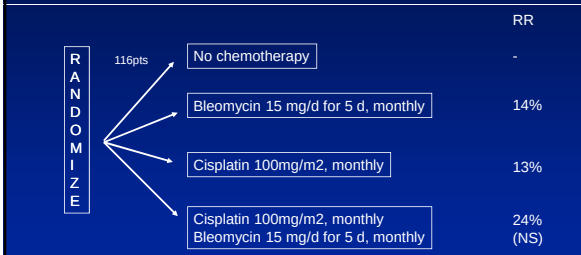
** Pooled data in advanced disease*

New Agent Activity in R/M-SCCHN

Drug	Response rates (%)
Edetrexate	6-21 *
Gemcitabine	11-13
Pemetrexed	26
Vinorelbine	6-22
Topotecan	0-14
Irinotecan	21
Paclitaxel	20-40
Docetaxel	21-42

** Schornagel et al, 1985 (Phase III study in 264 pts of MTX vs EDX, showing RR 16% vs 21% and OS 6 mo vs 6 mo, respectively*

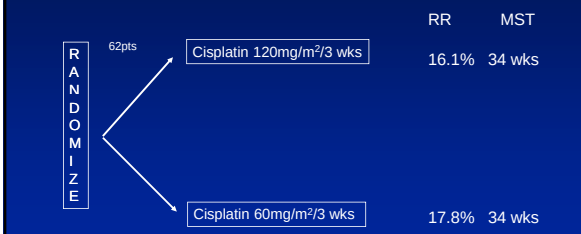
Cisplatin and Bleomycin for Advanced or Recurrent Squamous Cell Carcinoma of the Head and Neck: a Randomized Factorial Phase III Controlled Trial



Survival benefit: Cis vs control (P<0.05)
Cis arms vs non-Cis arms (P<0.01)

Morton RP, et al. Cancer Chemother Pharmacol 1985

High-Dose versus Low-Dose Cisplatin in Advanced Head and Neck Squamous Carcinoma: a Randomized Study.



Veronesi A, et al. J Clin Oncol 1985

Randomized Single Agent Trials in R/M-SCCHN

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

Methotrexate vs Two Schedules of Paclitaxel R/M disease

Stratification

- Institution
- WHO-PS
- Site
- Prior TRT

RANDOM

Treatment arms

- MTX 40 mg/m²/week
- PAC 175 mg/m²/3h/q 3 weeks
- PAC 175 mg/m²/24-h/q 3 weeks

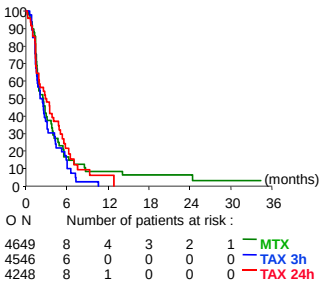
Vermorken et al, 1999

Methotrexate vs Two Schedules of Paclitaxel R/M disease

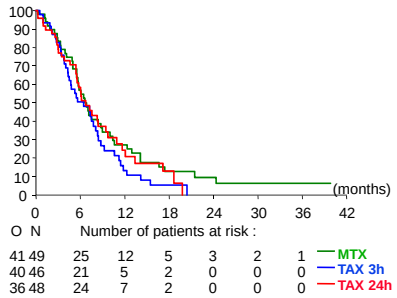
	MTX n=49	PAC-3h n=46	PAC-24h n=48
Response (% CR + PR)	16	11	23
- 95% CI:%	7-30	4-24	12-37
Toxicity (% grade ≥ 3)			
- Alopecia (moderately/severe)	2	65	68
- Stomatitis	11	2	4
- Leucopenia	10	13	57
- Neutropenia	15	17	72
- Febrile neutropenia	6	0	28

Vermorken et al, 1999

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



Cisplatin/5FU (PF) Combinations in R/M SCCHN
Nonrandomized trials

Reference (yr)	No. of pts	Response rate (%) CR	CR + PR
Kish (1984)	30	27	70
Rowland (1986)	30	17	60
Urba* (1989)	365	16	50

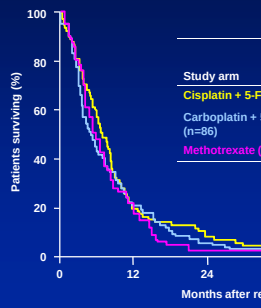
** Compiled results of 12 trials*

PF vs Single Agents or Other Pt-regimens
Randomized trials in R/M disease

Reference	No. of Pts	Agents	RR (%)	MS (mo)
Jacobs et al 1992	249	PF	32*	5.5
		P	17	5.0
		F	13	6.1
Forastiere et al 1992	277	PF	32**	6.6
		CF	21	5.0
		M	10	5.6
Clavel et al 1994	382	CABO	34+	7.0
		PF	31++	
		P	15	
Gibson et al 2005	218	PF	27	8.7
		PT	26	8.1

**β=0.035; **p<0.001; *p<0.001; **p=0.003*
(p=cisplatin; c=carboplatin; M=methotrexate; B=bleomycin; V=vincristine; T=paclitaxel; CABO=P+M+B+V)

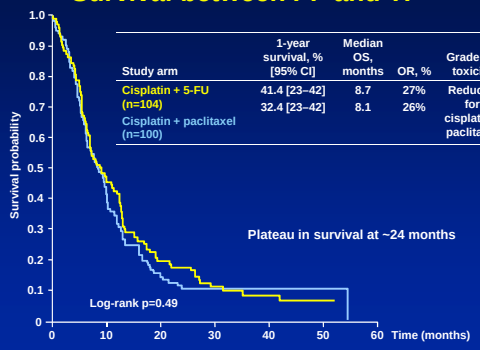
Phase III Trial of PF vs CF vs MTX in Recurrent and/or Metastatic SCCHN: No significant Difference in Survival



Study arm	Median OS, months	OR, %	Grade 3/4 toxicity
Cisplatin + 5-FU (n=87)	6.6	32	Neutropenia
Carboplatin + 5-FU (n=86)	5.0	21	Mucositis
Methotrexate (n=88)	5.6	10	

Forastiere A, et al. J Clin Oncol 1992;10:1245–1251

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	27%	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

Taxane Combinations in R/M SCCHN

		Response Rates (CR rates)	
		Paclitaxel	Docetaxel
2-drugs:	Cisplatin (P)	32-39 (7)	33-52 (9-11)
	Carboplatin (C)	33-33 (4-8)	-
	5-FU (F)	-	34 (9)
	Vinorelbine	-	44 (11)
3-drugs:	PF	38 (NR)	44 (12)
	IP	58 (17)	-
	IC	59 (17)	-

NR = not reported

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 OAS: 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 OAS: 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

Platinum-Refractory R/M SCCHN
Therapeutic options

- 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 Proc. ASCO, 2003: updated in 2005)
- 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)

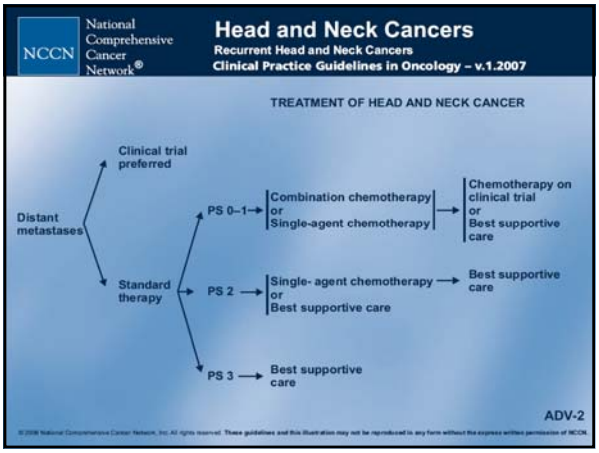
Single Agent Palliative Docetaxel for R/M-SCCHN 2nd line

Author	Prior CT		Pt-R	Regimen	ORR (%)
	Overall	for R/M			
Numico 2002 n=18	100%	61%	NR	80 mg/m² q 3 w	11
Zenda 2007 N-20	100%	NR	100%	60 mg/m² q 3 w	10
Specenier* N=30	90%	77%	80%	36 mg/m²/w	7

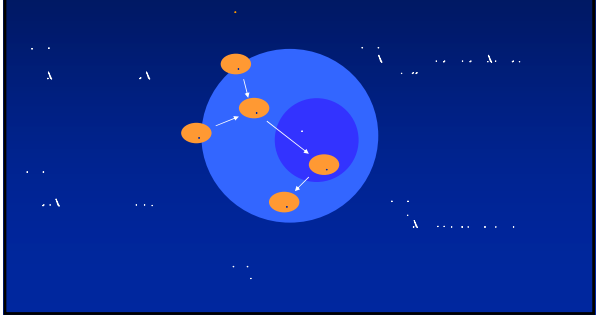
** UZA experience (submitted): median PFS 7.4 weeks (95% CI: 5.5 – 9.3 weeks); median OS 17.9 weeks (95% CI: 10.1-25.6 wks)*

Chemotherapy in R/M-SCCHN: Summary

- 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



EGFR Expression in Human Tumors

EGFR expression

NSCLC	40-80%
Prostate	40-80%
Head & Neck	90-100%
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-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/gastrointesinal (GI)
Erlotinib	OSI-774	reversible	EGFR	skin/GI
	PKI-166	reversible	EGFR/ERbB2	skin/GI/systemic/hepatic
Lapatinib	GW-572016	reversible	EGFR/ERbB2	skin/GI/systemic
Canertinib	CI-0033	irreversible	EGFR	skin/oral/GI/systemic

Specenier and Vermorken, Targ Oncol 2007; 2: 73-88

Non-Randomized Studies in Recurrent/Metastatic HNC

Treatment (Reference)	N	RR (%)	Median overall survival (months)
Cetuximab (Vermorken 2007)*°	103	13	5.9
Cet + Pt (Baselga 2005)*°	96	10	6.2
Cet + CDDP (Herbst 2005)*°	79	10	5.2
Cet + PF (Bourhis 2006)+	53	36	9.8
Cet + PAC (Hitt 2007)+	42	60	NR
Gefitinib 500 mg (Cohen 2003)	52	10.6	8.1
Gefitinib 250 mg (Cohen 2005)	70	1.4	5.5
Gefitinib 500 mg (Kirby 2006)	47	8	4.3
Erlotinib 150 mg (Soulieres 2004)	115	4.3	6

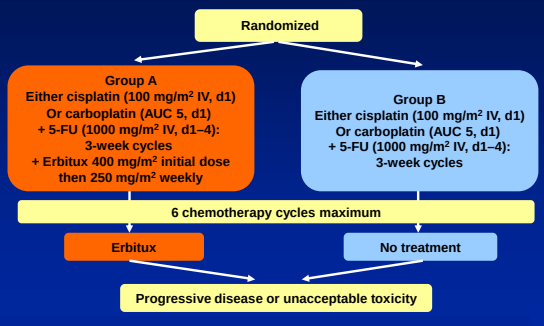
**chemorefractory disease (°Pt refractory); cetuximab 400 mg/m² initial dose, followed by 250 mg/m²/week*
+ first-line R/M-SCCHN

Completed Randomized Trials in Recurrent/Metastatic HNC

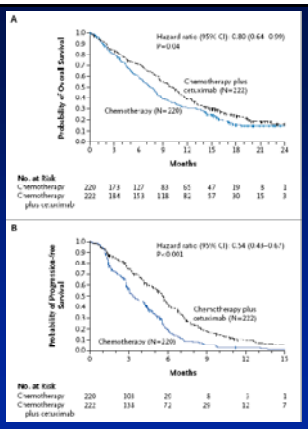
Study/Reference	N	Regimen	Population	RR (%)	OS (mo)
EXTREME/ Vermorken et al 2008	442	PFC vs PF	1st-line	36 vs 20	10.1 vs 7.4
ECOG 5397/ Burtness et al 2005	117	CisPtC vs cisPt	1st-line	26 vs 10	9.2 vs 8.0
IMEX/ Stewart et al, 2009*	486	Gefitinib (250 mg) Gefitinib (500 mg) Methotrexate	2nd-line	2.7 vs 7.6 vs 3.9	5.6 vs 6.0 vs 6.7

*PF=cisplatin or carboplatin plus 5-FU; C=cetuximab; * in press (JCO)*

EXTREME: Study design



Vermorken et al. N Engl J Med 2008: 359: 1116-27



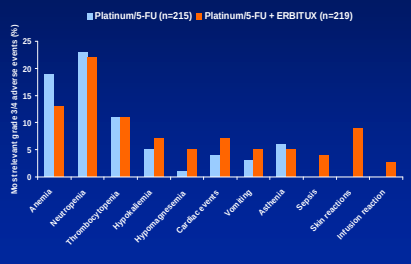
Vermorken et al. N Engl J Med 2008: 359: 1116-27

EXTREME: Responses to Treatment and Survival

Variable	PF+cetuximab n=222	PF n=220	HR or OR (95% CI)	P value
Survival – mo				
overall	10.1 (8.6 -11.2)	7.4 (6.4-8.3)	HR 0.80 (0.60-0.99)	0.04
progression-free	5.6 (5.0 - 6.0)	3.3 (2.9-4.3)	HR 0.54 (0.43-0.67)	<0.001
Best response - %				
overall	36 (29-42)	20 (15-25)	OR 2.33 (1.50-3.60)	<0.001
disease control	81 (75-86)	60 (53-67)	OR 2.88 (1.87-4.44)	<0.001
Time to TRT failure-mo	4.8 (4.0-5.6)	3.0 (2.8-3.4)	HR 0.59 (0.48-0.73)	<0.001
Duration of response	5.6 (4.7-6.0)	4.7 (3.6-5.9)	HR 0.76 (0.50-1.17)	0.21

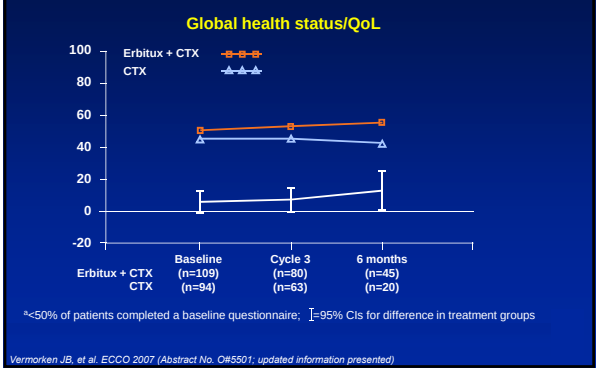
PF=cisplatin or carboplatin + 5-FU; HR=hazard ratio; OR: odds ratio
Vermorken et al. N Engl J Med 2008: 359: 1116-27

EXTREME: Most relevant grade 3/4 adverse events



Modified from Vermorken et al, N Engl J Med 2008: 359: 1116-27

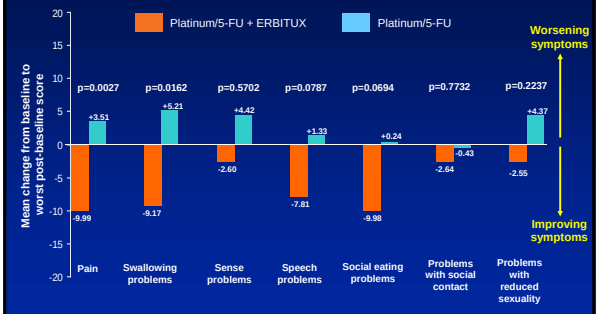
EXTREME: Quality of life[a]



[a]<50% of patients completed a baseline questionnaire; I=95% CIs for difference in treatment groups

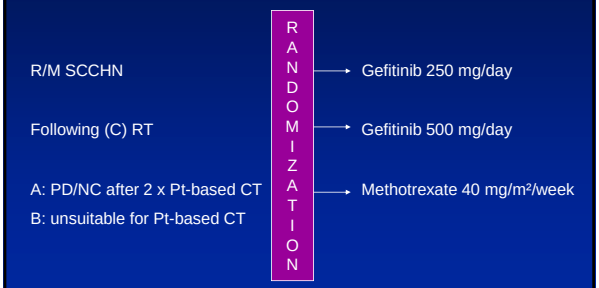
Vermorken JB, et al. ECCO 2007 (Abstract No. O#5501; updated information presented)

EXTREME: Symptom Control



Rivera F, et al. ESMO 2008

IMEX: Phase III Trial of Two Dose Levels of Gefitinib versus Weekly Methotrexate in SCCHN

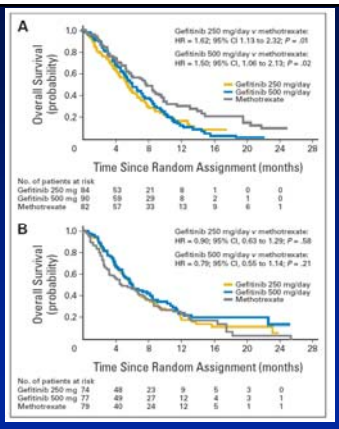


Stewart JSW, et al, JCO 2009

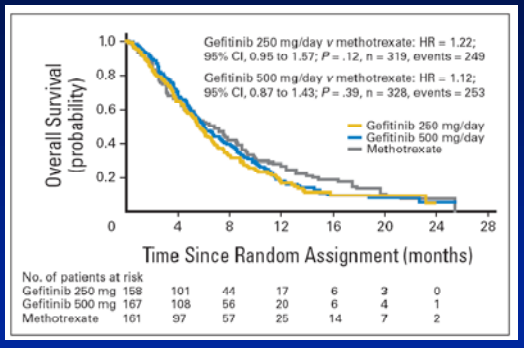
Two Dose-levels of Gefitinib vs IV Methotrexate in R/M-SCCHN
Phase III study

	Gefitinib 250 mg/d	Gefitinib 500 mg/d	MTX 40-60 mg/m²/w
Median survival	5.6 mo	6.0 mo	6.7 mo
Overall response	2.7 %	7.6 %	3.9 %
Disease-control	50.3 %	51.5 %	47.3 %
Tumor hemorrhage	8.9 %	11.4 %	1.9 %
Cancer pain	19.0 %	18.1 %	11.3 %
FACT-HH-score	13.4 %	18.0 %	6.0 %
FHNSI score	14.4 %	37.8 %	22.6 %

Stewart JSW, et al, JCO 2009



Stewart JSW, et al, JCO 2009

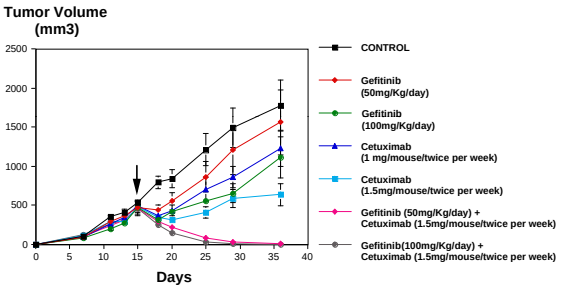


Stewart JSW, et al, JCO 2009

Ongoing Randomised Studies with MoAbs and TKIs
Recurrent/metastatic disease

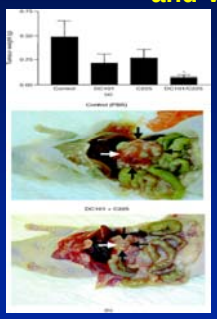
Study	Phase	N	End-point
SPECTRUM	III	650	0S
Cisplatin + 5FU			
Cisplatin + 5FU + panitumumab			
PARTNER	II	150	PFS
Docetaxel + cisplatin			
Docetaxel + Cis + panitumumab			
ECOG-E1302	III	330	OS
Docetaxel weekly + placebo			
Docetaxel weekly + gefitinib			
Hx-EGFR-202			
Zalutumumab + best supportive care			
Best supportive care	III	273	OS

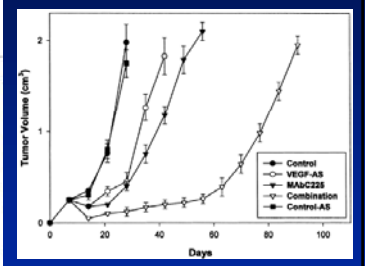
Combined anti-EGFR Treatment with Gefitinib and Cetuximab



P. Matar et al Clin Cancer Res 2004; 10: 6487-6501
Courtesy of Dr. Baselga, 2006

Experimental Evidence for Combined EGFR and VEGF Inhibition





Courtesy of Dr. Baselga

Jung et al. Eur J Cancer 2002;38:1133-1140.
Ciardiello et al. Clin Cancer Res 2000;6:3739-3747.

Erlotinib and Bevacizumab in R/M SCCHN: Phase I/II Study*

Phase I
4 patients given 5 mg/kg (1 NA)
3 patients given 10 mg/kg
3 patients given 15 mg/kg (patients induced in phase II assessment)

↓

Phase II
44 patients given 15 mg/kg (1 NA)
(first 3 patients also used in MTD assessment)
(N=3+44-1=46 assessable patients)

↓

2 additional patients accrued
(N=46+2=48 patients assessable in phase II)

Rash 41/48: diarrhea 168

Three patients → ≥ G3 bleeding

Response in 7 (15%), CR in 4

Median OS 7.1 months

Median PFS 4.1 months

Cohen et al., www.thelancet.com/oncology published on line, Feb 9, 2009

	Tumour cells			Endothelial cells		
	CR (n=2)	Non-CR (n=9)	p value	CR (n=2)	Non-CR (n=9)	p value
pVEGFR2	58539 (9004)	55174 (44069)	0·15	370783 (241961)	219250 (79903)	0·44
VEGFR2	83278 (6992)	175032 (167250)	0·33	1820000 (1940000)	1320000 (1100000)	0·91
pVEGFR2/VEGFR2	0·704 (0·054)	0·386 (0·142)	0·036*	0·329 (0·225)	0·247 (0·126)	0·73
pEGFR	107136 (72501)	70496 (71119)	0·22	1180000 (1240000)	314131 (97564)	0·44
EGFR	158498 (150977)	111355 (116596)	0·73	1680000 (1770000)	1190000 (754280)	1·00
pEGFR/EGFR	1·035 (0·063)	0·737 (0·298)	0·33	0·649 (0·351)	0·332 (0·184)	0·036*
pERK	115717 (54199)	65116 (38143)	0·22	753679 (97636)	416210 (301296)	0·22
ERK	218506 (100022)	136504 (67670)	0·33	2760000 (2430000)	1730000 (696229)	0·91
pERK/ERK	0·4844 (0·3065)	0·5896 (0·4870)	0·91	0·4948 (0·4833)	0·3245 (0·3591)	0·58
pAKT	36063 (17860)	38126† (26483)	0·89	546422 (69846)	442206† (306892)	0·71
AKT	140788 (40578)	84943† (63429)	0·18	2400000 (1090000)	1470000† (4700000)	0·53
pAKT/AKT	0·2502 (0·0581)	0·8177† (1·0483)	0·40	0·2446 (0·080)	0·209† (0·345)	0·71

CR=complete response. Non-CR=stable or progressive disease. *p<0·05, two-sided exact permutation test. †n=8.

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Conclusions

- Better understanding of the biology of SCCHN has led to change in treatment approaches
- Better selection of patients for specific treatment approach may become an important issue in future trials
- Finally a breakthrough in R/M SCCHN after 30 years