Cetuximab-based Treatment of Advanced Non-small Cell Lung Cancer

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Cetuximab (Erbitux®, [C225]):

Definition: chimeric genetically engineered IgG1 EGFR-targeted monoclonal antibody

Mechanism of Action:

1. targets the extracellular domain of the human EGFR
2. blocks signal transduction
3. interferes with cell growth:
   a. blocks cells at G1/S through induction of p27
   b. triggers an antibody-dependent cellular cytotoxic (ADCC) reaction
   c. produces irreversible downregulation of the receptor by internalization and degradation

Cetuximab:

Indications:

Cetuximab was approved:

- **In advanced, EGFR+ mCRC**: alone or in combination with irinotecan (CPT-11), based on improvement in ORR and TTP, but not in OS, compared with chemotherapy alone

- **In stage III/IV SqCC of the oropharynx, hypopharynx, and larynx:** in combination with XRT followed by surgery, based on improvement in local control, median survival, and 2-years PFS compared with radiation alone

Cetuximab:

in advanced NSCLC

Initial phase I/II trials testing first line cetuximab with platinum-based doublets:

a. carboplatin/paclitaxel
b. carboplatin/gemcitabine
c. cisplatin/gemcitabine
d. cisplatin/ vinorelbine

	RR (%)	Median PFS (mo)	Median OS (mo)
CHEMO + Cetuximab	**23 - 35**	4.0 - 5.5	**8.3 - 11.99**
CHEMO	18.2 - 28.0	4.2 - 4.6	7.3 - 9.26

Carboplatin/Paclitaxel and Cetuximab:
SWOG

225 pts.
Stg IIIB/IV

Tax-225/Carbo-6 q 3wks
C225-400>>250 q week

Tax-225/Carbo-6 q 3wks

	RR	DC	PFS median	OS median
C225-250 q week	**37%**	75%	4.2mo	**10.5mo**
Observ.	26%	71%	4.4mo	8.7mo

K Kelly et al, PASCO 2006, #7015

Carboplatin/Paclitaxel & Cetuximab in Advanced NSCLC:

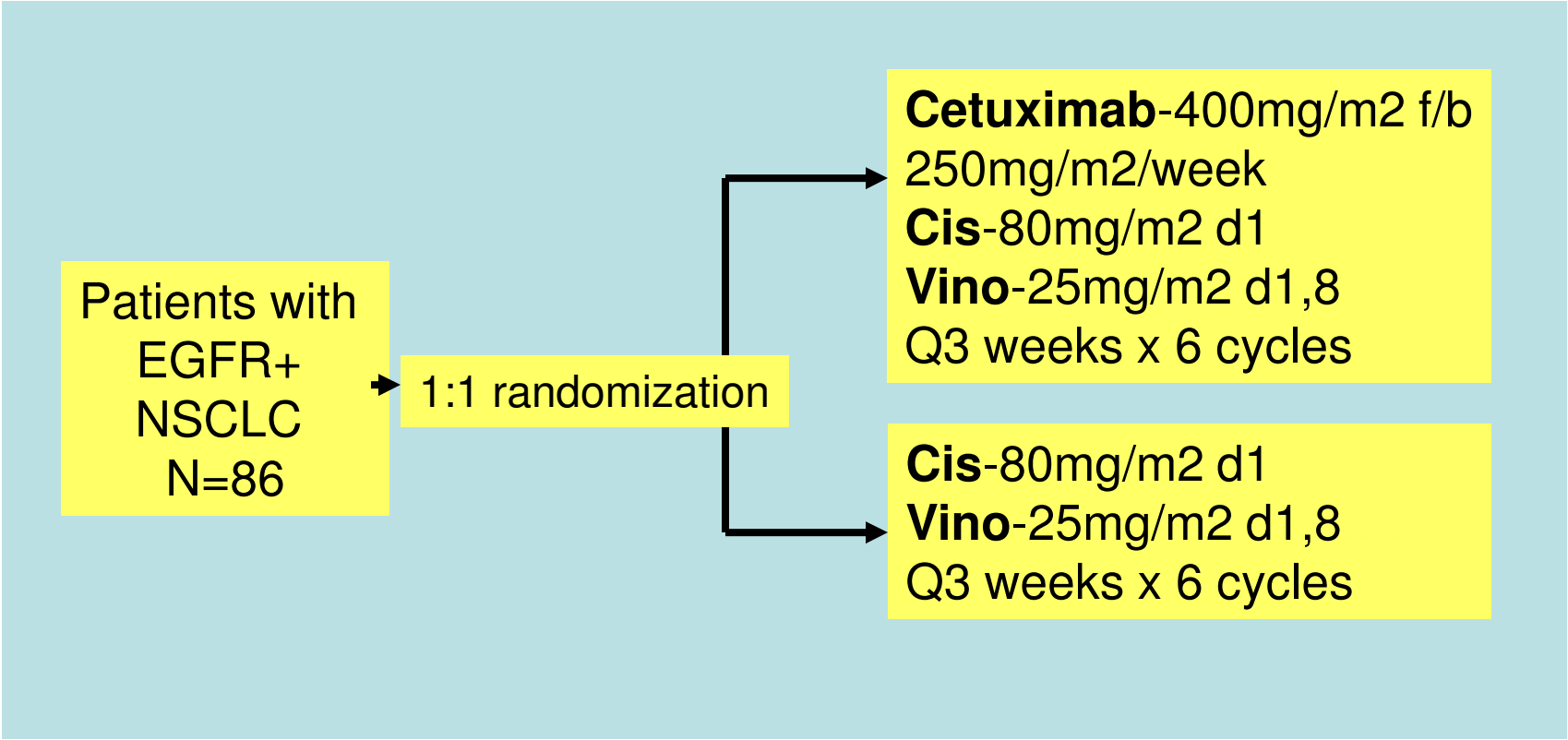
UNC/GCS

	ORR (%)	SD (%)	PFS median (mo)	OS median (mo)	1-yr survival (%)
C225 Carb-AUC 6 Pacl-**225** **q21d** →	23.4	43	4.2	11.7	45.9
C225 Carb-AUC 6 Pacl-**100** **q28d** →	24.5	38	3.9	10.2	40.4

MN Saleh et al. ASCO 2007, # 7586

Randomized Phase II: Cisplatin/Vinorelbine +/- Cetuximab

SLCG



Rosell et al. Ann Oncol 2008; ASCO #7012,2004

Randomized Phase II: Cisplatin/Vinorelbine +/- Cetuximab

SLCG

Efficacy	Cis/Vino (N=43)	CV+Cetux (N=43)
RR	28%	35%
Median PFS	4.6 m	5.0 m
Median OS	7.3 m	8.3 m
1-yr Survival	26%	33%
2-yr Survival	0%	16%

Rosell et al. AnnOncol 2008; ASCO #7012,2004

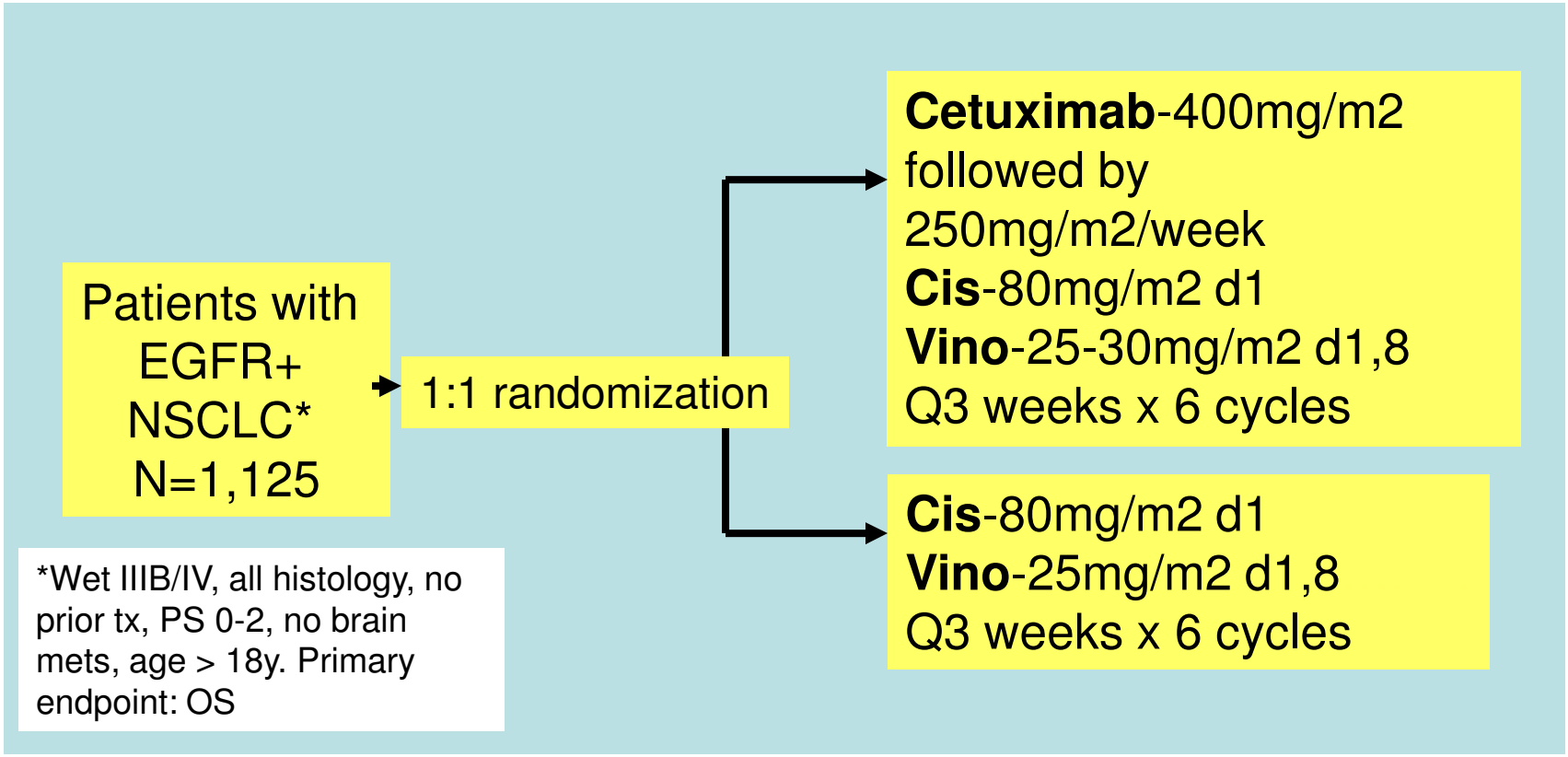
Cetuximab:

advanced NSCLC – Phase I/II

Author ***(EGFR status)***	**Patient No**	**Phase**	**Chemotherapy**	**ORR (%)**	**OS (mo)**	**PFS (mo)**
Thienelt	32	I/II	C225/carb/pacl	--	11	5
Robert *(EGFR+)*	35	I/IIa	C225/carb/gem	29	10.3	5.5
Butts	131	IIr	C225/cis/gem Cis/Gem	27.7 18.2	11.99 9.26	5.09 4.21
Rosell *(EGFR+)*	86	IIr	C225/Cis/vinor Cis/vinor	35 28	8.3 7.3	5.0 4.6
Herbst	242	II	C225/seq. carb/pacl C225/conc. carb/pacl	31 34	11 11	4 4
Bradford	57	II	C225/carb	5.3	8.2	3.0
Socinski	165	II	C225/carb/pacl Q3w C225/carb/pacl Weekly	23.4 24.5	11.7 10.0	4.4 4.2
Total:	**748**	**--**	**C225 +** **C225 -**	**29.86** **23.10**	**10.28** **8.28**	**5.07** **4.41**

Randomized Phase III: Cisplatin/Vinorelbine +/- Cetuximab

FLEX



Pirker et al. ASCO, June 1, 2008

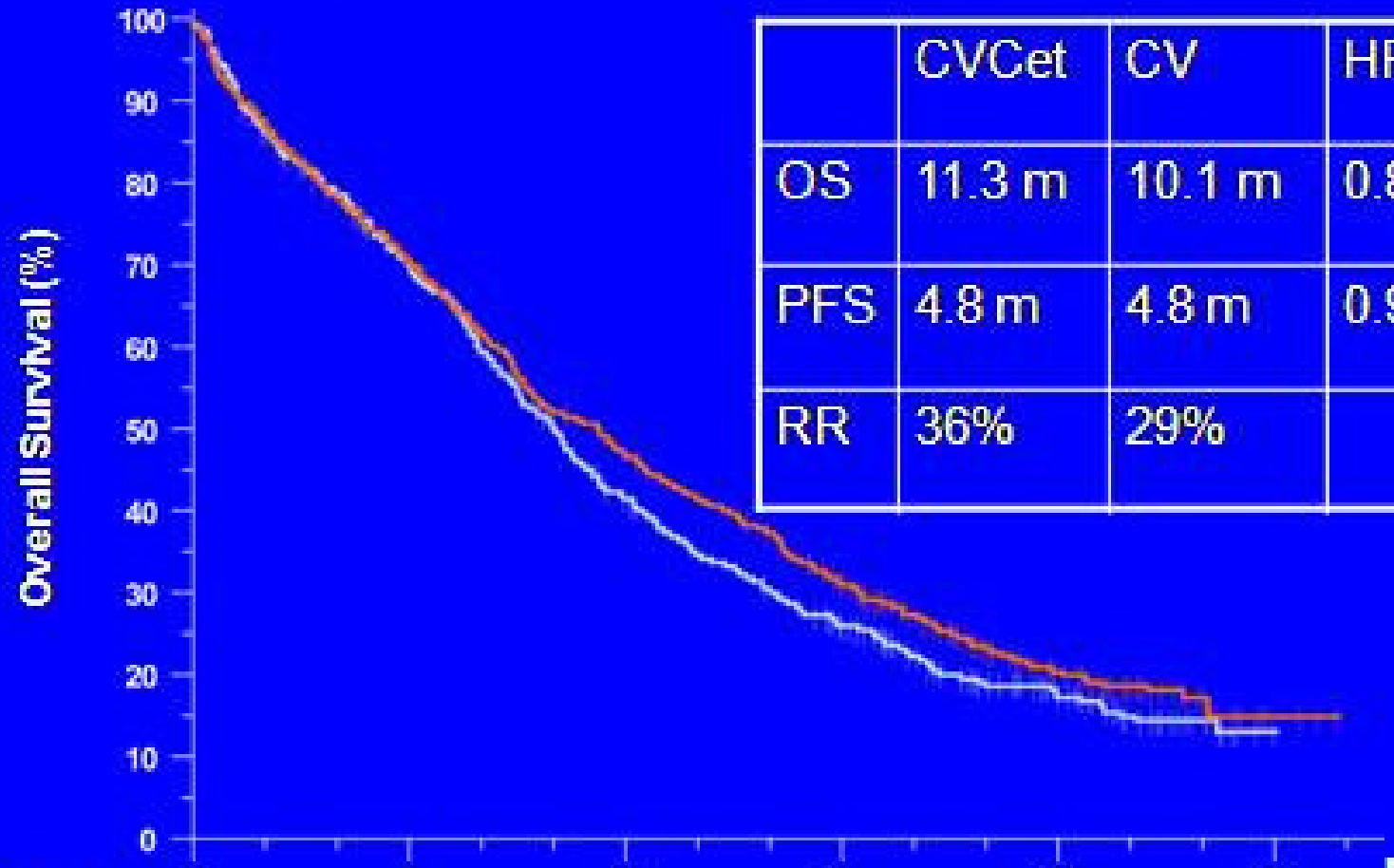
Randomized Phase III: Cisplatin/Vinorelbine +/- Cetuximab

FLEX- Overall Survival

	CVCet	CV	HR	*P*
Med OS (mo)	**11.3**	**10.1**	**0.871**	***0.044***
Med PFS (mo)	4.8	4.8	0.943	*NS*
RR	36%	29%		*0.012*

Pirker et al. ASCO, June 1, 2008

FLEX: Overall Survival



	CVCet	CV	HR	*p*
OS	11.3 m	10.1 m	0.871	.044
PFS	4.8 m	4.8 m	0.943	ns
RR	36%	29%		.012

Patients at risk						
CT + Cetuximab	557	383	251	155	53	3
CT	568	383	225	134	48	0

Pirker et al., ASCO, June 1, 2008

Randomized Phase III: Cisplatin/Vinorelbine +/- Cetuximab

FLEX- Toxicity

Adverse Events Grade ¾ (%)	CT + cetuximab (n=548)	CT (n=562)
Any event	**91**	**86**
Neutropenia	53	51
Febrile neutropenia	22	15*
Anemia	14	17
Acne-like rash	10	<1*
Diarrhea	5	2*
Infusion-related reactions	4	<1*
Treatment-related death	3	2

** P < 0.05*

Predictors of Response and Survival

Cetuximab:

predictive markers of response and survival

- Specific EGFR mutations do **NOT** correlate with response to cetuximab

EGFR as a Prognostic Marker in NSCLC:
IHC

101:130 ***(78%)*** of resected Stage I-III NSCLC had EGFR(+) expression (*) by IHC

	EGFR expression
Stage I	20%
Stage II	25%
Stage III	54%
PValue	*< 0.03*

	Median OS	5-yr Surv
EGFR **>10**	18 mo	31%
EGFR **<10**	50 mo	46%
	P < 0.001	

G Selvaggi et al., ASCO 2002; #1345

EGFR Mutation:

ATP-binding pocket of TK domain, in exons 19 and 21

- Of 275 pts treated with gefitinib; **25** reached **PR**
- 9 of these 25 *(all AdenoCa & BAC)* had pre-treatment tissue available for evaluation of EGFR gene mutations in the entire gene coding region
- Median OS in these 9 was > 18 months

	Cancer Tissue		Normal Tissue from Gefitinib-responders
	Responders	Non-Responders	
Mutation	8 of 9 (88.9%)	0 of 7	0 of 4
	P < 0.001		

Lynch T et al., NEJM,2004;350:2129

EGFR Gene Copy Number by *FISH* and Gefitinib in BAC:

81 pts, gefitinib-500 *(SWOG S0126)*

	CR/PR/S	Median OS	Median PFS
FISH (+): 19	12 (63%)	NR (~18 mo)	9 mo
FISH (-): 36	14 (39%)	8 mo	4 mo
P Value	***0.099***	***0.042***	***0.072***

Conclusion: strong association between increased EGFR copy number by FISH and sensitivity to gefitinib in pts with advanced BAC, after accounting for smoking status, sex, histology and PS

Hirsch FR et al., ASCO 2005, Abstract # 7030

Prospective Erlotinib Trial in Advanced NSCLC with EGFR-mutation:

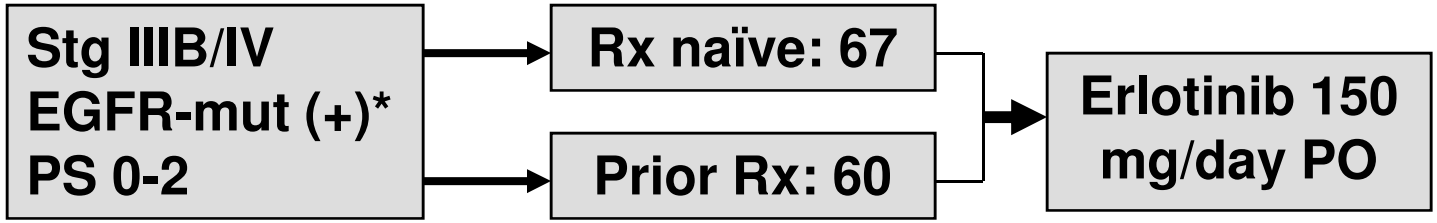
SLCG

Rationale: EGFR-mut predicts response (60-90%) and long TTP (12-21 mo) to the tk-inhibitors erlotinib & gefitinib.

Population: 127 (15.1%):1047 pts. ERGF-mut (+) ***(exon 19 & 21)***

M-age	68	Stg-IV	90%
Female/male	65%	AdenoCa	75%

Eligibility & treatment:



L Paz-Ares et al., PASCO 2006 Abstr7020

Prospective Erlotinib Trial in Advanced NSCLC with EGFR-mutation:

SLCG

Results:

	Median OS (mo)	1-yr S (%)	CR (%)	RR (%)
Exon-19-mut	33	82	**20**	**95**
Exon-21-mut			5.5	68

ORR: 83%

POOR Response:	GOOD Response:
Lung	CNS
Lymph nodes	Liver
	Bone

L Paz-Ares et al., PASCO 2006 Abstr7020

Prospective Erlotinib Trial in Advanced NSCLC with EGFR-mutation:

SLCG

Conclusions:

Prospective predictors of response to tk-inhibitors:

a. EGFR-mut (exon-19 > 21) $P = 0.038$

b. Non-smoking history $P = 0.043$

c. Female gender $P = 0.203$

L Paz-Ares et al., PASCO 2006 Abstr7020

Cetuximab:

predictive markers of response and survival

- Specific **EGFR mutations** do **NOT** correlate with response to cetuximab

EGFR Extracellular Domain **Polymorphism** May Be Associated with Survival Benefit in mCRC Pts on Cetuximab-based Treatment:

BACKGROUND: KRAS mutation and EGFR copy number may predict response to cetuximab in mCRC

METHODS:

32 EGFR+ mCRC pts on cetuximab/irinotecan have tissue analysis done:

1. EGFR copy number by FISH
2. KRAS mutation analysis
3. EGFR mutation analysis

Gonçalves A, et al. BMC Cancer. 2008 Jun 10;8:169.

EGFR Extracellular Domain **Polymorphism** May Be Associated with Survival Benefit in mCRC Pts on Cetuximab-based Treatment:

RESULTS:

PFS and OS were significantly better in patients with this EGFR exon 13 variant

	High EGFR polysomy	EGFR mutations	KRAS mutations
Responders ***(PR 9)***	**2 pts**	**exon 13 (R521K)** ***12 pts (11 PR/SD)***	**2:9 (22%)**
Non-responders ***23 (SD 12; PD 11)***			**12:23 (52%)**

Gonçalves A, et al. BMC Cancer. 2008 Jun 10;8:169.

EGFR Extracellular Domain **Polymorphism** May Be Associated with Survival Benefit in mCRC Pts on Cetuximab-based Treatment:

CONCLUSION:

1. Increase in **EGFR copy number** may be associated with cetuximab response

2. **KRAS mutations** are associated with low response rate

3. **EGFR exon 13** variant (R521K) may predict for cetuximab benefit

Gonçalves A, et al. BMC Cancer. 2008 Jun 10;8:169.

Cetuximab:

predictive markers of response and survival

- Specific **EGFR mutations** do **NOT** correlate with response to cetuximab

- **Polymorphism of EGFR** extracellular domain may be associated with PFS in mCRC patients on cetuximab-based treatment

Gonçalves A, et al. BMC Cancer. 2008 Jun 10;8:169.