

# Bronchialkarzinom Internistische Therapie

Robert Pirker  
Medizinische Universität Wien

*Onkologie in Klinik und Praxis*  
*Wilhelminenspital, 7.-9.11.2011*

# Nichtkleinzelliges Bronchialkarzinom

## Therapie

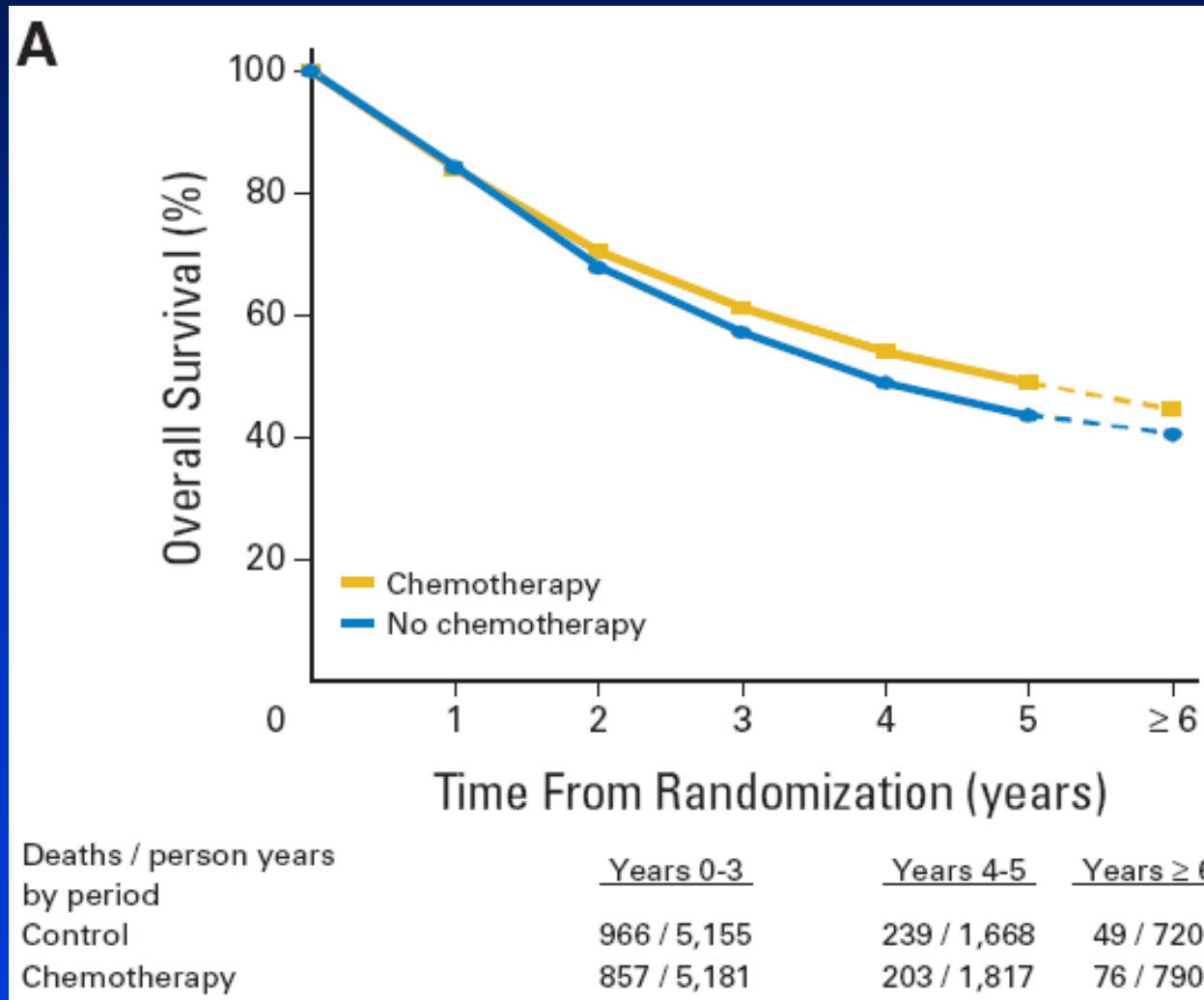
Stadium	Standardtherapie	In Studien
I, II	Operation Adjuvante Chemo	Adjuvante Therapien
IIIA	Lokaltherapie + Chemo	Multimodale Th.
IIIB	Chemoradiotherapie	Multimodale Th.
IV	Chemotherapie	Neue Substanzen

# Adjuvant Therapy of NSCLC

- Adjuvant chemotherapy improves survival
  - Survival benefit has been proven in recent trials: IALT, JBR10, ANITA
  - Meta-analyses confirm survival benefit:
    - LACE: HR 0.89 (0.82-0.96),  $p=0.005$   
OS gain at 5 years: 5%  
*Pignon JP et al. JCO 2008, 26, 3552*
    - LACE-Navelbine: HR 0.80 (0.70-0.91),  $p<0.001$   
OS gain at 5 years: 9%  
*Douillard JY et al. JTO 2010, 5, 220*
- Adjuvant radiotherapy
  - Decrease in survival: HR 1.21 (1.08-1.34)  
*PORT Meta-analysis, Lancet 1998, 352, 257*
  - Further trials required

# LACE Meta-Analysis

*Pignon JP et al. JCO 2008, 26, 3552*



# Adjuvant Therapy of NSCLC

- Adjuvant chemotherapy is standard of care in stages II, III
  - Cisplatin plus vinorelbine
  - 4 cycles
- Customized chemotherapy in clinical trials
- Targeted therapy in clinical trials
  - Erlotinib (RADIANT)
  - Bevacizumab
  - MAGE-A3 (MAGRIT)

# NSCLC Stadium III

## Chemotherapie und Radiotherapie

CT                      →                      RT  
CT-RT  
RT

Induktions-CT → CT-RT  
CT-RT → Konsolidierungs-CT

Inklusion der Operation (trimodale Therapie)  
Neue Strahlentherapietechniken  
PCI  
Zielgerichtete Therapien

# Advanced NSCLC

## Palliative therapy

- First-line Therapy
  - Chemotherapy
  - Targeted agents
- Maintenance therapy
- Therapy in pre-treated patients
- Supportive care

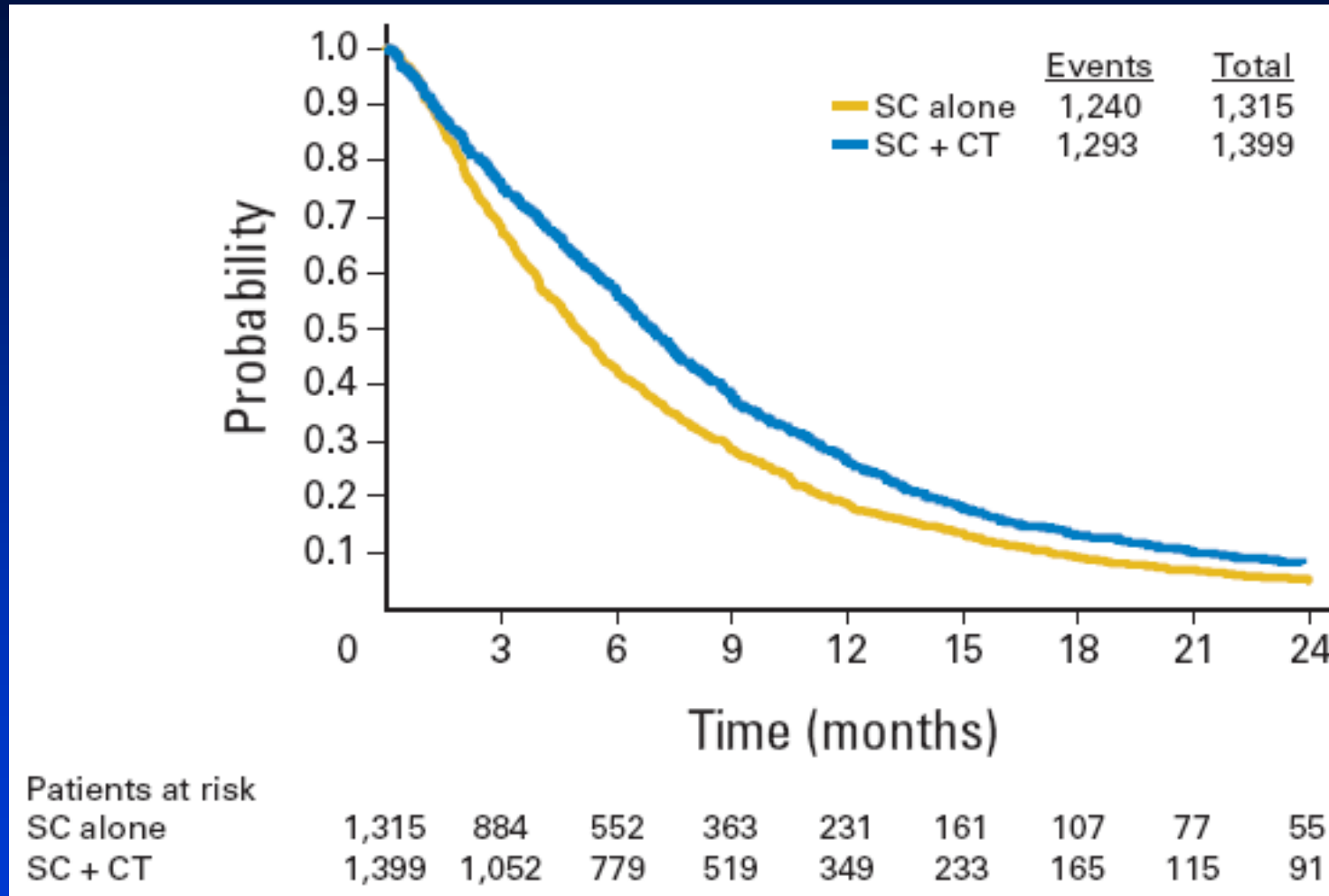
# NSCLC IIIB-IV

## Palliative 1<sup>st</sup> line chemotherapy

- **Platinum-based doublets** with 3<sup>rd</sup> generation drug (vinorelbine, gemcitabine, paclitaxel, docetaxel, pemetrexed); 4-6 cycles
- **Symptom relief in ~50-60%**  
**1-year survival rate increased by absolute ~10%**  
Improvement of quality of life (?)  
*NSCLC Collaborative Group. BMJ 1995;311:899-909*  
*NSCLC Meta-Analyses Collaborative Group. J Clin Oncol 2008;26:4617-25*
- ***Performance status affects outcome***
- **Elderly patients and patients with poor PS also benefit**
  - well tolerated protocols
  - enhanced supportive care

# Meta-Analysis: Overall survival

NSCLC Collaborative Group, JCO 2008, 26, 4617

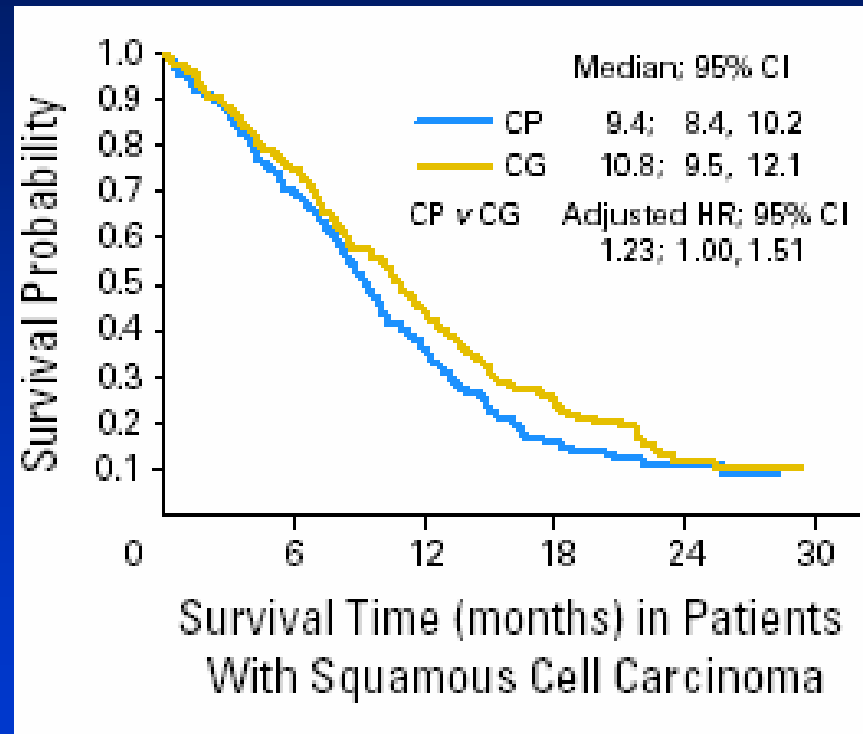
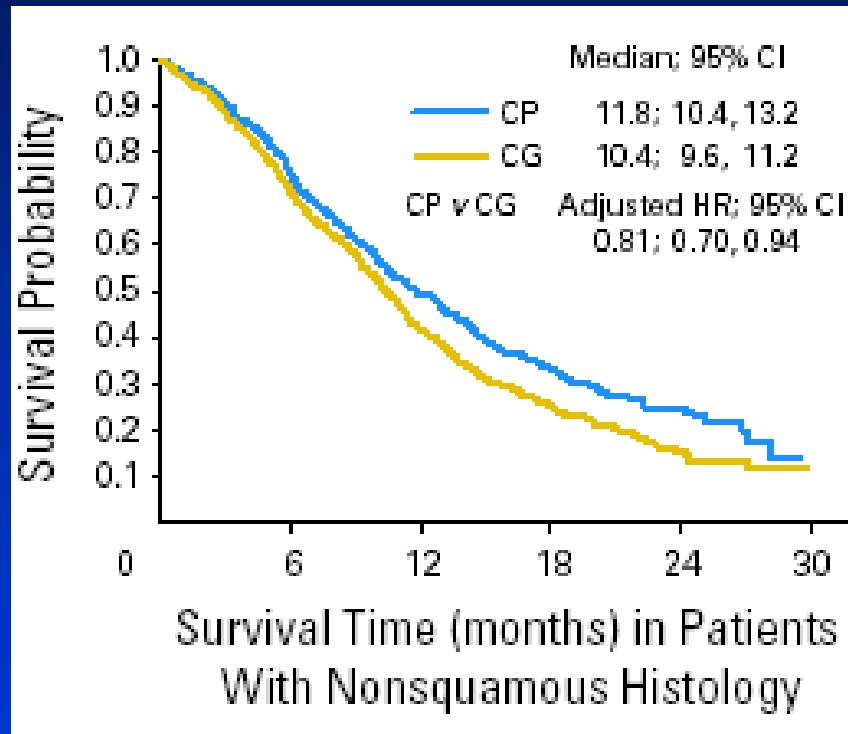


1-y survival rate increases from 21% to 29%.

Median survival increases from 4.5 to 6 months.

# Cisplatin/Pemetrexed versus Cisplatin/Gemcitabine

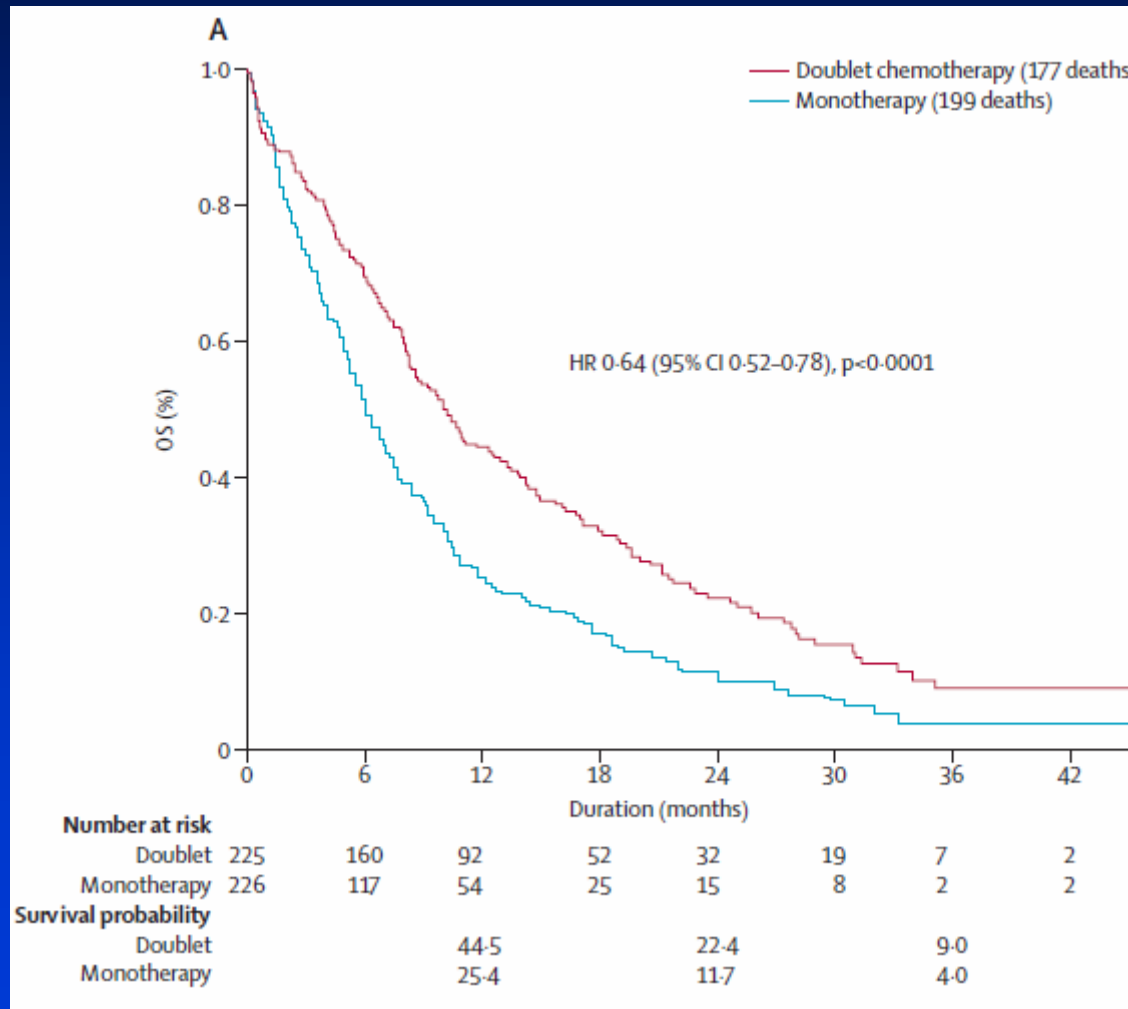
Scagliotti G et al. JCO online May 27, 2008



Superiority of pemetrexed/cisplatin in non-squamous cell carcinomas

# NSCLC IIB-IV

## 1<sup>st</sup> line chemotherapy in elderly patients *Quoix E et al. Lancet online Aug 9, 2011*



# NSCLC

## Progress through Personalized Medicine

- Customized chemotherapy
- Targeted therapies
  - EGFR-directed therapies
  - Angiogenesis inhibitors
  - Others
- Predictive biomarkers for patient selection
  - Patient characteristics
  - Tumour histology
  - Molecular tumour features

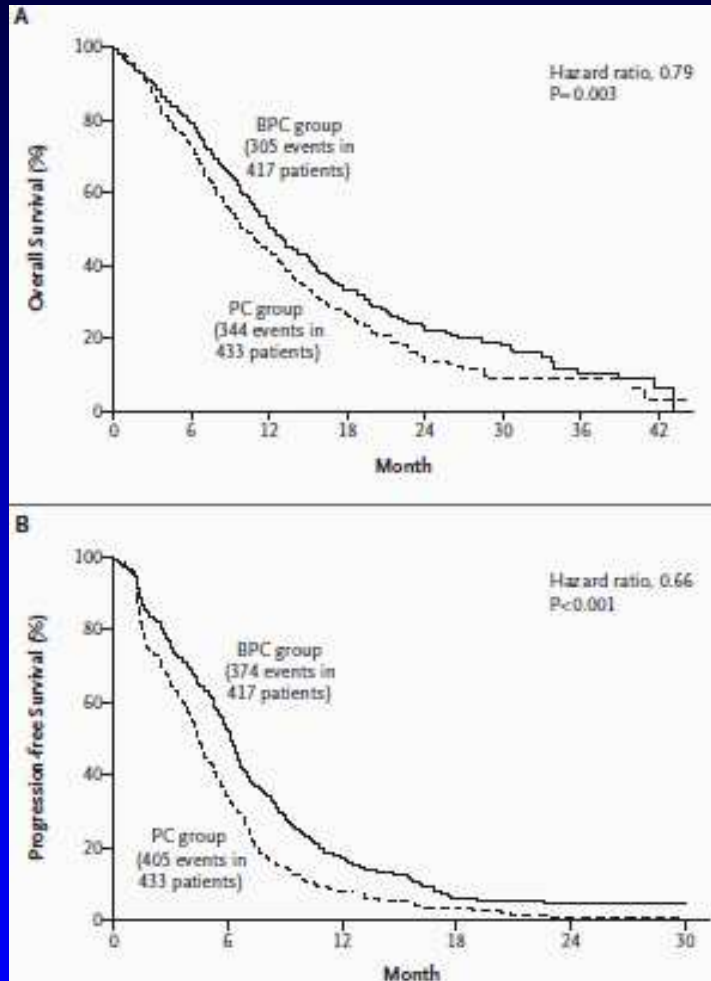
# Targeted therapies

- Angiogenesis inhibitors
- Inhibitors of growth factor receptor systems
- RAS / RAF pathway inhibitors
- Mammalian target of rapamycin (mTOR) inhibitors
- PI3K inhibitors
- Cyclooxygenase-2 (COX-2) inhibitors
- Proteasome inhibitors
- Histone deacetylase inhibitors
- PARP inhibitors
- Hedgehog pathway inhibitors
- Aurora B kinase inhibitors
- Vaccines

# Angiogenesis inhibitors

- Bevacizumab
- Tyrosine kinase inhibitors
  - Vandetanib                      BIBF1120
  - Sorafenib                        Pazopanib
  - Sunitinib                        Apatinib
  - Cediranib                        Axitinib
  - Motesanib
- Ramucirumab (VEGFR inhibitor)
- Aflibercept (VEGF trap)
- Vascular disrupting agents
  - Vadimezan (ASA404): ATTRACT-1 halted
  - Fosbretabulin tromethamine
  - Plinabulin (NPI-2358)
- Thalidomide

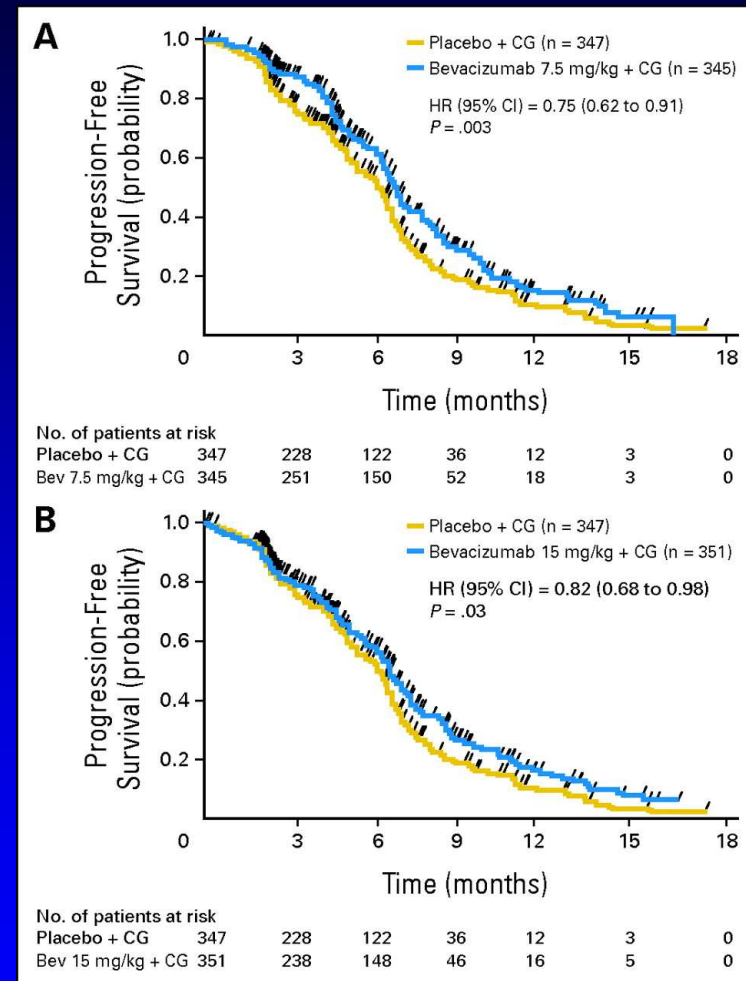
# Bevacizumab in advanced NSCLC



**ECOG 4599**

Sandler A et al.

NEJM 2006, 355, 2542



**AVAiL**

Reck M et al.

JCO 2009, 27, 1227

# Angiogenesis inhibitors in NSCLC

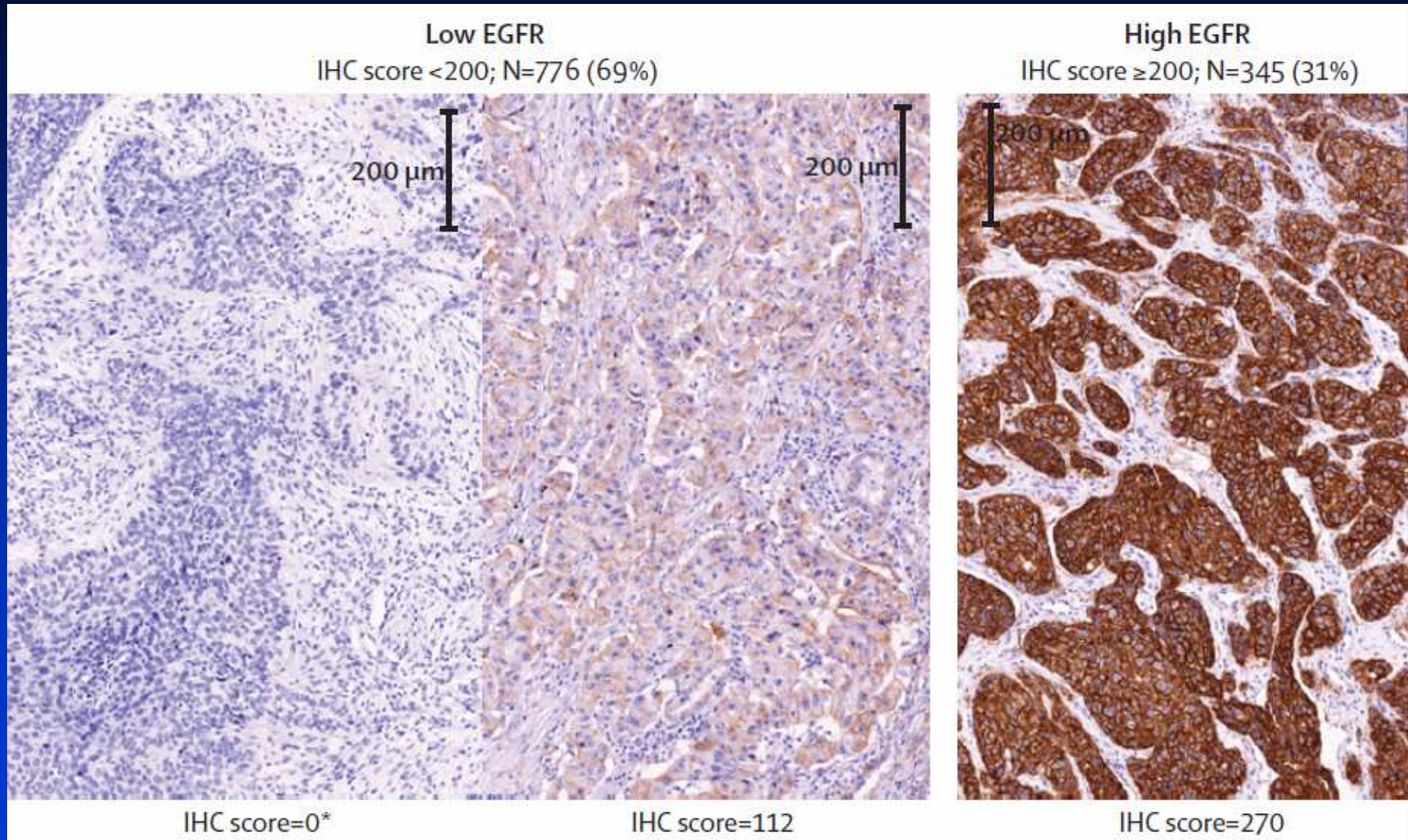
## Status 2011

- Bevacizumab (7.5 or 15 mg/kg every 3 weeks) is approved for non-squamous cell NSCLC
  - efficacy dependent on type of chemotherapy ?
  - dose & duration of treatment ?
  - biomarker ?
- Several trials failed
  - first-line treatment
    - sorafenib (ESCAPE, NExUS)
    - cediranib
    - motesanib
  - second-line treatment
    - vandetanib
- Ongoing trials
  - BIBF1120
  - others

# EGFR inhibitors

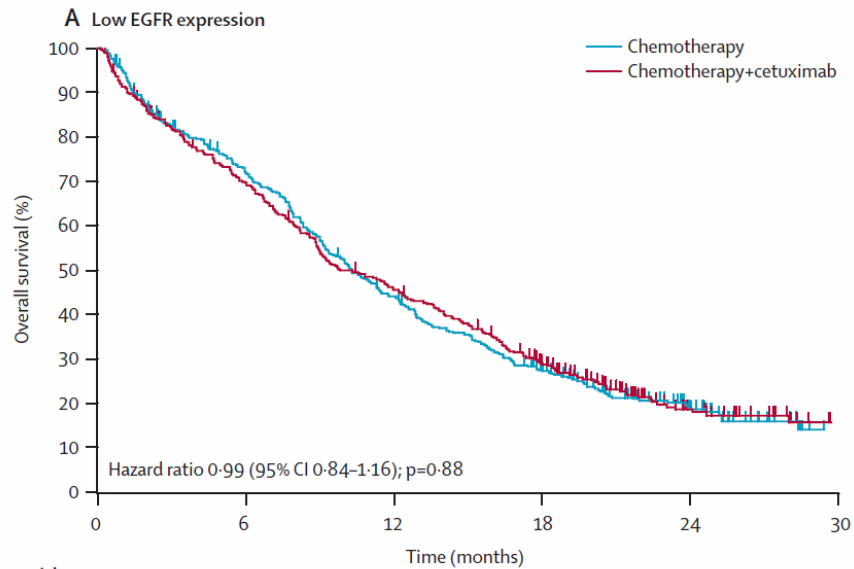
- **Monoclonal antibodies**
  - Cetuximab
  - Matuzumab
  - Nimotuzumab
  - Panitumumab
  - Necitumumab (IMC-11F8)
- **Tyrosine kinase inhibitors**
  - Gefitinib
  - Erlotinib
  - Afatinib (ErbB Family Blocker)
  - PF-299804 (pan-HER)
  - Lapatinib (EGFR, HER2)
  - AZD8931 (EGFR, HER2, HER3)
  - Vandetanib (EGFR, VEGFR)
  - Neratinib (HKI-272)
  - Icotinib

# Low and high EGFR expression

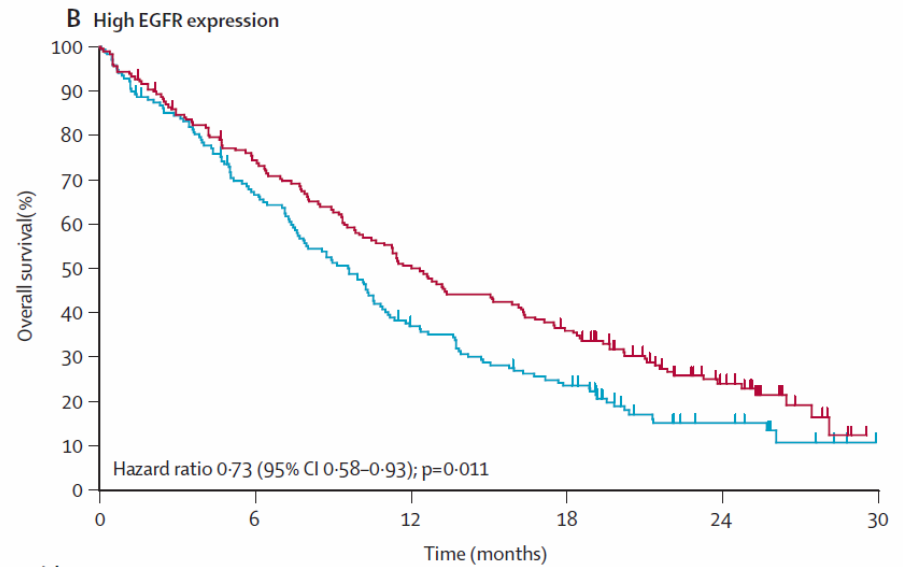


Pirker R et al. Lancet Oncol online Nov 4, 2011  
DOI:10.1016/S1470-2045(11)70318-7 Pirker OKP2011

# Low and high EGFR expression



Number at risk		0	6	12	18	24	30
Chemotherapy	399	275	167	98	37	0	
Chemotherapy+cetuximab	377	254	164	93	29	3	



Number at risk		0	6	12	18	24	30
Chemotherapy	167	108	58	36	11	0	
Chemotherapy+cetuximab	178	128	86	61	24	0	

*Pirker R et al. Lancet Oncol online Nov 4, 2011  
DOI:10.1016/S1470-2045(11)70318-7*

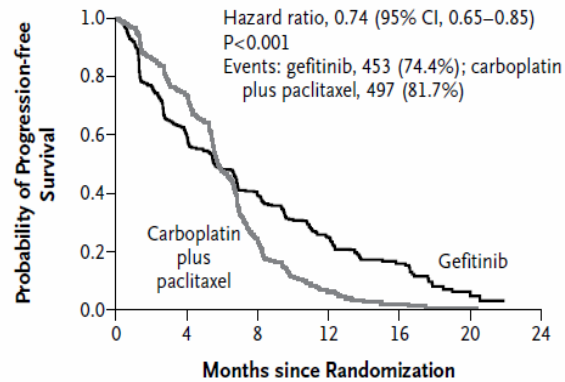
# EGFR-directed TKIs in advanced NSCLC

- Never-smokers or “light smokers” with adenocarcinomas
  - **IPASS**: Gefitinib vs. carboplatin/paclitaxel  
*Mok T et al. NEJM 2009, 361, 947*
  - **First Signal**: Gefitinib vs. carboplatin/paclitaxel  
*Lee et al. WCLC 2009*
- Patients with EGFR-activating mutations
  - **WJTOG 3405**: Gefitinib vs. cisplatin/docetaxel  
*Mitsudomi T et al. Lancet Oncology 2010, 11, 121*
  - **NEJ 002**: Gefitinib vs. carboplatin/paclitaxel  
*Maemondo M et al. NEJM 2010, 11, 121*
  - **OPTIMAL**: Erlotinib vs. carboplatin/gemcitabine  
*Zhou C et al. Lancet Oncology 2011, 12, 735*
  - **EU-TARC**: Erlotinib vs. chemotherapy in Caucasians  
*Rosell R et al. ASCO 2011*

# IPASS

Mok et al. NEJM 361, 947-957, 2009

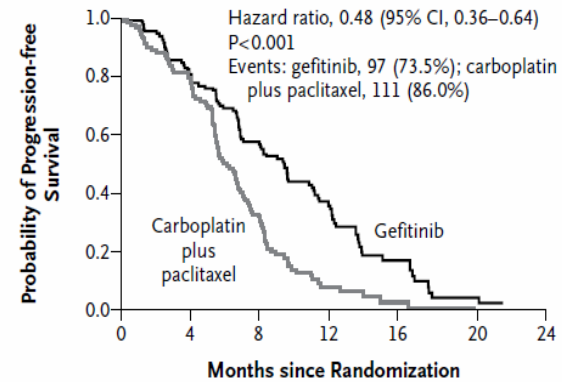
**A Overall**



**No. at Risk**

Gefitinib	609	363	212	76	24	5	0
Carboplatin plus paclitaxel	608	412	118	22	3	1	0

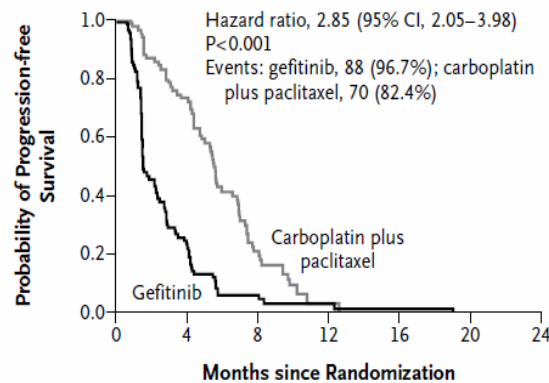
**B EGFR-Mutation-Positive**



**No. at Risk**

Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

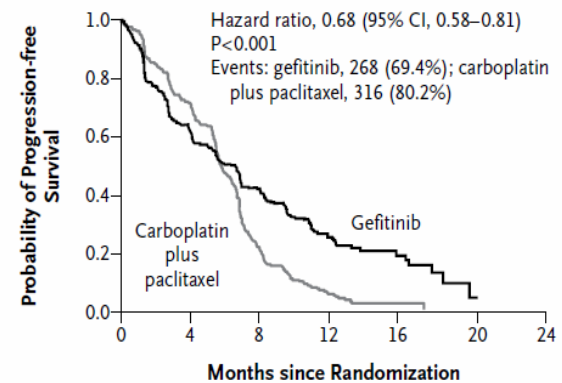
**C EGFR-Mutation-Negative**



**No. at Risk**

Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

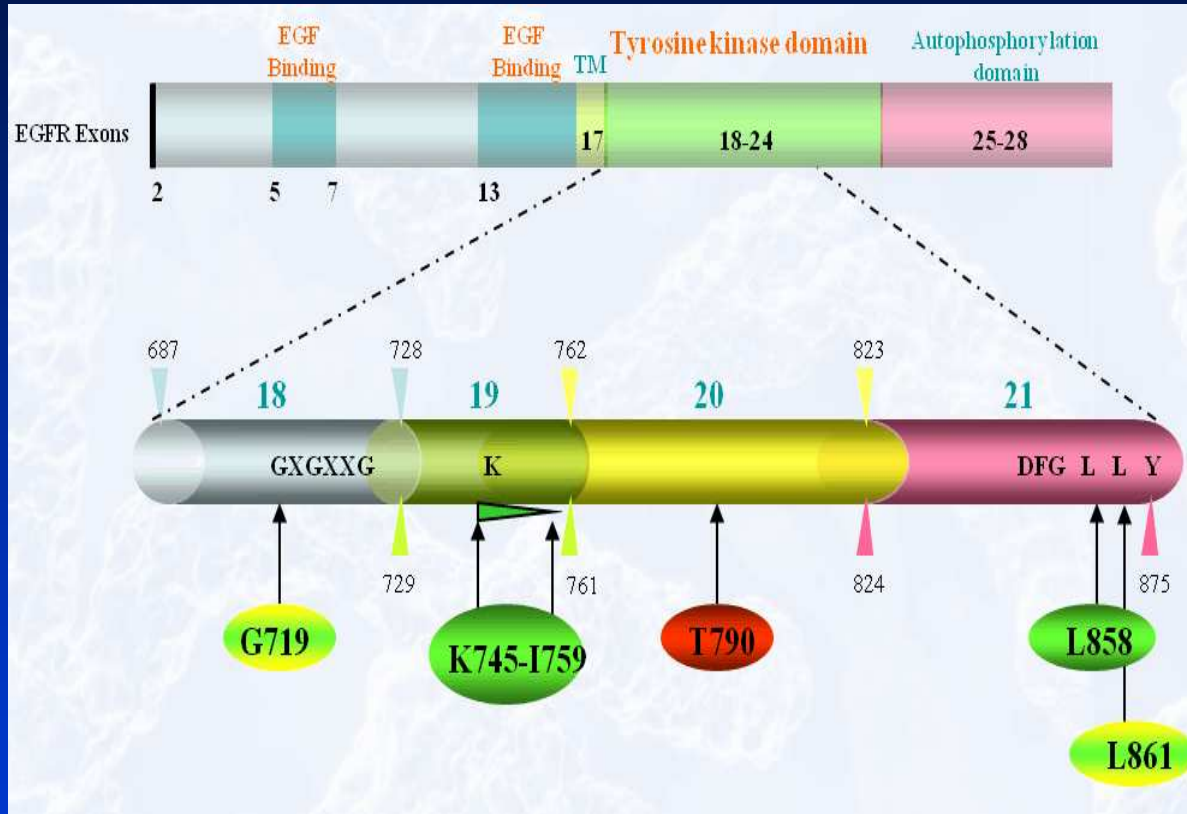
**D Unknown EGFR Mutation Status**



**No. at Risk**

Gefitinib	386	234	137	43	12	2	0
Carboplatin plus paclitaxel	394	251	67	14	1	0	0

# EGFR mutations and response to TKIs

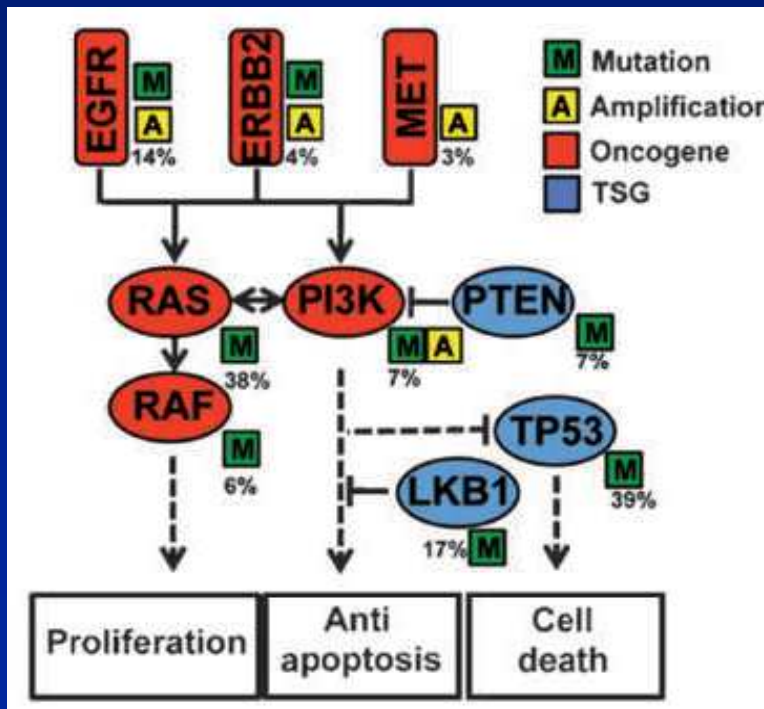


**Green** = responsive  
**Red** = non-responsive  
**Yellow-green** = mixed  
response outcomes

<http://www.somaticmutations-egfr.info>

# Resistance to EGFR-directed TKIs

- T790 mutations (~50%)
- MET amplification (~20%)

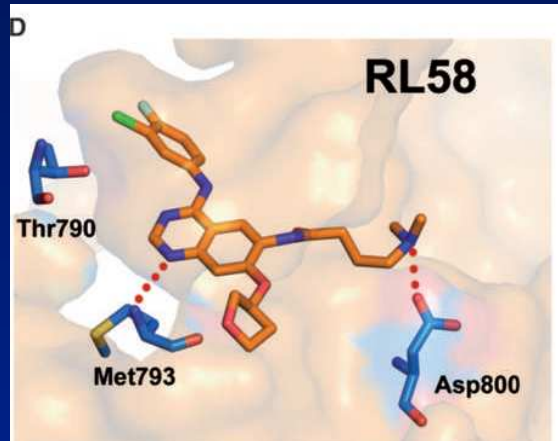


ML Sos et al.  
Cancer Res 2010, 70, 868

# EGFR-directed TKIs

## Reversal of Resistance

- Irreversible TKIs



ML Sos et al.  
Cancer Res 2010, 70, 868

- MET inhibitors

- ARQ-197 (TKI)
- Crizotinib (PF-02341066)
- PHA665752 (TKI)
- MetMAB
- Anti-hepatocyte growth factor antibody (SCH-900105)

# Crizotinib (PF-02341066) in advanced NSCLC

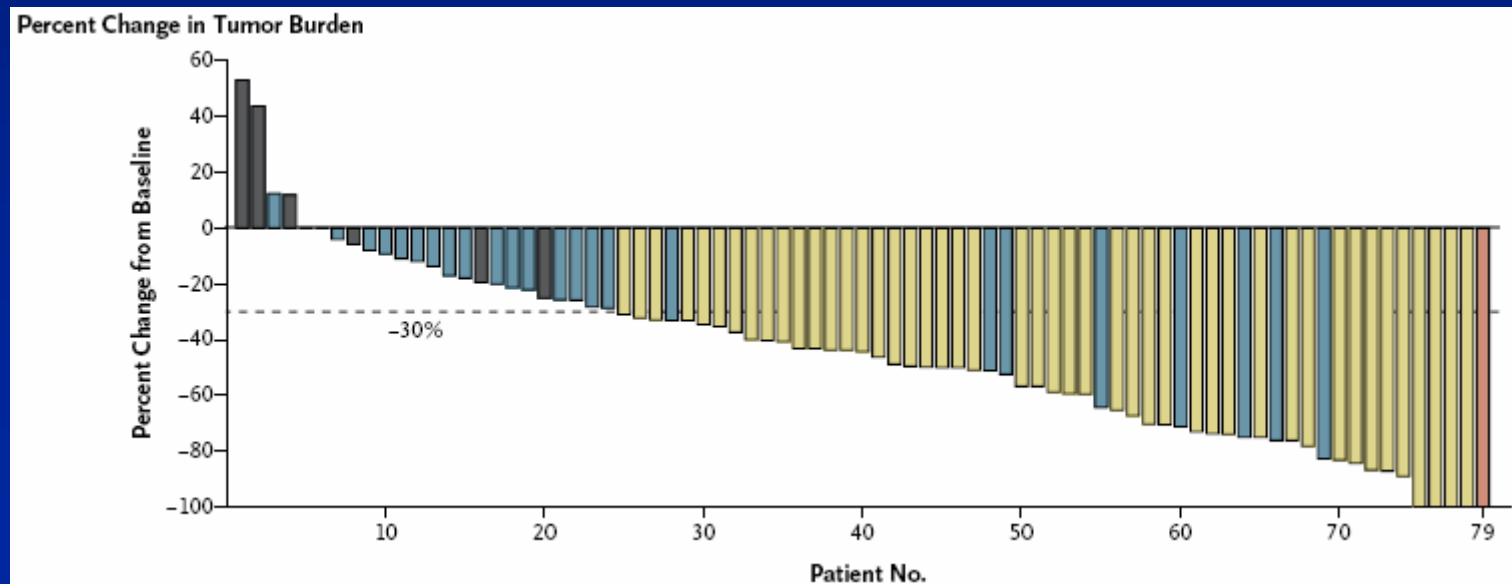
*EL Kwak et al. NEJM 2010, 363, 1693*

82 patients (out of 1500 screened)

Crizotinib 250 mg twice daily

ORR: 57%

6-month progression-free survival: 72%



# Maintenance Therapy

- **Chemotherapy**
  - Vinorelbine: no OS benefit  
Westeel V et al. JCN 2005;97:499-506
  - Gemcitabine: OS benefit in patients with good PS  
Brodowicz T et al. Lung Cancer 2006;52:155-163
  - Pemetrexed: PFS & OS benefit  
Ciuleanu T et al. Lancet 2009; 374: 1432
  - Pemetrexed (PARAMOUNT): PFS benefit  
Paz-Ares L et al. ASCO 2011
- **Early versus late 2<sup>nd</sup> line chemotherapy**
  - Docetaxel: benefit for early therapy  
Fidias P et al. J Clin Oncol 2009; 27: 591-598.
- **Targeted therapies**
  - Erlotinib: SATURN  
Cappuzzo F et al. . *Lancet Oncol* 2010;11:521
  - Bevacizumab + Erlotinib: ATLAS  
Miller V et al. J Clin Oncol 2009;27 (abstr. LBA8002)

# Advanced NSCLC

## Systemic Therapy in Pretreated Patients

- Docetaxel
- Pemetrexed
  - Non-squamous NSCLC
- Erlotinib
- Gefitinib in patients with EGFR-activating mutations
- Other chemotherapy protocols ?

# Advanced NSCLC Summary

- **First-line therapy with a platinum-based doublet**
  - Cisplatin preferred in patients with good PS
  - Pemetrexed preferred to gemcitabine in non-squamous NSCLC
  - plus bevacizumab in selected patients with non-squamous NSCLC
  - plus cetuximab\* in NSCLC with high EGFR expression
- **Patients with EGFR-activating mutations**
  - Gefitinib, erlotinib
- **Maintenance therapy**
  - Pemetrexed, erlotinib
- **Therapy in previously treated patients**
  - Docetaxel, pemetrexed, erlotinib

\* Not approved yet

# Kleinzelliges Bronchialkarzinom

- **Kombinationschemotherapie**  
Cisplatin/Etoposid  
Cyclophosphamid/Adriamycin/Vincristin  
andere Protokolle
- **Thorakale Strahlentherapie (simultan, sequentiell)**  
Patienten mit limitierter Erkrankung
- **Prophylaktische Ganzhirnbestrahlung**  
Patienten mit Therapieansprechen
- **Secondline Chemotherapie**  
Topotecan