



Implications for clinical practice

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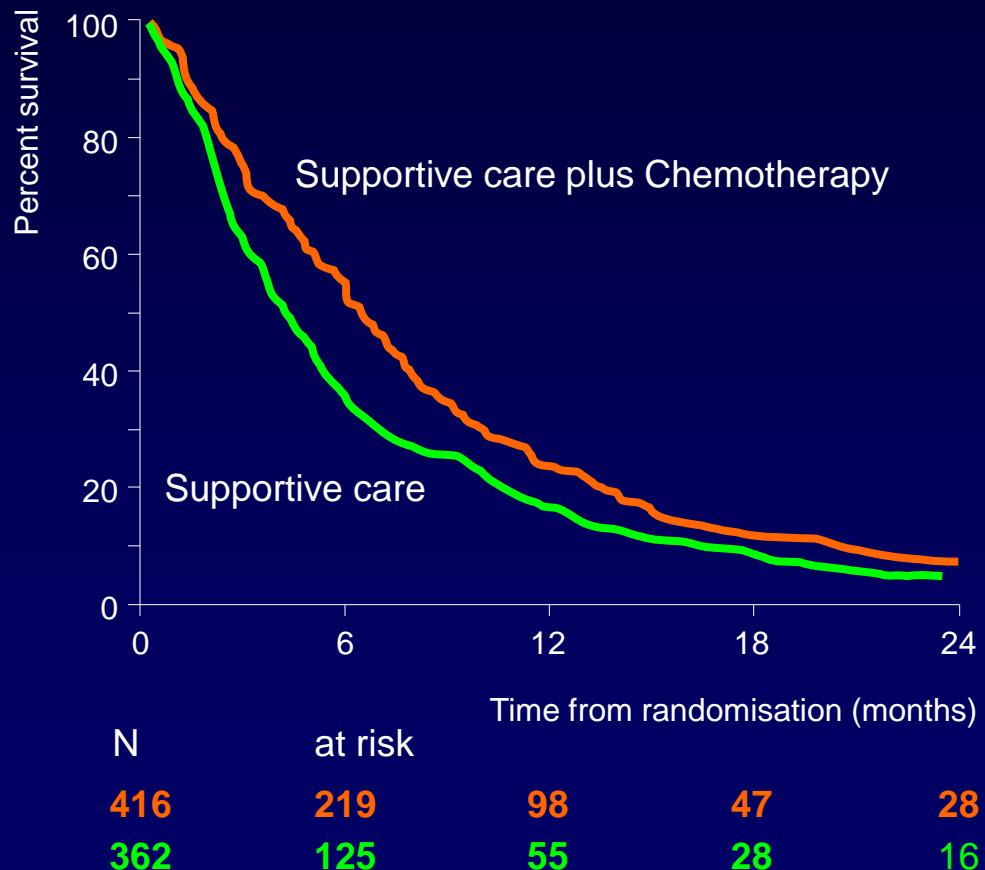
Disclosures

- Member of the advisory board: Roche, Lilly, Daichi-Sankyo, BMS, AstraZeneca
- Honoraria for lectures: Roche ,Lilly, Daichi-Sankyo, AstraZeneca

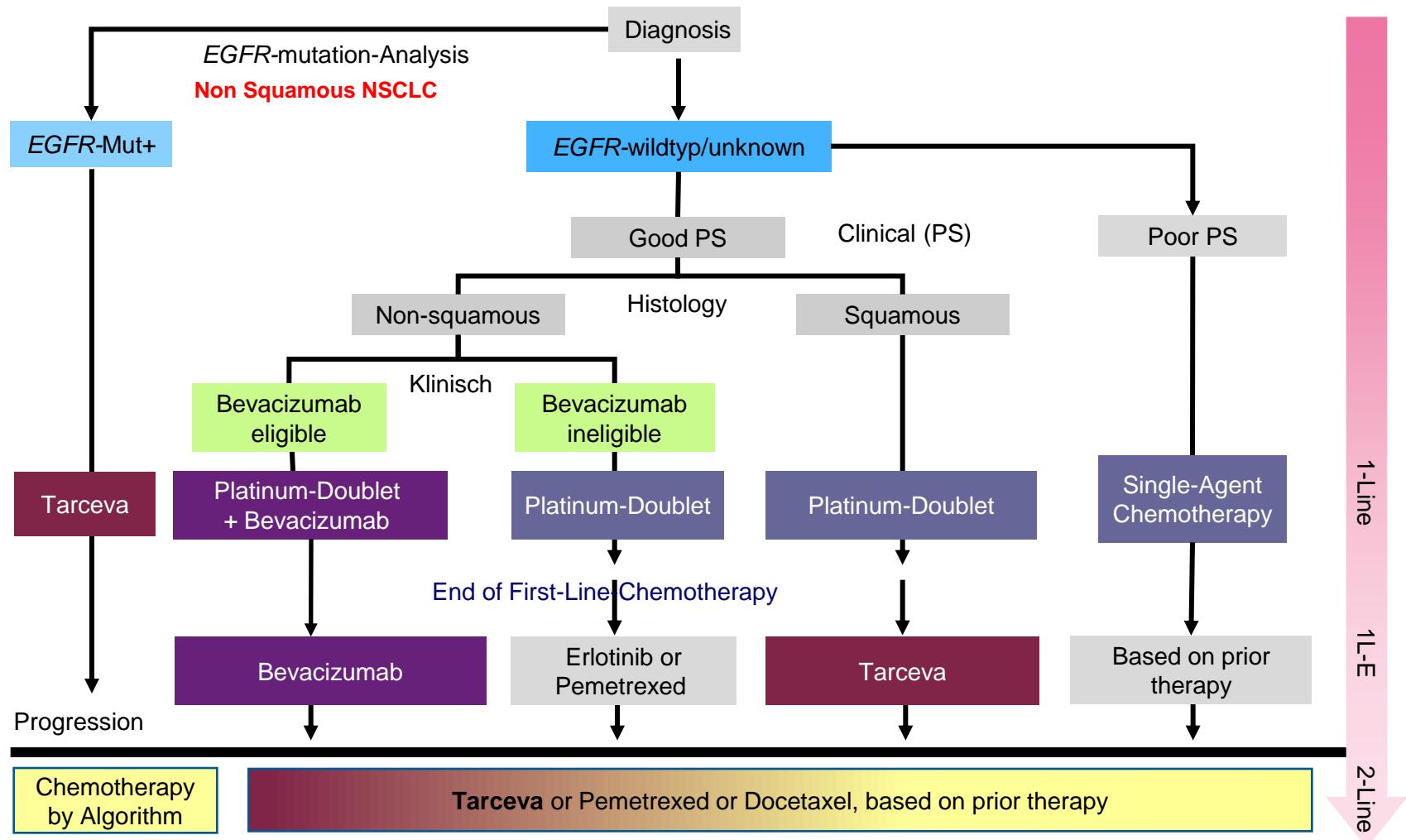
Chemotherapy has changed...

Meta-Analysis of 52 randomised trials

- 9387 patients
- 778 patients in randomised trials with platinum based chemotherapy
- **10% Increase in 1 year survival**
- Increase in median survival by 1,5 months (6 vs. 8 months)
- **Significant reduction of tumor associated symptoms**



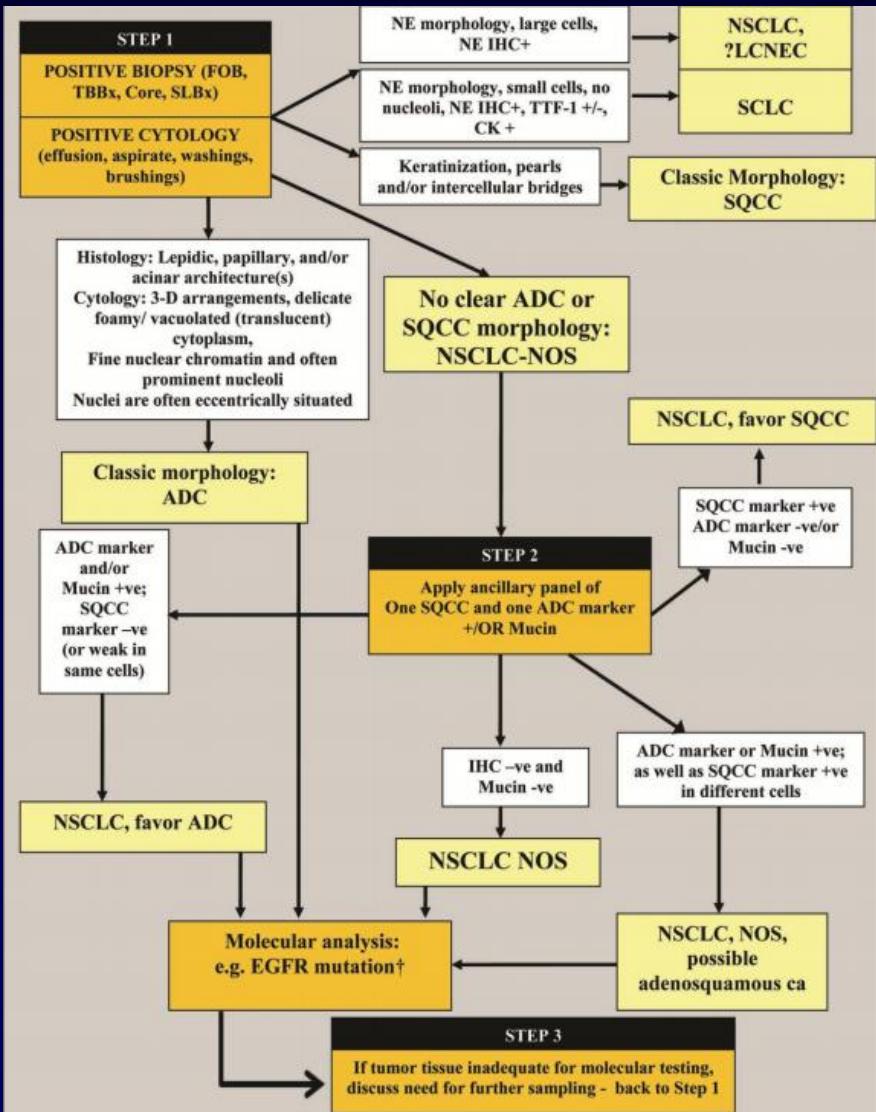
Proposed Treatment Algorithm – Advanced Stage NSCLC



**which indeed induces a couple of
implications....**

Implications

- Correct pathological diagnosis



1. Step: Conventional Criteria

Squamous Cell Carcinoma

SCLC

Adenocarcinoma

NSCLC

2. Step: Immunhistochemistry

Limited number of marker

Subtyping

3. Step: EGFR Mutation test

In appropriate settings

Reduction of NOS < 10%!

Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status

Clinical efficacy of EGFR-TKIs as first-line therapy

Trial	Pop.	Drug	EGFR Mut + (N)	ORR % TKI vs CT	PFS (HR, 95% CI)
IPASS ¹	Asia	Gefitinib	261	71.2 vs 47.3	0.48 (0.36, 0.64)
First-SIGNAL ²	Asia	Gefitinib	42	84.6 vs 37.5	0.61 (0.31, 1.22)
WJTOG 3405 ³	Asia	Gefitinib	172*	62.1 vs 32.2	0.49 (0.34, 0.71)
NEJGSG002 ⁴	Asia	Gefitinib	224**	73.7 vs 30.7	0.30 (0.22, 0.41)
OPTIMAL ⁵	Asia	Erlotinib	154***	83 vs 36	0.16 (0.10, 0.26)
EURTAC ^{6,7}	Europe	Erlotinib	174#	58.1 vs 14.9	0.37 (0.25, 0.54)
Lux Lung 38	Europe/Asia	Afatinib	345	56 vs 23 61 vs 22	0.58 (0.34, 0.65) 0.47 (0.34, 0.65)

* , modified ITT population; ** , PFS population;

*** , study population; # , ITT population

1. Mok et al 2009; 2. Lee, oral presentation at WCLC 2009; 3. Mitsudomi et al 2012; 4. Maemondo et al 2010; 5. Zhou et al 2011; 6. Rosell et al 2011; 7. Gervais, oral presentation at WCLC 2011; Yang et al, ASCO 2012

Clinical Consequence?

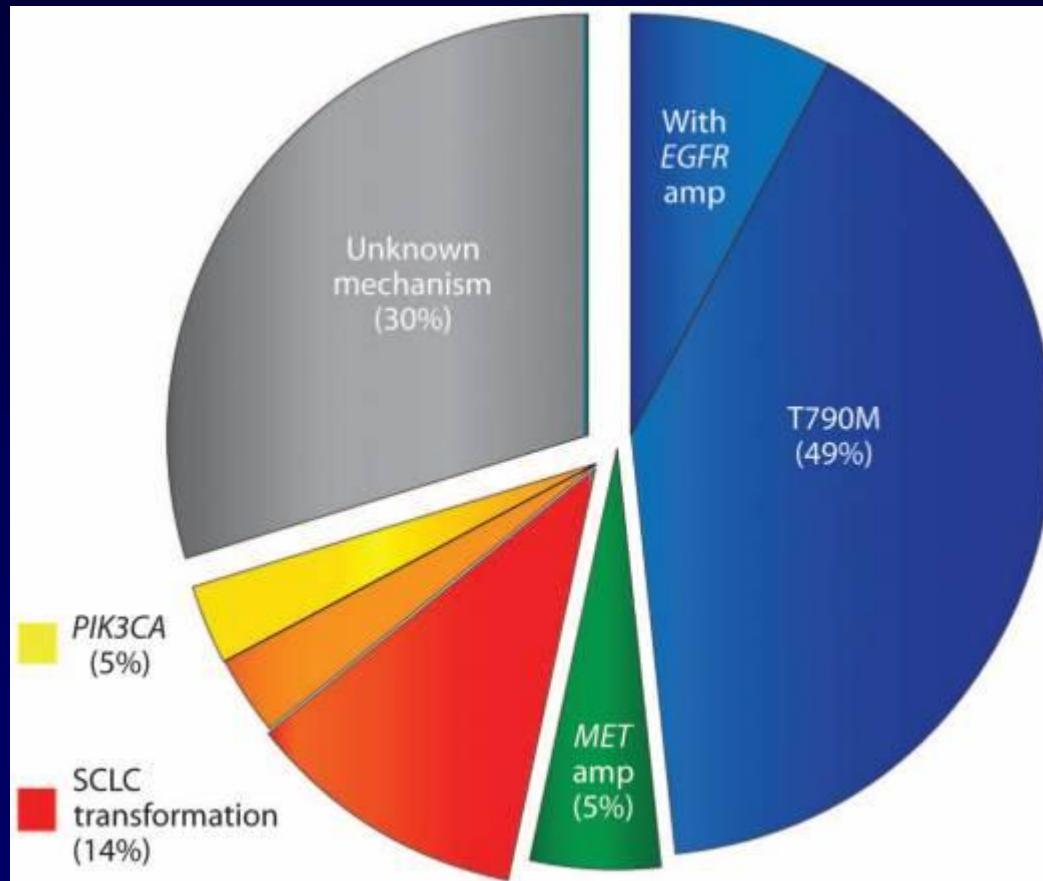
(The question of four A)

- **A**vailability (where can the test be done?)
- **A**ffordability (who has to pay how much?)
- **A**curateness (which test is used?)
- **A**cceleration (how many days to get the result?)
- **I**nteraction with pathologist / molecular pathologist will be crucial!

Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?

EGFR resistance mediating mechanisms



EGFR resistance mediating mechanisms

Combination chemotherapy + EGFR-TKI

Chemotherapy

IGF-Inhibitors

PIK3 TKI

HGF AB

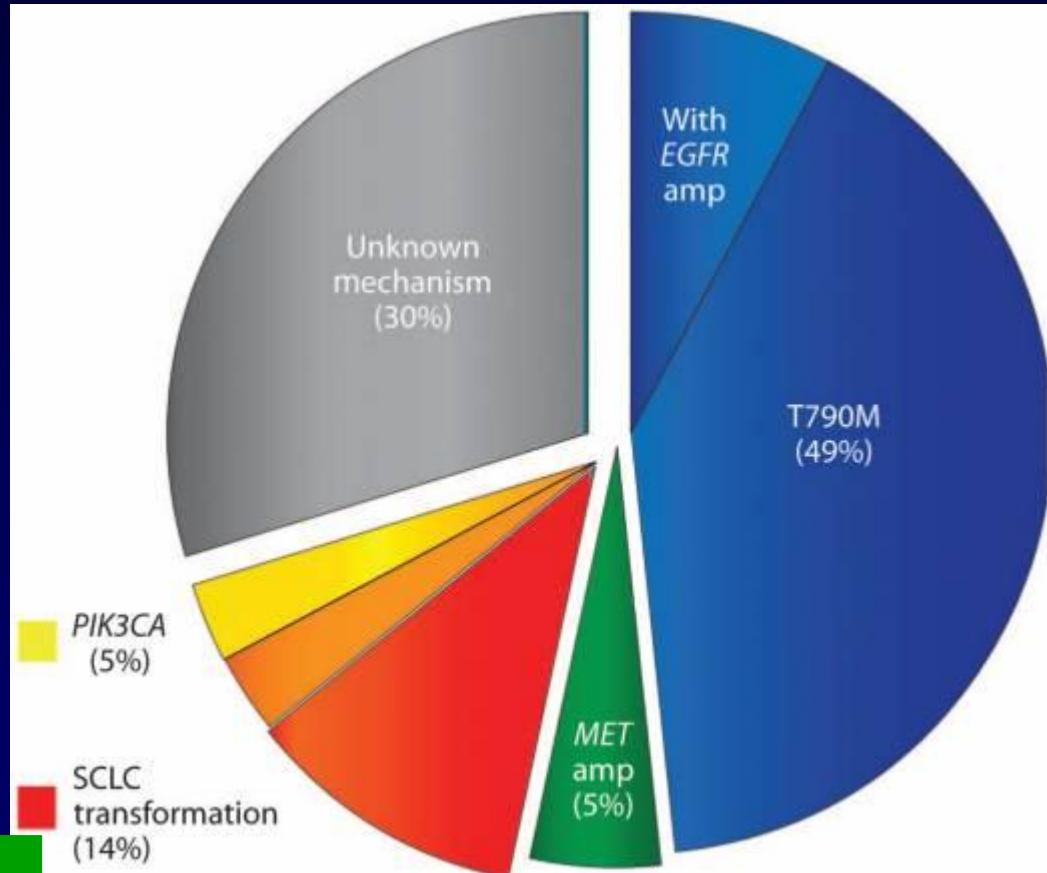
cMet TKI

Met Mab

Change of EGFR-TKI

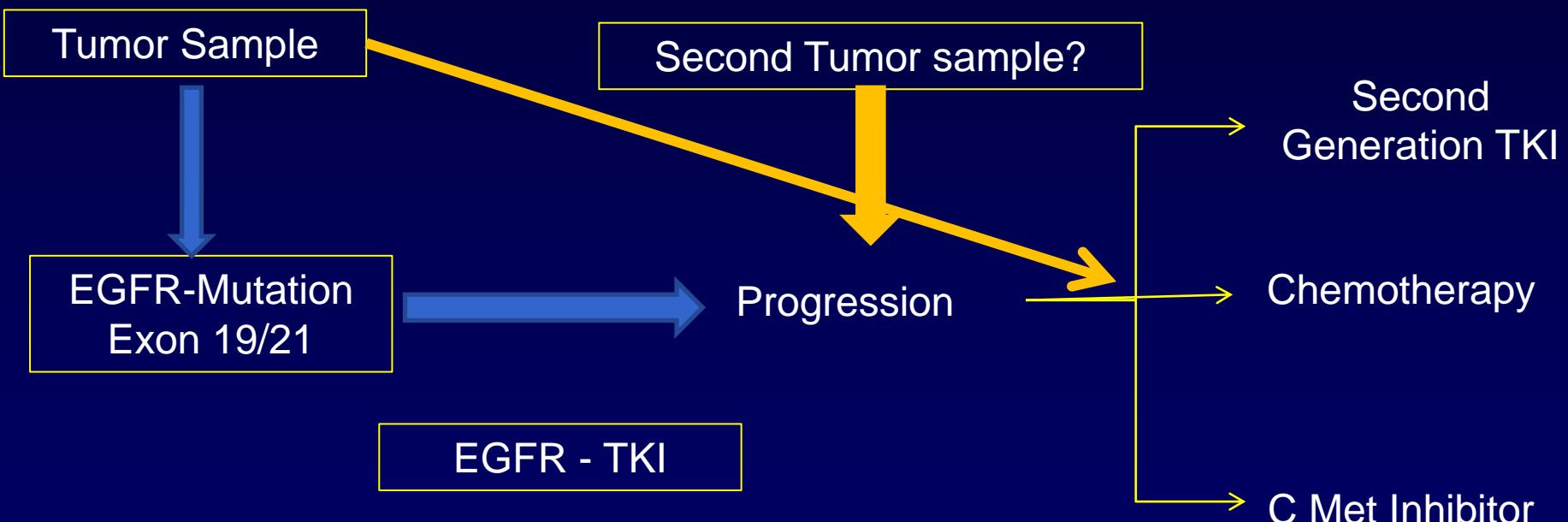
Second Generation EGFR-TKIs

Combination EGFR-TKI + EGFR AB



Sequist et al, Sci Transl Med 2011

Treatment of EGFR Resistance



Clinical consequence

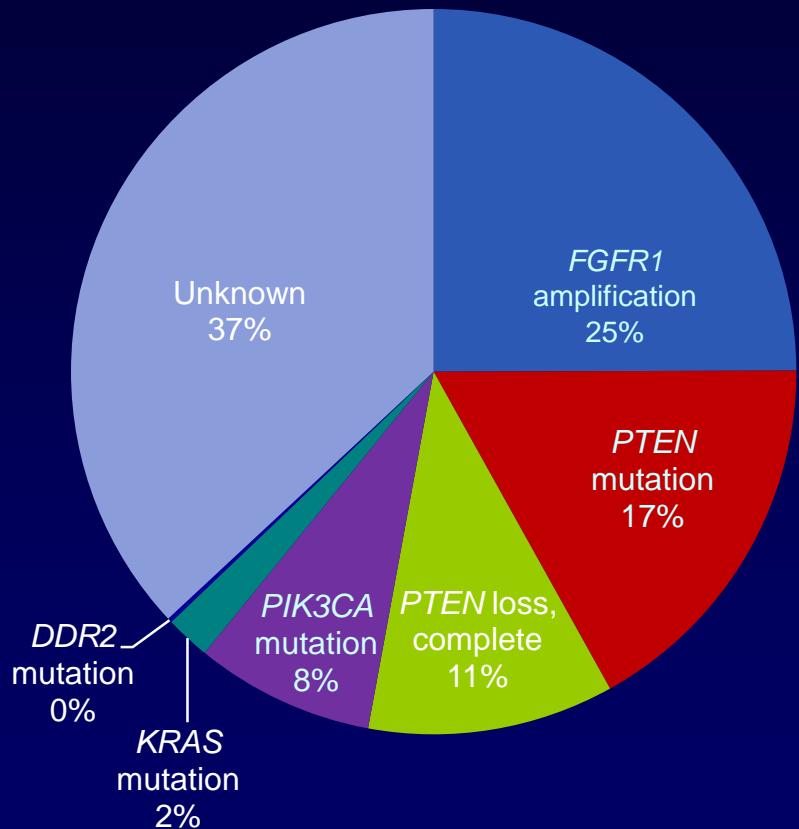
- Implementation of sequential biopsies in diagnostic algorithm of molecular characterized patients
- Balanced use of tumor material for morphological (transition to SCLC?) and molecular diagnosis (appearance of new driving mutation?)

Implications

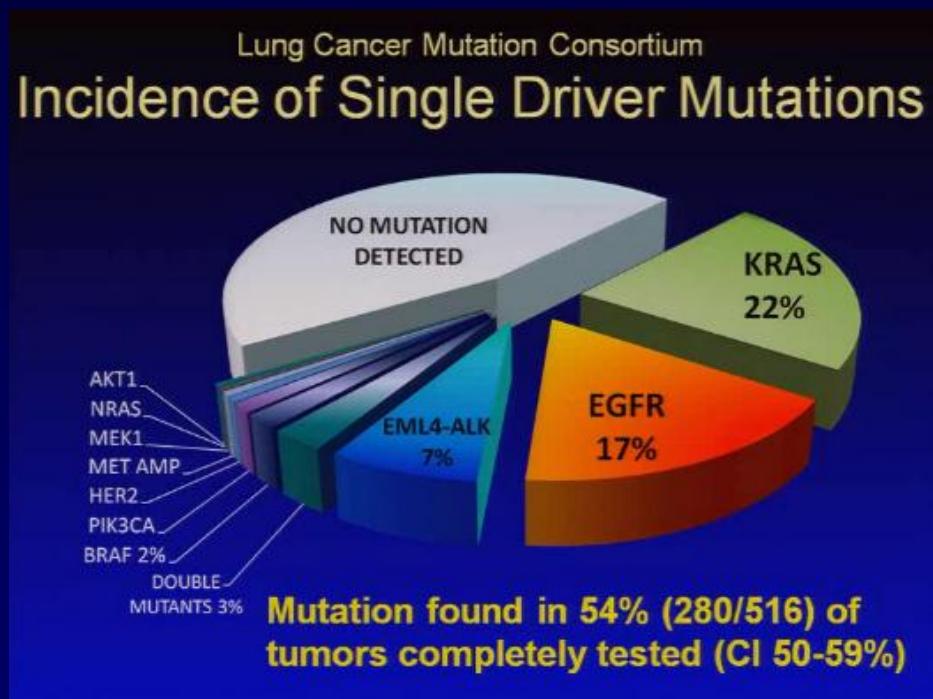
- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?
- New algorithms for molecular diagnosis?

Oncogenic mutations

Squamous Cell NSCLC



Adenocarcinoma



Clinical Consequences

- A lot of oncogenic mutations appear at a frequency of =/ $<$ 5%.
- Comprehensive testing is not feasible for all non academical sides – establishment of cooperationg network structures and databases will be necessary.
- Should we enrich populations for testing? – we got another lesson from the EGFR story
- Besides sophisticated molecular screening – still intelligent clinical validation will be gold standard.

Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?
- New algorithms for molecular diagnosis?
- New algorithms for treatment schedules?

The Switch Maintenance Registration Trials

Study	PFS HR p	OS HR p
JMEN		
Pem	0.5	0.79
Placebo	< 0.0001	0.012
SATURN		
Erlotinib	0.71	0.81
Placebo	< 0.0001	0.009

Switch maintenance:
TKI and pemetrexed show improved PFS and OS

Continuation Maintenance Trials

Study	PFS HR p	OS HR p
Paramount		
Pem	0.64	0.78
Placebo	0.0002	0.019
Avaperl		
Pemetrexed + Bevacizumab	0.48 < 0.001	Not reported
Bevacizumab		

Continuation maintenance:
Pemetrexed and Pemetrexed/Bevacizumab show improved PFS and OS

Clinical consequences and challenges

- Length of the induction therapy – how long can we give cisplatin?
- New treatment paradigm: no fixed number of treatment cycles
- New treatment to explain: Treatment as long as benefit is seen
- Different emphasis on adverse reactions: not every adverse reaction is included in the CTC – even CTC grade 2 fatigue can considerably influence quality of life.
- Principles of tumour measurement: How often? What should be done when progression is slow?

Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?
- New algorithms for molecular diagnosis?
- New algorithms for treatment schedules?
- New algorithms for management of side effects?

New agents – now toxicities

Agent	Toxicity
EGFR-TKI	Rash, Diarrhea, Paronychia
Sorafenib	Hand-Foot Syndrome, Rash, Fatigue
Sunitinib	Myalgia, Pain, Mucositis
Anti-VEGF Agents	Bleeding, Hypertension, Proteinuria, thrombembolic events
Crizotinib	Liver toxicity, Eye toxicity
Ganetespib	Diarrhea
Ipilimumab	Colitis, Skin toxicity, liver toxicity

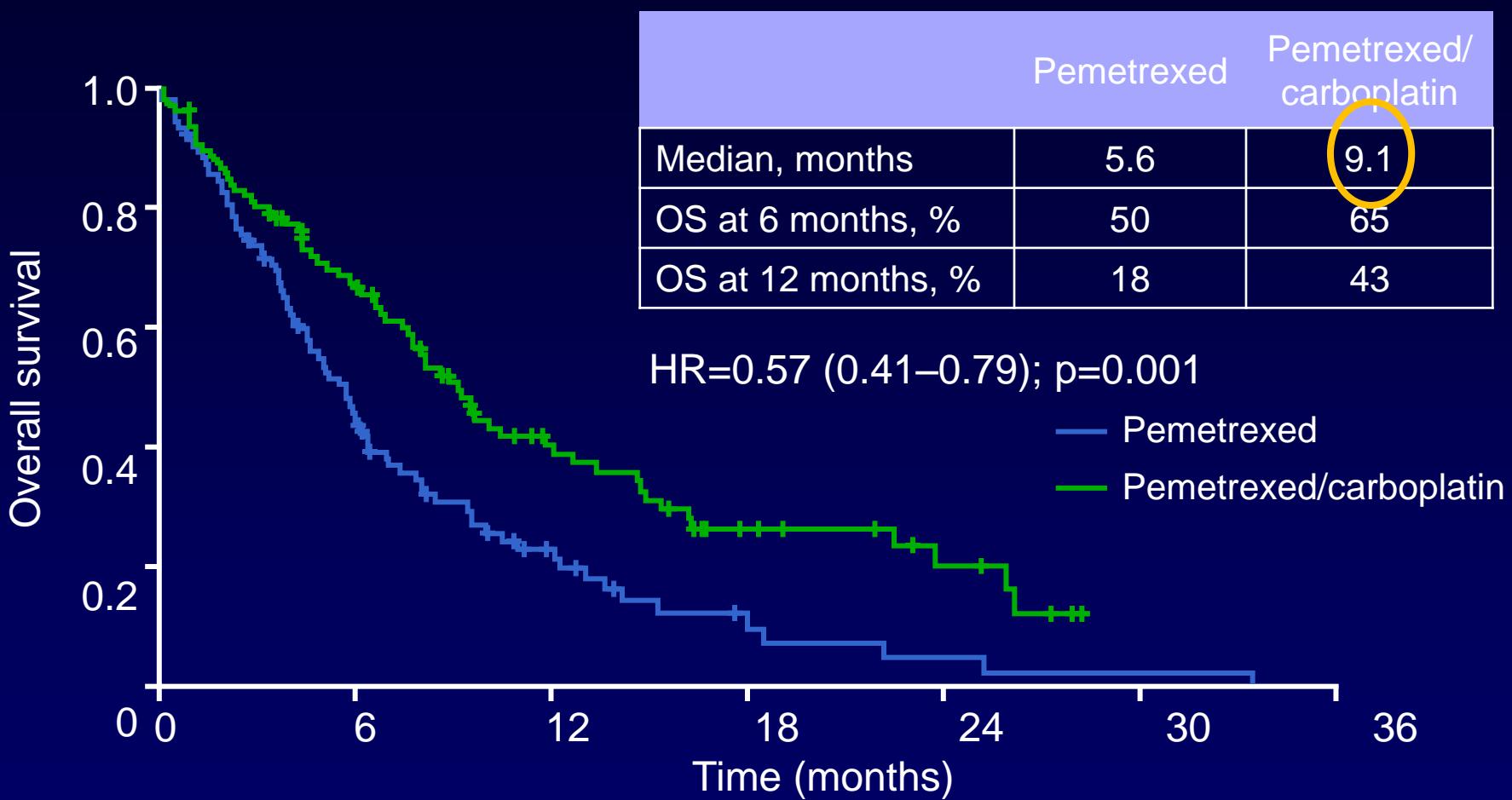
Clinical consequences

- Adequate information
- Adequate Management and Dose modification guidelines
- Adequate Grading system

Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?
- New algorithms for molecular diagnosis?
- New algorithms for treatment schedules?
- New algorithms for management of side effects?
- The forgotten patients?

New data in PS2?

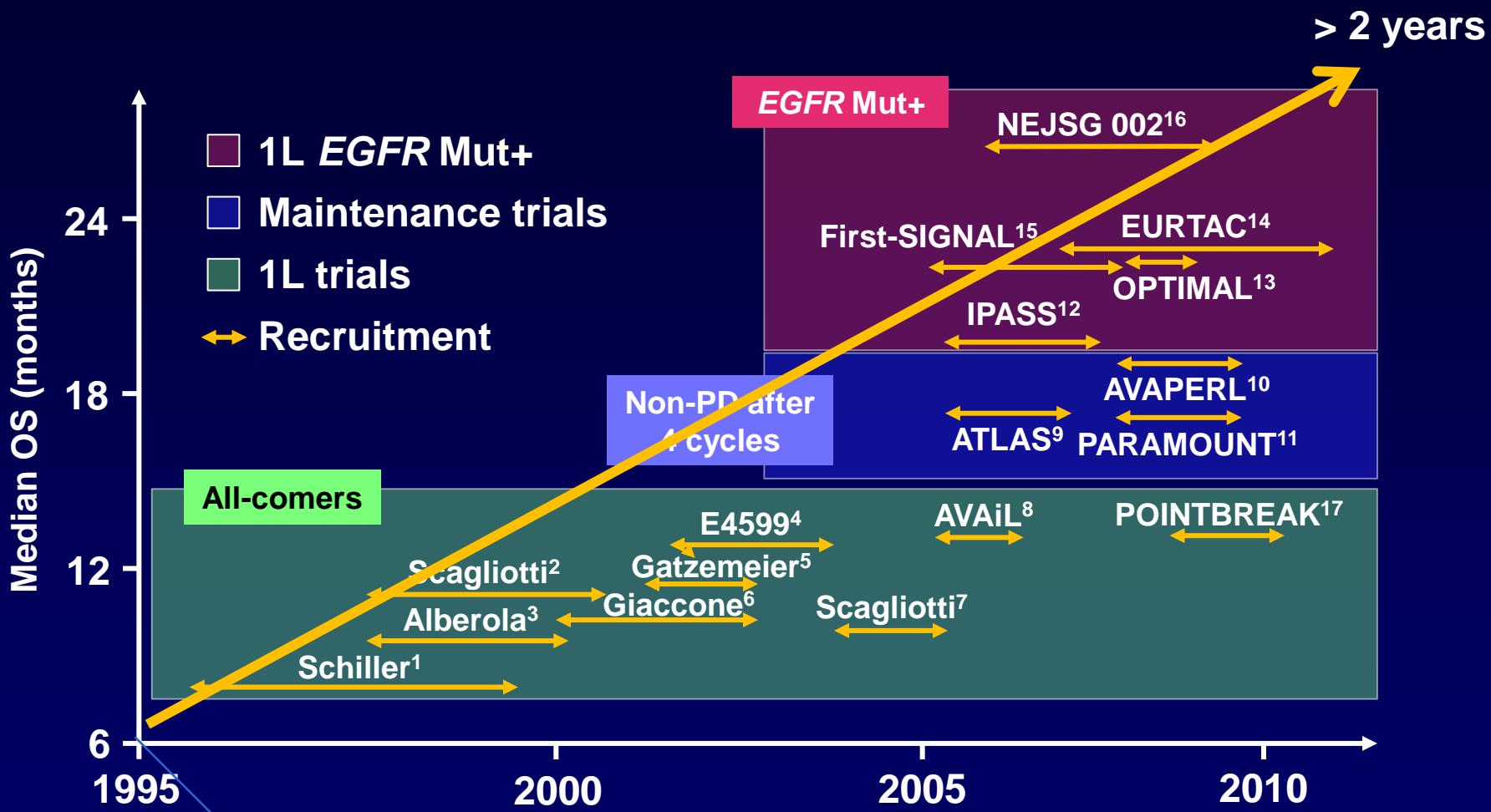


PS 2 = PS 2?

Clinical Consequences

- Clear definition of PS2 / Frail patients
- Further studies in this population are needed to get a **true** picture of lung cancer!

Studies in first-line NSCLC treatment



1. Schiller, et al. NEJM 2002; 2. Scagliotti, et al. JCO 2002; 3. Alberola, et al. JCO 2003; 4. Sandler, et al. NEJM 2006; 5. Gatzemeier, et al. JCO 2007
6. Giaccone, et al. JCO 2004; 7. Scagliotti, et al. Clin Cancer Res 2005; 8. Reck, et al. Ann Oncol 2010; 9. Kabbinavar, et al. ASCO 2010
10. Barlesi, et al. EMCC 2011; 11. Paz-Ares, et al. ASCO 2012; 12. Fukuoka, et al. JCO 2011; 13. Zhou, et al. ASCO 2012
14. de Marinis, et al. EMCC 2011; 15. Han, et al. JCO 2012; 16. Maemondo NEJM 2010; 17. Patel, et al. IASLC 2012 (Chicago)

Thoracic surgeon

Patient

Oncologist

Pathologist

Chest Physician

Radiologist

Radiotherapist

Basic researcher