LungCancerGroup Cologne

Network Genomic Medicine Lung Cancer

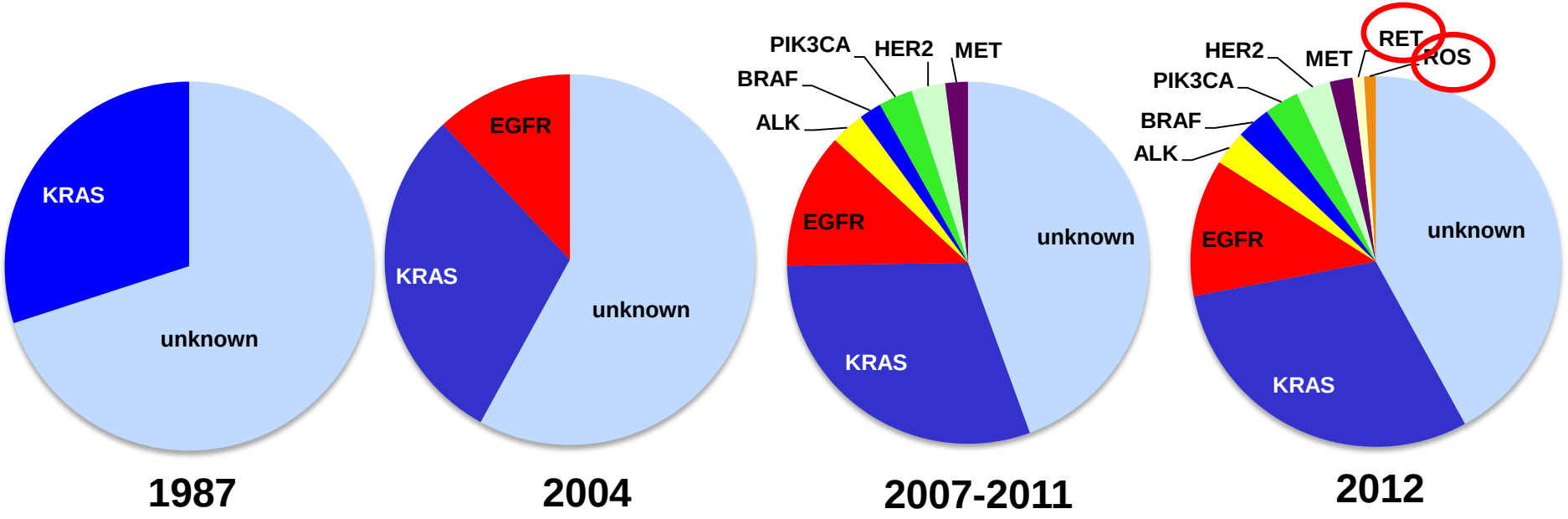
CIO Center for Integrated Oncology Köln Bonn

First Look Then Cook – Getting Molecular Testing into Clinical Routine

Jürgen Wolf
Center for Integrated Oncology and Department of Internal Med. I
University Hospital Köln

The molecular understanding of lung cancer increases

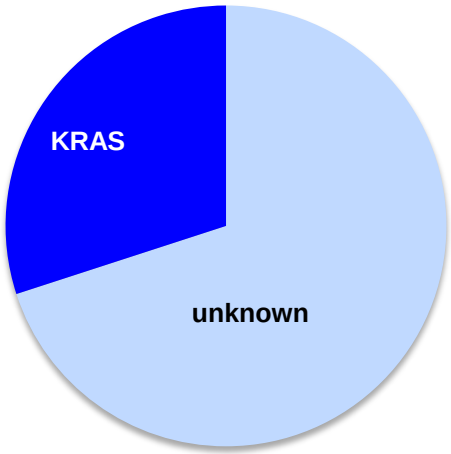
Driver mutations in adenocarcinoma



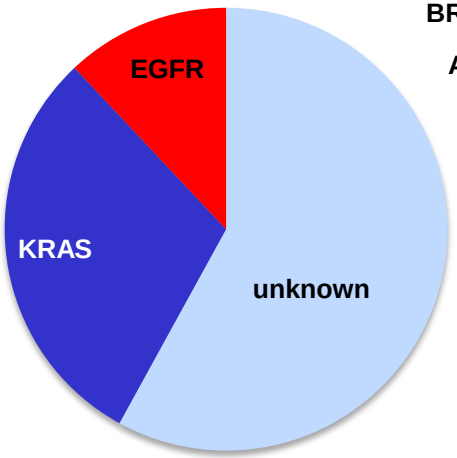
1987 2004 2007-2011 2012

The molecular understanding of lung cancer increases

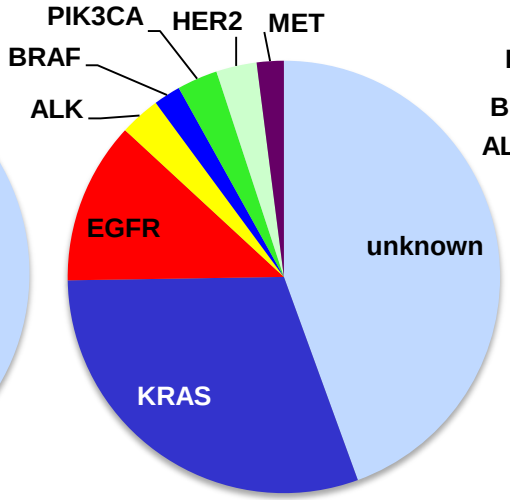
Driver mutations in adenocarcinoma



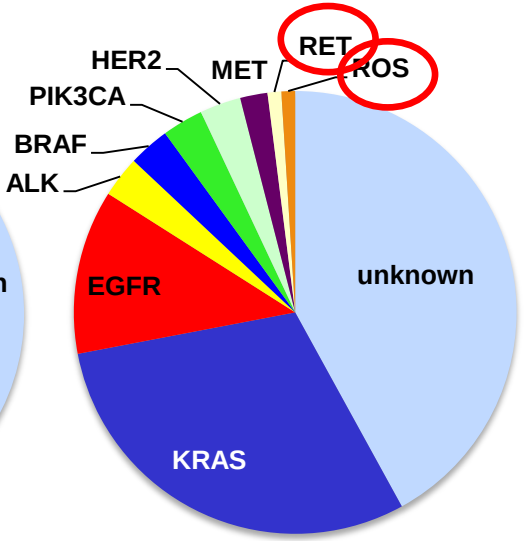
1987



2004

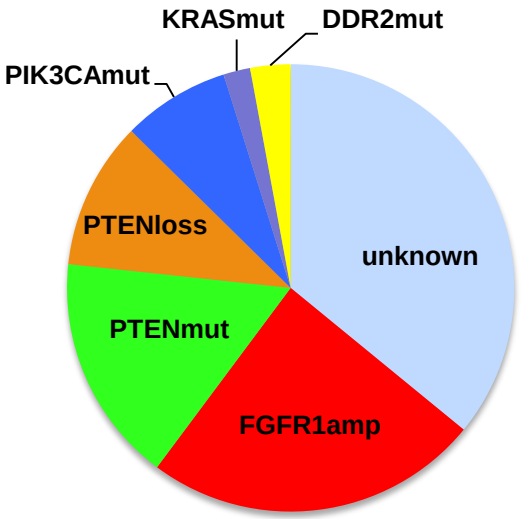


2007-2011



2012

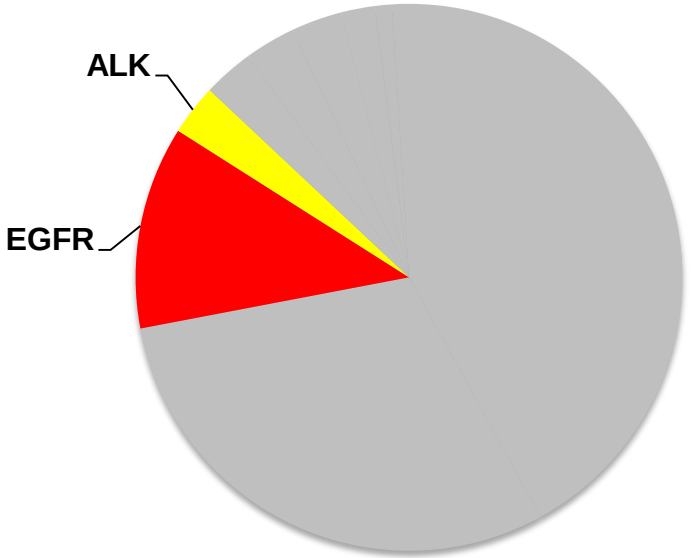
Driver mutations in squamous cell carcinoma



Currently 2 approved personalized treatment options: benefit for about 15% of all NSCLC patients

EGFR-TKIs EGFR mut. NSCLC
Gefitinib, Erlotinib (US, EU)
(Afatinib filed)

Crizotinib for ALK-positive NSCLC
(US, EU filed)



EGFR mutation testing: (not really) open questions

Why ?

When ?

Whom ?

How ?

How in the context of the

dramatic progress in the field ?

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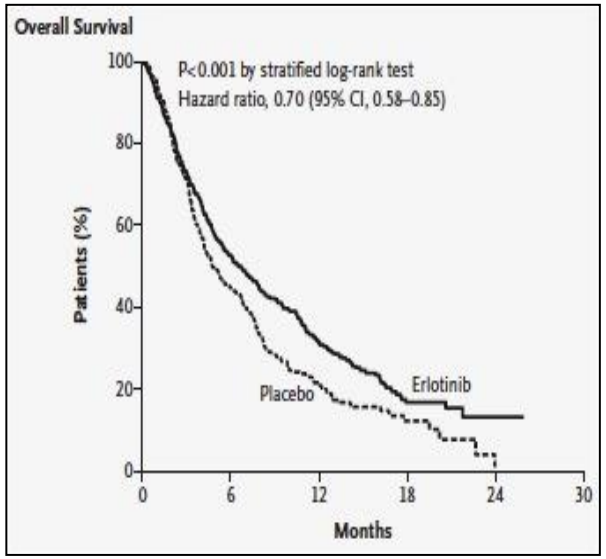
EGFR-TKI treatment of EGFR-mutated lung cancer: paradigm for the power of personalized therapy

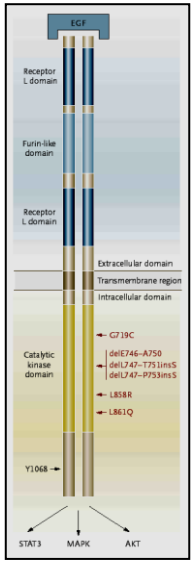
Erlotinib in unselected pts.



Shepherd, 2005

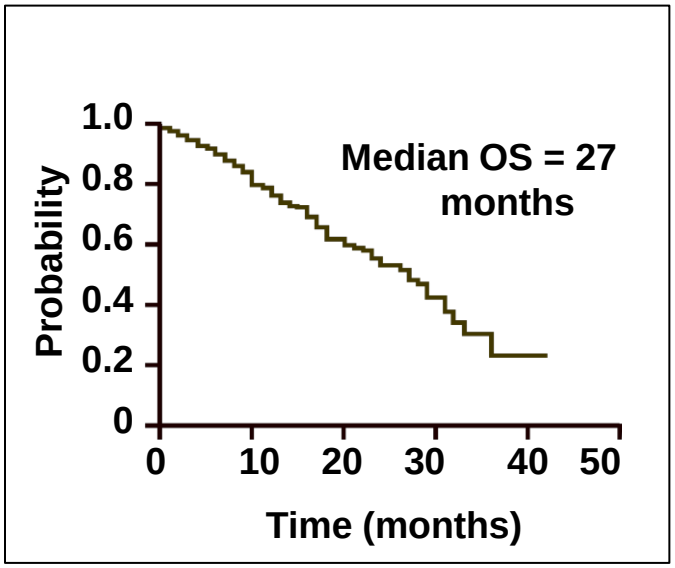
SV-gain: 2 mon.

mSV: < 1 year



Driver mutations in the EGFR

Erlotinib in pts. with EGFR mut.



Rosell, 2009

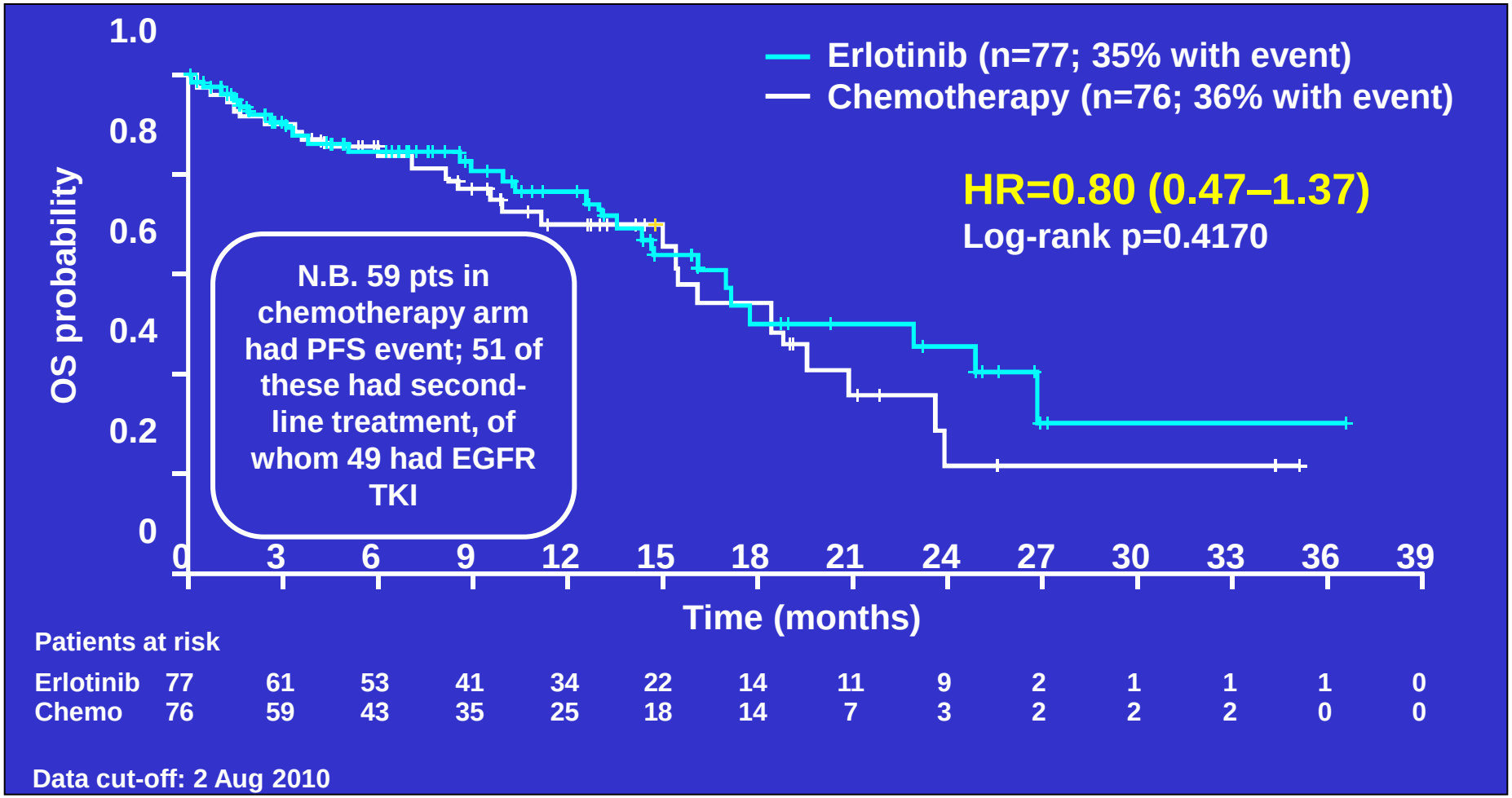
mSV: 27 months

Randomised trials confirm the superiority of 1st line EGFR-TKI vs. chemotherapy in EGFR-mut. NSCLC for RR, PFS and toxicity

Trial	EGFR TKI	n	EGFR mut.	RR (%)	PFS (m)	OS (m)
IPASS (Mok 2009)	gefitinib	1217	261	71 vs. 47 P=0.0001	9.5 vs. 6.3 HR 0.49	21.6 vs. 21.9 HR 1.0
NEJ002(Maemondo 2010)	gefitinib	224	224	74 vs. 31 P=0.0001	10.8 vs. 5.4 HR 0.30	27.7 vs. 26.8
WJTOG (Mitsudomi 2012)	gefitinib	192	192	62 vs. 32	9.2 vs. 6.3 HR 0.5	30.9 vs. n.r. HR 1.64
OPTIMAL (Zhou 2011)	erlotinib	164	164	83 vs. 36	13.7 vs. 4.6 HR 0.164	22.7 vs. 26.8 HR 1.04
EURTAC (Rosell 2012)	erlotinib	153	153	54.5 vs. 10.5	9.4 vs. 5.2 HR 0.37	22.9 vs. 18.8
LUX-LUNG3 (Yang 2012)	afatinib	345	345	56.1 vs. 22.6	11.1 vs. 6.0 HR 0.58	

Survival benefit unverifiable due to crossover

Example: EURTAC trial



Rosell et al., # 7503, ASCO 2011

EGFR mutation testing: (not really) open questions

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EGFR TKIs are the preferred 1st line treatment in EGFRmut NSCLC

Criteria:

- OS: unverifiable
- PFS: significantly better
- RR: significantly better
- Tox. / quality of life : significantly better
- Feasibility : yes

Is there any reason not to treat a patient first line with the more effective and less toxic drug?

Test before 1st line therapy (first look then cook) !

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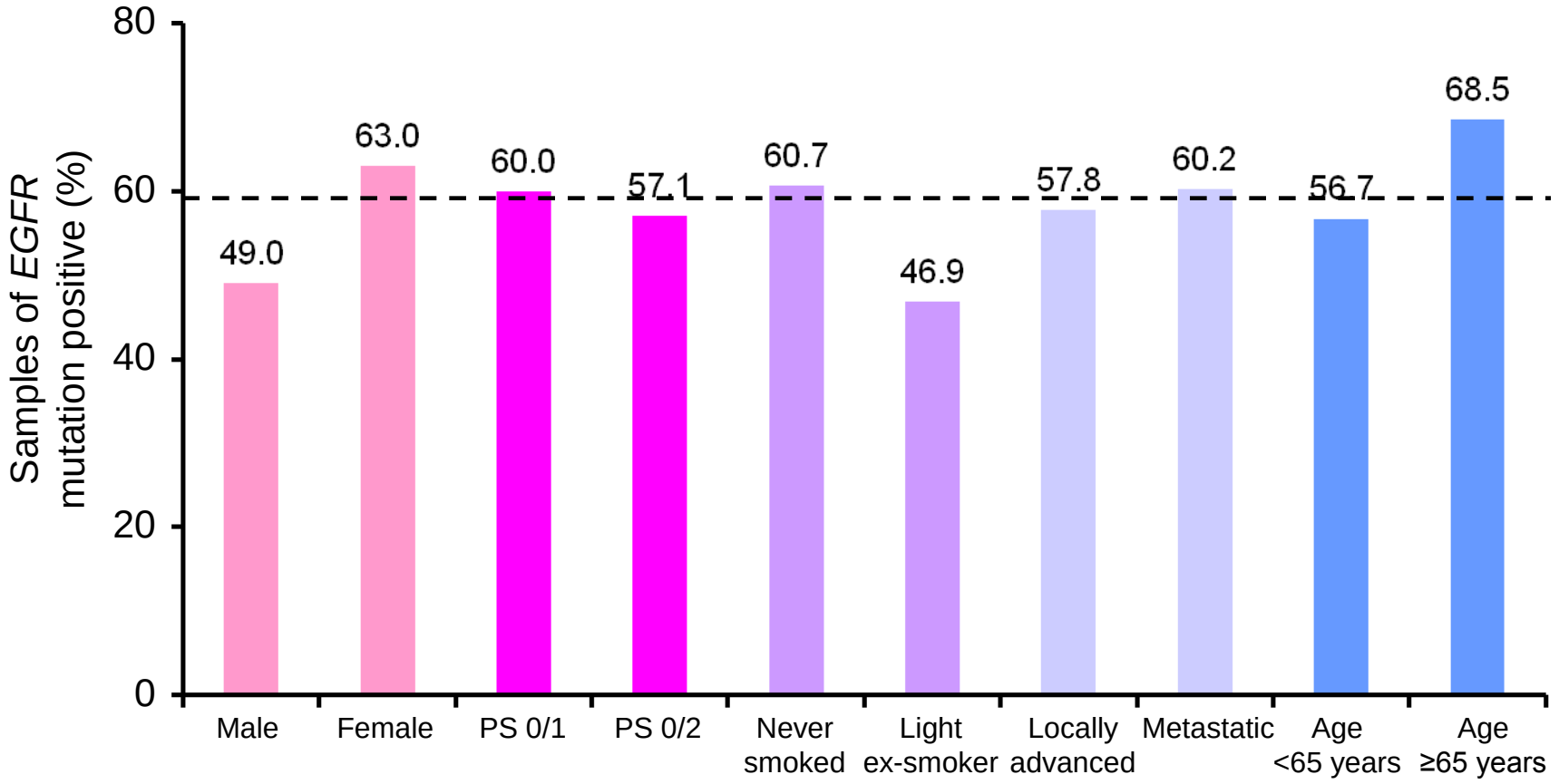
Epidemiological selection not acceptable

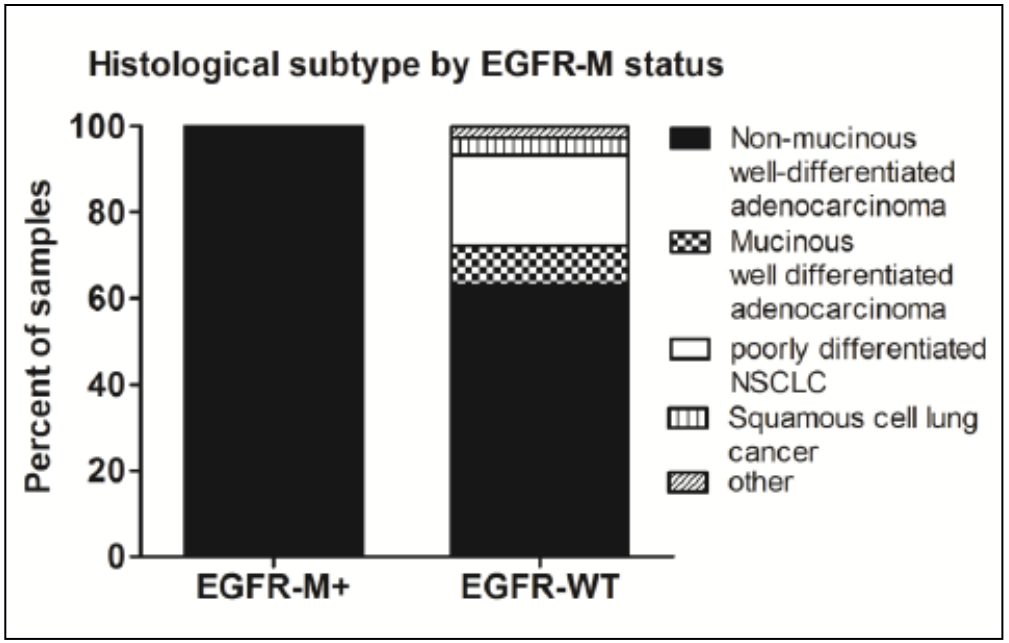
IPASS: Overall *EGFR* mutation rate = 59.7% (261/437)
– predominantly female, never smokers with adenocarcinoma



Mok T, et al. *Ann Oncol* 2008;19(Suppl. 8); Abstract LBA2.

EGFR mutations predominantly (only ?) in adenocarcinoma

Routine EGFR mutation diagnostics experience (n=907, f: 12.6%)
Leary, et al. Royal Marsden, London, WCLC 2011



EGFR mutation only in well-differentiated adenocarcinoma

30% of mutations in males are current or ex-smokers

EGFR mutations in squamous cell carcinoma?

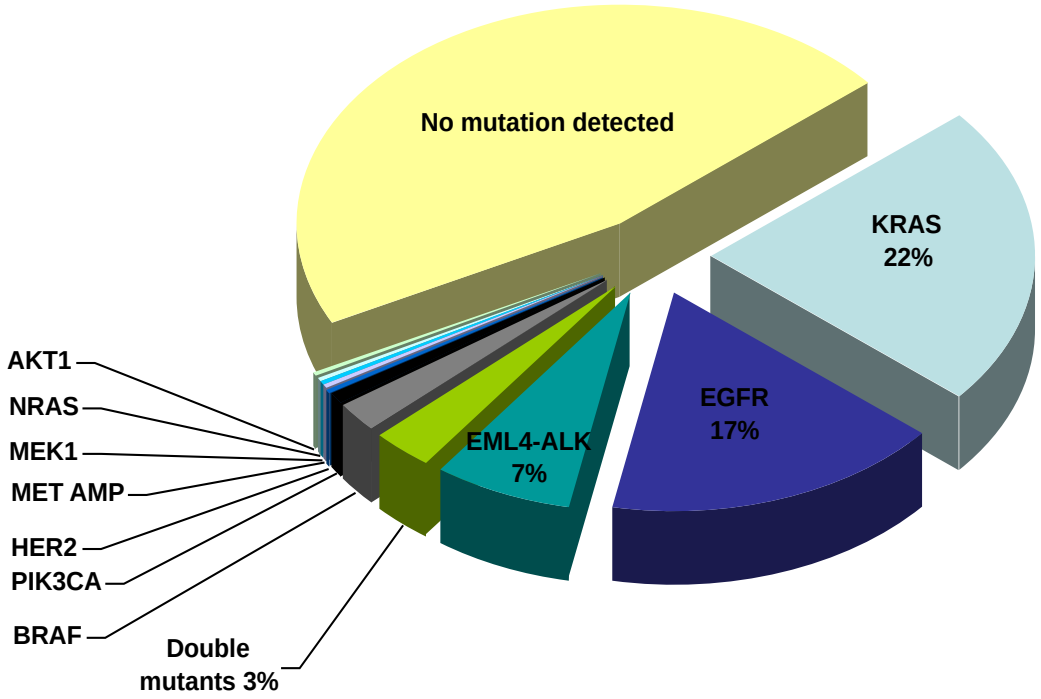
No.	Sex /Age	Smoking index	Initial diagnosis	EGFR mutation Type	EGFR mutation by direct sequencing	IHC			Alucian blue	Final diagnosis
						p63	TTF-1	Ex19 mut		
1	67/M	900	M/D SCC	L747-S752 del	Wild type	+	–	–	–	SCC
2	80/M	800	P/D SCC	L747-E749 del A750P	Wild type	+	–	–	–	SCC
3	50/M	60	M/D SCC	L747-E749 del A750P	mutant	+	–	–	–	SCC
4	60/F	0	P/D SCC	L746-A750 del	mutant	+	+	+	+	Ad with SCC differentiation
5	69/M	900	P/D SCC	L746-A750 del	mutant	+	+	+	+	Adsq
					5/89(6%)					3/87(3%)

Only one ‘pure’ SCC with EGFR mutation in a series of 89 SCCs

EGFR mutation in ‘pure’ SCC: A very rare event
no indication for routine testing

No EGFR mutations in KRAS mutated NSCLC

Analysis of driver mutations in 1000 patients with adenocarcinoma of the lung (Kris MG, et al. Memorial Sloan-Kettering Cancer Center, NY)



Kris M. American Society of Clinical Oncology Conference Proceedings 2011, Abstract CRA7506

Test before 1st line therapy

all non-squamous KRAS wildtype

NSCLC patients

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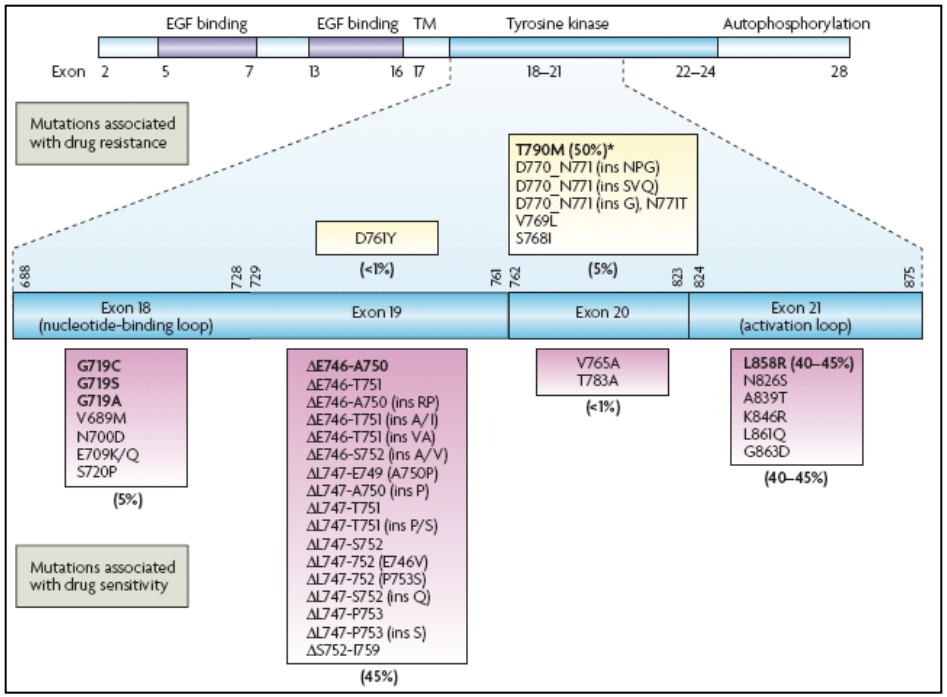
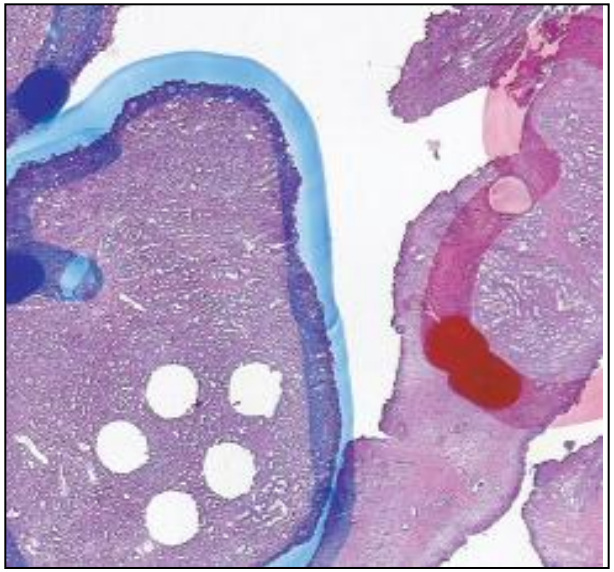
Challenges in EGFR mutation testing

- Various mutations
  - Activating
  - Resistance inducing
  - Of unknown function

- Heterogenous tissue
- Low tumour cell content





Lynch TJ, et al. N Engl J Med 2004;350:2129–2139; Paez JG, et al. Science 2004;304:1497–1500; Pao W, et al. Proc Natl Acad Sci U S A 2004;101:13306–13311

Methods

- Classical first generation sequencing
  - Sanger sequencing (exon 18, 19, [20], 21 + exon 20 T790M)
- Genotyping (mostly PCR based)
  - TaqMan real-time PCR (exon 20 T790M, exon 21 L858R)
  - High resolution melting analysis (HRMA)
- Next generation sequencing
  - Second generation sequencing: PCR-based clonal amplification
  - Third generation sequencing: single cell sequencing

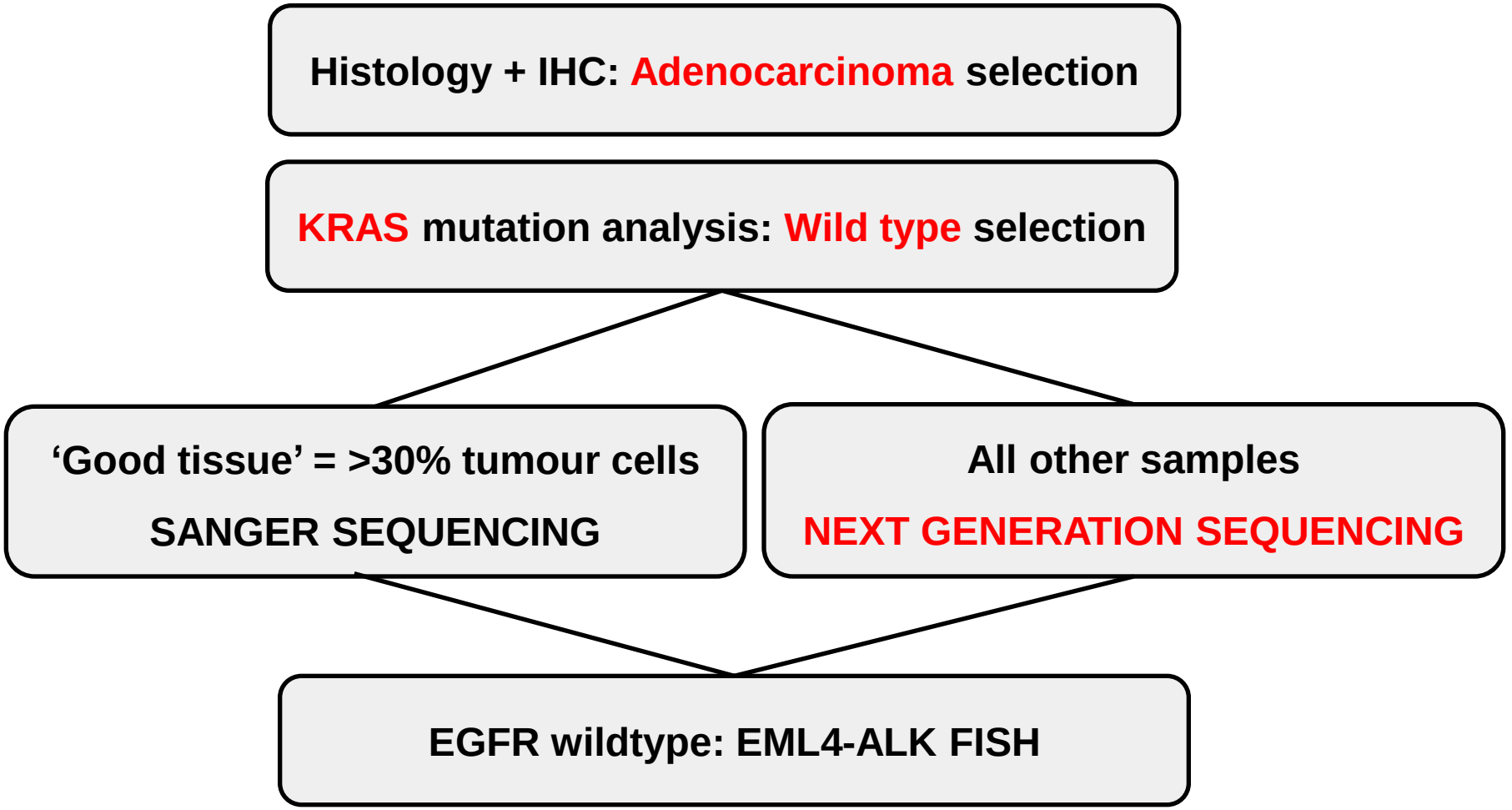
EGFR-mut. testing: interlaboratory comparison (German panel)

Institute	Mutated (Cases)	Exon 18	Exon 19	Exon 20	Exon 21
A	24 (14.3%)	1 (4.2%)	18 (75%)	0	5 (20.8%)
B	16 (12.3%)	2 (12.5%)	8 (50%)	0*	6 (37.5%)
C	24 (9.7%)	2 (7.7%)	13 (50%)	0†	11 (42.3%)
D	52 (25.9%)	2 (3.8%)	28 (53.8%)	7 (13.5%)	15 (28.9%)
E	5 (6.9%)	0	3 (60%)	0	2 (40%)
F	42 (18.6%)	10 (23.8%)	12 (28.6%)	2 (4.8%)	18 (42.8%)
Total	**163/1047 (15.6%)**	**17 (10.4%)**	**81 (49.7%)**	**9 (5.5%)**	**56 (34.4%)**
Sharma SV, et al. *Nat Rev Cancer* 2007		5%	45%	5%	40–45%

*30 cases analysed; †110 cases analyzed.

Penzel R, et al. *Virchows Arch* 2011;458:95–98.

Cologne algorithm for EGFR-mutation testing



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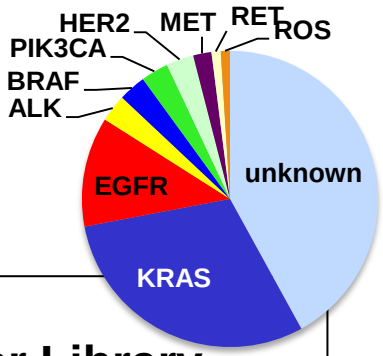
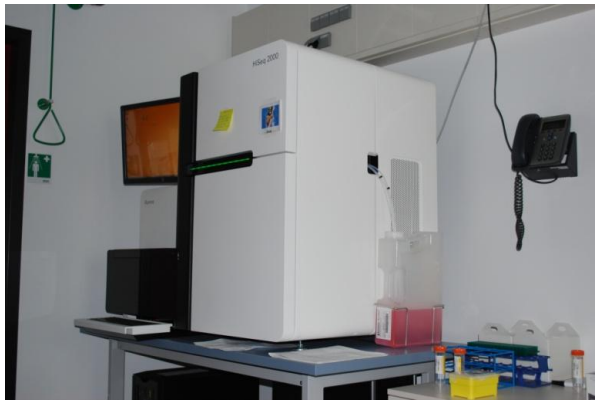
CIO Genome Scanner v2012.1



Next Generation Sequencing



Illumina HiSeq + MiSeq

Ion Torrent PGM

- **Cancer Hot Spot Primer Library**

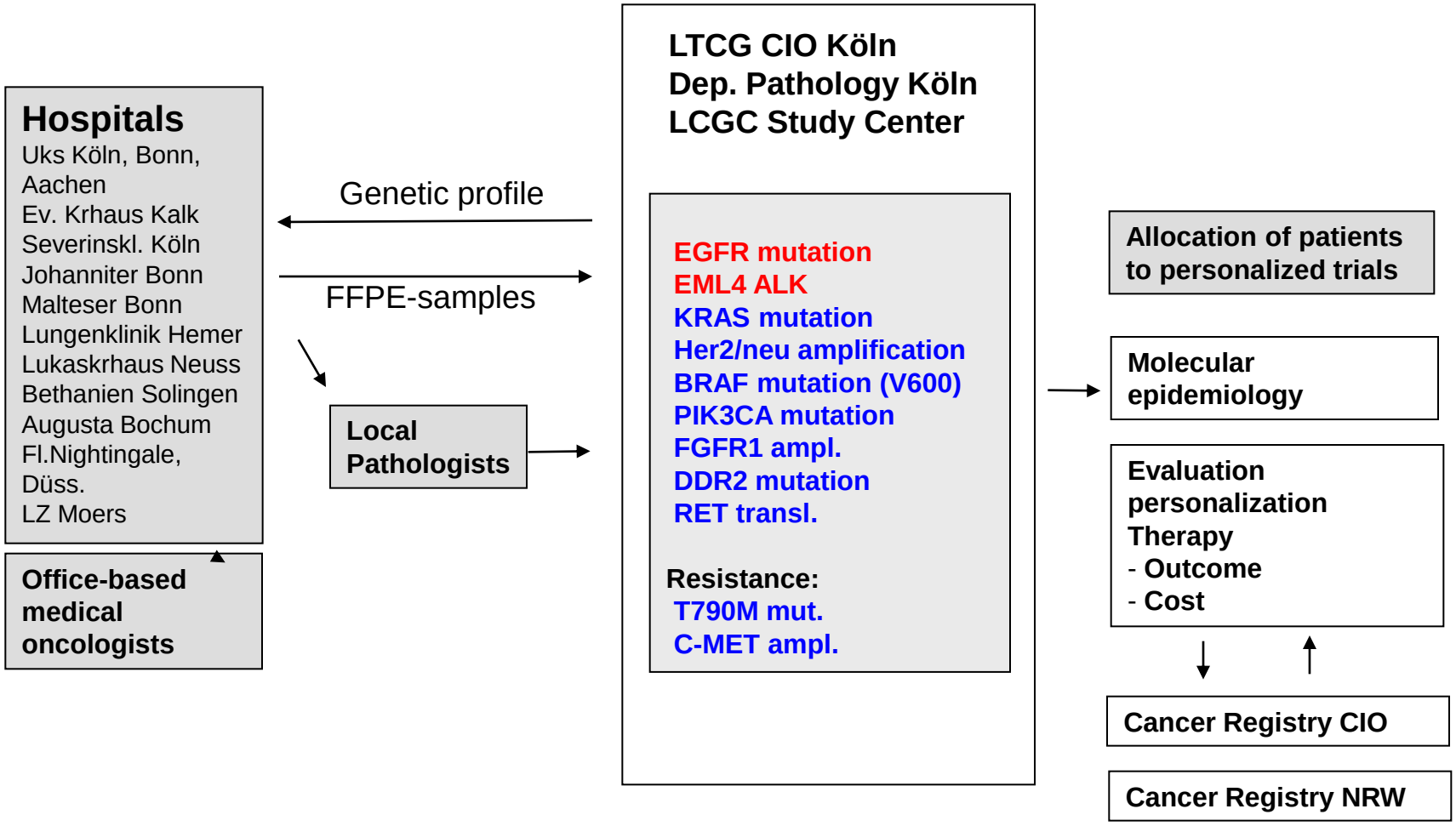
- **• 42 genes**
- **• 5,271 known mutations**
- • Pre-tailed Illumina amplicons

ABL1 CTNNB1 HRAS MLH1 PTEN TP53
APC EGFR IKBKB MSH2 RB1 VHL
BRAF ERBB2 JAK2 NF1 RET
BRCA1 FBXW7 JAK3 NF2 RUNX1
BRCA2 FGFR1 KIT NOTCH1 SMAD4
CDH1 FGFR2 KRAS NRAS SMO
CDKN2A FGFR3 MAP2K4 PDGFRA SRC
CSF1R FLT3 MET PIK3CA STK11

Active for lung in Aug. 2012 at the CIO

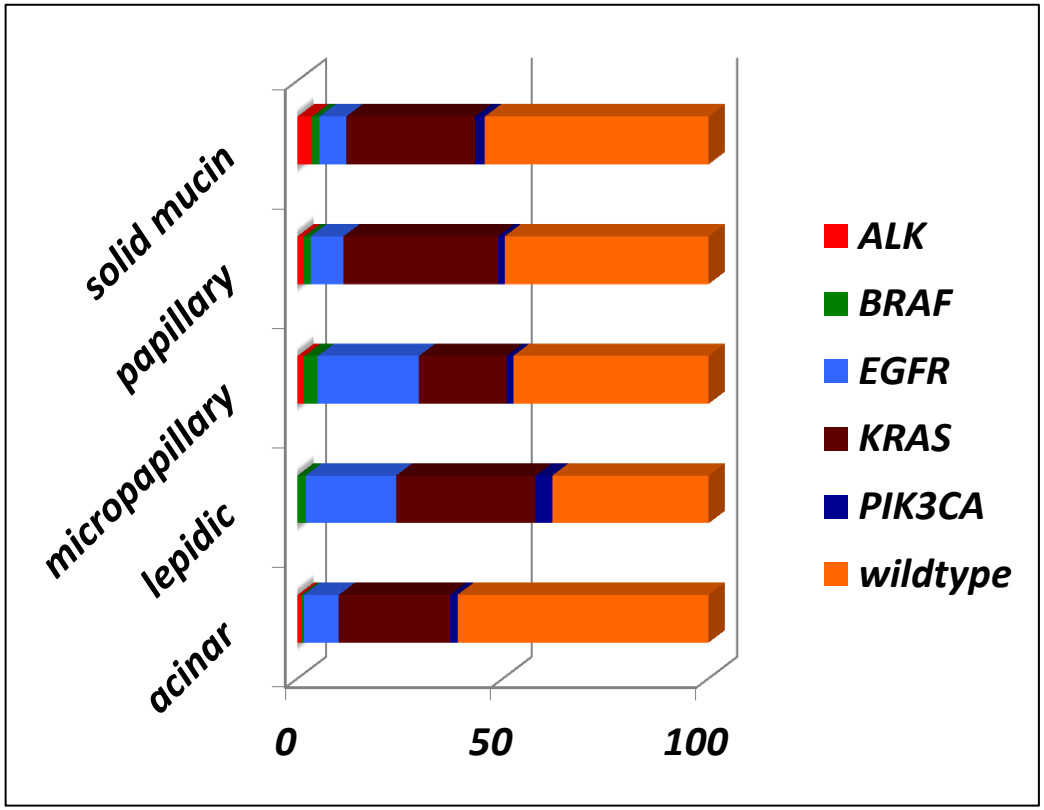
Regional Network Genomic Medicine Lung Cancer

March 2010 – Dezember 2011: 1990 patients analyzed
81 % evaluable for genotyping



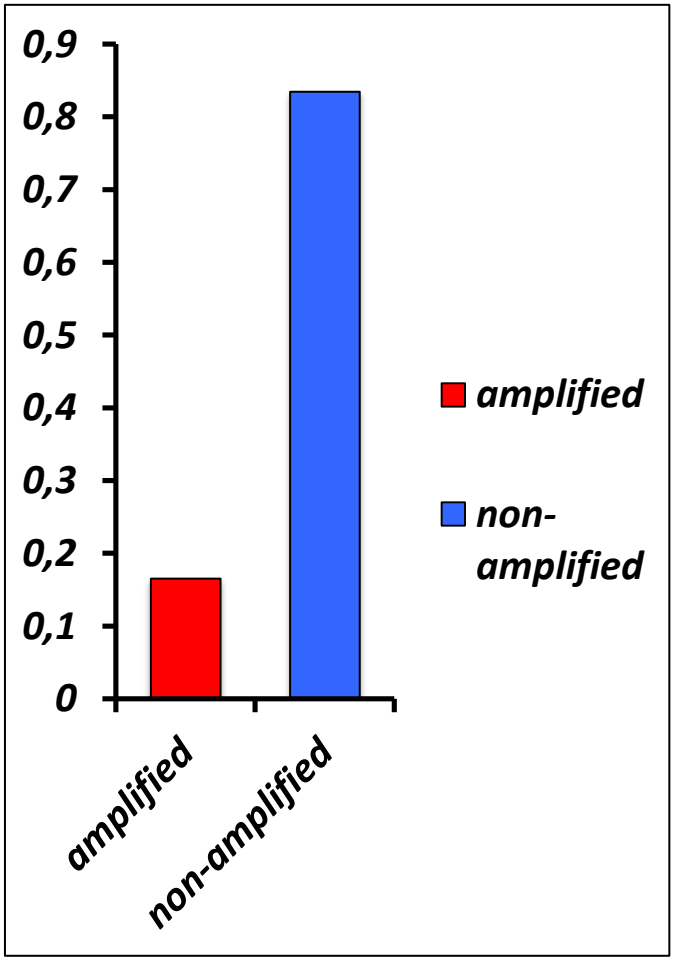
LTCG: Laboratory for Translational Cancer Genomics.

Evaluation of 1020 adenocarcinomas



Targetable lesions in 42%

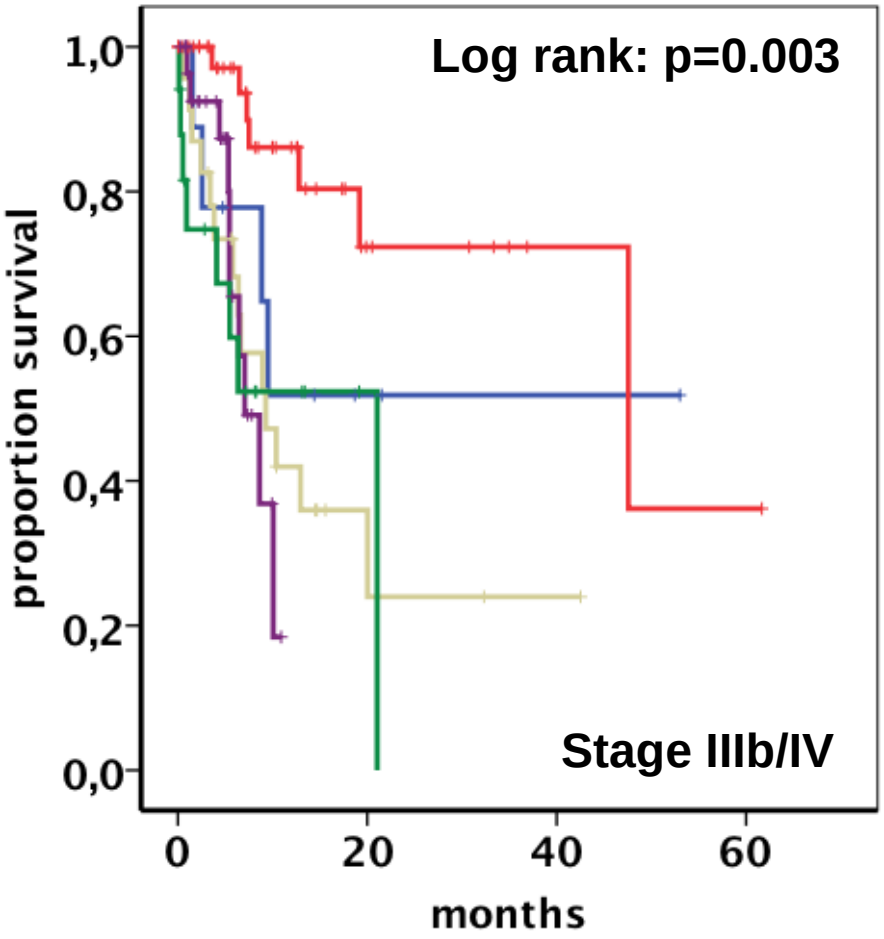
Evaluation of 427 Sqamous cell carcinomas



FGFR1 amplification: 15%

Heukamp, Zander...., Büttner, Wolf, submitted

Excellent survival of patients with EGFR mutations



Median OS of EGFR-mut pts: 47.5 mo

EGFR and ALK significant prognostic predictor in multivariate analysis

- 75% of all EGFR mutated patients received erlotinib or gefitinib
- 50% (11/22) EML4-ALK pos. pts. received crizotinib

Heukamp, Zander...., Büttner, Wolf, submitted

Summary

- **Substantial progress in lung cancer therapy by the consequent development of personalized approaches**

- **EGFR mutation testing**
  - before 1st line therapy
  - all non-squamous KRAS wildtype patiens

- **Near future: multiplex-testing assays based on NGS technology**

- **Close interaction of clinicians, basic scientists and molecular pathologists necessary for implementation**