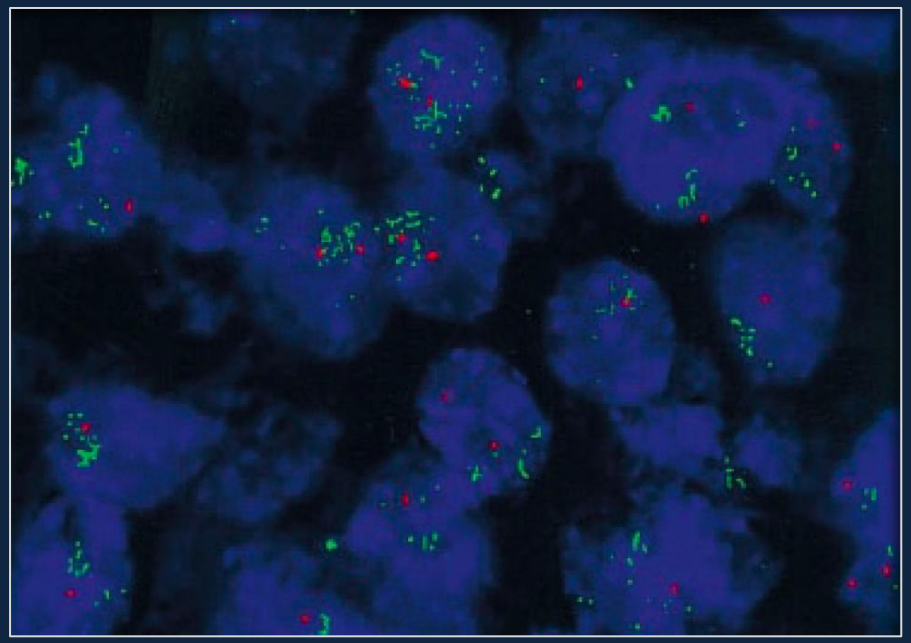
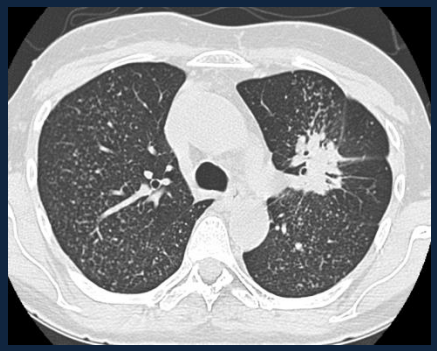
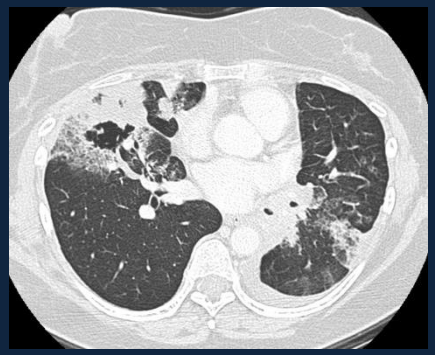
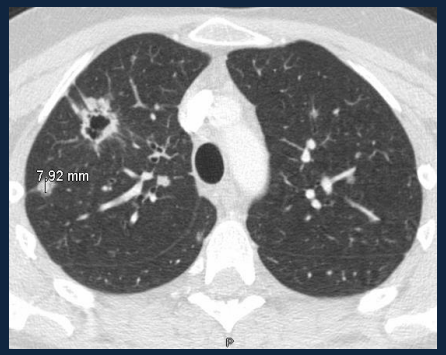


Solange Peters, MD-PhD
Cancer Center, Lausanne
Switzerland

# HER2





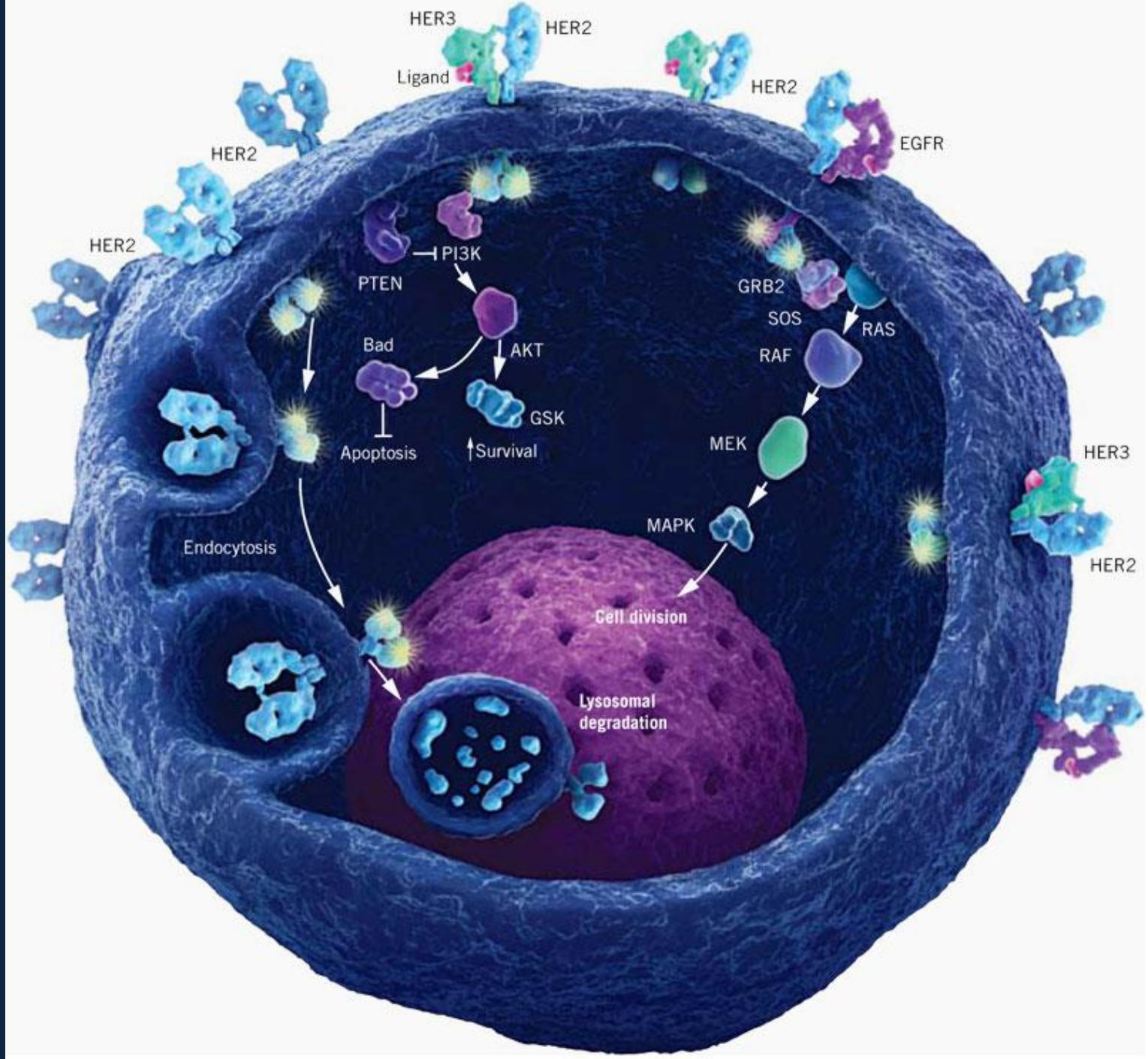


# Disclosures

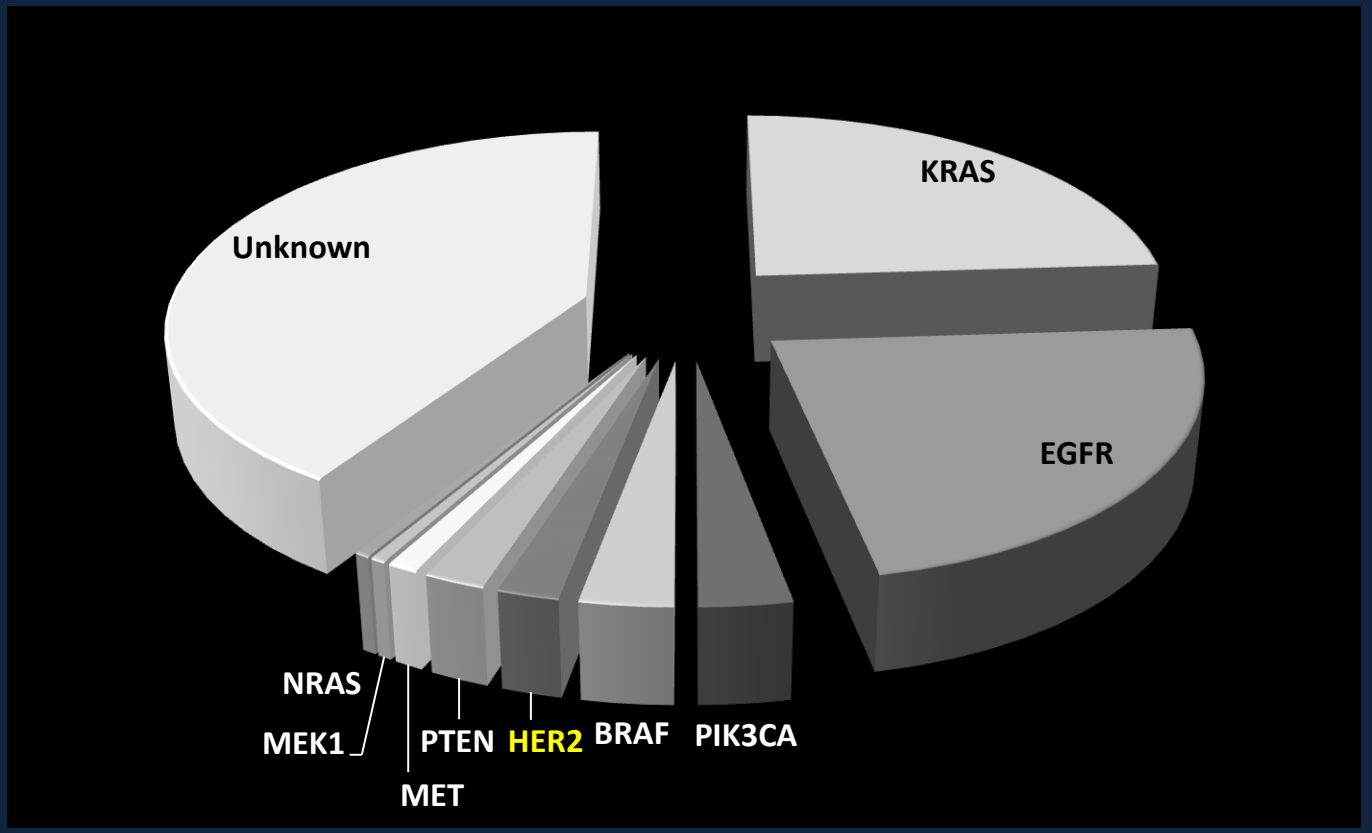
I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack , Merck Serono and Tesaro, for which I received honoraria.

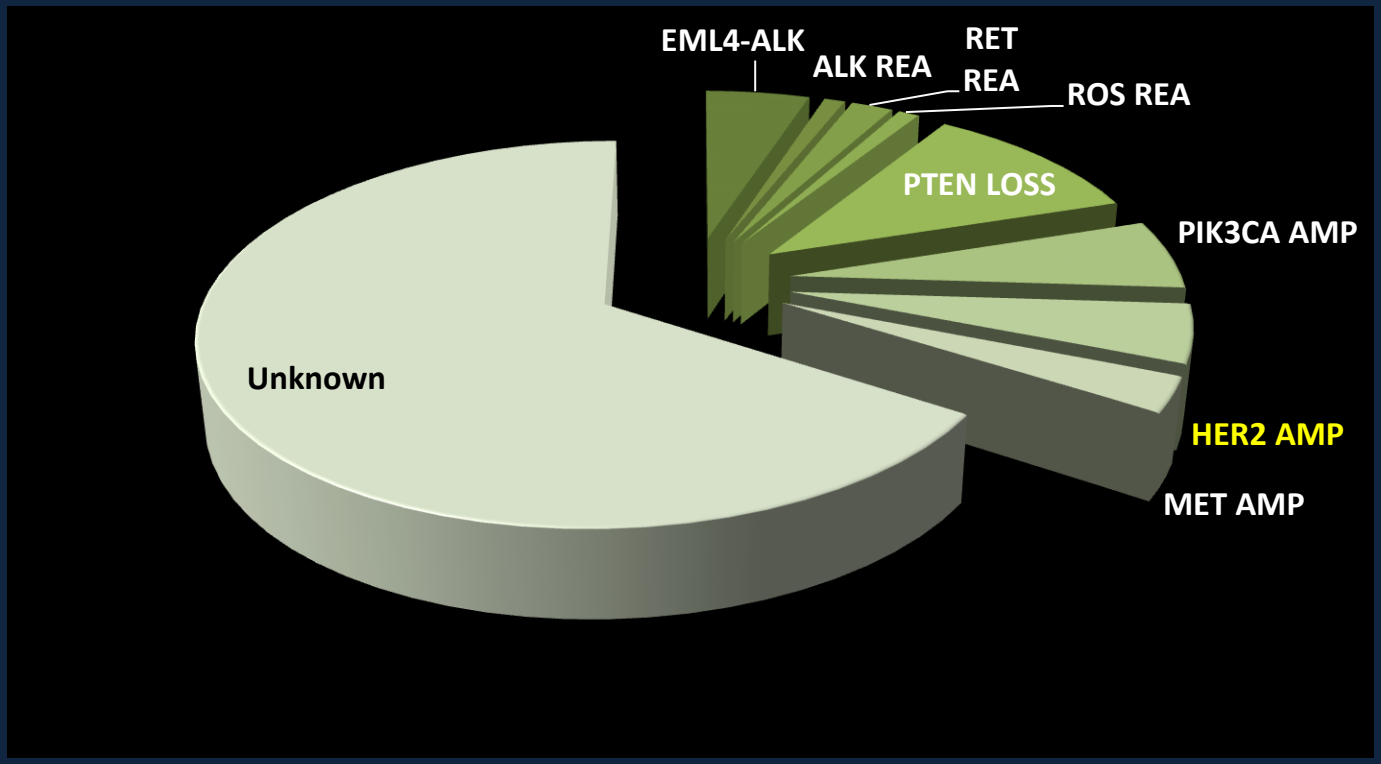
I declare no conflict of interest.


HER3
HER2
Ligand
HER2
HER2
EGFR
HER2
PI3K
PTEN
GRB2
SOS
RAS
Bad
AKT
RAF
GSK
Apoptosis
Survival
MEK
HER3
MAPK
Endocytosis
HER2
Cell division
Lysosomal degradation

# 2012 update on adenocarcinoma driver mutations

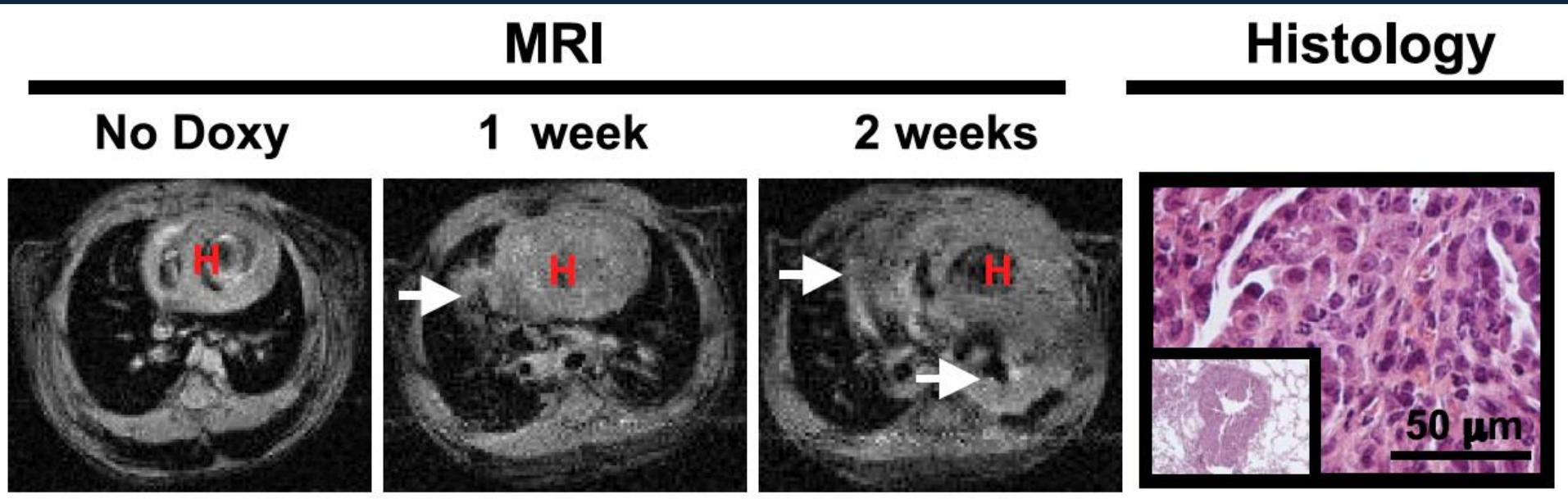


# 2012 update on adenocarcinoma driver gene alterations



# Definition of drivers?

Inducible expression of mutated HER2 (HER2YVMA):
Rapid development/maintenance of adenosquamous lung tumors in mice




Perera, PNAS 2009

# Epidemiology IHC/FISH (1)

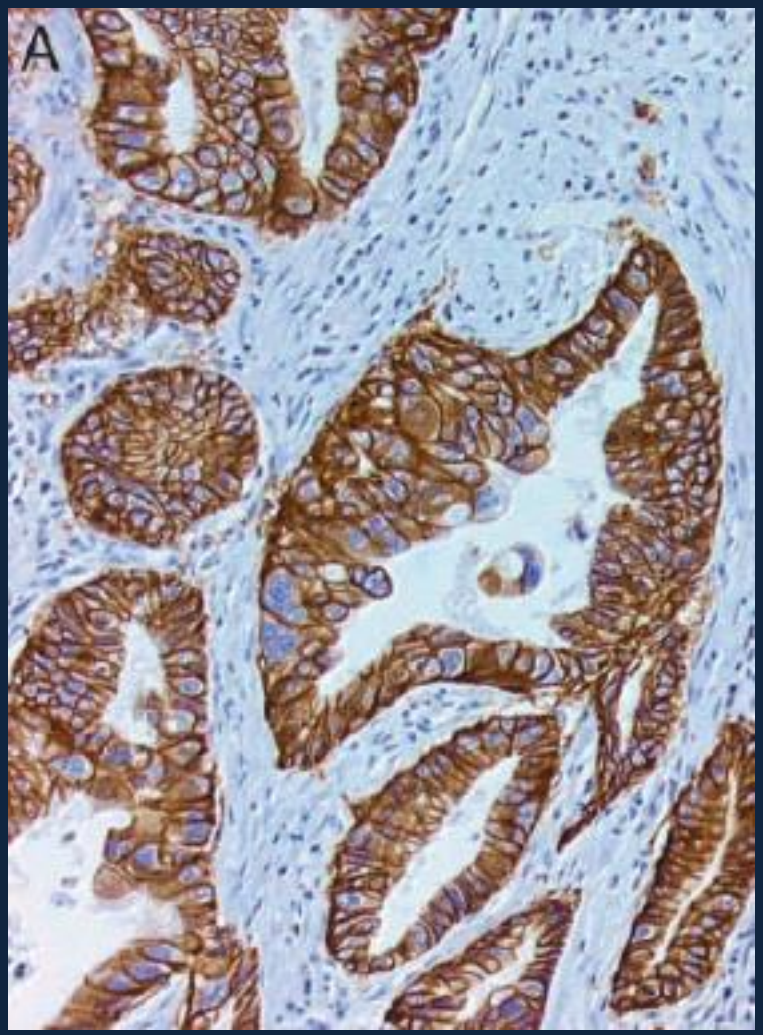
- HER2 overexpression by IHC in 20% (83 of 410) of stage IIIB-IV NSCLC, whereas 2% (7 of 378) positive by FISH

- Concordance between FISH and IHC 3+

| Carcinoma type | Total | Positive | IHC 2+ | IHC 3+ | FISH |
|---|---|---|---|---|---|
| Adenocarcinoma | 143 | 42 (29%) | 33 (23%) | 4 (3%) | 5 (4%) |
| Squamous cell carcinoma | 80 | 14 (18%) | 11 (14%) | 2 (3%) | 1 (1%) |

Heinmoller, CCR 2003

# Epidemiology IHC/FISH/RT-PCR (2)




115 stage I-III NSCLC.

- IHC positive in 23%, with 5 NSCLC (4%) showing intense staining

- RT-PCR with HER2 mRNA levels above normal in 54 of 115 of carcinomas (47%)

- FISH positive in 9 of 41 NSCLC (22%)

Pellegrini, CCR 2003

Lung cancer

# Intragenic ERBB2 kinase mutations in tumours

Table 1 **ERBB2 mutations in primary tumours**

| *Sample* | *Tumour/histology* | *Nucleotide** | *Amino acid** |
|---|---|---|---|
| PD1353a | NSCLC adenocarcinoma | 2322 ins/dup(GCATACGTGATG) | ins774(AYVM) |
| PD0258a | NSCLC adenocarcinoma | 2322 ins/dup(GCATACGTGATG) | ins774(AYVM) |
| PD0317a | NSCLC adenocarcinoma | 2322 ins/dup(GCATACGTGATG) | ins774(AYVM) |
| PD0319a | NSCLC adenocarcinoma | 2335 ins(CTGTGGGCT) | ins779(VGS) |
| PD0270a | NSCLC adenocarcinoma | TT2263-4CC | L755P |

- 120 primary NSCLC, 4.2% with mutations in HER2 kinase domain, 9.8% (5/51) in adenocarcinomas
- Overexpression probably does not accompany the mutation

Stephens, NATURE | VOL431 | 30 SEPTEMBER 2004 | www.nature.com/nature

# Epidemiology HER2 mutation (2)

- 403 stage I-III adenocarcinomas in caucasian patients: mutation in 9 (2.2%).
- Seven (78%) of the mutations were in frame duplications/ insertions at codons 776–779 (YVMA)
- Frequency higher in females (4.1% vs 1.8%) and in never smokers (3.1% vs 1.9%)

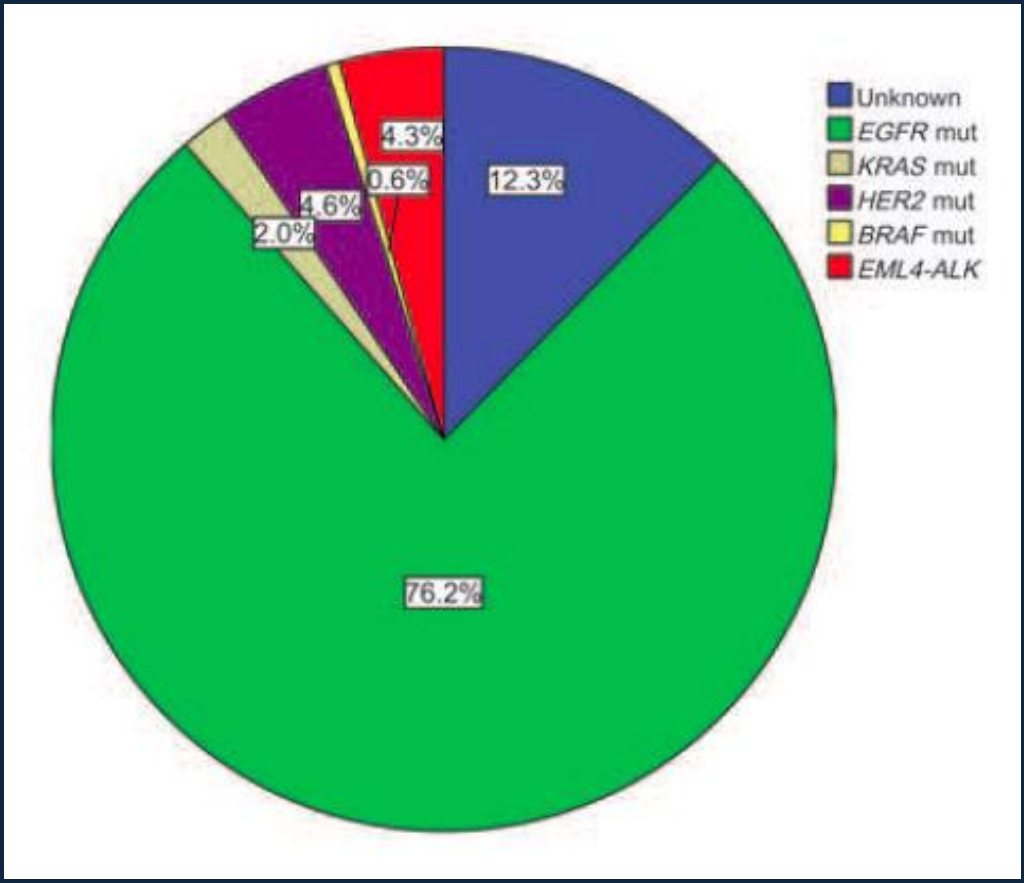
Buttitta, Int J Cancer 2006

- 394 adenocarcinoma, HER2 mutations preferentially in oriental ethnicity (3.9% vs 0.7%)
- All HER2 mutations were in-frame insertions in exon 20
- HER2 mutations significantly more frequent in never smokers (3.2%; P = 0.02) and adenocarcinoma histology (2.8%, P = 0.003)

Shigematsu, CCR 2005

# HER-2 mutation prevalence variability?

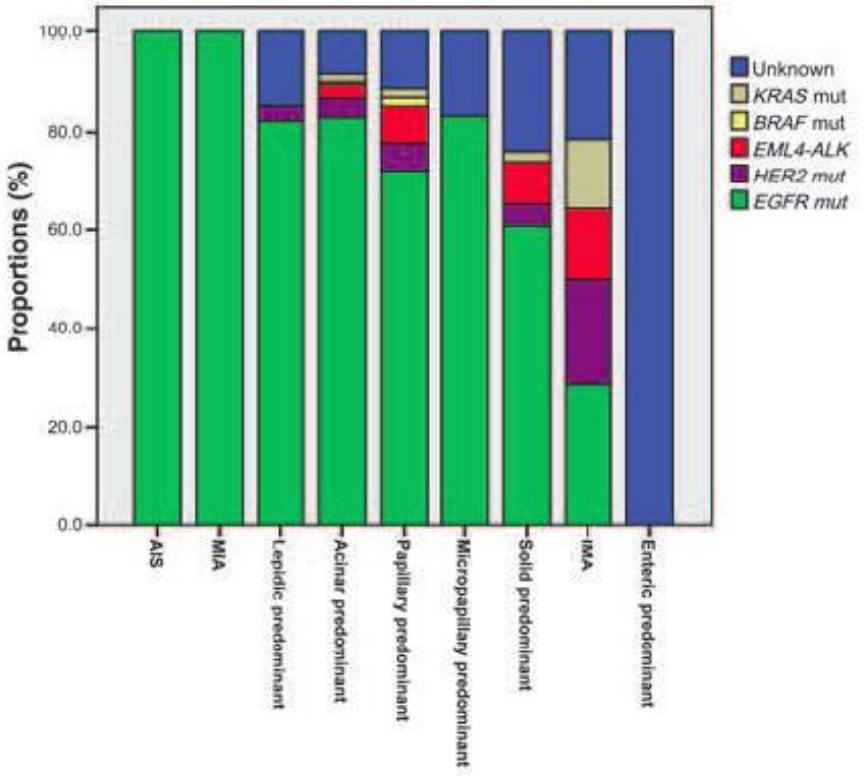
Frequency of Mutations in Lung Adenocarcinoma from Female Never-Smokers …

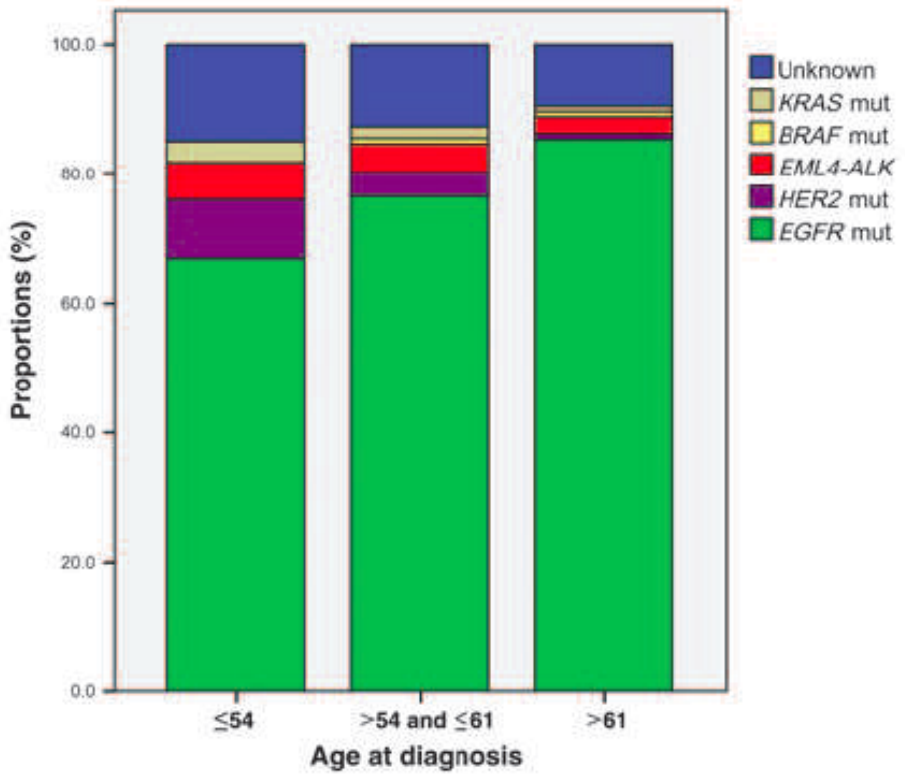



Zhang, CCR 2011

# HER-2 prevalence variability (2)?

Frequency of Mutations in Lung Adenocarcinoma from Female Never-Smokers … **varies with age, and histologic subtype**




Zhang, CCR 2011

# Similarity with EGFR insertions

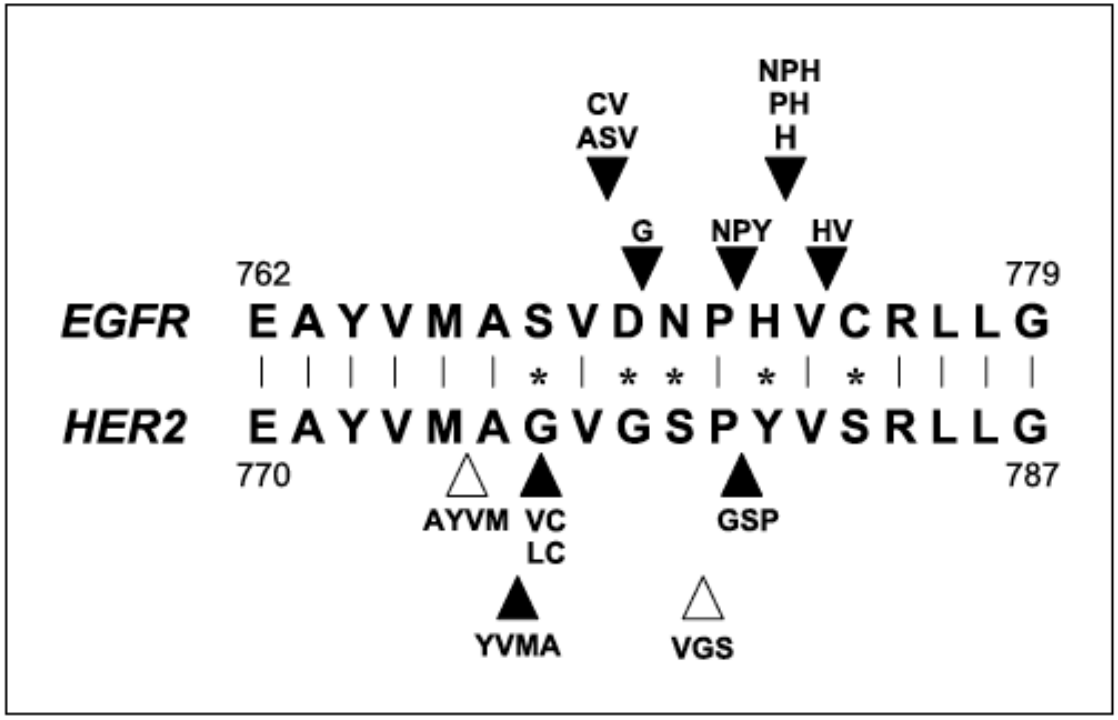
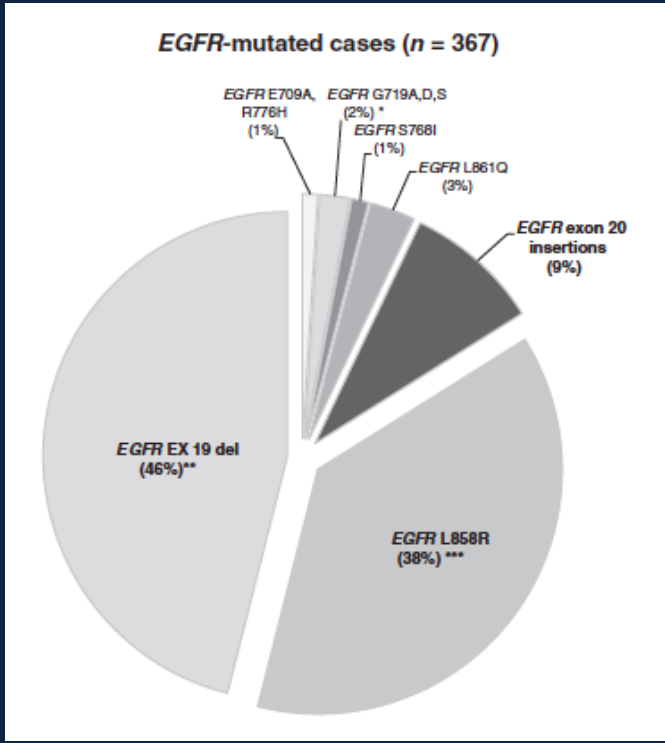
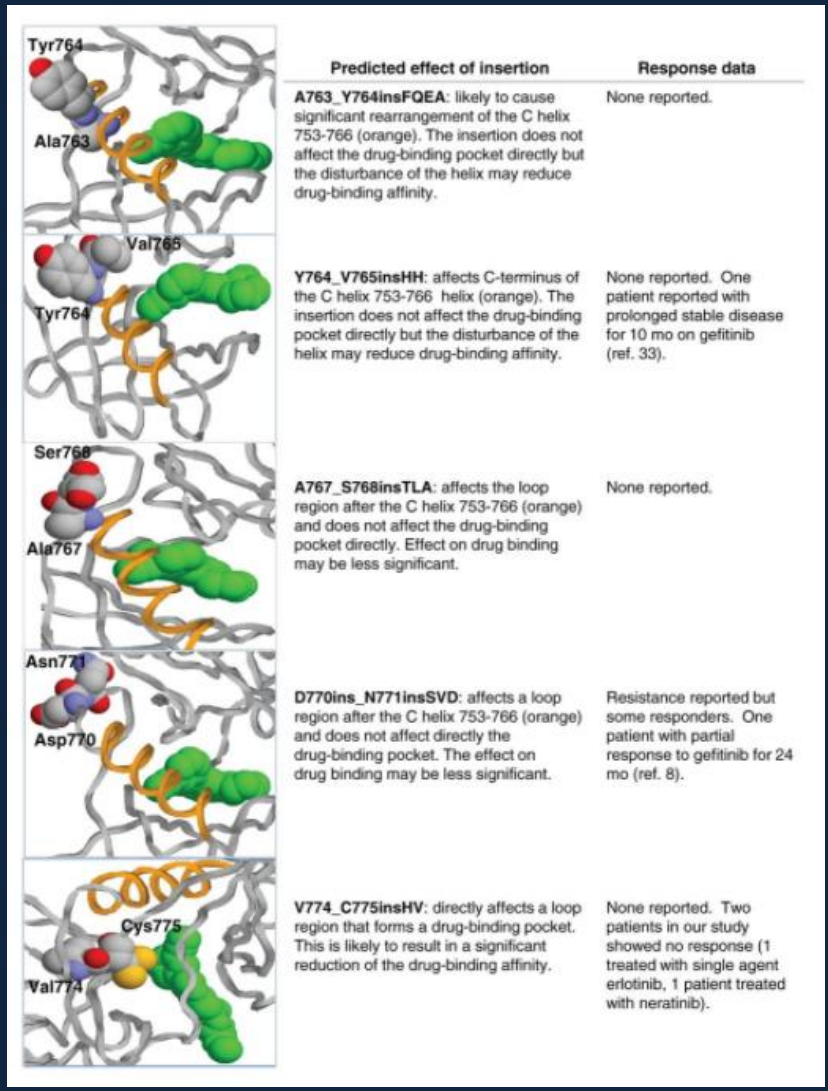



**Figure 2.** Amino acid alignments of the tyrosine kinase domain in EGFR and HER2. ▲ and ▼, duplications/insertions in this study (for *HER2*) or previously reported by us for *EGFR* (23). △, *HER2* duplications/insertions described by Stephens et al. (22). *, nonconserved amino acid.

Shigematsu, CCR 2005

# EGFR exon 20 insertions

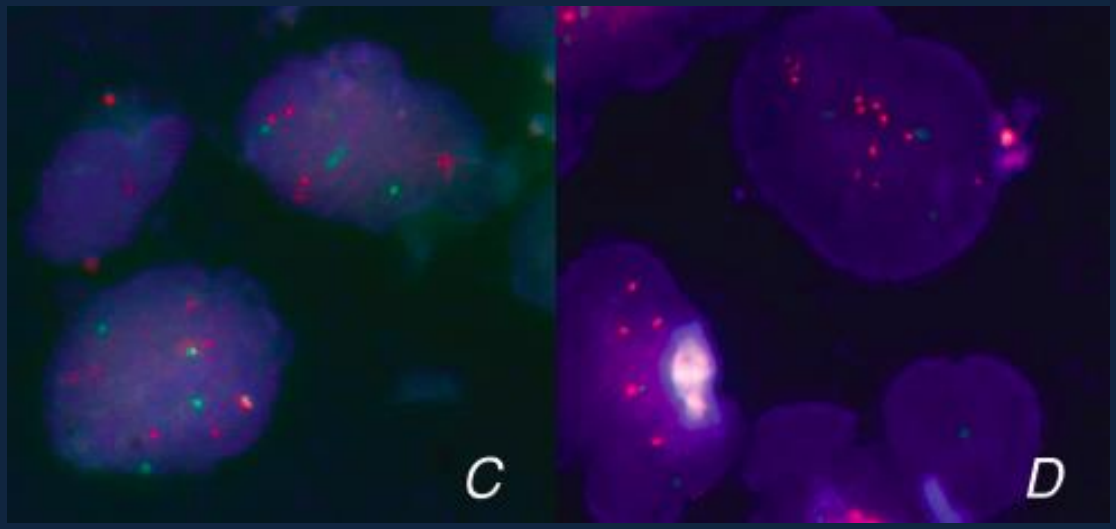



Arcila, Mol Cancer Ther 2013

# Correlation between HER2 mutation and amplification (1)

- HER2 mutation in 3.6% (8/224) = 11.1% without EGFR and KRAS mutations
- **Seven of eight HER2-mutated tumors showed HER2 copy number gains (CNGs)**




Li, JTO 2012

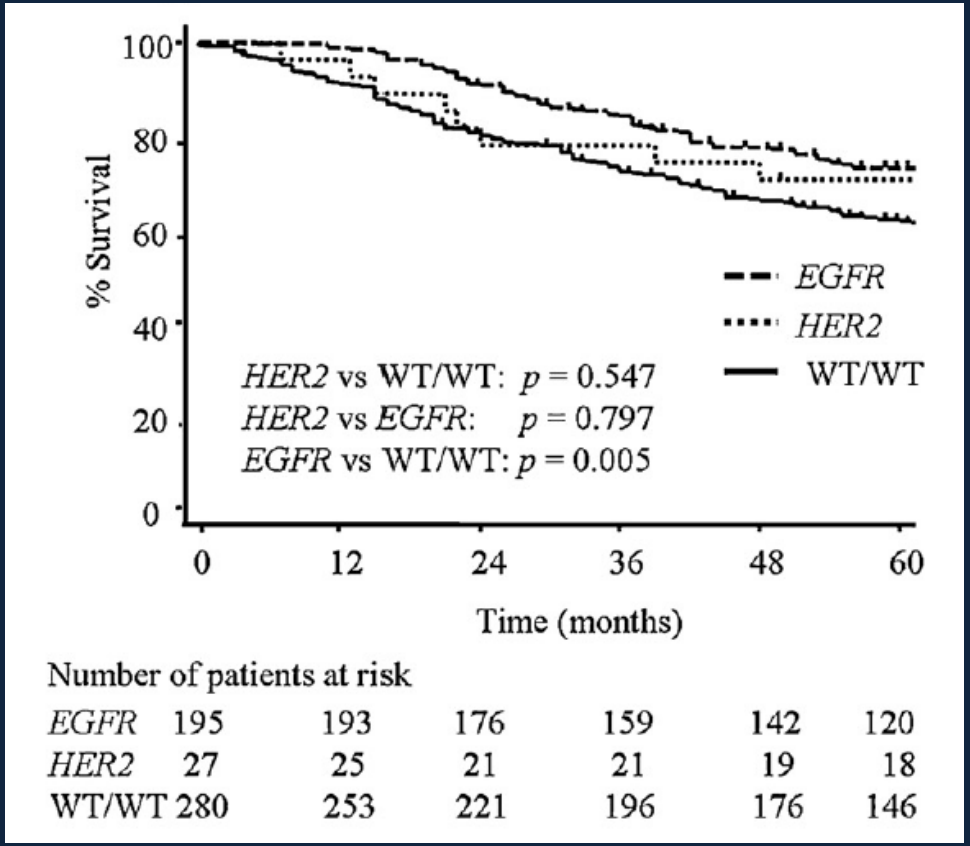
# Correlation between HER2 mutation and amplification (2)

- Identification of 25 cases with HER2 mutations, representing 6% of EGFR/KRAS/ALK-negative specimens
- HER2 mutations were more frequent among never-smokers ($P < 0.0001$) but there were no associations with sex, race, or stage
- **HER2 mutation was not associated with concurrent HER2 amplification in 11 cases tested for both**

Arcila, CCR 2012

# Pronostic impact of HER2 mutations

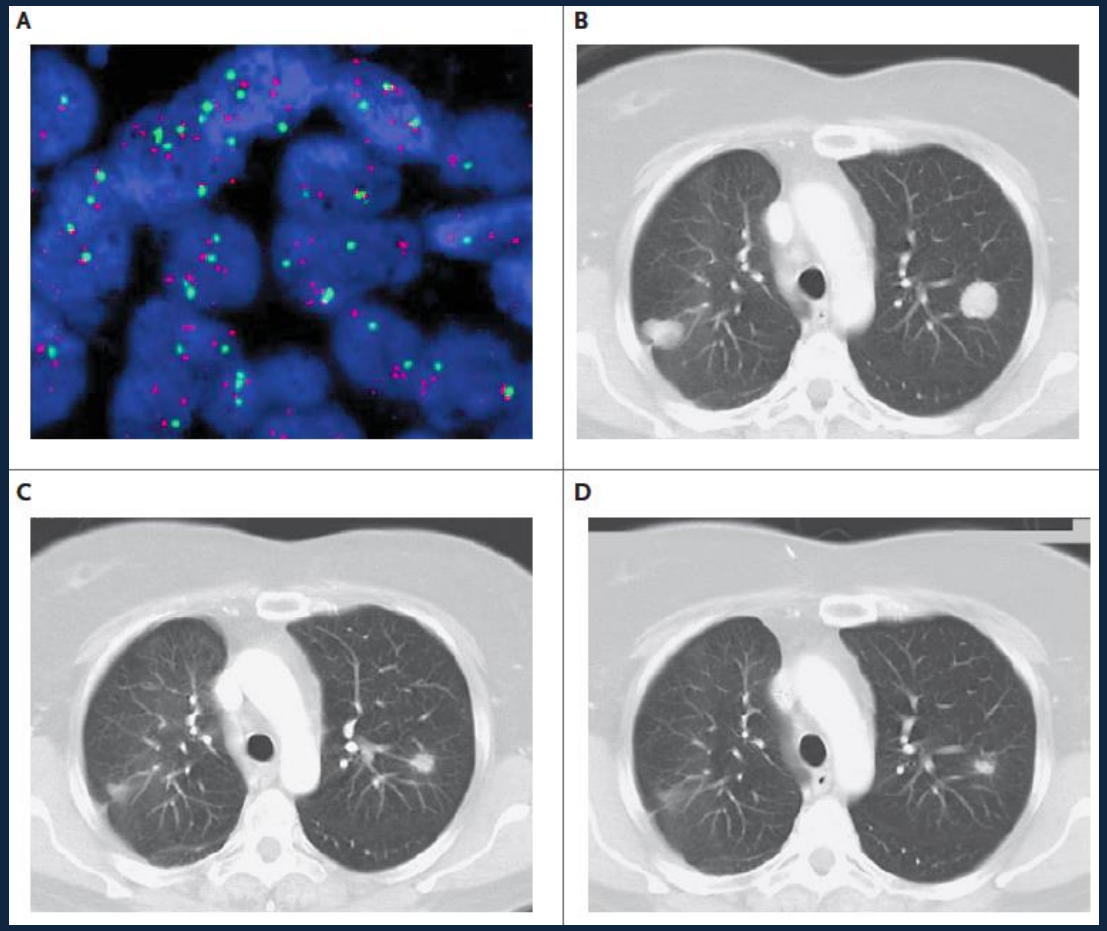
- HER2 mutations in 13 of 504 japanese patients (2.6%) undergoing surgery for NSCLC
- No difference in the overall survival of patients with HER2 mutations, compared with patients harboring EGFR mutations and patients harboring wild types for both EGFR and HER2




Tomizawa, Lung Cancer 2012

# The case report

HER2 mutation and response to trastuzumab (+ paclitaxel) therapy in non-small-cell lung cancer (increased HER2 and EGFR GCN and HER2 exon 20 mut+)




Cappuzzo, N Engl J Med 2006

# HER2 dedicated clinical trial in NSCLC (1)

Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer

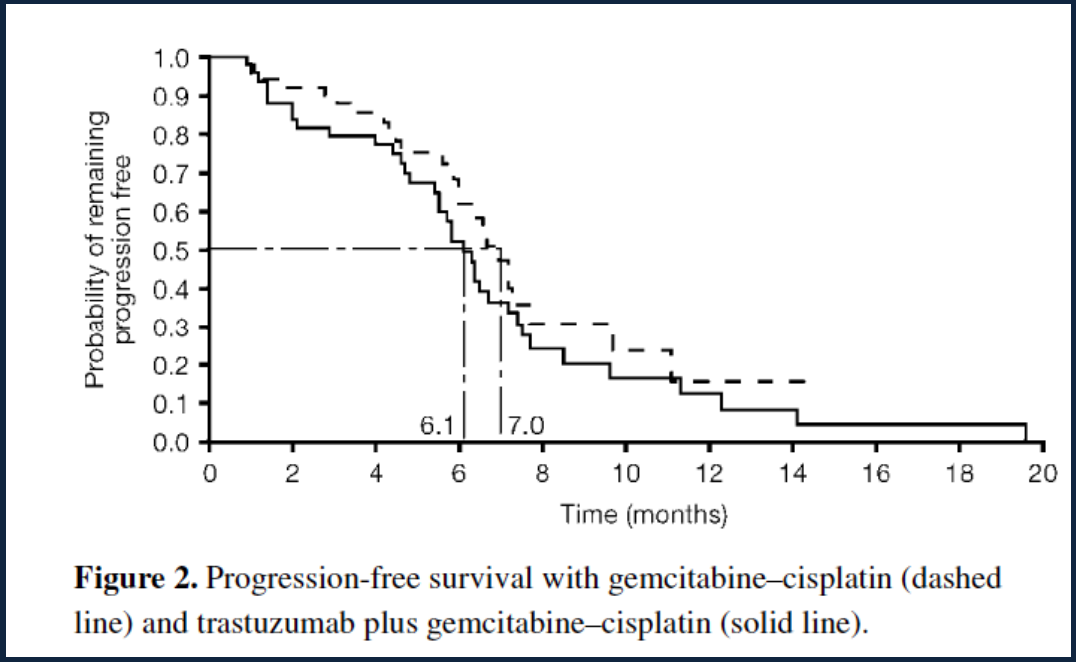



**Figure 2.** Progression-free survival with gemcitabine–cisplatin (dashed line) and trastuzumab plus gemcitabine–cisplatin (solid line).

- Clinical benefit was not observed
- Although HER2 3+/FISH-positive patients may benefit from trastuzumab, the subgroup was too small to provide definitive information

Gatzemeier, Ann Oncol 2004

# HER2 dedicated clinical trial in NSCLC (2)

Trastuzumab + docetaxel in HER2 positive non-small-cell lung cancer

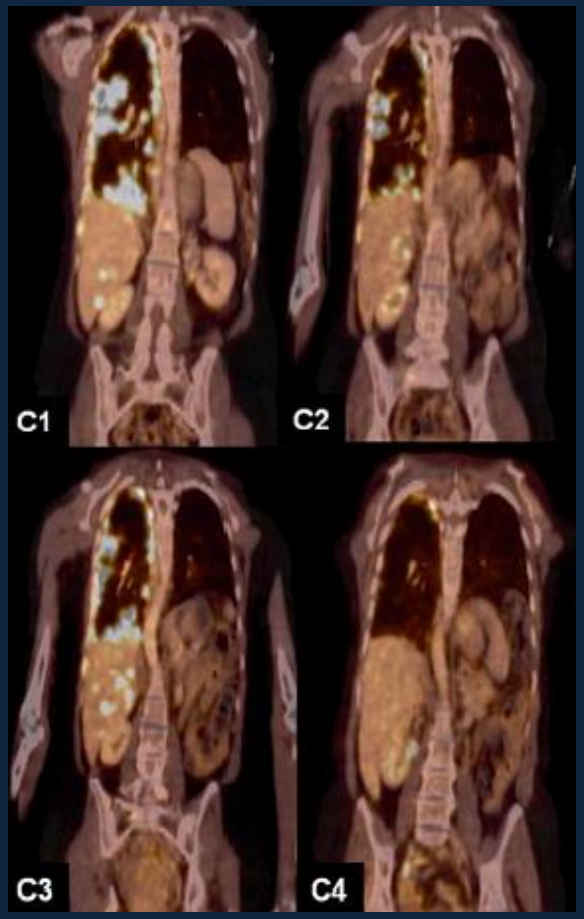
- Patients with HER2 2+ or 3+ randomized to either single-agent trastuzumab or docetaxel -> after 2 cycles, all receive the trastuzumab/docetaxel combination
- Only 13 patients (19%) had HER2-positive disease
- None responded to trastuzumab alone

*« In view of the limited target population for HER2 inhibition, future efforts and resources should be directed toward molecular targets other than HER2 in NSCLC »*

Lara, Clin Lung Cancer 2004

# HER2 dedicated clinical trial in NSCLC (3)

Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2




Five patients with metastatic HER2 mutated adenocarcinomas were identified, three of which were evaluable for response

Objective response was observed in all three patients, even after failure of other EGFR- and/or HER2-targeted treatments

De Greve, Lung Cancer 2012

# Our French/European experience (1)

- *HER2* mutation was identified in 65 patients out of 3800 patients (1.7%)
- Exclusive driver, except one single case with a concomitant *KRAS* mutation
- Median age of 60 years (31-86), high proportion of women (45 *vs*. 20 men, 69%), and of never smokers (34, 52.3%)
- All tumors were adenocarcinomas and 50% were stage IV at diagnosis

Mazieres and Peters, JCO in press

# Our French/European experience (2)

22 anti-HER2 treatments were administered after conventional chemotherapy in 16 patients:

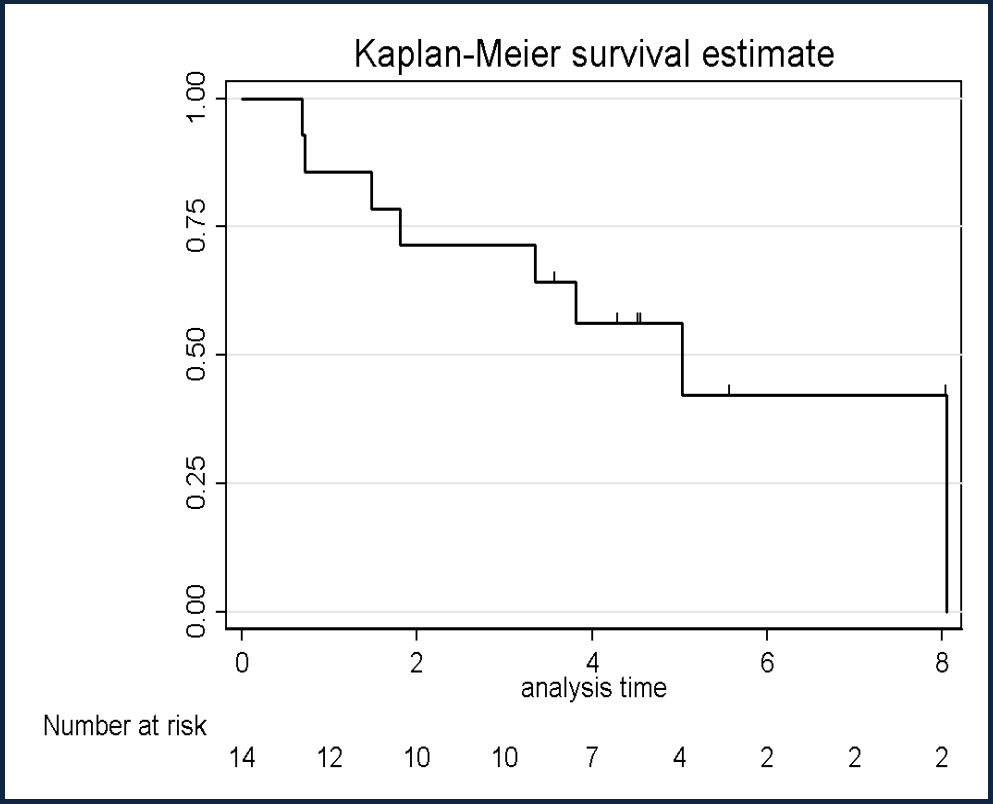
- 4 PD
- 7 SD
- 11 PR
- overall response rate ORR 50%; disease control rate DCR 82%
  - DCR of 93% for trastuzumab-based therapies (n = 15)
  - 100 % for afatinib (n = 3)
  - 0% to other HER2-targeted drugs (n = 3)

| Patient | 1st line treatment | Best disease response | 2nd line treatment | Best disease response | 3rd line treatment | Best disease response | 4th line treatment | Best disease response |
|---|---|---|---|---|---|---|---|---|
| 11 | VIN-HER | PR | | | | | | |
| 15 | CAR-PAC-TRAS | SD | | | | | | |
| 19 | TXT-MASA | PD | | | | | | |
| 24 | VIN-TRAS | PR | | | | | | |
| 26 | CAR-PAC-TRAS | PR | | | | | | |
| 27 | VIN-TRAS | PR | | | | | | |
| 28 | VIN-TRAS | SD | | | | | | |
| 30 | LAP | PD | | | | | | |
| 31 | NVB-HER | PR | | | | | | |
| 32 | LAP | PD | TRAS-VIN | PR | AFA | SD | CAR-TRAS | SD |
| 37 | VIN-TRAS | PD | | | | | | |
| 41 | DOC-TRAS | PR | | | | | | |
| 43 | VIN-TRAS | PR | AFA | PR | | | | |
| 44 | VIN-TRAS | PR | AFA | SD | | | | |
| 45 | VIN-TRAS | SD | PAC-TRAS | SD | | | | |
| 47 | TRAS | PR | | | | | | |

Mazieres and Peters, JCO in press

# Our French/European experience (3)

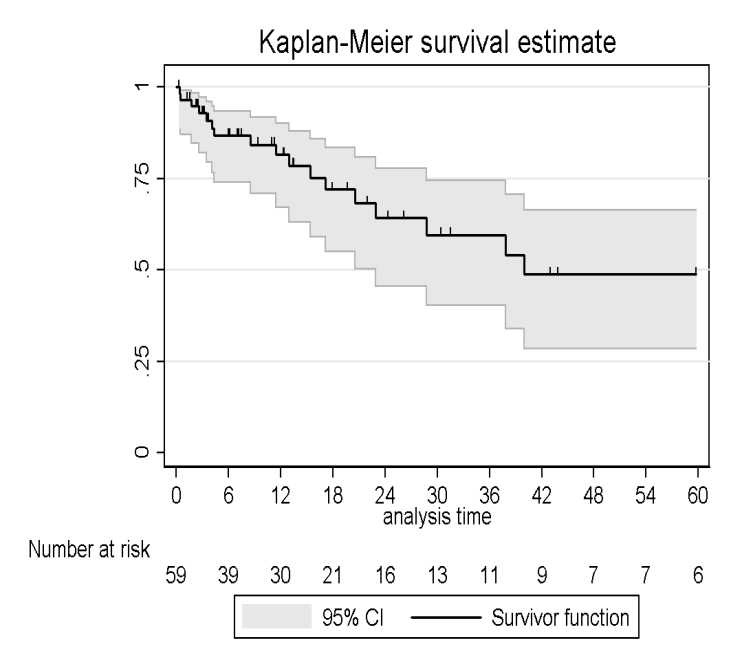
Progression free survival for patients with HER2-therapies was 5.1 mos

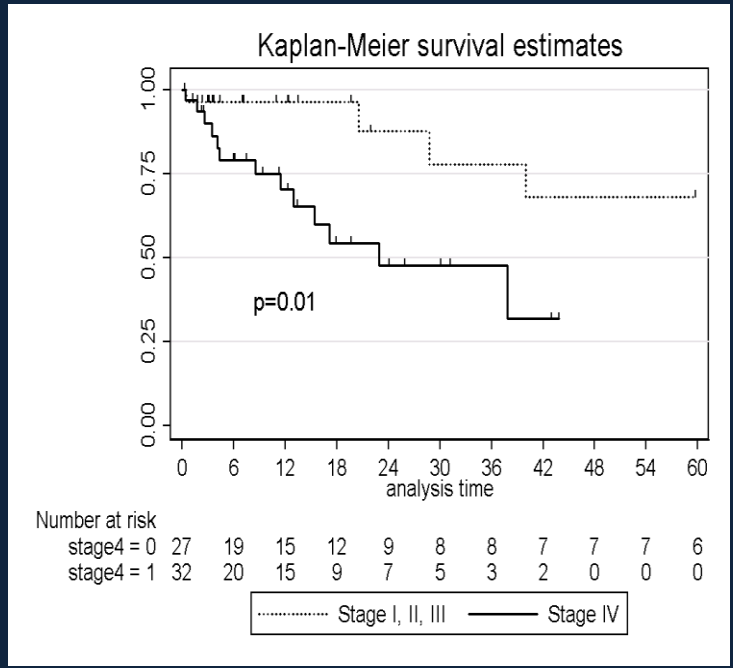



Mazieres and Peters, JCO in press

# Our French/European experience (4)

Median survival was of 89.6 and 22.9 months for early stage and stage IV patients, respectively




Mazieres and Peters, JCO in press

# Conclusions (1)

HER2 mutated NSCLC represent a small distinct subgroup of oncogene addicted cancers with specific demographics and potentially outcomes

Prognostic features related to HER2 mutations remains to be studied in large cohorts of patient

NSCLC patients with mutated *HER2* are mainly female, non-smokers, exclusively suffering from adenocarcinoma subtype

We identified some men and heavy smokers (up to 60 packs-year) suggesting that *HER2* testing should not be restricted to clinically defined subgroups

# Conclusions (2)

Trastuzumab is currently tested as a single-agent in patients with HER2-IHC positive, *HER2*-mutated or *HER2*-amplified NSCLC (NCT00004883 and NCT00758134), as well as in combination with carboplatin and paclitaxel

Pertuzumab is currently tested in a phase II trial in patients with advanced, pretreated NSCLC (NCT00063154)

The relative efficacy of trastuzumab as well as afatinib clearly deserves prospective evaluation in larger prospective international clinical trials

Such a prospective phase II trail is currently under preparation within European Thoracic Oncology Platform in collaboration with large national collaborative groups

# Thanks for your attention

# HER2 mutation description

**TABLE II – *HER2* MUTATIONS IN LUNG ADENOCARCINOMA**

| Case no. | Ethnicity (country) | Mutation (nucleotide) | Mutation (aminoacid) | Reference |
|---|---|---|---|---|
| 60 | Oriental (Japan) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | 28 |
| 79 | Oriental (Japan) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | 28 |
| 438 | Oriental (Taiwan) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | 28 |
| n.i. | Oriental (Japan) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | 29 |
| 189 | Oriental (Japan) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | 28 |
| 276 | Oriental (Japan) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | 28 |
| 11 | Oriental (Taiwan) | 2327–2329 ins (TTT) | G776V, C ins | 28 |
| 135 | Oriental (Japan) | 2327–2329 ins (TTT) | G776V, C ins | 28 |
| 153 | Oriental (Japan) | 2327–2329 ins (TTT), 2326 (G>C) | G776L, C ins | 28 |
| 154 | Oriental (Japan) | 2340–2348 ins (GGGCTCCCC) | GSP 781–783 ins | 28 |
| 254 | Oriental (Japan) | 2341–2349 ins (GGCTCCCCA) | GSP 781–783 ins | 28 |
| 23T | Caucasian (Italy) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | Current study |
| 62T | Caucasian (Italy) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | Current study |
| 157T | Caucasian (Italy) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | Current study |
| 302T | Caucasian (Italy) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | Current study |
| 375T | Caucasian (Italy) | 2325–2336 ins (ATACGTGATGGC) | YVMA 776–779 ins | Current study |
| 478 | Caucasian (Australia) | 2326–2337 ins (TACGTGATGGCT) | YVMA 776–779 ins | 28 |
| 81T | Caucasian (Italy) | 2326–2337 ins (TACGTGATGGCT) | YVMA 776–779 ins | Current study |
| 391T | Caucasian (Italy) | 2326–2337 ins (TACGTGATGGCT) | YVMA 776–779 ins | Current study |
| PD1353a | Not available | 2323–2334 ins (GCATACGTGATG) | AYVM 775–778 ins | 27 |
| PD0258a | Not available | 2323–2334 ins (GCATACGTGATG) | AYVM 775–778 ins | 27 |
| PD0317a | Not available | 2323–2334 ins (GCATACGTGATG) | AYVM 775–778 ins | 27 |
| 525T | Caucasian (Italy) | 2329 (G>T) | V777L | Current study |
| PD0319a | Not available | 2336–2344 (CTGTGGGCT) | VGS 779–781 ins | 27 |
| PD0270a | Not available | 2263–2264 (TT>CC) | L755P | 27 |
| 260T | Caucasian (Italy) | 2263–2264 (TT>CC) | L755P | Current study |

Buttitta, Int J Cancer 2006