# Abstract discussion

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First generation TKI
Gefitinib
Erlotinib

Second generation TKI
Afatinib
Dacomitinib

Third generation TKI
AZ9192
CO1686

Porsche 911

Porsche 911 Turbo

Porsche 911 GT3

Abst 91O

Abst 92O

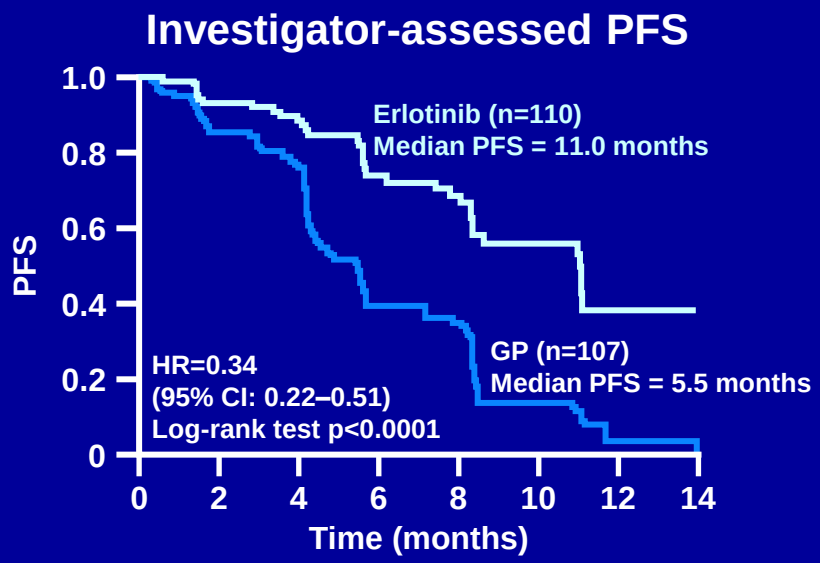
Abst 93O

First generation TKI
Gefitinib
Erlotinib

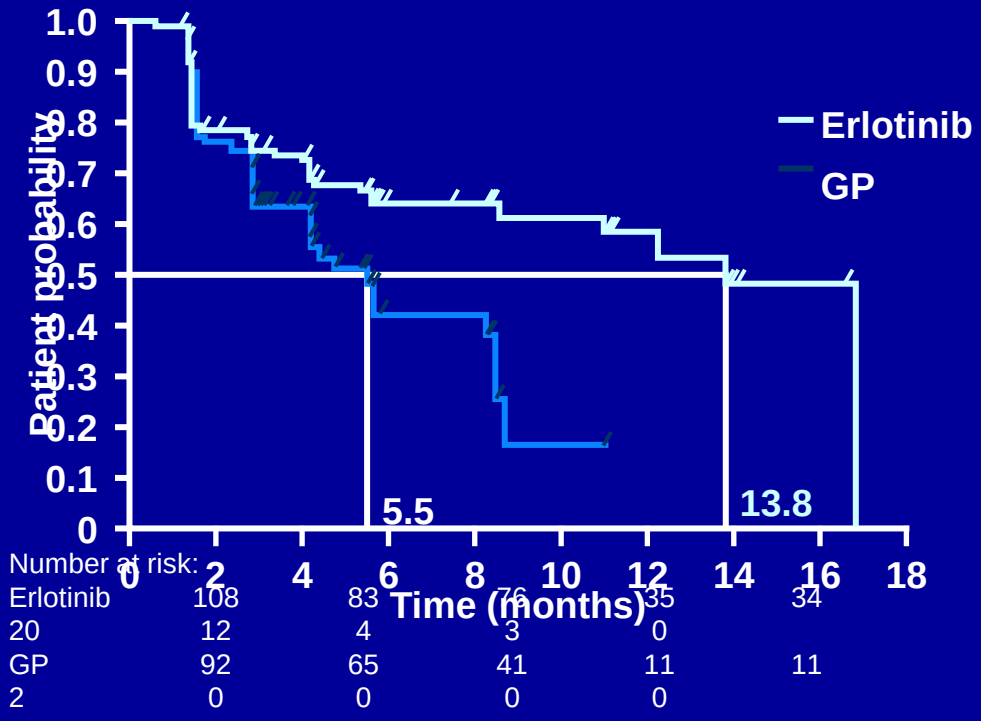
Porsche 911

Abst 91O

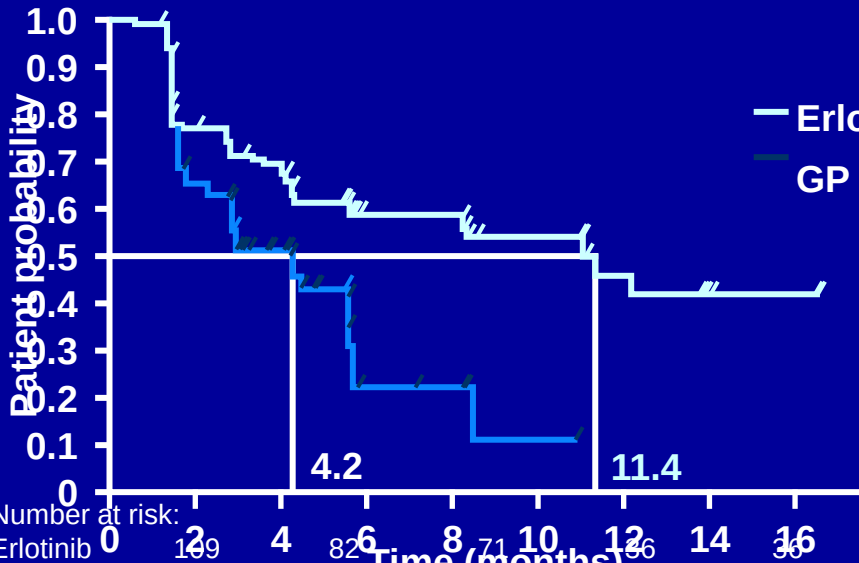
# Abst 91O
# ENSURE study



# Time to deterioration of symptoms and TOI



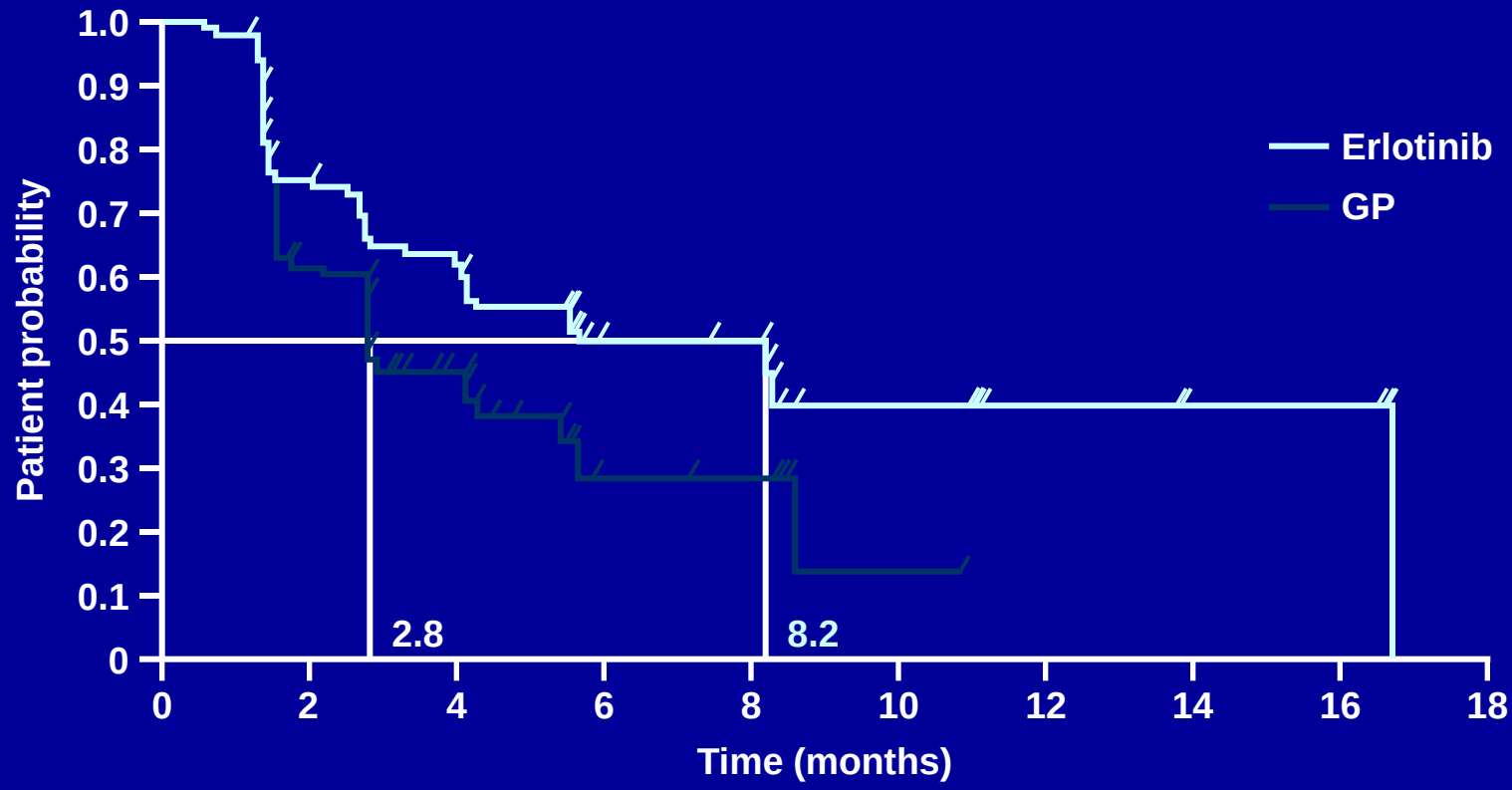

| Number at risk: | | | | | |
|---|---|---|---|---|---|
| Erlotinib | 108 | 83 | 76 | 35 | 34 |
| 20 | 12 | 4 | 3 | 0 | |
| GP | 92 | 65 | 41 | 11 | 11 |
| 2 | 0 | 0 | 0 | 0 | |




| Number at risk: | | | | | |
|---|---|---|---|---|---|
| Erlotinib | 109 | 82 | 71 | 36 | 36 |
| 21 | 11 | 4 | 3 | 0 | |
| GP | 92 | 56 | 31 | 5 | 4 |
| 1 | 0 | 0 | 0 | 0 | |

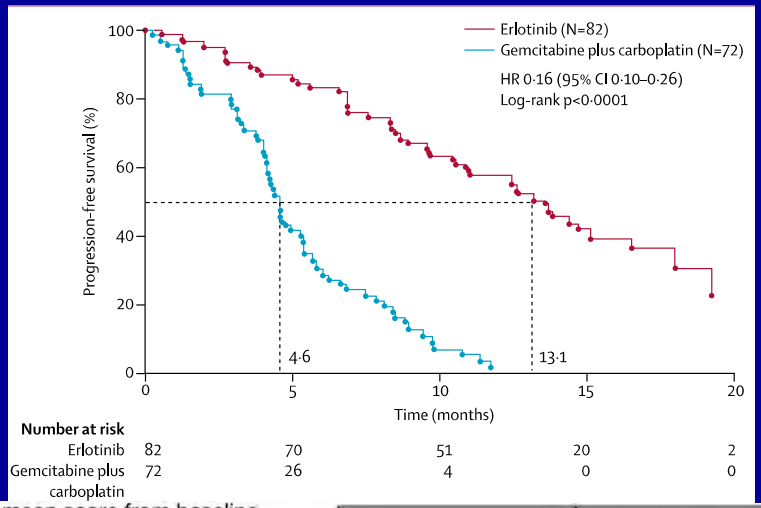
# Time to deterioration in QoL

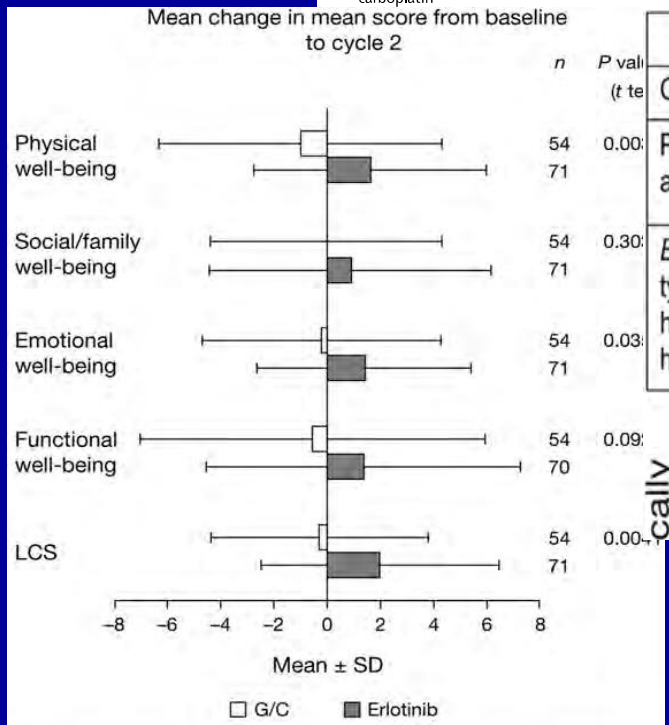
- Median time to deterioration in QoL was 8.2 months for erlotinib and 2.8 months for GP (HR=0.64, 95% CI: 0.44–0.93; p=0.0168)




| Number at risk: | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Erlotinib | 109 | 79 | 66 | 33 | 32 | 14 | 7 | 4 | 4 | 0 |
| GP | 92 | 51 | 27 | 7 | 6 | 1 | 0 | 0 | 0 | 0 |

# Twin findings as OPTIMAL

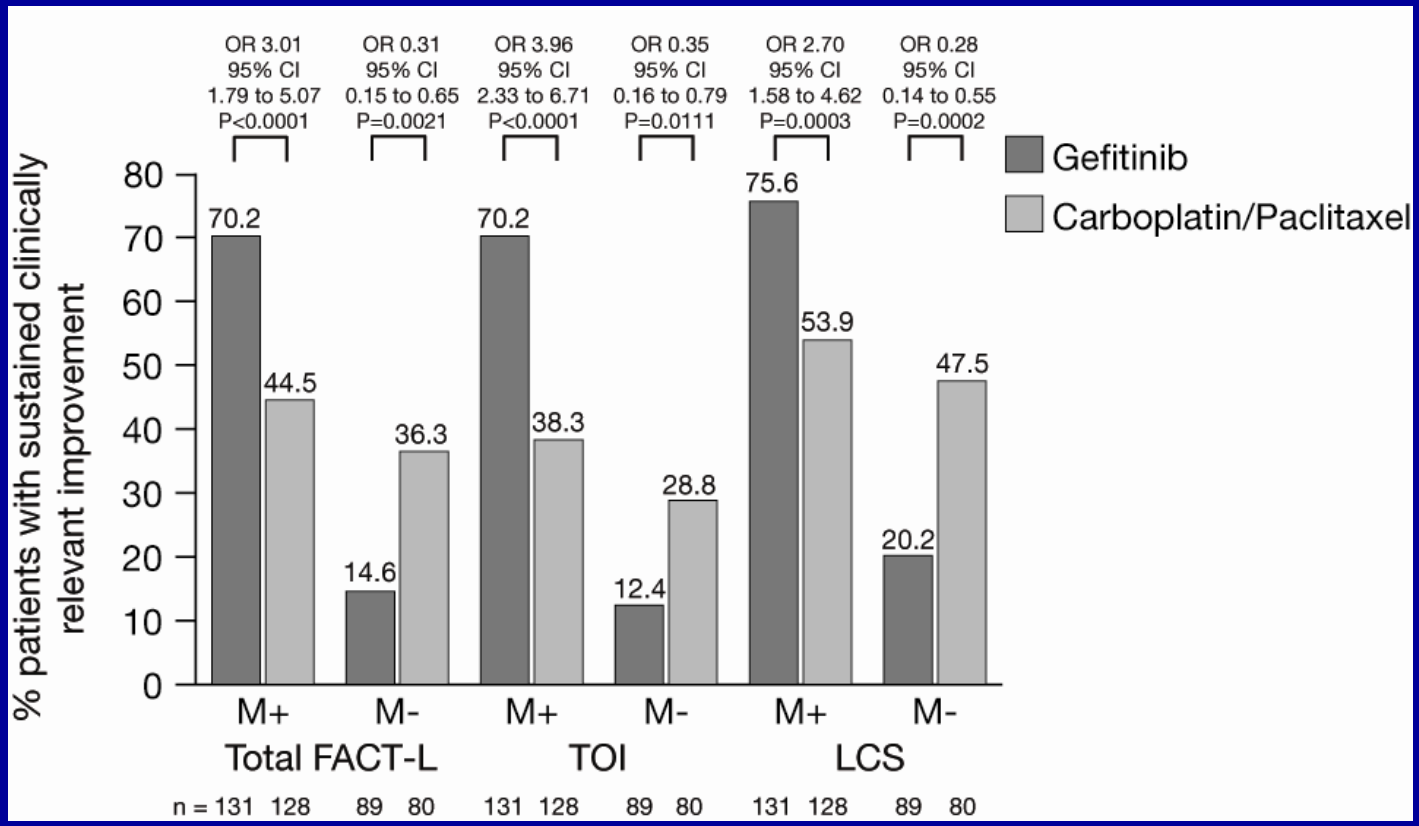



| Covariates | Odds ratio (95% CI) | | |
|---|---|---|---|
| | Total FACT-L | TOI | LCS |
| PS, smoking history and gender | 6.73 (3.01–15.04), $P < 0.0001$ | 7.46 (3.33–16.72), $P < 0.0001$ | 7.22 (3.23–16.13), $P < 0.0001$ |
| *EGFR* mutation type, smoking history and histological type | 6.69 (3.01–14.85), $P < 0.0001$ | 8.07 (3.57–18.26), $P < 0.0001$ | 7.54 (3.38–16.85), $P < 0.0001$ |

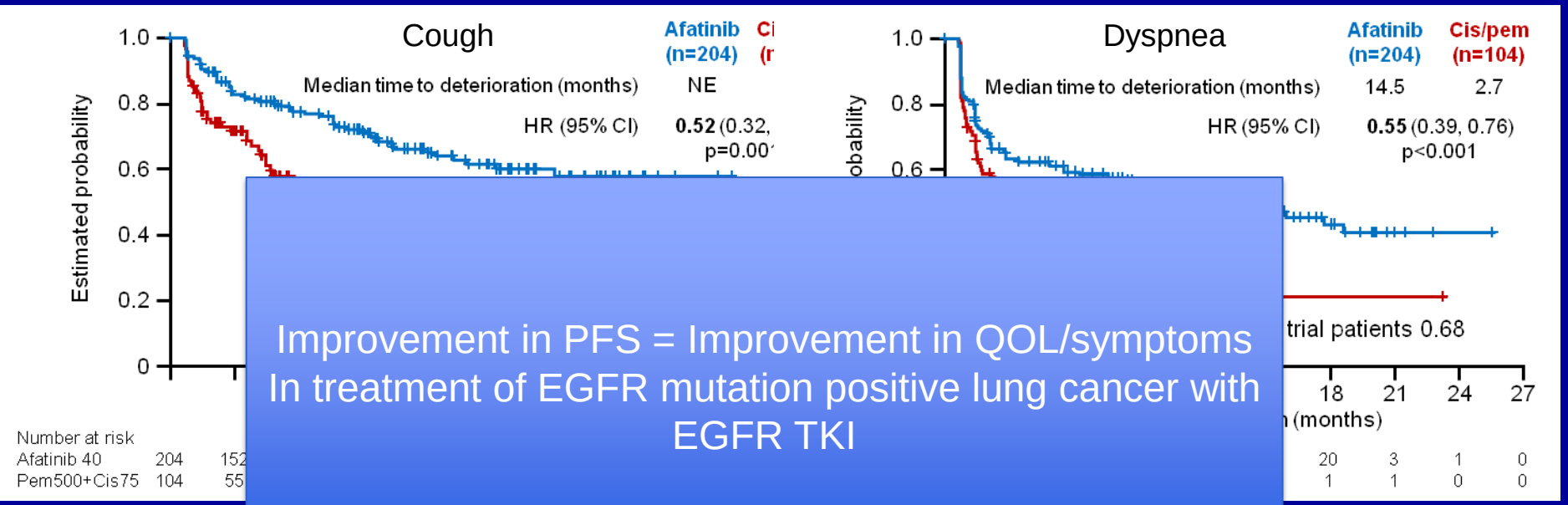

Zhou et al Lancet Oncology 2012
Chen et al Annals Oncology 2013

# Improvement in QOL in IPASS

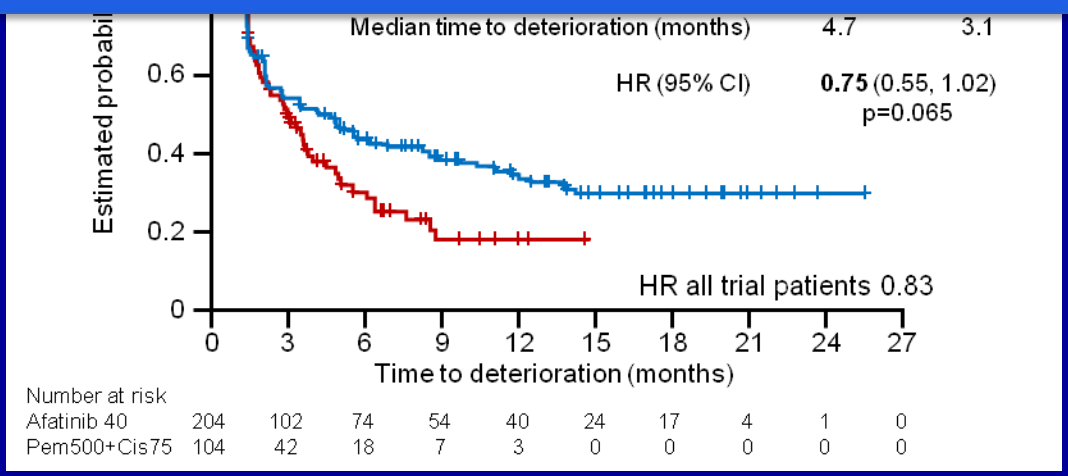



Mok et al NEJM 2009

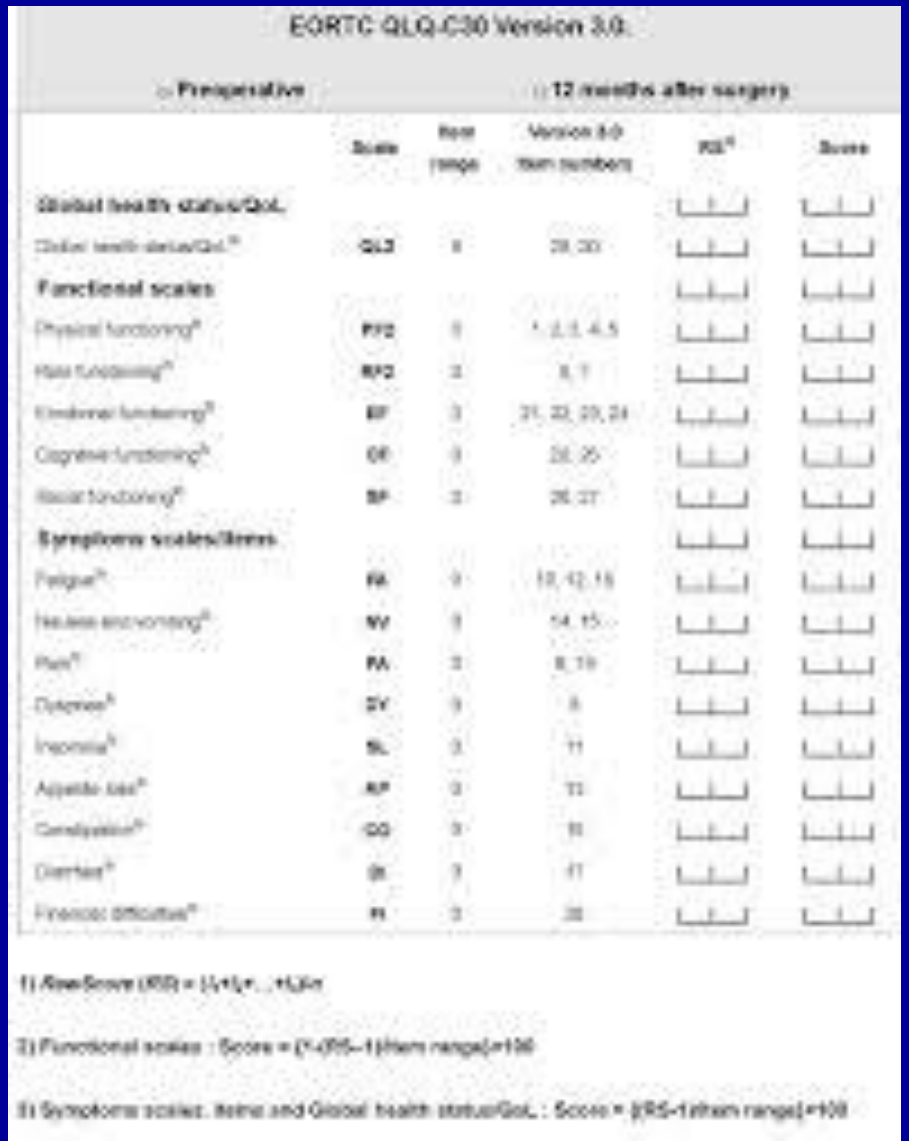
# Improvement in QOL in LUX Lung 3




Improvement in PFS = Improvement in QOL/symptoms
In treatment of EGFR mutation positive lung cancer with EGFR TKI



# Common tool: QLQ-C30



EORTC QLQ-C30 Version 3.0

| Preoperative | | | 12 months after surgery | | |
|---|---|---|---|---|---|
| | Scale | Item range | Version 3.0 item numbers | RS[1] | Score |
| **Global health status/QoL** | | | | | |
| [illegible] | QL2 | 6 | 29, 30 | | |
| **Functional scales** | | | | | |
| Physical functioning[2] | PF2 | 5 | 1, 2, 3, 4, 5 | | |
| Role functioning[2] | RF2 | 2 | 6, 7 | | |
| Emotional functioning[2] | EF | 3 | 21, 22, 23, 24 | | |
| Cognitive functioning[2] | CF | 2 | 20, 25 | | |
| Social functioning[2] | SF | 2 | 26, 27 | | |
| **Symptoms scales/items** | | | | | |
| Fatigue[3] | FA | 3 | 10, 12, 18 | | |
| Nausea and vomiting[3] | NV | 2 | 14, 15 | | |
| Pain[3] | PA | 2 | 8, 19 | | |
| Dyspnoea[3] | DY | 1 | 9 | | |
| Insomnia[3] | SL | 1 | 11 | | |
| Appetite loss[3] | AP | 1 | 13 | | |
| Constipation[3] | CO | 1 | 16 | | |
| Diarrhoea[3] | DI | 1 | 17 | | |
| Financial difficulties[3] | FI | 1 | 28 | | |

1) RawScore (RS) = (x1+x2+...+xn)/n

2) Functional scales : Score = (1-(RS-1)/item range)*100

3) Symptoms scales, items and Global health status/QoL : Score = [(RS-1)/item range]*100

# New tool: QLQ-D5

Quality of life questionnaire for Doctor

# QLQ-D5

| | Score1 | Score2 | Score 3 |
|---|---|---|---|
| Number of golf game per week | 0 | <2 | >2 |
| Nu[illegible] C[illegible] | | | |
| Numb[illegible] call at night per week | | | |
| My nurse hates me | Yes | Not sure | No |
| I rather be a dentist | Yes | Not sure | No |

If score <7, the doctor should use more first line EGFR TKI

First generation TKI
Gefitinib
Erlotinib

Second generation TKI
Afatinib
Dacomitinib

Porsche 911

Porsche 911 Turbo

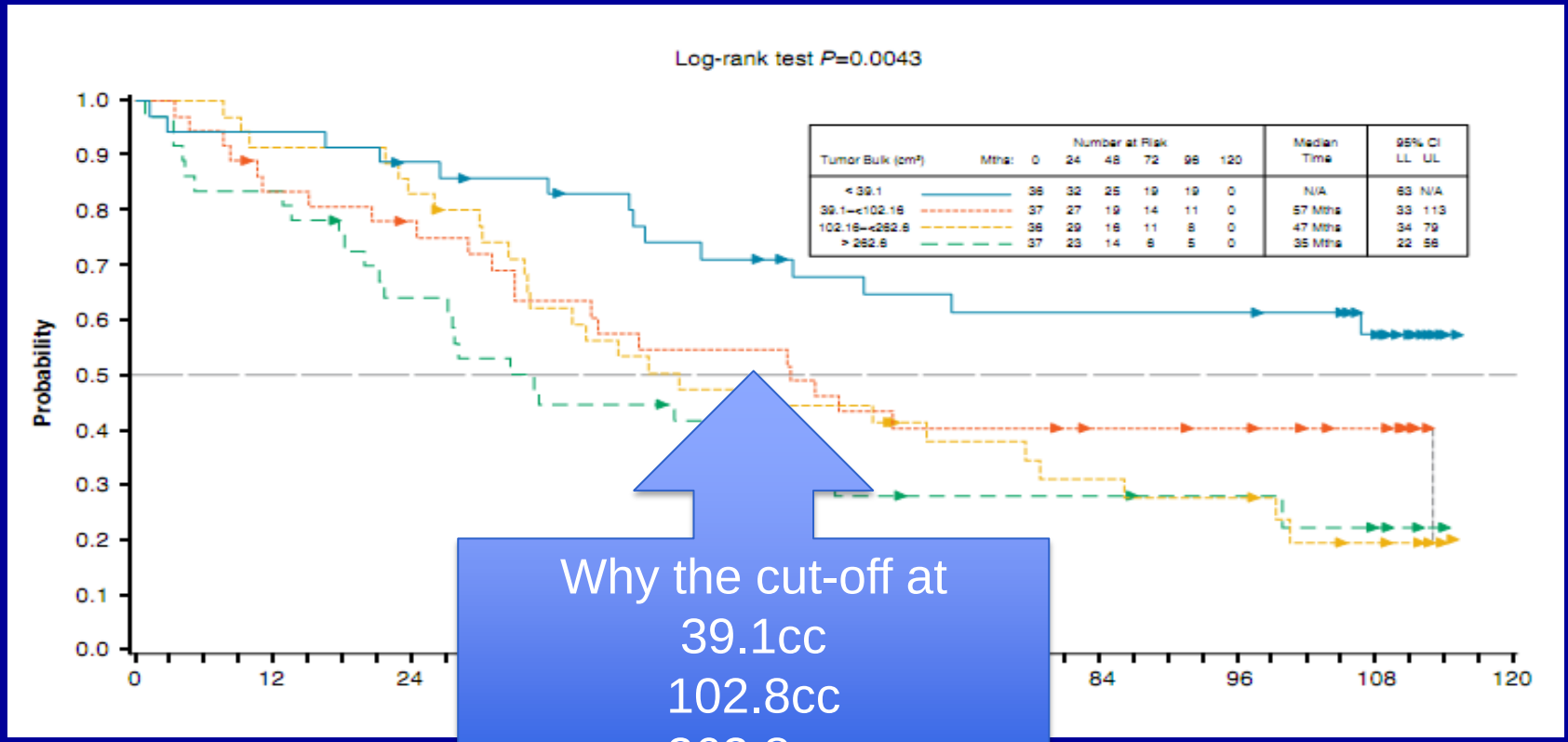
Abst 91O

Abst 92O

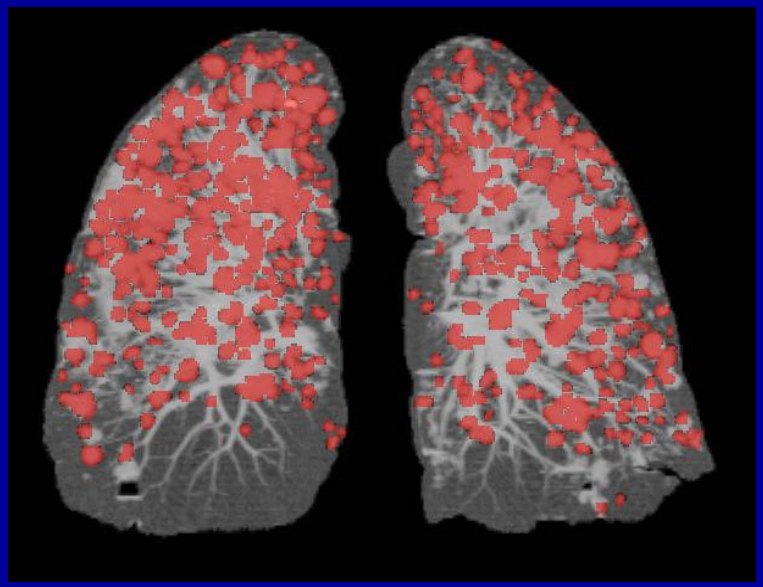
# Abst 92O: Bigger is worse

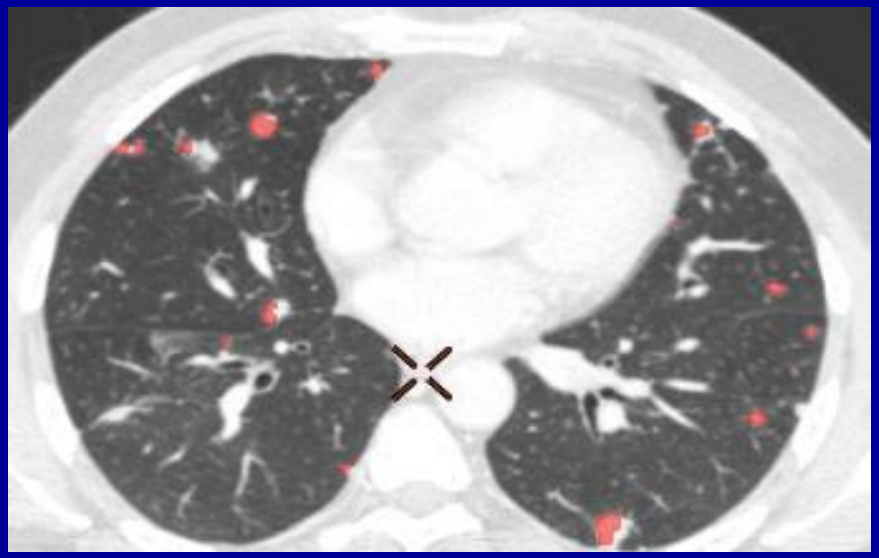
True or False?

# True in GIST

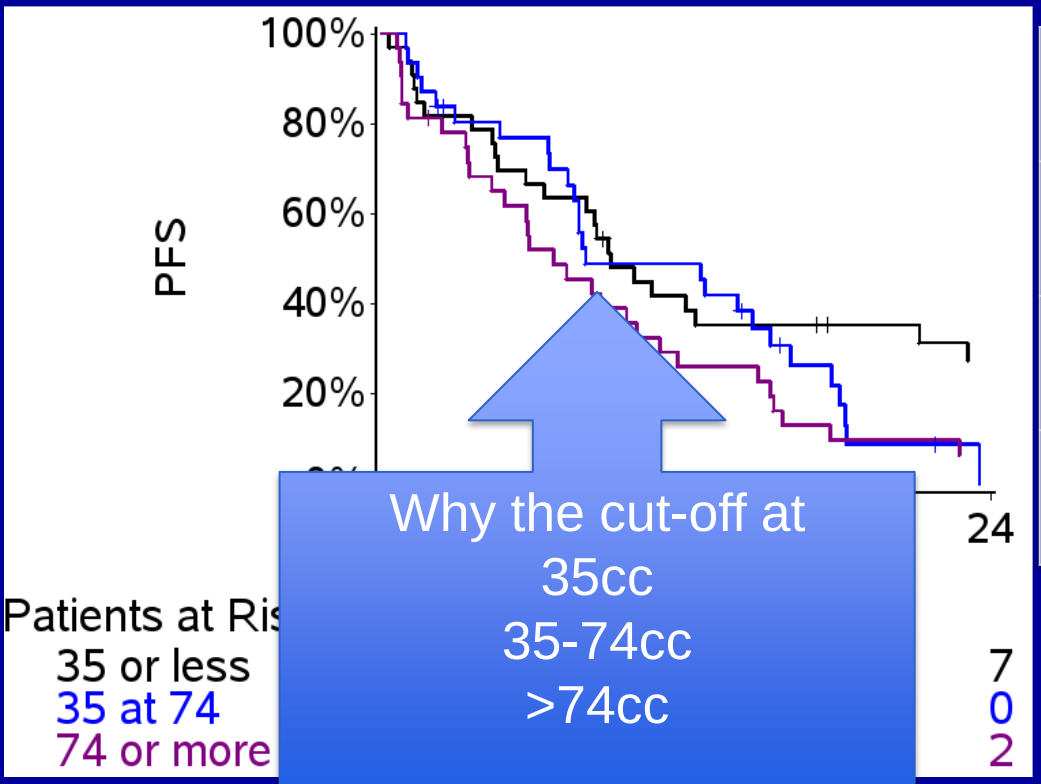

Log-rank test P=0.0043
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
84
96
108
120
Tumor Bulk (cm³)
Mths:
Number at Risk
0 24 48 72 96 120
Median Time
95% CI LL UL
< 39.1 36 32 25 19 19 0 N/A 63 N/A
39.1–<102.16 37 27 19 14 11 0 57 Mths 33 113
102.16–<262.8 36 29 16 11 8 0 47 Mths 34 79
> 262.8 37 23 14 8 5 0 35 Mths 22 56
Why the cut-off at
39.1cc
102.8cc
262.8cc

# My hat off to Charlotte for a painful job well done





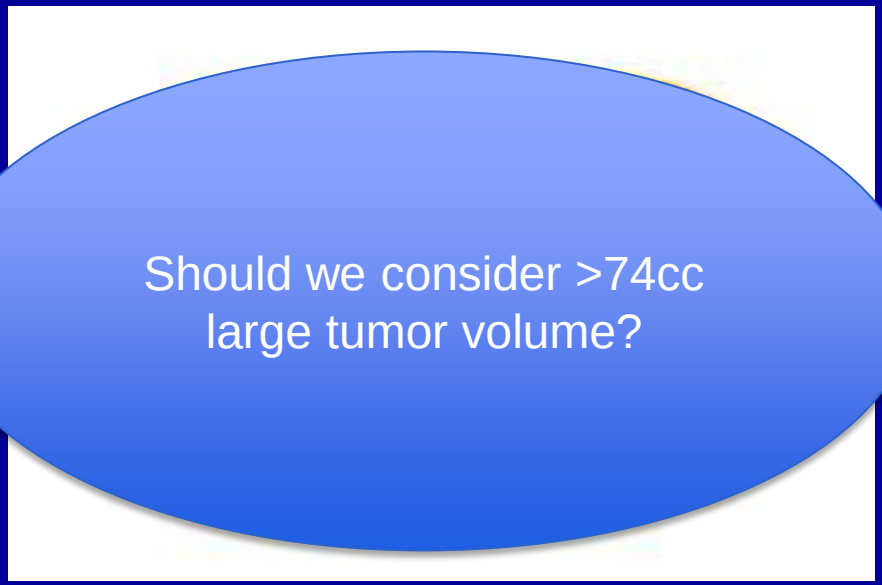
# True for oncogene driven lung cancer?




| | Median PFS (IC95%) | HR (p=0.04*) |
|---|---|---|
| ≤ 35 cm3 | 9.02 (5.67-21.18) | 1 |
| 35 – 74 cm3 | 8.03 (7.34-15.31) | 1.34 [0.77-2.33] |
| > 74 cm3 | 7.28 (4.33-10.07) | 1.70 [1.01-2.84] |

*** Test for trend**

# Volume of an orange?

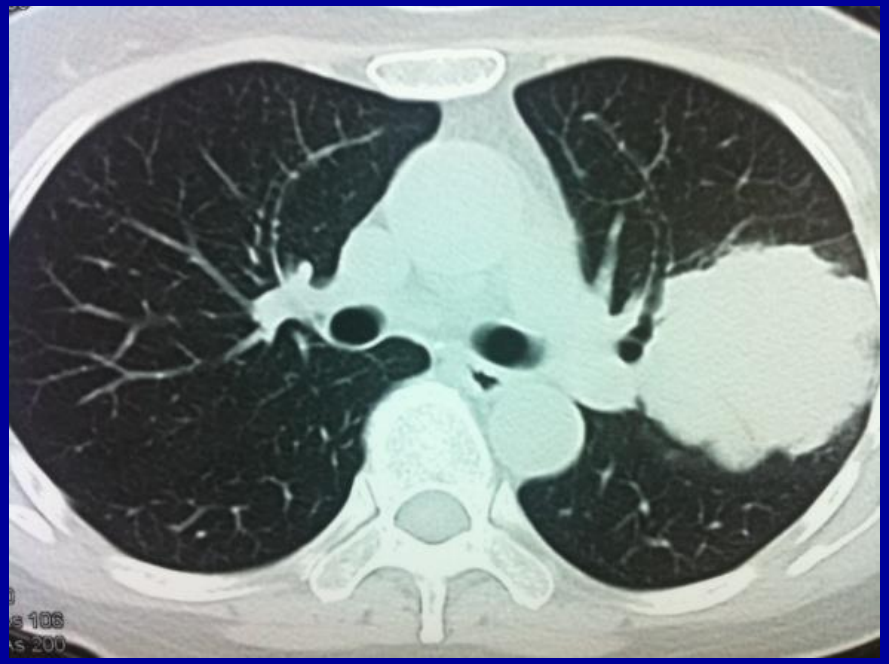



Radius = 4cm

Vol = $(4/3) \times \pi \times R^3$

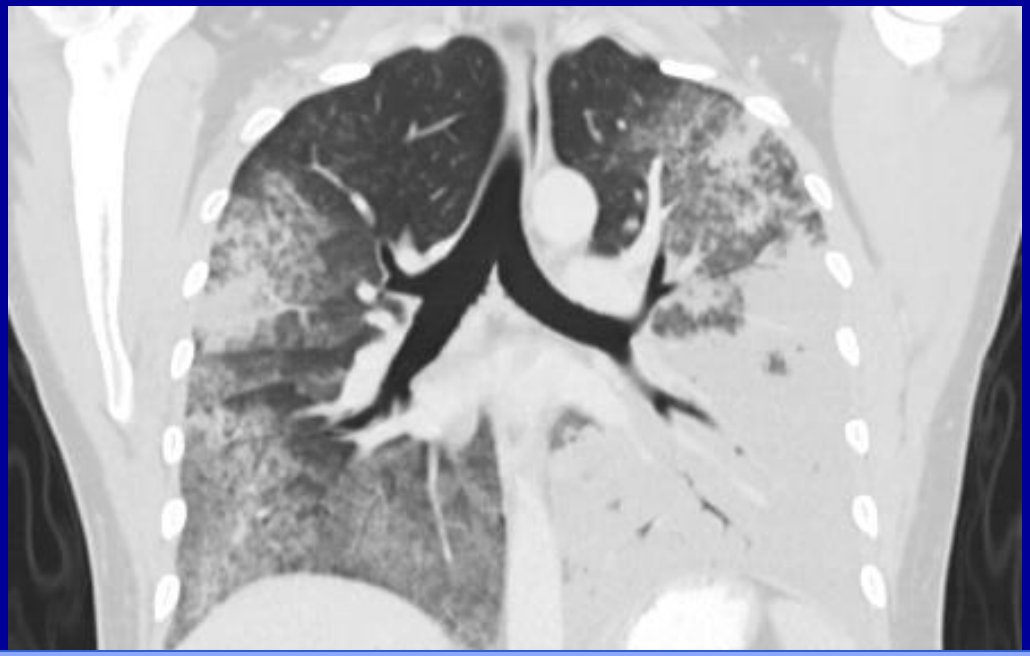
Volume of an average orange = 268 cc

# This is a big tumor in size of an orange



A quarter size may
not be that large

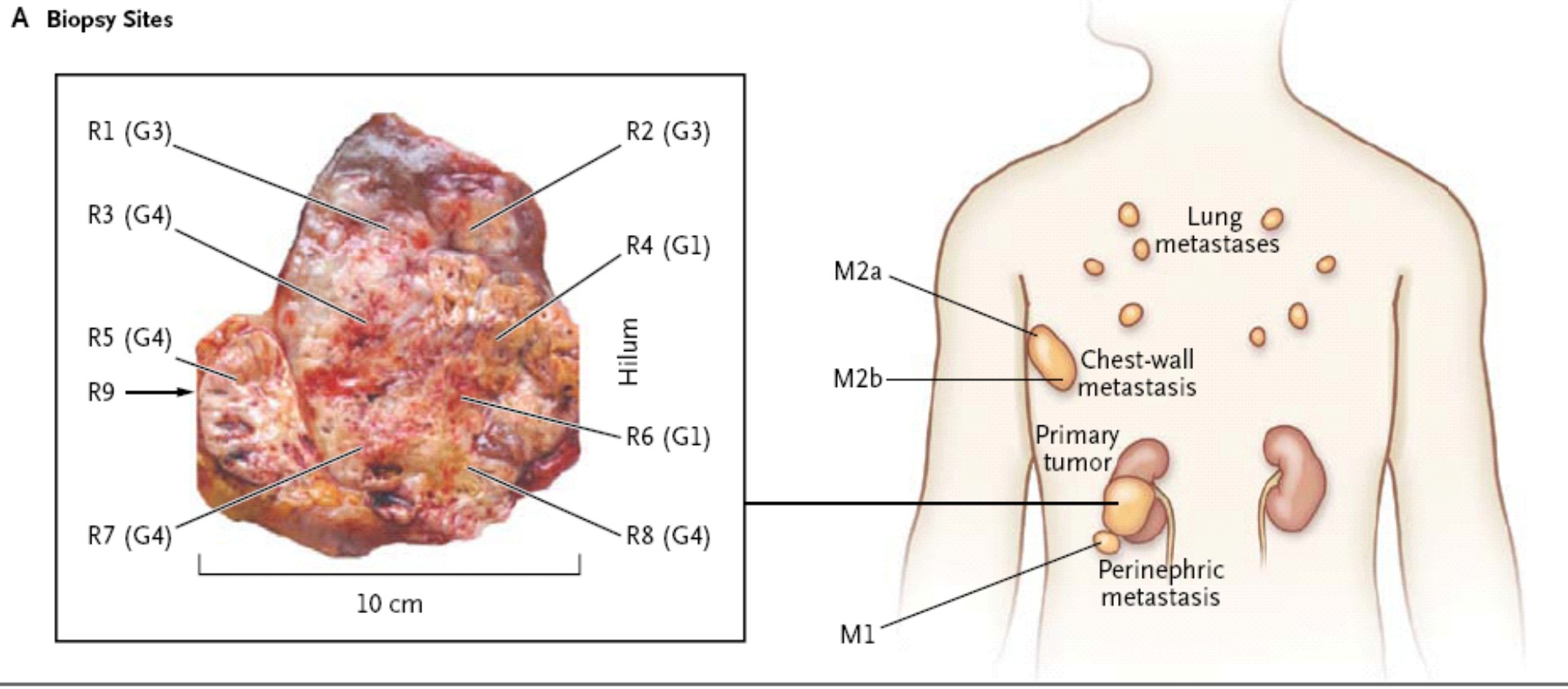
# How to measure volume for this ALK positive tumor?

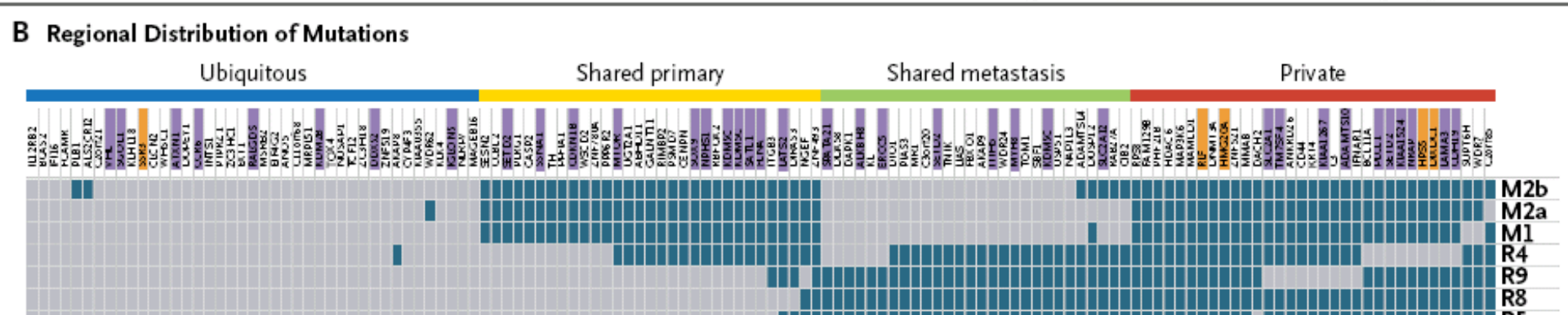


How “big” is big and sometime we cannot measure “big”?

# Why bigger is worse?

# Cancer is heterogenous

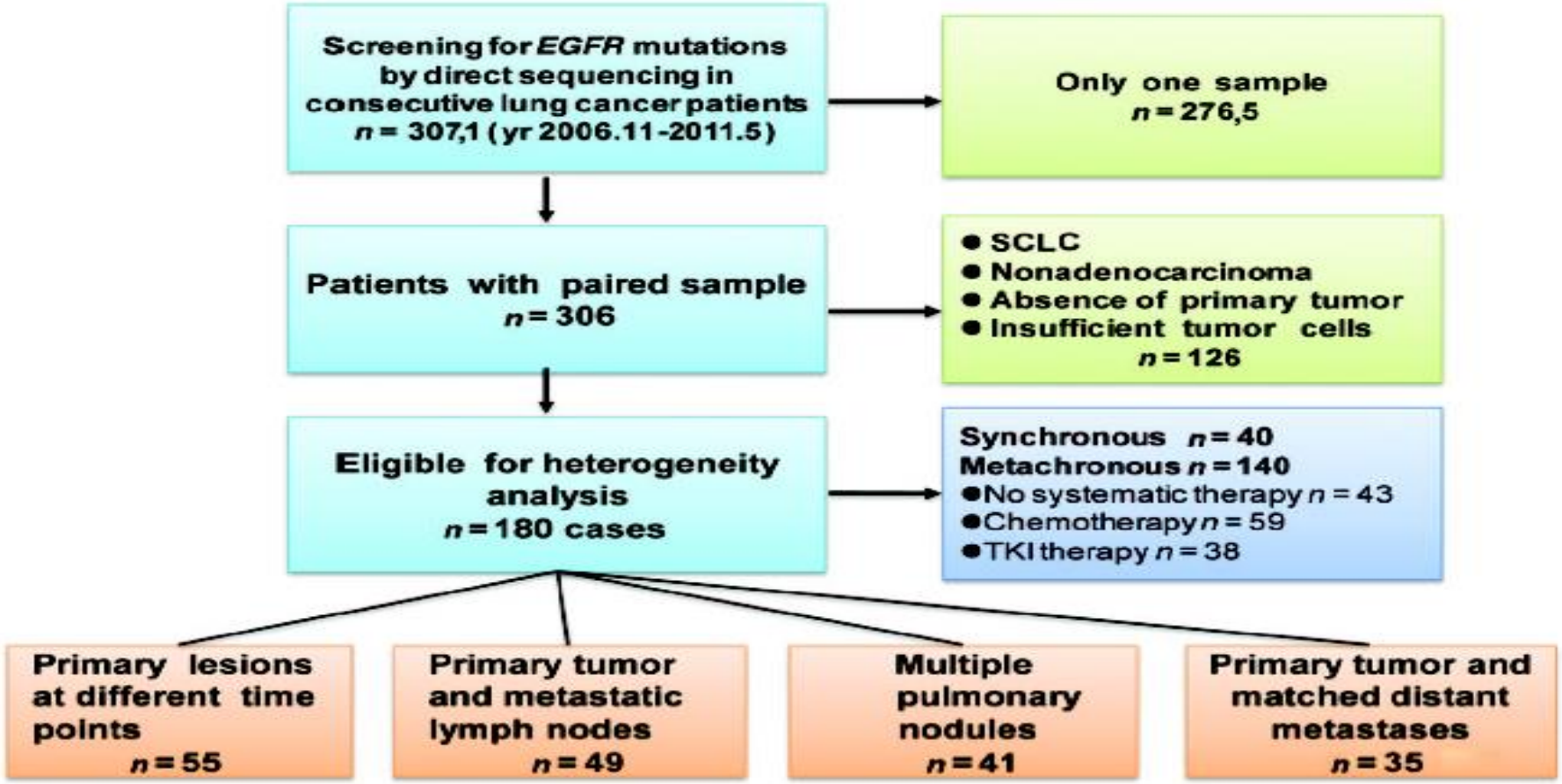


The Oncologist®

# *EGFR* Mutation Heterogeneity and the Mixed Response to EGFR Tyrosine Kinase Inhibitors of Lung Adenocarcinomas

ZHI-YONG CHEN,[a] WEN-ZHAO ZHONG,[a] XU-CHAO ZHANG,[a] JIAN SU,[a] XUE-NING YANG,[a] ZHI-HONG CHEN,[a] JIN-JI YANG,[a] QING ZHOU,[a] HONG-HONG YAN,[a] SHE-JUAN AN,[a] HUA-JUN CHEN,[a] BEN-YUAN JIANG,[a] TONY S. MOK,[b] YI-LONG WU[a]

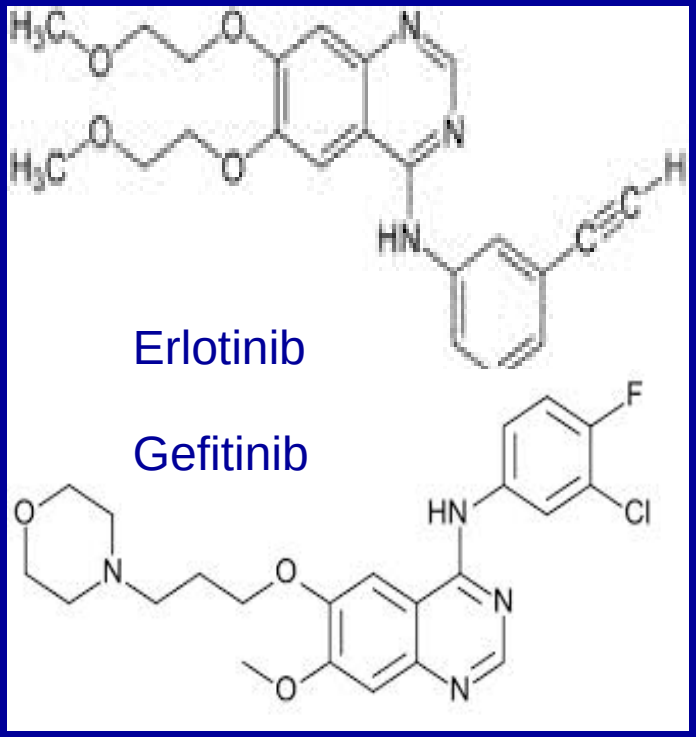



A.
Frequency(%)
60
50
40
30
20
10
0
5(9.1%)
5(10.2%)
(24.4%)
5(14.3%)
85.7%
Considering the bigger size and potential heterogeneity, should we consider second generation TKI?
A: Primary lesions at different time points (n=55)
B: Primary tumor and metastatic lymph nodes (n=49)
C: Multiple pulmonary nodules (n=41)
D: Primary tumor and matched distant metastases (n=35)
Heterogeneity 5 5 10 5
Homogeneity 50 44 31 30

# Unanswered questions

- How to develop better tool to measure tumor volume?
- What is the correlation between “incidence” of T790M mutation and tumor volume?
- What is the correlation between tumor heterogeneity and tumor volume?
- Should we use second generation TKI for bigger tumor?

# Different car, different engine

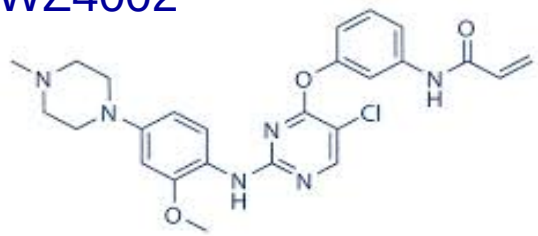


Erlotinib

Gefitinib

CO1686

WZ4002



IMPRESSIVE!!!

# Price to pay

| | CO-1686 HBr all doses TEAEs (N=43) | Placebo arm LUX LUNG-1 TEAEs (N=195)[1] | Placebo arm BR.21 TEAEs (N=242)[2] |
|---|---|---|---|
| Diarrhea | 9 (21%) | 9% | 19% |
| Rash | 2 (5%) | 16% | 17% |

19% Grade 3 hyperglycemia????

# Finding the T790M at time of resistance?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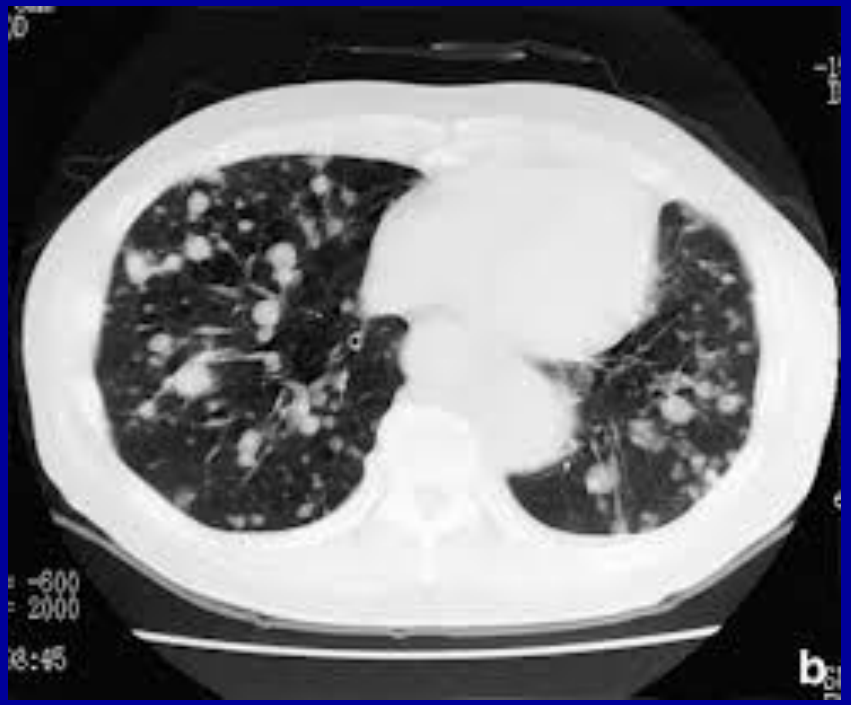


# Detection of T790M by Digital PCR

- Retrospective study of 135 pts on EGFR TKI
  - Test by EGFR T790M mutation (Amoy Diagnostic, China) using Fluidigm digital array chip
  - ARMS
- 11 paired tumor and plasma samples at baseline (by D-PCR)
  - 8/11 tumor positive for T790M
  - 4/8 (50%) detected in plasma

Chen et al WCLC 2013

# T790M Mutations Detected by ARMS and Digital PCR

| ITEM | ARMS No. | ARMS % | Digital PCR No. | Digital PCR % | *P value* |
|---|---|---|---|---|---|
| Pre-TKI patients(109) | | | | | ＜0.001 |
| T790M positive | 6 | 5.5 | 32 | 29.4 | |
| T790M negative | 103 | 94.5 | 77 | 70.6 | |
| Post-TKI patients(135) | | | | | 0.001 |
| T790M positive | 34 | 25.2 | 58 | 43 | |
| T790M negative | 101 | 74.8 | 77 | 57 | |

Digital PCR was more sensitive than ARMs to detect the T790M mutation in plasma

Chen et al WCLC 2013

# Use of Digital PCR for T790M in CO1686 population

| | | Tissue | | | |
|---|---|---|---|---|---|
| | | Activating Mutations | | T790M | |
| | | positive | negative | positive | negative |
| Plasma | positive | 57 | 0 | 21 | 2 |
| | negative | 21 | 23 | 13 | 61 |
| *total* | | 78* | 23 | 34 | 63 |

| | Activatin | T790M |
|---|---|---|
| **PPA (Positive Percent Agreement)** | **73%** | **62%** |
| **NPA (Negative Percent Agreement)** | **100%** | **97%** |
| **(tissue as reference method)** | | |

- Two T790M plasma+/tumor- patients were confirmed plasma-positive by BEAMing
  - May reflect tumor heterogeneity and highlights potential advantages of plasma

- Plasma-/tumor+ patients likely plasma-negative due to biology (low/no ctEGFR$^{mut}$)
  - Several T790M plasma-neg samples also negative by BEAMing (sensitivity <0.02%)

Wakelee et al WCLC 2013

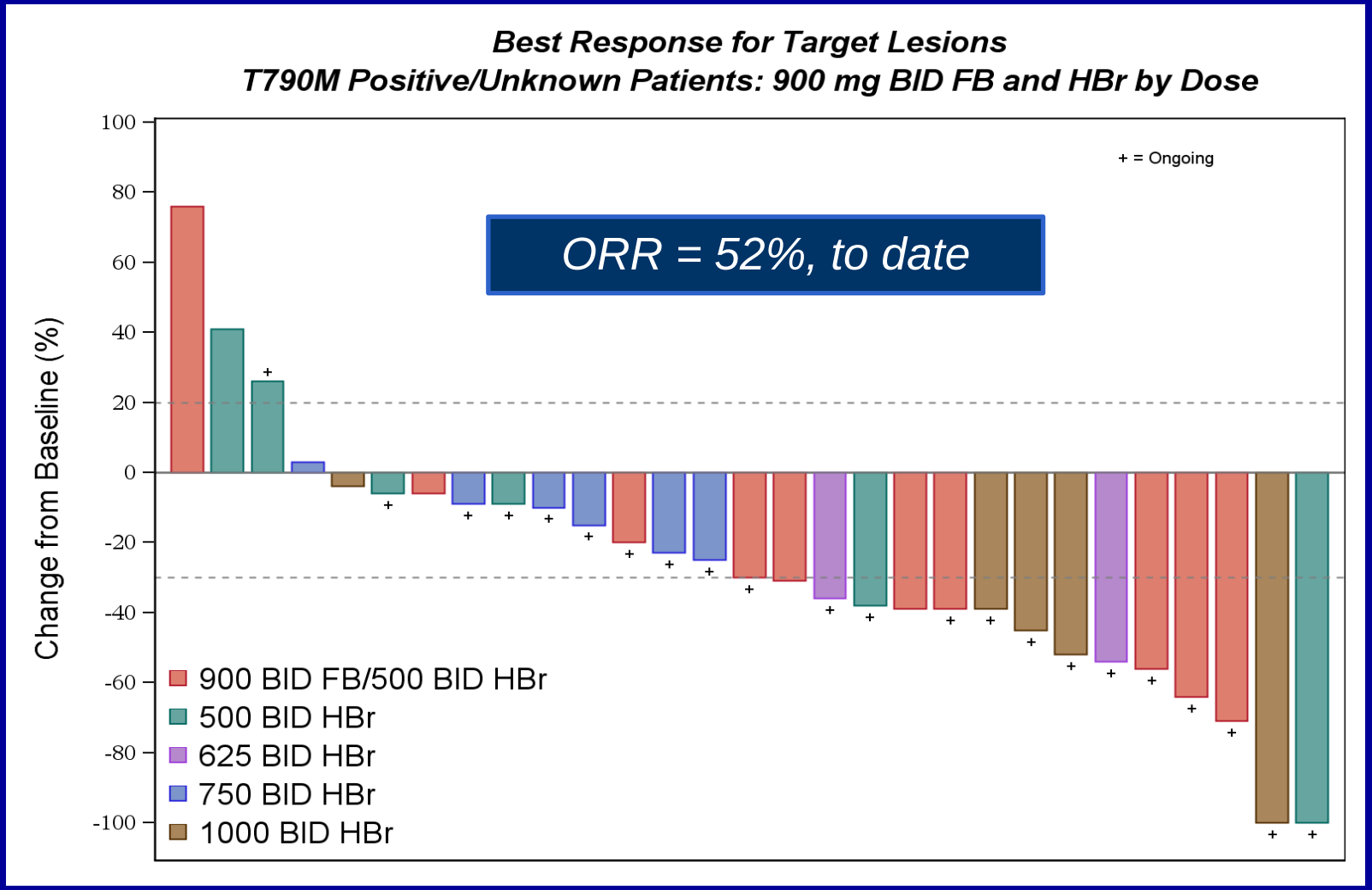
# Strong overall agreement observed between cobas and BEAMing *EGFR* plasma tests

| T790M in plasma | | BEAMing | |
|---|---|---|---|
| | | positive | negative |
| **cobas** | positive | 16 | 1 |
| | negative | 3 | 10 |

- 87% overall agreement between platforms for T790M (n = 30)
  - Similar overall agreement seen for activating mutations (90%)

- 63% of patients with detectable plasma T790M had levels <1% (range: 0.046 – 12%) which supports requirement for highly sensitive detection methods in plasma

# Does CO1686 works in T790M mutation negative patients?



# Unanswered questions

- Should T790M be the standard biomarker for CO1686?
- If so, can we accept T790M positive plasma fDNA analysis?
- Does CO1686 work in T790M negative tumor? If so, why?
- Should a T790M EGFR TKI be used as first line treatment for pts with only sensitizing EGFR mutation?

# Finding answers from a TIGER

A Young Heather Wakelee??

# TIGER Programs

## TIGER1 (Phase 2/3)
- Newly diagnosed EGFRmut NSCLC
- Randomized 1:1 CO-1686:erlotinib
- Primary EP = PFS

CO1686 as first line therapy

## TIGER2 (Phase 2)
- Progression upon 1st and only TKI
- Biopsy-proven T790M+
- Primary EP = ORR

T790M as biomarker

## TIGER3 (Phase 3)
- Progression upon doublet chemotherapy or TKI; and T790M-
- Randomize to CO-1686 vs chemotherapy

Does it work in T790M negative?

## TIGER4 (Phase 2)
- TIGER2-like patients; plasma T790M+

Plasma DNA as serogate biomarker

# Summary

- Yes, we knew that first line EGFR TKI is associated with better QOL (91O)
- Bigger is likely worse (92O)
  - We don’t know how big is big
  - We need to know why big is worse
- T790M specific EGFR TKI is very promising (93O)
  - Need to develop T790M as companion biomarker
  - TIGER is pretty robust

# My Porsche and I