# Disclosures

- Professor Baohui Han
  - *Speakers bureau* – AstraZeneca
  - *Consultant* – Boehringer Ingelheim

# Determining the prevalence of *EGFR* mutations in Asian and Russian patients with advanced NSCLC of adenocarcinoma (ADC) and non-ADC histology: IGNITE study (#233)

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**15-18 April 2015, Geneva, Switzerland**

**Organisers** IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

**Partners** ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop

# Background

- In patients with advanced non-small-cell lung cancer (aNSCLC), accurate / accessible epidermal growth factor receptor (*EGFR*) mutation testing is important to guide treatment decisions[1,2]
- Activating *EGFR* mutations in patients with NSCLC is associated with female gender, Asian ethnicity, never-smokers and tumours of adenocarcinoma (ADC) histology[3]
- Mutation testing is commonly performed using tumour biopsy or cytology samples; however, a proportion of patients do not have a suitable sample available for testing
- The large, multicentre, interventional, non-comparative IGNITE diagnostic study (NCT01788163) will assess the current status of *EGFR* mutation testing in patients with locally advanced or metastatic NSCLC of ADC / non-ADC histology in a real-world setting (Asia-Pacific [AsiaPac] and Russia)

[1]NCCN 2012; [2]NICE 2013; [3]Dearden et al. 2013

# Study design

*Patients were enrolled from China (n=1458), Russia (n=972), Indonesia (n=302), Taiwan (n=271), Singapore (n=102), Thailand (n=94), Australia (n=71), South Korea (n=62) and Malaysia (n=50)*

## Patients

- Patients with newly diagnosed, locally advanced / metastatic chemotherapy-naïve NSCLC not suitable for curative treatment (including surgery and chemoradiotherapy) or
- Recurrent disease after surgical resection with / without adjuvant chemotherapy

## Objectives

To determine:

- *EGFR* mutation frequency (ADC and non-ADC histology) [primary endpoint]
- Concordance between *EGFR* mutation status obtained via tissue / cytology and blood (plasma)-based testing
- Correlations between *EGFR* mutation status and demographic data / disease status
- *EGFR* mutation testing practices
- Treatment decisions following *EGFR* mutation testing

## Statistical analysis

- Sample size: 2500 patients from AsiaPac / 1000 patients from Russia needed to be tested to give similar precision of ADC and non-ADC mutation frequency estimate
- Descriptive summary statistics described *EGFR* mutation frequency, sampling / mutation testing methodologies and treatment decisions
- Concordance rate of *EGFR* mutation status between matched tissue / cytology and plasma samples, pooled test sensitivity, specificity, PPV and NPV; exact 2-sided 95% CIs
- Correlation between *EGFR* mutation status and demographic / disease data analysed with multivariate logistic regression model of *EGFR* mutation status at baseline

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; WHO, World Health Organization
Summary statistics collated for evaluable populations (all patients with known tumour [tissue / cytology] and / or plasma sample *EGFR* mutation status)

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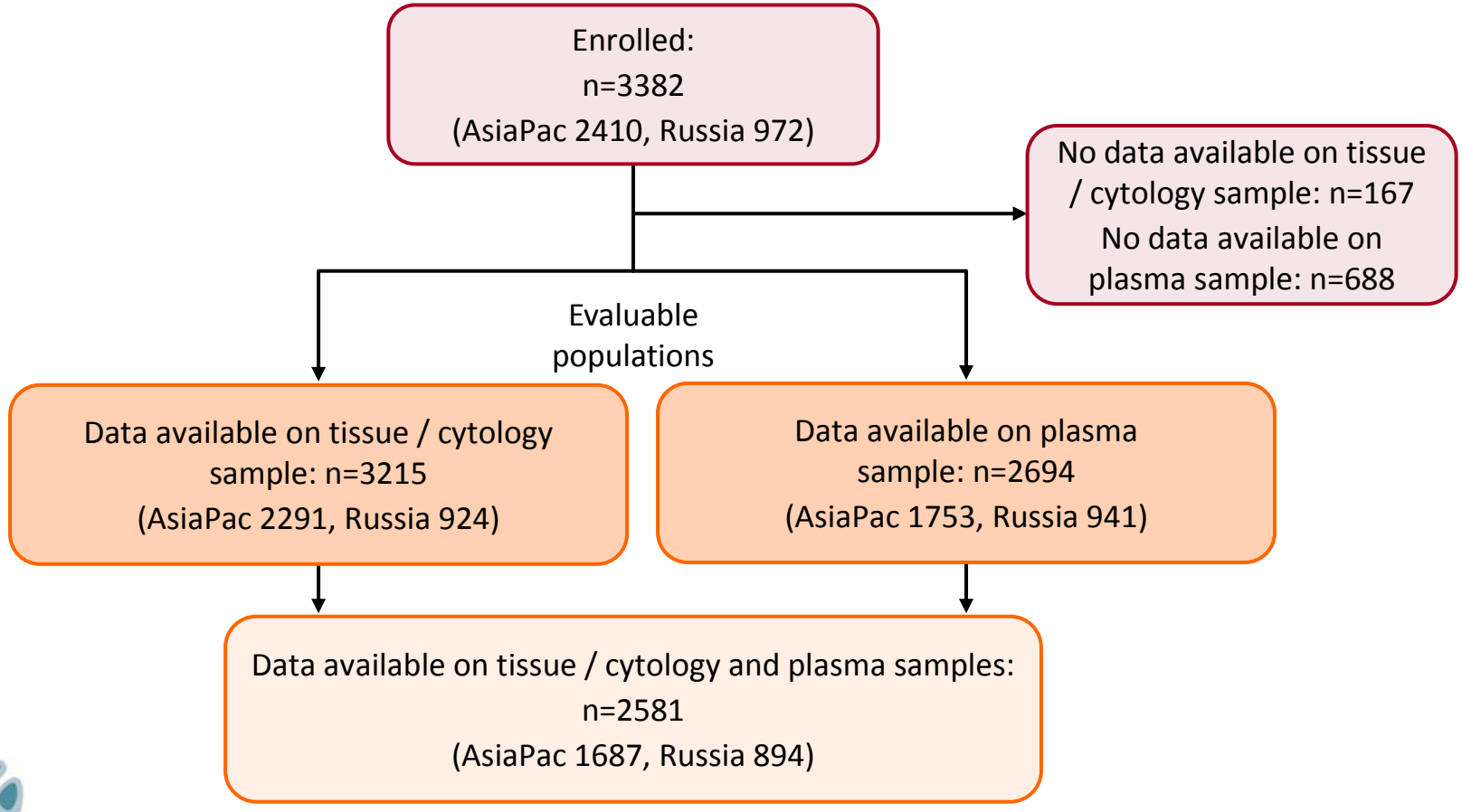
# Patient flow diagram

*First patient enrolled: 27 February 2013; last patient last visit: 25 August 2014*



# Patient demographics

| | Enrolled population | | | Tissue / cytology evaluable | | | Plasma evaluable | | |
|---|---|---|---|---|---|---|---|---|---|
| | AsiaPac (N=2410) | Russia (N=972) | Overall (N=3382) | AsiaPac (N=2291) | Russia (N=924) | Overall (N=3215) | AsiaPac (N=1753) | Russia (N=941) | Overall (N=2694) |
| Age, mean | 60.7 | 59.8 | 60.4 | 60.7 | 59.6 | 60.4 | 61.0 | 59.8 | 60.6 |
| Male, % | 62.8 | 74.8 | 66.2 | 62.7 | 74.7 | 66.2 | 62.8 | 74.6 | 66.9 |
| ***Stage of disease, %*** | | | | | | | | | |
| IIIA | 6.5 | 17.4 | 9.6 | 6.5 | 17.3 | 9.6 | 6.8 | 17.1 | 10.4 |
| IIIB | 12.1 | 18.7 | 14.0 | 12.3 | 19.0 | 14.2 | 13.4 | 18.6 | 15.2 |
| IV | 81.4 | 63.9 | 76.3 | 81.3 | 63.6 | 76.2 | 79.8 | 64.3 | 74.4 |
| ***WHO performance status, %*** | | | | | | | | | |
| 0-1 | 80.8 | 88.2 | 82.9 | 81.3 | 87.8 | 83.2 | 87.1 | 88.1 | 87.5 |
| 2 | 13.2 | 10.9 | 12.5 | 13.1 | 11.3 | 12.6 | 10.1 | 10.9 | 10.4 |
| >2 | 6.0 | 0.9 | 4.5 | 5.5 | 1.0 | 4.2 | 2.8 | 1.0 | 2.2 |
| ***Smoking status*** | | | | | | | | | |
| Never-smoker, % | 47.0 | 29.1 | 41.8 | 47.4 | 28.9 | 42.1 | 48.9 | 29.3 | 42.1 |
| Pack-years, median | 30.0 | 37.0 | 34.0 | 30.0 | 37.0 | 35.0 | 40.0 | 37.0 | 39.0 |

Pack-years: (number of cigarettes smoked per day x number of years smoked) / 20

# *EGFR* mutation frequency

| | Tissue / cytology samples | | Plasma samples | |
|---|---|---|---|---|
| Overall | ADC<br>952/2249 (42.3%) | non-ADC<br>89/927 (9.6%) | ADC<br>397/1814 (21.9%) | non-ADC<br>60/854 (7.0%) |
| AsiaPac | ADC<br>862/1749 (49.3%) | non-ADC<br>75/525 (14.1%) | ADC<br>342/1301 (26.3%) | non-ADC<br>31/445 (6.9%) |
| Russia | ADC<br>90/500 (18.0%) | non-ADC<br>15/402 (3.7%) | ADC<br>55/513 (10.7%) | non-ADC<br>29/409 (7.1%) |

- Immunohistochemistry analyses showed that:
  - 43.9% (351/799) of TTF-1-positive patient samples were *EGFR* mutation-positive
  - 9.8% (25/256) of TTF-1-negative patient samples were *EGFR* mutation-positive

TTF-1, thyroid transcription factor 1

# Correlations between *EGFR* mutation status and demographic / disease status

- Multivariate regression analyses indicated that:
  - ADC histology, never-smoking status, Asian ethnicity significantly correlated with *EGFR* mutation-positive tissue / cytology and plasma sample (all $p<0.01$)
  - female gender significantly correlated with *EGFR* mutation-positive tissue / cytology sample ($p=0.0075$)
  - an association was also seen between plasma *EGFR* mutation and increasing number of metastases ($p<0.0001$) and being aged ≤65 years ($p=0.0009$)

# *EGFR* mutation subtype frequency

*Tissue / cytology*

| | | ADC n/N (%) | non-ADC n/N (%) |
|---|---|---|---|
| ***Subtype (% of overall positive)*** | | | |
| Exon 19 deletion only | AsiaPac | 420/862 (48.7) | 29/74 (39.2) |
| | Russia | 53/90 (58.9) | 6/15 (40.0) |
| L858R only | AsiaPac | 366/862 (42.5) | 41/74 (55.4) |
| | Russia | 23/90 (25.6) | 3/15 (20.0) |
| Exon 20 insertions only | AsiaPac | 20/862 (2.3) | 0/74 (0.0) |
| | Russia | 0/90 (0.0) | 0/15 (0.0) |
| G719X only | AsiaPac | 10/862 (1.2) | 1/74 (1.4) |
| | Russia | 0/90 (0.0) | 0/15 (0.0) |
| L861Q only | AsiaPac | 11/862 (1.3) | 1/74 (1.4) |
| | Russia | 0/90 (0.0) | 2/15 (1.3) |
| Other rare / double mutations[a] | AsiaPac | 35/862 (4.1) | 2/74 (2.7) |
| | Russia | 14/90 (15.5) | 4/15 (26.7) |

*'Other' mutations including T790M*

Exon 19 Del +T790M:
AsiaPac n=1,
Russia n=0

T790M only / T790M + other mutation:
AsiaPac n=4,
Russia n=0

[a]Including L858R + other or Exon 19 deletion + other

# *EGFR* mutation status concordance

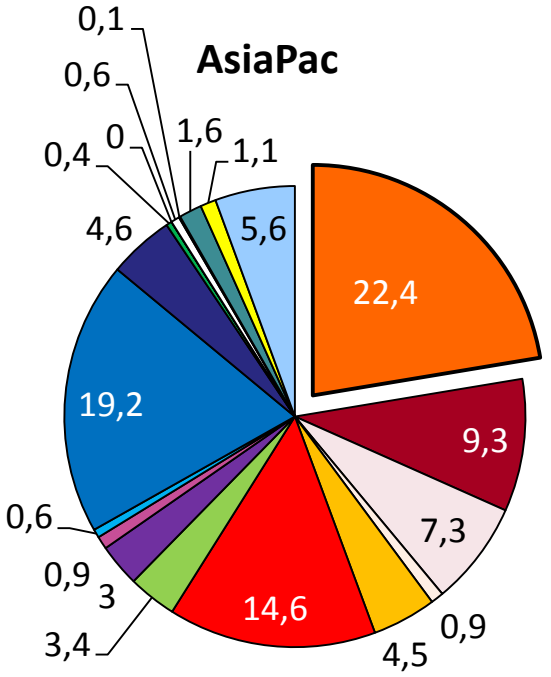
*Matched tissue / cytology and plasma samples*

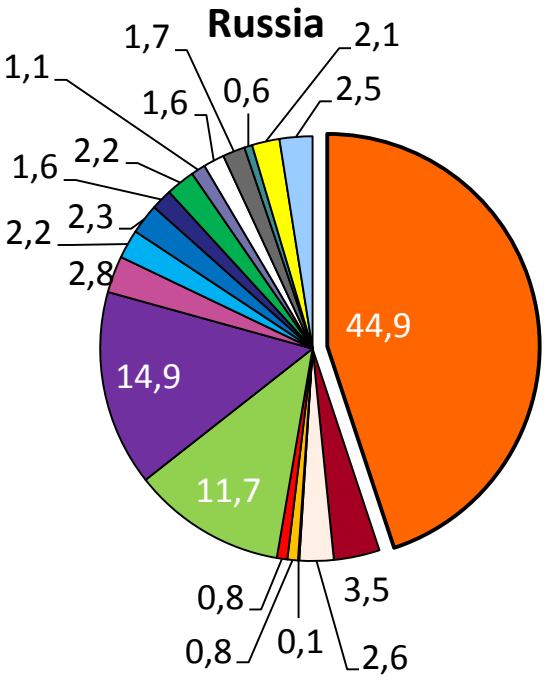
| | Concordance | | Sensitivity | | Specificity | | PPV | | NPV | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n/N (%) | 95% CI | n/N (%) | 95% CI | n/N (%) | 95% CI | n/N (%) | 95% CI | n/N (%) | 95% CI |
| AsiaPac (n=1687) | 1310/1687 (77.7) | 75.6, 79.6 | 343/692 **(49.6)** | 45.8, 53.4 | 967/995 (97.2) | 96.0, 98.1 | 343/371 **(92.5)** | 89.3, 94.9 | 967/1316 (73.5) | 71.0, 75.8 |
| Russia (n=894) | 767/894 (85.8) | 83.3, 88.0 | 33/109 **(30.3)** | 21.8, 39.8 | 734/785 (93.5) | 91.5, 95.1 | 33/84 **(39.3)** | 28.8, 50.5 | 734/810 (90.6) | 88.4, 92.5 |

- Plasma test sensitivity varied by country (30.3–53.8%); however, it was lowest in Russia
- Furthermore, PPV was higher in AsiaPac (92.5%) compared with Russia (39.3%)

# Sampling / *EGFR* mutation testing

*Tissue / cytology – sample collection methods*




- Bronchoscopic
- Core biopsy (NOS)
- Cytology
- Cytology: bronchial washings
- Cytology: fine needle aspiration
- Image-guided core biopsy
- Incisional biopsy
- Lobectomy
- Localisation biopsy
- Mediastinascopic
- Needle biopsy
- Percutaneous core biopsy
- Pneumonectomy: extra pericardial
- Pneumonectomy: intra pericardial
- Segmental excision
- Segmentectomy
- Transbronchial
- Wedge resection
- Other

***Median test turnaround time***

AsiaPac: 6 days (95% CI 8.8, 10.1); Russia: 9 days (95% CI 12.6, 16.0)

***Average test success rate***

AsiaPac: 99.5%; Russia: 98.7%

# 1st-line treatment decisions

*Following* EGFR *mutation testing; tissue / cytology*

| *EGFR* mutation status | AsiaPac | | Russia | |
|---|---|---|---|---|
| | Positive n/N (%) | Negative n/N (%) | Positive n/N (%) | Negative n/N (%) |
| Total | 809/941 (85.9) | 1004/1350 (74.4) | 86/110 (78.2) | 555/814 (68.2) |
| **Therapy** | | | | |
| Gefitinib | 299/809 (37.0) | 11/1004 (1.1) | 24/86 (27.9) | 9/555 (1.6) |
| Erlotinib | 83/809 (10.3) | 7/1004 (0.7) | 3/86 (3.5) | 1/555 (0.2) |
| Afatinib | 18/809 (2.2) | 0/1004 (0.0) | 13/86 (15.1) | 0/555 (0.0) |
| Crizotinib | 0/809 (0.0) | 10/1004 (1.0) | 0/86 (0.0) | 3/555 (0.5) |
| Cisplatin | 131/809 (16.2) | 350/1004 (34.9) | 15/86 (17.4) | 286/555 (51.5) |
| Carboplatin | 128/809 (15.8) | 368/1004 (36.7) | 28/86 (32.6) | 207/555 (37.3) |
| Gemcitabine | 74/809 (9.1) | 291/1004 (29.0) | 2/86 (2.3) | 44/555 (7.9) |
| Paclitaxel | 58/809 (7.2) | 168/1004 (16.7) | 18/86 (20.9) | 148/555 (26.7) |
| Pemetrexed | 143/809 (17.7) | 249/1004 (24.8) | 1/86 (1.2) | 27/555 (4.9) |
| Etoposide | 4/809 (0.5) | 24/1004 (2.4) | 18/86 (20.9) | 226/555 (40.7) |

# Conclusions

- IGNITE is the largest, multicentre real-world observational study of *EGFR* mutation frequency in patients with NSCLC of ADC and non-ADC histologies
- IGNITE further confirms that ADC histology, never-smoking status and Asian ethnicity are significantly correlated with *EGFR* mutation-positive status
- Plasma ctDNA may be used for patients whose tumour sample is not available / evaluable to determine *EGFR* mutation status for patients from AsiaPac
- Investigation of Russian concordance data is ongoing
- *EGFR* mutation status and histology data indicate that *EGFR* mutation testing should be considered in patients with NSCLC of ADC and non-ADC histology

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# IGNITE study PIs

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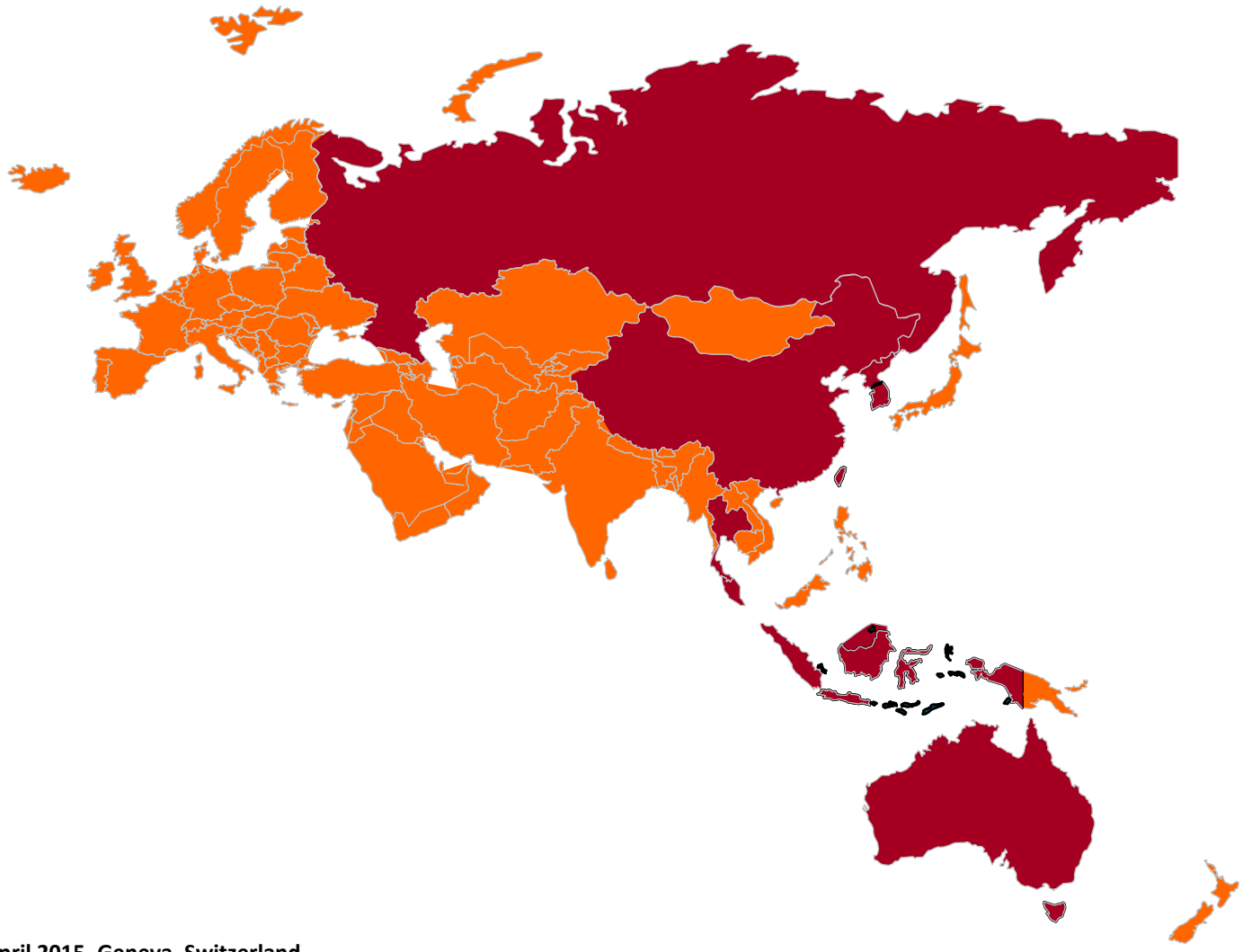
# Additional slides

# Study sites map



Russia (n=972)
Australia (n=71)
China (n=1458)
Indonesia (n=302)
Malaysia (n=50)
Singapore (n=102)
South Korea (n=62)
Taiwan (n=271)
Thailand (n=94)

# Correlations between demographic / disease status factors and *EGFR* mutation status

| Demographic /disease status | Tissue / cytology | | | | Plasma (China / South Korea / Russia / Taiwan only) | | | |
|---|---|---|---|---|---|---|---|---|
| | % | p-value | OR | 95% CI | % | p-value | OR | 95% CI |
| ADC vs non-ADC | 42.3 vs 9.6 | <0.0001 | 3.973 | 2.943, 5.364 | 21.9 vs 7.0 | 0.0002 | 1.955 | 1.377, 2.774 |
| AsiaPac vs Russia | 41.1 vs 11.9 | <0.0001 | 3.929 | 2.977, 5.151 | 21.4 vs 9.2 | <0.0001 | 2.084 | 1.525, 2.848 |
| Never- vs ever-smoker | 52.1 vs 18.6 | <0.0001 | 2.515 | 1.957, 3.233 | 26.3 vs 10.5 | <0.0001 | 2.077 | 1.624, 2.656 |
| Female vs male | 52.5 vs 22.6 | 0.0075 | 1.409 | 1.096, 1.811 | 26.3 vs 12.6 | N/A | N/A | N/A |
| Greater number of organs with metastases, % of patients with *EGFR* mutation-positive NSCLC with 1/2/3/≥4 metastatic organs | 34/39/46/48 | 0.0909 | 1.086 | 0.987, 1.195 | 15/22/30/42 | <0.0001 | 1.386 | 1.242, 1.546 |
| ≤65 vs ≥65 years old | N/A | N/A | N/A | N/A | 18.8 vs 13.8 | 0.0009 | 1.561 | 1.201, 2.028 |

N/A, not applicable; OR, odds ratio

# 1st-line treatment decisions

*Most common treatment choice (mutation status derived from tissue / cytology)*

| | *EGFR* mutation-positive n/N (%) | *EGFR* mutation-negative n/N (%) |
|---|---|---|
| Overall | Gefitinib 323/895 (36.1) | Cisplatin 636/1559 (40.8)<br>Carboplatin 575/1559 (36.9) |
| AsiaPac | Gefitinib 299/809 (37.0) | Carboplatin 368/1004 (36.7)<br>Cisplatin 350/1004 (34.9) |
| Russia | Carboplatin 28/86 (32.6)<br>Gefitinib 24/86 (27.9)<br>Paclitaxel 18/86 (20.9)<br>Etoposide 18/86 (20.9) | Cisplatin 286/555 (51.5)<br>Etoposide 226/555 (40.7) |

Where chemotherapy was most common, two most common chemotherapies reported to reflect doublet-chemotherapy

# 2nd-line *EGFR* mutation-positive NSCLC treatment decisions

*Tissue / cytology*

| | AsiaPac n/N (%) | Russia n/N (%) | Overall n/N (%) |
|---|---|---|---|
| Gefitinib | 25/157 (15.9) | 12/29 (41.4) | 37/186 (19.9) |
| Pemetrexed | 29/157 (18.5) | 1/29 (3.4) | 30/186 (16.1) |
| Erlotinib | 18/157 (11.5) | 4/29 (13.8) | 22/186 (11.8) |
| Cisplatin | 15/157 (9.6) | 1/29 (3.4) | 16/186 (8.6) |
| Carboplatin | 13/157 (8.3) | 1/29 (3.4) | 14/186 (7.5) |
| Docetaxel | 12/157 (7.6) | 0/29 (0.0) | 12/186 (6.5) |
| Afatinib | 3/157 (1.9) | 6/29 (20.7) | 9/186 (4.8) |
| Paclitaxel | 3/157 (1.9) | 3/29 (10.3) | 6/186 (3.2) |
| Bevacizumab | 1/157 (0.6) | 1/29 (3.4) | 2/186 (1.1) |

# *EGFR* mutation status concordance

*Matched tissue / cytology samples: same vs different mutation test methods*

| | Overall (N=2581) | | Same method (N=946) | | Different methods (N=1635) | |
|---|---|---|---|---|---|---|
| | % | Exact 95% CI for % | % | Exact 95% CI for % | % | Exact 95% CI for % |
| Concordance | 80.5 | 78.9, 82.0 | 79.4 | 76.7, 81.9 | 81.1 | 79.1, 83.0 |
| Sensitivity | 46.9 | 43.4, 50.5 | 49.6 | 44.2, 54.9 | 44.9 | 40.2, 49.6 |
| Specificity | 95.6 | 94.5, 96.5 | 97.0 | 95.3, 98.2 | 94.9 | 93.4, 96.0 |
| PPV | 82.6 | 78.8, 86.0 | 90.6 | 85.6, 94.3 | 76.8 | 71.2, 81.8 |
| NPV | 80.0 | 78.2, 81.7 | 76.5 | 73.3, 79.5 | 81.9 | 79.8, 83.9 |

Same methods were either QIAGEN Therascreen® (141/173) or PNA-LNA Clamp (32/173)

Identical methods used in a subset of 173 matched samples from Russia only had minimal / no improvement in sensitivity (30.0% vs 25.9% in original sample vs Russian subset sample) and PPV (39.3% vs 46.7% in original sample vs Russian subset sample)

# Tissue / cytology *EGFR* mutation-negative and plasma *EGFR* mutation-positive samples

| | Russia (n=51) | AsiaPac (n=28) |
|---|---|---|
| Patient characteristics | • 31% never-smokers<br>• 53% ADC histology<br>• 25% female<br>Low proportion have characteristics associated with *EGFR* mutation-positive status | • 57% never-smokers<br>• 82% ADC histology<br>• 43% female<br>High proportion have characteristics associated with *EGFR* mutation-positive status |
| Tumour sampling / mutation test methods | • 8% cytology / needle biopsy<br>• 10% tested by DNA sequencing | • 39% cytology / needle biopsy<br>• 18% tested by DNA sequencing / pyrosequencing |

False-negative tumour results likely accounted for a small proportion of discordant results in Russia and a substantial proportion of discordant results in AsiaPac

# Concordance data from Russian cohort

*QIAGEN Therascreen® EGFR RGQ PCR kit performance*

| | QIAGEN Therascreen® EGFR RGQ PCR kit used for tissue / cytology and plasma testing | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Russia (n=941) | | China (n=193) | | Taiwan (n=137) | | IFUM[1] (n=652) | |
| | n/N (%) | 95% CI | n/N (%) | 95% CI | n/N (%) | 95% CI | % | 95% CI |
| Concordance | 119/141 (84.4) | 77.3, 90.0 | 150/193 (77.7) | 71.2, 83.4 | 107/137 (78.1) | 70.2, 84.7 | 94.3 | 92.3, 96.0 |
| Sensitivity | 2/21 **(9.5)** | 1.2, 30.4 | 40/81 **(49.4)** | 38.1, 60.7 | 32/61 **(52.5)** | 39.3, 65.4 | **65.7** | 55.8, 74.7 |
| Specificity | 117/120 (97.5) | 92.9, 99.5 | 110/112 (98.2) | 93.7, 99.8 | 75/76 (98.7) | 92.9, 100.0 | 99.8 | 99.0, 100.0 |
| PPV | 2/5 **(40.0)** | 5.3, 85.3 | 40/42 **(95.2)** | 83.8, 99.4 | 32/33 **(97.0)** | 84.2, 99.9 | **98.6** | 92.3, 100.0 |
| NPV | 117/136 (86.0) | 79.0, 91.4 | 110/151 (72.8) | 65.0, 79.8 | 75/104 (72.1) | 62.5, 80.5 | 93.8 | 91.5, 95.6 |

- Sensitivity and PPV are higher when used in China and Taiwan compared with Russia; may be due to pre-analytics (e.g. plasma sample handling) or differences in DNA extraction method
- Further analysis of Russian concordance data ongoing

IFUM study: Phase IV, open-label, study of *EGFR* mutation status of both tissue / cytology and ctDNA samples from Caucasian patients with *EGFR* mutation-positive NSCLC

[1]Douillard et al. 2014

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# Sampling methodologies

*Tissue / cytology*

The majority of tissue / cytology samples were:

- obtained during **current diagnosis** (AsiaPac 93.7%, Russia 74.1%)
- derived from the **primary tumour** (AsiaPac 67.1%, Russia 80.3%)
- sampled from the **lung / lymph nodes** (AsiaPac 68.3%, Russia 79.8% / AsiaPac 14.1%, Russia 10.2%)
- collected via **bronchoscopy** (AsiaPac 22.4%, Russia 44.9%)

Tissue / cytology samples were predominantly stored as **FFPE tissue blocks** (AsiaPac 74.6%, Russia 91.2%) and fixed with **10% neutral buffered formalin** (AsiaPac 74.4%, Russia 84.4%)

- Mutation tests not performed on the tissue / cytology samples of 262 patients
- Most common reason for not testing was insufficient material provided for the test (AsiaPac 84.0%, Russia 50.0%)

FFPE, formalin-fixed paraffin embedded

**15-18 April 2015, Geneva, Switzerland**

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# Sampling methodologies

*Sample site*

| | AsiaPac | Russia |
|---|---|---|
| Adrenal | 0 (0.0) | 4 (0.4) |
| Ascites | 0 (0.0) | 0 (0.0) |
| Bone | 45 (1.9) | 19 (2.0) |
| Brain | 13 (0.5) | 15 (1.5) |
| Liver | 8 (0.3) | 6 (0.6) |
| Lung | 1646 (68.3) | 776 (79.8) |
| Lymph nodes | 340 (14.1) | 99 (10.2) |
| Pericardial effusion | 16 (0.7) | 0 (0.0) |
| Pleura | 92 (3.8) | 30 (3.1) |
| Pleural effusion | 192 (8.0) | 8 (0.8) |
| Skin / soft tissue | 12 (0.5) | 8 (0.8) |
| Other | 46 (1.9) | 7 (0.7) |

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