Disclosures

- Dr Martin Reck
  - *Speakers bureaux* – F Hoffmann-La Roche, Lilly, Bristol-Myers Squibb, AstraZeneca, Pfizer, Daiichi-Sankyo, Boehringer Ingelheim
  - *Consultant* – F Hoffmann-La Roche, Lilly, Bristol-Myers Squibb, AstraZeneca, Pfizer, Daiichi-Sankyo, Boehringer Ingelheim, MSD

Investigating the utility of ctDNA in plasma for the detection of *EGFR* mutation status in European and Japanese patients with advanced NSCLC: ASSESS study (#229)

Martin Reck,[1] Koichi Hagiwara,[2] Baohui Han,[3] Sergei Tjulandin,[4] Christian Grohé,[5] Takashi Yokoi,[6] Alessandro Morabito,[7] Rose McCormack,[8] Marianne Ratcliffe,[8] Nicola Normanno[9]

[1]Department of Thoracic Oncology, LungenClinic Grosshansdorf, Grosshansdorf, Airway Research Center North (ARCN), Member of the German Centre for Lung Research (DZL), Germany; [2]Jichi Medical University, Saitama Medical Center, Saitama-ken, Japan; [3]Department of Respiratory Medicine, Shanghai Chest Hospital, Jiao Tong University, Shanghai, China; [4]Department of Clinical Pharmacology and Chemotherapy, Russian Cancer Research Centre, Moscow, Russia; [5]Arzt für Innere Medizin, Pneumologie und Kardiologie, Evangelische Lungenklinik Berlin, Germany; [6]The Department of Thoracic Oncology, Kansai Medical University Hirakata Hospital, Osaka, Japan; [7]Thoraco-Pulmonary Department, Instituto Nazionale Tumori-Fondazione Pascale, Napoli, Italy; [8]AstraZeneca, Macclesfield, UK; [9]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori "Fondazione Giovanni Pascale", IRCCS, Napoli, Italy

elcc

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 and accessible epidermal growth factor receptor *(EGFR)* mutation testing is important to guide treatment decisions[1-2]
  - EGFR tyrosine kinase inhibitors have demonstrated superior efficacy to doublet chemotherapy in patients with *EGFR* mutation-positive aNSCLC[3-7]
  - Global testing practices and processes are unknown, as they vary between hospitals, within and between countries, and across different regions or continents
- Mutation status is commonly tested via tissue or cytology samples; however not all patients have an available and evaluable sample
  - *EGFR* mutations can be detected in circulating free tumour-derived DNA (ctDNA) present in the plasma of patients with aNSCLC as an alternative sample type[8-11]
  - Further work is required to ascertain the utility of ctDNA for EGFR mutation analysis in real-world practice
- The large, multicentre, non-interventional, non-comparative ASSESS diagnostic study (NCT01785888) evaluated the utility of ctDNA for *EGFR* mutation testing in patients with aNSCLC in a real-world setting (Europe and Japan)

[1]NCCN 2012; [2]NICE 2013; [3]Maemondo et al. 2010; [4]Mitsudomi et al. 2010; [5]Mok et al. 2009; [6]Rosell et al. 2012; [7]Zhou et al. 2011; [8]Aung et al. 2010; [9]Douillard et al. 2014; [10]Goto et al. 2012; [11]Liu et al. 2011

Study design

Patients were enrolled from Japan (n=300), France (n=145), Germany (n=346), Italy (n=259), Netherlands (n=27), Spain (n=158), Sweden (n=17), UK (n=59)

Patients

- Patients with newly diagnosed, locally advanced (stage IIIA/B) / metastatic chemotherapy-naïve NSCLC not suitable for curative treatment[a]

or

- Recurrent disease after surgical resection with / without adjuvant chemotherapy

Objectives

Primary

- Concordance between *EGFR* mutation status obtained via tissue / cytology and blood (plasma) based testing

Secondary

- *EGFR* mutation frequency
- Correlations between *EGFR* mutation status and demographic data / disease status
- *EGFR* mutation testing practices
- 1st-line therapy (all patients)
- 2nd-line therapy (patients with *EGFR* mutation-positive NSCLC)

Samples

- Provision of tumour and plasma samples for *EGFR* mutation testing

Assessments

Tissue / cytology[b]

- *EGFR* mutation testing according to local practices following histopathological review (WHO classification)

Blood (plasma)[b]

- Samples processed to plasma and transported to designated laboratories for *EGFR* mutation testing

WHO, World Health Organization

[a]Including surgery and chemoradiotherapy

[b]Europe: central / regional expert laboratories conducted blood testing; Japan: commercial laboratories conducted blood and tissue / cytology testing

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Statistical analysis

Sample size estimates

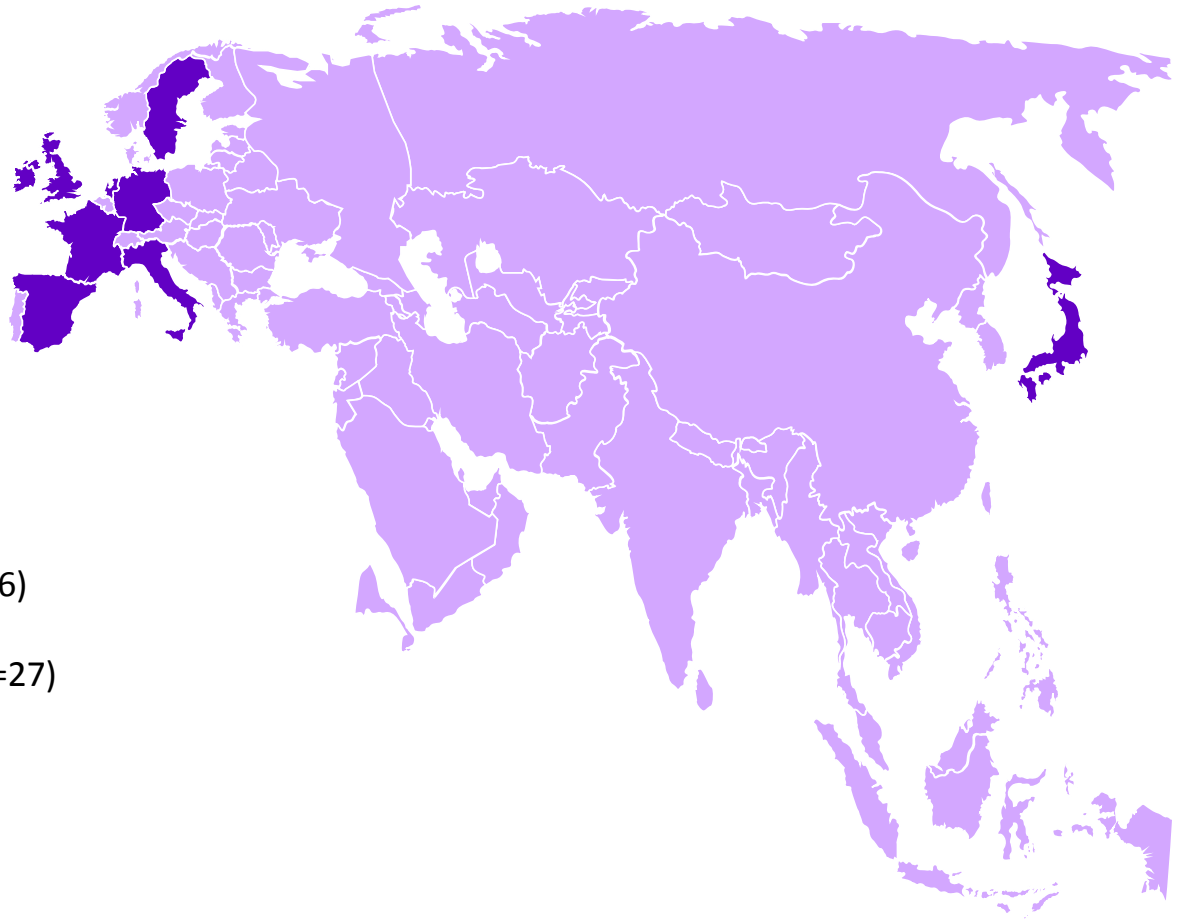
- 1000 patients from Europe / 300 patients from Japan required to determine adequate sensitivity for each region
- 1000 patients in Europe / 300 patients in Japan needed to be tested to obtain 100 patients with *EGFR* mutation-positive NSCLC in each region

Endpoint analysis

- Primary endpoint: concordance rate between matched tissue / cytology and plasma samples; pooled test sensitivity, specificity, PPV and NPV; exact 2-sided 95% CIs
- Descriptive summary statistics used to describe sampling / mutation testing methodologies and *EGFR* mutation frequency
- Correlation between *EGFR* mutation status and demographic / disease data analysed with multivariate logistic regression model of *EGFR* mutation status at baseline
  - Covariates: histology (ADC, non-ADC), smoking status (never-, ever-smoker), gender (female, male), age (≤65, >65 years) and WHO performance status (0-1, 2); disease status characteristics

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

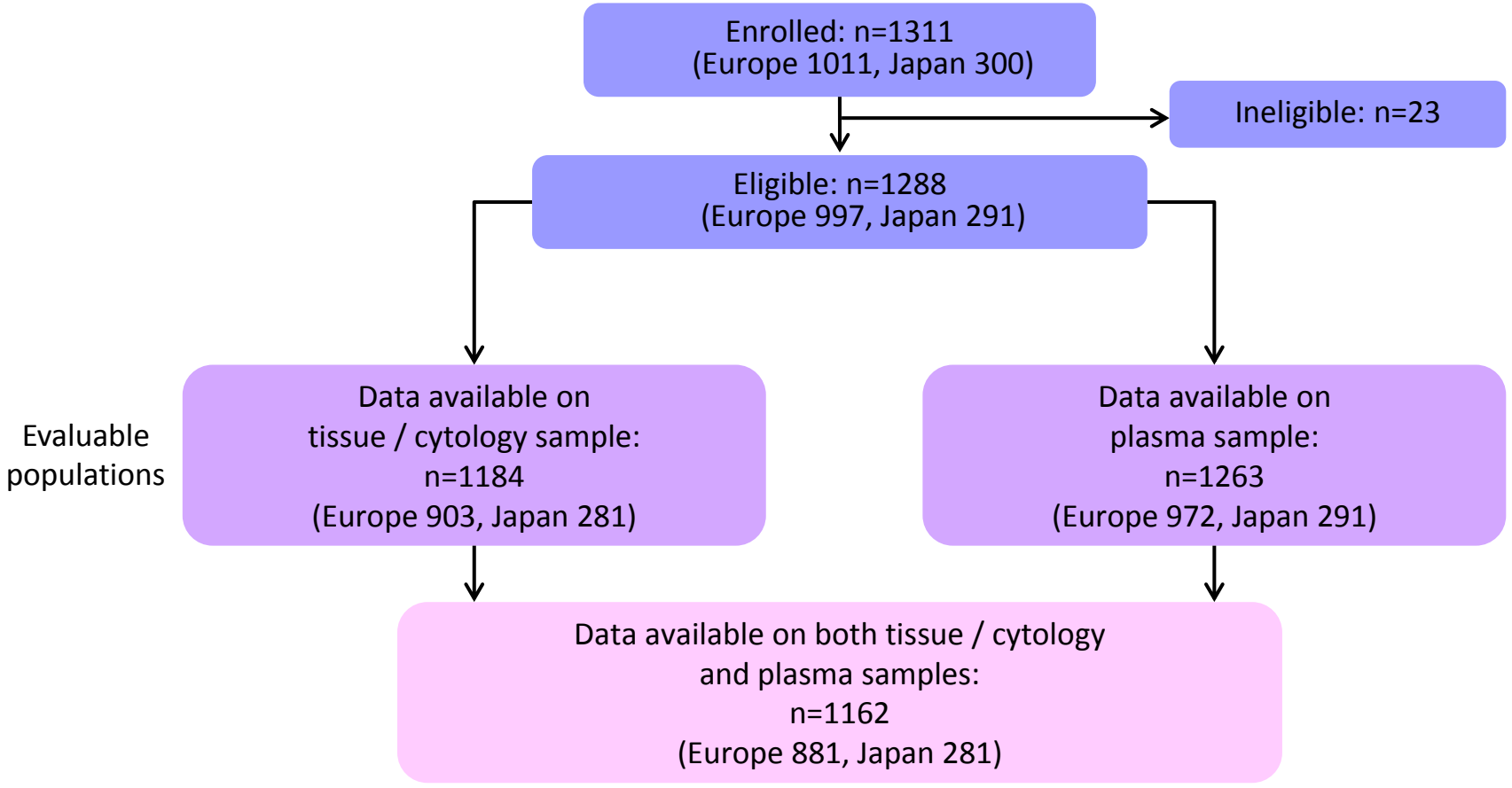
Study sites map



Japan (n=300)
France (n=145)
Germany (n=346)
Italy (n=259)
Netherlands (n=27)
Spain (n=158)
Sweden (n=17)
UK (n=59)

Patient flow diagram

First patient enrolled: 11 April 2013; last patient last visit: 17 April 2014



Patient demographics

	Enrolled population			Tissue / cytology evaluable			Plasma evaluable		
	Europe (N=997)	Japan (N=291)	Overall (N=1288)	Europe (N=903)	Japan (N=281)	Overall (N=1184)	Europe (N=972)	Japan (N=291)	Overall (N=1263)
Age, mean (SD)	65.4 (9.7)	70.2 (9.0)	66.5 (9.8)	65.4 (9.9)	70.4 (8.9)	66.6 (9.9)	65.4 (9.7)	70.2 (9.0)	66.5 (9.8)
Male, %	67.7	66.0	67.3	66.8	65.8	66.6	67.7	66.0	67.3
Race, %									
Caucasian	97.9	0.0	75.8	97.8	0.0	74.6	97.8	0	75.3
Asian	0.5	100.0	23.0	0.6	100	24.2	0.5	100	23.4
WHO performance status									
0-1	84.4	79.4	83.2	84.2	79.4	83.0	84.3	79.4	83.1
2	13.6	12.7	13.4	13.7	13.2	13.6	13.7	12.7	13.5
>2	2.0	7.9	3.3	2.1	7.5	3.4	2.1	87.9	3.4
Disease stage, %	(N=990)	(N=291)	(N=1281)	(N=896)	(N=281)	(N=1177)	(N=966)	(N=291)	(N=1257)
IIIA	5.3	7.9	5.9	4.8	8.2	5.6	5.4	7.9	6.0
IIIB	8.6	12.7	9.5	8.1	11.4	8.9	8.5	12.7	9.5
IV	86.2	79.4	84.6	87.1	80.4	85.5	86.1	79.4	84.6
Smoking status	(N=996)	(N=291)	(N=1287)	(N=903)	(N=281)	(N=1184)	(N=971)	(N=291)	(N=1262)
Never-smoker, %	17.5	26.8	19.6	18.7	27.0	20.7	17.7	26.8	19.8
Pack-years, median	40.0	45.0	40.0	40.0	45.0	40.0	40.0	45.0	40.0

SD, standard deviation

Sampling methodologies

Tissue / cytology; enrolled population

The majority of tissue / cytology samples were:

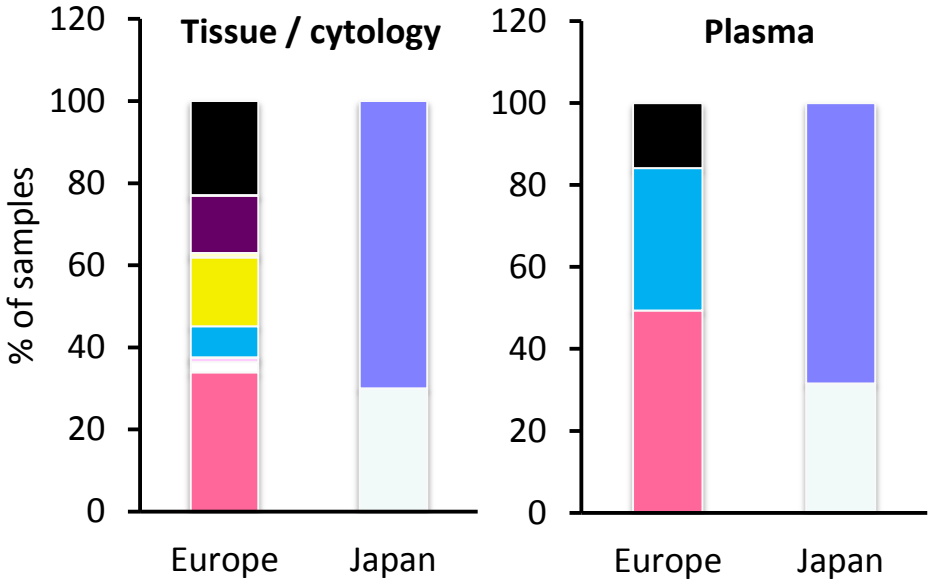
- obtained during **current diagnosis** (Europe 71.1%, Japan 84.9%)
- derived from the **primary tumour** (Europe 78.9%, Japan 83.5%)
- collected via **bronchoscopy** (Europe 38.9%, Japan 68.4%)

Samples were predominantly prepared as **FFPE tissue blocks** (Europe 71.4%, Japan 64.6%) and fixed with **4% neutral buffered formalin** (Europe 50.1%, Japan 25.1%)

- Mutation tests were not performed on the tissue / cytology samples of 110 patients; results were not yielded from tested samples of 17 patients
- Most common reason for not testing was insufficient material provided for the test (Europe 60.3%, Japan 55.6%)

FFPE, formalin-fixed paraffin embedded

EGFR mutation testing practices



- Other
- Sequenom
- Pyrosequencing
- Cycleave
- PNA LNA clamp
- Fragment length analysis
- DNA sequencing
- Roche cobas® EGFR Mutation Test
- Amoy EGFR 29 Mutation Detection Kit
- Qiagen Therascreen® EGFR PCR Kit (28 mutations)
- Qiagen Therascreen® EGFR Pyro Kit
- Qiagen Therascreen® EGFR RGQ PCR Kit

- Median test turnaround time
  Europe: 11 days (95% CI 14.0, 17.3) ; Japan: 8 days (95% CI 8.2, 14.1)
- Average test success rate
  Europe: 98.3% ; Japan: 99.6%

EGFR mutation status concordance (1)

Same vs different mutation test methods used in corresponding tissue / cytology and plasma samples

	Overall (n=1162)		Same method (n=254)		Different methods (n=908)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Concordance	1035/1162 (89.1)	87.1, 90.8	221/254 (87.0)	82.2, 90.9	814/908 (89.6)	87.5, 91.6
Sensitivity	87/189 (46.0)	38.8, 53.4	25/56 (44.6)	31.3, 58.5	62/133 (46.6)	37.9, 55.5
Specificity	948/973 (97.4)	96.2, 98.3	196/198 (99.0)	96.4, 99.9	752/775 (97.0)	95.6, 98.1
PPV	87/112 (77.7)	68.8, 85.0	**25/27 (92.6)**	75.7, 99.1	**62/85 (72.9)**	62.2, 82.0
NPV	948/1050 (90.3)	88.3, 92.0	196/227 (86.3)	81.2, 90.5	752/823 (91.4)	89.2, 93.2

Same methods: QIAGEN Therascreen®, PNA-LNA PCR clamp or Roche cobas® EGFR Mutation Test

EGFR mutation status concordance (2)

QIAGEN Therascreen® RGQ PCR Kit

	ASSESS overall (n=1162)		ASSESS (QIAGEN Therascreen® RGQ PCR Kit data only)		IFUM[1] (QIAGEN Therascreen® RGQ PCR Kit)	
	n/N (%)	95% CI	n/N (%)	95% CI	%	95% CI
Concordance	1035/1162 (89.1)	87.1, 90.8	131/138 (94.9)	89.8, 97.9	94.3	92.3, 96.0
Sensitivity	87/189 (46.0)	38.8, 53.4	16/22 **(72.7)**	49.8, 89.3	**65.7**	55.8, 74.7
Specificity	948/973 (97.4)	96.2, 98.3	115/116 **(99.1)**	95.3, 100.0	**99.8**	99.0, 100.0
PPV	87/112 (77.7)	68.8, 85.0	16/17 **(94.1)**	71.3, 99.9	**98.6**	92.3, 100.0
NPV	948/1050 (90.3)	88.3, 92.0	115/121 (95.0)	89.5, 98.2	93.8	91.5, 95.6

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

EGFR mutation status concordance (3)

Characteristics of patients with possible false-positive results

- Samples from 25 patients believed to have yielded false-positive results (*EGFR* mutation-positive plasma sample and *EGFR* mutation-negative tissue / cytology sample)
  - Patients from multiple sites / countries, indicating no specific lab-based issues
  - 56% of tumours were tested by DNA sequencing / pyrosequencing (vs 25% of overall population)
  - 76% of patients never-, former- or light-smokers (vs 45% of overall population)
  - 32% of tumour samples were needle biopsies / cytology (vs 21% of overall population)
  - Tissue / cytology and corresponding plasma sample from 1 patient not genuinely discordant[a]

Possible over-representation of cytology samples (inadequate tumour sample) and / or use of less-sensitive DNA sequencing methodology (inadequate mutation analysis to detect mutation) may have contributed to false-positive rate

[a]Reported as Exon 20 mutation-positive in plasma, but Exon 20 had not been screened in tumour assay

EGFR mutation frequency

Tissue / cytology		Overall n/N (%)	ADC n/N (%)	Non-ADC n/N (%)
Overall *EGFR* mutation-positive (n=189)	Japan	86/281 (30.6)	78/195 (40.0)	6/77 (7.8)
	Europe	105/903 (11.6%)	99/712 (13.9)	6/180 (3.3)
Subtype (% of overall positive)[a]				
Exon 19 deletion	Japan		40 (51.3)	-
	Europe		54 (54.5)	-
L858R only	Japan		37 (47.4)	-
	Europe		28 (28.3)	-
T790M + other	Japan		0 (0)	-
	Europe		1 (1.0)	-
Exon 20 insertion	Japan		0 (0)	-
	Europe		4 (4.0)	-
Exon 18	Japan		1 (1.3)	-
	Europe		4 (4.0)	-
Other rare / double mutations[b]	Japan		0 (0)	-
	Europe		8 (8.1)	-

- Female gender, ADC histology, never-smoking status, and Japanese ethnicity significantly correlated with *EGFR* mutation-positive tissue / cytology and plasma sample (all $p<0.001$)
- There was a trend between increasing number of metastases and *EGFR* mutation-positive plasma sample ($p=0.054$)

- Immunohistochemistry analyses showed that 4.3% (10 / 231) of TTF-1-negative tissue / cytology samples were *EGFR* mutation-positive
  - Exon 19 deletion (n=4), L858R (n=4), G719X (n=1), S768I & V769L (n=1)

TTF-1, thyroid transcription factor 1; [a]The number of patients with *EGFR* mutation-positive NSCLC of non-ADC histology was too small to interpret mutation subtype frequency data; [b]Including L858R + other or Exon 19 deletion + other

1st-line treatment decisions

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

	Europe		Japan		Overall	
	***EGFR* mutation-positive, n/N (%)**	***EGFR* mutation-negative, n/N (%)**	***EGFR* mutation-positive, n/N (%)**	***EGFR* mutation-negative, n/N (%)**	***EGFR* mutation-positive, n/N (%)**	***EGFR* mutation-negative, n/N (%)**
Total who received treatment	93/105 (88.6)	676/798 (84.7)	81/86 (94.2)	133/195 (68.2)	174/191 (91.1)	809/993 (81.5)
Therapy						
Gefitinib	42/105 (40.0)	0/798 (0.0)	55/86 (64.0)	0/195 (0.0)	97/191 (50.8)	0/993 (0.0)
Erlotinib	25/105 (23.8)	5/798 (0.6)	14/86 (16.3)	0/195 (0.0)	39/191 (20.4)	5/993 (0.5)
Afatinib	15/105 (14.3)	0/798 (0.0)	0/86 (0.0)	0/195 (0.0)	15/191 (7.9)	0/993 (0.0)
Pemetrexed	10/105 (9.5)	358/798 (44.9)	8/86 (9.3)	65/195 (33.3)	18/191 (9.4)	423/993 (42.6)
Radiotherapy	9/105 (8.6)	103/798 (12.9)	3/86 (3.5)	26/195 (13.3)	12/191 (6.3)	129/993 (13.0)
Carboplatin	2/105 (1.9)	264/798 (33.1)	9/86 (10.5)	75/195 (38.5)	11/191 (5.8)	339/993 (34.1)
Cisplatin	8/105 (7.6)	256/798 (32.1)	1/86 (1.2)	26/195 (13.3)	9/191 (4.7)	282/993 (28.4)
Bevacizumab	1/105 (1.0)	56/798 (7.0)	3/86 (3.5)	22/195 (11.3)	4/191 (2.1)	78/993 (7.9)

2nd-line treatment decisions

Patients confirmed with EGFR mutation-positive NSCLC via tissue / cytology

	Europe (n=13)	Japan (n=19)	Overall (n=32)
Erlotinib	6	7	13
Gefitinib	2	5	7
Afatinib	1	0	1
Pemetrexed	3	2	5
Cisplatin	2	3	5
Carboplatin	2	2	4
Docetaxel	0	2	2
Bevacizumab	0	2	2
Paclitaxel	0	2	2

- *EGFR* mutation status was the largest driver of choice for both patients with *EGFR* mutation-positive (77.0%) and mutation-negative (40.4%) NSCLC
  - Non-squamous cell carcinoma histology (13.1%) and patient preference (5.8%) were also key drivers of treatment choice in patients with *EGFR* mutation-negative NSCLC

Conclusions

- These first real-world data from the large, observational ASSESS study suggest ctDNA may be a feasible, suitable sample for *EGFR* mutation analysis
  - Improvements are required in real-world mutation analysis practices of both tissue / cytology and plasma samples
- Overall *EGFR* mutation status concordance of tumour and plasma results was 89% (sensitivity 46%, specificity 97%, PPV 78% and NPV 90%)
  - False-negative results in tumour samples likely contributed to low PPV; subsequently increased to 93% in subgroup of samples when identical, highly sensitive methods were used
  - Concordance data for the QIAGEN Therascreen® RGQ PCR Kit demonstrated sensitivity of 73% and specificity of 99%, similar to that reported for the Phase IV IFUM clinical trial[1] which utilised this method (sensitivity 66%, specificity 100%)
- It is important to use robust and sensitive methodologies when analysing tissue / cytology and plasma samples to ensure that patients receive the most appropriate treatments to address the molecular features of their disease

[1]Douillard et al. 2014

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ASSESS study PIs

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Additional / potential back-up slides

EGFR mutation status concordance (4)

Modified DNA re-extraction methods (Japanese subset; n=94)

	Overall (n=1162)		DNA extraction method:	Mutation detection: PNA-LNA PCR Clamp					
				QIAamp MinElute Virus Spin Kit for DNA[a]		QIAamp Circulating Nucleic Acid Kit[b]		Overall + QIAamp Circulating Nucleic Acid Kit data	
	n/N (%)	95% CI		%	95% CI	%	95% CI	%	95% CI
Concordance	1035/1162 (89.1)	87.1, 90.8		72.5	62.2, 81.4	83.5	74.3, 90.5	89.5	87.6, 91.2
Sensitivity	87/189 (46.0)	38.8, 53.4		**17.2**	5.8, 35.8	**51.7**	32.5, 70.6	50.0	42.8, 57.2
Specificity	948/973 (97.4)	96.2, 98.3		98.4	91.3, 100.0	98.4	91.3, 100.0	97.4	96.2, 98.3
PPV	87/112 (77.7)	68.8, 85.0		83.3	39.5, 99.6	93.8	69.8, 99.8	79.5	71.3, 86.3
NPV	948/1050 (90.3)	88.3, 92.0		71.8	61.0, 81.0	81.3	70.7, 89.4	90.6	88.7, 92.3

[a]400 µL plasma; [b]3 mL plasma

EGFR mutation status concordance

Europe vs Japan

	Overall (n=1162)		Europe		Japan	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Concordance	1035/1162 (89.1)	87.1, 90.8	808/881 (91.7)	89.7, 93.4	227/281 (80.8)	75.7, 85.2
Sensitivity	87/189 (46.0)	38.8, 53.4	53/103 (51.5)	41.4, 61.4	**34/86 (39.5)**	29.2, 50.7
Specificity	948/973 (97.4)	96.2, 98.3	755/778 (97.0)	95.6, 98.1	193/195 (99.0)	96.3, 99.9
PPV	**87/112 (77.7)**	68.8, 85.0	53/76 (69.7)	58.1, 79.8	34/36 (94.4)	81.3, 99.3
NPV	948/1050 (90.3)	88.3, 92.0	755/805 (93.8)	91.9, 95.4	193/245 (78.8)	73.1, 83.7

Sampling methodologies (1)

	Europe		Japan	
	n/N	%	n/N	%
Source of biopsy sample				
Current diagnosis	709/997	71.1	247/291	84.9
Prior diagnosis	227/997	22.8	13/291	4.5
Prior surgery	60/997	6.0	31/291	10.7
Other	1/997	0.1	0/291	0.0
Sample site				
Adrenal	4/996	0.4	0/291	0.0
Ascites	0/996	0.0	0/291	0.0
Bone	20/996	2.0	2/291	0.7
Brain	14/996	1.4	3/291	1.0
Liver	17/996	1.7	1/291	0.3
Lung	725/996	72.8	230/291	79.0
Lymph nodes	87/996	8.7	25/291	8.6
Pericardial effusion	2/996	0.2	1/291	0.3
Pleura	61/996	6.1	5/291	1.7
Pleural effusion	35/996	3.5	15/291	5.2
Skin / soft tissue	17/996	1.7	1/291	0.3
Other	14/996	1.4	8/291	2.7

Sampling methodologies (2)

	Europe		Japan	
	n/N	%	n/N	%
Sample lesion type				
Primary tumour	786/996	78.9	243/291	83.5
Metastatic site	196/996	19.7	40/291	13.7
Other	14/996	1.4	8/291	2.7
Sample collection method				
Bronchoscopic	387/995	38.9	199/291	68.4
Core-biopsy (NOS)	83/995	8.3	2/291	0.7
Cytology	45/995	4.5	14/291	4.8
Cytology: bronchial washings	12/995	1.2	7/291	2.4
Cytology: fine needle aspiration	93/995	9.3	1/291	0.3
Image-guided core biopsy	59/995	5.9	5/291	1.7
Incisional biopsy	31/995	3.1	1/291	0.3
Lobectomy	50/995	5.0	21/291	7.2
Localisation biopsy	25/995	2.5	5/291	1.7
Mediastinascopic	11/995	1.1	0/291	0.0
Needle biopsy	82/995	8.2	15/291	5.2
Percutaneous core biopsy	18/995	1.8	0/291	0.0
Pneumonectomy: extra pericardial	1/995	0.1	1/291	0.3
Pneumonectomy: intra pericardial	1/995	0.1	0/291	0.0
Segmental excision	2/995	0.2	11/291	3.8
Segmentectomy	3/995	0.3	0/291	0.0
Sleeve	0/995	0.0	0/291	0.0
Transbronchial	30/995	3.0	1/291	0.3
Wedge resection	10/995	1.0	0/291	0.0
All other combined	52/995	5.2	8/291	2.7

NOS, not otherwise specified

EGFR mutation frequency

Sample type	Tissue / cytology n (%)	Plasma n (%)
Overall	191/1184 (16.1)	119/1263 (9.4)
Country		
Europe	105/903 (11.6)	82/972 (8.4)
Japan	86/281 (30.6)	37/291 (12.7)
Histology		
ADC	177/907 (19.5)	109/952 (11.4)
Non-ADC	12/257 (4.7)	9/288 (3.1)
***EGFR* mutation subtype**		
Exon 19 deletions	96/191 (50.3)	68/119 (57.1)
Exon 19 deletions + T790M	0/191 (0.0)	0/119 (0.0)
L858R	71/191 (37.2)	38/119 (31.9)
L858R + T790M	0/191 (0.0)	2/119 (1.7)
T790M only	0/191 (0.0)	3/119 (2.5)
T790M + other[a]	1/191 (0.5)	1/119 (0.8)
Other[b]	23/191 (12.0)	7/119 (5.9)

ADC, adenocarcinoma

[a]Any other mutation that occurred in combination with T790M that is not L858R or Exon 19 deletion

[b]This category included double mutations not specified

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

Demographic / disease status factor	Tissue / cytology				Plasma			
	%	p-value	OR	95% CI	%	p-value	OR	95% CI
ADC vs non-ADC	19.5 vs 4.7	0.0001	4.020	1.994, 8.107	11.4 vs 3.1	0.0075	3.005	1.342, 6.731
Never- vs ever-smoker	46.1 vs 8.3	<0.0001	6.182	4.035, 9.473	26.8 vs 5.1	<0.0001	4.407	2.746, 7.071
Female vs male	29.3 vs 9.5	0.0028	1.903	1.248, 2.902	17.7 vs 5.4	0.0048	1.976	1.232, 3.170
Japanese vs European	30.6 vs 11.6	<0.0001	5.159	3.394, 7.841	12.7 vs 8.4	0.0905	1.520	0.936, 2.469
Number of organs with metastases, median	N/A	N/A	N/A	N/A	2 vs 1	0.0540	1.202	0.997, 1.450

ADC, adenocarcinoma; CI, confidence interval; N/A, not applicable; OR, odds ratio