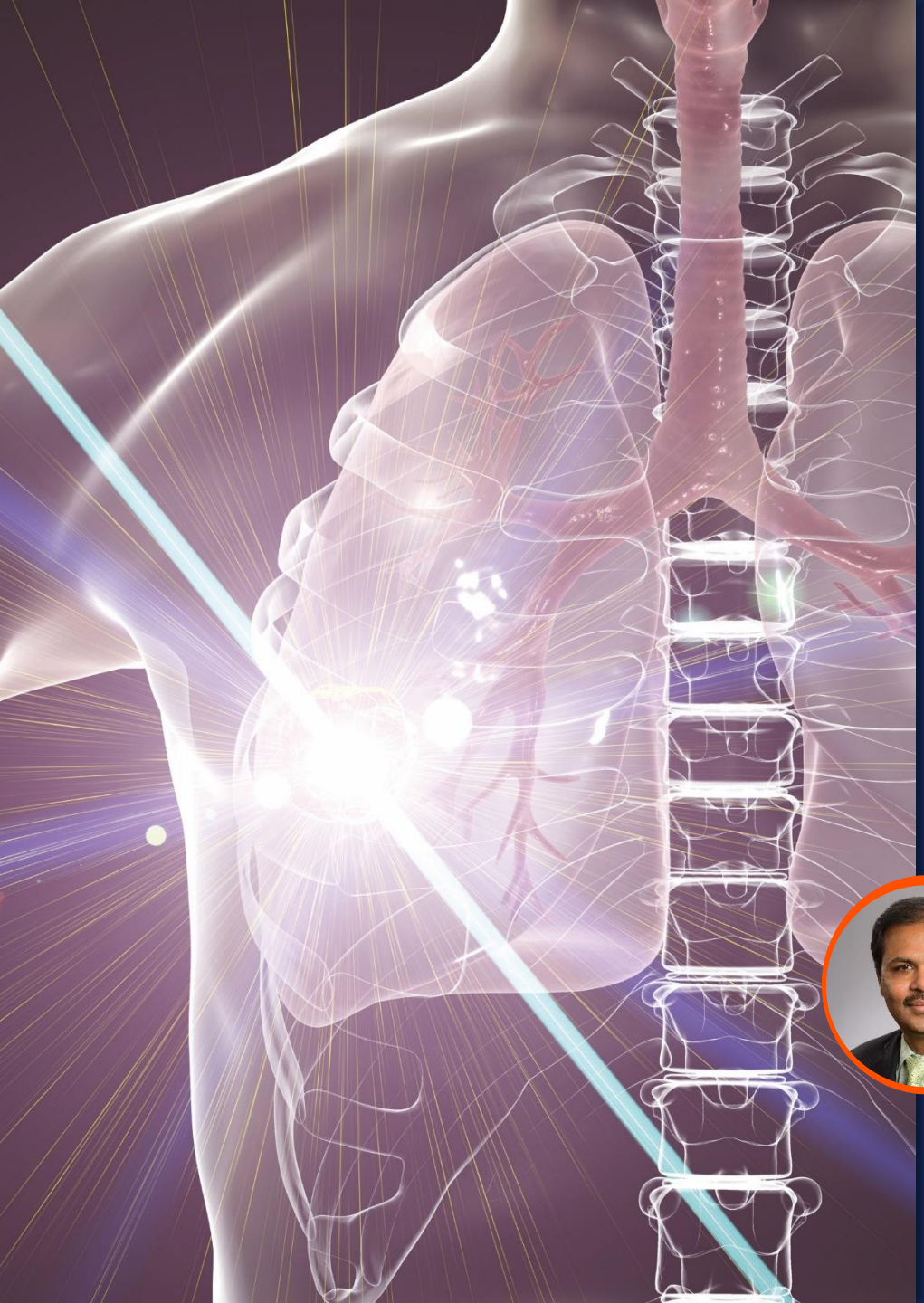

touchCONGRESS Webinar

Should we use third-generation TKIs up front in EGFR+ NSCLC?

Professor Suresh Ramalingam
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Webinar recorded: September 2019

Funded by an independent medical education request from Astra Zeneca

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Webinar overview

Should we use third-generation TKIs up front in EGFR+ NSCLC?

- ESMO Congress 2019 – What are the key clinical data for EGFR TKIs that will inform daily practice?
- ESMO Congress 2019 – Can we determine an optimal sequencing of treatment for patients with EGFR+ NSCLC?
- ESMO Congress 2019 – How can we tailor care to the individual?

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

ESMO Congress 2019 – What are the key clinical data for EGFR TKIs that will inform daily practice?

Focus on the different efficacy and safety profiles of third-generation agents, compared with first- and second-generation TKIs

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

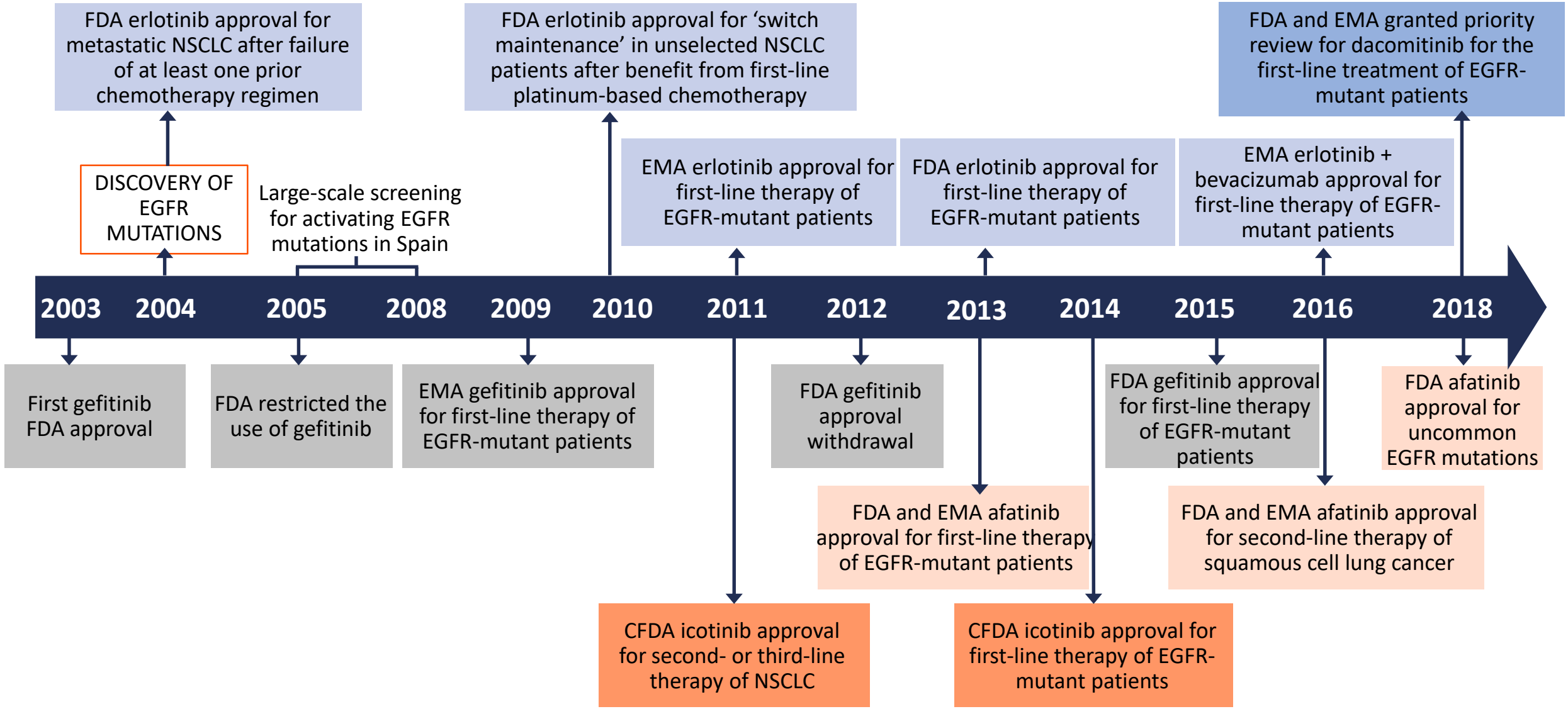
EGFR mutant lung cancer

Incidence	Present in 10–15% Caucasian compared with 40–50% of Asian patients with NSCLC[1]
Agents	Gefitinib, erlotinib, afatinib, dacomitinib and osimertinib approved for first-line EGFR TKI therapy[2]
Trial landscape	Several direct comparison trials of EGFR TKIs[2]

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Hirsch FR, Bunn PA. *Lancet Oncol.* 2009;**10**:432–433; 2. NCCN. Non-Small Cell Lung Cancer Version 7.2019; August 30, 2019.

First- and second-generation EGFR TKIs



CFDA, China Food and Drug Administration; EGFR, epidermal growth factor receptor; EMA, European Medical Agency; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

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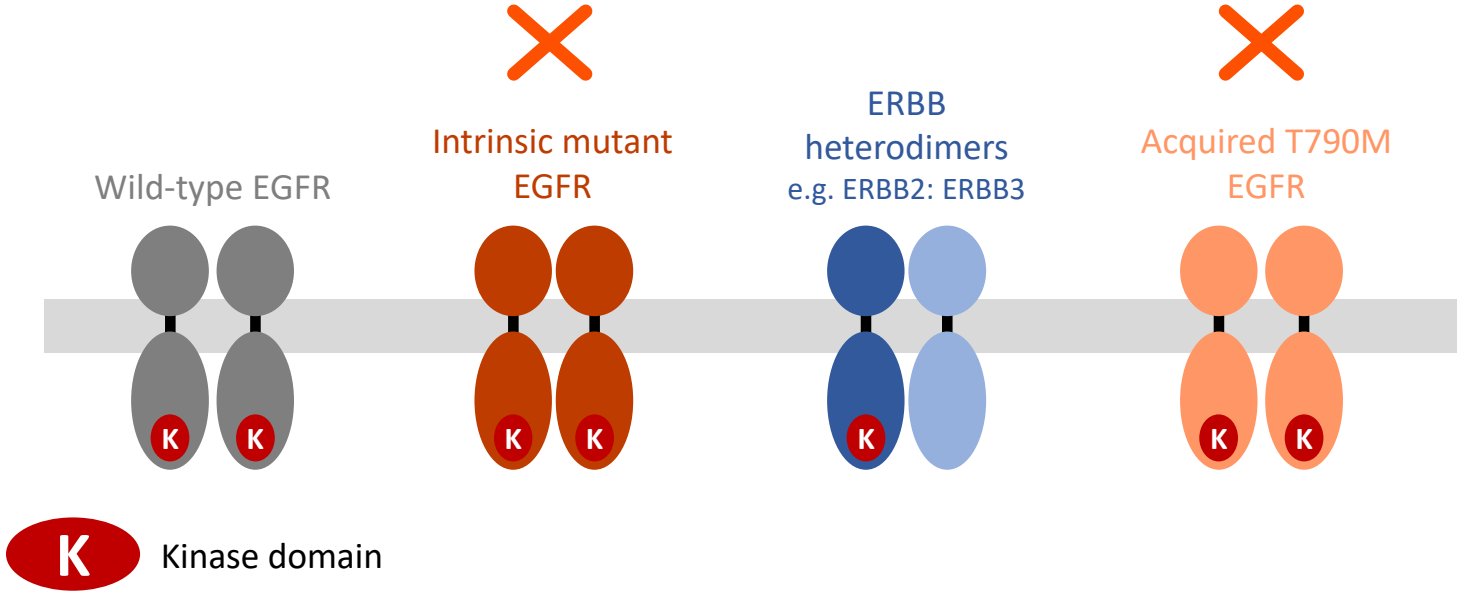
Third-generation EGFR TKIs

Acquired resistance to first- and second-generation EGFR TKIs is inevitable

Most common mechanism is emergence of the T790M mutation



Third-generation EGFR TKIs, such as osimertinib, target the T790M mutation

The FDA and EMA have approved osimertinib as monotherapy for the first-line treatment of adult patients with locally-advanced or metastatic NSCLC with activating EGFR mutations

EGFR, epidermal growth factor receptor; EMA, European Medical Agency; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Osimertinib vs. comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis

S. Ramalingam

Final OS analysis of the Phase II FLAURA study which evaluated the efficacy of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation who failed standard chemotherapy vs. comparator EGFR TKI

≥18 years (Japan ≥20)

Treatment-naïve with Ex19del/L858R EGFRm advanced NSCLC

WHO performance status 0–1

Stable CNS metastases not requiring steroids for ≥2 weeks was allowed

Randomized 1:1 to osimertinib 80 mg qd po (n=279) or comparator EGFR TKI (gefitinib 250 mg qd/erlotinib 150 mg qd po; n=277), stratified by mutation status (Ex19del/L858R) and race (Asian/non-Asian)

Crossover was allowed for patients in the comparator EGFR TKI arm upon central confirmation of progression and T790M positivity (25% of patient crossed over)

Primary endpoint was PFS by RECIST v1.1, per investigator

Secondary endpoint was OS

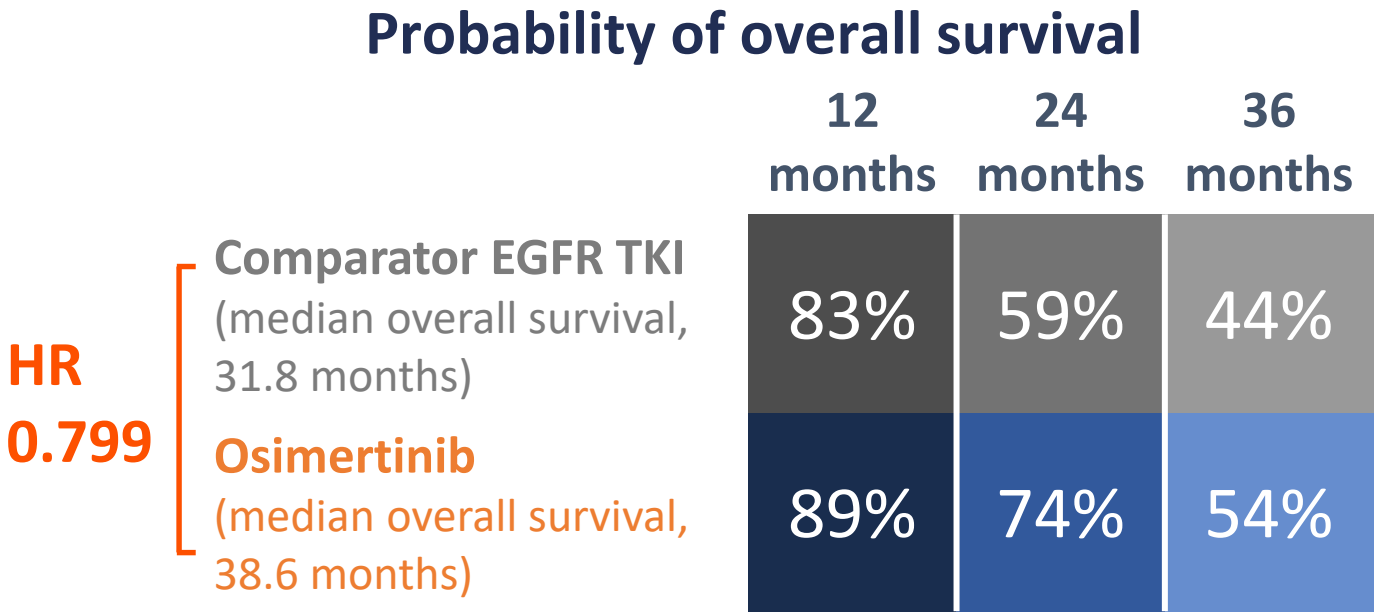
CNS, central nervous system; EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; qd, once daily; po, orally; RECIST, response evaluation criteria in solid tumours; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

Ramalingam S, et al. Presented at the ESMO Congress 2019; abstract no. LBA5_PR.

Osimertinib vs. comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis

S. Ramalingam

Probability of overall survival



Median duration of exposure was 20.7 months for the osimertinib arm and 11.5 months in the comparator EGFR TKI arm

Adverse events ≥Grade 3 were reported in 18% of patients in the osimertinib arm and 29% of patients in the comparator EGFR TKI arm

Osimertinib provided a statistically significant and clinically meaningful improvement in OS vs. comparator EGFR TKI in first-line patients with EGFRm advanced NSCLC with a favourable and consistent toxicity profile

EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

Ramalingam S, et al. Presented at the ESMO Congress 2019; abstract no. LBA5_PR.

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CTONG 1509: Phase III study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC

Q. Zhou

Open-labelled, randomized, multicentre Phase III study to investigate the efficacy and safety of bevacizumab with or without erlotinib in Chinese EGFR-mutated NSCLC patients

311 patients (from 14 centres) with advanced non-squamous NSCLC harbouring EGFR mutation were randomly (1:1) assigned to receive either combination with erlotinib (150 mg daily) plus bevacizumab (15 mg/kg iv q3w) or erlotinib (150 mg daily)

Random assignment was stratified by sex (female/male), disease stage (stage IIIb vs. stage IV vs. recurrence) and EGFR gene mutation (exon 19 deletion vs. exon 21 L858R)

Primary endpoint was PFS as determined by an IRC

Secondary endpoints were PFS by investigator, tumour response (by IRC and investigator), OS, TTF, safety, PRO and exploratory biomarker analysis

Next-generation sequencing of a 448-gene panel and transcriptome sequencing was used for resistance biomarker analysis of paired frozen tissue samples

EGFR, epidermal growth factor receptor; IRC, independent review committee; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; q3w, every 3 weeks; TKI, tyrosine kinase inhibitor; TTF, time to failure.

Zhou Q, et al. Presented at the ESMO Congress 2019; abstract no. 14800.

CTONG 1509: Phase III study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC

Q. Zhou

	Median PFS by IRC (months)	Median PFS by investigator (months)	ORR by IRC
Bevacizumab plus erlotinib (n=157)	18.0	18.0	86.3%
	HR = 0.55	HR = 0.57	p=0.741
Erlotinib alone (n=154)	11.3	11.2	84.7%

The most common Grade 3 or worse adverse events in the bevacizumab plus erlotinib group were: hypertension, proteinuria and rash; and in the erlotinib-alone group: rash, elevated alanine aminotransferase and elevated aspartate aminotransferase

Compared with erlotinib alone, bevacizumab plus erlotinib showed superior efficacy with acceptable tolerability

EGFR, epidermal growth factor receptor; IRC, independent review committee; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; TKI, tyrosine kinase inhibitor; TTF, time to failure.

Zhou Q, et al. Presented at the ESMO Congress 2019; abstract no. 14800.

JIPANG study: Randomized Phase III study of pemetrexed/cisplatin (PEM/Cis) versus vinorelbine/cisplatin (VNR/Cis) for completely resected p-stage II-IIIA non-squamous non-small cell lung cancer (Ns-NSCLC): Outcomes based on EGFR mutation status

M. Tsuboi

The VNR/Cis chemotherapy doublet has been evaluated in prior positive adjuvant trials in patients with completely resected Ns-NSCLC, whereas no Phase III study has so far evaluated PEM/Cis in this population

Patients with completely resected Ns-NSCLC were randomized 1:1 to receive PEM/Cis (500 mg per m^2/75 mg per m^2; day 1; n=389) or VNR/Cis (25 mg per m^2; days 1 and 8/80 mg per m^2; day 1; n-395)

Patients were stratified according to sex, age, pathologic stage, EGFRm status and institution

The primary endpoint was RFS

The planned sample size was 800 patients in total

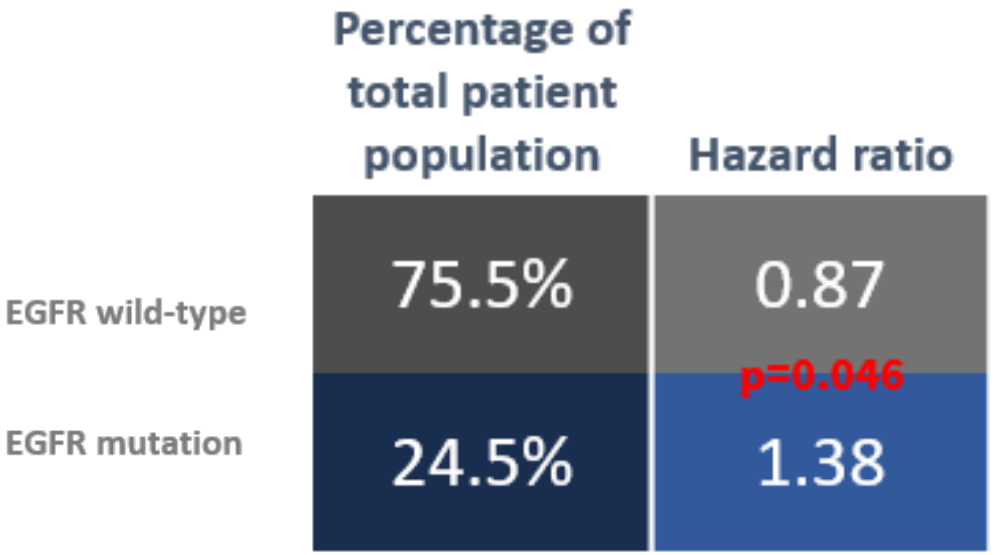
EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; Ns-NSCLC, non-squamous non-small cell lung cancer; PEM/Cis, pemetrexed/cisplatin; RFS, recurrence free survival; VNR/Cis, vinorelbine/cisplatin.

Tsuboi M, et al. Presented at the ESMO Congress 2019; abstract no. 1440PD.

JIPANG study: Randomized Phase III study of pemetrexed/cisplatin (PEM/Cis) versus vinorelbine/cisplatin (VNR/Cis) for completely resected p-stage II-IIIA non-squamous non-small cell lung cancer (Ns-NSCLC): Outcomes based on EGFR mutation status

M. Tsuboi

- **Results suggest that PEM/Cis can be an option for post-operative chemotherapy in stage II-IIIA non-squamous NSCLC**
- **Sub-group analysis with unbalanced patient characteristics does not allow the recommendation of any platinum-based doublet based on EGFR status**
- **Role of adjuvant EGFR TKIs (with without chemotherapy) needs to be defined**



Although this Phase III study did not meet the primary endpoint, PEM/Cis had a similar efficacy to VNR/Cis with a better tolerability as postoperative adjuvant chemotherapy for Ns-NSCLC patients

EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; Ns-NSCLC, non-squamous non-small cell lung cancer; PEM/Cis, pemetrexed/cisplatin; RFS, recurrence free survival; TKI, tyrosine kinase inhibitor; VNR/Cis, vinorelbine/cisplatin.
Tsuboi M, et al. Presented at the ESMO Congress 2019; abstract no. 1440PD.

Phase II study of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation: A multicenter trial of the Korean Cancer Study Group (LU17-19)

T.M. Kim

Phase II study to evaluate the efficacy of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation who failed on standard chemotherapy

Patients received osimertinib 80 mg orally once daily until disease progression, unacceptable toxicities, withdrawal or no clinical benefits

Primary end point was investigator-assessed, confirmed ORR as defined by RECIST version 1.1

Secondary end points were safety profiles, PFS, OS and duration of response

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumours.

Kim TM, et al. Presented at the ESMO Congress 2019; abstract no. 1529P.

Phase II study of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation: A multicenter trial of the Korean Cancer Study Group (LU17-19)

T.M. Kim

- ORR was 0% with mostly disease stabilization (stable disease, 46.7%, n=7)
- Three patients who had EGFR exon 20 insertions at M766, A767 and unknown sites were still receiving osimertinib at the cut-off date (disease stabilization, 12, 7 and 7 months, respectively)
- Median PFS and OS were 3.5 months (95% CI 1.6-not reached) and not reached (1-year OS rate, 56.3%), respectively
- Disease control rate at 6 months was 31.1%
- The most frequently observed adverse events were nausea (20%, n=3), vomiting (20%, n=3), anaemia (13.3%, n=2) and fever (13.3%, n=2)

Osimertinib was well tolerated, but had limited clinical activity in NSCLC patients with EGFR exon 20 insertion mutation who failed to standard chemotherapy

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; RECIST, Response evaluation criteria in solid tumours.

Kim TM, et al. Presented at the ESMO Congress 2019; abstract no. 1529P.

Implications for practice

Data from the ESMO Congress 2019 show that, for front-line therapy of EGFR-mutated NSCLC, osimertinib 80 mg/day is the optimal therapy

This regimen improve PFS and OS while providing a safe toxicity profile

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

ESMO Congress 2019 – Can we determine an optimal sequencing of treatment for patients with EGFR+ NSCLC?

Focus on third-generation EGFR TKIs
with or without earlier-generation agents

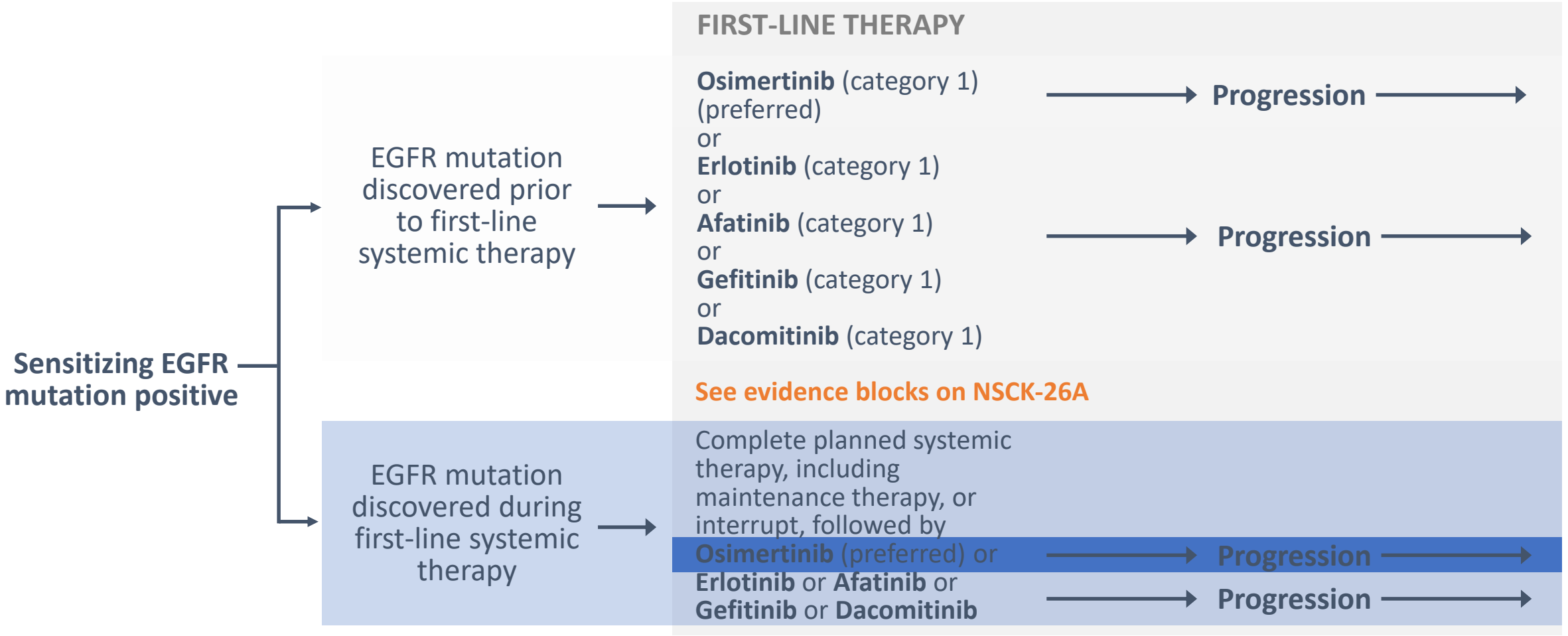
EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

EGFR TKI sequencing

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

NCCN Guidelines – August 2019

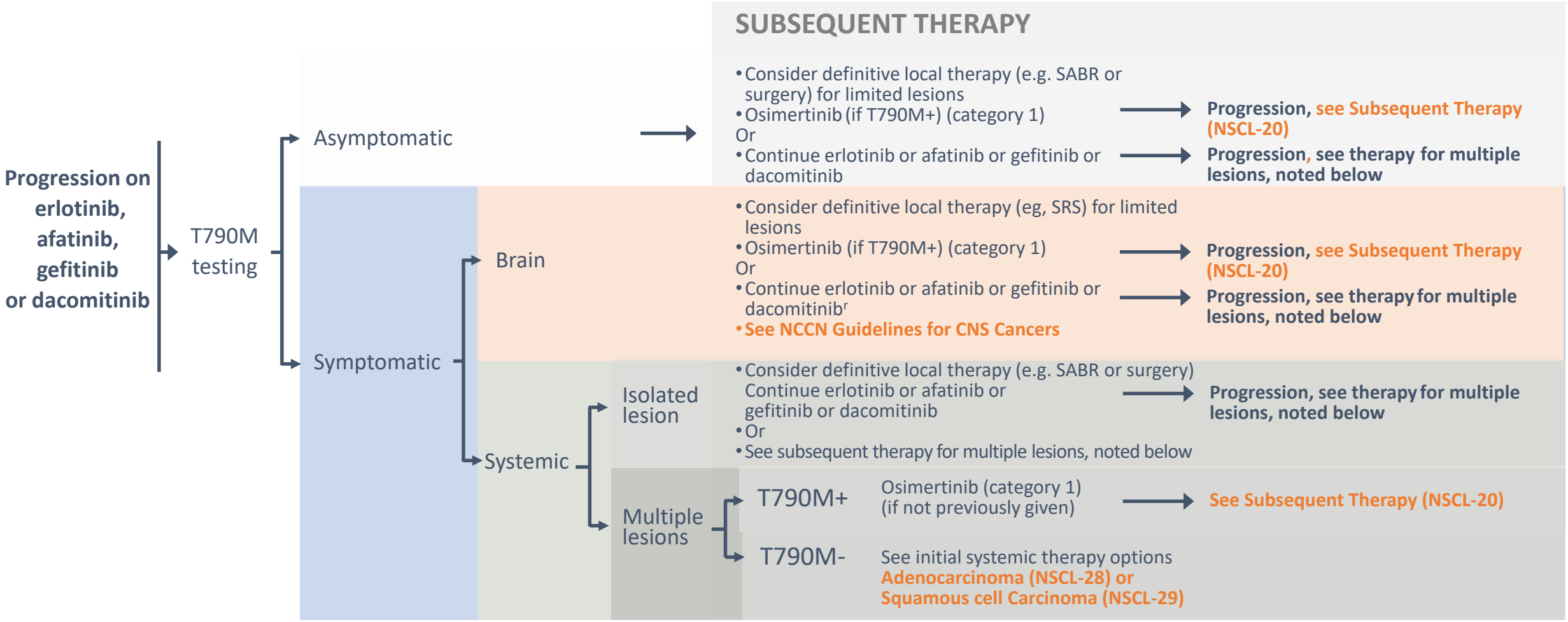
SENSITIZING EGFR MUTATION POSITIVE



EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network.
Adapted from NCCN. Non-Small Cell Lung Cancer Version 7.2019; August 30, 2019.

NCCN Guidelines – August 2019

SENSITIZING *EGFR* MUTATION POSITIVE



EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiotherapy; SRS, stereotactic radiosurgery.
Adapted from NCCN. Non-Small Cell Lung Cancer Version 7.2019; August 30, 2019.

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Effectiveness of sequencing TKIs in patients with EGFR mutation-positive non-small cell lung cancer (NSCLC): A French national medical-administrative claim database analysis

N. Girard

French National medical-administrative claim database (SNDS) assessment of the real-life effectiveness of the TKI sequencing approach first- or second-generation followed by osimertinib

576 patients treated with first- or second-generation EGFR TKI followed by osimertinib

	Overall population (n=576)
Gender	
• Men (n, %)	152 (26.4%)
• Women (n, %)	424 (73.6%)
Age	
• Median (min-max)	72 (27–93)
• Mean (SD)	70.7 (12.2)
• 18–50 years old	34 (5.9%)
• 50–60 years old	67 (11.6%)
• 60–70 years old	142 (24.7%)
• 70–80 years old	172 (29.9%)
• ≥80 years old	95 (16.5%)
Charlson comorbidity index [modified for cancer patients: mean (SD)]	0.4 (0.9)

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI tyrosine kinase inhibitor.
Girard N, et al. Presented at the ESMO Congress 2019; abstract no. 1528P.

Effectiveness of sequencing TKIs in patients with EGFR mutation-positive non-small cell lung cancer (NSCLC): A French national medical-administrative claim database analysis

N. Girard

- Median time on first- or second-generation EGFR TKI was 13.6 months
- Median time on third-generation EGFR TKI was 11.9 months
- Median overall survival for sequential first- or second-generation EGFR TKI followed by osimertinib was 37.1 months
- Proportion of patients still alive at end of analysis: 90.8% at 12 months. 71.0% at 24 months and 51.6% at 36 months

Examined cohort confirmed the prolonged time on TKI treatment and survival rates of patients receiving first- or second-generation EGFR TKI followed by osimertinib in a real-life setting

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI tyrosine kinase inhibitor.
Girard N, et al. Presented at the ESMO Congress 2019; abstract no. 1528P.

Treatment patterns of EGFR mt+ NSCLC IV pts: Real-world data of the NOWEL network

J. Roeper

Investigation of the treatment pattern and especially the attrition rate between first- and second-line therapy in EGFR+ patients from the NOWEL network

A retrospective study of 1539 pts with non-squamous NSCLC IV

Of 965 patients tested, 148 (15%) with an EGFR mt+ were identified

144/148 of these patients were treated with systemic therapy

EGFR mt+ patient characteristics:

- **55% exon 19 mutation vs. 36% exon 21 mutation**
- **64% female vs. 36% male**
- **64% never/light smoker vs. 33% ex-heavy/current smoker**
- **83% ECOG 0/1 vs. 13% ECOG 2/3**

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; mt+, mutation positive; NSCLC, non-small cell lung cancer; TKI tyrosine kinase inhibitor.
Roeper J, et al. Presented at the ESMO Congress 2019; abstract no. 1533P.

Treatment patterns of EGFR mt+ NSCLC IV pts: Real-world data of the NOWEL network

J. Roeper

- Of the 144 patients, 14 are still on first-line therapy, 9 were lost to follow-up and 3 died while on first-line therapy
- A total of 118 patients were candidates for second-line therapy, but only 84 (70%) actually received this treatment
- After availability of third-generation EGFR TKIs, 72 patients were candidates for second-line treatment and 51 (71%) received this treatment
- Median OS of patients receiving second-line therapy after access to third-generation EGFR TKIs was 35 months vs. 10 months without second-line therapy ($p<0.000$)
- Of the 20 positive for T790M mutation, 16 received third-generation EGFR TKI for second-line therapy with a median OS of 51 months vs. 25 months for patients not receiving a third-generation EGFR TKI ($p<0.002$)

- A significant number of patients treated with first- or second-generation TKI did not reach second-line therapy even with broad accessibility of third-generation TKI
- Reasons for not receiving second-line therapy were in most cases deterioration of PS, death and no testing for T790M in a minority of cases

EGFR, epidermal growth factor receptor; mt+, mutation positive; NSCLC, non-small cell lung cancer; OS, overall survival; PS, performance status; TKI tyrosine kinase inhibitor.
Roeper J, et al. Presented at the ESMO Congress 2019; abstract no. 1533P.

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Implications for practice

Data from the ESMO Congress 2019 show that one-third of patients will be unable to receive second-line therapy following front-line EGFR TKI treatment

Important to use the third-generation EGFR TKIs first as they provide optimal outcomes for patients

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

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ESMO Congress 2019 – How can we tailor care to the individual?

Focus on biomarkers in EGFR+ NSCLC

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Biomarkers for EGFR+ NSCLC

Early biomarker testing is central to the ability to prescribe first-line EGFR TKIs in EGFR+ NSCLC, and testing for T790M mutations following resistance to first- and second-generation EGFR TKIs is crucial to enable prolonged EGFR TKI treatment (via third-generation agents), before resorting to chemotherapy or other options[1]

Despite guideline recommendations, access to EGFR testing is not universally available and disparities exist concerning which patients receive molecular testing[2]

Real-world data show that many patients do not receive second-line therapy after progression on first- or second-generation TKIs partly as a result of access to T790M testing[3]

Increased awareness of the need for, and correct timing of, biomarker testing in EGFR+ NSCLC is therefore crucial to the implementation of best practice[1]

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Garinet S, et al. J Clin Med 2018;7:144; 2. Roeper J, et al. Ann Oncol 2018;29:1447P; 3. Roper N, et al. J Clin Oncol 2019;37;9049.

Longitudinal circulating tumour DNA (ctDNA) monitoring for early detection of disease progression and resistance in advanced NSCLC in FLAURA

J.E. Grey

Exploratory analysis of ctDNA for the early detection of disease progression of the Phase III FLAURA study which evaluated the efficacy of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation who failed to standard chemotherapy vs. comparator EGFR TKI

Treatment-naïve patients (pts) with EGFRm (ex19del/L858R) locally advanced/metastatic NSCLC (n=556) were randomized 1:1 (osimertinib 80 mg qd: comparator [gefitinib 250 mg qd/erlotinib 150 mg qd])

Plasma samples were collected on days 1, 8 and 15, then every 21 days for weeks 3–18, then every 6 weeks thereafter

In patients who had a plasma sample on PD and/or discontinuation, ctDNA droplet digital PCR for EGFRm (ex19del/L858R/T790M) was performed at all available timepoints and C797S for post-week 6 timepoints. C797S and T790M were the only resistance mutations assayed

ctDNA progression was defined with respect to the nadir ctDNA result and its proximity to the ddPCR detection and quantification limits

ctDNA, circulating tumour DNA; ddPCR, double drop polymerase chain reaction; EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; NSCLC, non-small cell lung cancer; PD, disease progression; qd, once daily; TKI, tyrosine kinase inhibitor.

Grey JE, et al. Presented at the ESMO Congress 2019; abstract no. LBA85.

Longitudinal circulating tumour DNA (ctDNA) monitoring for early detection of disease progression and resistance in advanced NSCLC in FLAURA

J.E. Grey

- The ctDNA progression analysis included 122/556 (22%) patients with valid longitudinal monitoring ddPCR data and RECIST PD by DCO1 (12 June 2017)
- Across both arms, ctDNA progression preceded or co-occurred with PD in 80/122 (66%) patients with 2.7 months median lead time; 9.5 months median PFS (n=80)
- Acquired C797S or T790M was detected in 57/122 (47%) patients with ctDNA progression (osimertinib 4/50 [8%] C797S, comparator 53/72 [74%] T790M); median time to detection was 16.7 and 8.4 months for the osimertinib and comparator arms, respectively, mirroring overall median PFS
- In patients with ctDNA progression and PD (n=106), acquired T790M and C797S were detected either at the same time as, or earlier than PD in 41/106 (38%) patients (osimertinib 2/39 [5%], comparator 39/67 [58%]); median lead time was 1.4 months

ctDNA monitoring may allow for earlier identification of pts who progress on first-line EGFR TKI therapy and the detection of EGFR-mediated resistance mechanisms in advance of PD in EGFRm NSCLC

ctDNA, circulating tumour DNA; ddPCR, double drop polymerase chain reaction; EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; NSCLC, non-small cell lung cancer; PD, disease progression; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; TKI, tyrosine kinase inhibitor.

Grey JE, et al. Presented at the ESMO Congress 2019; abstract no. LBA85.

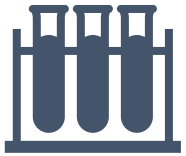
Differential expression of B7-H4, VISTA, B7-H6, HHLA2, IDO-1, PD-L1 and CD8 in EGFR mutant and wild-type lung adenocarcinoma

S. Yu

Investigation to describe the expression profiles of newly discovered B7 family (B7-H4, VISTA, B7-H6, HHLA2), IDO-1, PD-L1 and CD8 in resected lung adenocarcinoma tumour tissues and try to find potential immune target for lung cancer with EGFR mutation

A total of 372 adenocarcinoma lung cancer patients who underwent lung cancer resection were selected in the discovery cohort

The validation cohort contains another 231 adenocarcinoma lung cancer patients



Expression of B7-H4, VISTA, B7-H6, HHLA2, IDO-1, PD-L1 and CD8 was determined by immunohistochemical staining

CD8, cluster of differentiation 8; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death ligand 1.

Yu S, et al. Presented at the ESMO Congress 2019; abstract no. 1740PD.

Differential expression of B7-H4, VISTA, B7-H6, HHLA2, IDO-1, PD-L1 and CD8 in EGFR mutant and wild-type lung adenocarcinoma

S. Yu

B7-H4 expression was significantly higher in EGFR-mutated than wild-type patients ($p<0.05$)

IDO-1, PD-L1 and CD8 expression was significantly lower in EGFR-mutated than wild-type patients

B7-H6, IDO-1, PD-L1 and CD8 expression was significantly lower in EGFR-mutated than wild-type patients

No anti-B7-H4 agents are currently available

For wild-type patients, clinical trials investigating anti-IDO-1 therapy in melanoma and NSCLC have had poor results

B7-H4 is a potential new immune target for patients with EGFR mutation positive NSCLC

CD8, cluster of differentiation 8; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1.

Yu S, et al. Presented at the ESMO Congress 2019; abstract no. 1740PD.

Frequency of epidermal growth factor receptor (EGFR) mutations in stage IB–IIIA EGFR mutation positive non-small cell lung cancer (NSCLC) after complete tumour resection

M. Tsuboi

Report of the frequency of the most common EGFR activating mutations from patients screened for the Phase III ADAURA trials assessing osimertinib as adjuvant therapy in early-stage NSCLC after complete resection

ADAURA is a Phase III, double-blind, randomized, placebo-controlled study assessing efficacy and safety of osimertinib vs. placebo of 2447 patients

At screening, 1087 patients had EGFR mutations associated with EGF TKI sensitivity [ex19del (53%), L858R (42%)], alone or in combination with exon 20 insertion (3%), G719X (2%), S768I (1%), T790M (2%) or L861Q (1%) were centrally assessed from resected tumour samples using the cobas® EGFR Mutation Test

Some patients may have been pre-screened for EGFR mutations using local tests

Adult patients with mainly non-squamous histology, stage IB–IIIA EGFRm NSCLC, following complete tumour resection, without or after adjuvant chemotherapy

EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Tsuboi M, et al. Presented at the ESMO Congress 2019; abstract no. 1440PD.

Frequency of epidermal growth factor receptor (EGFR) mutations in stage IB–IIIA EGFR mutation positive non-small cell lung cancer (NSCLC) after complete tumour resection

M. Tsuboi

Overall frequency of EGFR mutations (44%) should be treated with caution owing to differences in pre-screening between countries

High prevalence of EGFRm mutations in Asian and female patients with stage IB–IIIA NSCLC following complete resection, which is consistent with the advanced setting

	Number (%) of patients			
	Asian (n=681)		Non-Asia (n=402)	
Mutation	Male	Female	Male	Female
Ex19del	129 (19)	209 (31)	55 (14)	177 (44)
L858R	103 (15)	216 (32)	29 (7)	107 (27)
S768I	4 (1)	4 (1)	1 (<1)	2 (1)
G719X	4 (1)	9 (1)	2 (1)	9 (2)
Ex20ins	2 (<1)	7 (1)	4 (1)	15 (4)
T790M	3 (<1)	6 (1)	3 (1)	7 (2)
L861Q	3 (<1)	1 (<1)	0	4 (1)

Screening for EGFR mutations may be considered in the adjuvant setting although EGFR TKIs are not recommended as the current standard of care in this setting

EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.
Tsuboi M, et al. Presented at the ESMO Congress 2019; abstract no. 1440PD.

Impact of ramucirumab (RAM) + erlotinib (ERL) on EGFR mutations in circulating tumour DNA – The 1st report of a biomarker study in Japanese patients from RELAY: Global Phase III study of ERL + RAM or placebo (PL) in 1L metastatic NSCLC with EGFR activating mutations

K. Nishio

Liquid biopsy exploratory sub-study of the RELAY trial to investigate acquired resistance to EGFR TKIs, including whether RAM+ERL affects the occurrence of T790M and/or other mutations of acquired resistance

RELAY study found RAM+ERL improved PFS compared with PL+ERL in EGFR mutation-positive metastatic NSCLC

Biomarker population 1: patients with results from baseline (with no T790M detected) and post-progression 30-day follow-up (42 patients; 19 RAM+ERL and 23 PL+ERL)

Biomarker population 2: patients with EGFR activation mutations detected in post-progression 30-day follow-up sample (23 patients; 8 RAM+ERL and 15 PL+ERL)

EGFR, epidermal growth factor receptor; ERL, erlotinib; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PL, placebo; RAM, ramucirumab; TKI, tyrosine kinase inhibitor.

Nishio K, et al. Presented at the ESMO Congress 2019; abstract no. 1523P.

Impact of ramucirumab (RAM) + erlotinib (ERL) on EGFR mutations in circulating tumour DNA – The 1st report of a biomarker study in Japanese patients from RELAY: Global Phase III study of ERL + RAM or placebo (PL) in 1L metastatic NSCLC with EGFR activating mutations

K. Nishio

The ddPCR population included 42 patients and had a similar PFS HR to the full ITT population

The rates of EGFR T790M mutation positivity at the 30-day follow-up were not different between treatment groups: 26% (5 of 19) (95% CI 12-49%) in RAM+ERL and 30% (7 of 23) (95% CI, 16-51%) in PL+ERL (p=1.0)

When evaluating the cumulative post-progression T790M rates according to the number of cycles received prior to disease progression, the rates for patients who had progressed by Cycle 4, Cycle 12, or Cycle 53 were 0%, 17% and 26% for RAM+ERL, and 0%, 33% and 30%, respectively for PL+ERL

Preliminary results suggest that RAM+ERL may potentially delay the occurrence of resistance from T790M mutation

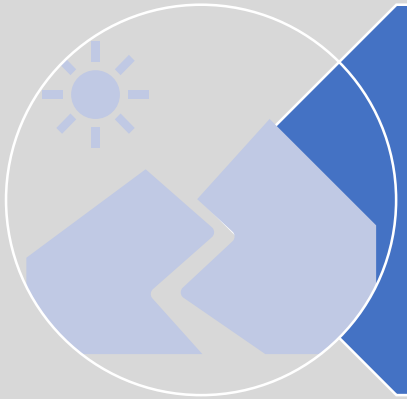
Treatment with RAM+ERL resulted in superior PFS, with similar T790M rates at progression as compared to PL+ERL, suggesting the potential for effective EGFR-directed therapy after progression on RAM+ERL

EGFR, epidermal growth factor receptor; ERL, erlotinib; ITT, intention to treat; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PL, placebo; RAM, ramucirumab; TKI, tyrosine kinase inhibitor.

Nishio K, et al. Presented at the ESMO Congress 2019; abstract no. 1523P.

Implications for practice

Data from the ESMO Congress 2019 have changed the treatment landscape for EGFR-mutated NSCLC



On the horizon are new combination therapies involving third-generation EGFR TKIs to further improve outcomes for patients

EGFR, epidermal growth factor receptor; NSCLC, non-squamous non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

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