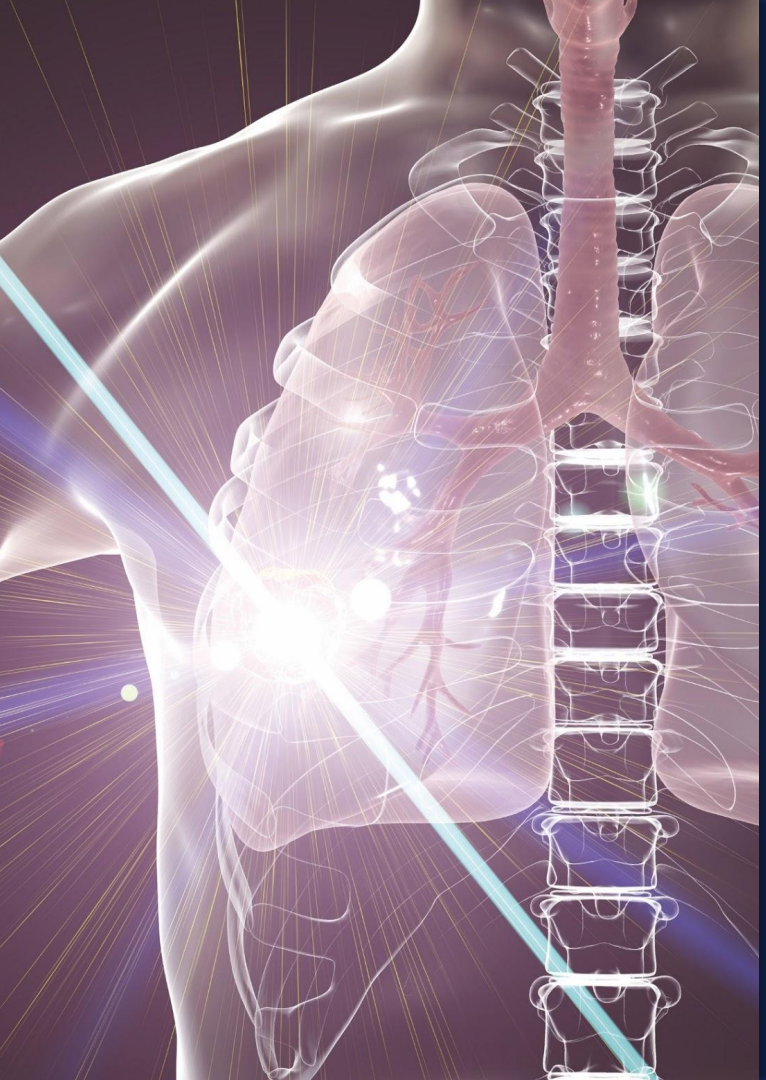

touchPANEL DISCUSSION

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

Funded by an independent medical education request from Astra Zeneca

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Expert panel

Prof. Ross Camidge (Chair)

Division of Medical Oncology,
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Japan

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Learning objectives

- Discuss issues related to biomarker testing, including timing and access
- Describe treatment sequencing options and the paradigms for therapy of EGFR+ NSCLC
- Recall recent data for 3rd-generation EGFR TKIs in first-line EGFR+ NSCLC and describe real-world evidence

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

Agenda

Barriers to accessing biomarker testing

Presentation: Ross Camidge
Panel discussion: Byoung Chul Cho, Niels Reinmuth and Yasushi Goto; moderated by Ross Camidge

What are possible approaches to treatment sequencing for EGFR+ NSCLC?

Presentation: Ross Camidge
Panel discussion: Byoung Chul Cho, Niels Reinmuth and Yasushi Goto; moderated by Ross Camidge

What did we learn about 3rd-generation EGFR TKIs in 2019 and how will it affect our patients?

Presentation: Ross Camidge
Panel discussion: Byoung Chul Cho, Niels Reinmuth and Yasushi Goto; moderated by Ross Camidge

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

Barriers to accessing biomarker testing

Prof. Ross Camidge (Chair)

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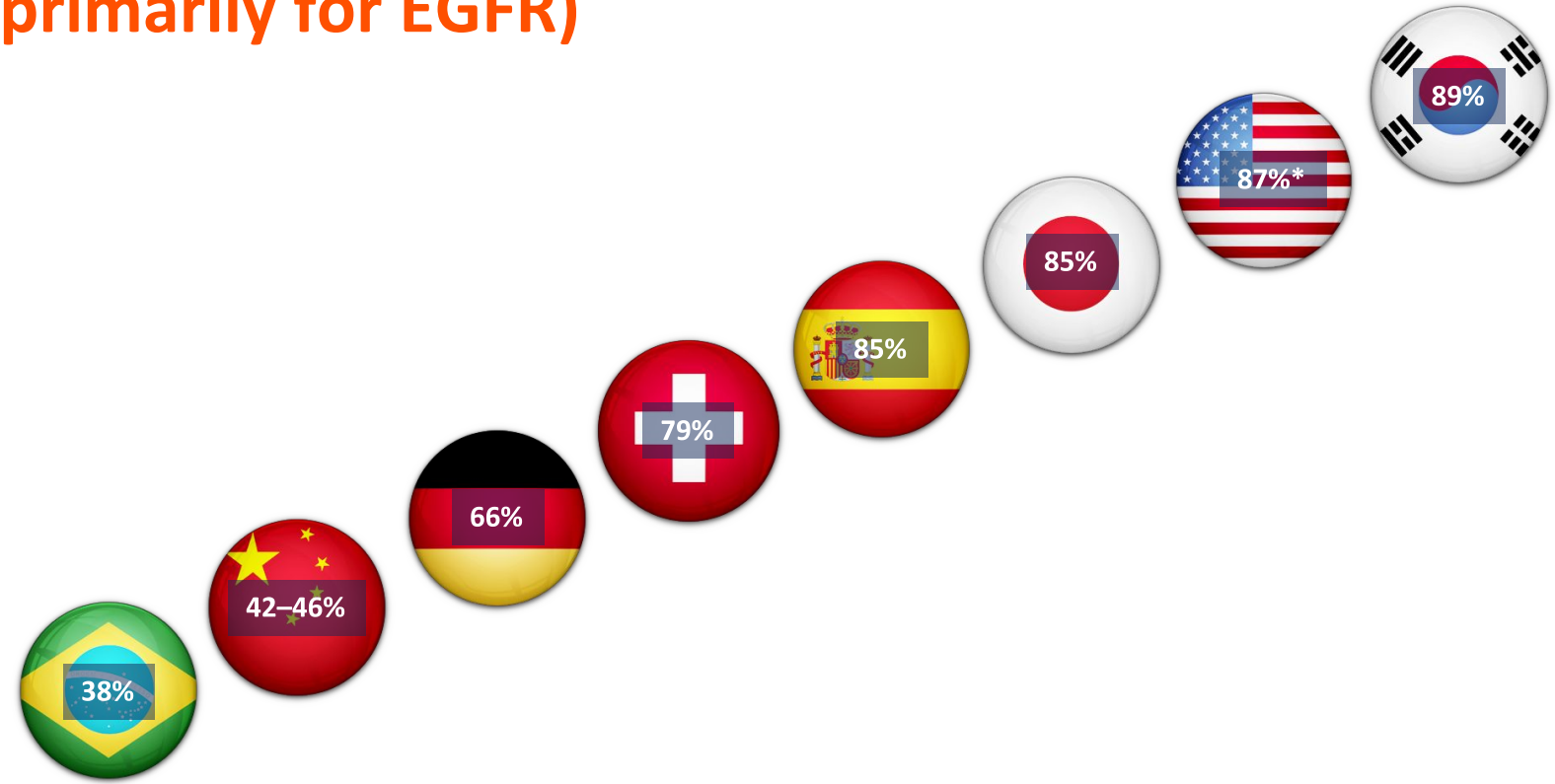
Biomarker testing across the globe (primarily for EGFR)



*In academic centres.

Pennell NA, et al . American Society of Clinical Oncology Educational Book 2019;39:531–542; Audibert CM, et al. Trends in the Molecular Diagnosis of Lung Cancer;2018.

Resistance mechanisms to osimertinib and first-/second-generation EGFR TKIs

- CNS progression
- On target resistance – T790M, C797S, others
- Bypass pathways (MET, ALK, KRAS, BRAF, etc)
- Phenotypic change (EMT, small cell transition)

CNS, central nervous system; EGFR, epidermal growth factor; EMT, epithelial–mesenchymal transition; TKI, tyrosine kinase inhibitor.

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

Exploratory analysis of ctDNA for the early detection of original EGFR mutation +/- T790M/C797S disease progression of the phase III FLAURA study which evaluated the efficacy of osimertinib vs. first generation EGFR TKI in NSCLC patients with typical activating EGFR mutations

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

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

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.

Panel discussion

Byoung Chul Cho, Niels Reinmuth and Yasushi Goto

Moderated by Ross Camidge

What is the standard approach for initial biomarker testing in your region, and do you incorporate liquid biopsy?

How do you monitor patients with EGFR-mutated NSCLC during therapy?

- **What kind of scans and at what frequency?**
- **Do you also use blood tests (CBC/CMP, serum tumour markers, cfDNA)?**

CBC, complete blood count; CMP, comprehensive metabolic panel; cfDNA, circulating free DNA.

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What are possible approaches to treatment sequencing for EGFR+ NSCLC?

Prof. Ross Camidge (Chair)

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Denver,
USA

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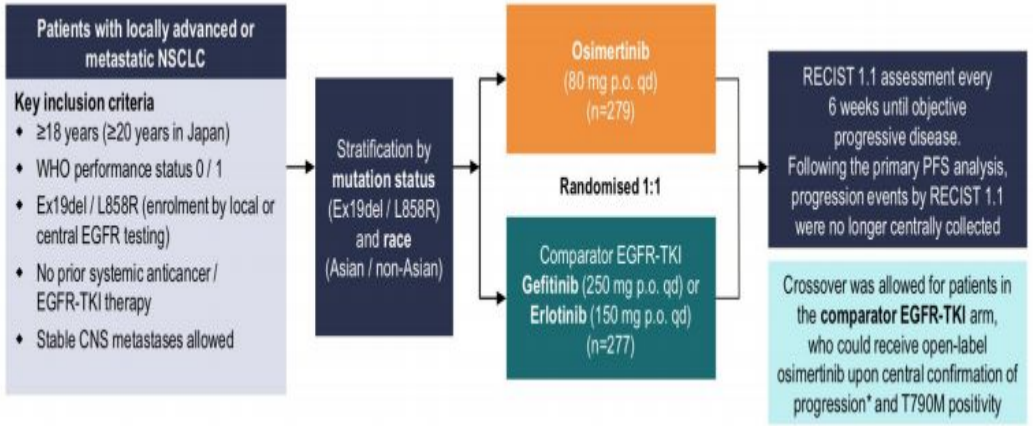
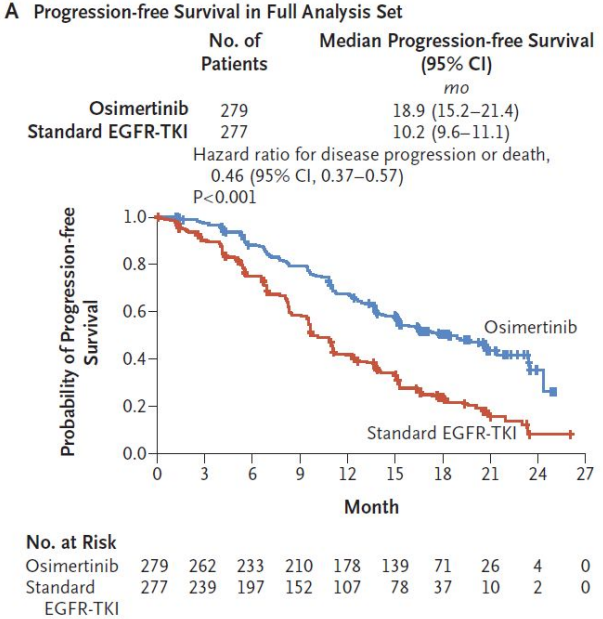
Therapeutic options for patients with advanced EGFR mutant NSCLC (all lines)

- Platinum-doublet chemotherapy, +/- antiangiogenics +/- anti-PD1/L1
- Other cytotoxic chemotherapies
- First- or second-generation EGFR TKIS
- Third-generation EGFR TKIs
- Local ablative therapies (radiation/surgery)
- Combinatorial approaches – TKI + chemo, TKI + antiangiogenic, TKI + TKI, TKI + local ablative approaches

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

Osimertinib in untreated EGFR-mutated advanced NSCLC





CNS, central nervous system; EGFR, epidermal growth factor; EGFRm, mutated EGFR; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.
Soria JC, et al. N Engl J Med 2018;378:113–125.

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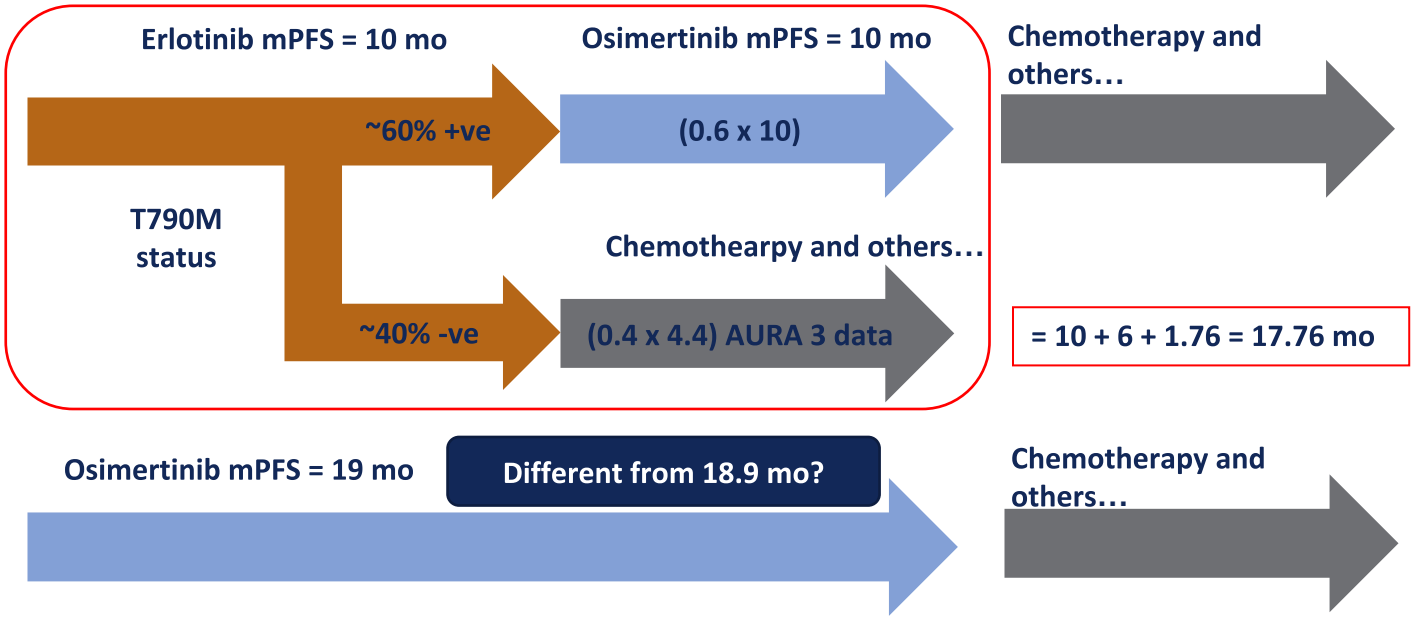
PFS of TKI based options

Regimen	Trials	Median PFS (Months)	Reference(s)
Gefitinib	WJTOG3405, NEJ002, LUX-Lung 7, ARCHER 1050	9.2–10.9	1–4
Erlotinib	EURTAC, OPTIMAL, NEJ026	10.4–13.3	5–7
Afatinib	LUX-Lung 3, LUX-Lung 6, LUX-Lung 7	11.0–11.1	8–10
Dacomitinib	ARCHER 1050	14.7	4
Erlotinib and bevacizumab	NEJ026	16.9	7
Osimertinib (second line)	AURA3	10.1	11
Osimertinib (first line)	FLAURA	18.9	12

PFS, progression free survival; TKI, tyrosine kinase inhibitor.

1. Maemondo M, et al. N Engl J Med 2010;362:2380–2388; 2. Mitsudomi T, et al. Lancet Oncol 2010;11:121–128; 3. Park K, et al. Lancet Oncol 2016;17:577–589; 4. Wu YL, et al. Lancet Oncol 2017;18:1454–1466; 5. Zhou C, et al. Lancet Oncol 2011;12:735–742; 6. Rosell R, et al. Lancet Oncol 2012;13:239–246; 7. Furuya N, et al. ASCO Ann Meet Proc 2018;27:9006; 8. Sequist LV, et al. J Clin Oncol 2013;31:3327–3334; 9. Wu YL, et al. Lancet Oncol 2014;15:213–222. 10. Park K, et al. Lancet Oncol 2016;17:577–589; 11. Mok T.S, et al. N Engl J Med 2017;376:629–640; 12. Soria JC, et al. N Engl J Med 2018:378;113–125.

Sequencing of EGFR TKIs: which strategy is best?



EGFR, epidermal growth factor receptor; mo, months; mPFS, median progression free survival; TKI, tyrosine kinase inhibitor.

Zhou C, et al. Lancet Oncol 2011;12:735–742; Rosell R, et al. Lancet Oncol 2012;13:239–246; Furuya N, et al. ASCO Ann Meet Proc 2018;27:9006; Sequist LV, et al. J Clin Oncol 2013;31:3327–3334; Wu YL, et al. Lancet Oncol 2014;15:213–222. Park K, et al. Lancet Oncol 2016;17:577–589; Mok T.S, et al. N Engl J Med 2017;376:629–640; Soria JC, et al. N Engl J Med 2018:378;113–125

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Panel discussion

Byoung Chul Cho, Niels Reinmuth and Yasushi Goto

Moderated by Ross Camidge

What is the rationale behind your choice of therapy sequence in patients with advanced EGFR mutant NSCLC?

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

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What are the considerations clinicians need to make following progression at each line if therapy for patients with advanced EGFR mutant NSCLC?

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

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What did we learn about 3rd-generation EGFR TKIs in 2019 and how will it affect our patients?

Prof. Ross Camidge (Chair)

Division of Medical Oncology,
University of Colorado School of Medicine,
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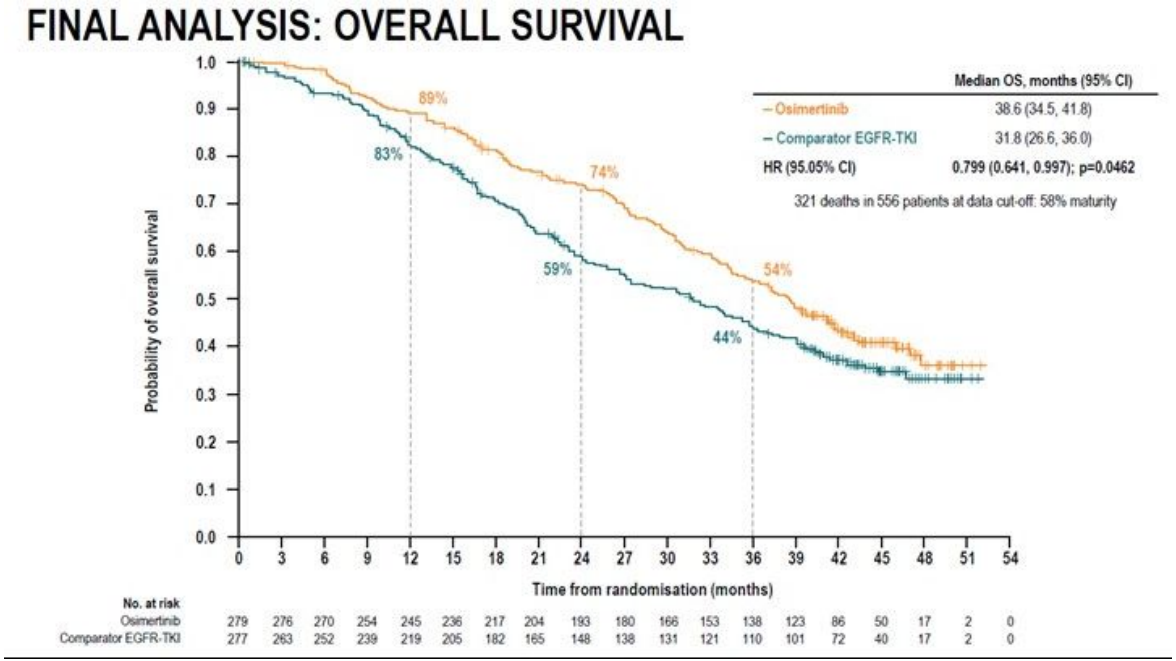
Third generation EGFR TKIs in development

Name	Status of development	Off-target kinase inhibition	Reference
Osimertinib (AZD-9291)	FDA licensed post first/second generation TKIs in presence of T790M; first-line use in advanced EGFR mutant NSCLC	>60% of a limited number of additional kinases, including ErbB2/4, ACK1, ALK, BLK, BRK, MLK1 and MNK2	1
Olmutinib (HM61713)	Phase I/II trial showed potential in T790M-positive NSCLC after failing ≥1 prior EGFR TKI	Unknown	2
Nazartinib (EGF816)	Phase II. Recent phase I combination trials	ALK, ABL1, BRAF, FGFR3, FLT3, KIT, LRRK2, MET, PIK3CA, RET	3
Lazertinib (YH25448)	Phase I/II	AXL, FER, MLK1, MER, RET	4
CK-101 (RX518)	Phase I/II. Phase III planned	Unknown	5

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

1. Santarpia M, et al. Lung Cancer (Auckl) 2017;8:109–125. 2. Kim DW, et al. Lung Cancer 2019;135:66–72; 3. Jia Y, et al. Cancer Res 2016;76:1591–1602. 4. Yun J, et al. Clin Cancer Res 2019; Epub ahead of print; 5. Johnson M, et al. J Thorac Oncol. 2018;13:S323.

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



Median follow-up for OS in all patients was 35.8 months in the osimertinib arm and 27.0 months in the comparator EGFR TKI arm

Cross-over was allowed within trial upon central confirmation of progression and T790M positivity and 25% of patients crossed over from the comparator EGFR TKI to osimertinib

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

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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Panel discussion

Byoung Chul Cho, Niels Reinmuth and Yasushi Goto

Moderated by Ross Camidge

Will the improvements in overall survival following used of third-generation EGFR TKIs reported in 2019 change clinical practice?

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

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Given the failure of many previous EGFR TKI studies to show a benefit to overall survival why is FLAURA different?

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

With osimertinib and the other third generation EGFR TKIs in development, what are the unmet needs we should be focussing on in the future?

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

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Conclusions

Ross Camidge

Thank you for watching this on-demand event

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