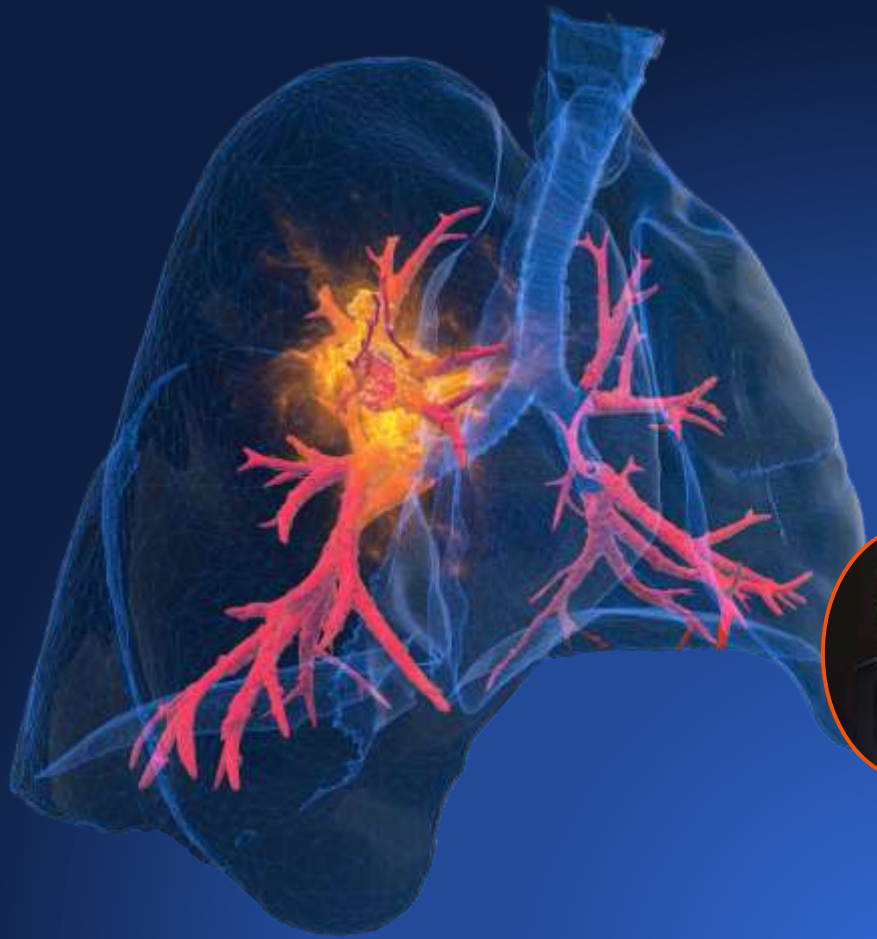

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

touchCONGRESS webinar

Progress in the management of *EGFR*-mutant NSCLC in 2020: Where are we now?

Dr Roy S Herbst
Professor of Medicine and Pharmacology, Chief of Medical Oncology, Director of the Thoracic Oncology Research Program; Associate Director for Translational Science, Yale School of Medicine and Yale Cancer Center
New Haven, Connecticut, USA

Webinar recorded: June 2020

Funded by an independent medical education request from AstraZeneca

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Learning objectives

- Recall efficacy and safety data for EGFR-TKIs for patients *EGFR*-mutant NSCLC, including those with early-stage disease
- Describe how molecular testing can help guide appropriate therapy approaches for patients with *EGFR*-mutant NSCLC
- Discuss how the treatment pathway for the use of targeted therapies in the management of *EGFR*-mutant NSCLC is evolving now and in the future

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

Webinar overview

EGFR-mutant NSCLC

- The clinical efficacy and safety of EGFR-TKIs – where are we now?
- ASCO20 Virtual – Role of targeted therapies in the adjuvant setting
- ASCO20 Virtual – Novel treatment strategies in the metastatic setting
- ASCO20 Virtual – Advances in genomic testing in NSCLC

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

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EGFR-mutant NSCLC: Where are we now?

Key questions for translating current evidence into clinical practice

- Following the results of the phase III FLAURA trial, should overall survival be the primary efficacy endpoint in the metastatic setting?
- Can we improve survival outcomes using combination therapies in the first-line setting?
- Is there a role for using targeted therapy earlier?

Without genotyping we are not able to personalize treatment

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

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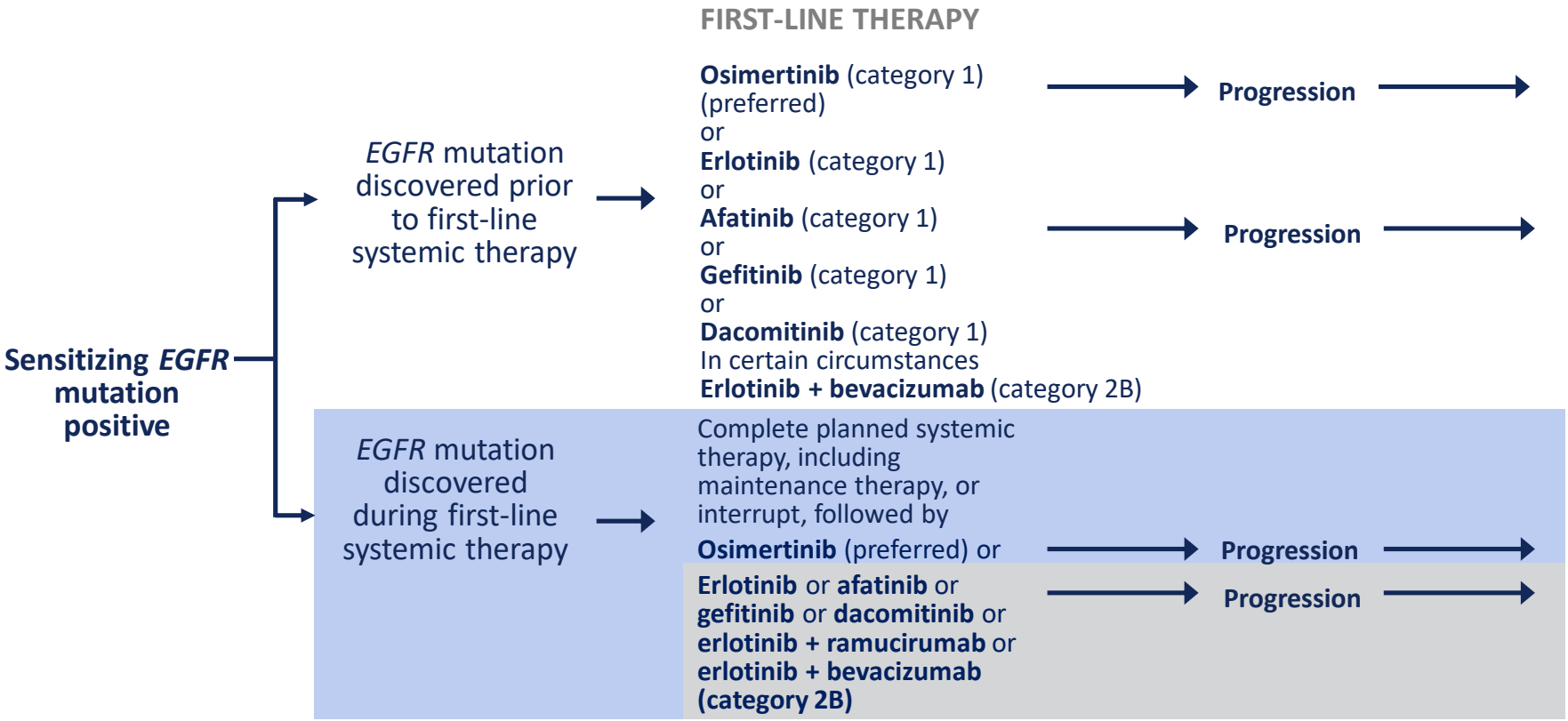
NCCN Guidelines – May 2020

SENSITIZING *EGFR*-MUTANT NSCLC



EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.
Adapted from NCCN. Non-Small Cell Lung Cancer Version 5. 2020; May 27, 2020.

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Will targeted therapies play a significant role in the adjuvant setting?

Progress in the management of *EGFR*-mutant NSCLC in 2020: Where are we now?

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

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Early-stage NSCLC

- Although surgery is regarded as the best possible treatment, only 20–25% of tumours are suitable for potentially curative resection[1]
- Adjuvant cisplatin is the standard of care in stage II-IIIA completely resected NSCLC[2]
- Stage III NSCLC at diagnosis is associated with poor prognosis
  - The 5-year survival rate is between 35% and 50% depending on the time interval between surgery and the first course of chemotherapy[3]
  - Survival rate is the poorest when chemotherapy is delayed beyond 60 days after surgical resection ($p<0.001$)[3]

- Is there a role for targeted therapy earlier?

NSCLC, non-small Cell lung cancer.

1. Arriagada R, et al. *Lancet.* 2010; 375:1267–1277. 2. Burdett S, et al. *Cochrane Database of Systematic Reviews.* 2015;Issue 3. Art. No.: CD011430.
3. Wang B-Y, et al. *PLoS ONE.* 2016;11: e0163809.

KINDLE: Contemporary management and associated outcomes of patients with stage III NSCLC in a real-world setting: A multicounty observational study

Jazieh AR, et al.

To characterize patients, treatment patterns and their associated outcomes for stage III NSCLC in a real-world setting in the pre-IO era

Study enrolment period: January 1st, 2013 to December 31st, 2017

- KINDLE is a retrospective, multicountry, multicentre study capturing data on patient and disease characteristics, treatments and outcomes for stage III NSCLC

- 3151 patients enrolled at 125 centres in three geographical regions (≥9 months follow up):
  - Middle East and North Africa, n=1046
  - Asia, n=1874
  - Latin America, n=231

Baseline characteristics	
Median age	63 years (range 21–92)
Males	76.5%
Smoking history	69.2%
Stage IIIA (AJCC 7th ed.)	55.9%
Adenocarcinoma	53.7%
Squamous cell carcinoma	36.6%
Curative surgical resection	21.4%

- **>25 first-line regimens**: cCRT = 29.4%, CT alone = 17%, sCRT = 10.4%, RT alone = 8.5%
- **Stage IIIA patients**: those eligible for and undergoing surgery + CT had longer mOS and mPFS than patients not undergoing surgery, and received other treatments
- **Stage IIIB patients**: mOS and mPFS significantly improved for cCRT vs CT alone or RT alone or sCRT
- Overall mOS in stage IIIA and stage IIIB were 43.8 mos and 27.7 mos, respectively
- Patients with complete resections had mPS and mOS of 21 months

Real-world data reveal diversity of treatment practices in stage III NSCLC. Survival outcomes remain poor in stage III disease and there is a need for implementation of guidelines and improved access to innovative treatments to optimize outcomes

cCRT, concurrent chemo-radiotherapy; CI, confidence interval; CT, chemotherapy; IO, immunotherapy; mos, months; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; RT, radiotherapy; sCRT, sequential chemo-radiotherapy.

Jazieh AR, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9043).

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ALCHEMIST: Adjuvant targeted therapy or immunotherapy for high-risk resected NSCLC

Sands J, et al.

To report updated enrolment to the ALCHEMIST platform: a trial offering concurrent immunotherapy with adjuvant chemotherapy

- ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)
- Screening trial A151216 enrols patients (n=5362 registered) with completely resected stage IB (≥4 cm)–IIIA (per AJCC 7) NSCLC – 3 studies ongoing:

Study	Biomarker	Patients	Adjuvant vs observation
A081105	*EGFR* mutations	367	Erlotinib
E4512	*ALK* fusions	109	Crizotinib
EA5142	PD-L1 status	935	Nivolumab

- New adjuvant study A081801 (Spring 2020)
- Patients randomized to 1 of 3 treatment arms:
  - Chemo-IO with pembrolizumab during and after chemotherapy
  - Sequential chemotherapy followed by pembrolizumab
  - Chemotherapy alone

Early biomarker testing used to facilitate enrolment to targeted therapy trials

Inclusion criteria:
- Enrolled to A151216, negative for *EGFR* and *ALK* alterations, and with PD–L1 testing completed
- Aged >18 years, Eastern Cooperative Oncology Group performance status 0-1, standard organ function values

Exclusion criteria:
- Prior lung cancer therapy except surgery
- Pregnancy/ breastfeeding, active second malignancy <3 years

By building off the ongoing ALCHEMIST platform, study aims to facilitate rapid enrolment to A081801 across participating NCTN sites

ALK, anaplastic lymphoma kinase; Chemo-IO, chemo-immunotherapy; EGFR, epidermal growth factor receptor; NCTN, National Clinical Trials Network; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1.

Sands J, et al. *J Clin Oncol.* 2020;38:(suppl; abstr TPS9077).

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CTONG1104: Adjuvant gefitinib versus chemotherapy for stage II-IIIA *EGFR*-mutant NSCLC – final overall survival analysis randomized phase III trial

Wu, Y-L et al.

To report OS data from the phase III ADJUVANT/CTONG1104 study*

Data cut-off: January 2020

Patients (n=222) with *EGFR*-activating mutation stage II-IIIA (N1–N2) NSCLC were randomized 1:1 to:

GEF	VIN + CIS
Gefitinib 250 mg once per day for 24 months (n=111)	Vinorelbine 25 mg/m^2, d1 and d8 plus cisplatin (75 mg/m^2, d1) every 3 weeks for 4 cycles (n=111)

- Median follow-up was 80.0 months
- All predefined subgroups had no significant difference. However, trend in favour of gefitinib

Results	GEF	VIN + CIS	
mOS, months	**75.5**	**62.8**	HR=0.92 95% CI, 0.62–1.36 p=0.674
3-year OS, %	**68.6**	**67.5**	-
5-year OS, %	**53.8**	**52.4**	-
3-year DFS, %	**30.8**	**19.8**	$p_{3\text{-}y}$=0.001
5-year DFS, %	**23.4**	**23.7**	$p_{5\text{-}y}$=891

No novel unexpected SAE were observed during follow up

*Primary endpoint: DFS in the ITT population. Secondary endpoints included: OS, 3- and 5-year DFS rate, 5-year OS rate.

The DFS survival advantage observed in the ADJUVANT trial did not translate to significant OS difference. The duration of GEF adjuvant treatment ≥18 months may provide longer OS benefit.

CI, confidence interval; CIS, cisplatin; d, day; DFS, disease-free survival; EGFR, epidermal growth factor receptor; GEF, gefitinib; HR, hazard ratio; ITT, intention-to-treat; mOS, median overall survival; NSCLC, non-small cell lung cancer; OS, overall survival; SAE, serious adverse events; VIN, vinorelbine.

Wu Y-L, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9005).

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ADAURA: Osimertinib as adjuvant therapy in patients with stage IB-IIIA *EGFR*-mutant NSCLC after complete tumour resection

Herbst, R et al.

To report an unplanned interim analysis from the ADAURA trial: study was unblinded early due to efficacy of osimertinib

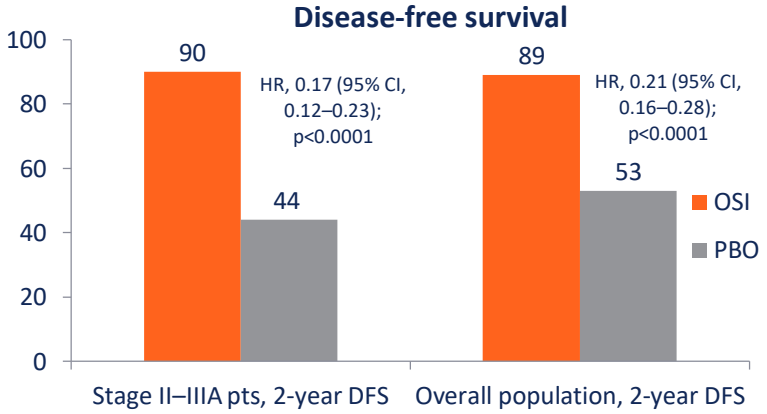
Data cut-off: January 2020

- Phase III, double-blind, randomized study assessing efficacy and safety of OSI vs PBO in pts with stage IB–IIIA *EGFR*-mutant NSCLC after complete tumour resection and adjuvant CT

OSI	PBO
OSI 80 mg once daily orally (n=339)	Placebo 80 mg once daily orally (n=343)

1º endpoint: DFS by investigator in stage II–IIIA pts
2º endpoints: OS and safety

- Treatment: ≤3 years, stratified by stage (IB/II/IIIA), mutation type (ex19del/L858R), and race (Asian/non-Asian); eligible pts: ≥18 years (Japan/Taiwan: ≥20), WHO PS 0/1



- OS was immature (4% maturity) with 29/682 deaths (OSI, n=9, PBO n=20) at DCO

Safety profile was consistent with the known safety profile of OSI

Adjuvant osimertinib provided statistically significant and clinically meaningful improvement in DFS in patients with stage IB/II/IIIA *EGFR*-mutant NSCLC after complete tumour resection and adjuvant CT

CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; DCO, data cut-off; EGFR, epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; OS, overall survival; OSI, osimertinib; PBO, placebo; PS, performance status; pts, patients.

Herbst R, et al. *J Clin Oncol.* 2020;38:(suppl; abstr LBA5).

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Summary

This can be based on Dr Herbst's commentary

How is the treatment landscape evolving in metastatic *EGFR*-mutant NSCLC?

Progress in the management of *EGFR*-mutant NSCLC in 2020: Where are we now?

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

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EGFR-mutant metastatic NSCLC

- The survival outcomes of the FLAURA phase III trial support osimertinib as the first-line standard of care for patients with *EGFR*-mutant advanced-stage NSCLC. However, knowledge of novel mechanisms of resistance to osimertinib is a challenge for clinicians in determining optimal sequential treatment options.[1]
- There is a need to maximise the response to treatment in the first-line setting for optimal outcomes.[2] Are combination approaches the way forward?
- The question is which combination strategy and for which patients?
- The recent results of the phase III ADAURA study, mean that the treatment paradigm for NSCLC continues to evolve rapidly.

- What do the latest data tell us about the evolving treatment paradigm in advanced NSCLC?

NSCLC, non-small-cell lung cancer.

1. Remon J, et al. *Nat Rev Clin Oncol.* 2020;17:202–203; 2. Planchard D, et al. *Clin Can Res.* 2019;25:2058–2063.

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ATLAS: Phase III, open-label, randomized study of atezolizumab in combination with carboplatin + paclitaxel + bevacizumab compared with pemetrexed + cisplatin or carboplatin with stage IV NSCLC with activating *EGFR* mutation or *ALK* translocation

Park S, et al.

Outline design of new study of atezolizumab combined with VEGF inhibitor and conventional cytotoxic chemotherapy in patients with activating *EGFR* mutation and *ALK* translocation

Study period: treatment initiated August 2019 (n=19); primary analyses in Q3, 2022[1]

- Phase III, open-label, multicenter, two-arm study – population stratified based on *EGFR* vs *ALK* and presence of brain metastases (n=228) and randomized in a 2:1 ratio

ARM A	ARM B
4 or 6 cycles of ABCP followed by maintenance atezolizumab and bevacizumab every 3 weeks	4 or 6 cycles of pemetrexed + cisplatin/carboplatin and pemetrexed maintenance every 3 weeks

Inclusion criteria:

- Diagnosis of stage IV non-squamous NSCLC, with activating *EGFR* mutation or *ALK* translocation
- Cytotoxic chemotherapy-naïve
- Disease progression to treatment with ≥1 EGFR- or ALK-TKI
- If T790M mutation present after 1st or 2nd generation EGFR-TKI, second line 3rd generation EGFR-TKI mandatory
- T790M positive patients restricted to <30% of study population
- Primary endpoint: PFS
- Secondary endpoints include: OS, ORR, DCR and QoL

Study is designed and conducted to confirm the recent key subgroup analyses from IMpower 150, which showed positive outcomes of atezolizumab combined with VEGF inhibitor and conventional cytotoxic chemotherapy[2]

ABCP, atezolizumab plus bevacizumab + carboplatin + paclitaxel; ALK, anaplastic lymphoma kinase; DR, disease control rate; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

1. Park S, et al. *J Clin Oncol.* 2020;38:(suppl; abstr TPS9636). 2. Reck M, et al. *Lancet Respir Med.*2019;7:387–401.

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RELAY+: Exploratory study of ramucirumab plus gefitinib in untreated patients with *EGFR*-mutant metastatic NSCLC

Nishio M, et al.

To report initial results from RELAY+ (Part C), an open-label, single-arm, exploratory study evaluating RAM plus GEF in East Asian patients

- Part C of RELAY is an open-label single arm study investigating RAM + GEF in untreated patients (n=82)

RAM 10 mg/kg Q2W plus GEF 250 mg/day until disease progression or unacceptable toxicity

Patients with metastatic NSCLC and *EGFR* exon 19 deletions (Ex19del) or exon 21 substitution mutation (Ex21.L858R)

- 1-year PFS rate* (assuming a 1-year PFS rate of 55% for RAM + GEF), tumour response, biomarkers, and safety were assessed
- *EGFR* T790M status (baseline/30-day follow-up) assessed

Baseline characteristics	
Female	65.9%
Never-smokers	65.9%
Ex19del	43.9%

Post-progression *EGFR* T790M was seen in 7 of 9 (78%) patients with 30-day follow-up NGS results in which *EGFR* activating mutation was detected

Results	
Median follow-up	13.8 months
PFS	
• Overall	65.0%
• Ex19del	67.2%
• Ex21.L858R	63.4%
ORR	70.7%
DCR	98.8%

Grade ≥3 treatment-emergent AEs reported in >5% of patients were ALT increased (23.2%), hypertension (22.0%), and AST increased (12.2%)

Study met primary endpoint: efficacy of RAM + GEF in RELAY+ similar to RAM + ERL in RELAY, with the safety profile of the combination similar to that of the individual drugs

*Primary endpoint . AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCR, disease control rate; EGFR, epidermal growth factor receptor; ERL, erlotinib; GEF, gefitinib; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RAM, ramucirumab.

Nishio M, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9564).

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NEJ026: Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harbouring activating *EGFR*-mutations

Maemondo M, et al.

To report overall survival in patients with *EGFR*-mutated NSCLC treated with bevacizumab + erlotinib vs erlotinib monotherapy

Data cut-off: November 2019

- Phase III, randomized trial in which CT-naïve patients (n=226) with advanced non-squamous EGFR-mutant NSCLC were randomly assigned to:

Bevacizumab + erlotinib (n=112)	**Erlotinib (n=112)**
Erlotinib 150 mg daily + bevacizumab 15 mg/kg iv q3w	Erlotinib 150 mg daily

1º endpoint: PFS; 2º endpoints: OS, RR, safety and QoL

	Bevacizumab + erlotinib (BE)	**Erlotinib (E)**	**HR (95% CI)**
Median OS	50.7 months (37.3–NR)	46.2 months (38.2–NR)	1.00 (0.68 to 1.49)
Median PFS2*	28.6 months (22.1–35.9)	24.3 months (20.4–29.1)	0.773 (0.562 to 1.065)
Median OS 2nd line OSI	50.7 months (38.0–50.7)	40.1 months (29.5–NR)	0.645 (0.40 to 1.03)

- Median follow-up time 39.2 months

BE treatment induces T790M resistance. OSI treatment was equally efficacious after either BE or E treatment

Additional effect of bevacizumab on erlotinib monotherapy for *EGFR*-mutant NSCLC, its efficacy gradually decreased in the order of PFS, PFS2 and OS, with no significant differences. Findings are concordant with J025567 study

*PFS2, median survival time between enrolment and progressive disease of second-line treatment. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; NR, not reached; OS, overall survival; OSI, osimertinib; PFS, progression-free survival; QoL, quality of life; RR, response rate.

1. Maemondo M, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9506). 2. Seto T, et al. *Lancet Oncol.* 2014;15:1236–44.

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High-dose osimertinib for CNS progression in *EGFR*-mutant NSCLC: A multi-institutional experience

Piper-Vallillo A, et al.

To report multi-institutional experience with dose-escalation of osimertinib up to a maximum dose of 160 mg daily

- Patients (n=105) with advanced *EGFR*-mutant NSCLC treated with OSI 160 mg daily were retrospectively reviewed to assess the CNS efficacy of dose escalation for CNS progression (CNS PD) – analysis focused on 3 cohorts:

A (n=24)	B (n=34)	C (n=11)
		
OSI 80 mg to 160 mg for CNS PD without CT and/or RT	OSI 80 mg to 160 mg for CNS PD while receiving CT and/or RT	OSI 160 mg for CNS PD as initial dose without CT and/or RT

- MedDurCNSCon defined as time from start of OSI 160 mg to CNS PD or discontinuation
- 69 (26 male, median age 57 years) *EGFR*-mutant NSCLC patients received OSI 160 mg for CNS PD
- 61 patients had isolated CNS/LMD PD, without systemic PD

	MedDurCNSCon (mos)
Cohort A	
• OSI 160 mg monotherapy	3.8 (95% CI, 1.7–5.8)
• Isolated LMD	5.8 (95% CI, 1.7–9.1)
• Parenchymal metastases only	2 (95% CI, 1–4.9)
Cohort B	5.1 (95% CI, 3.1–6.5)
Cohort C	4.2 (95% CI, 1.6–NA)

Dose escalation to OSI 160 mg daily provided modest benefit with median 3.8 months added CNS disease control, with no severe or life-threatening side effects

CI, confidence interval; CT, chemotherapy; EGFR, epidermal growth factor receptor; LMD, leptomeningeal disease; MedDurCNSCon, median duration of central nervous system (CNS) disease control; NSCLC, non-small cell lung cancer; OSI, osimertinib; PD, progressive disease; RT, radiotherapy.

Piper-Vallillo A, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9586).

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Nazartinib in treatment-naïve *EGFR*-mutant NSCLC: Updated phase II results

Shao-Weng Tan D, et al.

To report updated phase II results, including OS, from a study of third-generation EGFR-TKI, nazartinib, in patients with treatment-naïve patients with locally advanced/metastatic *EGFR*-mutant NSCLC (with and without BM)

Oral nazartinib 150 mg once daily (continuous schedule)

Treatment-naïve adult (n=45) with activating *EGFR*-mutations (L858R or ex19del), stage IIIB/IV advanced NSCLC with neurologically stable and controlled BM

- Median age 64 yrs; 26 pts ECOG PS 1; 19 pts had BM
- *EGFR* mutations: 56% ex19del, 40% L858R, 4% other

- 1º : ORR by BIRC per RECIST v1.1
- 2º : DCR, DOR, TTR, PFS, OS, safety

	BM: Yes (n=18)	BM: No (n=27)	All patients (n=45)
ORR, n (%) (95% CI)	12 (67) (41–87)	19 (70) (50–86)	31 (69) (53–82)
DCR, n (%) (95% CI)	18 (100) (82–100)	23 (85) (66–96)	41 (91) (79–98)
Median DOR, mo (95% CI)	15 (9–25)	NE (15–NE)	25 (14–NE)
Median PFS, mo (95% CI)	17 (11–21)	NE (15–NE)	18 (15–NE)
Median OS, mo (95% CI)			NE (23–NE)

Most frequent grade 3/4 AEs (≥10%, all causality): maculopapular rash (11%; all grade 3), increased lipase (11%]; no clinical pancreatitis

In treatment-naïve patients with advanced *EGFR*-mutant NSCLC, median OS with nazartinib was not reached at 33 months and the safety profile was manageable. Nazartinib is a promising new therapy, including in patients with BM

AEs, adverse events; BIRC, blinded independent review committee; BM, brain metastasis; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ECOG PS, performance status; EGFR, epidermal growth factor receptor; mo, month; NSCLC, non-small cell lung cancer; OS, overall survival; TTR, time to response; PFS, progression-free survival.

Shao-Weng Tan D, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9574).

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Summary

This can be based on Dr Herbst's commentary

What advances in mutation testing will further support precision medicine in *EGFR*-mutant NSCLC?

Progress in the management of EGFR-mutant NSCLC in 2020: Where are we now?

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

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Genotyping in NSCLC

- Genotyping is required to identify patients with advanced cancer eligible for targeted therapy
- However, many patients do not receive biomarker testing due to limitations of tissue analysis
- Next-generation sequencing (NGS) and liquid biopsy may overcome some of these limitations
- Guidelines discuss the option of broad NGS for efficiency. However, little is known about the contemporary patterns and clinical features of NGS and other testing technologies

- What do the latest data tell us about the clinical utility of newer testing methods to detect *EGFR*-mutant NSCLC?

NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell cancer.
Ettinger DS, et al. *J Natl Compr Canc Netw.* 2019;17:1464–1472.

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Genomic testing among patients with newly-diagnosed advanced NSCLC in the United States: A contemporary clinical practice patterns study

Gondos A, et al.

To report on contemporary clinical patterns of guideline-mandated genomic testing in newly diagnosed patients with advanced NSCLC in a US setting

- Newly-diagnosed patients with advanced NSCLC who had received 1st-line treatment included from the Flatiron Health EHR-derived de-identified database

NGS* group

n=1355 received NGS (CGP: 18.8%, n=429)

Non-NGS group

n=926 received non-NGS tests

- Analysis defined successful biomarker testing in *ALK*, *EGFR*, *BRAF* and *ROS1* and described occurrence of testing, patterns of use of technologies, occurrence of successful testing/inadequate testing, test failures, and percentage of patients who potentially missed targeted therapy

- 79.7% of patients in the CGP subgroup received no other type of test compared with 29.8% of patients in the other NGS group

	NGS group (CGP)	Non-NGS group
Inadequate testing	13.4% (CGP: 4.9%)	52.5%
Test failures/ unsuccessful testing	4.2% (CGP: 1.2%)	6.8%
Potentially missed a targeted therapy	10.1% (CGP: 3.0%)	40.3%

- *EGFR* and *ALK* testing were performed in ≥95% of patients (all testing groups); however, in the non-NGS group, only 83.6% and 55.7% of patients received tests for *ROS1* and *BRAF,* respectively

Use of NGS, particularly CGP, may help to avoid suboptimal testing, minimize test failures, and improve uptake of testing for newly introduced biomarkers, enabling individualized, targeted therapy

*Included a subgroup using comprehensive genomic profiling (CGP). EHR, electronic health record; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ROS1, receptor tyrosine kinase 1.

Gondos A, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9592).

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Clinical performance of a comprehensive novel liquid biopsy test for identifying patients with NSCLC for treatment with osimertinib

Gray JE, et al.

To report on a liquid biopsy test based on NGS of ctDNA to identify patients with *EGFR*-mutant NSCLC (ex19del, L858R mutations) or *EGFR* T790M eligible for treatment with osimertinib (OSI)

n=441/556 FLAURA trial	**n=300/419 AURA3 trial**
1st-line OSI vs EGFR TKI in *EGFR*m NSCLC	OSI vs CT in NSCLC with T790M at progression on EGFR TKI

- Patients from FLAURA and AURA3 retrospectively tested with Guardant360 (G360), a 74-gene ctDNA NGS assay assessing single nucleotide variants, insertion-deletions, amplifications and fusions
- PFS of patients with *EGFR*m or T790M detected by G360 was compared with patients detected by cobas® *EGFR* Mutation Test using tissue or plasma

FLAURA (ex19del/L858R)	PFS Hazard Ratio (95% CI)	p-value
• **G360**	0.42 (0.31, 0.55)	<0.0001
• **cobas plasma**	0.45 (0.35, 0.58)	<0.0001
• **cobas tissue**	0.43 (0.34, 0.54)	<0.001
AURA3 (T790M)		
• **G360**	0.39 (0.28, 0.57)	<0.0001
• **cobas plasma**	0.42 (0.28, 0.62)	<0.0001
• **cobas tissue**	0.37 (0.29, 0.48)	<0.0001

- G360 demonstrated clinical performance similar to that for cobas EGFR Mutation Test for identifying patients with *EGFR*-mutant or T790M
- Efficacy analyses were limited to tissue-positive patients

G360 accurately identifies patients with *EGFR*-mutant NSCLC for osimertinib therapy while providing comprehensive genotyping for other therapeutic molecular targets. Liquid biopsy complements tissue-based testing

CI, confidence interval; ctDNA, circulating tumour DNA; EGFRm, epidermal growth factor receptor mutant; ex19del, exon 19 deletions; HR, hazard ratio; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; OSI, osimertinib; PFS, progression-free survival.

Gray JE, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9553).

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A model comparing the value of broad next-generation sequencing-based testing to single gene testing in patients with NSCLC in the US

Pennell NA, et al.

To report on plausible testing configurations for actionable driver oncogenes and discuss their implications for the US population

- Simulation evaluated various testing with SGT or NGS on the basis of LYG and cost per LYG
- Expected prevalence of ADOs among nsNSCLC patients and survival distribution in the presence/absence of an ADO treatment strategy were calibrated

- Survival duration generated from Weibull distributions fit to statistical estimates of median and 5-year survival
- Weibull distributions with appropriate match between ADO and targeted treatment generated median additional 2 years of life

- **nsNSCLC patients for testing in US annually = 89,000**

- ADOs in NGS: *EGFR, ALK, ROS1, BRAF, RET, MET, NTRK*
- ADOs in SGT: *EGFR* and *ALK*

Estimated patients with ADOs (*EGFR/ALK/ROS1/BRAF/RET/MET/NTRK*)	**26,300**
CMS reimbursement for NGS	$627.50
CMS reimbursement for SGTs (*EGFR*+*ALK*)	$732.30
Cost of treatment for 2 years	$10K/year = $20,000
Estimated median and 5-year survival of patients with ADO with highly-effective treatment	39 months and 25%
Estimated median and 5-year survival of patients with ADO who goes unidentified	14 months and 5%

- Each 10% increase in NGS instead of SGT = 2630 additional LYG and cost savings per LYG of -$49 to -$109
- At current 80% testing rate, replacing SGT with NGS = additional 21,019 LYG with reduced cost per LYG of -$599
- Increasing testing from 80% to 100% of patients would increase LYG by 15,017
- If 100% of patients were tested with NGS and every patient received treatment, cost per LYG of this strategy would be $16,641.57

Broad NGS testing compared to SGT for *EGFR/ALK* leads to large gains in life years at reduced cost per LYG, supporting universal NGS testing for all patients with advanced non-squamous NSCLC

ADOs, actionable driver oncogenes; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; LYG, life year gained; NGS, next-generation sequencing; nsNSCLC, non-squamous non-small cell lung cancer; NTRK, non-receptor tyrosine kinase; ROS1, receptor tyrosine kinase 1; SGT, single-gene testing.

Pennell NA, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9529).

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Residual circulating tumour DNA after two months of therapy to predict progression-free and overall survival in patients on S1403 randomized to afatinib +/- cetuximab

Mack PC, et al.

To report on the predictive value of ctDNA clearance at Cycle 3 Day 1 (C3D1) following treatment with afatinib with/without cetuximab in patients with *EGFR*-mutant NSCLC

- S1403: a 1st-line phase III study of afatinib with/without cetuximab in patients with *EGFR*-mutant NSCLC (n=168)
- Study closed early due to futility

- Plasma specimens prospectively collected at baseline, Cycle 3 Day 1 (C3D1; 8 weeks) and at progression
- Samples processed for batch analysis of ctDNA by NGS (Guardant360) – complete case analysis approach used

- Survival distributions (Kaplan-Meier) and HRs + CIs (Cox model) were estimated, and distributions compared (log-rank test); landmark analysis assessed predictive value of ctDNA clearance at C3D1
- 104 patients (62%) had analyzable baseline plasma specimens, with *EGFR* mutations detected in 83 (80%)

Baseline			
	Detectable	**Not-detectable**	**HR (CI)**
PFS	10.2 (7.3–13.5)	14.7 (10.1–NR)	1.80 (0.29–2.01) [p=0.03]
OS	30.2 (25–NR)	NR	2.10 (0.82–5.39) [p=0.1]
Landmark analysis			
	C3D1: clearance	**C3D1: residual**	**HR (CI)**
PFS	15.1	2.8	0.24 (0.13–0.44) [p=0.00001]
OS	27.2	15.0	0.30 (0.14–0.66) [p=0.003]

- Of 62 cases with detectable ctDNA at baseline, 68% (42/62) became undetectable at C3D1 (ctDNA clearance)
- 70 patients had matching at-progression samples
- T790M mutations were observed at progression in 18/70 (25%) cases

Clearance of *EGFR* ctDNA after 60 days of therapy was associated with a substantial and statistically significant improvement in subsequent PFS and OS

CI, confidence interval; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; NR, not reached; OS, overall survival; PFS, progression-free survival.

Mack PC, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9532).

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Summary

This can be based on Dr Herbst's commentary

Implications for practice

Alternative slide to capture implications for practice – key take away

Data from ASCO20 Virtual show

Important to do x

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

Thank you for watching this on-demand event

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