# *Evolving Precision Medicine Addresses Acquired Resistance and Identifies New Therapeutic Targets in*

# NON-SMALL CELL LUNG CANCER-

## A WHITEBOARD ANIMATION VIEW

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*The activity is supported by an educational grant from Daiichi Sankyo.*

# *Evolving Precision Medicine Addresses Acquired Resistance and Identifies New Therapeutic Targets in Non-Small Cell Lung Cancer – A Whiteboard Animation View*


**PROGRAM CHAIR**
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**SPEAKER FACULTY**


| | | |
|---|---|---|
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| **Jonathan Riess, MD, MS**<br>Associate Professor<br>UC Davis Comprehensive Cancer Center<br>Sacramento, CA | **Jared Weiss, MD**<br>Associate Professor, School of Medicine<br>Section Chief of Thoracic and<br>Head/Neck Oncology<br>Lineberger Comprehensive Cancer Center<br>University of North Carolina - Chapel Hill<br>Chapel Hill, NC | **Vamsidhar Velcheti, MD**<br>Medical Director Thoracic<br>Oncology Program<br>NYU Langone Perlmutter Cancer Center<br>New York University School of Medicine<br>New York, NY |


## PROGRAM OVERVIEW

This activity will cover the treatment and management of patients with non-small cell lung cancer (NSCLC).

## TARGET AUDIENCE

This activity is intended to meet the educational needs of medical oncologists, pathologists, and other academic, federal and community-based healthcare practitioners who care for patients with lung cancer.

## LEARNING OBJECTIVES

On completing the program, attendees should be able to:

- Review the current treatment options for patients with EGFR-mutation positive non-small cell lung cancer and resultant therapy resistance
- Discuss antibody-drug conjugates and their evolving role in patients with EGFR resistant, non-small cell lung cancer (NSCLC)

- Explore the new transmembrane marker, TROP2, its role in tumorigenesis, and potential targeted agents to inhibit its effects in patients with NSCLC

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## NURSING CREDIT INFORMATION

Purpose:
This program would be beneficial for nurses involved and/or interested in the therapeutic management of patients with lung cancer.

CNE Credits:
1.0 ANCC Contact Hour

CNE Accreditation Statement:
Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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|---|---|
| **Jacob Sands, MD** | Dr. Sands discloses consulting/advisory board honoraria from Abbvie, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Foundation Medicine, Guardant, Jazz Pharmaceuticals, Loxo, Medtronic, and Pharma Mar; and research support in the form of drug provided by Merck for NCI-sponsored study. |
| **Rebecca Heist, MD, MPH** | Dr. Heist reports that she serves as a consultant for Novartis, Apollomics, Tarveda, Boehringer Ingelheim, and Roche. She has done medical writing for Pfizer and also contracted research on behalf of her institution for Novartis, Abbvie, Agios, Daichii Sankyo, Corvus, Genentech Roche, Mirati, Exelixis, Debiopharm, Incyte, Takeda, and Lilly. |
| **Shayma Master Kazmi, MD, RPh** | Dr. Kazmi reports that she serves as a consultant for Merck, Eisai, Takeda, Immunomedics, and Lilly. She also serves on the speakers bureau for Merck, Eisai, Takeda, Immunomedics, and Lilly. |
| **Aaron Lisberg, MD** | Dr. Lisberg reports that he serves as a consultant for AstraZeneca, Bristol-Myers Squibb, Leica Biosystems, Jazz Pharmaceuticals, Novocure, Pfizer, and MorphoSys. He has also done contracted research grants with Daiichi Sankyo, Calithera Biosciences, AstraZeneca, Dracen Pharmaceuticals, and WindMIL. |
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| **Jared Weiss, MD** | Dr. Weiss reports that he serves as a consultant for G1, Eli Lilly, Vesselon, Pfizer, Azitra, Nanobiotix, Blueprint, Saaatchi, AZ, Celgene, Jounce, Rakuten, EMD Serono, Genentech, Inivata, and Abbvie. He also has stock with Vesselon and Nektar. |
| **Vamsidhar Velcheti, MD** | Dr. Velcheti reports that he serves as a consultant for BMS, Foundation Medicine, Novartis, Merck, AstraZeneca, Blueprint Medicine, Eli Lilly, and Novocure. |

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To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures
2. Participate in the live virtual activity
3. Complete posttest and evaluation form online.

You will receive your certificate as a downloadable file.

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This activity is supported by an educational grant from Daiichi Sankyo.


## AGENDA

**I. First-line Systemic Therapy for Patients with EGFR mutation-positive, Advanced or Metastatic NSCLC**

- a. Diagnostics and mutation testing in the community setting
  - i. Identifying the EGFR-positive patient
  - ii. Pretreatment mutation results and treatment decisions
- b. EGFR tyrosine kinase inhibitors
  - i. Monotherapy options
  - ii. Clinical trials data – efficacy and safety
  - iii. EGFR mutations and therapy options
    1. Resistance and therapy decisions

**II. Addressing EGFR-Inhibitor Resistance – Evolving Options Beyond TKIs**

- a. Aberrantly upregulated in NSCLC
  - i. Human Epidermal Growth Factor Receptor 3 – data describing role in TKI resistance
  - **ii. Whiteboard theme – depiction of the role HER3 plays in EGFR-TKI resistance in NSCLC**
- b. Clinical trials data describing the role of HER3
  - **i.** Study outcomes in patients with NSCLC resistant to EGFR-TKI therapy
  - **ii.** Ongoing development and clinical trials findings

**III. New Transmembrane Antigen – Trophoblast-Cell Surface Antigen 2**

- a. Why TROP2?
  - i. Over expression promotes proliferation and invasion in lung adenocarcinoma
  - ii. TROP2 antibody associated with tumor size – novel marker?
  - **iii. Whiteboard theme – depiction of the TROP2 cell-surface antigen in tumors and role in tumorigenesis**
- b. Clinical trials findings in NSCLC
  - i. Efficacy and tolerability of TROP2-targeted ADC
  - ii. Ongoing trials and outcomes

**IV. Conclusions**

**V. Questions and Answers**

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**Jacob Sands, MD**
Physician, Dana-Farber Cancer Institute
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## Disclosures

- Dr. Jacob Sands discloses consulting/advisory board honoraria from Abbvie, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Foundation Medicine, Guardant, Jazz Pharmaceuticals, Loxo, Medtronic, and Pharma Mar; and research support in the form of drug provided by Merck for NCI-sponsored study.

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## Learning Objectives

- Review the current treatment options for patients with *EGFR*-mutation–positive NSCLC and resultant therapy resistance
- Discuss ADCs and their evolving role in patients with EGFR-resistant NSCLC
- Explore the new transmembrane marker, TROP2, its role in tumorigenesis, and potential targeted agents to inhibit its effects in patients with NSCLC

**ADC = antibody-drug conjugate; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; TROP2 = trophoblast cell-surface antigen 2.**

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## *EGFR*-Mutation–Positive Advanced or Metastatic NSCLC

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## EGFR: Identification and Impact on Treatment

- Facilitates targeted treatment in advanced NSCLC (tumor tissue or ctDNA)
- Acquired resistance in first- and second-generation TKI therapy (can be detected by plasma monitoring of ctDNA)
  - *EGFR*-T790M mutation is one of the most frequent resistance mechanisms at progression (≈50%-60%)
- Acquired resistance to third-generation TKI in first and second line
  - Potential mechanisms include *EGFR*, SNV, MET and HER2 amplifications, and genetic fusions
- Early detection of mutation(s) involved in resistance may help further stratify treatment decisions

**ctDNA = circulating tumor DNA; HER = human epidermal growth factor receptor; SNV = single nucleotide variant; TKI = tyrosine kinase inhibitor.**

**Douillard JY, et al. *J Thorac Oncol.* 2014;9:1345-1353. Buttitta F, et al. *Oncotarget.* 2020;11:982-991.**

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## EGFR-TKI Landscape

- First generation
  - Gefitinib
  - Erlotinib
- Second generation
  - Afatinib
  - Dacomitinib
- Third generation
  - Osimertinib

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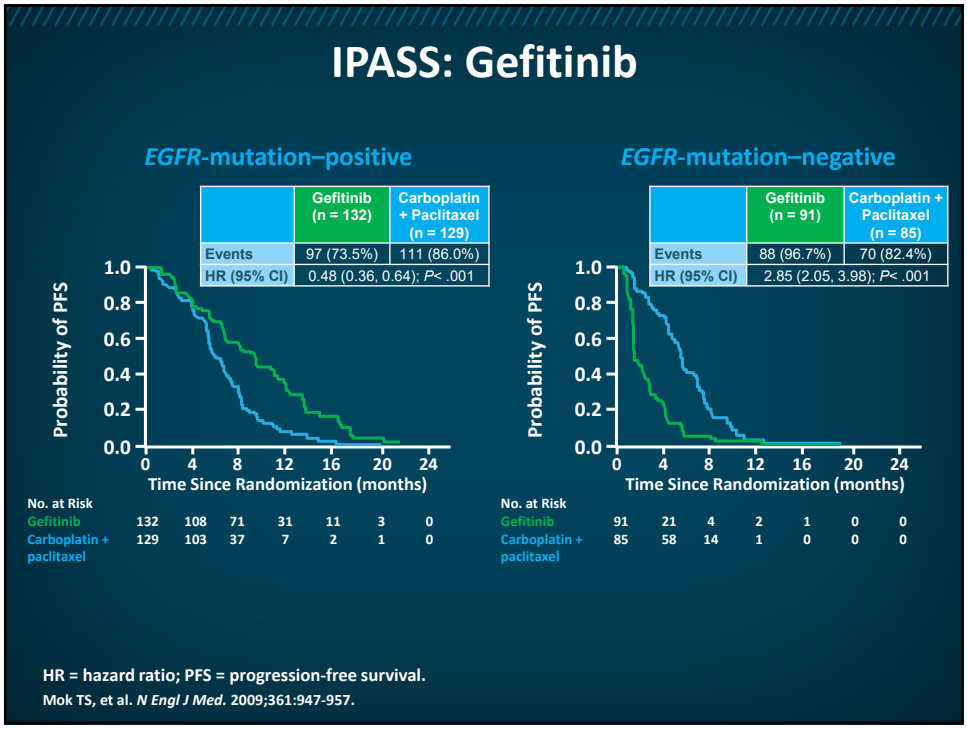
IPASS: Gefitinib
EGFR-mutation–positive
Gefitinib (n = 132)
Carboplatin + Paclitaxel (n = 129)
Events
97 (73.5%)
111 (86.0%)
HR (95% CI)
0.48 (0.36, 0.64); P< .001
Probability of PFS
Time Since Randomization (months)
No. at Risk
Gefitinib 132 108 71 31 11 3 0
Carboplatin + paclitaxel 129 103 37 7 2 1 0
EGFR-mutation–negative
Gefitinib (n = 91)
Carboplatin + Paclitaxel (n = 85)
Events
88 (96.7%)
70 (82.4%)
HR (95% CI)
2.85 (2.05, 3.98); P< .001
Probability of PFS
Time Since Randomization (months)
No. at Risk
Gefitinib 91 21 4 2 1 0 0
Carboplatin + paclitaxel 85 58 14 1 0 0 0
HR = hazard ratio; PFS = progression-free survival.
Mok TS, et al. N Engl J Med. 2009;361:947-957.

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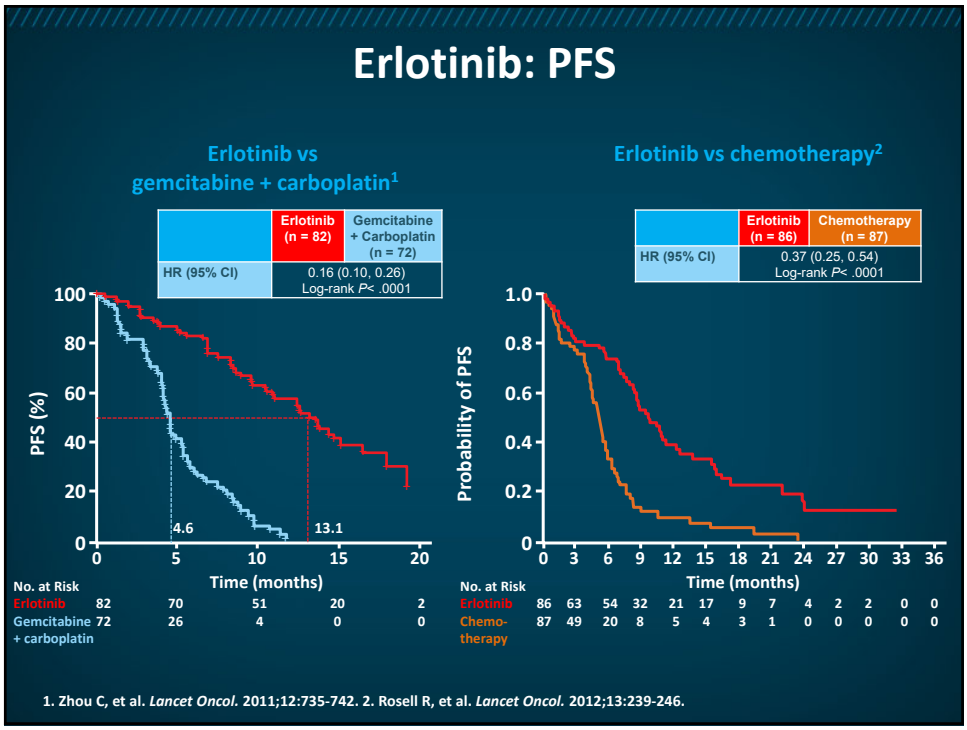
Erlotinib: PFS
Erlotinib vs gemcitabine + carboplatin1
Erlotinib (n = 82)
Gemcitabine + Carboplatin (n = 72)
HR (95% CI)
0.16 (0.10, 0.26)
Log-rank P< .0001
PFS (%)
4.6
13.1
Time (months)
No. at Risk
Erlotinib 82 70 51 20 2
Gemcitabine + carboplatin 72 26 4 0 0
Erlotinib vs chemotherapy2
Erlotinib (n = 86)
Chemotherapy (n = 87)
HR (95% CI)
0.37 (0.25, 0.54)
Log-rank P< .0001
Probability of PFS
Time (months)
No. at Risk
Erlotinib 86 63 54 32 21 17 9 7 4 2 2 0 0
Chemo-therapy 87 49 20 8 5 4 3 1 0 0 0 0 0
1. Zhou C, et al. Lancet Oncol. 2011;12:735-742. 2. Rosell R, et al. Lancet Oncol. 2012;13:239-246.

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# Erlotinib: Safety Summary

**Most common AEs of all grades reported in ≥3% of patients in either treatment group**

| | Erlotinib (n = 83) | | Gemcitabine + Carboplatin (n = 72) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Neutropenia | 5 (6%) | 0 | 50 (69%) | 30 (42%) |
| Thrombocytopenia | 3 (4%) | 0 | 46 (64%) | 29 (40%) |
| Anemia | 4 (5%) | 0 | 52 (72%) | 9 (13%) |
| Infection | 14 (17%) | 1(1%) | 7 (10%) | 0 |
| Skin rash | 61 (73%) | 2 (2%) | 14 (19%) | 0 |
| Diarrhea | 21 (25%) | 1 (1%) | 4 (6%) | 0 |
| Stomatitis | 11 (13%) | 1 (1%) | 1 (1%) | 0 |
| Paronychia | 3 (4%) | 0 | 0 | 0 |
| Vomiting or nausea | 1 (1%) | 0 | 33 (46%) | 1 (1%) |
| Constipation | 0 | 0 | 11 (15%) | 0 |
| Increased ALT | 31 (37%) | 3 (4%) | 24 (33%) | 1 (1%) |
| Fatigue | 4 (5%) | 0 | 17 (24%) | 1 (1%) |

Data are n (%) and are for the safety population (all patients who received ≥1 dose of study drug); each patient was only counted once even though they might have had several events across different body systems.

AE = adverse event; ALT = alanine aminotransferase.

Zhou C, et al. *Lancet Oncol.* 2011;12:735-742.

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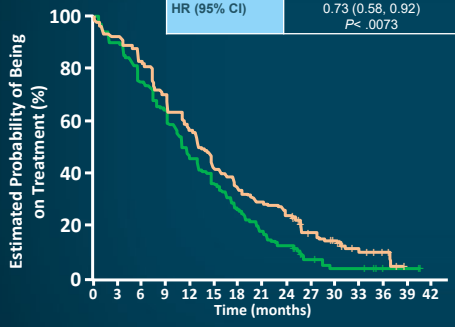
# Afatinib and Dacomitinib: PFS

## Afatinib[1]

| | Afatinib (n = 160) | Gefitinib (n = 159) |
|---|---|---|
| Median PFS (95% CI), mo | 13.7 (11.9, 15.0) | 11.5 (10.1, 13.1) |
| HR (95% CI) | 0.73 (0.58, 0.92) *P*< .0073 | |

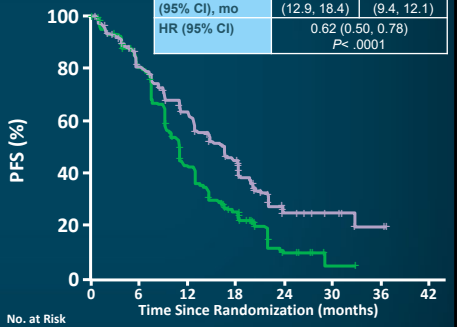



No. at Risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Afatinib | 160 | 148 | 133 | 113 | 91 | 68 | 56 | 48 | 40 | 25 | 18 | 9 | 5 | 0 | 0 |
| Gefitinib | 159 | 144 | 120 | 103 | 74 | 59 | 43 | 30 | 21 | 11 | 6 | 6 | 2 | 2 | 0 |

## Dacomitinib[2]

| | Dacomitinib (n = 227) | Gefitinib (n = 225) |
|---|---|---|
| Events | 140 | 177 |
| Median PFS (95% CI), mo | 16.6 (12.9, 18.4) | 11.0 (9.4, 12.1) |
| HR (95% CI) | 0.62 (0.50, 0.78) *P*< .0001 | |




No. at Risk (no. censored)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dacomitinib | 227 (0) | 166 (21) | 124 (28) | 85 (32) | 19 (69) | 7 (81) | 2 (85) | 0 (87) |
| Gefitinib | 225 (0) | 172 (12) | 89 (17) | 48 (23) | 9 (40) | 1 (47) | 0 (48) | 0 (48) |

1. Park K, et al. *Lancet Oncol.* 2016.17:577-589. 2. Wu Y-L, et al. *Lancet Oncol.* 2017;18:1454-1466.

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# Afatinib and Dacomitinib: Safety Summary

**Dacomitinib Grade 3 SAE**

| | |
|---|---|
| Diarrhea | 8% |
| Rash | 4% |
| Dermatitis acneiform | 14% |
| Maculopapular rash | 4% |
| Stomatitis | 4% |
| Paronychia | 7% |

**Afatinib Grade 3 SAE**

| | |
|---|---|
| Diarrhea | 14.4% |
| Rash | 16.2% |
| Stomatitis/ mucositis | 8.7% |
| Paronychia | 11.4% |

| | omitinib (n = 227) | | | Gefitinib (n = 224) | | | |
|---|---|---|---|---|---|---|---|
| | ade 3 | Grade 4 | Grade 5 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 |
| | (51%) | 5 (2%) | 22 (10%) | 128 (57%) | 67 (30%) | 5 (2%) | 20 (9%) |
| | (8%) | 0 | 1 (<1%) | 123 (55%) | 2 (1%) | 0 | 0 |
| | (7%) | 0 | 0 | 42 (19%) | 3 (1%) | 0 | 0 |
| | (14%) | 0 | 0 | 64 (29%) | 0 | 0 | 0 |
| | (4%) | 0 | 0 | 39 (17%) | 1 (<1%) | 0 | 0 |
| | (3%) | 0 | 0 | 54 (24%) | 1 (<1%) | 0 | 0 |
| | (1%) | 0 | 0 | 38 (17%) | 0 | 0 | 0 |
| | (2%) | 0 | 0 | 36 (16%) | 1 (<1%) | 0 | 0 |

| | atinib (n = 160) | | | Gefitinib (n = 159) | | | |
|---|---|---|---|---|---|---|---|
| | ade 3 | Grade 4 | Grade 5 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 |
| | (29%) | 3 (2%) | 0 | 124 (78%) | 26 (16%) | 2 (1%) | 1 (1%) |
| | (12%) | 1 (1%) | 0 | 95 (60%) | 2 (1%) | 0 | 0 |
| | (9%) | 0 | 0 | 124 (78%) | 5 (3%) | 0 | 0 |
| | (4%) | 0 | 0 | 38 (24%) | 0 | 0 | 0 |
| | (2%) | 0 | 0 | 26 (16%) | 1 (1%) | 0 | 0 |
| | 0 | 0 | 0 | 59 (37%) | 0 | 0 | 0 |
| | 0 | 0 | 0 | 36 (23%) | 0 | 0 | 0 |
| Fatigue§ | 24 (15%) | 9 (6%) | 0 | 23 (14%) | 0 | 0 | 0 |

*Includes acne, blister, dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash pruritic, rash pustular, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, and skin ulcer. †Includes aphthous stomatitis, mucosal erosion, mucosal inflammation, mouth ulceration, and stomatitis. ‡Includes nail bed infection, nail infection, and paronychia. §Includes asthenia, fatigue, and lethargy. SAE = serious AE.

Wu Y-L, et al. *Lancet Oncol.* 2017;18:1454-1466. Park K, et al. *Lancet Oncol.* 2016.17:577-589.

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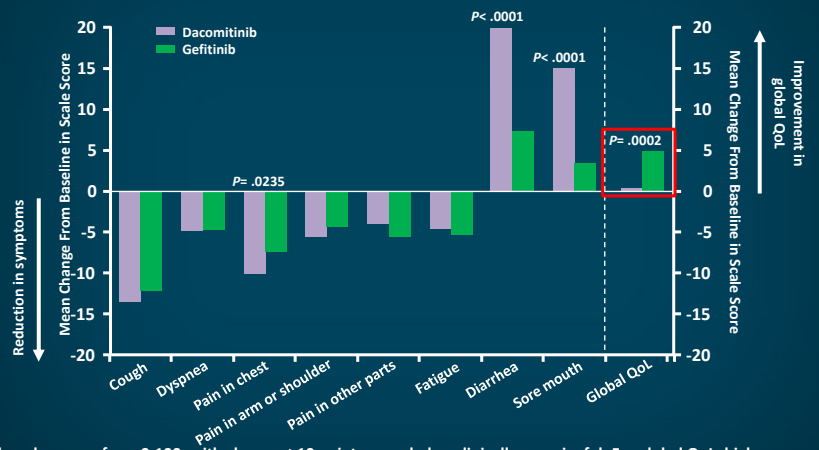
# Dacomitinib: Impact on QoL

## Overall change from baseline in key lung cancer-associated symptoms, fatigue, diarrhea, sore mouth, and global QoL




Each scale ranges from 0-100, with changes ≥10 points regarded as clinically meaningful. For global QoL, higher scores indicate better global QoL; for symptoms, higher scores indicate greater severity of symptoms. *P* values (unadjusted for multiple testing) are for the between-group comparison of overall change from baseline, calculated using repeated-measures mixed-effects modelling. QoL = quality of life.

Wu Y-L, et al. *Lancet Oncol.* 2017;18:1454-1466.

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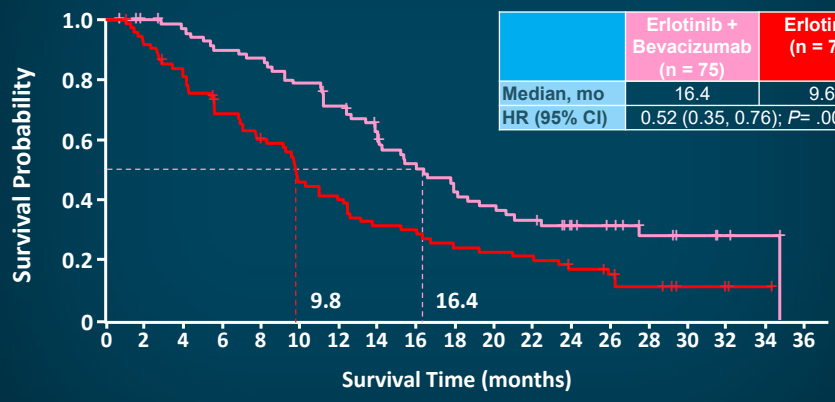
# JO25567: Erlotinib + Bevacizumab PFS

## Updated PFS: investigator-assessed




| | Erlotinib + Bevacizumab (n = 75) | Erlotinib (n = 77) |
|---|---|---|
| Median, mo | 16.4 | 9.6 |
| HR (95% CI) | 0.52 (0.35, 0.76); *P*= .0073* | |

*Log-rank test, 2-sided.

Yamamoto N, et al. ASCO 2018. Presentation.

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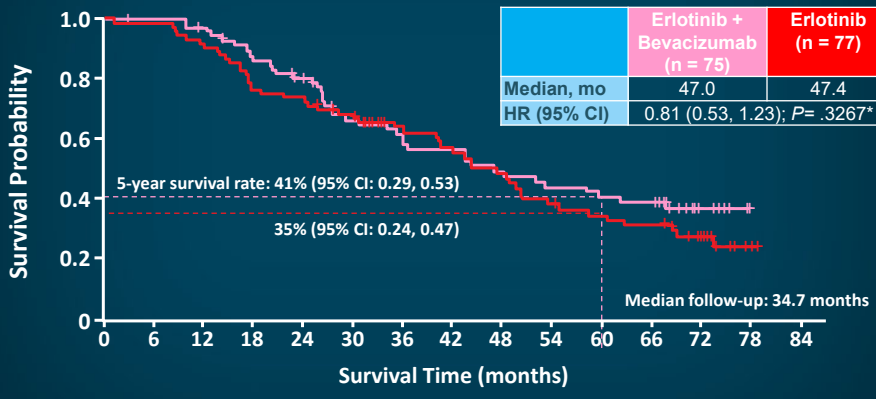
# JO25567: Erlotinib + Bevacizumab OS

## Final OS




| | Erlotinib + Bevacizumab (n = 75) | Erlotinib (n = 77) |
|---|---|---|
| Median, mo | 47.0 | 47.4 |
| HR (95% CI) | 0.81 (0.53, 1.23); *P*= .3267* | |

*Log-rank test, 2-sided.

OS = overall survival.

Yamamoto N, et al. ASCO 2018. Presentation.

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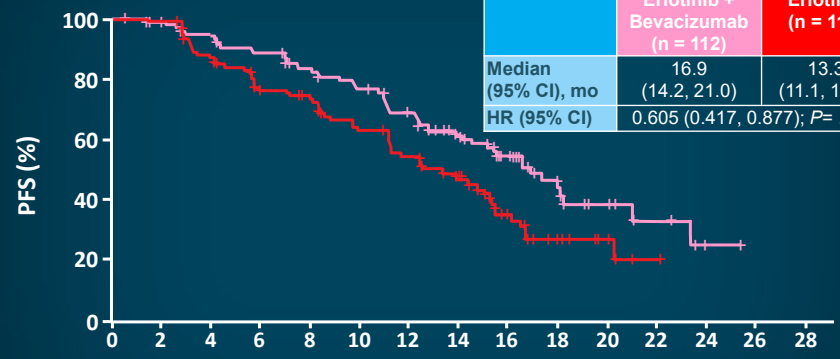
# NEJ026: Erlotinib + Bevacizumab PFS

## PFS in modified ITT population




| | Erlotinib + Bevacizumab (n = 112) | Erlotinib (n = 112) |
|---|---|---|
| Median (95% CI), mo | 16.9 (14.2, 21.0) | 13.3 (11.1, 15.3) |
| HR (95% CI) | 0.605 (0.417, 0.877); *P*= .016 | |

| No. at Risk (no. censored) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Erlotinib + bevacizumab | 112 (0) | 100 (6) | 83 (7) | 64 (17) | 34 (35) | 10 (52) | 1 (59) | 0 (60) |
| Erlotinib | 112 (0) | 94 (4) | 73 (12) | 51 (15) | 18 (34) | 5 (43) | 0 (47) | 0 (47) |

ITT = intent-to-treat.

Saito H, et al. *Lancet Oncol.* 2019;20:625-635.

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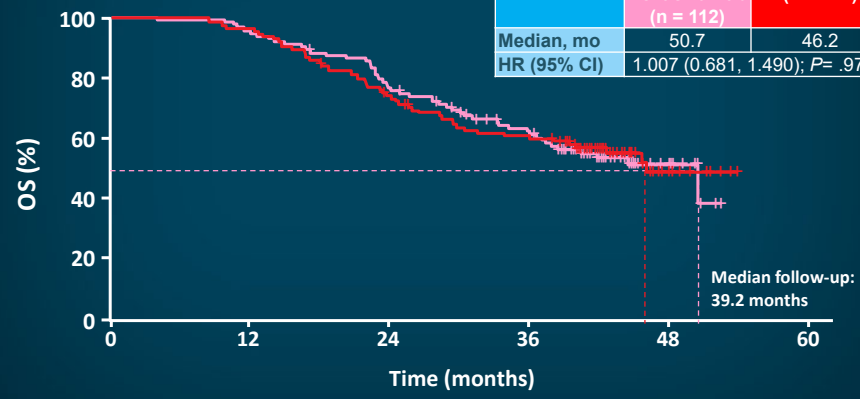
# NEJ026: Erlotinib + Bevacizumab OS

## Final OS




| | Erlotinib + Bevacizumab (n = 112) | Erlotinib (n = 112) |
|---|---|---|
| Median, mo | 50.7 | 46.2 |
| HR (95% CI) | 1.007 (0.681, 1.490); *P*= .973* | |

*Log-rank test.

Maemondo M, et al. ASCO 2020. Presentation.

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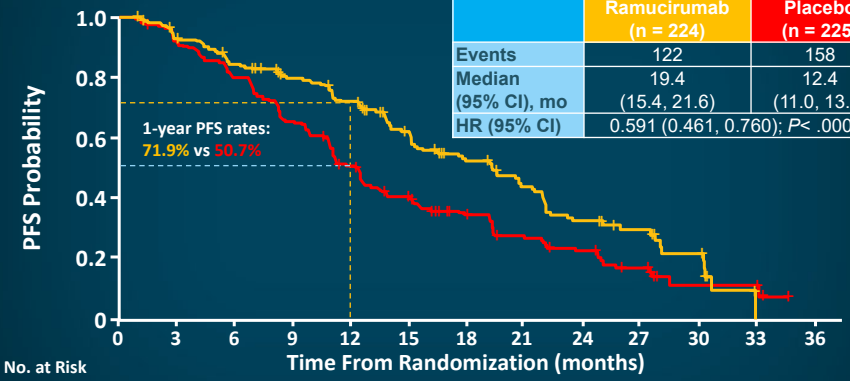
# Erlotinib + Ramucirumab

## RELAY primary endpoint: PFS (investigator-assessed)

| | Erlotinib + Ramucirumab (n = 224) | Erlotinib + Placebo (n = 225) |
|---|---|---|
| Events | 122 | 158 |
| Median (95% CI), mo | 19.4 (15.4, 21.6) | 12.4 (11.0, 13.5) |
| HR (95% CI) | 0.591 (0.461, 0.760); *P*< .0001 | |




| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Erlotinib + ramucirumab | 224 | 196 | 170 | 154 | 133 | 103 | 69 | 49 | 32 | 20 | 10 | 1 | 0 |
| Erlotinib + placebo | 225 | 196 | 167 | 136 | 99 | 72 | 52 | 37 | 27 | 15 | 4 | 4 | 0 |

Consistent PFS benefit by independent, blinded central review (HR, 0.671 [95% CI: 0.518, 0.869]; *P*= .0022).

Nakagawa K, et al. ASCO 2019. Presentation.

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# NEJ009: Gefitinib + Carboplatin + Pemetrexed

- Non-squamous NSCLC
- Previously untreated stage IIIB, IV, recurrence
- Aged 20-75 years
- PS 0-1
- Positive *EGFR* mutation

RANDOMIZATION

Stratified by sex, stage, type of *EGFR* mutation, and smoking history

**Induction Phase**

Gefitinib (daily) + Carboplatin + Pemetrexed (4-6 cycles, Q21D)

Gefitinib (daily)

Continue until PD

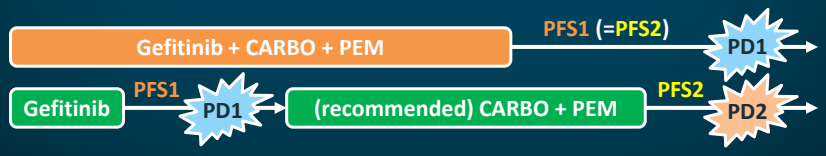
**Maintenance Phase**

Gefitinib (daily) Pemetrexed (Q21D)

Repeat until PD

Platinum-based regimen*

*Recommended by the protocol




PD = progressive disease; PEM = pemetrexed; PS = performance status; Q21D = every 21 days, CARBO = carboplatin.

Nakamura A, et al. ASCO 2018. Presentation.

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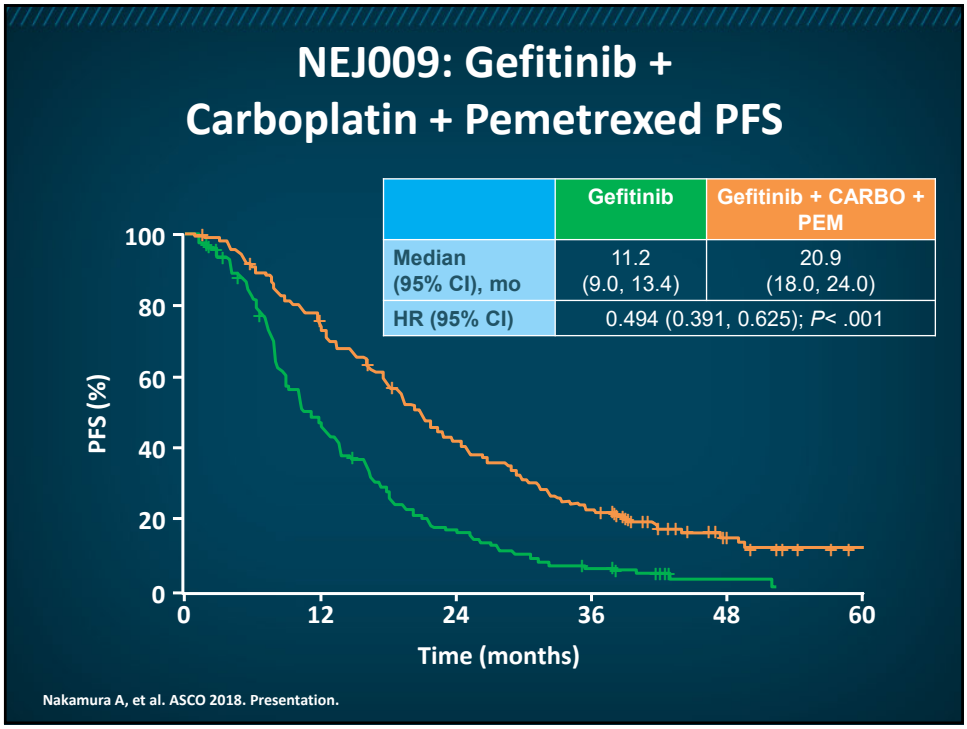
NEJ009: Gefitinib + Carboplatin + Pemetrexed PFS
Gefitinib
Gefitinib + CARBO + PEM
Median (95% CI), mo
11.2 (9.0, 13.4)
20.9 (18.0, 24.0)
HR (95% CI)
0.494 (0.391, 0.625); P< .001
PFS (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
Nakamura A, et al. ASCO 2018. Presentation.

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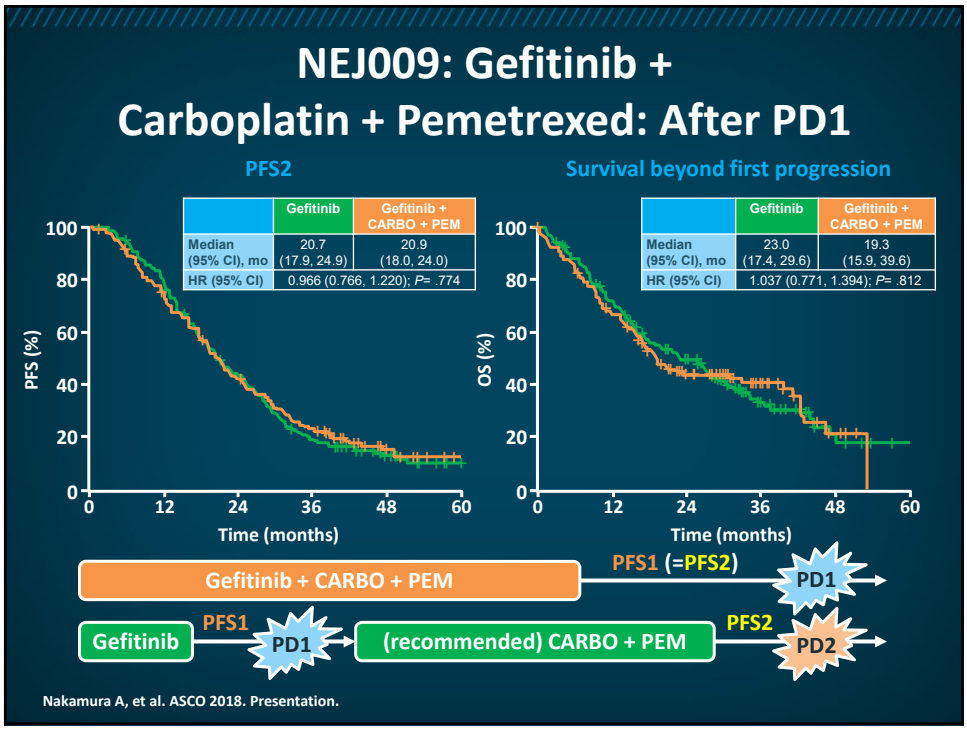
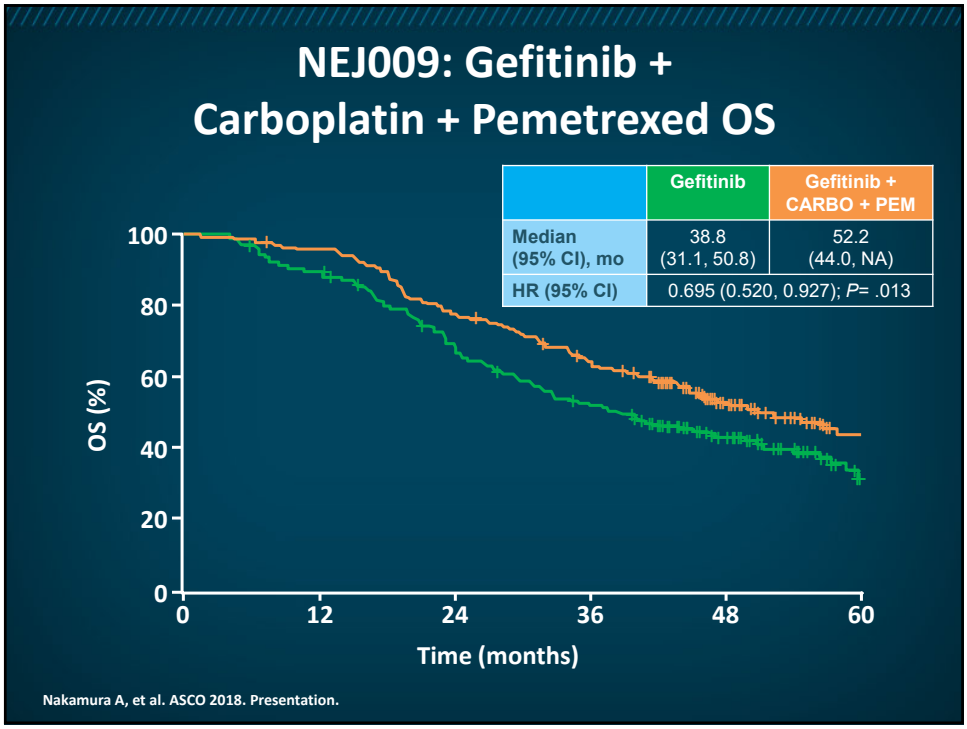

NEJ009: Gefitinib + Carboplatin + Pemetrexed: After PD1
PFS2
Gefitinib
Gefitinib + CARBO + PEM
Median (95% CI), mo
20.7 (17.9, 24.9)
20.9 (18.0, 24.0)
HR (95% CI)
0.966 (0.766, 1.220); P= .774
PFS (%)
Time (months)
Survival beyond first progression
Gefitinib
Gefitinib + CARBO + PEM
Median (95% CI), mo
23.0 (17.4, 29.6)
19.3 (15.9, 39.6)
HR (95% CI)
1.037 (0.771, 1.394); P= .812
OS (%)
Time (months)
Gefitinib + CARBO + PEM
PFS1 (=PFS2)
PD1
Gefitinib
PFS1
PD1
(recommended) CARBO + PEM
PFS2
PD2
Nakamura A, et al. ASCO 2018. Presentation.

20


NEJ009: Gefitinib + Carboplatin + Pemetrexed OS
Gefitinib
Gefitinib + CARBO + PEM
Median (95% CI), mo
38.8 (31.1, 50.8)
52.2 (44.0, NA)
HR (95% CI)
0.695 (0.520, 0.927); P= .013
OS (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
Nakamura A, et al. ASCO 2018. Presentation.

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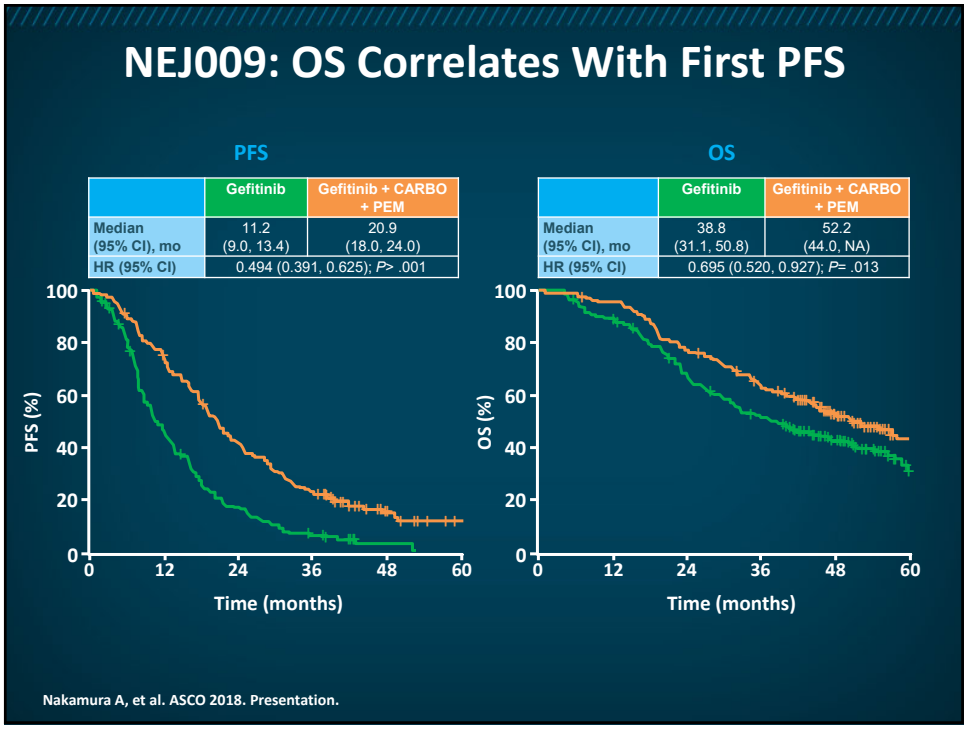
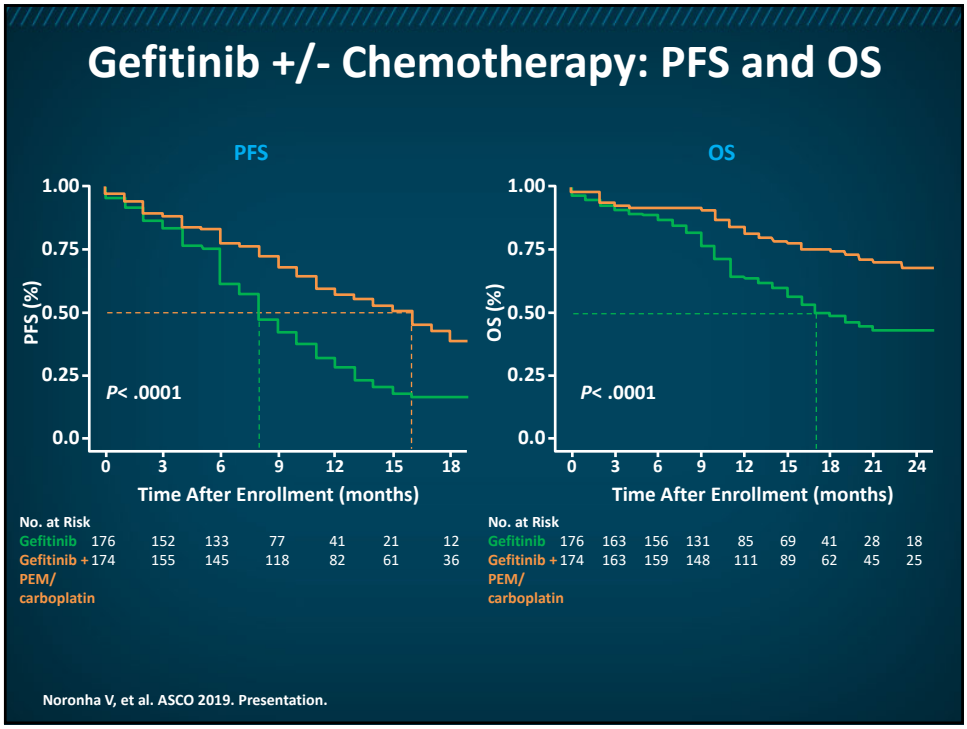

NEJ009: OS Correlates With First PFS
PFS
Gefitinib
Gefitinib + CARBO + PEM
Median (95% CI), mo
11.2 (9.0, 13.4)
20.9 (18.0, 24.0)
HR (95% CI)
0.494 (0.391, 0.625); P> .001
PFS (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
OS
Gefitinib
Gefitinib + CARBO + PEM
Median (95% CI), mo
38.8 (31.1, 50.8)
52.2 (44.0, NA)
HR (95% CI)
0.695 (0.520, 0.927); P= .013
OS (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
Nakamura A, et al. ASCO 2018. Presentation.

22


Gefitinib +/- Chemotherapy: PFS and OS
PFS
PFS (%)
1.00
0.75
0.50
0.25
0.0
P< .0001
0 3 6 9 12 15 18
Time After Enrollment (months)
No. at Risk
Gefitinib 176 152 133 77 41 21 12
Gefitinib + PEM/ carboplatin 174 155 145 118 82 61 36
OS
OS (%)
1.00
0.75
0.50
0.25
0.0
P< .0001
0 3 6 9 12 15 18 21 24
Time After Enrollment (months)
No. at Risk
Gefitinib 176 163 156 131 85 69 41 28 18
Gefitinib + PEM/ carboplatin 174 163 159 148 111 89 62 45 25
Noronha V, et al. ASCO 2019. Presentation.

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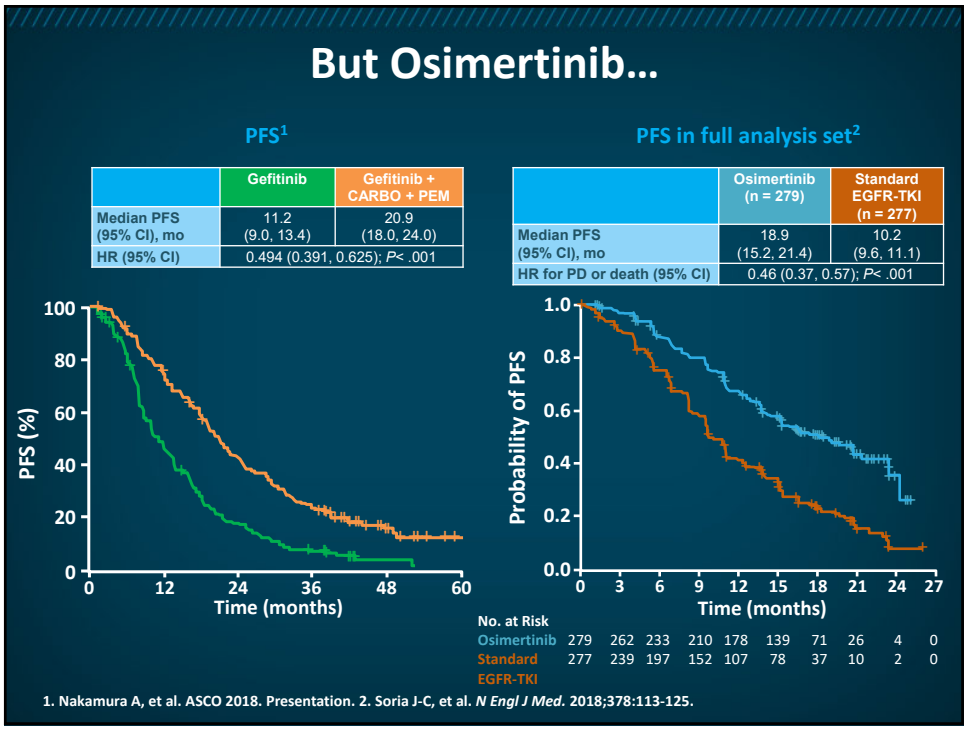
But Osimertinib…
PFS[1]
Gefitinib
Gefitinib + CARBO + PEM
Median PFS (95% CI), mo
11.2 (9.0, 13.4)
20.9 (18.0, 24.0)
HR (95% CI)
0.494 (0.391, 0.625); P< .001
PFS (%)
100
80
60
40
20
0
0 12 24 36 48 60
Time (months)
PFS in full analysis set[2]
Osimertinib (n = 279)
Standard EGFR-TKI (n = 277)
Median PFS (95% CI), mo
18.9 (15.2, 21.4)
10.2 (9.6, 11.1)
HR for PD or death (95% CI)
0.46 (0.37, 0.57); P< .001
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0.0
0 3 6 9 12 15 18 21 24 27
Time (months)
No. at Risk
Osimertinib 279 262 233 210 178 139 71 26 4 0
Standard EGFR-TKI 277 239 197 152 107 78 37 10 2 0
1. Nakamura A, et al. ASCO 2018. Presentation. 2. Soria J-C, et al. N Engl J Med. 2018;378:113-125.

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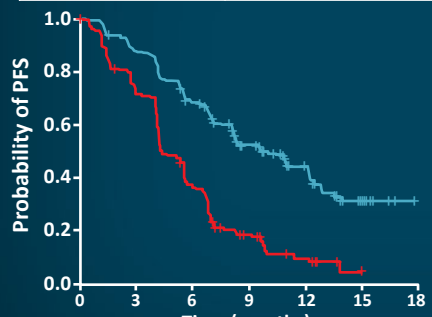
# EGFR T790M (CNS Disease)

## Patients in ITT population

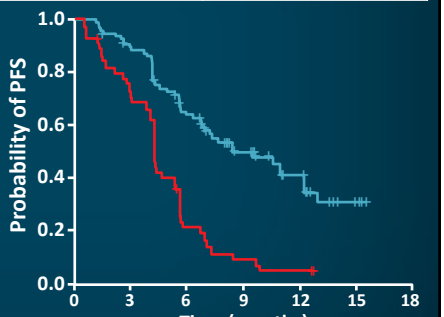
| | Osimertinib (n = 279) | Platinum-PEM (n = 140) |
|---|---|---|
| Median PFS (95% CI), mo | 10.1 (8.3, 12.3) | 4.4 (4.2, 5.6) |
| HR for PD or death (95% CI) | 0.30 (0.23, 0.41); *P*< .001 | |




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 240 | 162 | 88 | 50 | 13 | 0 |
| Platinum-PEM | 140 | 93 | 44 | 17 | 7 | 1 | 0 |

## Patients with CNS metastases

| | Osimertinib (n = 93) | Platinum-PEM (n = 51) |
|---|---|---|
| Median PFS (95% CI), mo | 8.5 (6.8, 12.3) | 4.2 (4.1, 5.4) |
| HR for PD or death (95% CI) | 0.32 (0.21, 0.49) | |




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Osimertinib | 93 | 80 | 46 | 27 | 14 | 4 | 0 |
| Platinum-PEM | 51 | 32 | 9 | 4 | 2 | 0 | 0 |

CNS = central nervous system.

Mok TS, et al. *N Engl J Med.* 2017;376:629-640.

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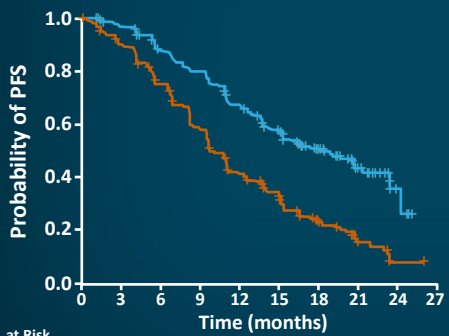
# FLAURA: PFS and OS

## PFS in full analysis set

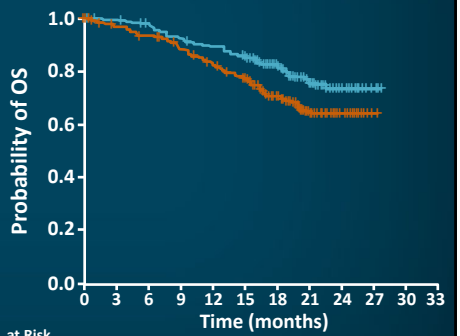
| | Osimertinib (n = 279) | Standard EGFR-TKI (n = 277) |
|---|---|---|
| Median PFS (95% CI), mo | 18.9 (15.2, 21.4) | 10.2 (9.6, 11.1) |
| HR for PD or death (95% CI) | 0.46 (0.37, 0.57); *P*< .001 | |




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 262 | 233 | 210 | 178 | 139 | 71 | 26 | 4 | 0 |
| Standard EGFR-TKI | 277 | 239 | 197 | 152 | 107 | 78 | 37 | 10 | 2 | 0 |

## OS

| | Osimertinib (n = 279) | Standard EGFR-TKI (n = 277) |
|---|---|---|
| Median OS (95% CI), mo | NC (NC, NC) | NC (NC, NC) |
| HR for PD or death (95% CI) | 0.63 (0.45, 0.88); *P*= .007 | |




| No. at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 276 | 269 | 253 | 243 | 232 | 154 | 87 | 29 | 4 | 0 | 0 |
| Standard EGFR-TKI | 277 | 263 | 252 | 237 | 218 | 200 | 126 | 64 | 24 | 1 | 0 | 0 |

NC = not calculated.

Soria J-C, et al. *N Engl J Med.* 2018;378:113-125.

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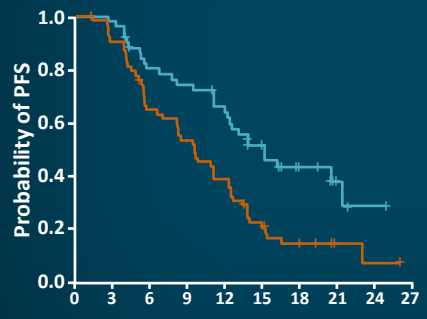
# FLAURA (CNS Disease)

## PFS in patients with CNS metastases

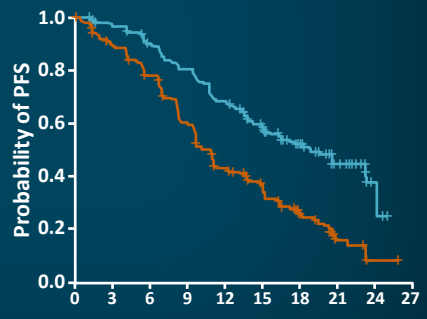
| | Osimertinib (n = 53) | Standard EGFR-TKI (n = 63) |
|---|---|---|
| Median PFS (95% CI), mo | 15.2 (12.1, 21.4) | 9.6 (7.0, 12.4) |
| HR for PD or death (95% CI) | 0.47 (0.30, 0.74); *P*< .001 | |




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 53 | 51 | 40 | 37 | 32 | 22 | 9 | 4 | 1 | 0 |
| Standard EGFR-TKI | 63 | 57 | 40 | 33 | 24 | 13 | 6 | 2 | 1 | 0 |

## PFS in patients without CNS metastases

| | Osimertinib (n = 226) | Standard EGFR-TKI (n = 214) |
|---|---|---|
| Median PFS (95% CI), mo | 19.1 (15.2, 23.5) | 10.9 (9.6, 12.3) |
| HR for PD or death (95% CI) | 0.46 (0.36, 0.59); *P*< .001 | |




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 226 | 211 | 193 | 173 | 146 | 117 | 62 | 22 | 3 | 0 |
| Standard EGFR-TKI | 214 | 182 | 157 | 119 | 83 | 65 | 31 | 8 | 1 | 0 |

Soria J-C, et al. *N Engl J Med.* 2018;378:113-125.

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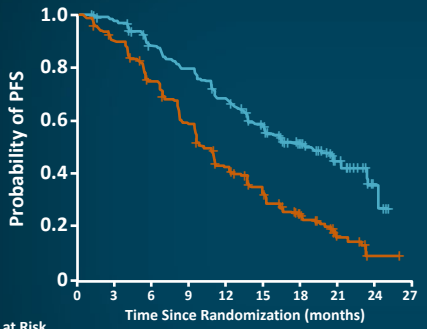
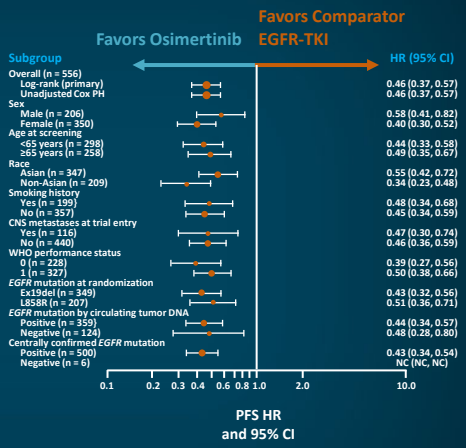
# FLAURA: PFS




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 262 | 233 | 210 | 178 | 139 | 71 | 26 | 4 | 0 |
| Comparator EGFR-TKI | 277 | 239 | 197 | 152 | 107 | 78 | 37 | 10 | 2 | 0 |




WHO = World Health Organization.

Ramalingam S, et al. ESMO 2019. Presentation.

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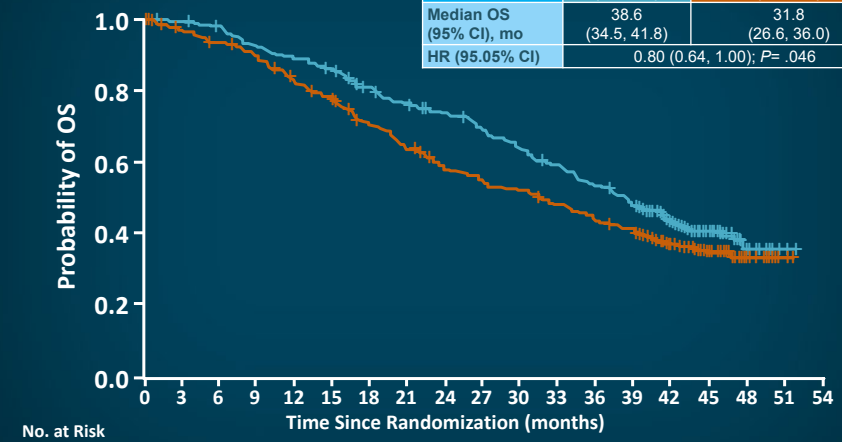
# FLAURA: OS

| | Osimertinib (n = 279) | Comparator EGFR-TKI (n = 277) |
|---|---|---|
| Median OS (95% CI), mo | 38.6 (34.5, 41.8) | 31.8 (26.6, 36.0) |
| HR (95.05% CI) | 0.80 (0.64, 1.00); *P*= .046 | |




No. at Risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 276 | 270 | 254 | 245 | 236 | 217 | 204 | 193 | 180 | 166 | 153 | 138 | 123 | 86 | 50 | 17 | 2 | 0 |
| Comparator EGFR-TKI | 277 | 263 | 252 | 239 | 219 | 205 | 182 | 165 | 148 | 138 | 131 | 121 | 110 | 101 | 72 | 40 | 17 | 2 | 0 |

Ramalingam SS, et al. *N Engl J Med.* 2020;382:41-50.

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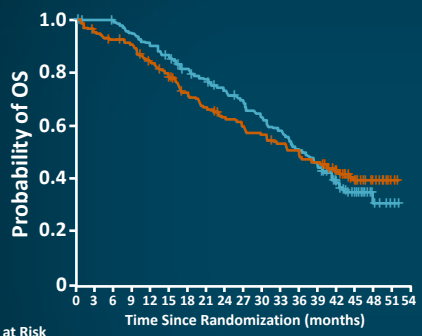
# FLAURA: OS by Subgroup Comparison

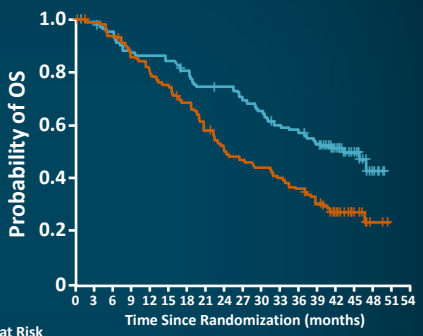
Asian patients




No. at Risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 174 | 172 | 156 | 135 | 118 | 100 | 81 | 48 | 8 | 0 |
| Comparator EGFR-TKI | 173 | 156 | 137 | 113 | 97 | 87 | 74 | 52 | 15 | 0 |

Non-Asian patients




No. at Risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 105 | 98 | 89 | 82 | 75 | 66 | 57 | 38 | 9 | 0 |
| Comparator EGFR-TKI | 104 | 96 | 82 | 69 | 51 | 44 | 36 | 20 | 2 | 0 |

Ramalingam S, et al. ESMO 2019. Presentation.

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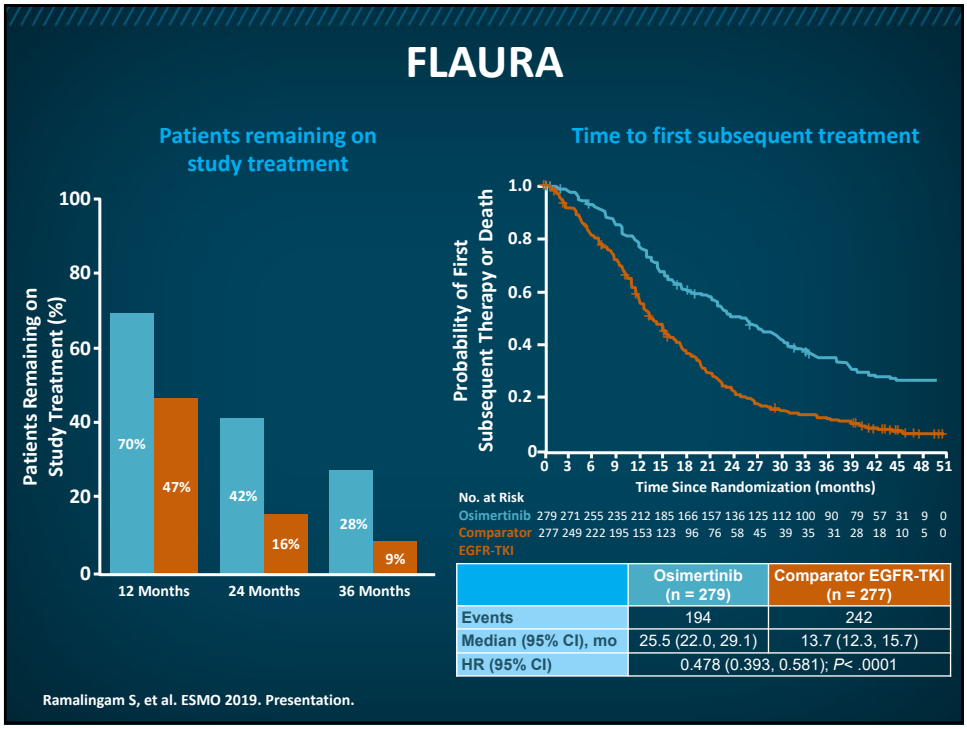
FLAURA
Patients remaining on study treatment
Patients Remaining on Study Treatment (%)
100
80
60
40
20
0
70%
47%
42%
16%
28%
9%
12 Months
24 Months
36 Months
Time to first subsequent treatment
Probability of First Subsequent Therapy or Death
1.0
0.8
0.6
0.4
0.2
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time Since Randomization (months)
No. at Risk
Osimertinib 279 271 255 235 212 185 166 157 136 125 112 100 90 79 57 31 9 0
Comparator EGFR-TKI 277 249 222 195 153 123 96 76 58 45 39 35 31 28 18 10 5 0
Osimertinib (n = 279)
Comparator EGFR-TKI (n = 277)
Events 194 242
Median (95% CI), mo 25.5 (22.0, 29.1) 13.7 (12.3, 15.7)
HR (95% CI) 0.478 (0.393, 0.581); P< .0001
Ramalingam S, et al. ESMO 2019. Presentation.

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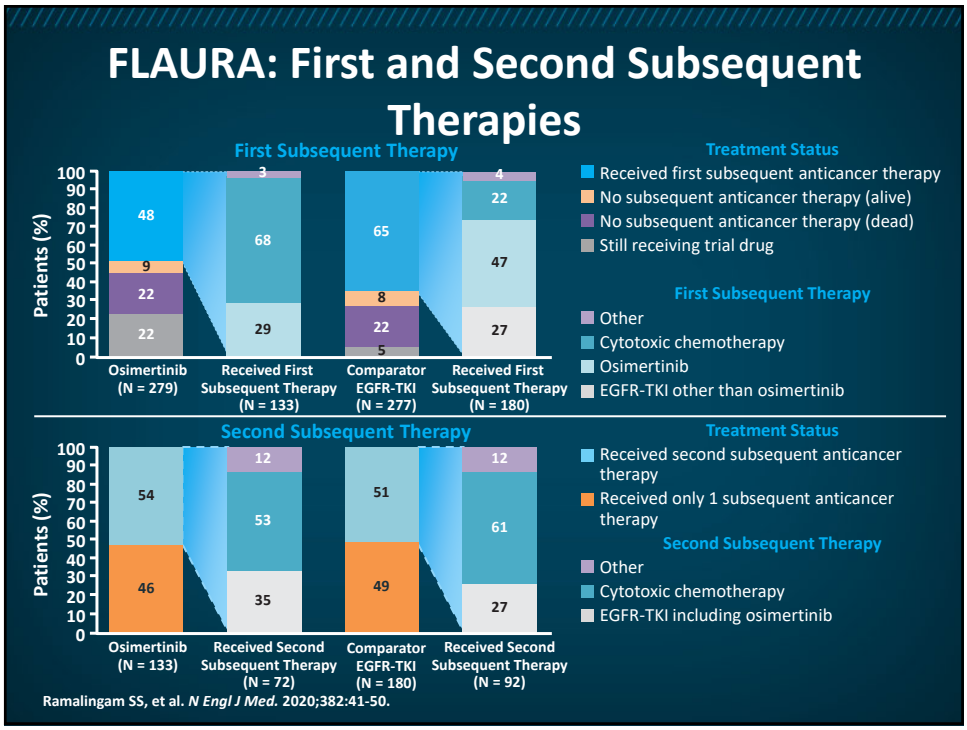
FLAURA: First and Second Subsequent Therapies
First Subsequent Therapy
Patients (%)
Osimertinib (N = 279)
Received First Subsequent Therapy (N = 133)
Comparator EGFR-TKI (N = 277)
Received First Subsequent Therapy (N = 180)
48
9
22
22
3
68
29
65
8
22
5
4
22
47
27
Treatment Status
Received first subsequent anticancer therapy
No subsequent anticancer therapy (alive)
No subsequent anticancer therapy (dead)
Still receiving trial drug
First Subsequent Therapy
Other
Cytotoxic chemotherapy
Osimertinib
EGFR-TKI other than osimertinib
Second Subsequent Therapy
Patients (%)
Osimertinib (N = 133)
Received Second Subsequent Therapy (N = 72)
Comparator EGFR-TKI (N = 180)
Received Second Subsequent Therapy (N = 92)
54
46
12
53
35
51
49
12
61
27
Treatment Status
Received second subsequent anticancer therapy
Received only 1 subsequent anticancer therapy
Second Subsequent Therapy
Other
Cytotoxic chemotherapy
EGFR-TKI including osimertinib
Ramalingam SS, et al. N Engl J Med. 2020;382:41-50.

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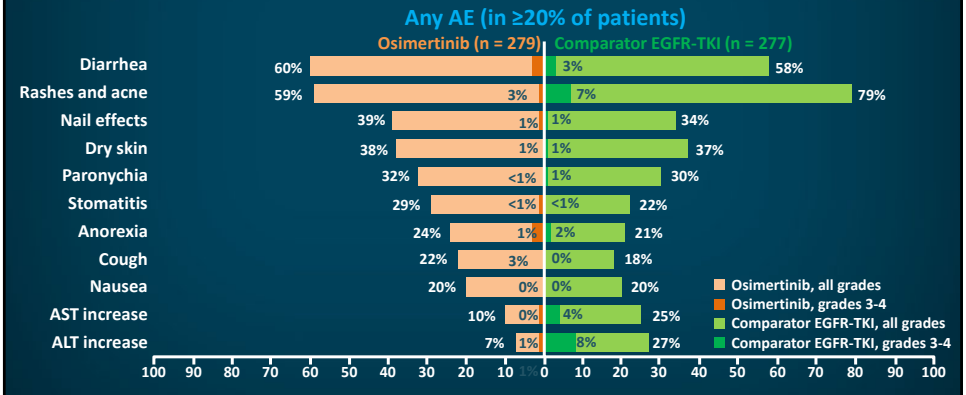
# FLAURA: Safety Summary

- Median duration of exposure: osimertinib, 20.7 months; comparator EGFR-TKI, 11.5 months
- Grade ≥3 possibly causally related AEs: osimertinib, 51 patients (18%); comparator EGFR-TKI, 79 patients (29%)




AST = aspartate aminotransferase.

Ramalingam S, et al. ESMO 2019. Presentation.

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# Impact to Clinical Practice?

- Osimertinib is the standard of care first-line treatment in the United States
  - Better PFS, CNS penetration, and side-effect profile
  - FLAURA updated data further support this with OS benefit
  - EGFR-TKI sequencing strategy is not supported
- Will vascular endothelial growth factor or chemotherapy added to osimertinib improve outcomes?
  - Future studies will provide data

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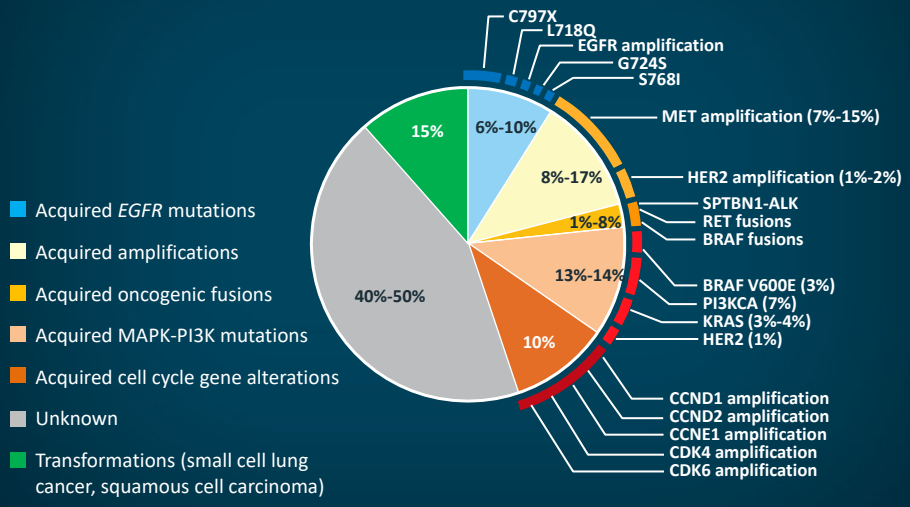
# Resistance Mechanisms to First-line Osimertinib




CDK = cyclin-dependent kinase; MAPK = mitogen-activated protein kinase; PI3K = phosphatidylinositol 3-kinase.

Ramalingam S, et al. ESMO 2019. Presentation.

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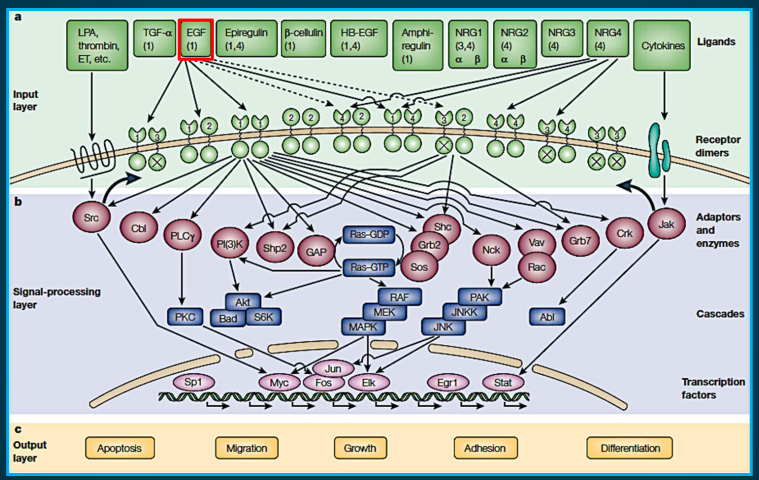
# EGFR, HER2, and ErbB Collaborate Within a Framework of a Layered Signaling Network




Egr = early growth response protein; HB-EGF = heparin-binding EGF-like growth factor; LPA = lysophosphatidic acid; Stat = signal transducer and activator of transcription; TGF = tumor growth factor.

Yarden Y, Sliwkowski MX. *Nature Rev Mol Cell Biol.* 2001;2:127-137.

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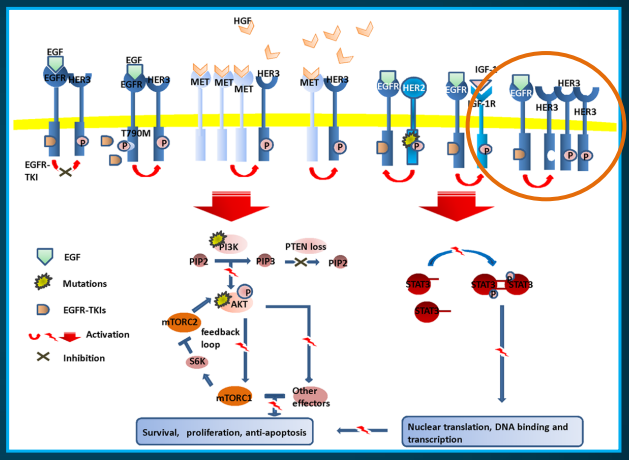
# EGFR and HER3

- Targeted therapy to EGFR can lead to HER3 overexpression. HER3 cannot be autophosphorylated, but HER3 dimerizes with EGFR, which activates the pathway previously inhibited by EGFR TKIs. This is a mechanism for resistance




IGF = insulin-like growth factor; mTOR = mammalian target of rapamycin; HER3 = human epidermal growth factor receptor 3.
Lin Y, et al. *Am J Cancer Res.* 2014;4:411-435.

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# Whiteboard Presentation

**We will now watch a brief depiction of the role of HER3 in EGFR-TKI resistance in NSCLC**

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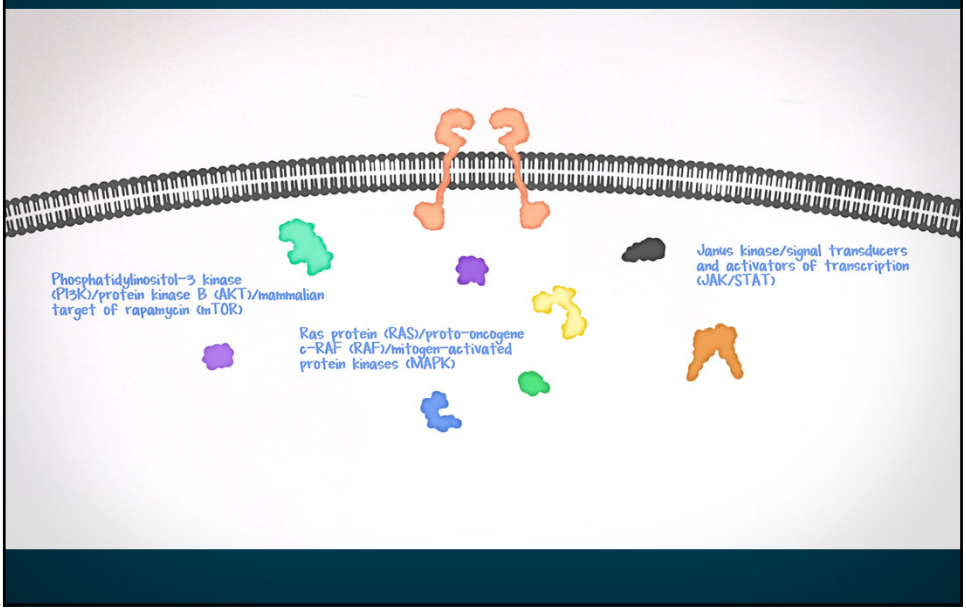
## The role of HER3 in EGFR-TKI resistance in NSCLC

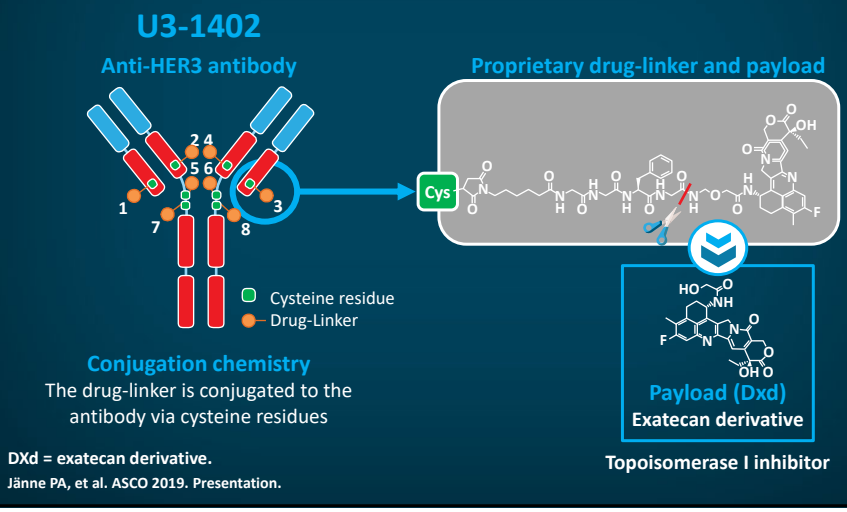
https://youtu.be/vtVZxzOUwIg




39

## Targeting HER3

- HER3 expression on cells can serve as a door to the cell for cytotoxic therapy in the form of ADCs




DXd = exatecan derivative.

Jänne PA, et al. ASCO 2019. Presentation.

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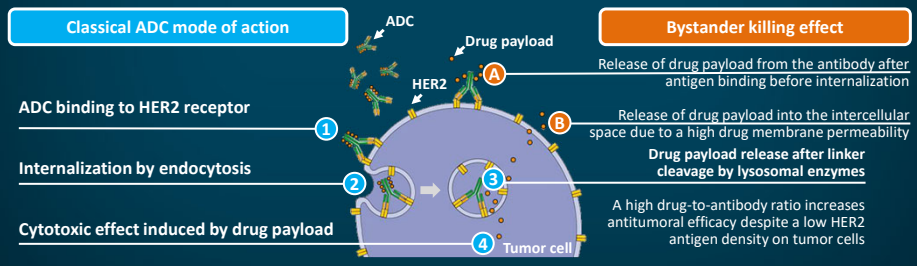
# Antibody-Drug Conjugates

- ADCs bind to a surface receptor leading to endocytosis
- Lysosomal degradation releases the cytotoxic payload
- Higher drug-to-antibody ratios deposit more drug into the cell
- Payloads that are membrane permeable may lead to bystander effects by entering neighboring cells after release from the first targeted cell

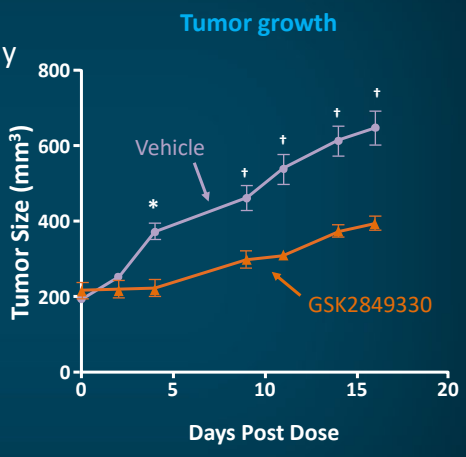



Rinnerthaler G, et al. *Int J Mol Sci.* 2019;20:1115.

41

# GSK2849330

- IgG1/Gg3 glyco-engineered humanized monoclonal antibody
- Engineered for 3 mechanisms of action
  - Blocking ligand-dependent signaling, inhibiting HER3 signaling and function
  - Cell-mediated cytotoxicity
  - Complement-dependent cytotoxicity
- Demonstrated compelling *preclinical data* targeting HER3




*$P$< .01; †$P$< .001 using 2-way analysis of variance.
Alsaid H, et al. *PLoS One*. 2017;12:e0176075.

*Not FDA-approved for NSCLC.

42

# U3-1402

- Features of HER3-directed ADC
  - High potency of the topoisomerase I inhibitor payload
  - Drug-to-antibody ratio of about 8:1
  - Payload has short systemic half-life
  - The payload is membrane permeable, allowing entry to nearby cells (bystander effect)

Jänne PA, et al. ASCO 2019. Presentation.

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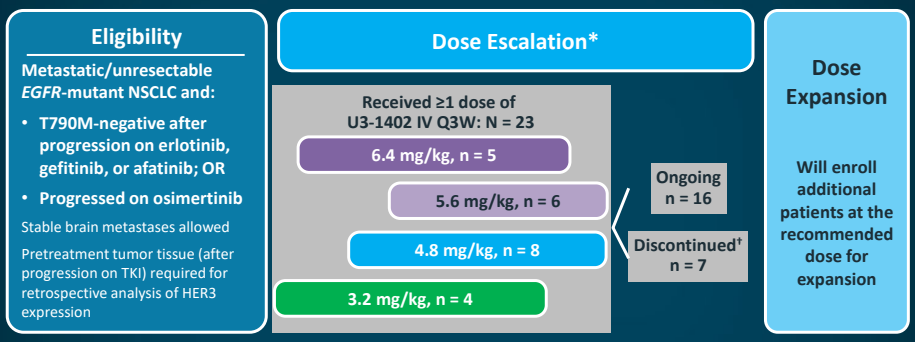
# U3-1402: Study Schema

## U3-1402 phase 1 dose escalation and expansion study




| Study Objectives | Primary: Safety and tolerability of U3-1402 | Secondary: Antitumor activity of U3-1402 | Exploratory: Biomarkers of U3-1402 antitumor activity |
|---|---|---|---|

Data cutoff of February 25, 2019. *Dose escalation was guided by the modified continuous reassessment method with escalation with overdose control. Additional doses may be added. †Reasons for discontinuation included PD per RECIST v1.1, n = 5; clinical progression (definitive clinical signs of PD, but did not meet RECIST criteria), n = 1; and AE, n = 1. clinicaltrials.gov NCT03260491. Q3W = every 3 weeks.

Jänne PA, et al. ASCO 2019. Presentation.

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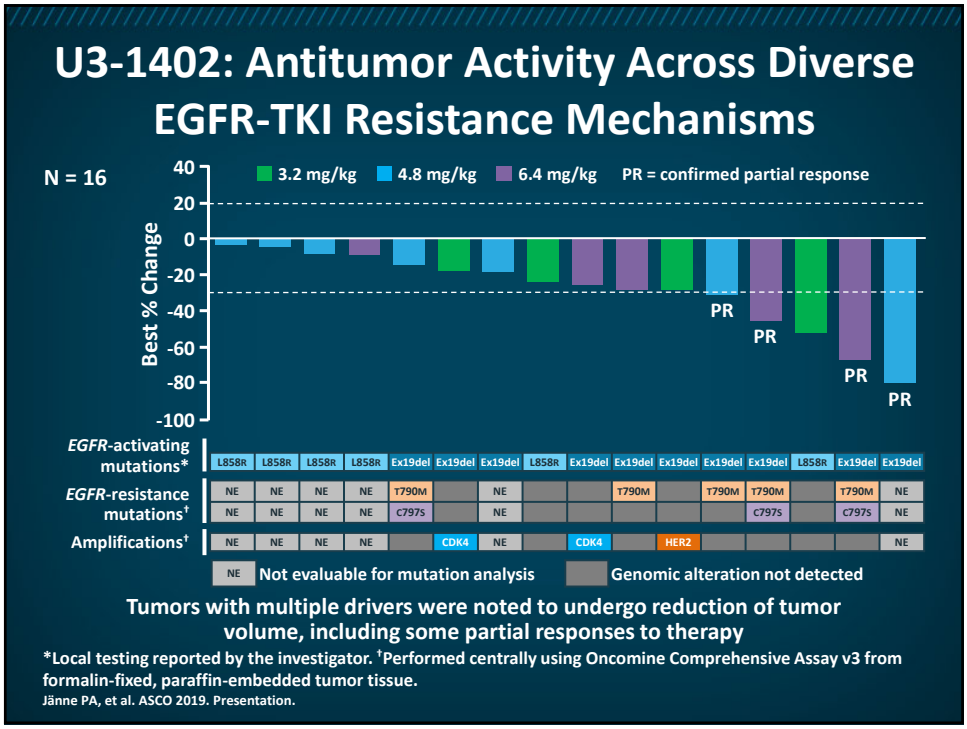
U3-1402: Antitumor Activity Across Diverse EGFR-TKI Resistance Mechanisms
N = 16
3.2 mg/kg
4.8 mg/kg
6.4 mg/kg
PR = confirmed partial response
Best % Change
40
20
0
-20
-40
-60
-80
-100
PR
PR
PR
PR
EGFR-activating mutations*
EGFR-resistance mutations†
Amplifications†
L858R
Ex19del
T790M
C797S
CDK4
HER2
NE
Not evaluable for mutation analysis
Genomic alteration not detected
Tumors with multiple drivers were noted to undergo reduction of tumor volume, including some partial responses to therapy
*Local testing reported by the investigator. †Performed centrally using Oncomine Comprehensive Assay v3 from formalin-fixed, paraffin-embedded tumor tissue.
Jänne PA, et al. ASCO 2019. Presentation.

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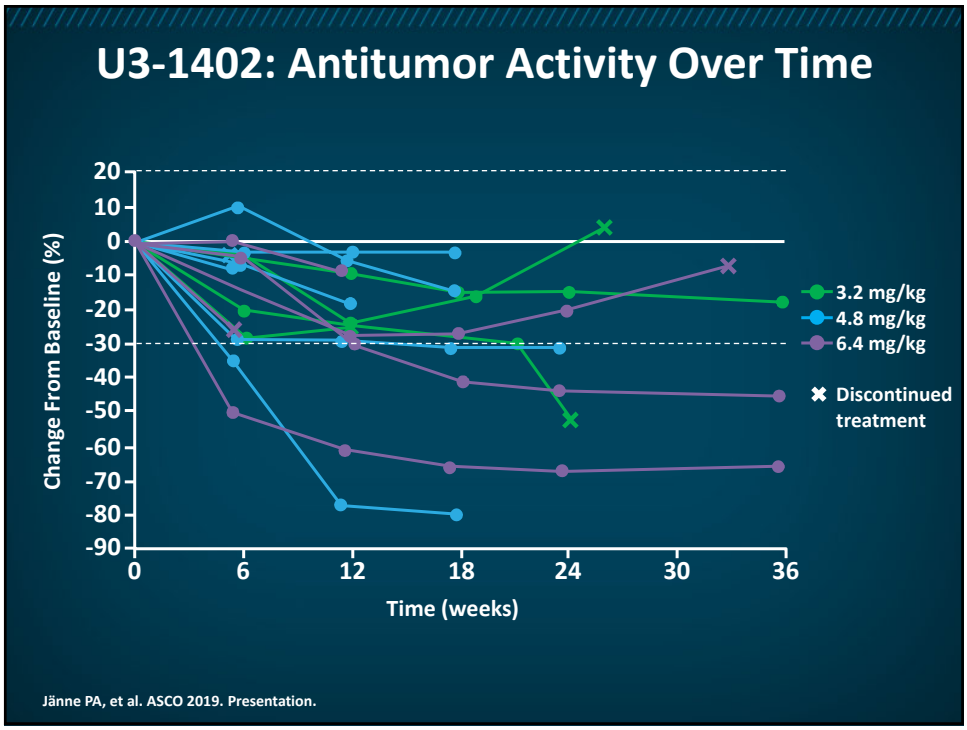
U3-1402: Antitumor Activity Over Time
Change From Baseline (%)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
0
6
12
18
24
30
36
Time (weeks)
3.2 mg/kg
4.8 mg/kg
6.4 mg/kg
Discontinued treatment
Jänne PA, et al. ASCO 2019. Presentation.

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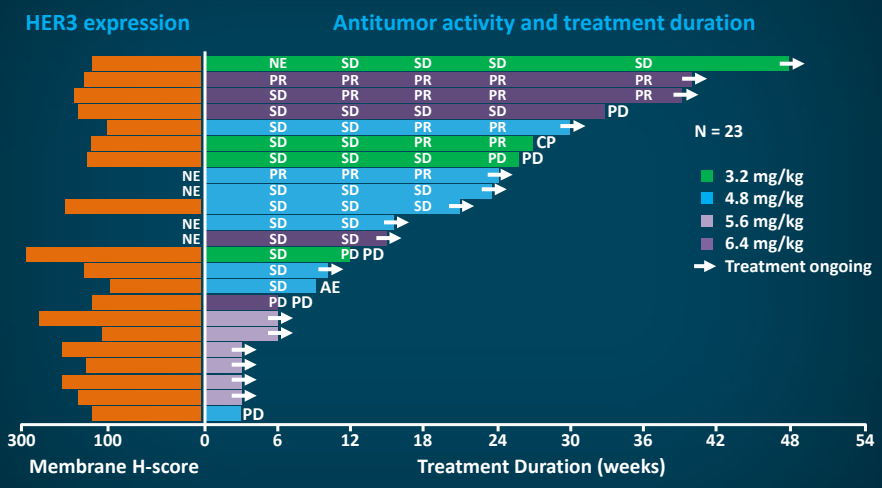
# U3-1402: Treatment Duration




CP = clinical progression; SD = stable disease.

Jänne PA, et al. ASCO 2019. Presentation.

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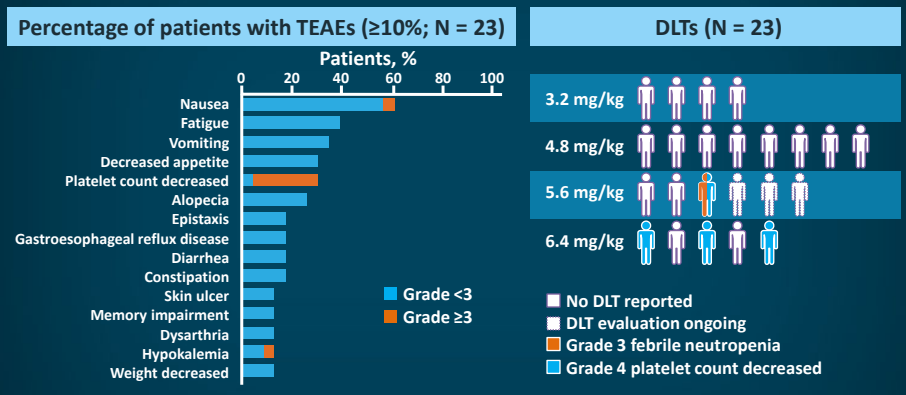
# U3-1402: Safety Summary

## TEAEs and DLTs in patients treated with U3-1402




Data cutoff date of February 25, 2019. TEAE analysis used the safety analysis set, which includes all patients who received ≥1 dose of U3-1402 (N = 23). For TEAEs in <10% of patients, there were 5 grade 3 events: ALT increased, n = 1; troponin increased, n = 1; confusional state, n = 1; hypoxia, n = 1; febrile neutropenia, n = 1.

DLT = dose-limiting toxicity; TEAE = treatment-emergent AE.

Jänne PA, et al. ASCO 2019. Presentation.

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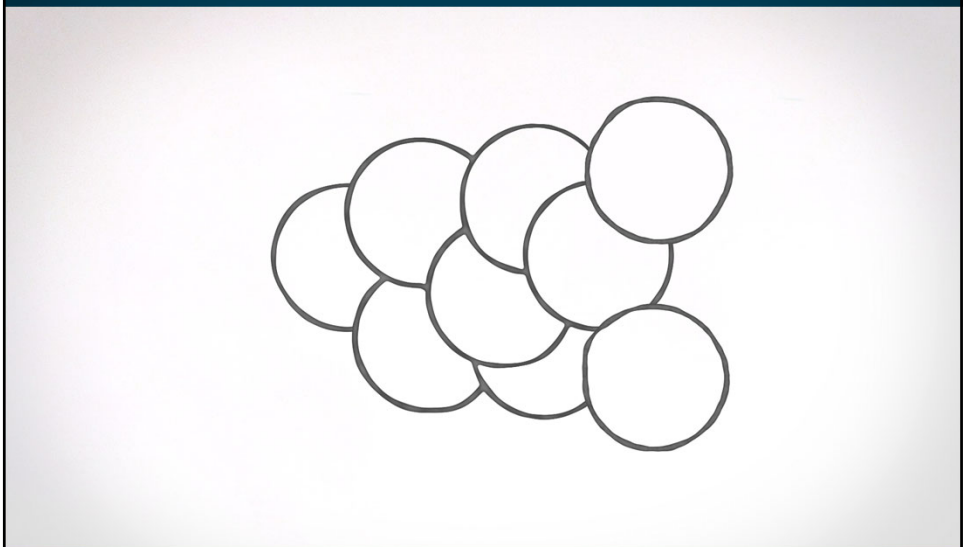
# Whiteboard Presentation

**We will now watch a brief depiction of trophoblast cell-surface antigen 2 (TROP2) and the role it plays in tumorigenesis**

49

Trophoblast Cell-Surface Antigen 2 (TROP2) and the Role it Plays in Tumorigenesis

https://youtu.be/qEqHUT7apkY



50

# Trophoblast Cell-Surface Antigen 2 (TROP2)

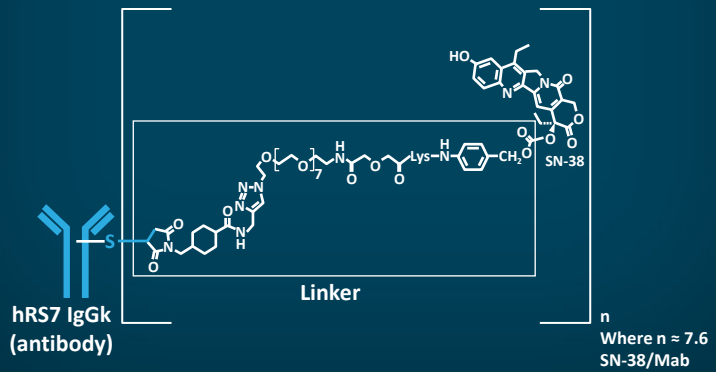
- A glycoprotein overexpressed in various epithelial cancers[1]
- Portends poor prognosis[2]
- Intracellular calcium signal transducer[2]
- Has oncogenic properties[1]

1. Wang J, et al. *Mol Cancer Ther*. 2008;7:280-285. 2. Shvartsur A, Bonavida B. *Genes Cancer*. 2015;6:84-105.

51

# Sacituzumab Govitecan

- TROP2-directed ADC
- Payload is SN-38 (topoisomerase I inhibitor)

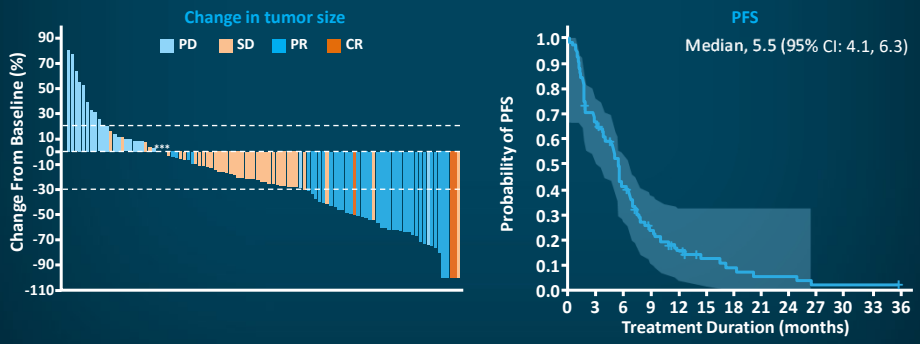



Syed YY. *Drugs* 2020;80:1019-1025

52

# Sacituzumab Govitecan in TNBC[1]

- April 2020: FDA granted accelerated approval for treatment of metastatic triple-negative breast cancer after ≥2 prior therapies for metastatic disease[2]
- ORR 33.3%
- Median DOR 7.7 months



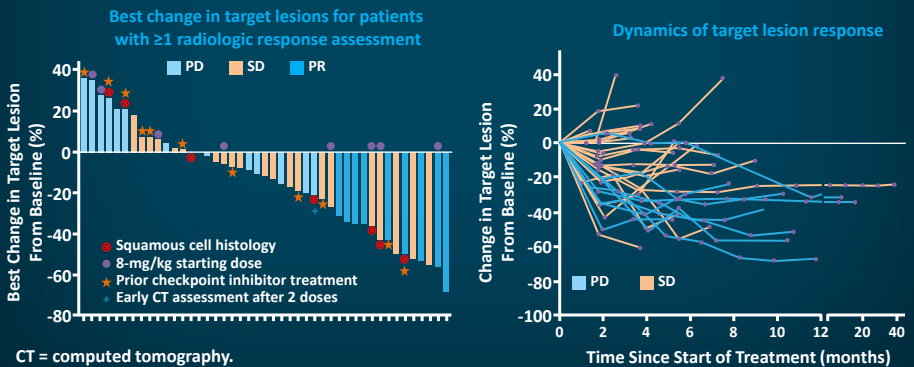

TNBC = triple negative breast cancer; CR = complete response; DOR = duration of response; ORR = objective response rate.

1. Bardia A, et al. *N Engl J Med.* 2019;380:741-751. 2. FDA approval (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer). Accessed August 17, 2020.

53

# Sacituzumab Govitecan in NSCLC

- ORR 19%
- Median DOR 6.0 months
- Clinical benefit rate 43%
- Demonstrated evidence of efficacy




CT = computed tomography.

Heist RS, et al. *J Clin Oncol.* 2017;35:2790-2797.

54

# TROP2 (cont)

- TROP2: an intracellular calcium-signaling transducer
  - Overexpressed in epithelial cancers, including NSCLC, which portends poor survival
- DS-1062 is an ADC
  - TROP2 antibody bound to DXd (topoisomerase I inhibitor)

**Phase 1 study of DS-1062**

- **Patients aged ≥18 (US) or 20 (Japan) years with metastatic/unresectable advanced NSCLC and**
  - Disease relapsed from/refractory to standard treatment (or for which no standard treatment is available)
  - ECOG PS 0-1
  - Measurable disease per RECIST v1.1
- **Patients were enrolled without selection for TROP2**
  - Pretreatment tumor tissue required for retrospective analysis of TROP2 expression

**Dose escalation**

DS-1062 dose Q3W

- 10 mg/kg (n ≈ 3-6)
- 8 mg/kg (n ≈ 3-6)
- 6 mg/kg[a] (n ≈ 3-6)
- 4 mg/kg[a] (n ≈ 3-6)
- 2 mg/kg (n ≈ 3-6)
- 1 mg/kg (n ≈ 3-6)
- 0.5 mg/kg (n ≈ 3-6)
- 0.27 mg/kg (n ≈ 3-6)

**Dose expansion**

- **Enrollment of approximately 50 patients at 4 mg/kg, 50 patients at 6 mg/kg, and 80 patients at 8 mg/kg is ongoing**
- **Up to 40 patients each in 2 additional indications may also be enrolled if DS-1062 demonstrates acceptable safety, tolerability, and efficacy from previously treated patients in this study**

ECOG = Eastern Cooperative Oncology Group.

Lisberg AE, et al. ASCO 2020. Poster 9619.

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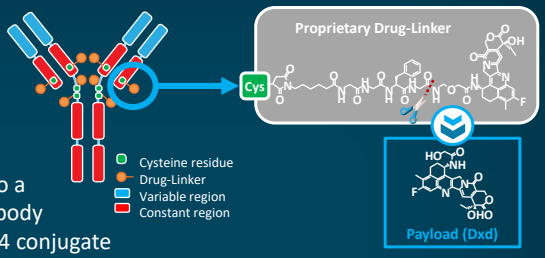
# DS-1062

## DS-1062a structure

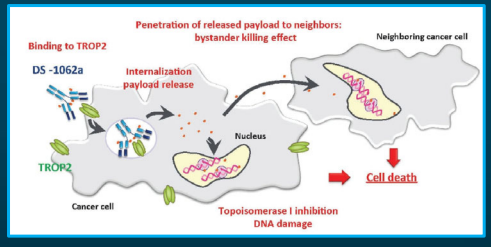
- TROP2-targeting ADC with a novel topoisomerase I inhibitor (DXd)

## Conjugation chemistry

- Tetrapeptide linker bound to a cysteine residue of the antibody
- DS-1062a is a selective DAR4 conjugate




## Proposed mechanism of action




Sands JM, et al. ASCO 2018. Poster 374. Lisberg AE, et al. ASCO 2020. Poster 9619.

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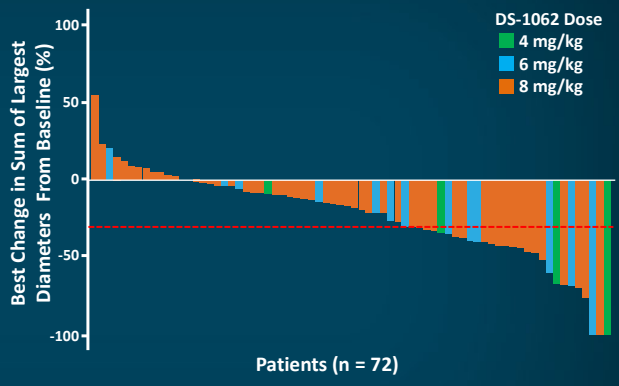
# DS-1062: Tumor Response

- Maximum tolerated dose: 8 mg/kg
- Responses have been noted at multiple dose levels




Lisberg AE, et al. ASCO 2020. Poster 9619.

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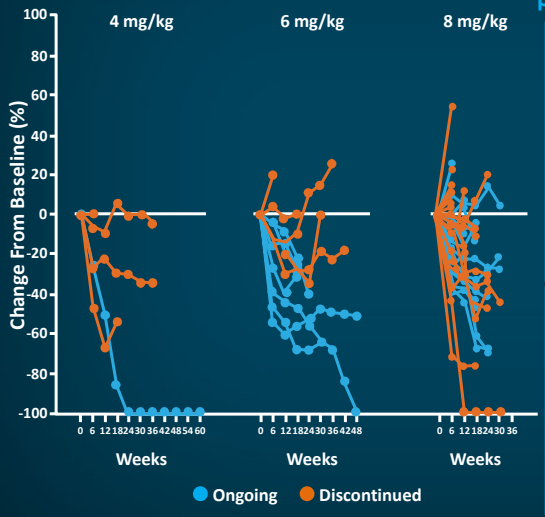
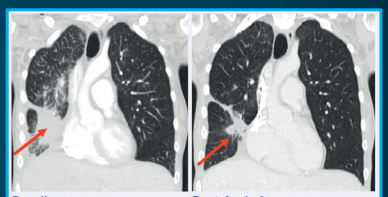
# DS-1062: Tumor Response by Dose

**Change in tumor burden by DS-1062 dose[1]**



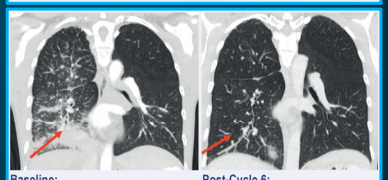

**Reduction in target lesion size in patient treated with 4-mg/kg DS-1062a[2]**



**Baseline:** Begin 4.0-mg/kg DS-1062a

**Post-Cycle 6:** After 4.5 months of treatment

*Maximum percent decrease in tumor size 36.6%*



**Baseline:** Begin 4.0-mg/kg DS-1062a

**Post-Cycle 6:** After 4.5 months of treatment

*Maximum percent decrease in tumor size 36.6%*

1. Lisberg AE, et al. ASCO 2020. Poster 9619. 2. Sands JM, et al. ASCO 2018. Poster 374.

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# DS-1062: Safety Summary

- Tolerable safety profile up to 8 mg/kg in first in-human study
- ORR 27%
- Responses were noted irrespective of TROP2 expression

| | Patients Treated With DS-1062 (N = 138) | |
|---|---|---|
| | All Grades, n (%) | Grade ≥3, n (%) |
| Any TEAE | 129 (94) | 62 (45) |
| TEAEs in ≥15% of patients, by preferred term | | |
| Nausea | 60 (44) | 0 |
| Fatigue | 56 (41) | 4 (3) |
| Stomatitis | 47 (34) | 4 (3) |
| Alopecia | 46 (33) | 0 |
| Vomiting | 37 (27) | 0 |
| Decreased appetite | 31 (23) | 0 |
| Infusion-related reaction | 29 (21) | 0 |
| Anemia | 26 (19) | 4 (3) |
| Constipation | 26 (19) | 1 (1) |
| Cough | 26 (19) | 1 (1) |
| Mucosal inflammation | 25 (18) | 4 (3) |
| Rash | 25 (18) | 0 |
| Dyspnea | 23 (17) | 6 (4) |
| Diarrhea | 20 (15) | 0 |

Lisberg AE, et al. ASCO 2020. Poster 9619.

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# Conclusions

- First-line treatment for sensitizing *EGFR* mutation
  - Osimertinib: Improved PFS, OS, and good CNS activity
- Various mechanisms for resistance to osimertinib
  - HER3 expression can serve as a receptor to access point for cancer cells. Delivery of cytotoxic agent via ADCs, such as U3-1402, appears promising
- DS-1061 is another ADC in an ongoing early phase trial with compelling results

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# Case Studies

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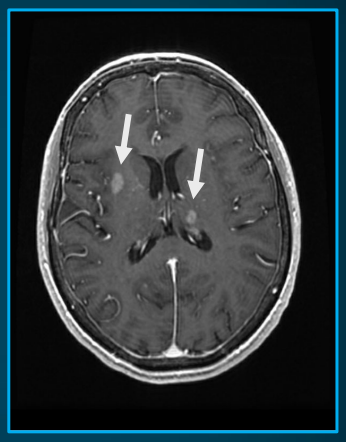
## Case Study

- A 52-year-old woman presented to her primary care physician with persistent cough for the past month
- CT revealed multiple lung nodules and radiographic findings consistent with bone and liver metastases; however, no radiographic findings threatening impending symptoms
- She reported good appetite and energy level without any other significant symptoms. Although the cough was bothersome at times, it did not limit her physical activity
- Brain MRI revealed evidence of brain metastases
- Biopsy of liver nodule showed adenocarcinoma lung



MRI = magnetic resonance imaging.

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## Case Study: Question 1

What is the next, most appropriate intervention for this patient?

A) Carboplatin + pemetrexed + pembrolizumab

B) Carboplatin + pemetrexed

C) Pembrolizumab

D) Hold treatment and test for genomic alterations of the cancer

E) Whole-brain radiation

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## Case Study: Question 2

Given her ongoing good functional status, low overall tumor burden, and suspicion for a targetable genomic alteration, a NGS test was sent and showed an L858R *EGFR* mutation. Which treatment do you recommend?

A) Erlotinib

B) Gefitinib

C) Dacomitinib

D) Afatinib

E) Osimertinib

**NGS = next-generation sequencing.**

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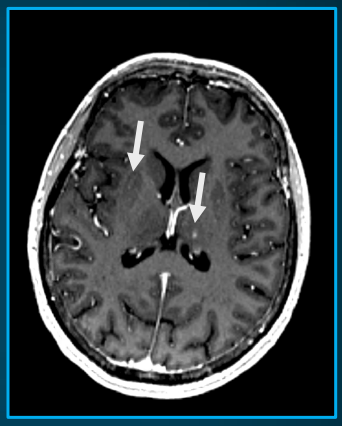
## Case Study: First-line Treatment

- She started osimertinib 80 mg daily. Within 2 weeks she noted resolution of her cough. Significant improvement in brain metastases was also noted on follow-up imaging



65

## Case Study: Question 3

She did well on osimertinib for 2 years before CT showed evidence of progression in her liver and lungs. What is the best course of action?

A) Send cfDNA as a blood based test to evaluate for targetable genomic alterations

B) Get a biopsy to test tissue for targetable genomic alterations

C) Start carboplatin + pemetrexed + pembrolizumab

D) Start carboplatin + paclitaxel + atezolizumab + bevacizumab

E) Hospice care

cfDNA = circulating free DNA.

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## Case Study: Question 4

A blood sample was collected and sent for cfDNA testing. No alterations were identified. Given the negative cfDNA testing, biopsy was obtained and tissue was sent for NGS testing. What are some possible mechanisms of resistance to osimertinib?

A) MET amplification

B) *HER2* mutation

C) *C797S* mutation

D) RET fusion

E) All of the above

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## Thank you!

Questions and Answers

68

## Overview of NSCLC and Treatment

| Citation | Address |
|---|---|
| **American Cancer Society (ACS). Non-Small Cell Lung Cancer stages. Revised October 1, 2019.** | https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/staging-nsclc.html |
| **American Cancer Society (ACS). Treating Non-Small Cell Lung Cancer. Revised June 10,2020.** | https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell.html |
| **Cancer.Net. Lung cancer – Non-Small Cell: Statistics. Approved May, 2020.** | https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics |
| **National Institutes of Health. National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. Updated May 7, 2020.** | https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq |

## EGFR Mutation

| Citation | Address |
|---|---|
| **Douillard JY, Ostoros G, Cobo M, et al. Gefitinib treatment in *EGFR* mutated Caucasian NSCLC: Circulating-free tumor DNA as a surrogate for determination of EGFR status. *J Thorac Oncol*. 2014;9:1345-1353.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4224589/ |
| **Buttitta F, Felicioni L, Di Lorito A, et al. Early prediction of resistance to tyrosine kinase inhibitors by plasma monitoring of *EGFR* mutations in NSCLC: A new algorithm for patient selection and personalized treatment. *Oncotarget*. 2020;11:982-991.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7082112/ |

**EGFR TKIs**

| Citation | Address |
|---|---|
| **Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.** | https://www.nejm.org/doi/10.1056/NEJMoa0810699 |
| **Maemondo M, Fukuhara T, Saito H, et al. NEJ026: Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR-mutations. *J Clin Oncol*. 2020;38(15 suppl):9506.** | https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.9506 |
| **Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.** | https://www.nejm.org/doi/10.1056/NEJMoa1612674 |
| **Nakagawa K, Garon EB, Seto T, et al. RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2019;37(15 suppl):9000.** | https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.9000 |
| **Nakamura A, Inoue A, Morita S, et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). *J Clin Oncol*. 2018;36(15 suppl):9005.** | https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.9005 |
| **Noronha V, Patel VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in *EGFR*-mutated lung cancer. *J Clin Oncol*. 2020;38:124-136.** | https://ascopubs.org/doi/10.1200/JCO.19.01154 |

| | |
|---|---|
| **Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. *Lancet Oncol*. 2016;17:577-589.** | https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30033-X/fulltext |
| **Ramalingam SS. Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRM advanced NSCLC (FLAURA): Final overall survival analysis. *Ann Oncol*. 2019;30(suppl 5):v914-v915** | https://www.annalsofoncology.org/article/S0923-7534(19)60436-9/fulltext |
| **Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41-50.** | https://www.nejm.org/doi/10.1056/NEJMoa1913662 |
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