# Drawing the map: molecular characterization of NSCLC

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# Disclosures

- Honoraria for advisory board/consultancy/speakers fee
  - Eli Lilly
  - Roche
  - Boehringer Ingelheim
  - Bristol-Myers Squibb
  - MSD
  - Amphera B.V.
  - Verastem
  - AstraZeneca
- Research funding department
  - Eli Lilly
  - Roche
  - Boehringer Ingelheim
- Patents pending
  - Tumour lysate antigen
- Stock owner
  - Amphera B.V. immunotherapy

# Learning objective

- After this presentation, participants will be able to
  - identify molecular pathways that drive malignancy in advanced NSCLC
  - understand the importance of genetic testing in improving diagnosis and identifying opportunities for treatments
  - recognize the limited treatment options available for advanced squamous NSCLC

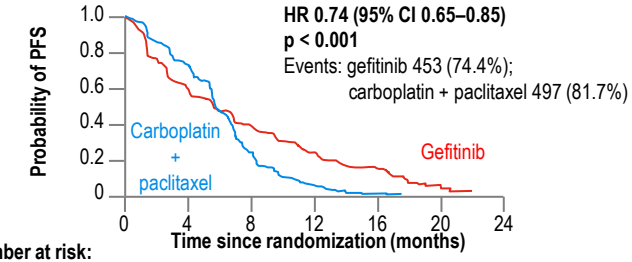
# Question 1

Should molecular profiling be part of the diagnostic work-up in a patient with advanced squamous NSCLC who is a smoker?

1. Yes
2. No

# First-line therapy with gefitinib prolongs PFS in patients with *EGFR* mutation

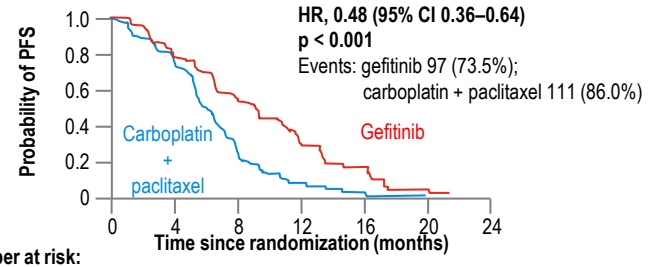
**Overall**




Number at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gefinitib | 609 | 363 | 212 | 76 | 24 | 5 | 0 |
| Carboplatin + paclitaxel | 608 | 412 | 118 | 22 | 3 | 1 | 0 |

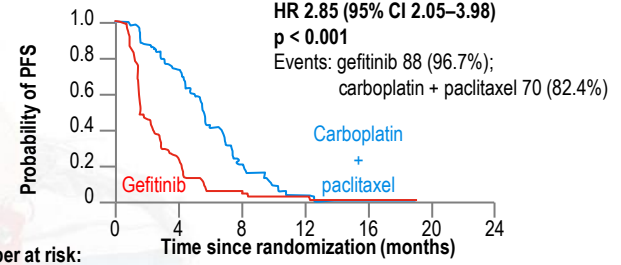
***EGFR*-mutation-positive**




Number at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gefinitib | 132 | 108 | 71 | 31 | 11 | 3 | 0 |
| Carboplatin + paclitaxel | 129 | 103 | 37 | 7 | 2 | 1 | 0 |

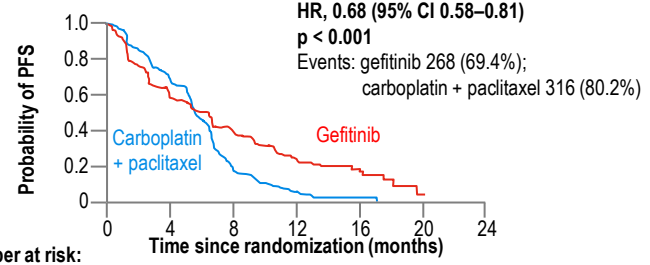
***EGFR*-mutation-negative**




Number at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gefinitib | 91 | 21 | 4 | 2 | 0 | 0 | 0 |
| Carboplatin + paclitaxel | 85 | 58 | 14 | 1 | 0 | 0 | 0 |

**Unknown *EGFR* mutation status**



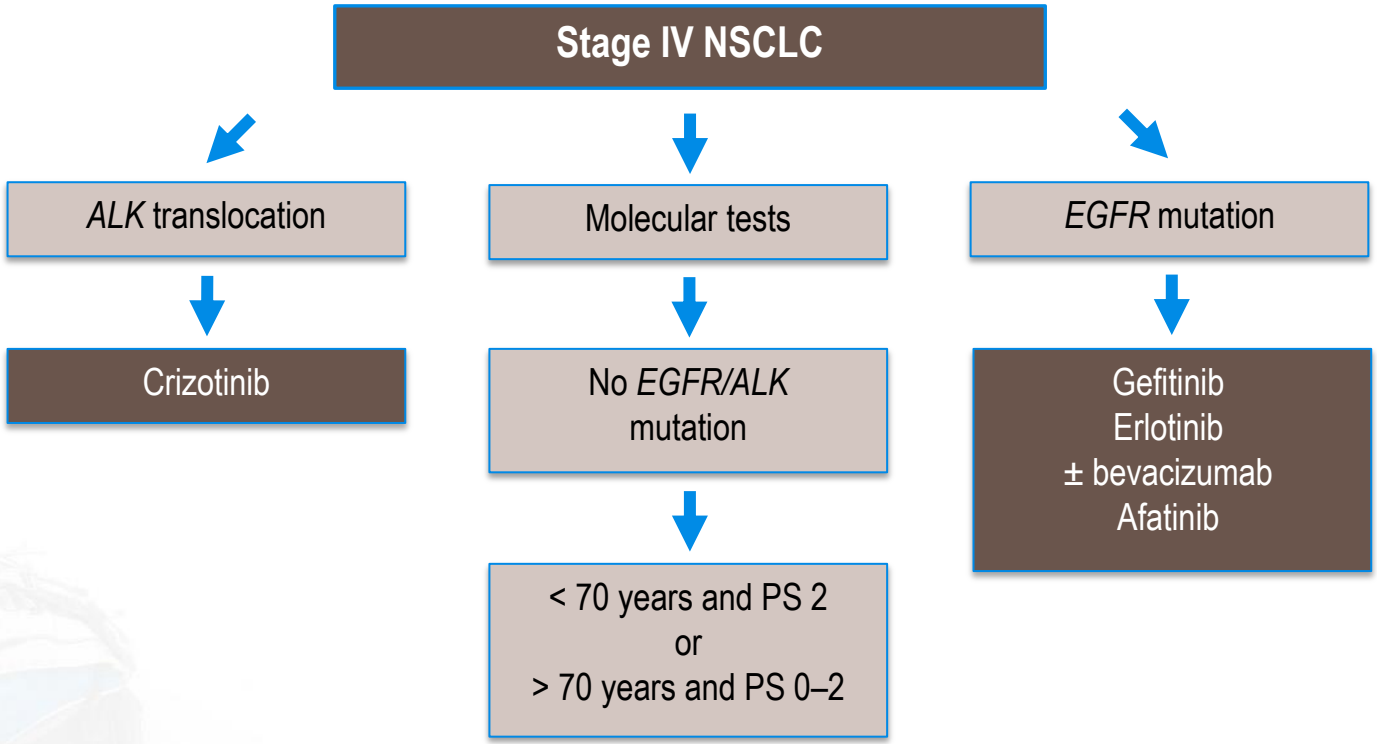

Number at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gefinitib | 386 | 234 | 137 | 43 | 12 | 2 | 0 |
| Carboplatin + paclitaxel | 394 | 251 | 67 | 14 | 1 | 0 | 0 |

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival.

# ESMO Guidelines 2016

Non-squamous

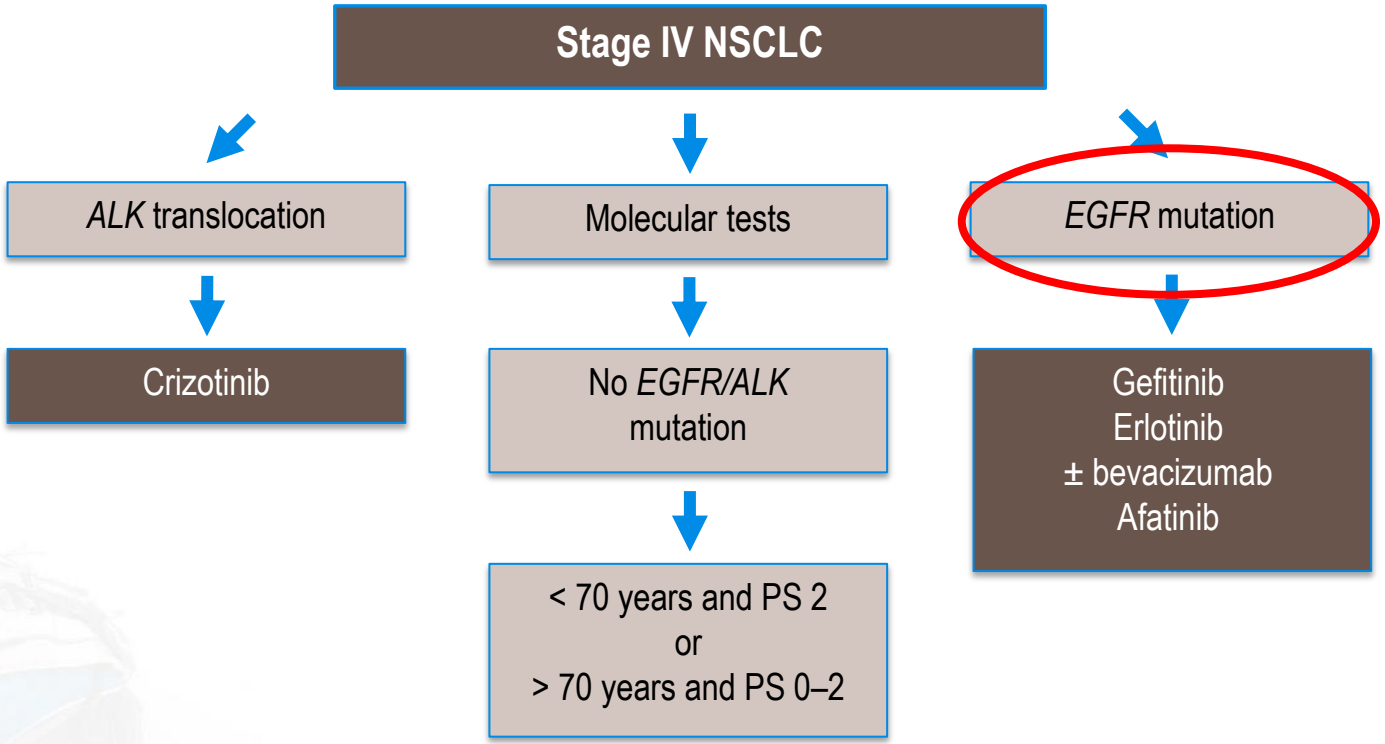



ALK, anaplastic lymphoma kinase; PS, performance status.

Based on Novello S, et al. Ann Oncol. 2016;27 Suppl 5:v1-v27.

# ESMO Guidelines 2016

Non-squamous

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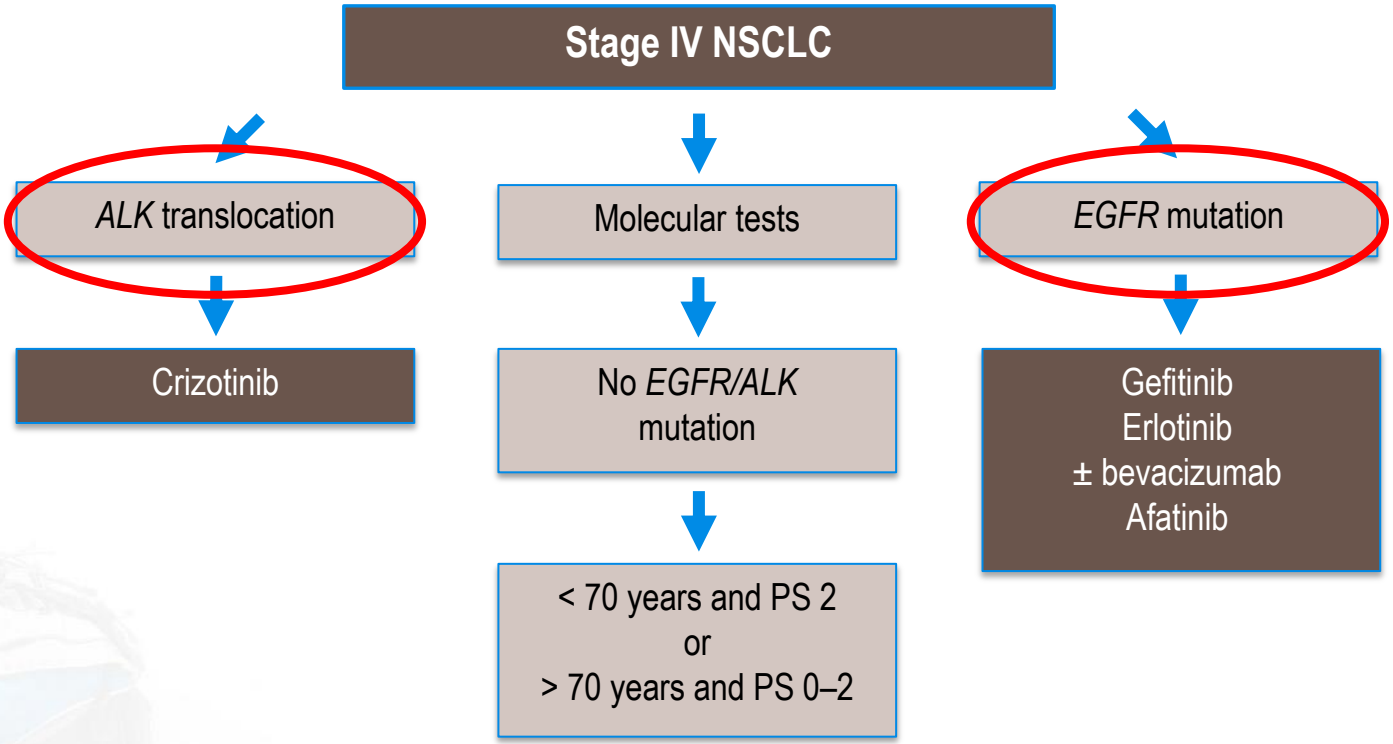
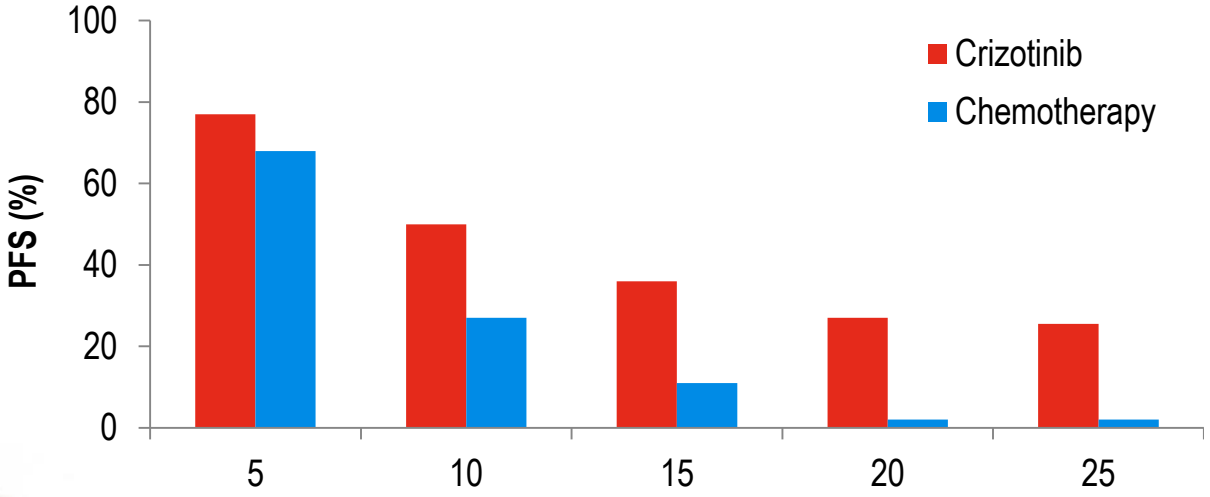
Non-squamous




ALK, anaplastic lymphoma kinase; PS, performance status.

Based on Novello S, et al. Ann Oncol. 2016;27 Suppl 5:v1-v27.

# Crizotinib as first-line therapy prolonged PFS in patients with advanced *ALK*-positive NSCLC




| Number at risk: | | | | | |
|---|---|---|---|---|---|
| Crizotinib | 120 | 65 | 38 | 19 | 7 |
| Chemotherapy | 105 | 36 | 12 | 2 | 1 |

**HR for progression or death in crizotinib group**
**0.45 (95% CI 0.35–0.60); p < 0.001***

* 2-sided stratified log rank test.

Solomon BJ, et al. N Engl J Med. 2014;371:2167-77.

# Tumour responses to crizotinib in *ROS1*-rearranged NSCLC

- *ROS1* rearrangements represent a second molecular subgroup of NSCLC that can be targeted with crizotinib
- Response rates to crizotinib are high in *ROS1*-rearranged NSCLC

| Type of response (n = 50) | ROS1 cohort, number (%) |
|---|---|
| Complete response | 3 (6) |
| Partial response | 33 (66) |
| Stable disease | 9 (18) |
| Progressive disease | 3 (6) |

- Duration of response was 17.6 months (95% CI 14.5−NR)
  - 64% of responses were ongoing at the time of data cutoff

NR, not reached; *ROS1*, ROS1 proto-oncogene receptor tyrosine kinase.

Shaw AT, et al. N Engl J Med. 2014;371:1963-71.

# Case discussion

Second opinion: no treatment options?

- 65-year-old male
- Adenocarcinoma of the RUL
  - liver and left adrenal gland metastasis
  - *EGFR* testing negative
  - no *ALK* translocation
- 2013
  - started treament with cisplatin + pemetrexed with partial response
  - progressive disease after 8 cycles of pemetrexed maintenance

RUL, right upper lobe of lung.

Courtesy of J. Aerts.

# Case (continued)

- Started on docetaxel (75 mg/m$^2$/3 weeks)
  - hospitalized for cardiac arrest after the second cycle
- Docetaxel discontinued



Courtesy of J. Aerts.

# Question 2

What would you do?

1. BSC
2. Restart on another chemotherapy
3. Check mutation testing
4. Consider phase 1 study
5. Immunotherapy after PD-L1 testing

PD-L1, programmed death-ligand 1.

# Case (continued)

- Check mutation testing
  - referring hospital tested for *EGFR* in:
    - exon 19
    - exon 21
- NGS testing
  - *EGFR* mutation positivity:
    - exon 18

NGS, next-generation sequencing.

Courtesy of J. Aerts.

# Case (continued)

- 2014
  - started on erlotinib (150 mg/day) with a partial response
- 2016
  - progressive disease in liver and lung



Courtesy of J. Aerts.

# Question 3

What would your next step be?

1. Start on immunotherapy with PD-L1 inhibitors
2. Restart chemotherapy
3. BSC
4. Perform new mutation testing

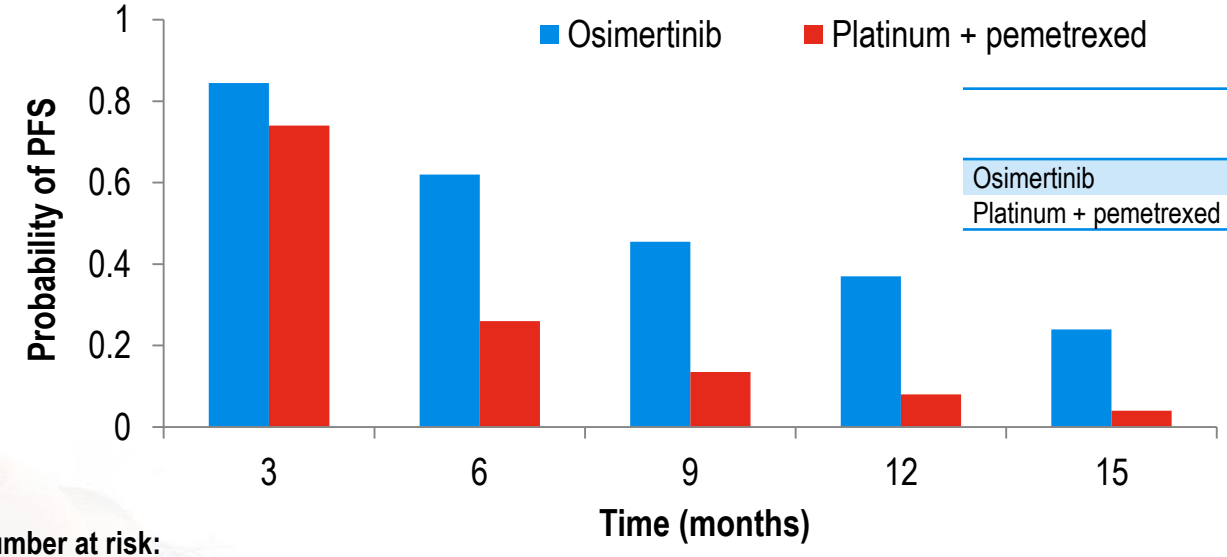
# Case (continued)

- Additional liver biopsy and cfDNA (liquid biopsy) testing
  - T790M positivity
- Started on osimertinib (80 mg/day)
  - partial response up to present

cfDNA, cell-free DNA.

Courtesy of J. Aerts.

# Osimertinib vs platinum + pemetrexed in T790M-positive advanced NSCLC: PFS




| | Patients, n | Median PFS, months (95% CI) |
|---|---|---|
| Osimertinib | 116 | 8.2 (6.8–9.7) |
| Platinum + pemetrexed | 56 | 4.2 (4.1–5.1) |

HR for disease progression or death
0.42 (95% CI 0.29–0.61)

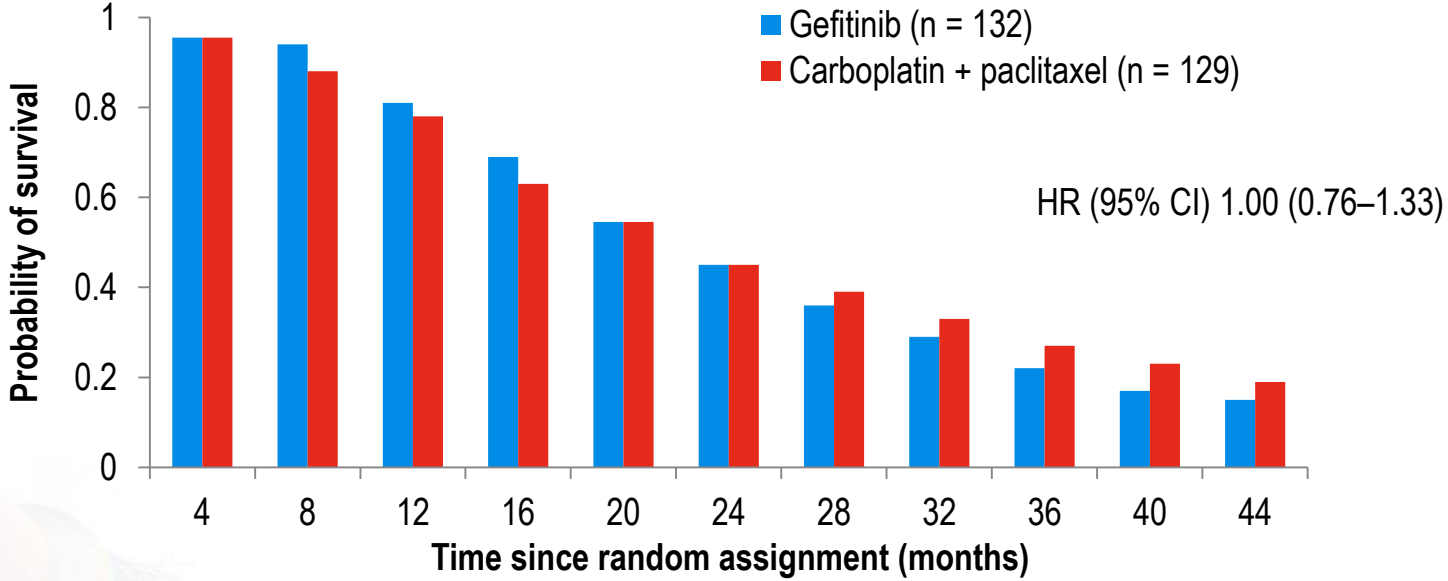
| Number at risk: | | | | | |
|---|---|---|---|---|---|
| Osimertinib | 95 | 63 | 35 | 20 | 5 |
| Platinum + pemetrexed | 39 | 13 | 5 | 2 | 1 |

**Duration of PFS among patients with T790M-positive status after first-line EGFR-TKI therapy**

EGFR-TKI, EGFR tyrosine kinase inhibitor.

Mok TS, et al. N Engl J Med. 2017;376:629-40.

# Follow up targeted therapy: gefitinib in EGFR-positive patients




**Number at risk:**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gefitinib | 126 | 121 | 103 | 88 | 70 | 58 | 46 | 38 | 24 | 11 | 6 |
| Carboplatin + paclitaxel | 123 | 112 | 95 | 80 | 68 | 55 | 48 | 40 | 26 | 15 | 7 |

**No difference in OS for gefitinib vs carboplatin + paclitaxel in patients with *EGFR* mutation status**

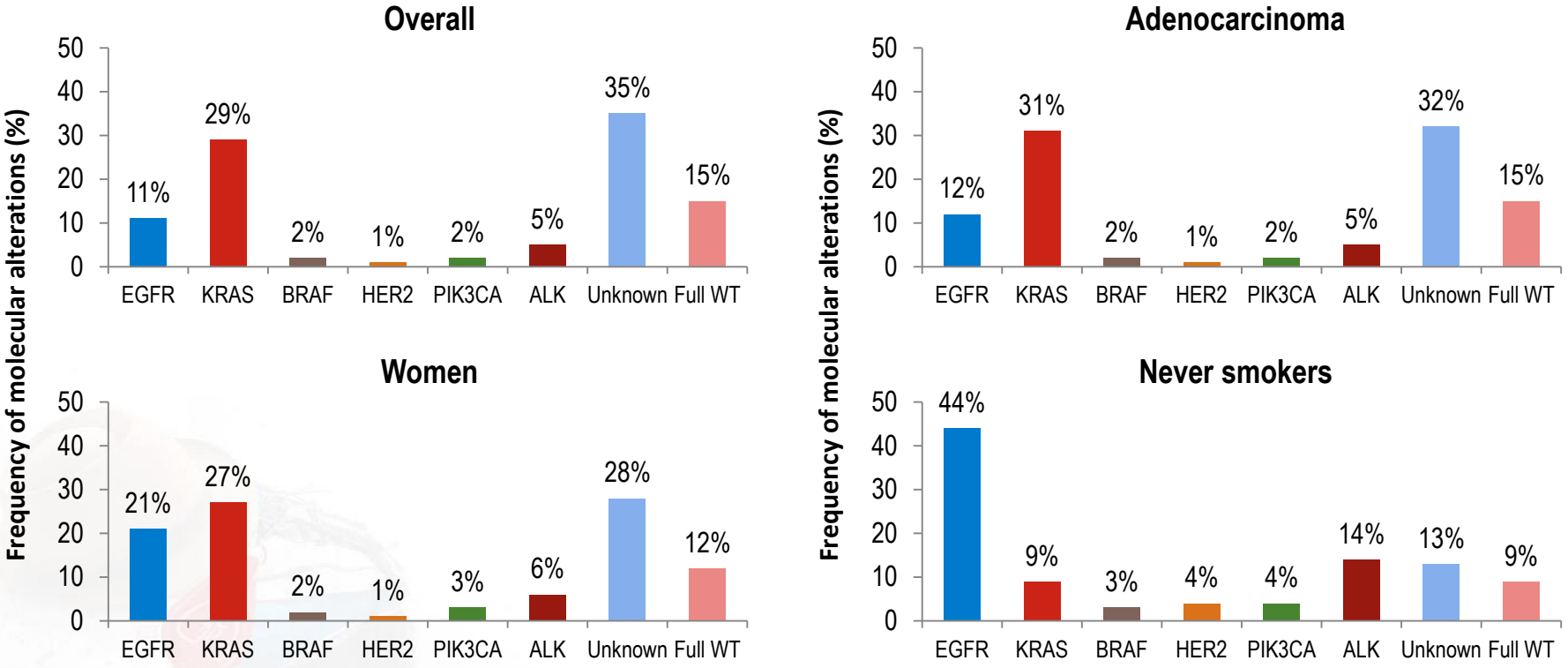
OS, overall survival.

Fukuoka M, et al. J Clin Oncol. 2011;29:2866-74.

# Acquired resistance also develops

- Patient example with resistance to ALK mutation and subsequent treatments can be found:
  - Shaw AT, et al. N Engl J Med. 2016;374:54-61 (Figure 1)

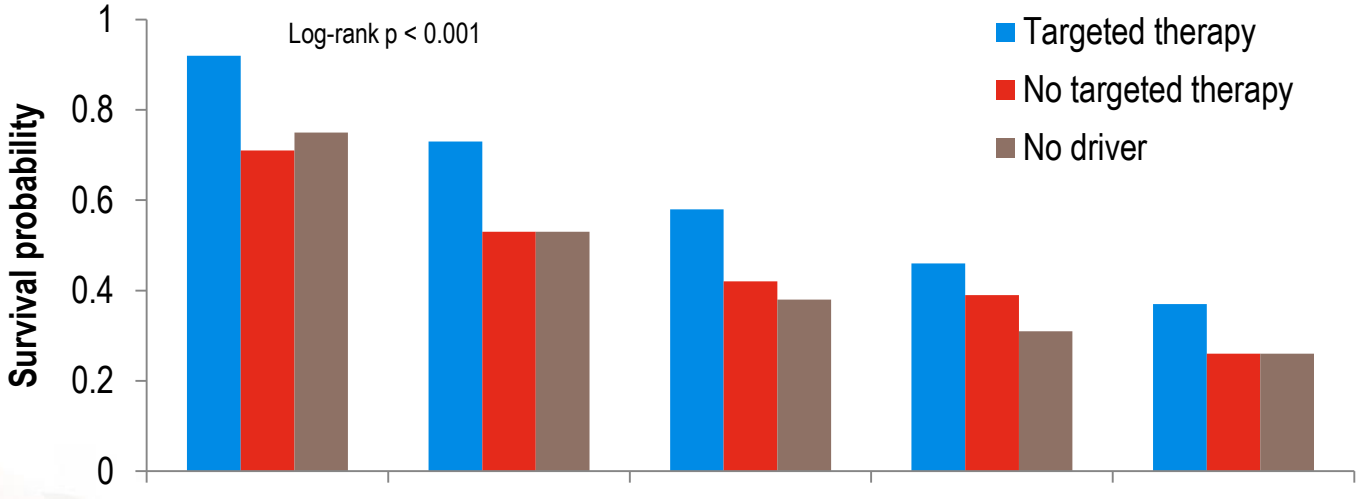
# Performing NGS for a more comprehensive molecular screening




WT, wild type.

Barlesi F, et al. Lancet. 2016;387:1415-26.

# Survival of patients with drivers: targeted therapy versus no targeted therapy




| Number at risk: | | | | | |
|---|---|---|---|---|---|
| Patients with oncogenic driver | | | | | |
| No targeted therapy | 205 | 110 | 64 | 43 | 20 |
| Targeted therapy | 225 | 143 | 72 | 36 | 23 |
| Patients with no driver | 250 | 122 | 59 | 36 | 23 |

Kris MG, et al. JAMA. 2014;311:1998-2006.

# Oncogenic drivers in NSCLC

*Controversy*

## Parachute approach to evidence based medicine

Malcolm Potts, Ndola Prata, Julia Walsh, Amy Grossman

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

Sometimes it's best just to jump in!

Potts M, et al. BMJ. 2006;333:701-3.

# Question 3 (continued)

What is your next step?

1. Start on immunotherapy with PD-L1 inhibitors
2. Restart chemotherapy
3. BSC
4. New mutation testing

# Question 3 (continued)

What is your next step?

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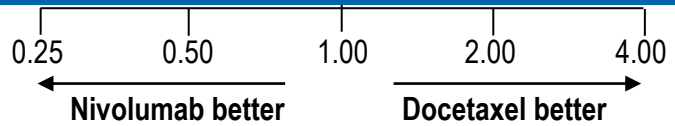
2. Restart chemotherapy
3. BSC
4. New mutation testing

# Second-line nivolumab in non-squamous NSCLC: OS by subgroup

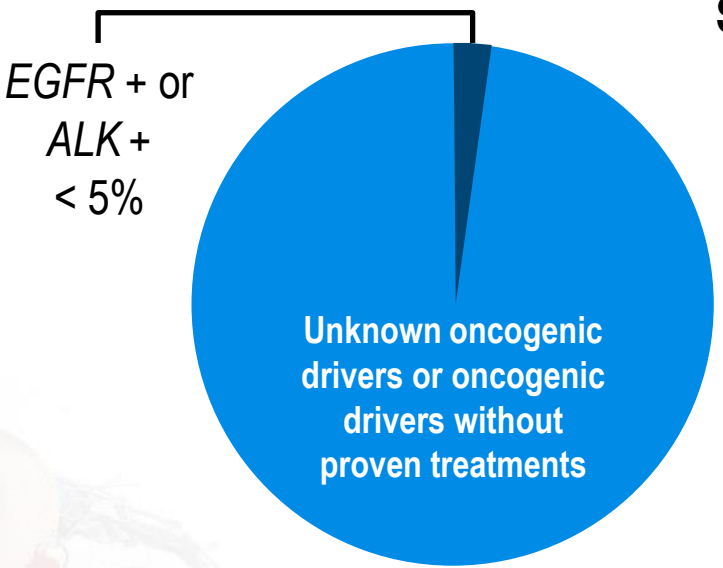
- Immunotherapy may not be an effective treatment option in patients with an *EGFR* mutation

| Subgroup | Patients, n | Unstratified hazard ratio (95% CI) |
|---|---|---|
| *EGFR* mutation status | | |
| Positive | 82 | 1.18 (0.69–2.00) |
| Not detected | 340 | 0.66 (0.51–0.86) |
| Not reported | 160 | 0.74 (0.51–1.06) |




Borghaei H, et al. N Engl J Med. 2015;373:1627-39.

# What about squamous cell carcinoma?



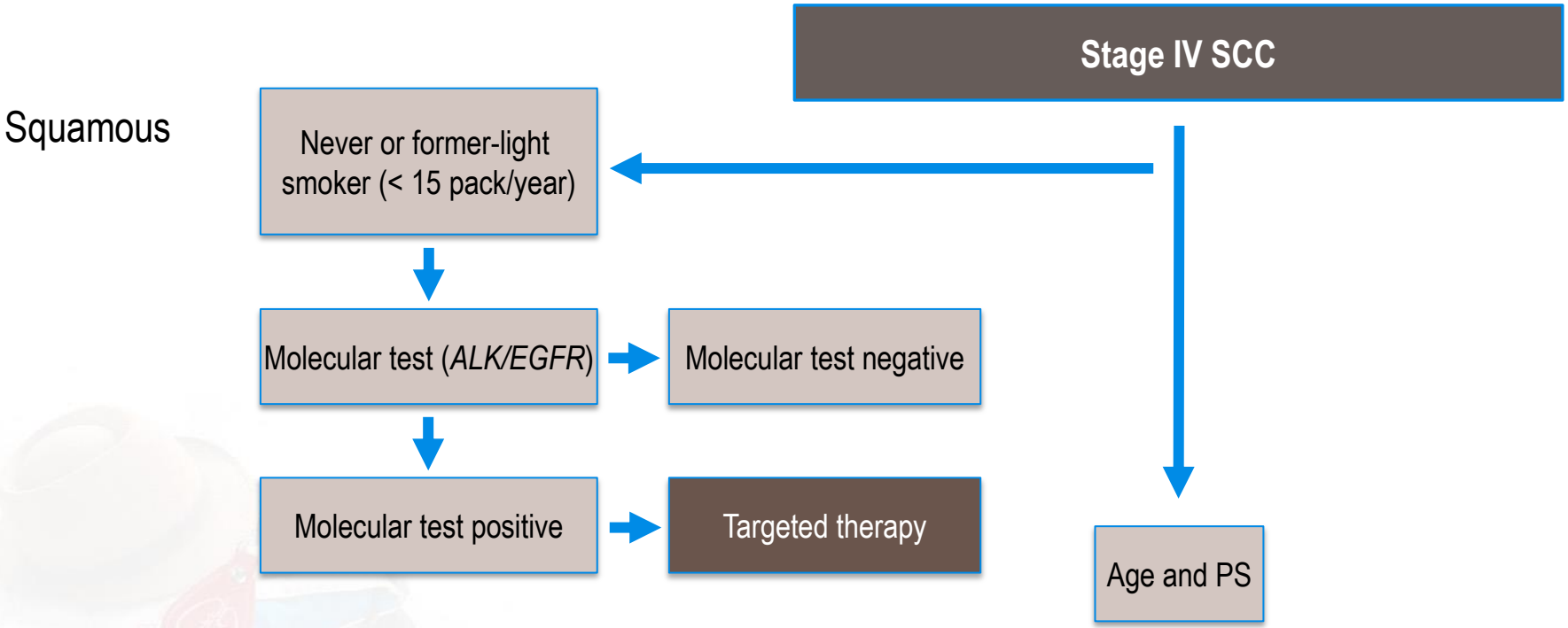

**Squamous NSCLC[1–3]**

The IASLC SqCLC education program[4]

IASLC, International Association for the Study of Lung Cancer; SqCLC, squamous cell lung cancer.

1. Kim HS, et al. Lung Cancer. 2013;80:249-55.
2. Pao W, Girard N. Lancet Oncol. 2011;12:175-80.
3. Perez-Moreno P, et al. Clin Cancer Res. 2012;18:2443-51.
4. SqCLC Resources. Available from: https://www.iaslc.org/squamous-lung-cancer-resources. Squamous Cell Lung Cancer Education Program, www.iaslc.org.

# ESMO Guidelines 2016




SCC, squamous cell carcinoma.

Based on Novello S, et al. Ann Oncol. 2016;27 Suppl 5:v1-v27.

# Conclusion

- Molecular profiling has increased the therapeutic potential in advanced NSCLC
- For the majority of patients, certainly for those with squamous cell NSCLC, targetable drivers are lacking

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