Third-Line and Beyond (Subsequent) Systemic Therapy in NSCLC

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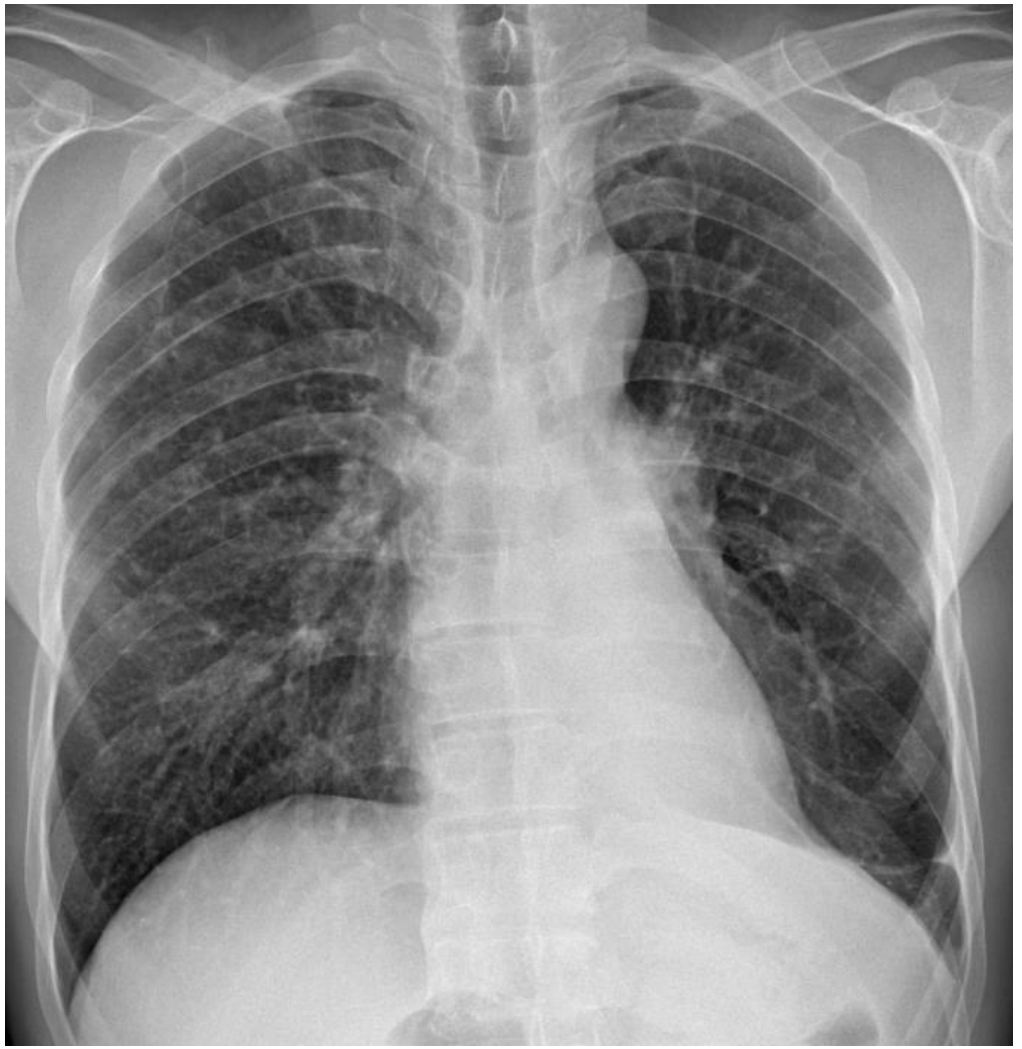
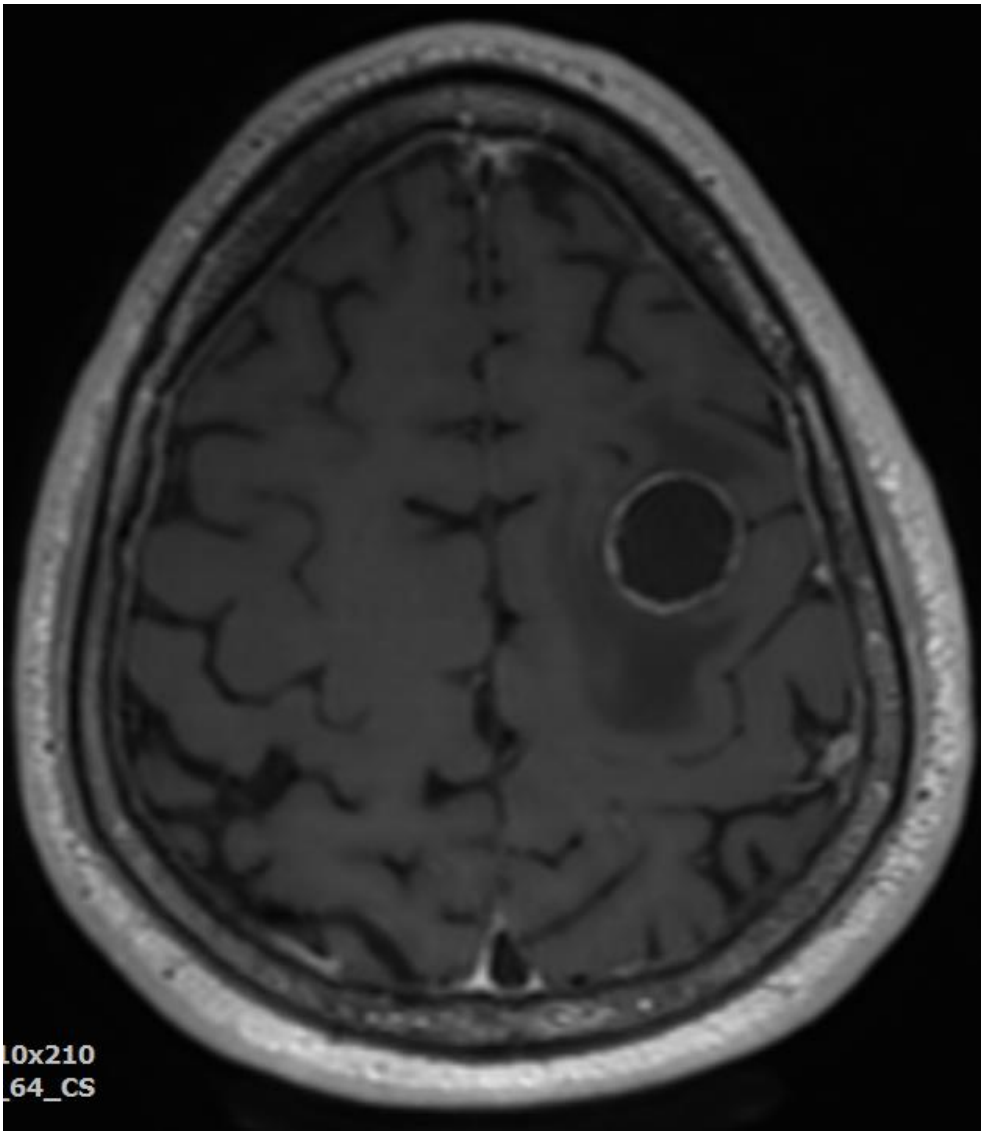
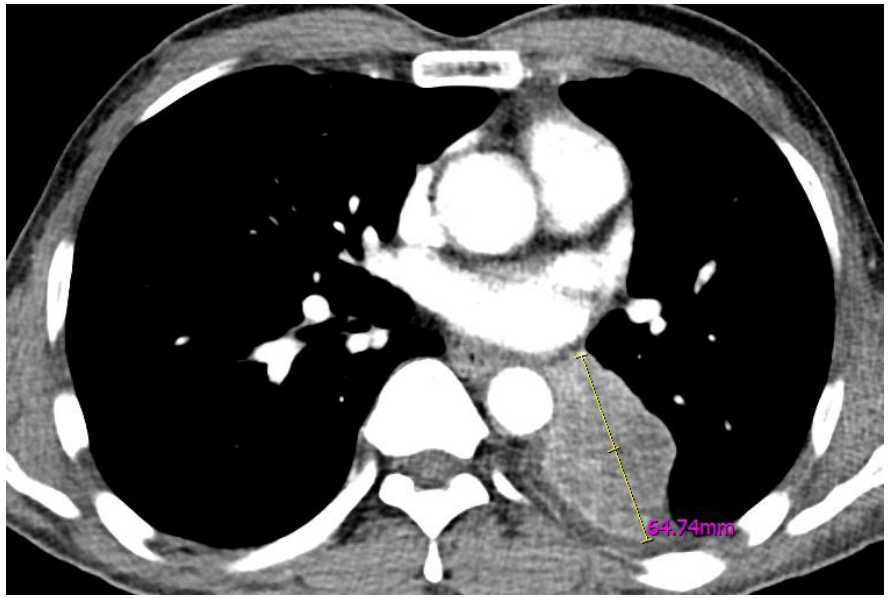
Case

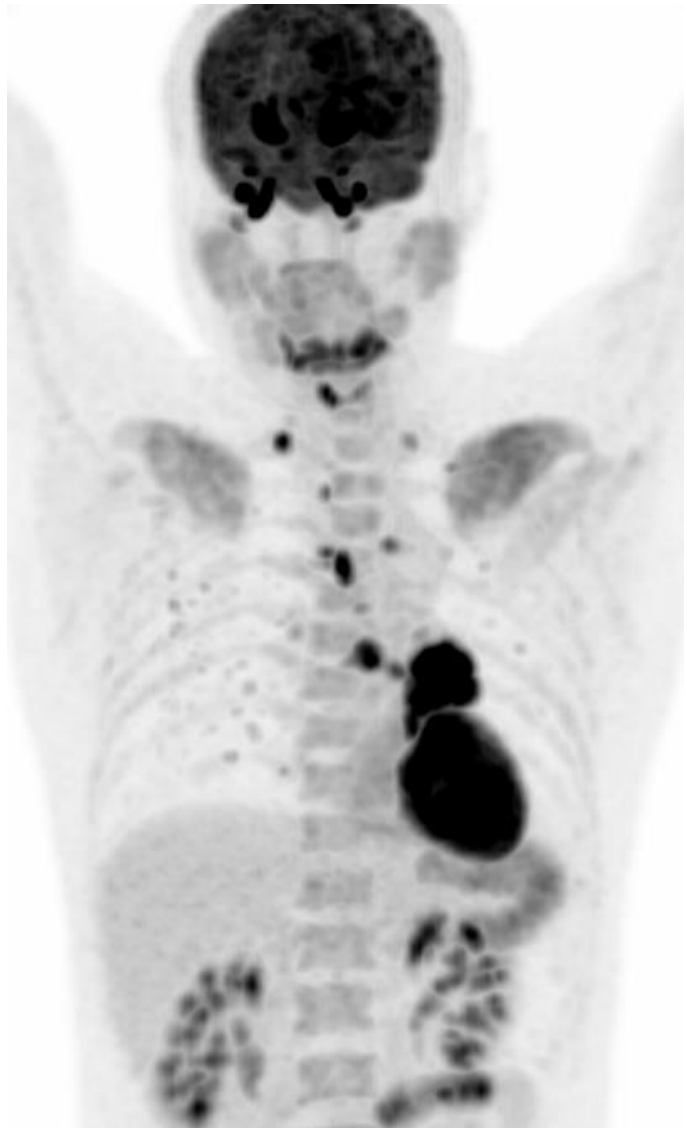
- Adm via ER
- 63/M
- C/C : Syncope & Rt. hemiparesis
- Never-Smoker
- PHx : DM (-), HTN (-), Tbc (-)



Radiology





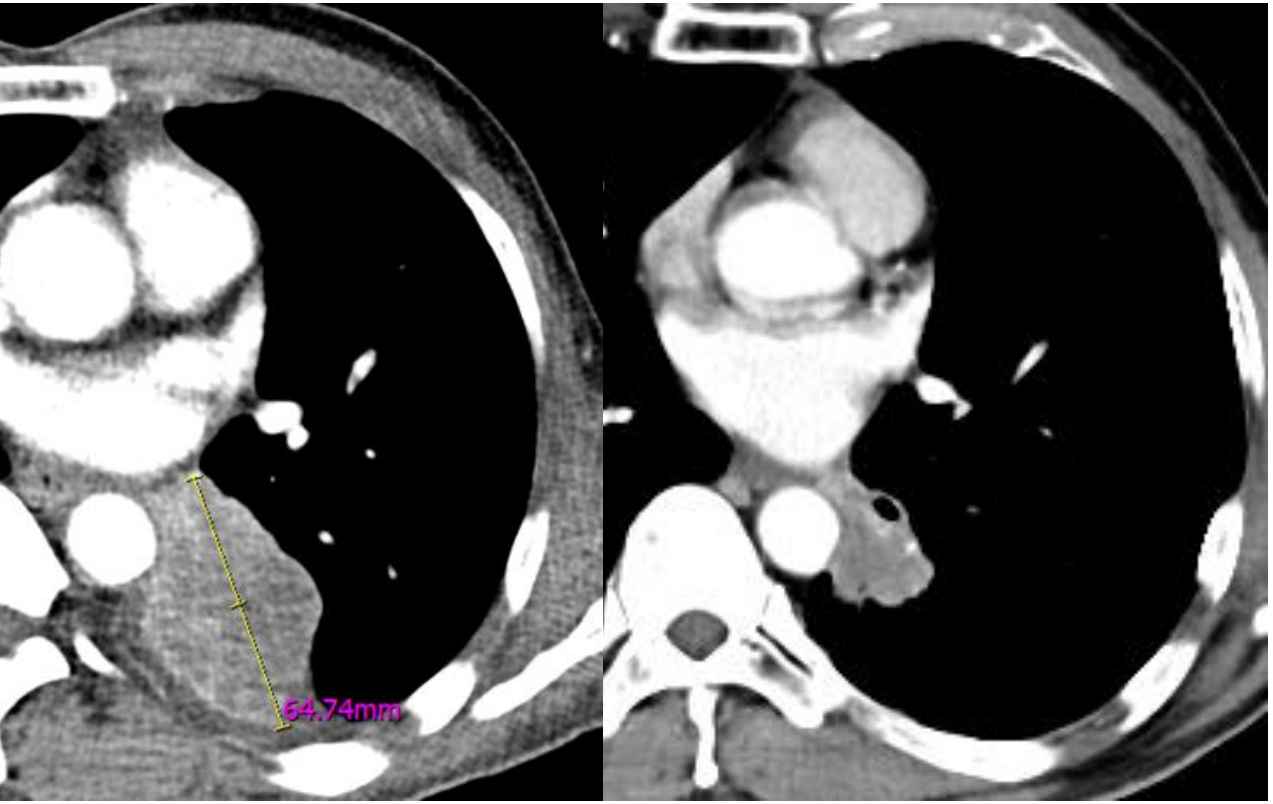


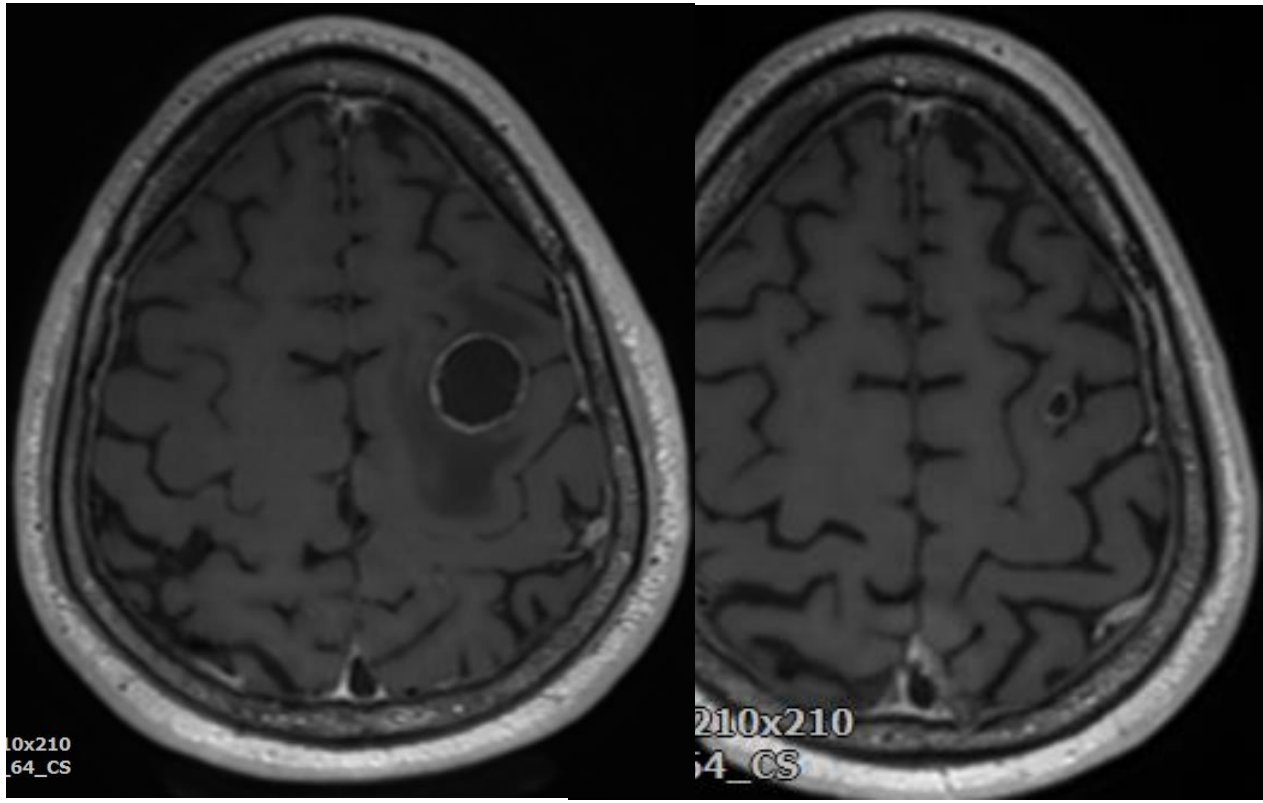
Diagnosis

- Pathology : Adenocarcinoma
- EGFR exon 19 del (+), ALK (-), ROS1 (-)
- PD-L1 SP263 : tumor proportion score 30%
- Stage IVb (cT4N3M1c) : lung to lung, bone, & brain metastasis

Progress Note

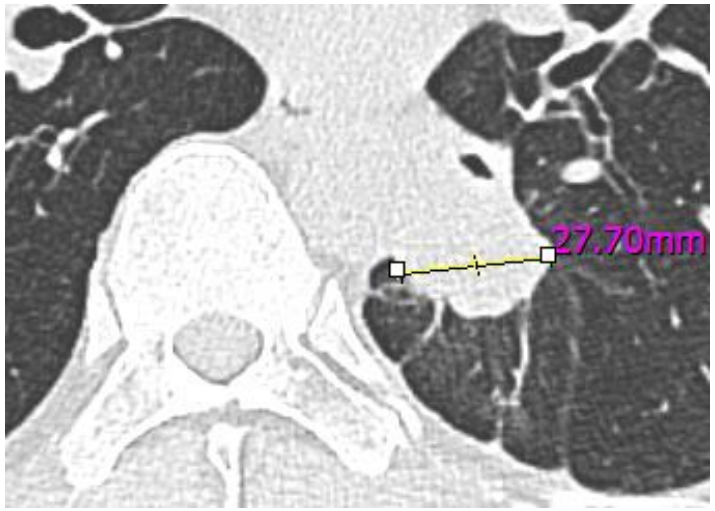
1. SRS on the brain lesions
2. 1st line systemic Tx.
   - Afatinib for 1 year (diarrhea, folliculitis on scalp)

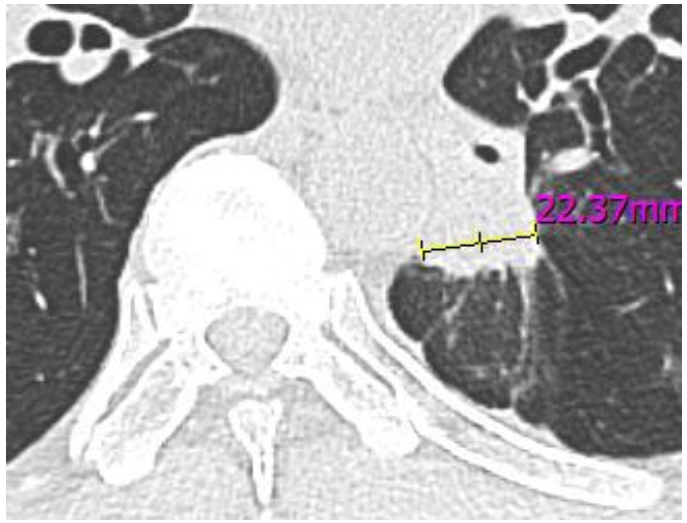


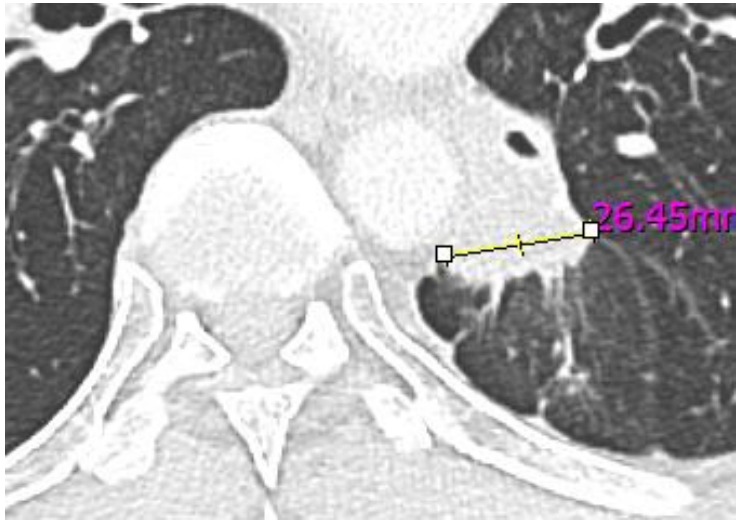


Progress Note

1. SRS on the brain lesions
2. 1st line systemic Tx.
   - Afatinib for 1 year (diarrhea, folliculitis on scalp) ➔ T790M (-)
3. 2nd line systemic Tx.
   - Gem-Cb. CTx. : 4 cycle (G3 toxicity of Hb & PLT)







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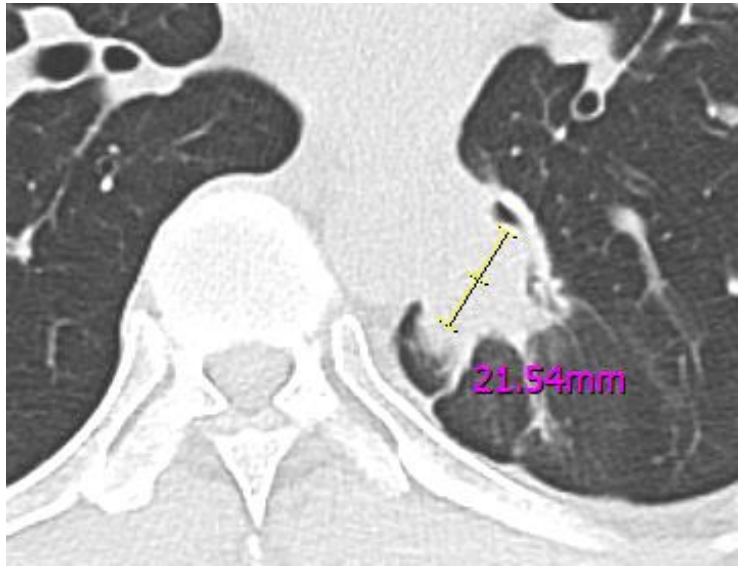
4. 3rd line systemic Tx.
   - Alimta monoTx. 3 cycle



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5. Cord compression, C5
   - Decompressive total laminectomy, C5
   - Postop. RTx.

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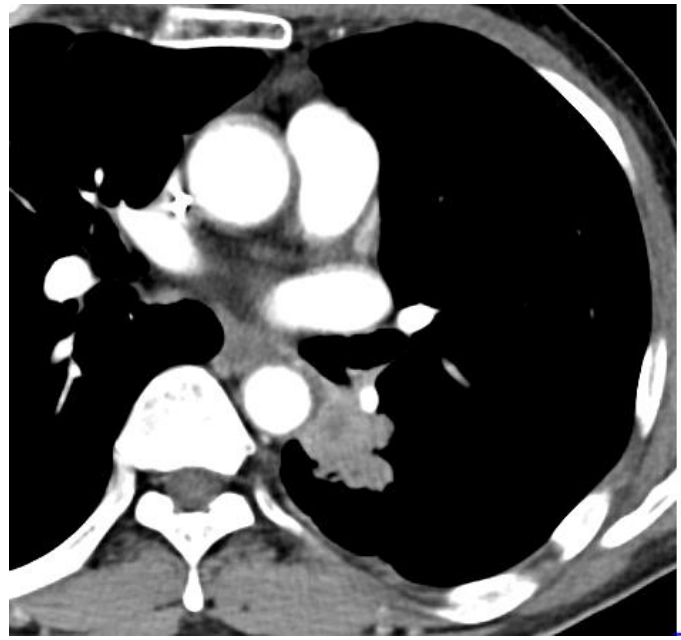
   - Decompressive total laminectomy, C5
   - Postop. RTx.
6. 4th line systemic Tx.
   - Atezolizumab : 3 cycle



Progress Note

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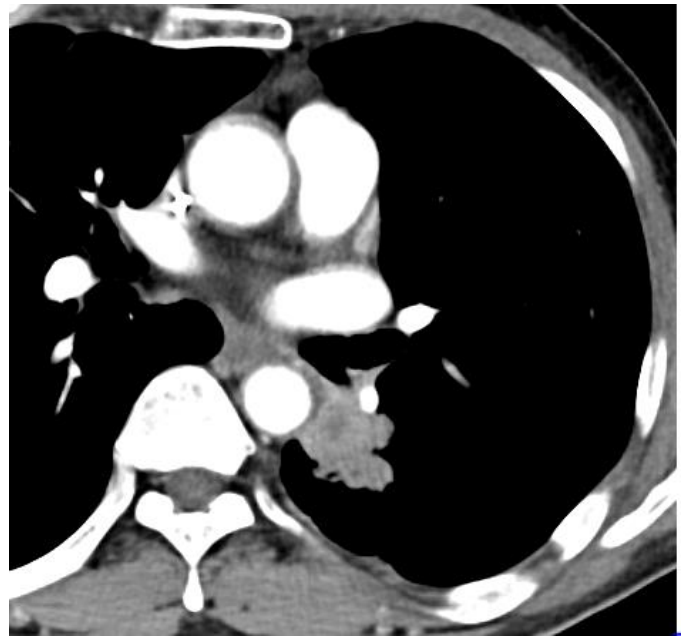
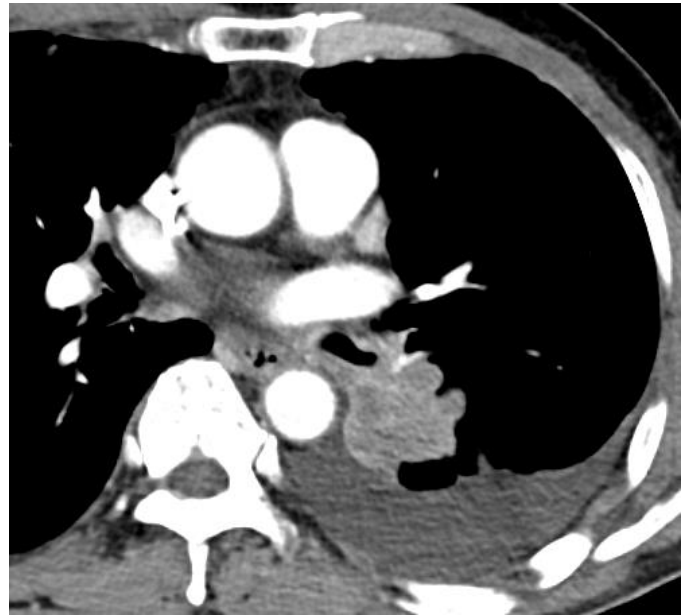
7. What's next?





Survey to patients treated with 1st-line platinum regimen

- 68% would choose CTx. Compared to BSC alone
  : If Sx. could be substantially improved
  : even if survival was not prolonged

- if patients' lives would be prolonged by 3 months
  : only 19% would choose an intensive Tx.

- 70% chance of symptom relief
  : 73% willing to choose an intensive CTx.

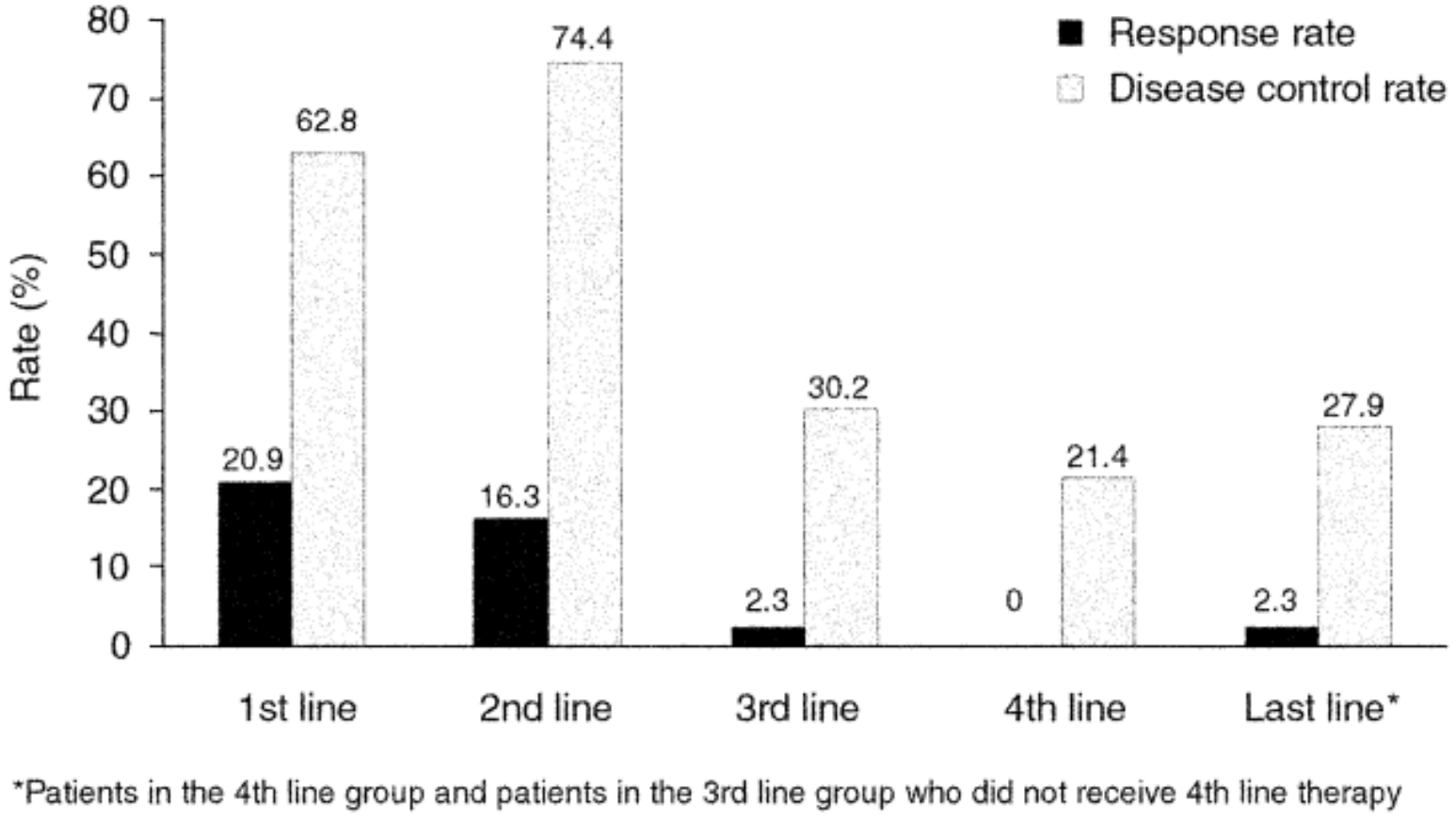
Br Med J 1998; 317: 771–775
Internal Medicine 2005; 44:107–113
Oncology 2009;77(suppl 1);113-121

Aim of 3rd-line Tx.

- Ultimate aim of systemic Tx.
  : improve survival and QoL

- Role of 3rd-line Tx. in NSCLC
  : remains controversial
  : overall survival, maintain stable disease,
  : QoL, disease-related symptom, treatment toxicity profile, maintenance of performance status

Response rates & DCRs for each line of Tx.



*Patients in the 4th line group and patients in the 3rd line group who did not receive 4th line therapy

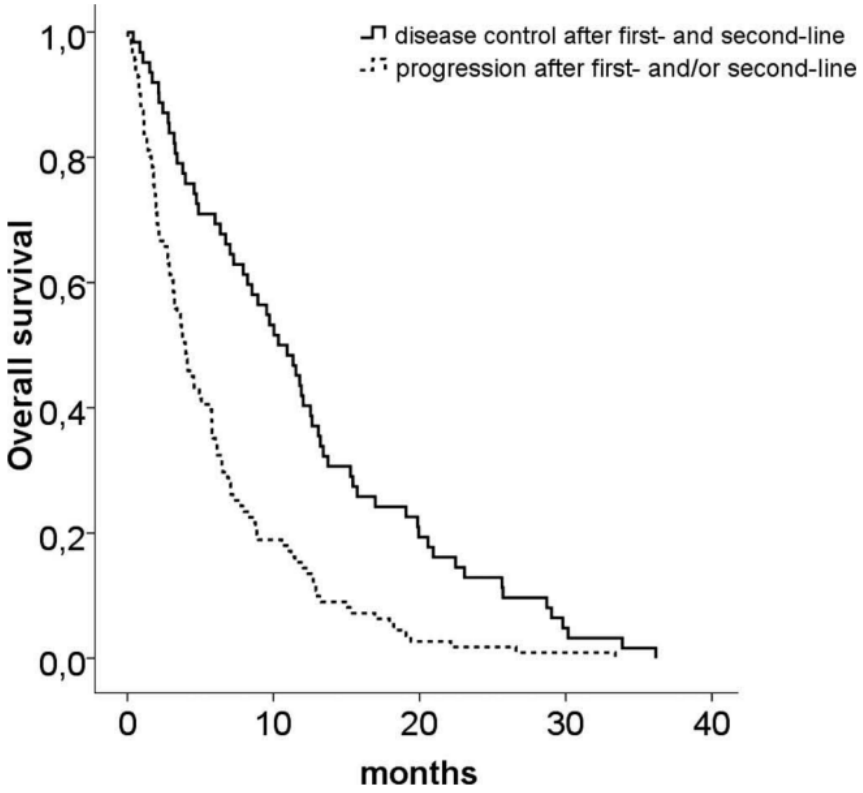
Lung Cancer. 2003;39(1);55-61

Clinical predictive factor for 3rd-line Tx.

- **Factors increasing survival after 3rd-line Tx.**

- Age : < 70 yrs
- Smoking : < 10 pack-year
- No cancer-related Sx.
- Wt. loss : < 5 kg after 2nd-line Tx
- PS : 0-1
- No extrathoracic tumor spread
- Disease control after both 1st – and 2nd-line Tx : strongest predictor

Overall survival

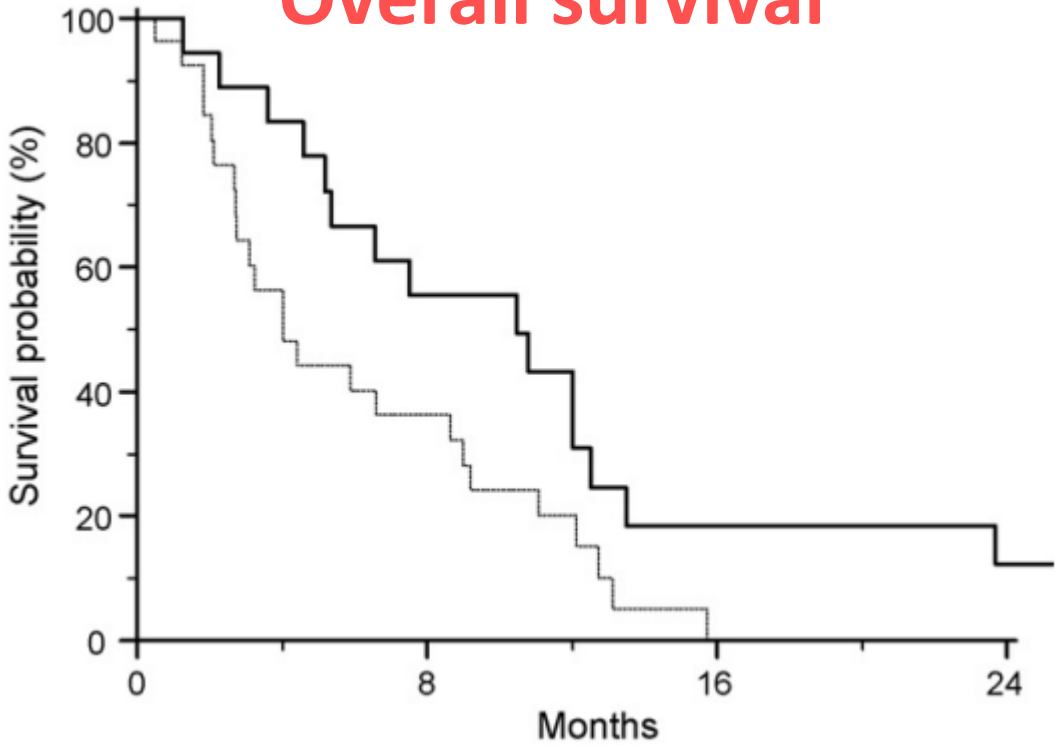


J Thorac Oncol. 2009;4(12);1544-9

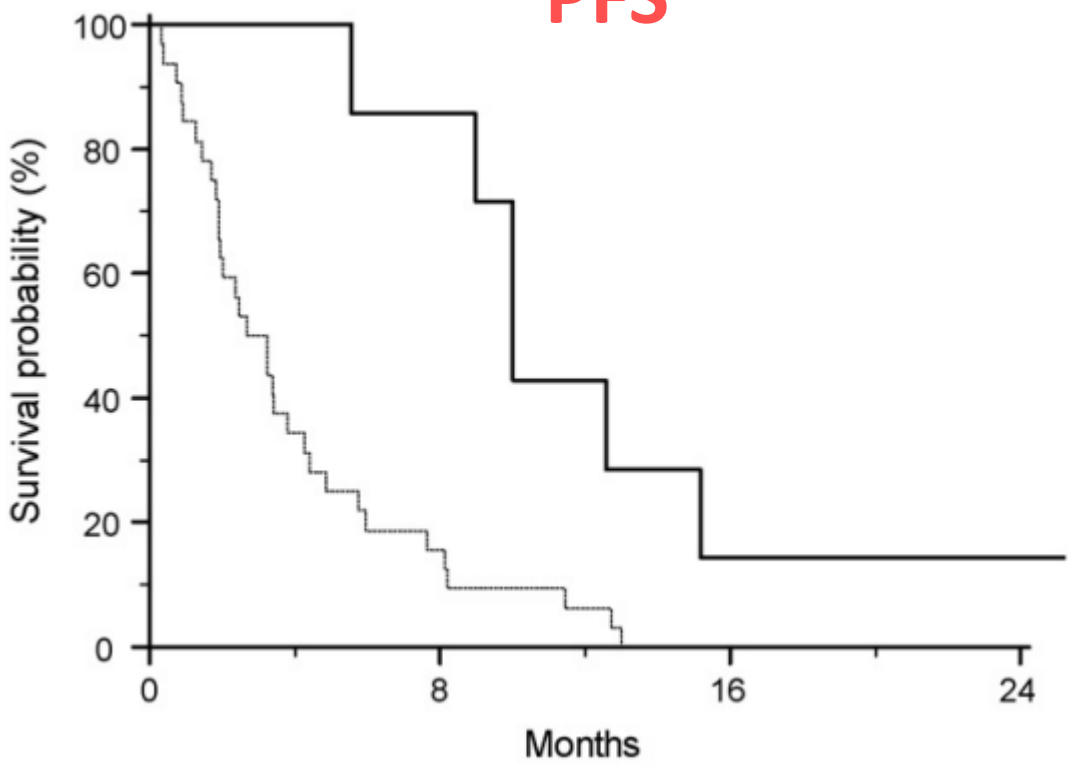
Clinical predictive factor for 3rd-line Tx.

- **Response to 2nd-line therapy**

Overall survival



PFS



Lung Cancer. 2010 Jun;68(3);433-7

Recommendation for recurrent and metastatic disease

- Histologic subtype

- Biomarker testing for genetic variants (ie, oncogenic driver events)
  - EGFR mutation (category 1) for nonsq. NSCLC or NSCLC NOS,
  - ALK fusions (category 1) for nonsq. NSCLC
  - ROS1 fusions (category 2A)
  - BRAF
  - PD-L1 expression (category 1)

NCCN Guidelines version 6.2021 NSCLC

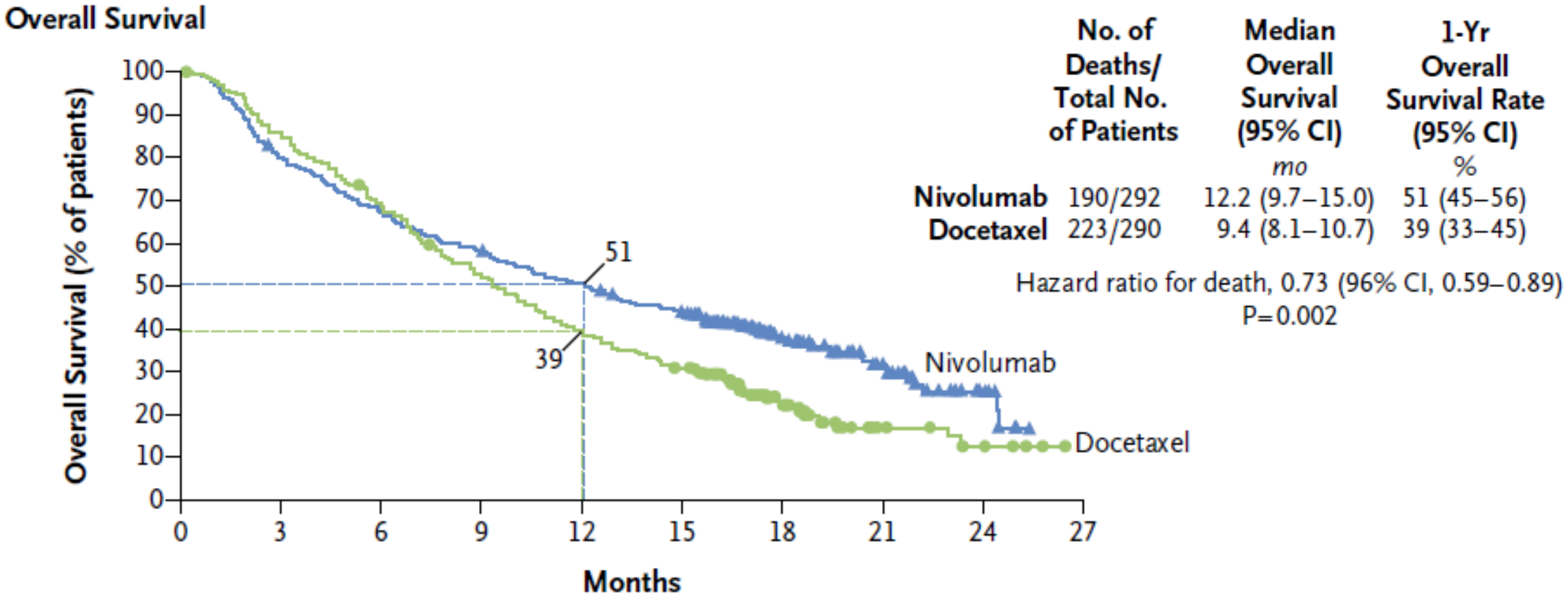
Subsequent Tx. for NSCLC

If patients have not previously received an ICI

- Pembrolizumab, nivolumab, or atezolizumab (category 1)
  - based on
    : improved survival rates
    : longer duration of response
    : fewer adverse events

    when compared with cytotoxic CTx.

Nivolumab vs Docetaxel : CheckMate 057



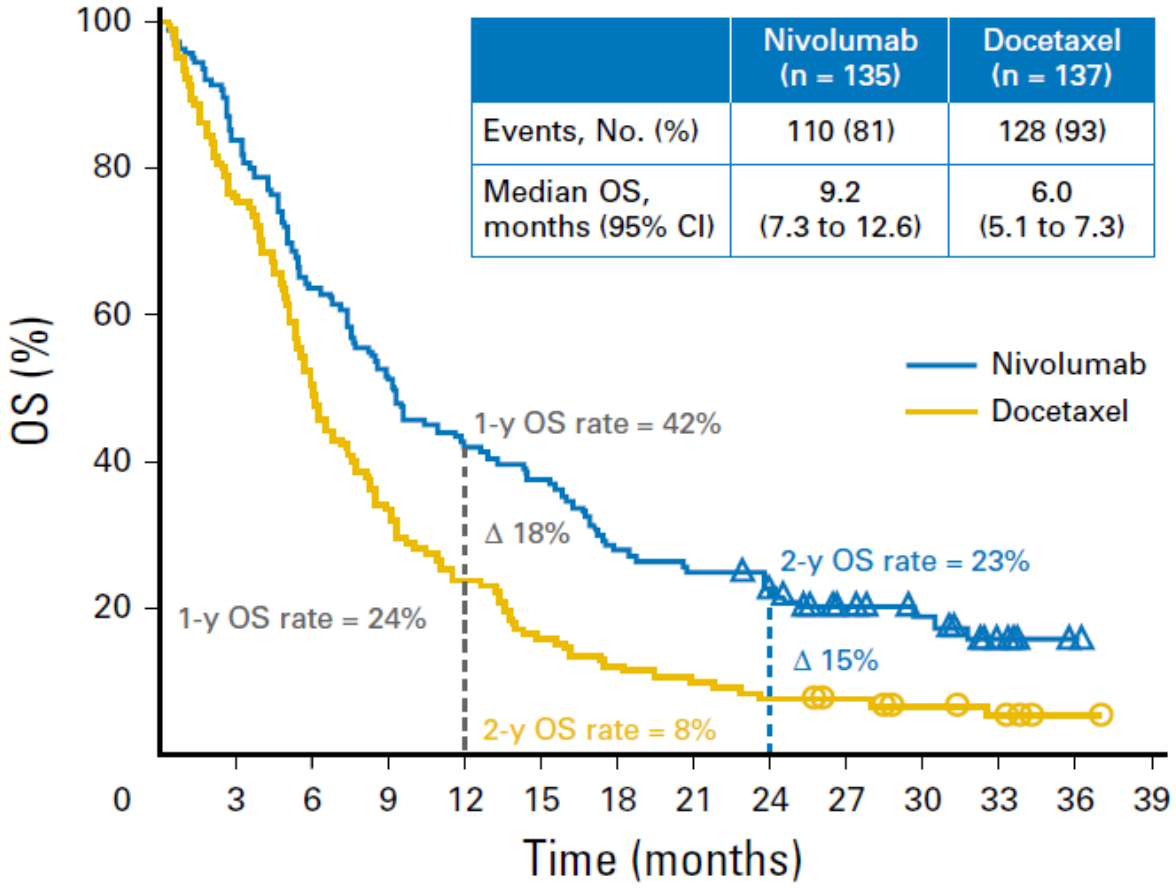
	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

N Engl J Med. 2015;373(17);1627–1639

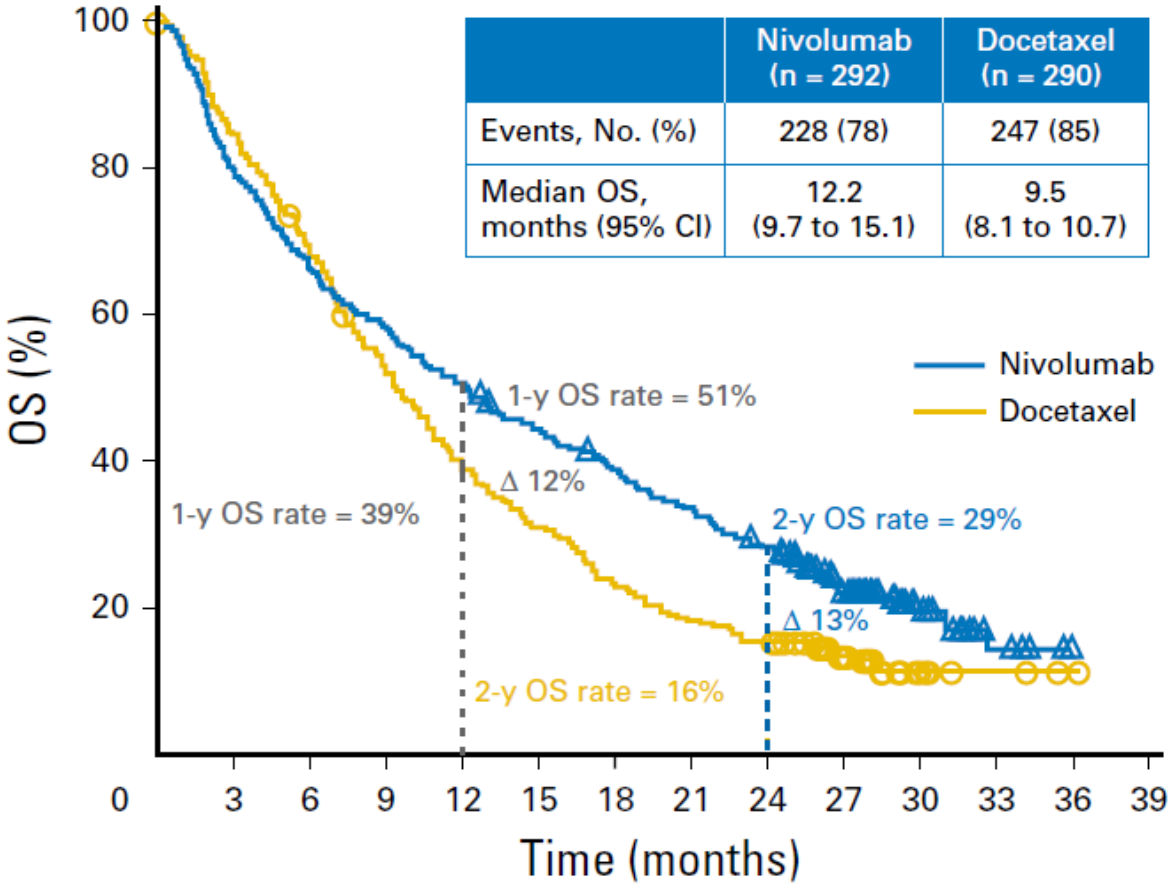
Nivolumab vs Docetaxel (CheckMate 017 & 057)

Squamous NSCLC



	Nivolumab (n = 135)	Docetaxel (n = 137)
Events, No. (%)	110 (81)	128 (93)
Median OS, months (95% CI)	9.2 (7.3 to 12.6)	6.0 (5.1 to 7.3)

Nonsquamous NSCLC

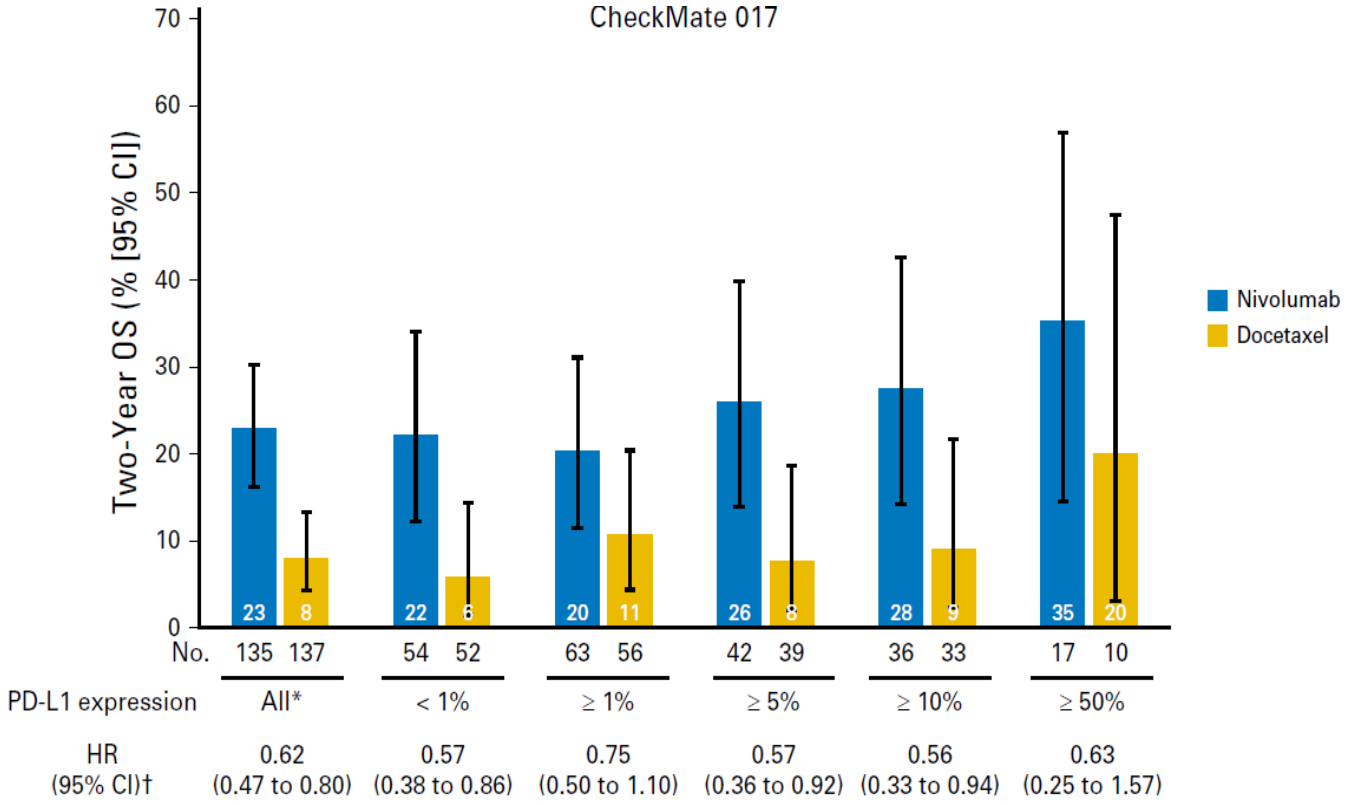


	Nivolumab (n = 292)	Docetaxel (n = 290)
Events, No. (%)	228 (78)	247 (85)
Median OS, months (95% CI)	12.2 (9.7 to 15.1)	9.5 (8.1 to 10.7)

J Clin Oncol 2017;35(35):3924-3933

Nivolumab vs Docetaxel (CheckMate 017 & 057)

Squamous NSCLC



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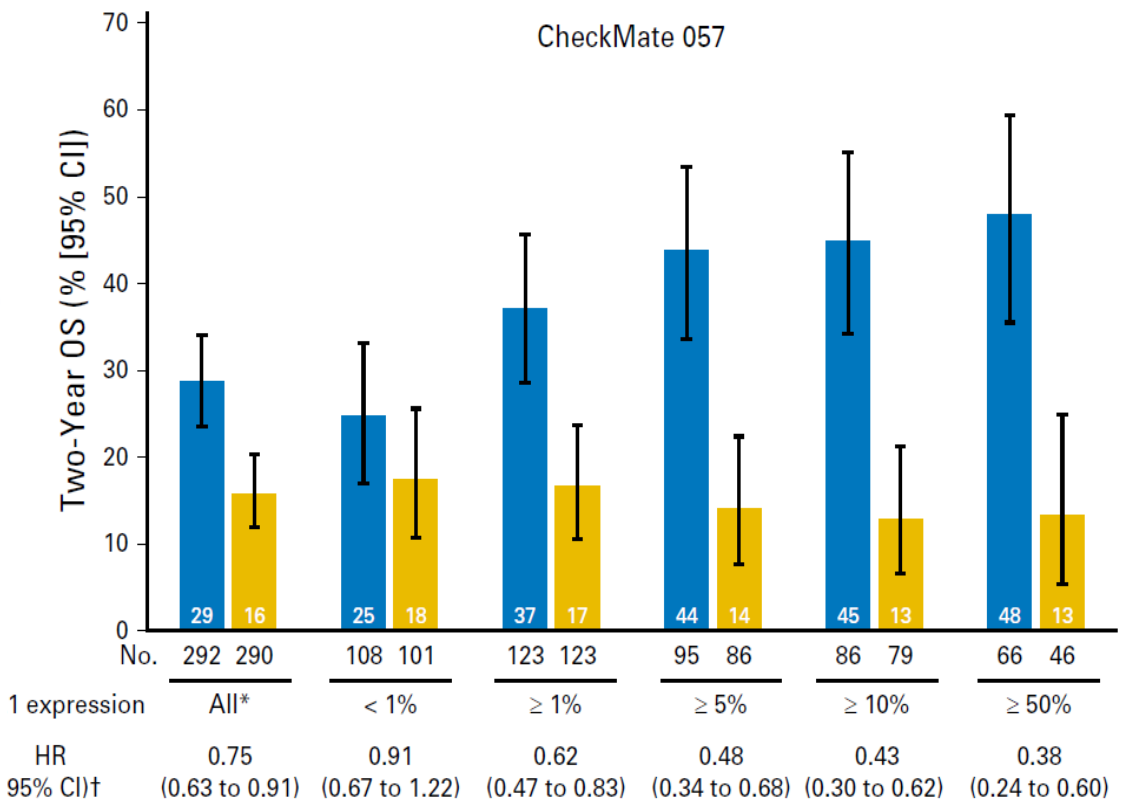
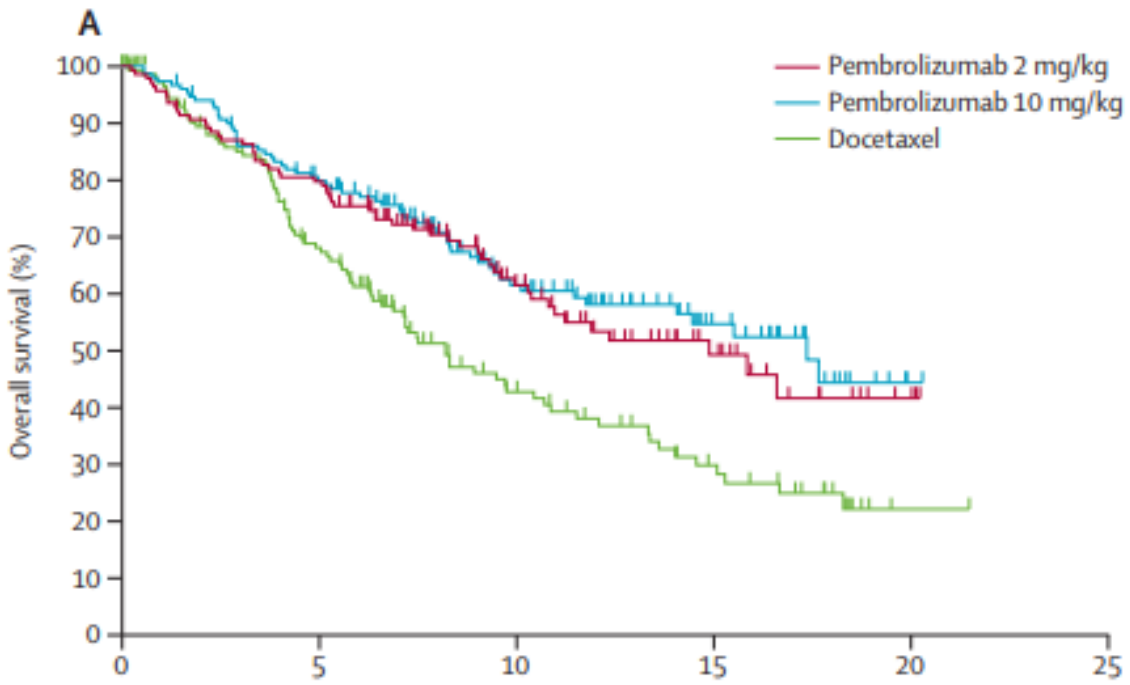


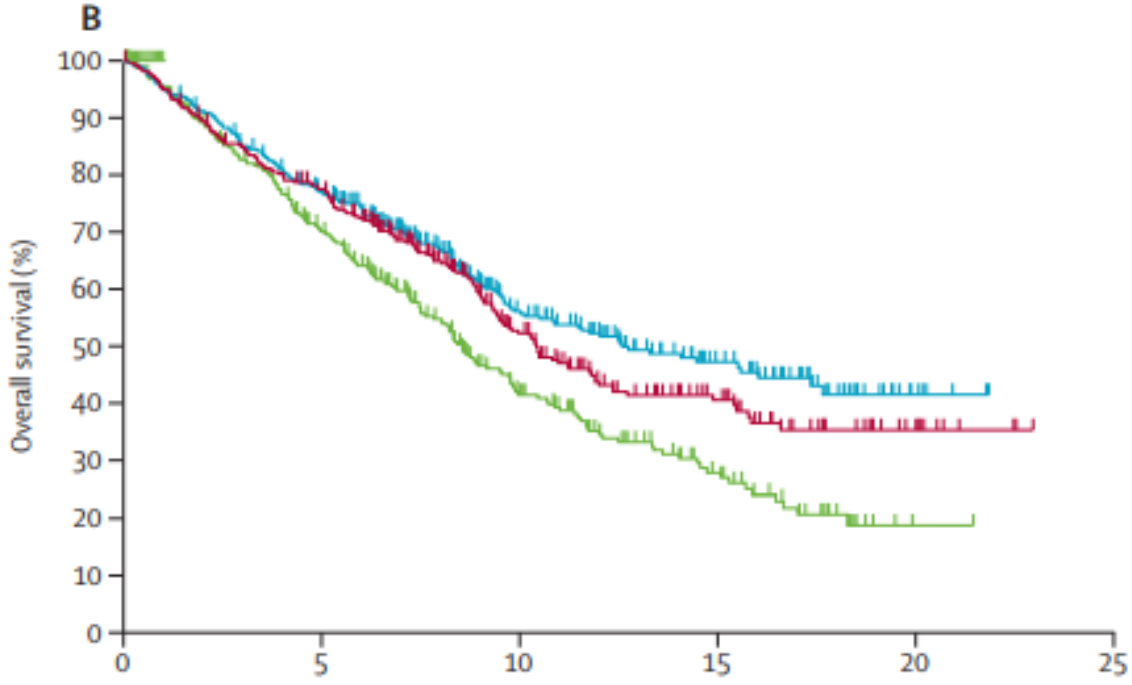
J Clin Oncol 2017;35(35):3924-3933

Pembrolizumab vs Docetaxel (Keynote-010) : OS

PD-L1 TPS≥50%



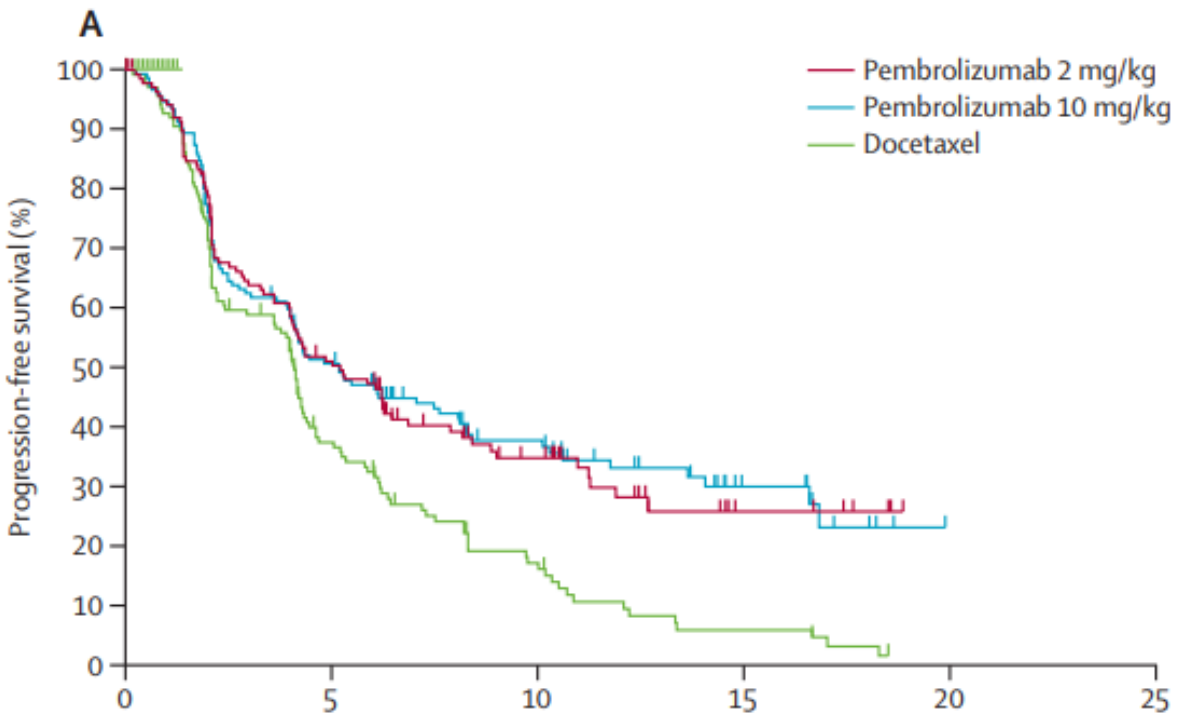
All patients



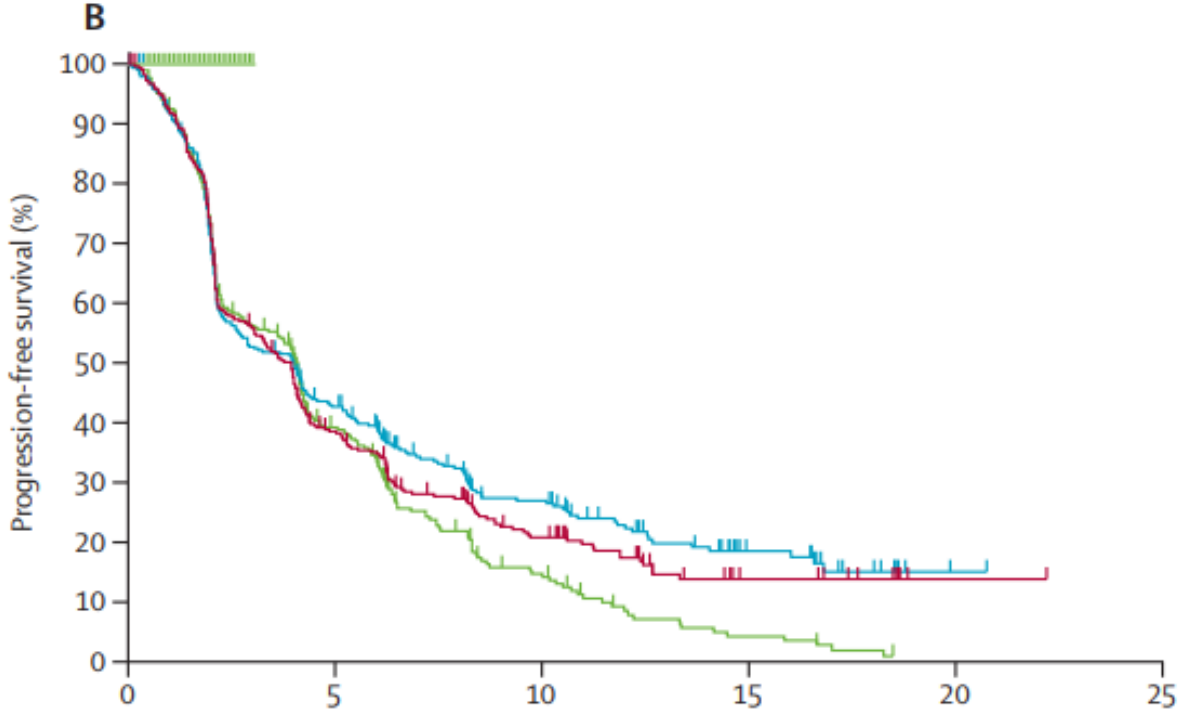
Lancet 2016;387(10027):1540-1550

Pembrolizumab vs Docetaxel (Keynote-010) : PFS

PD-L1 TPS≥50%



All patients



Lancet 2016;387(10027):1540-1550

NSCLC with Driver Mutation

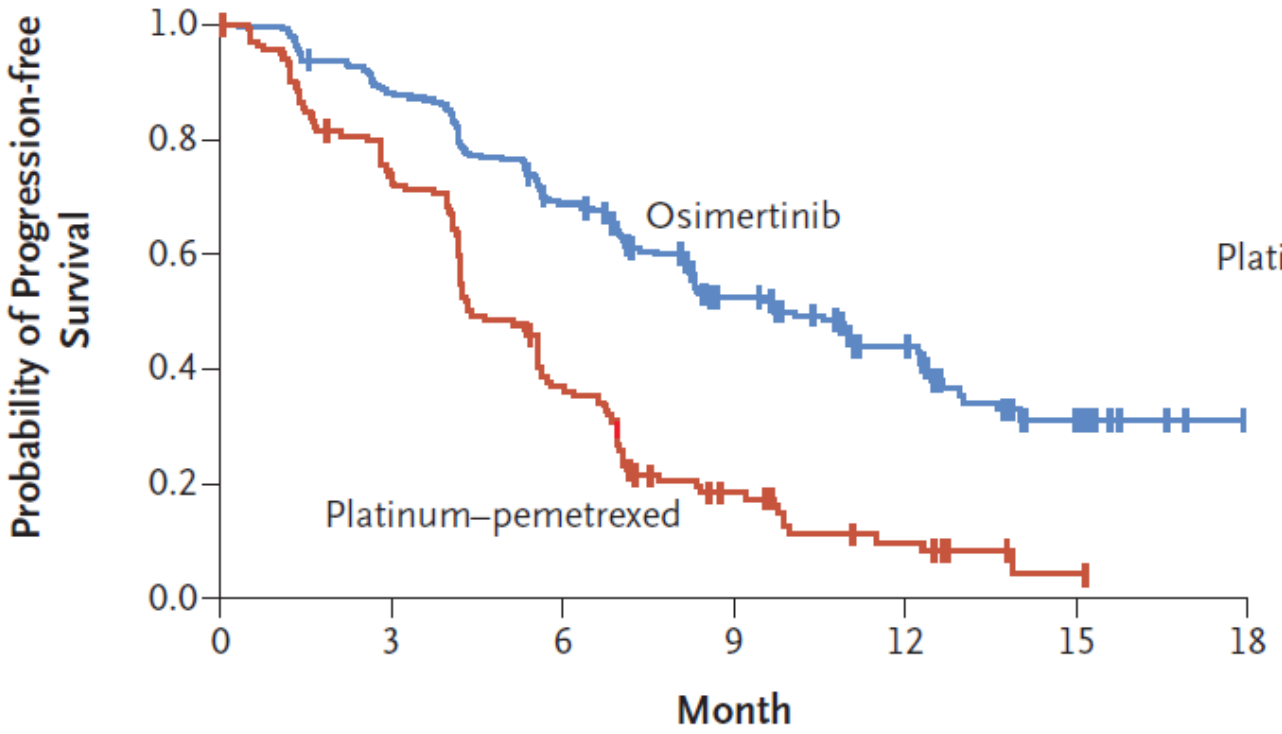
Subsequent Tx. After EGFR-TKI in sensitizing EGFR mutation

- Depends on asymptomatic or symptomatic
  - considering local Tx.
  - continuing current EGFR-TKI
  - Osimertinib if not previous given & T790M+
  - 1st line systemic Tx. for nonsq. NSCLC (eg. Pemetrexed/cisplatin)

- Osimertinib (category 1)
  - metastatic EGFR T790M+ NSCLC
  - progressed on erlotinib, gefitinib, dacomitinib, or afatinib

Osimertinib vs Pemetrexed-platinum in T790M+

Patients in Intention-to-Treat Population



No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

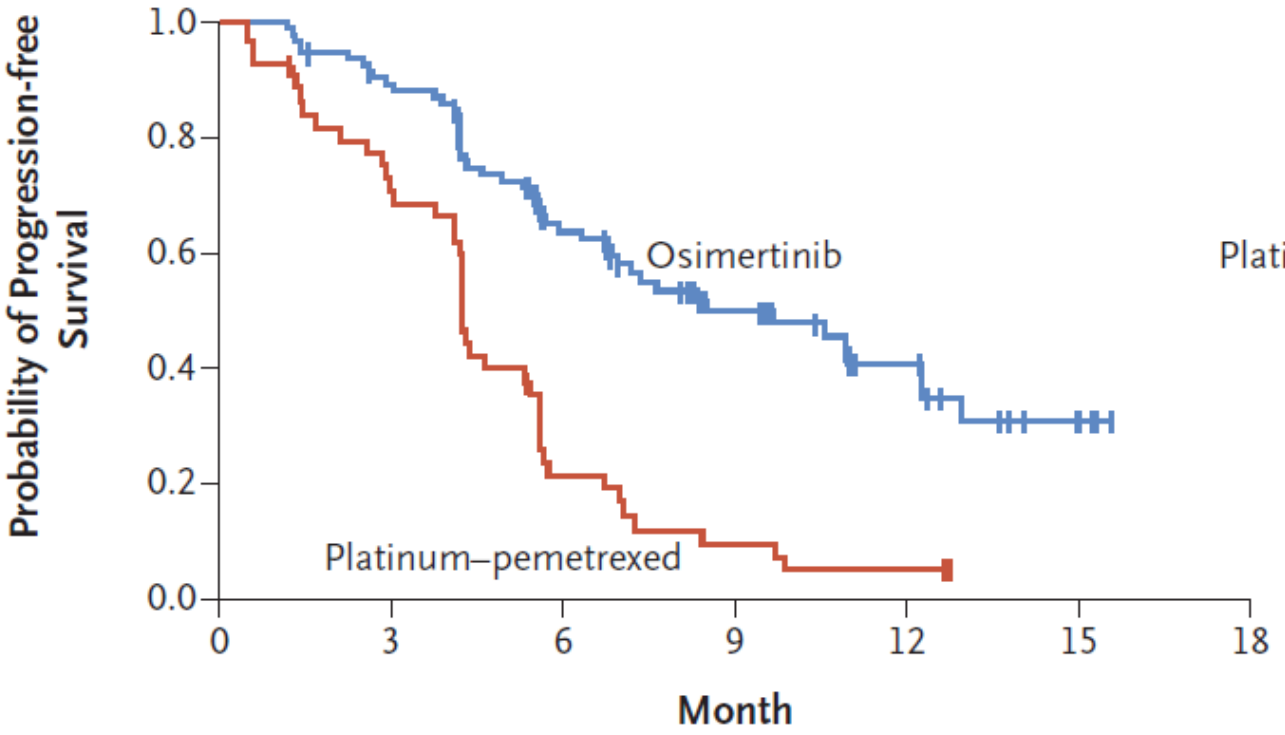
	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

N Engl J Med 2017;376(7);629-640

Osimertinib vs Pemetrexed-platinum in T790M+

Patients with CNS Metastases



No. at Risk							
Osimertinib	93	80	46	27	14	4	0
Platinum–pemetrexed	51	32	9	4	2	0	0

	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	93	8.5 (6.8–12.3)
Platinum–pemetrexed	51	4.2 (4.1–5.4)

Hazard ratio for disease progression or death, 0.32 (95% CI, 0.21–0.49)

N Engl J Med 2017;376(7);629-640

Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor-Resistant *EGFR*-Mutant Lung Cancer With and Without *T790M* Mutations

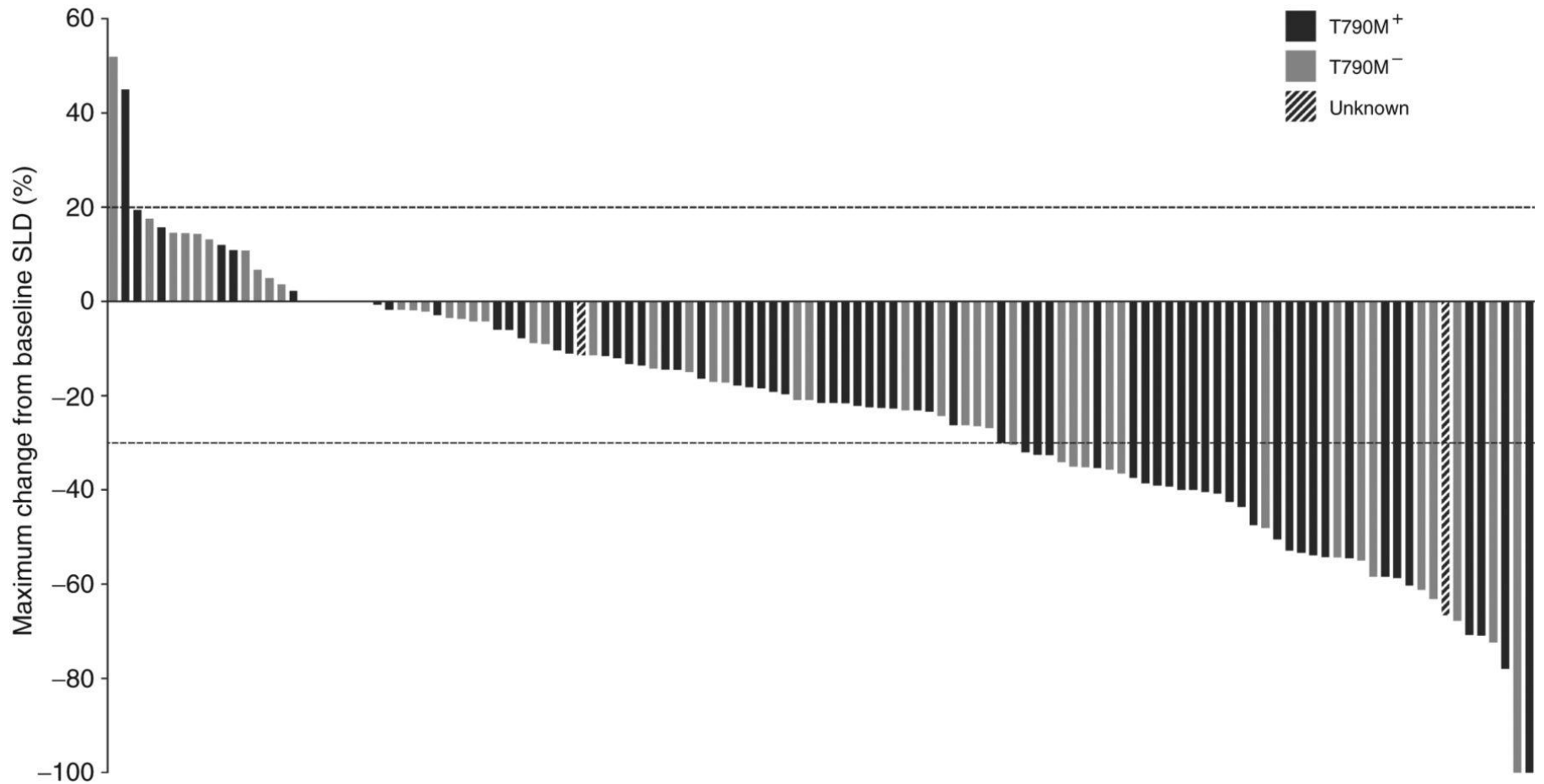
- Enrollment
  : heavily pretreated patients with advanced EGFR mutant NSCLC
  : acquired resistance to erlotinib/gefitinib

- Phase Ib
  : Afatinib/cetuximab for T790M+/- tumors

- Results
  - RR : overall 29% (32% for T790M+ vs 25% for T790M-)
  - PFS : 4.7 mo

Cancer discov 2014;4:1036-1045

Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor-Resistant *EGFR*-Mutant Lung Cancer With and Without *T790M* Mutations

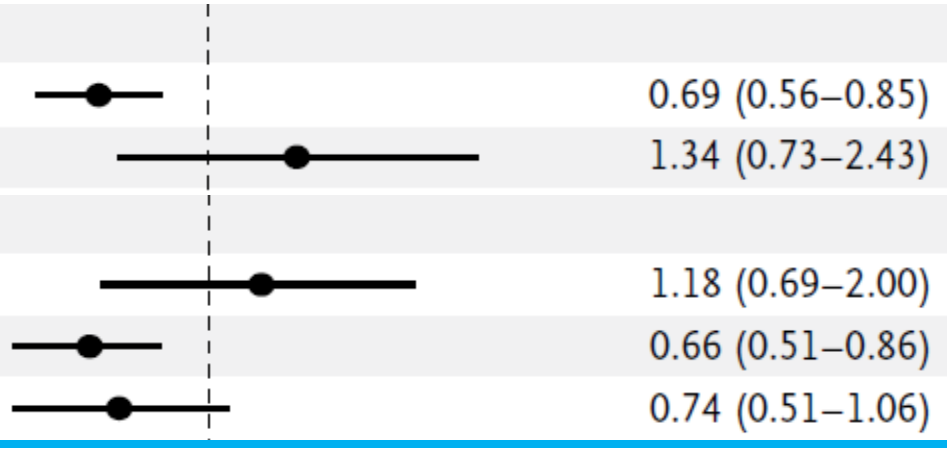


Cancer discov 2014;4:1036-1045

Nivolumab vs Docetaxel : CheckMate 057

Characteristic	Nivolumab (N = 292)	Docetaxel (N = 290)	Total (N = 582)
Positive *EGFR* mutation status — no. (%)§	44 (15)	38 (13)	82 (14)
Positive *ALK* translocation status — no. (%)§	13 (4)	8 (3)	21 (4)
No. of prior systemic regimens — no. (%)¶			
1	256 (88)	259 (89)	515 (88)
2	35 (12)	31 (11)	66 (11)

Subgroup	No. of Patients	Unstratified Hazard Ratio (95% CI)
Line of therapy		
Second line	515	0.69 (0.56–0.85)
Third line	66	1.34 (0.73–2.43)
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)

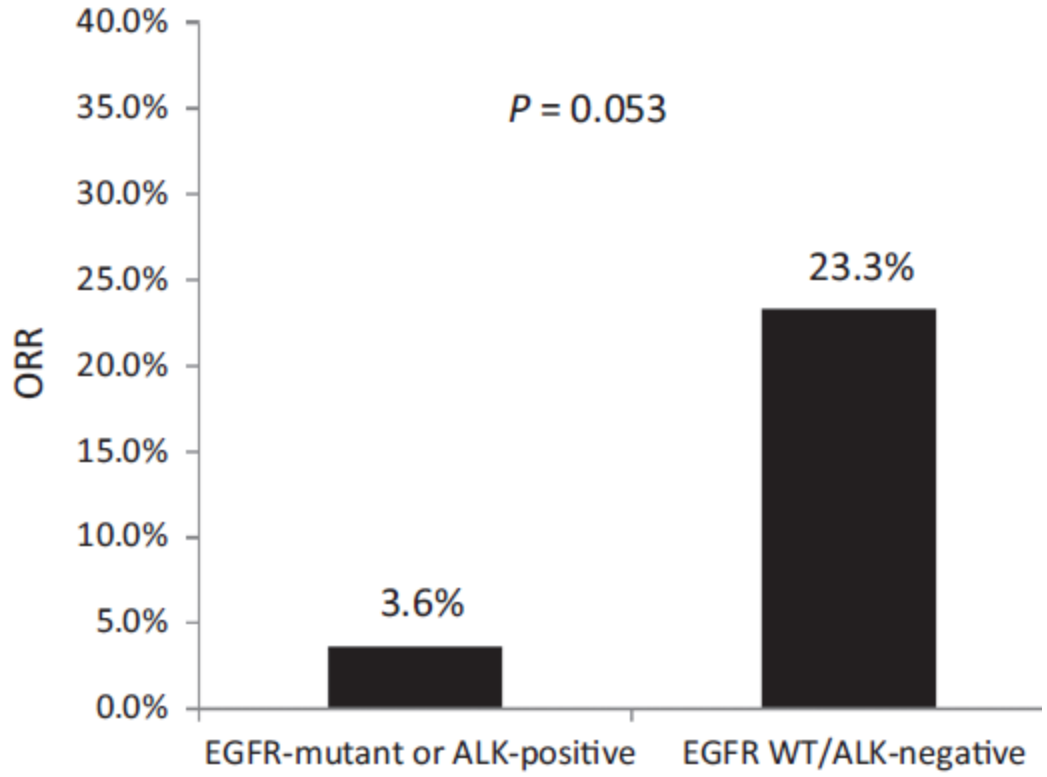


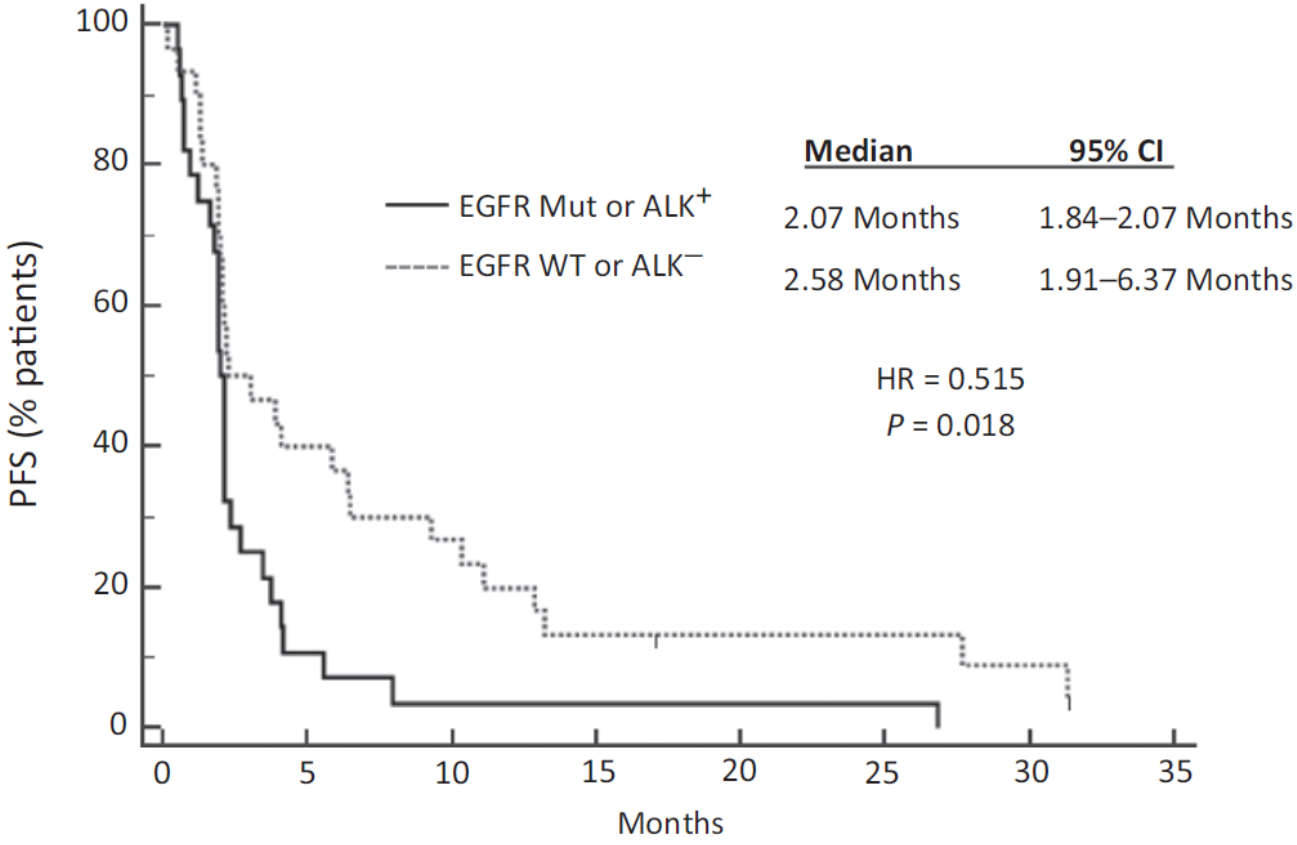
N Engl J Med. 2015;373(17);1627–1639

Cancer Therapy: Clinical

Clinical Cancer Research

EGFR Mutations and *ALK* Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non–Small Cell Lung Cancer: A Retrospective Analysis

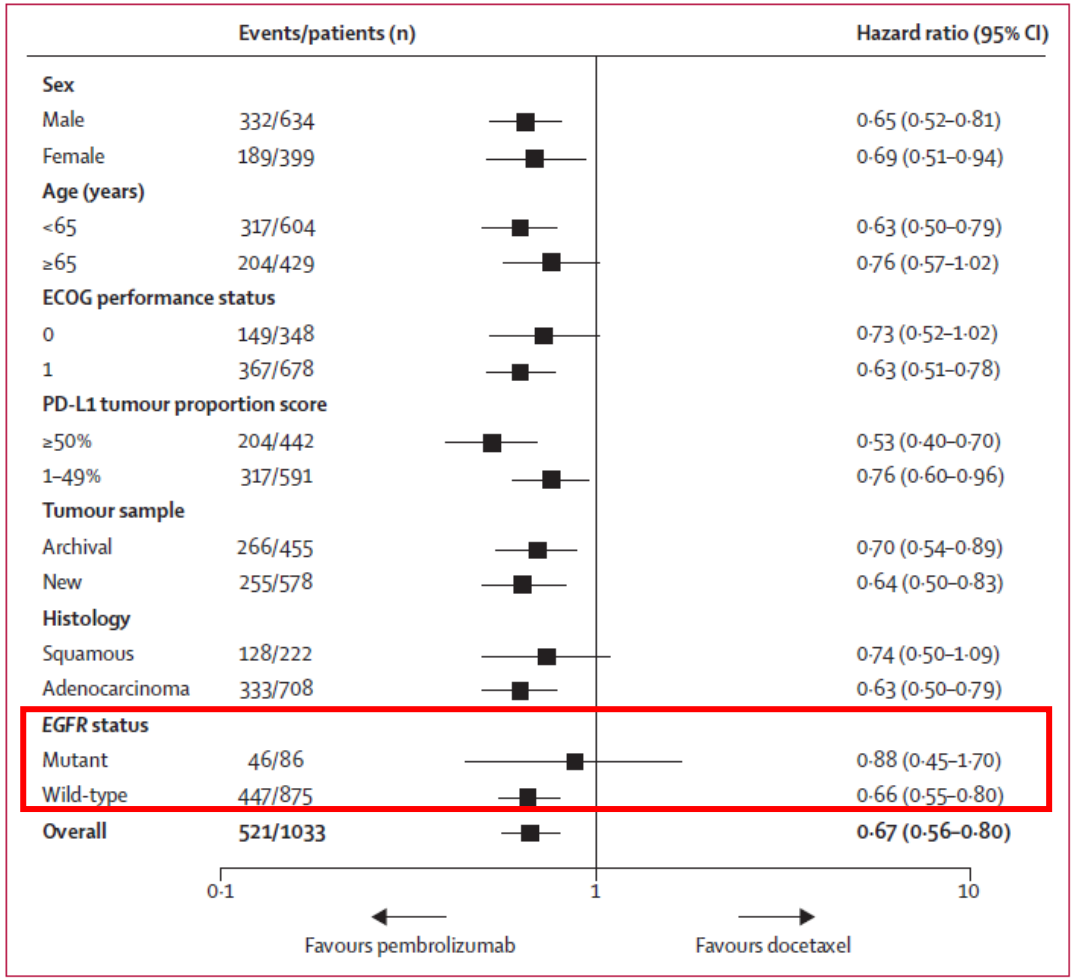




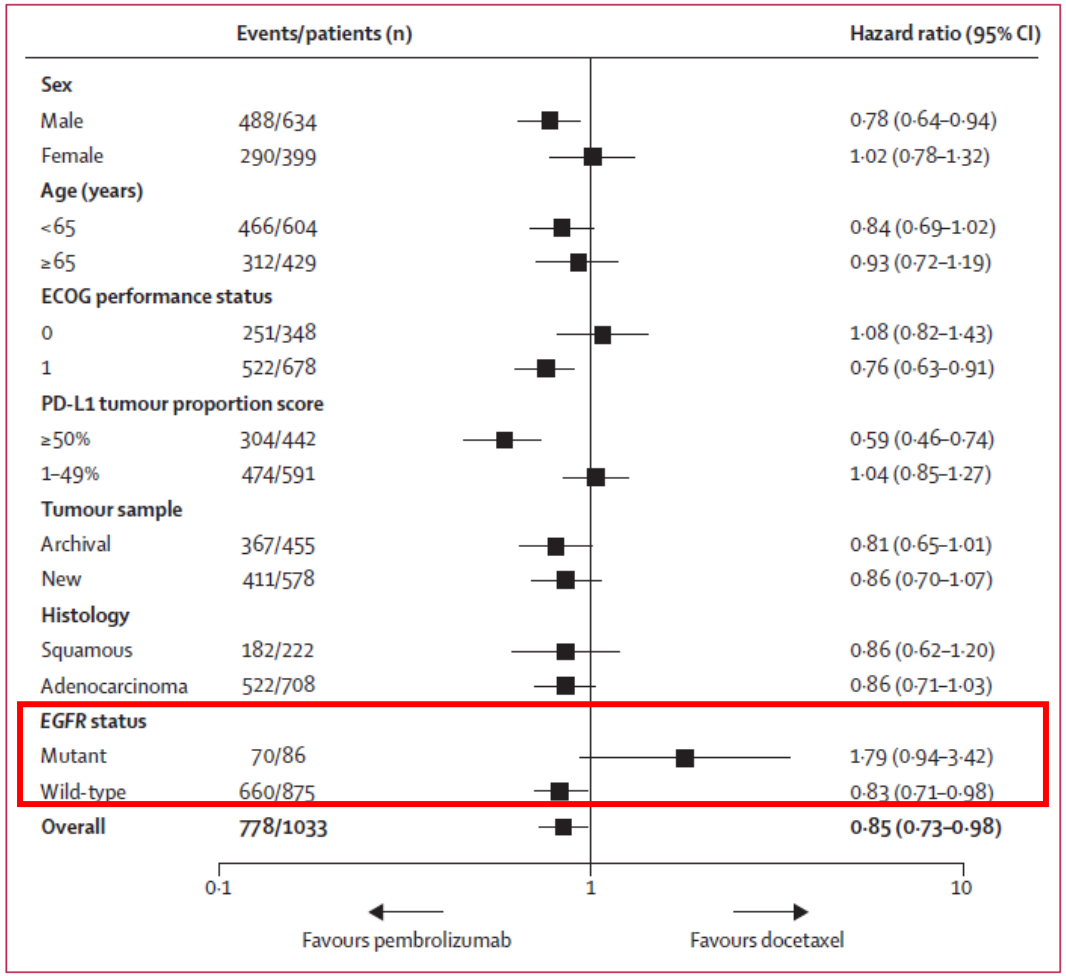
Clin Cancer Res 2016;22;4585-4593

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Overall Survival



PFS



Lancet 2016;387(10027);1540-1550

Subsequent ICI for EGFR (+) patients

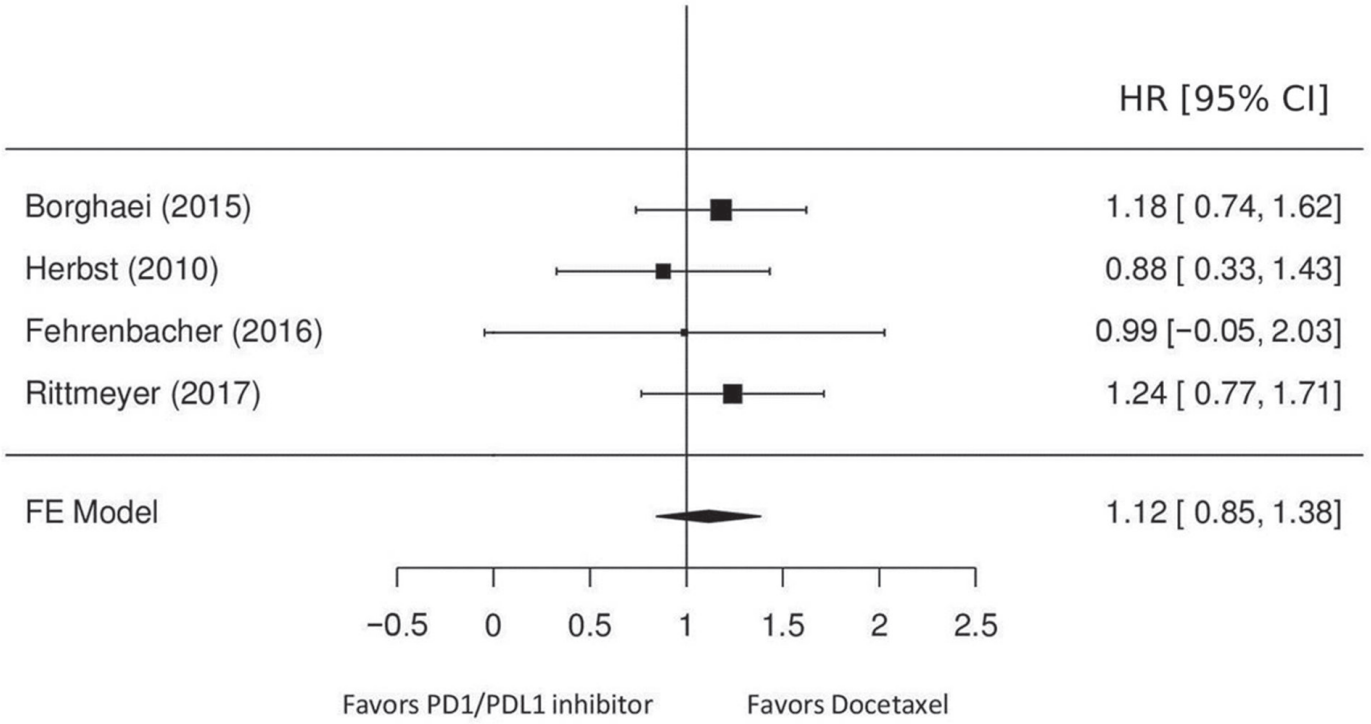
- HRs for overall survival
  - do not favor docetaxel over
    : nivolumab (HR, 1.18; CI, 0.69-2.0),
    : pembrolizumab (HR, 0.88; CI, 0.45-1.7), or
    : atezolizumab (HR, 1.24; CI, 0.7-2.2)
    but wide CIs due to few patients with EGFR mutations

- HRs for PFS
  - do favor docetaxel compared with
    : pembrolizumab (HR, 1.79; CI, 0.94-3.42) or
    : nivolumab (HR, 1.46; CI, 0.90-2.37)

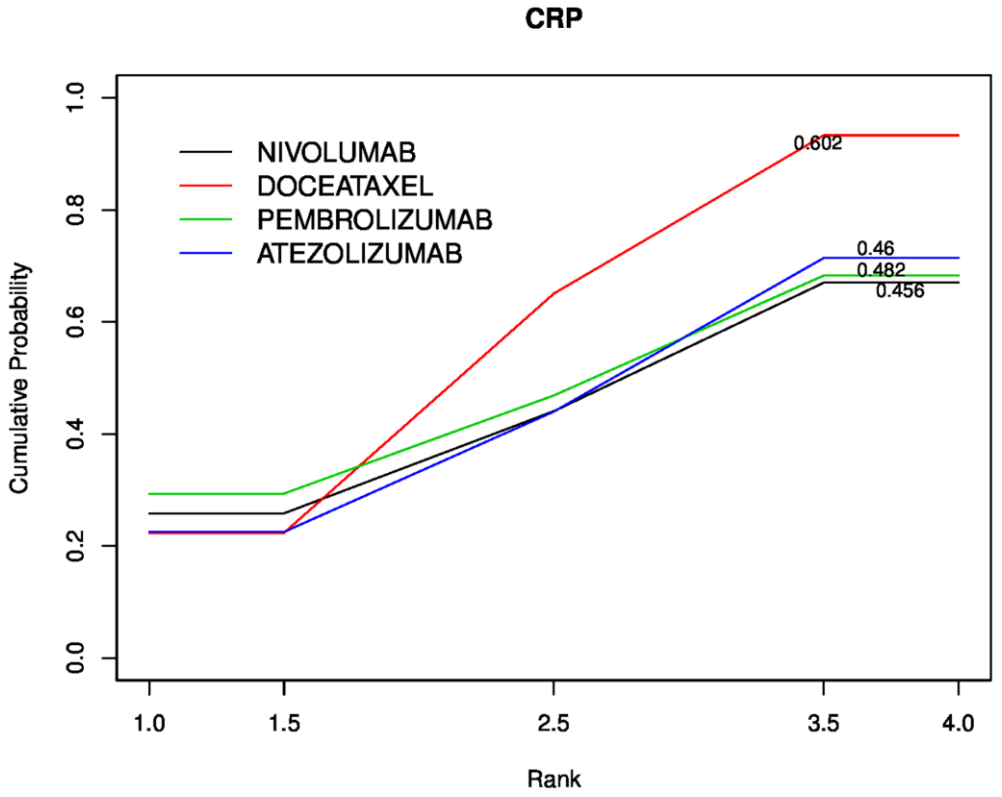
N Eng J Med 2015;373:1627-1639
Clin Cancer Res 2016;22:4585-4593
Lancet 216;387:1540-1550
Primary analysis from OAK. ESMO 1016 abstract LBA44

Meta-Analysis

Immune checkpoint inhibitors in EGFR-mutation positive TKI-treated patients with advanced non-small-cell lung cancer network meta-analysis



Hazard ratios for OS



SUCRA (SUrface under the Cumulative RAnking curve)

Oncotarget 2019;10:209-215

Subsequent ICI for EGFR, ALK, MET (+) patients

- Meta-analysis
  : docetaxel improves OS when compared with ICI

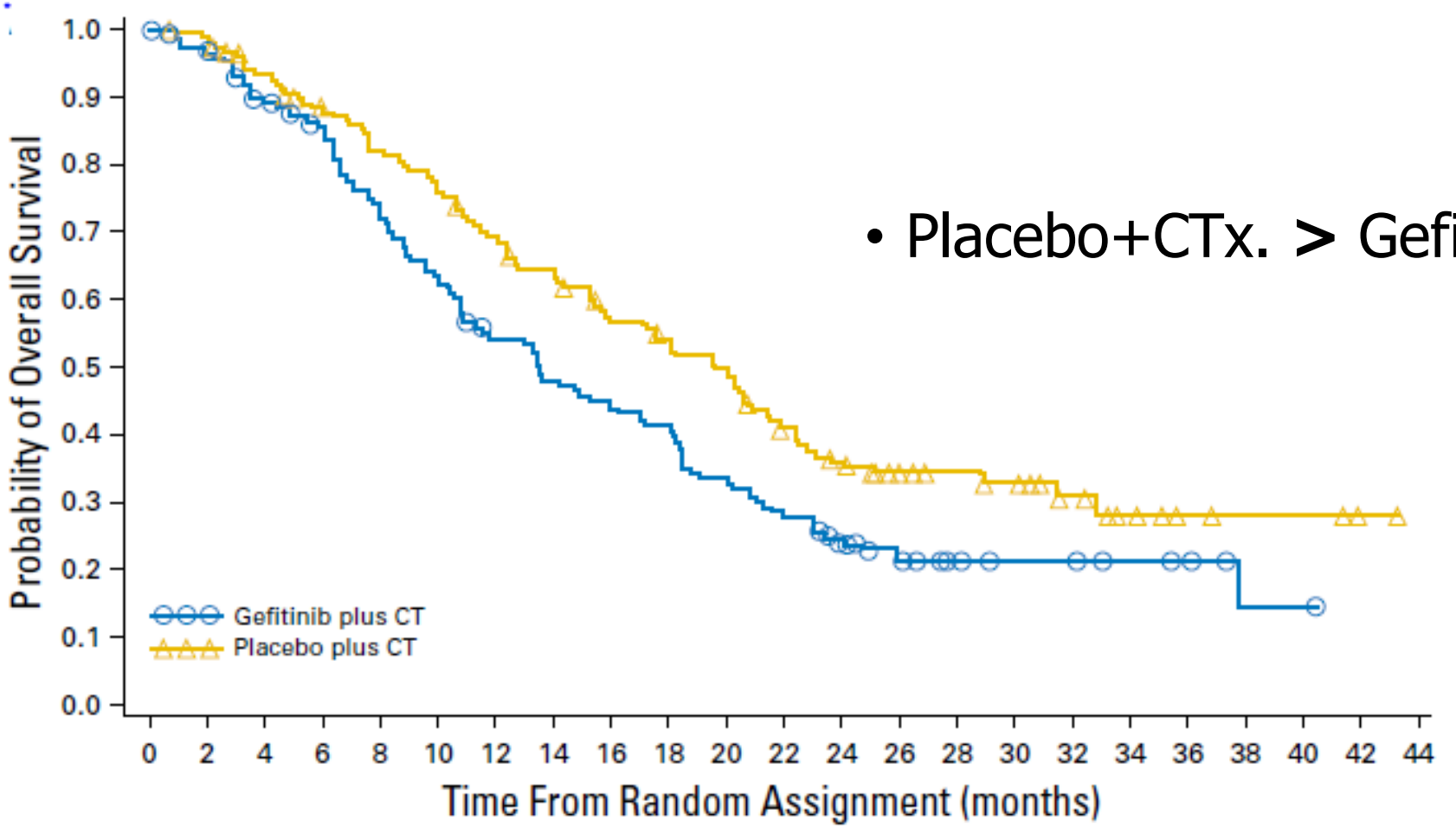
- Subsequent Tx. with pembrolizumab, nivolumab, or atezoluzumab
  : not recommended in patients with EGFR mutations or ALK fusions

- ALK (+) with very high PD-L1 expression
  : not respond to pembrolizumab

- Patients with METex14 mutations and high PD-L1 expression
  - not respond to immunotherapy

Oncotarget 2019;10:209-215
Clin Cancer Res 2016;22:4585-4593

Gefitinib+CTx. vs CTx. in EGFR+ resistant to 1st–line Gefitinib (IMPRESS)



- Placebo+CTx. **>** Gefitinib+CTx.

J Clin Oncol 2017;35:4027-4034

Subsequent Tx. for ALK+ metastatic NSCLC

- progression after Tx. with ALK inhibitors
  : lorlatinib (category 2A)

- Progression after 1st line target Tx.

- Considering local therapy
- Continuing alectinib, brigatinib, crizotinib, or ceritinib
- Taking alectinib, brigatinib, ceritinib (if all were not previously given) or lorlatinib
- Taking a 1st-line systemic Tx. regimen for nonsq. NSCLC

NCCN Guidelines version 6.2021 NSCLC

Subsequent Tx. for Pts. with ALK fusions

- After further progression on subsequent targeted Tx

1) Lorlatinib, or
2) 1st line combination CTx. (eg. Carbo/paclitaxel) for patients with PS 0 to 1
3) Other CTx. Option (eg. Docetaxel) for PS 2 patients

NCCN Guidelines version 6.2021 NSCLC

NSCLC without Driver Mutation

PS of 0 to 2 without genetic variants

- **If ICIs have not previously been given**

 - nivolumab, pembrolizumab, or atezolizumab

 : as preferred options for all histologic subtypes

 : based on improved survival rate

 : longer duration of response

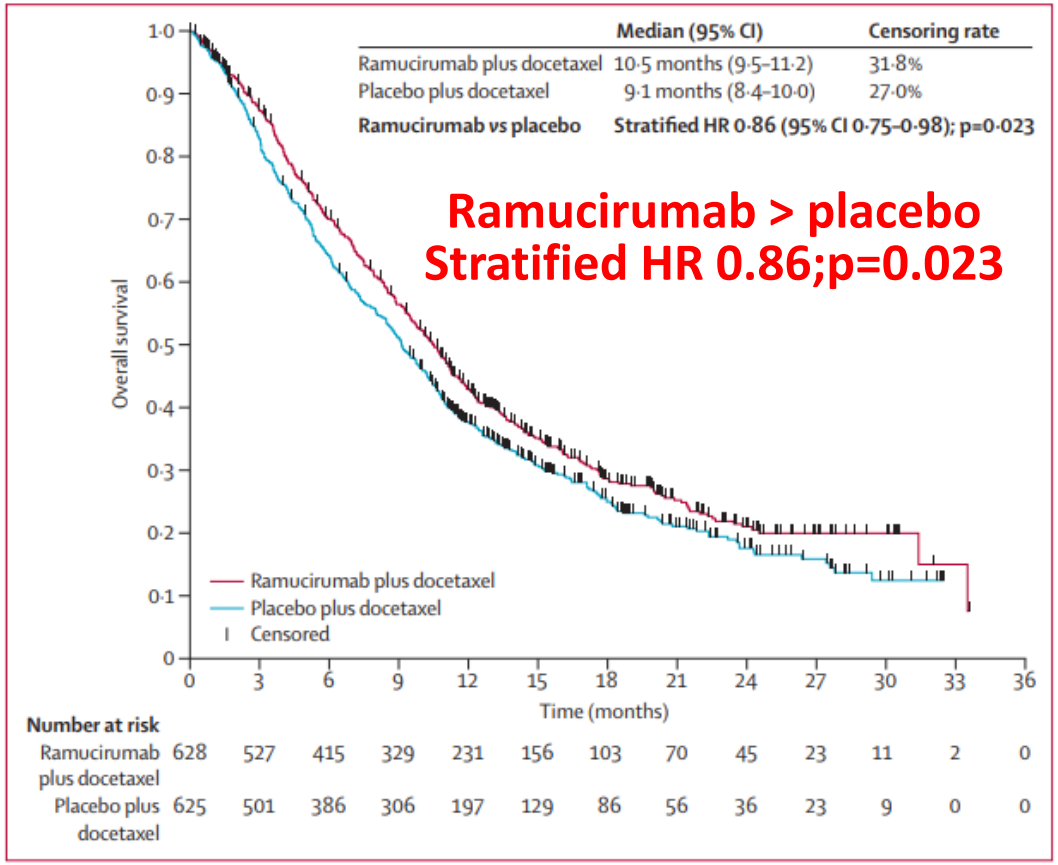
 : fewer adverse events

 when compared to cytotoxic CTx.

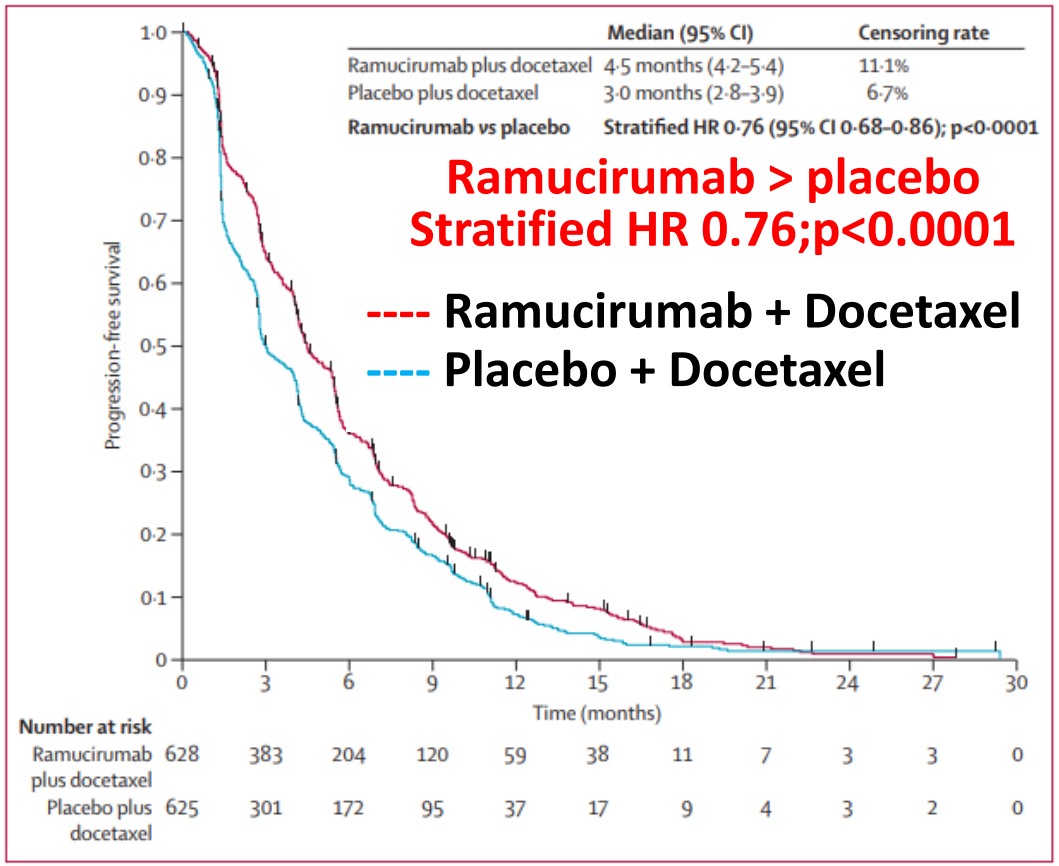
NCCN Guidelines version 6.2021 NSCLC

Ramucirumab/docetaxel for ICI intolerant Pts. (REVEL)

Overall survival



PFS



Lancet 2014;384(9944):665-73

PS of 0 to 2 without genetic variants

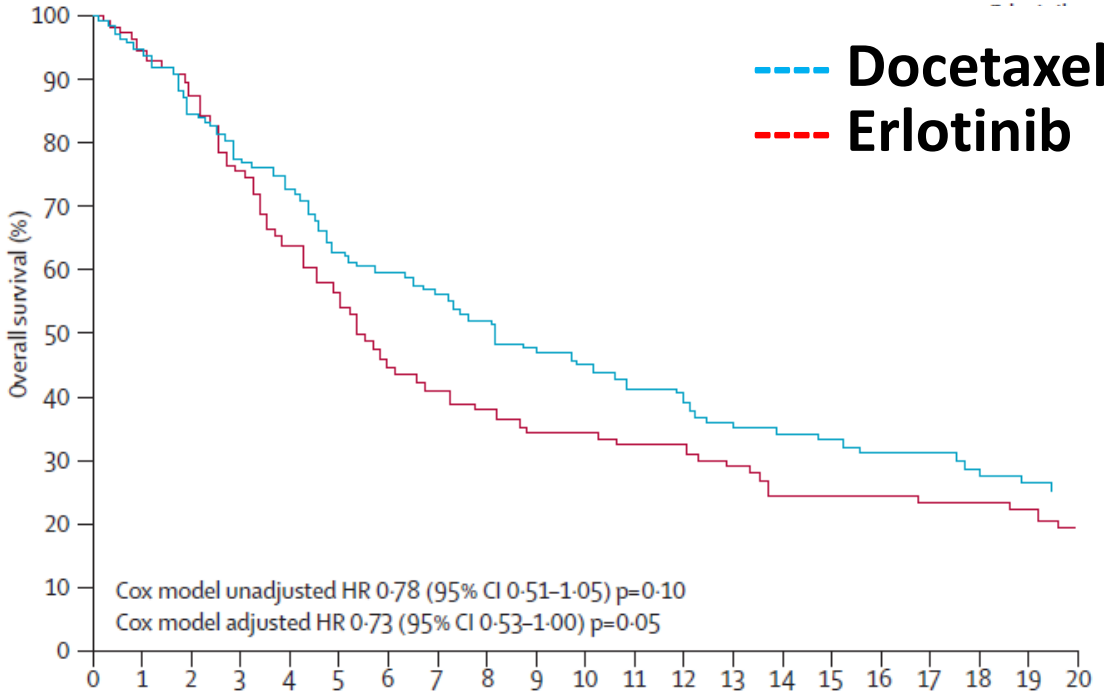
- **Docetaxel**
  - superior to BSC, vinorelbine, or ifosfamide
    : improved survival and QoL
  - superior to erlotinib for patients with wild-type EGFR tumors

- **Pemetrexed vs docetaxel**
  - similar median survival but less toxicity
  - recommended for patients with nonsq. NSCLC

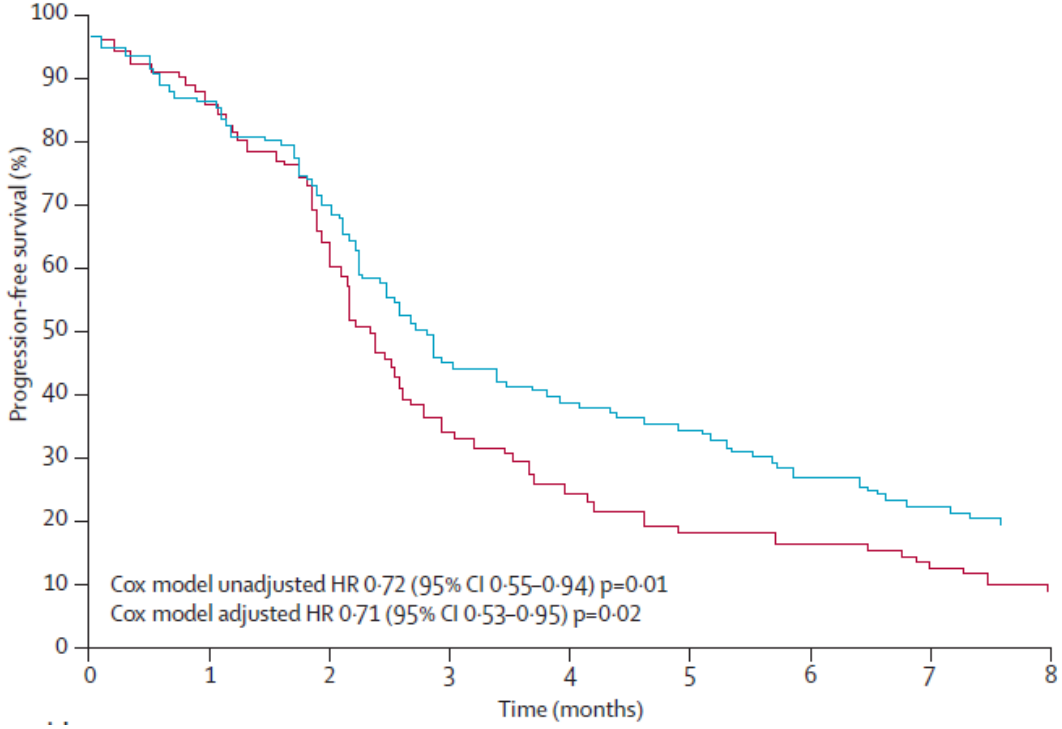
NCCN Guidelines version 6.2021 NSCLC

Erlotinib vs docetaxel for wild-type EGFR tumors (TAILOR)

Overall survival



PFS



Lancet 2013;14(10);981-8

Subsequent Tx. After 2nd progresssion

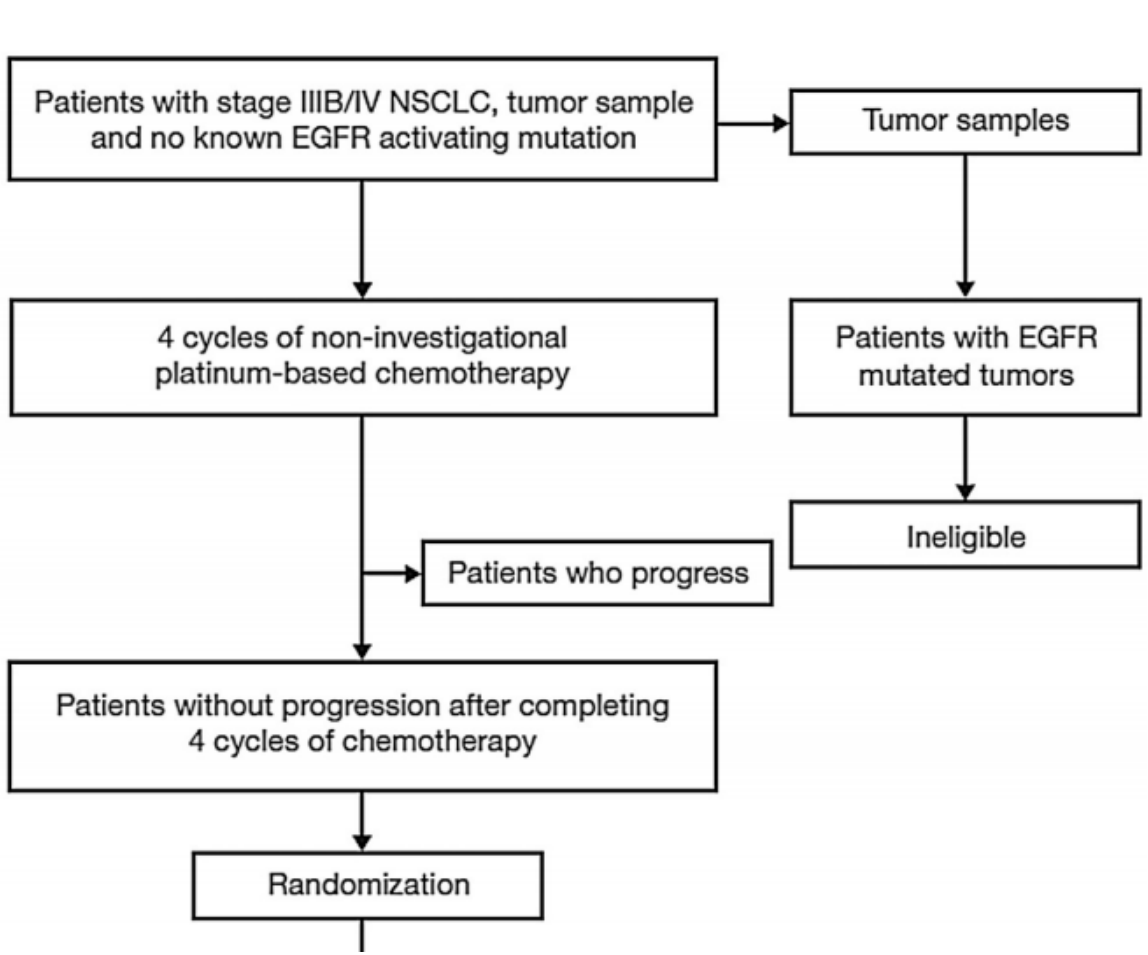
• If the following agents have not already been given

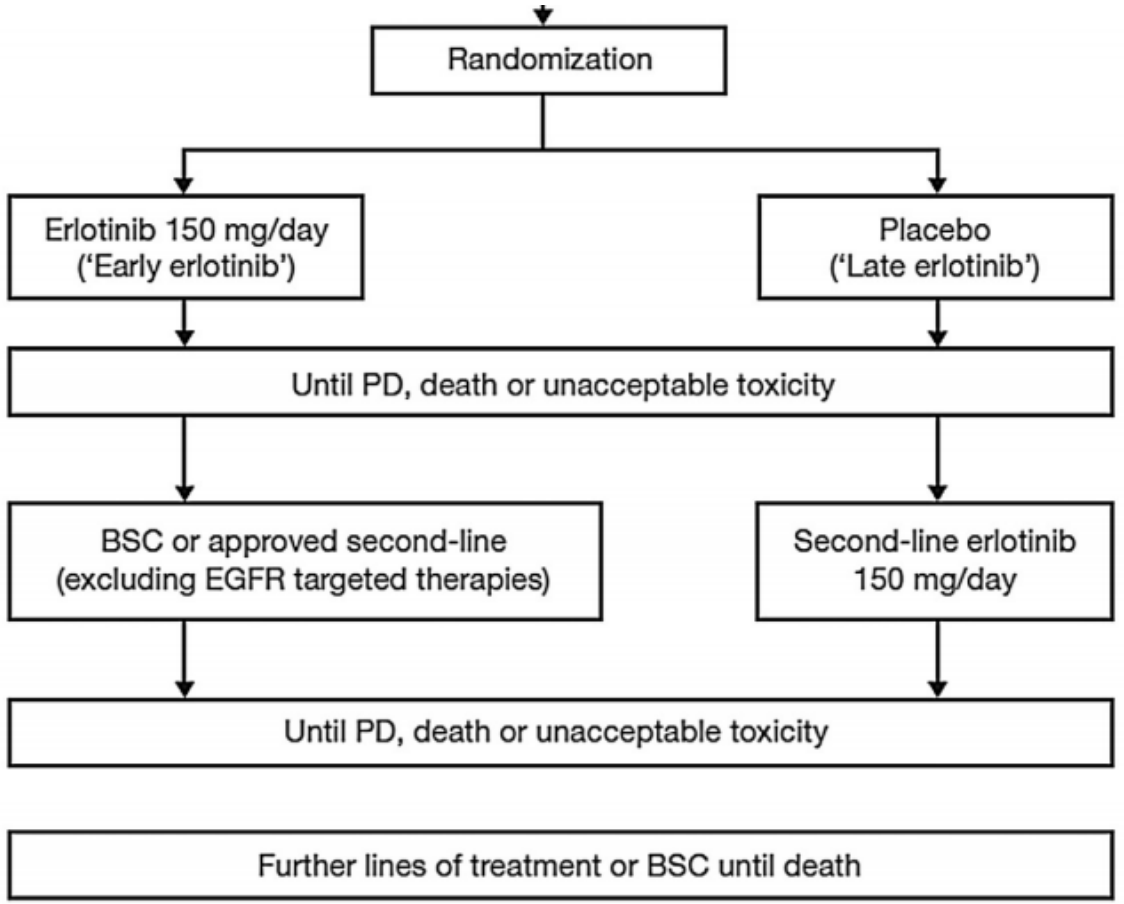
1) nivolumab, pembrolizumab, or atezolizumab (2A)
2) Docetaxel with or without ramucirumab (2B)
3) Gemcitabine (2B)
4) Pemetrexed for nonsquamous only (2B)

: include a PS 0 to 2 and PD-L1 less than 1%

NCCN Guidelines version 6.2021 NSCLC
J Clin Oncol 2014;32:1902-1908
J thorac Oncol 2006;1:1042-1058

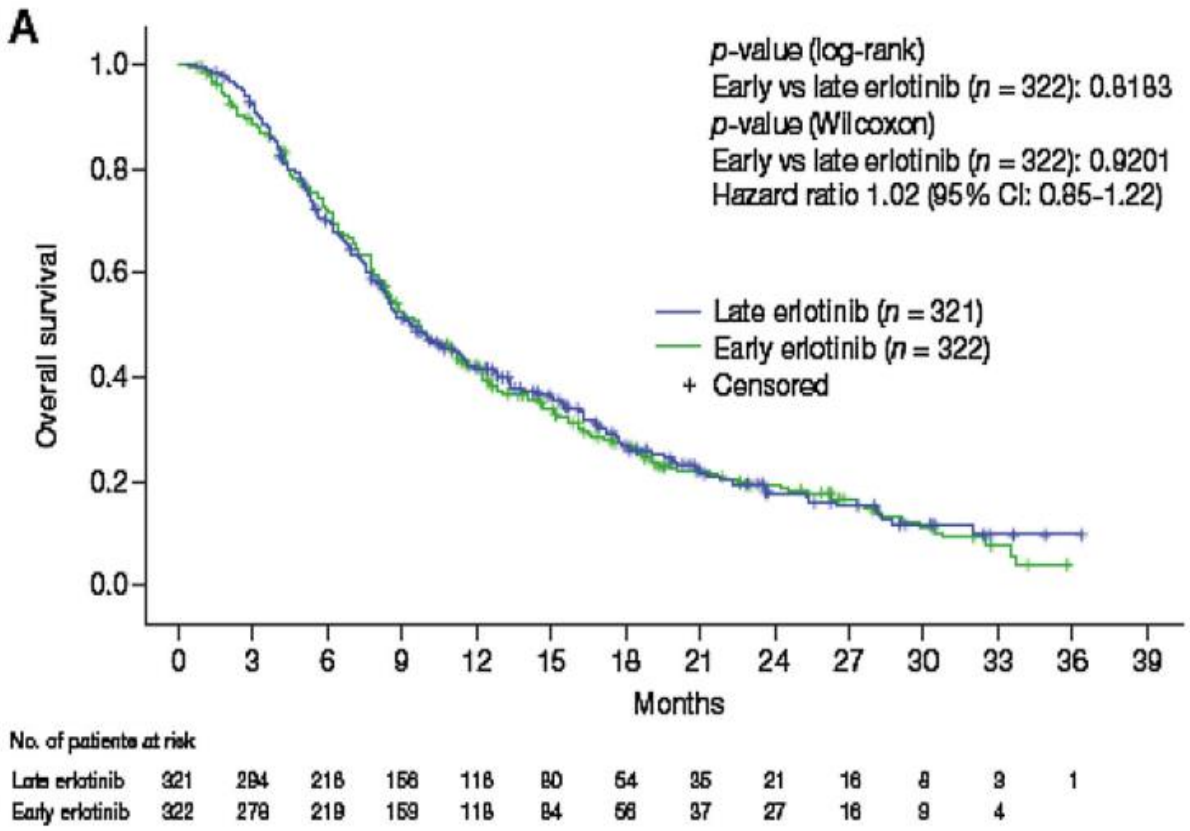
Maintenance erlotinib following CTx. (IUNO)

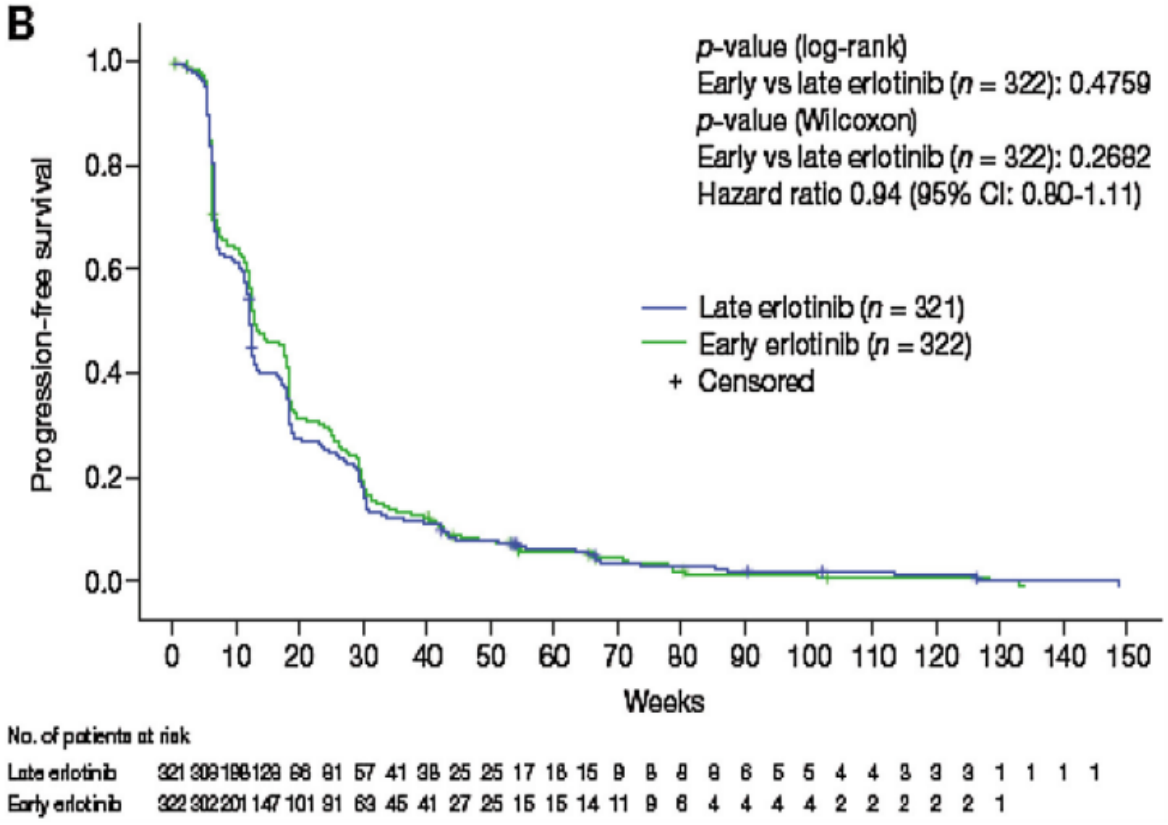




Lung Cancer 2016;102:30-37

Maintenance erlotinib following CTx. (IUNO)

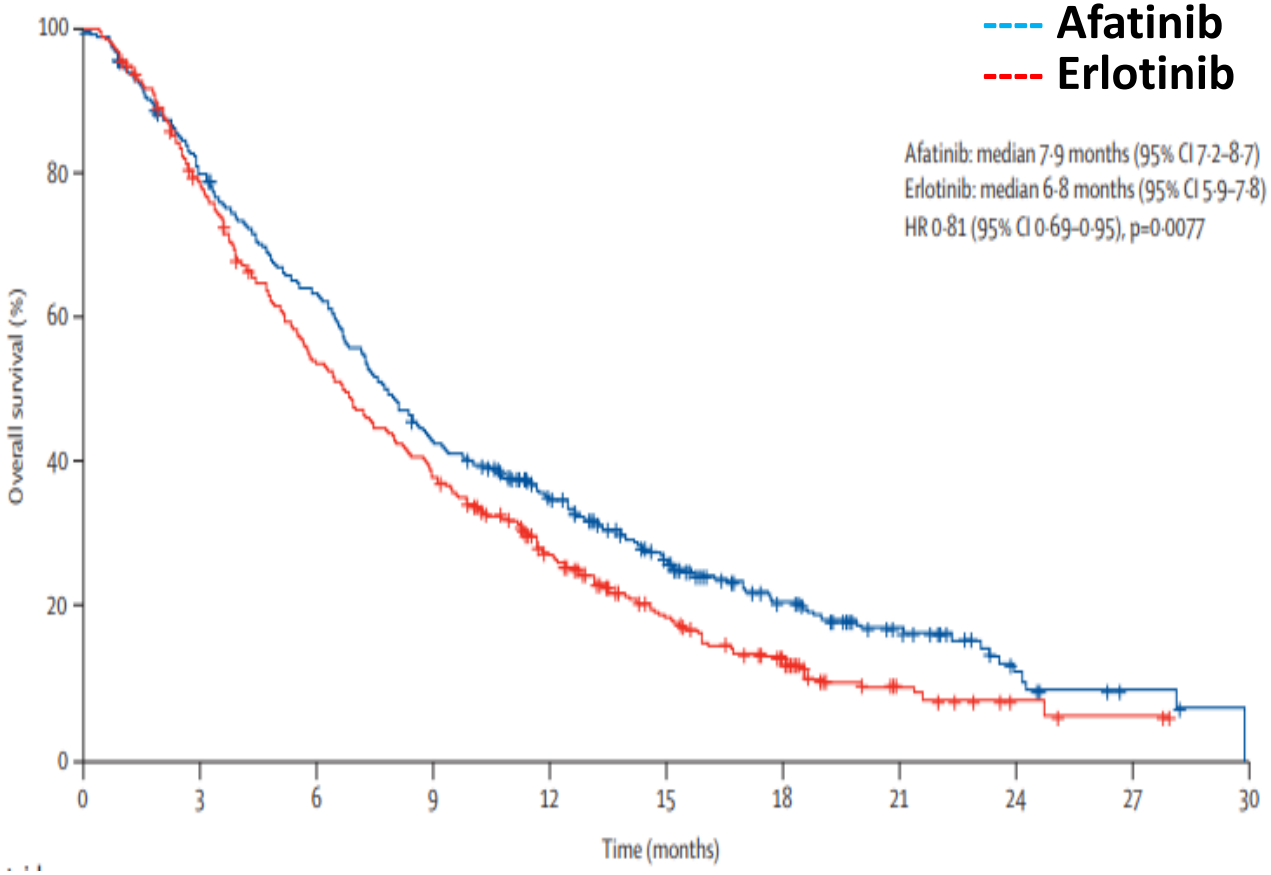




Lung Cancer 2016;102:30-37

Afatinib vs erlotinb as 2nd-line Tx. (LUX-Lung 8)

- Stage IIIB or IV
- Sq. cell Ca. of the lung
- Progressed after at least 4 cycles of platinum based CTx.
- Randomly assigned to afatinib or erlotinb until disease progression
- Grade ≥ 3 AE : almost 60% in each arm



Lancet Oncol 2015;16:897-907

Subsequent Tx. For patients without EGFR mutation

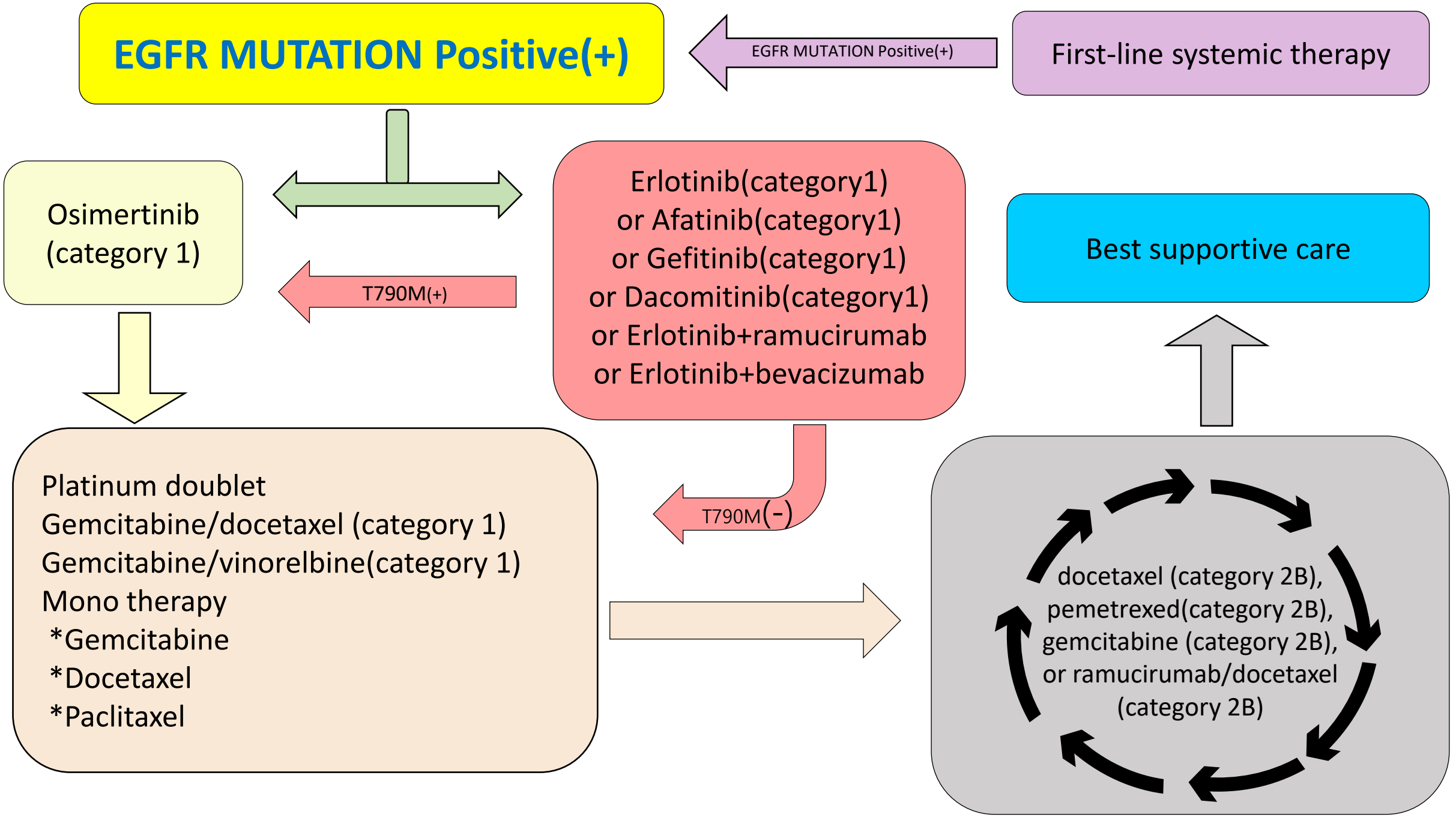
- Deleted erlotinib as subsequent therapy
  - for nonsquamous NSCLC &
  - PS of 0 to 2 but without EGFR mutation

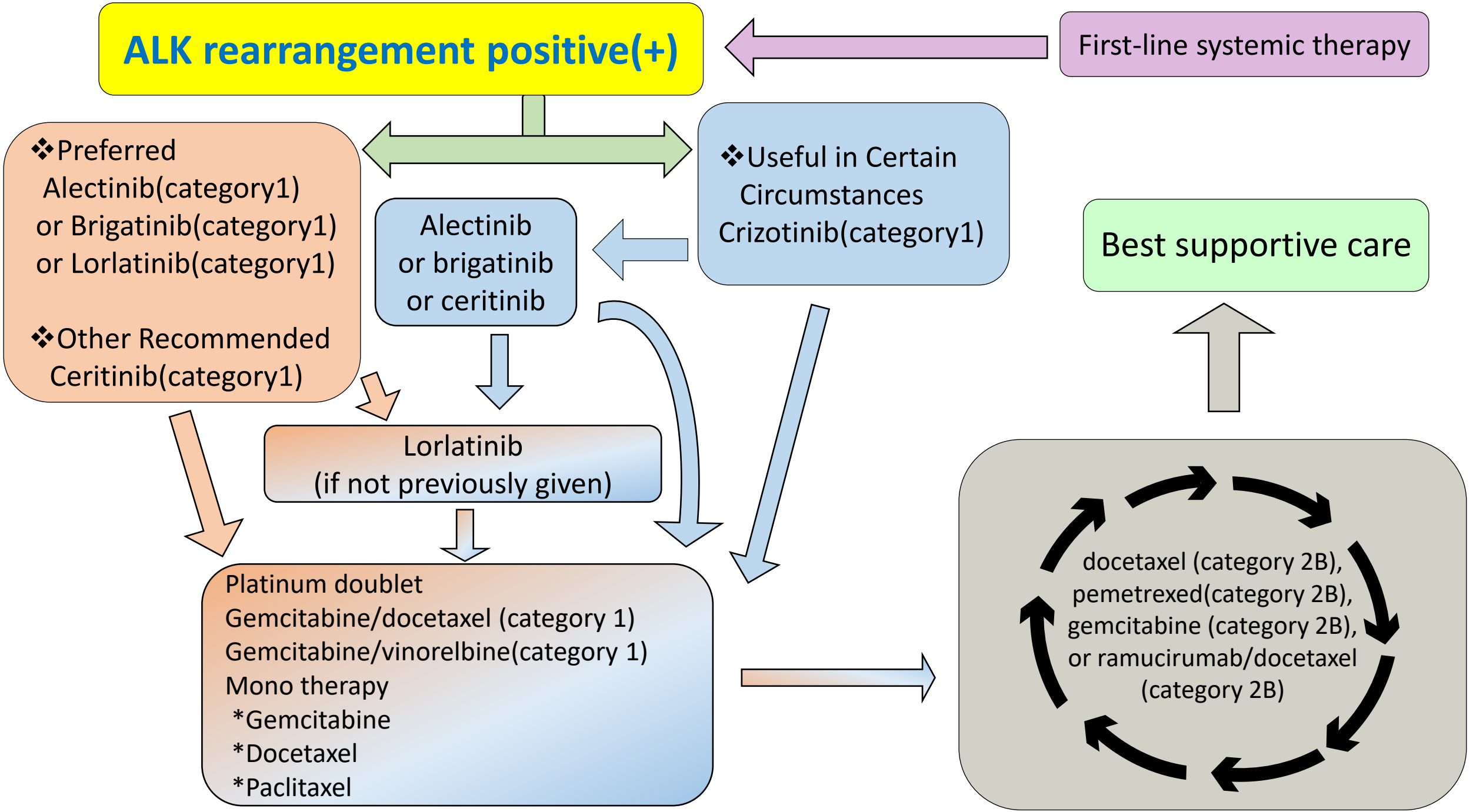
- Deleted erlotinib as an option for subsequent Tx
  - for squamous cell NSCLC

- Overall survivial
  - Nivolumab (9.2 mo), afatinib (7.9 mo), erlotinib (6.8 mo)
  - Nivolumab : only 7% experienced ≥ grade 3 AE

Lung Cancer 2016;102:30-37
Lancet Oncol 2015;16:897-907
N Engl J Med 2015;373(2);123-35

Summary


EGFR MUTATION Positive(+)
EGFR MUTATION Positive(+)
First-line systemic therapy
Osimertinib
(category 1)
T790M(+)
Erlotinib(category1)
or Afatinib(category1)
or Gefitinib(category1)
or Dacomitinib(category1)
or Erlotinib+ramucirumab
or Erlotinib+bevacizumab
Best supportive care
Platinum doublet
Gemcitabine/docetaxel (category 1)
Gemcitabine/vinorelbine(category 1)
Mono therapy
*Gemcitabine
*Docetaxel
*Paclitaxel
T790M(-)
docetaxel (category 2B),
pemetrexed(category 2B),
gemcitabine (category 2B),
or ramucirumab/docetaxel
(category 2B)


ALK rearrangement positive(+)
First-line systemic therapy
❖Preferred
Alectinib(category1)
or Brigatinib(category1)
or Lorlatinib(category1)
❖Other Recommended
Ceritinib(category1)
❖Useful in Certain
Circumstances
Crizotinib(category1)
Alectinib
or brigatinib
or ceritinib
Best supportive care
Lorlatinib
(if not previously given)
Platinum doublet
Gemcitabine/docetaxel (category 1)
Gemcitabine/vinorelbine(category 1)
Mono therapy
*Gemcitabine
*Docetaxel
*Paclitaxel
docetaxel (category 2B),
pemetrexed(category 2B),
gemcitabine (category 2B),
or ramucirumab/docetaxel
(category 2B)

NSCLC without Genetic Variants

- **Progression after initial cytotoxic Tx.**

  - PD-1 or PD-L1 inhibitor

    : nivolumab, pembrolizumab, or atezolizumab (category 1)

  - chemotherapy

  : docetaxel with/without ramucirumab

  : gemcitabine

  : pemetrexed for nonsquamous NSCLC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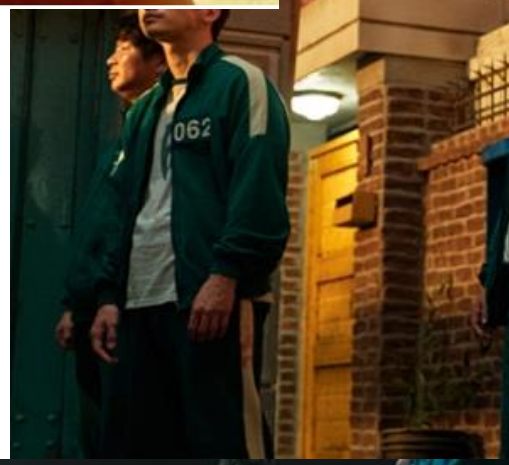
229

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