Systemic chemotherapy and targeted therapy in lung Cancer

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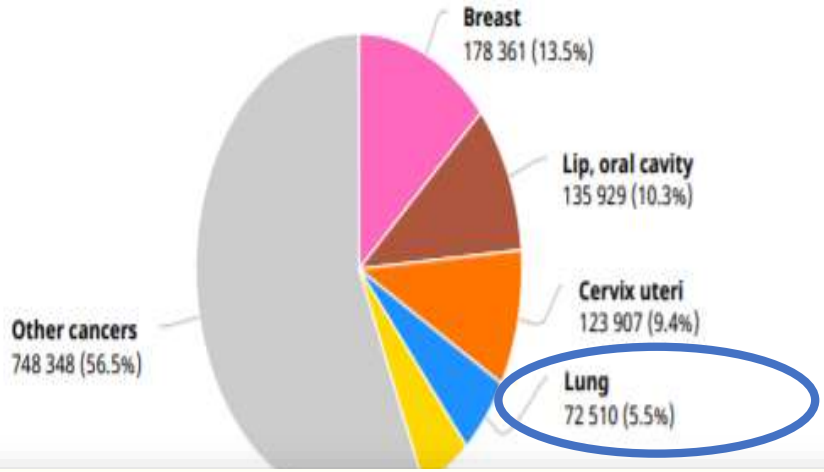
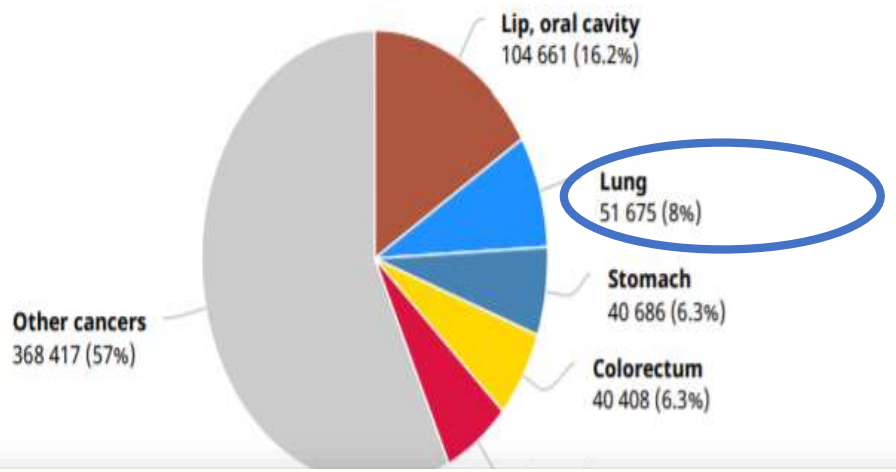
The burden of lung cancer in India: Globocan 2020

Number of new cases in 2020, both sexes, all ages



Number of new cases in 2020, males, all ages



Incidence, Mortality and Prevalence by cancer site

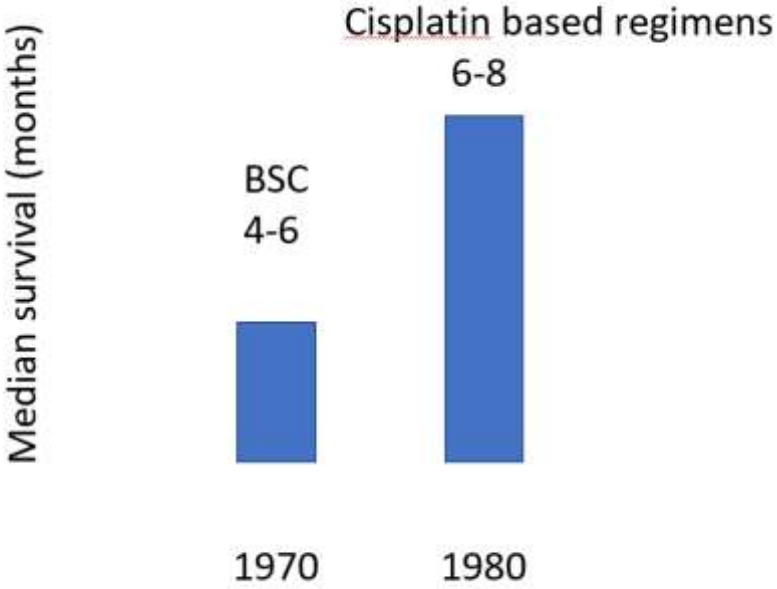
	New cases				Deaths				5-year prevalence (all ages)	
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop. (per 100 000)
Breast	178 361	1	13.5	2.81	90 408	1	10.6	1.49	459 271	69.28
Lip, oral cavity	135 929	2	10.3	1.09	75 290	3	8.8	0.62	300 413	21.77
Cervix uteri	123 907	3	9.4	2.01	77 348	2	9.1	1.30	283 842	42.82
Lung	72 510	4	5.5	0.67	66 279	4	7.8	0.61	80 817	5.86
Oesophagus	63 180	5	4.8	0.57	58 342	5	6.9	0.53	68 607	4.97
Stomach	60 222	6	4.5	0.53	53 253	6	6.3	0.48	81 270	5.89
Leukaemia	48 419	7	3.7	0.31	35 392	7	4.2	0.24	127 493	9.24

* 2021 projection: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf

Surgery mainstay of treatment for resectable disease.
Prognosis still poor i/v/o distant metastasis and local recurrence

Main Question 1980's

- Does chemotherapy prolong survival in Advanced stage disease ?
- Yes it does . Cisplatin based doublets do.
- If yes is it tolerable ?
  Toxicity
  Nausea , Vomiting ,
  Myelosuppresion



Adjuvant CT in NSCLC

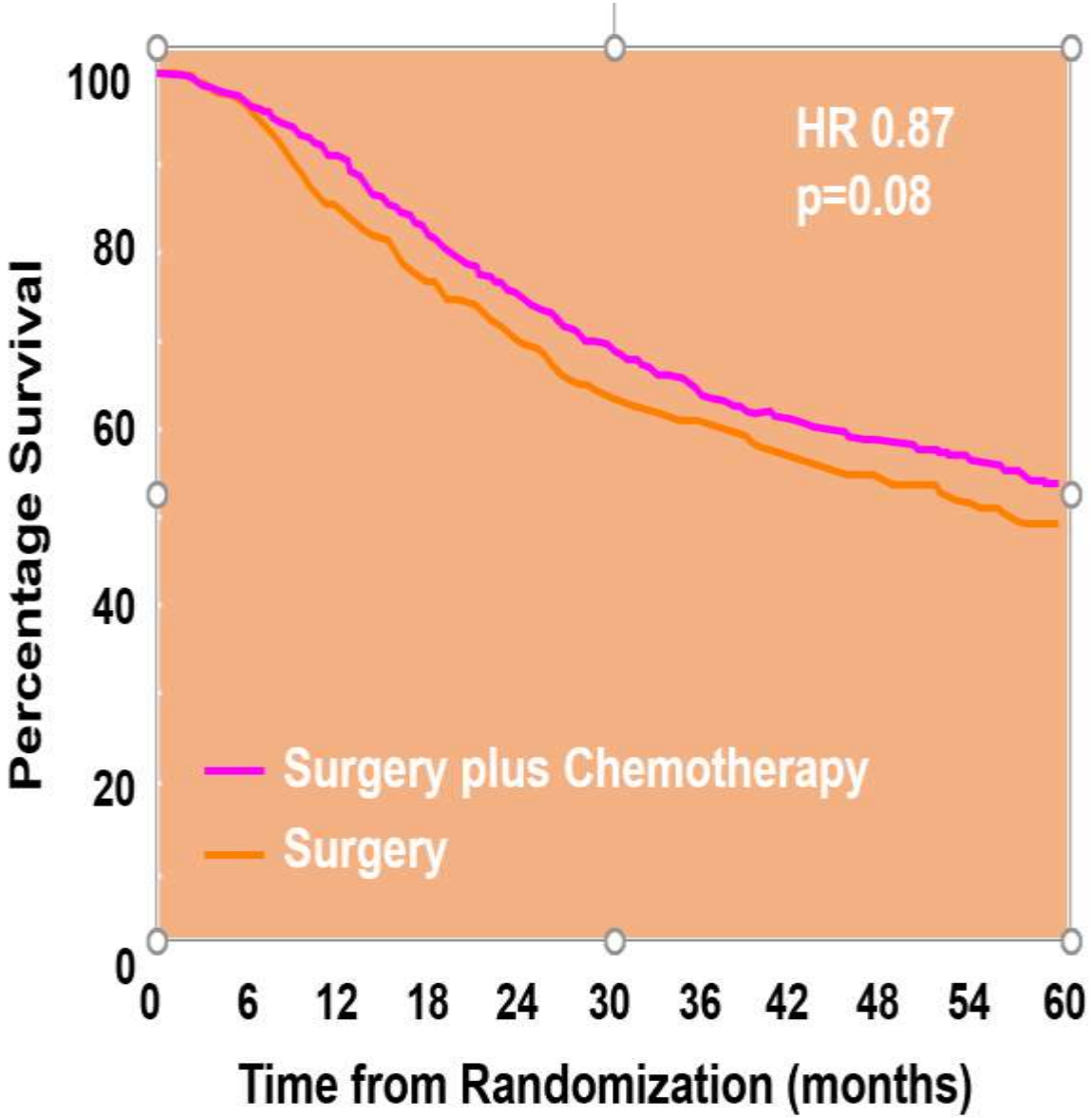
Meta-analysis of **eight cisplatin-based** adjuvant chemotherapy trials.

1,394 patients with NSCLC.

13% reduction in the **risk of death** (P = 0.08).

6% reduction in the risk of death in patients treated with postoperative cisplatin-based chemotherapy compared with patients who received only postoperative radiotherapy.
(P = 0.46).

Adjuvant chemotherapy with **long-term alkylating** agents was significantly **detrimental**.



NSCLC Collaborative Group BMJ 311:899,1995

The Adjuvant Lung Project Italy (ALPI)

On the basis of a previous meta-analysis, the International Adjuvant Lung Cancer Trial was designed to evaluate the effect of cisplatin-based adjuvant chemotherapy on survival after complete resection of non–small-cell lung cancer.

- 1209 cases
- Stage I-IIIA resected NSCLC
- Randomization .
  587 Observation

  592 CTx3
  (mitomycin , vindesine , cisplatin)

- CT Toxicity
- 30% grade 3
- 18% grade 4
- RT optional
- Median observation :63 months.
- 526 death, 1076 patients,
- HR:0.94 overall survival
- HR:0.87 PFS

Giorgio V. Scagliotti GV et al . J Nat Cancer Ins 2003

Randomized International Adjuvant Lung Cancer Trial (IALT): Design

- N=1867
- Select eligibility criteria:
- Stage I-III
- Complete surgical resection within 60 days
- Age ≤ 75.

RANDOMIZE

Cisplatin 80 mg/m² q 3 wk × 4 OR
Cisplatin 100 mg/m² q 4 wk × 3-4 OR
Cisplatin 120 mg/m² q 4 wk × 3

PLUS

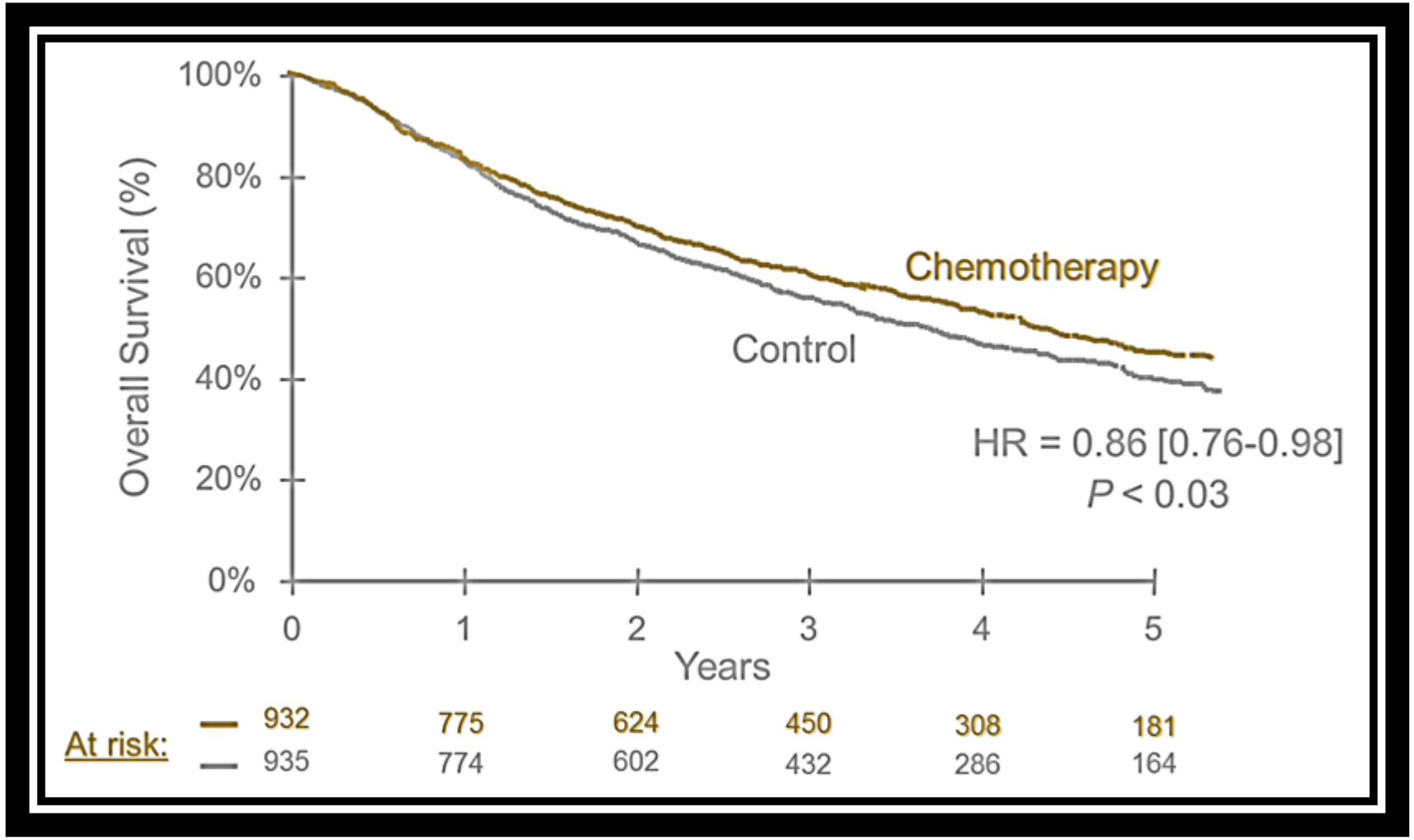
Etoposide 100 mg/m² × 3 days/cycle OR
Vinorelbine 30 mg/m² weekly OR
Vinblastine 4 mg/m² weekly OR
Vindesine 3 mg/m² weekly

± Thoracic Radiotherapy □ 60 Gy†

Each center selected chemotherapy regimen
†Optional, but predefined by N stage at each center

International Adjuvant Lung Cancer Trial Collaborative Group. N Engl J Med. 2004;350 (4):351-360

IALT: Overall Survival



Prospective Randomized Trial of Adjuvant Vinorelbine and Cisplatin in Completely Resected Stage IB/II NSCLC (JBR10)

JBR.10

Winton, ASCO 23:7018, 2004

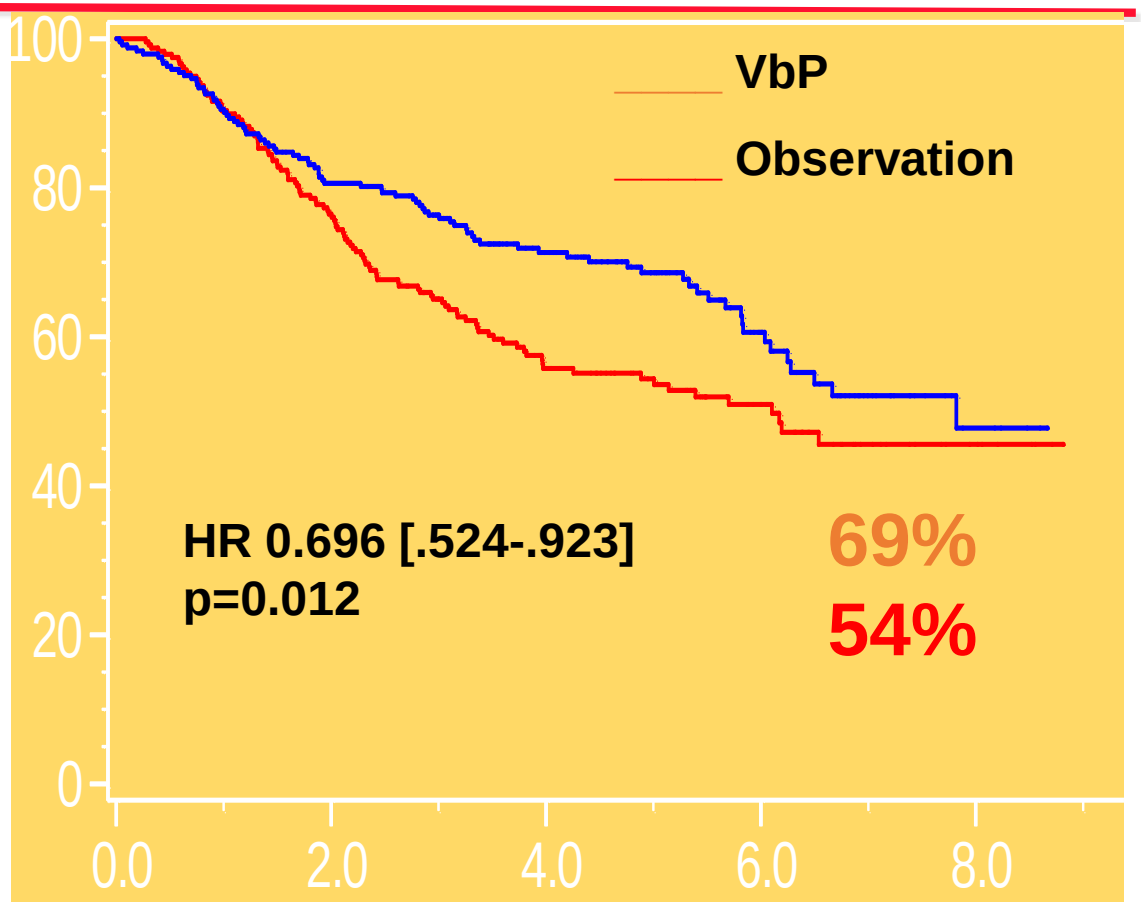
482 pts randomized after resection (stage IB/II)

- Lobectomy or pneumonectomy, N2 sampling
- Vin (25mg/m2 weekly) + Cis (50mg/m2 d1,8) q 4 weeks x 4 cycles versus observation
- Stratified: N status, ras mutation

Winton TL, et al. ASCO Abstract 7018

Prospective Randomized Trial of Adjuvant Vinorelbine and Cisplatin in Completely Resected Stage IB/II NSCLC (JBR10)

- 59% received 3 or more cycles
- Limited toxicity (neuro)
- Overall survival improved Vin/Cis (94m vs 73 m)
- 5-year survival longer for Vin/Cis (69% vs 54%)
- 15% survival improvement at 5 years
- 30% reduction in risk of death (p=0.012)



Winton TL, et al. ASCO Abstract 7018

UTF Meta – Analysis.

6 Trials: 2,003 pts.

UFT: Uracil and Tegafur

Tegafur - prodrug of fluorouracil

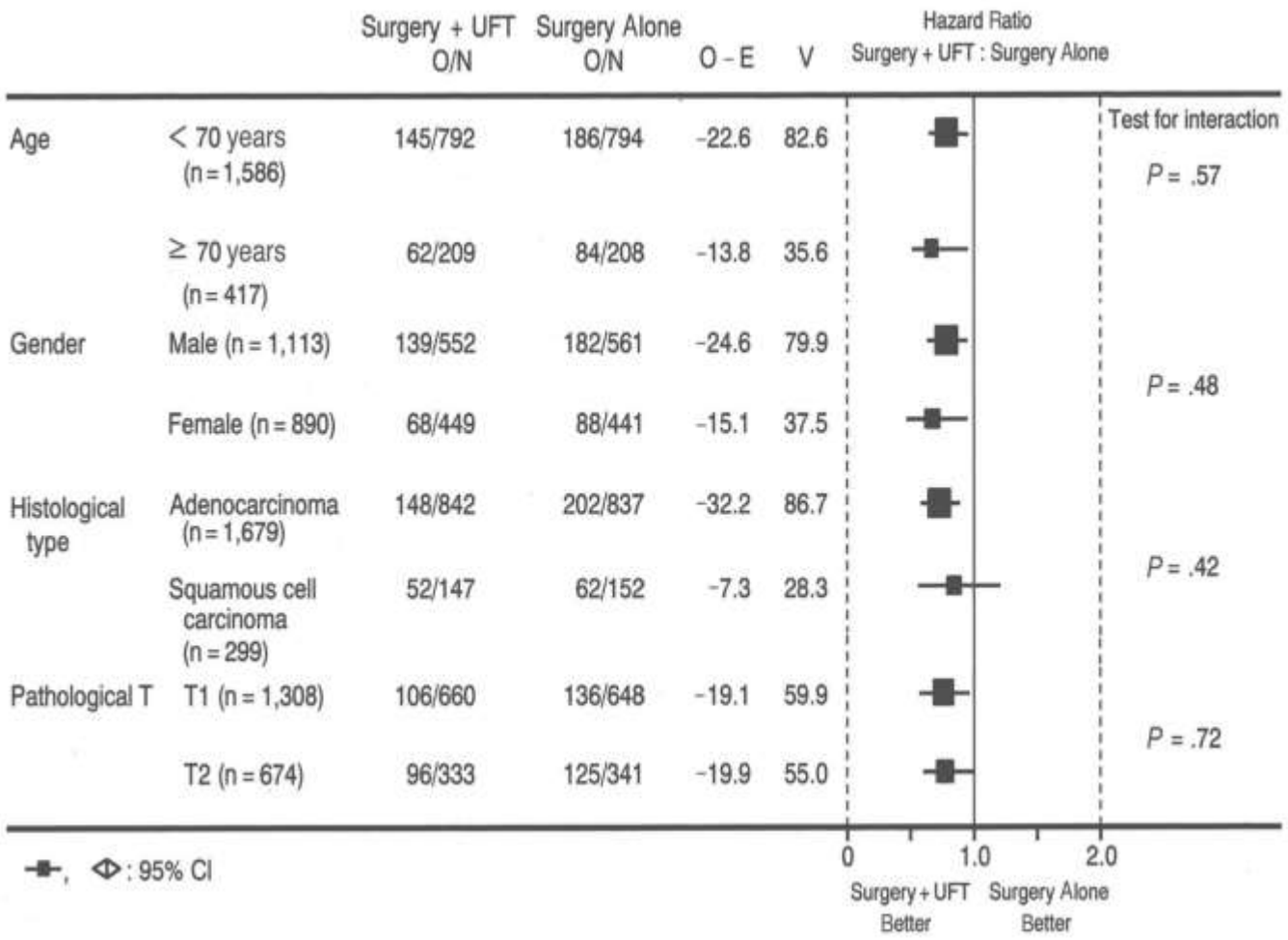
Uracil - inhibits DPD, ↑ serum FU

400 mg PO daily x 1-2 years

T1 :1,308(65.3%),T2 :674(33.6%),N0 :1,923 (96.0%)

Median duration of follow-up was 6.44 yrs.

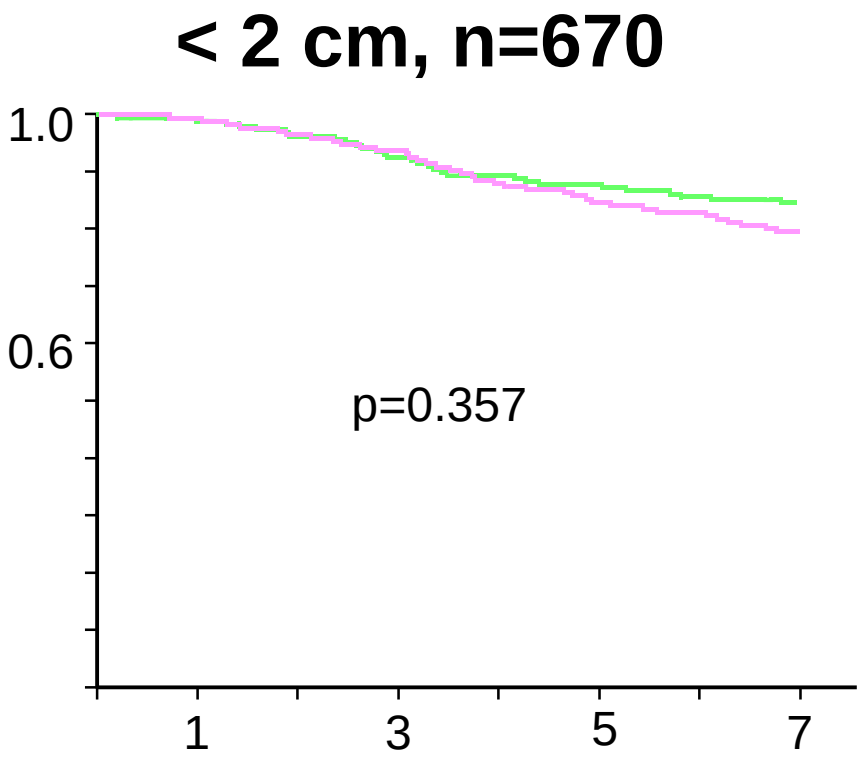
Survival	Sx + UFT5	Sx alone	
5yrs	81.5%	76.5%,	P = .011
7yrs	77.2%	69.5%,	P= .001

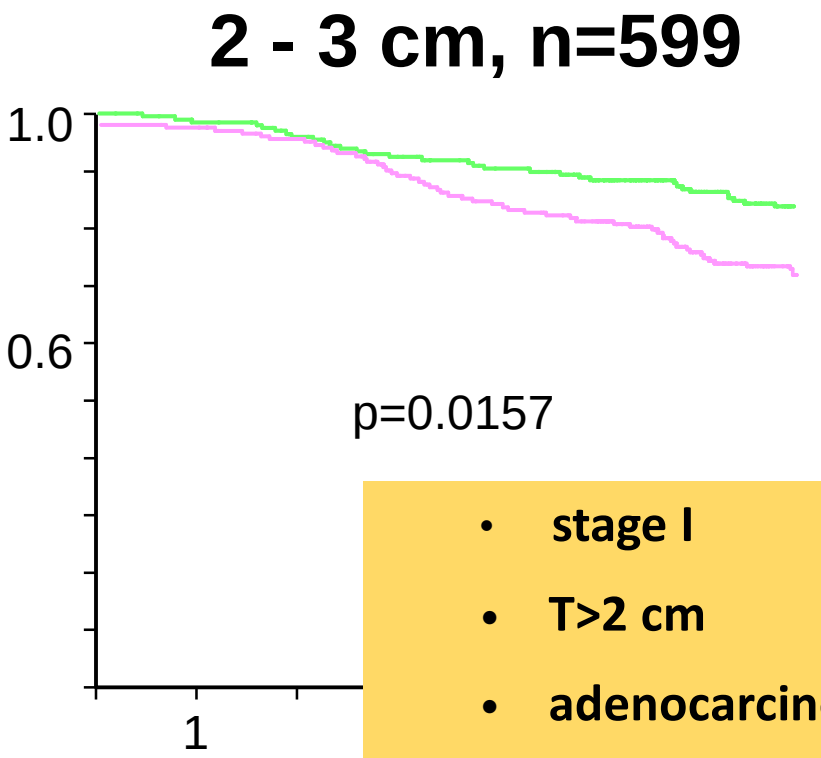


Pooled hazard ratio was 0.74, and its 95% CI was 0.61 to 0.88 (P .001).

Hamada et al ; J Clin Oncol 23:4999-5006. © 2005 by American Society of Clinical Oncology

UFT Meta-Analysis :Analysis T1





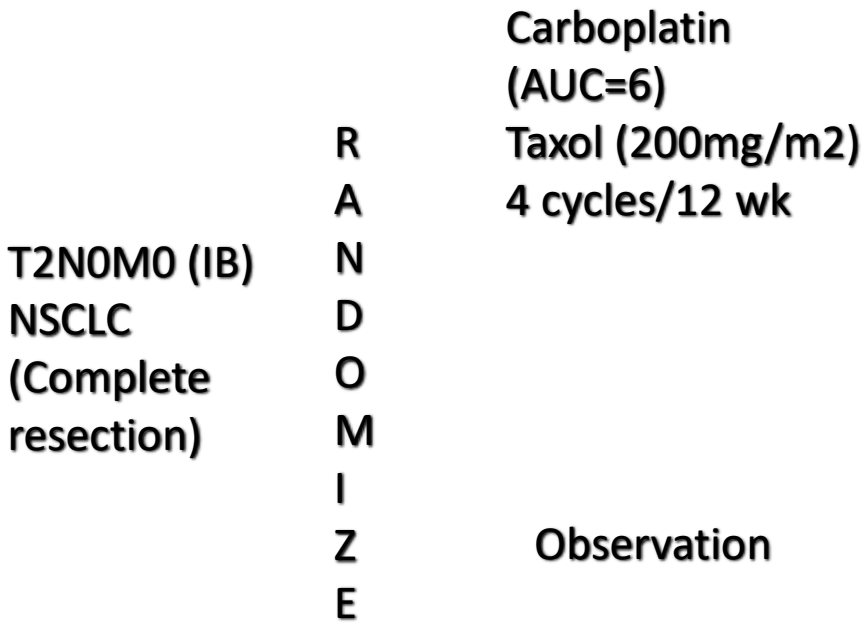
- **stage I**
- **T>2 cm**
- **adenocarcinoma**
- **a study population with 45% women**

Hamada, ASCO 23:7002, 2004

Randomized Clinical Trial :Adjuvant Chemotherapy with Paclitaxel and Carboplatin following Resection in Stage IB NSCLC (CALGB 9633)

CALGB 9633
Strauss, ASCO 23:7019, 2004

- High risk stage I patients (T2) after resection
- Stratified by histology, differentiation, mediastinoscopy
- Lobectomy or pneumonectomy; N2 sampling
- Closed by a planned interval analysis
- Accrual 344/384 planned (90%)

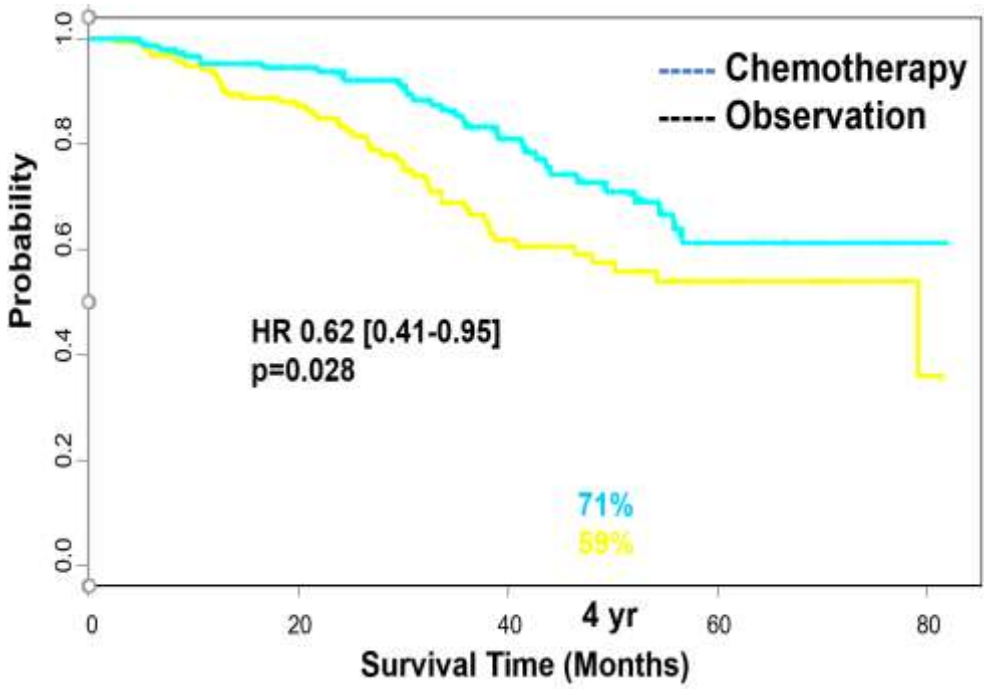


Strauss GM, et al. ASCO Abstract 7019

CALGB 9633

Variable	Chemo (n=173)	Control (n=171)	P value
Age	61 yr (34-78)	62 yr (40-81)	0.42
PS=0	55%	58%	0.92
Sx present	78%	74%	0.39
size	4.7cm (0-15)	4.6cm (1-12)	0.87
Squam	39%	39%	0.98
Poorly diff	50%	50%	0.99
Mediastin	80%	79%	0.78
Lobectom	89%	89%	0.98

All 4 cycles delivered in 85%
Dose modification in 35%
55% received all 4 cycles at full dose
Chemo well tolerated: no toxicity related deaths
Grade 3-4 neutropenia in 36%



Strauss GM, et al. ASCO Abstract 7019

NCIC & CALGB Adjuvant Chemotherapy Conclusions

The NCIC and CALGB studies confirm the positive IALT findings of a benefit for postoperative platin-based chemotherapy in completely resected NSCLC.

- Consistent reductions in the risk of death have been observed in recent adjuvant platin-based trials and the 1995 meta-analysis.
- Adjuvant platin-based chemotherapy should be recommended to completely resected NSCLC patients with good performance status.

NSCLC| Initial Systemic Therapy: Doublets

Meta-analysis: 65 trials (N = 13,601) between 1980-2001

–Compared efficacy of

- Doublet vs single-agent regimens
- Triplet vs doublet regimens

Survival Outcome	Doublet vs Single-Agent Regimens	Triplet vs Doublet Regimens
1-yr OS	Doublet > single-agent ▪ OR: 0.80; 95% CI: 0.70-0.91; *P* < .001 ▪ 5% absolute benefit	Triplet = doublet ▪ OR: 1.01; 95% CI: 0.85-1.21; *P* = .88
Median OS	Doublet > single-agent ▪ MR: 0.83; 95% CI: 0.79-0.89; *P* < .001	Triplet = doublet ▪ MR: 1.00; 95% CI: 0.94-1.06; *P* = .97

Delbaldo C, et al. JAMA. 2004;292:470-484.

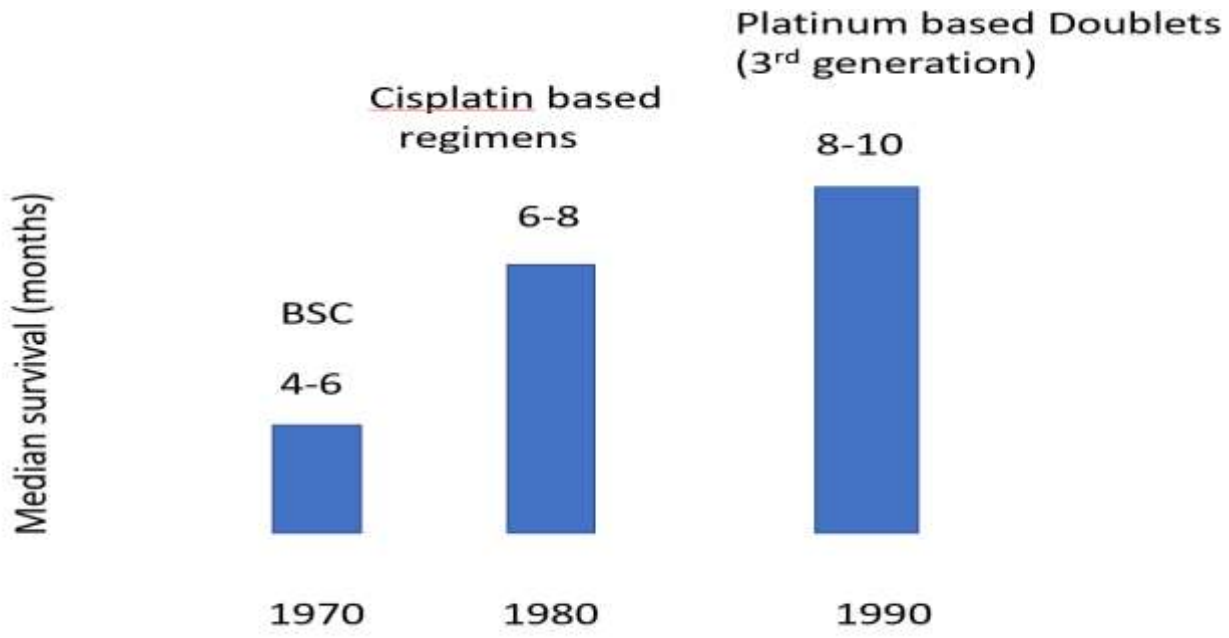
Central question in 1990's

- Are platinum based doublets with 3rd generation drugs superior?

- Middle 1990's Which of the new doublets are the best?

3rd generation agents.

Vinorelbine
Paclitaxel
Docetaxel
Gemcitabine



Mid-late 1990's - Advanced NSCLC

Central question in mid-late 90's

Which of the new doublets was the best ?

All of them have similar efficacy and safety

ECOG 1594

Coalition

ASCO guideline
NCCN guideline

<u>Dominant regimens in practice</u>

US

Carboplatin based regimens

EU

Cisplatin based regimens

ECOG 1594: Comparison of 4 First-line Doublet Regimens in Advanced NSCLC.

Advanced-stage, previously untreated NSCLC patients (N = 1207)

Reference Arm
Paclitaxel 135 mg/m^2 over 24 hrs on Day 1
Cisplatin 75 mg/m^2 on Day 2
3-wk cycle

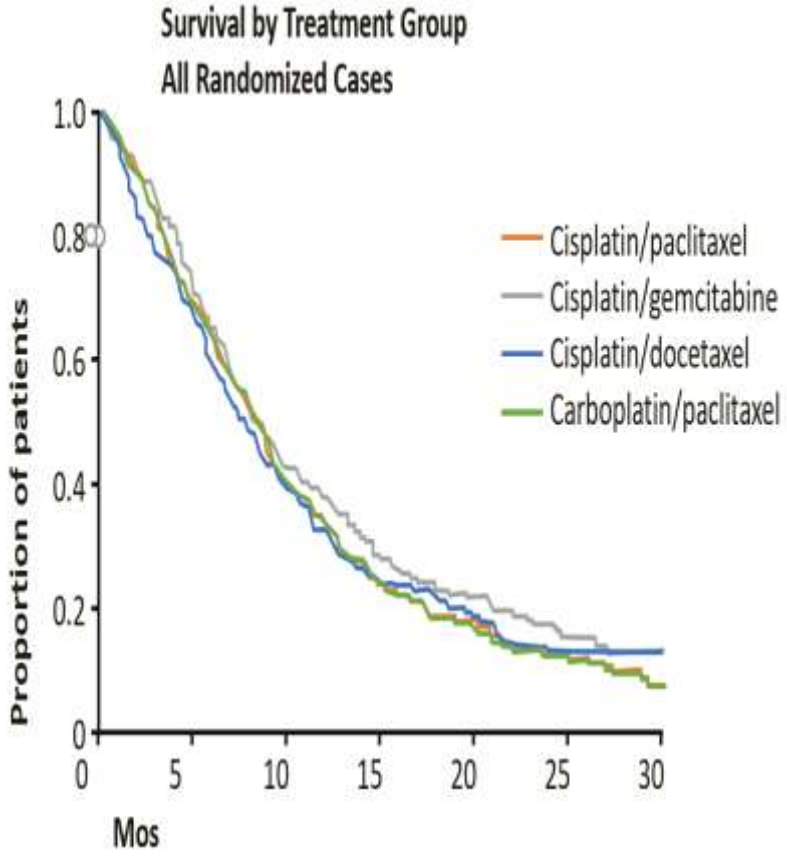
Gemcitabine 1000 mg/m^2 on Days 1, 8, 15
Cisplatin 100 mg/m^2 on Day 1
4-wk cycle

Docetaxel 75 mg/m^2 on Day 1
Cisplatin 75 mg/m^2 on Day 1
3-wk cycle

Paclitaxel 225 mg/m^2 over 3 hrs on Day 1
Carboplatin AUC 6.0 mg/mL/min on Day 1
3-wk cycle

Stratified by:

- ECOG PS (0/1 vs 2)
- Weight loss in previous 6 mos (< 5% vs ≥ 5%)
- Disease stage (IIIB vs IV or recurrent)
- Brain metastases (yes vs no)



Schiller JH, et al. N Engl J Med. 2002;346:92-98.

ANITA Schema: Randomized Phase III Trial of Adjuvant Chemotherapy

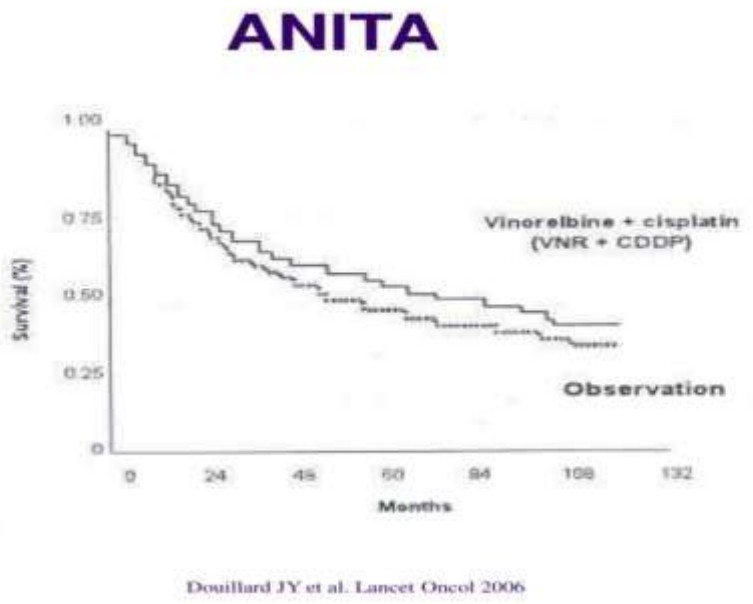
N=840
- Completely resected stage IB. II. Or IIIA NSCLC
- PS 0.1. or 2
- Age 18.75

R A N D O M I Z E

Vinorelbine 30 mg/m^2/week for 16 weeks + cisplatin 100 mg/m^2 on day 1 every 4 weeks for f cycles(n=407)

Observation (n=433)

Follow-up analysis



Douillard JY et al. Lancet Oncol 2006

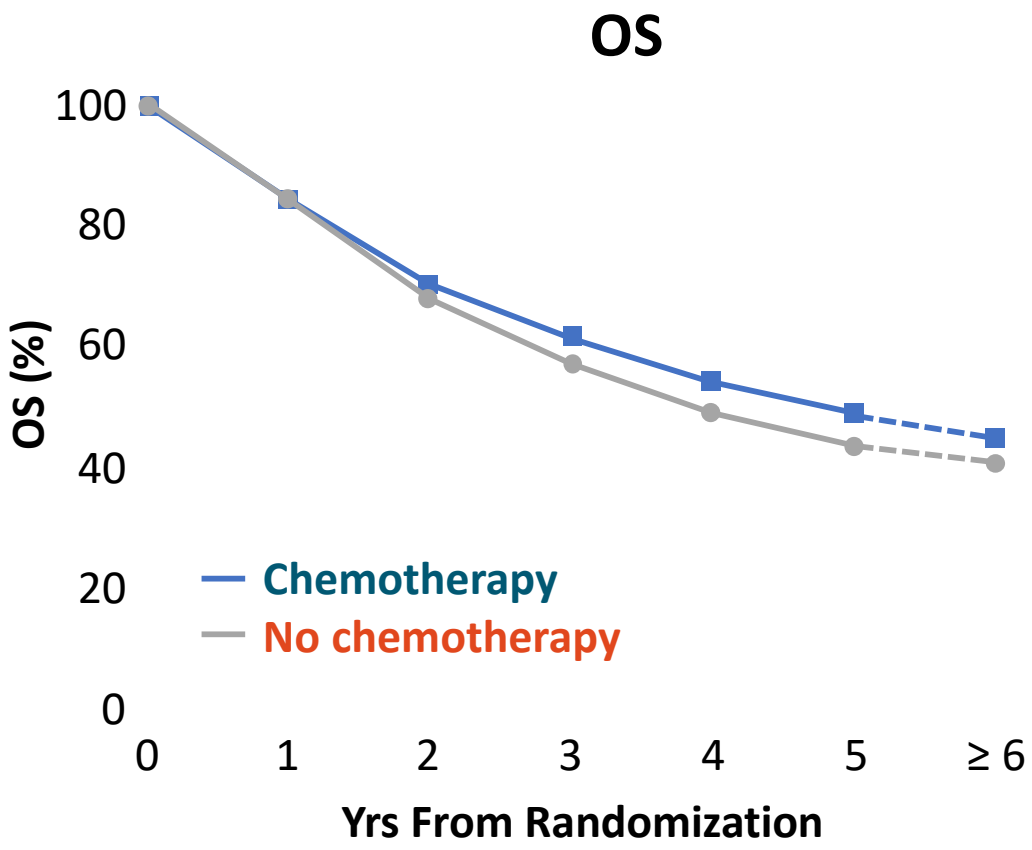
Efficacy of Adjuvant Chemotherapy vs Observation Alone

Outcome	Chemotherapy Group	Observation Group	Hazard Ratio (95%CI)	P-value
Median overall survival	65.8 months	43.8 months	0.79 (0.66-0.95)	0.013
7-year survival	45.2%	36.8%		

Douillard J. et al ASCO 2005. Abstract 7013

LACE Meta-Analysis: OS Benefit From Postoperative Cisplatin in Early-Stage NSCLC.

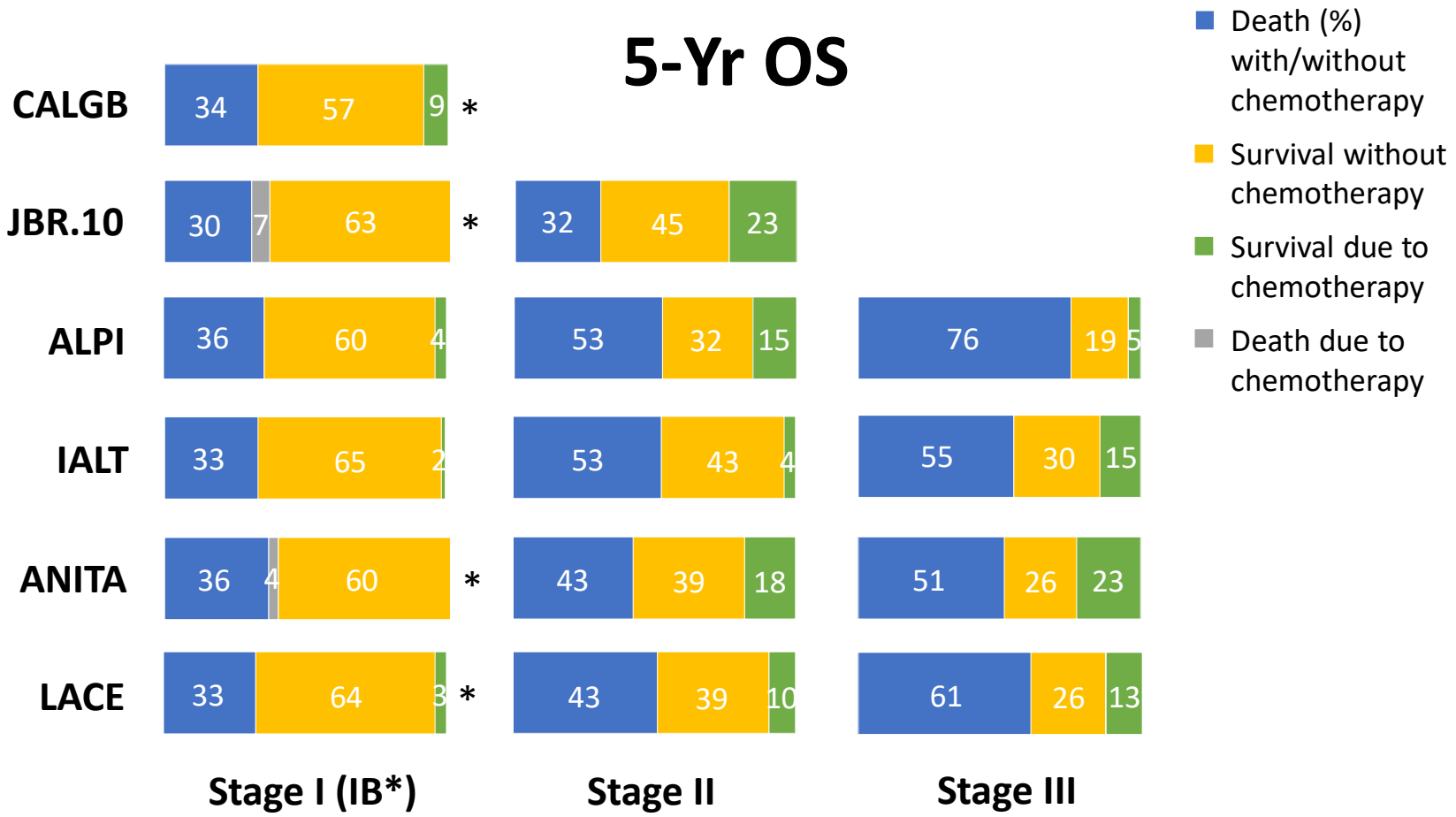
- Pooled analysis of 5 trials evaluating adjuvant cisplatin-based chemotherapy (N = 4584)
  - Cisplatin/vinorelbine most commonly used agent (only combination shown to prolong OS)
- Chemotherapy led to improved OS
  - HR: 0.89
  - Absolute benefit of 3.9% and 5.4% at 3 and 5 yrs, respectively.
  - No difference in chemotherapy regimens.
  - Benefit greater with stage II and III disease and with good performance status .
  - Also benefited elderly up to 80 yrs.



Pignon. JCO. 2016;26:3552.

Impact of Adjuvant Chemotherapy in Early-Stage NSCLC Depends on Stage.

- Retrospective analysis of estimated absolute risk/benefit for 100 patients treated with surgery and adjuvant CT based on reported, stage-specific 5-yr OS rates in the control arms of each clinical trial



*Trials that only included stage IB; ALPI and IALT included both IA and IB.

Kris. JCO. 2017;35:2960.

Adjuvant therapy adjuvant trials

Study	Treatment	5-year survival		p value
		Observation	Active treatment	
International Adjuvant Lung Trial (IALT)	Surgery ± platinum chemotherapy	40.4	44.5	<0.03
Cancer and Leukemia Group B (CALGB 9633)	Surgery ± carboplatin/paclitaxel	57	59	0.38
National Cancer Institute of Canada (NCIC JBR.10)	Surgery ± vinorelbine/cisplatin	54	69	0.03
Adjuvant Navelbine International Trialist Association (ANITA)	Surgery ± vinorelbine/cisplatin	43	51	0.013
Tegafur-uracil (UFT) meta-analysis	Surgery ± UFT	77	82	0.001
LACE meta-analysis	Surgery ± cisplatin-based chemotherapy	43.5	48.8	0.004

Late 1990's and 2000's - Advanced NSCLC

Central question in late 90's and 2000's

Does the addition of a third agent improve efficacy to a platin- based doublet?

Yes or NO

Targeted therapy

Target several new specific targets unique or largely unique to malignant cells

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKI)

Erlotinib
Gefitinib

Result: Negative
(TALENT, INTACT 1&2, TRIBUTE)

Vascular Endothelial Growth Factor (VEGF) Antibody
(Anti-angiogenesis agent)

Bevacizumab (Avastin)

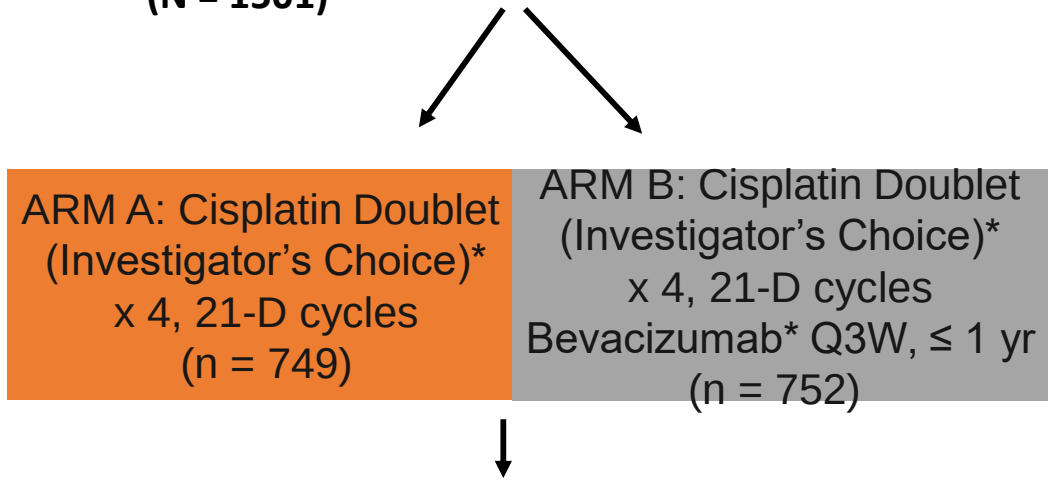
Result:
Positive (ECOG4599)

PFS advantage but no OS advantage (AVAIL)

E1505 Chemotherapy Subset Analysis in Early-Stage, Resected NSCLC

- Adjuvant cisplatin-based chemotherapy provides only modest OS benefit (~ 5%) in pts with early-stage, resected NSCLC[1]
- E4599: addition of bevacizumab to platinum-based chemotherapy improved outcomes in pts with advanced nonsquamous NSCLC[2]
- E1505: randomized phase III study evaluated bevacizumab plus cisplatin-based doublet chemotherapy in early stage resected NSCLC
  - Cisplatin partners: vinorelbine, docetaxel, gemcitabine, pemetrexed
  - Bevacizumab addition failed to improve OS (HR: 0.99; 95% CI: 0.82-1.19; *P* = .90) or DFS (HR: 0.99; 95% CI: 0.86-1.15; *P* = .95)[3]
  - Trial stopped early for futility
- Post hoc analysis of pooled E1505 outcomes data by chemotherapy subset reported here[4]

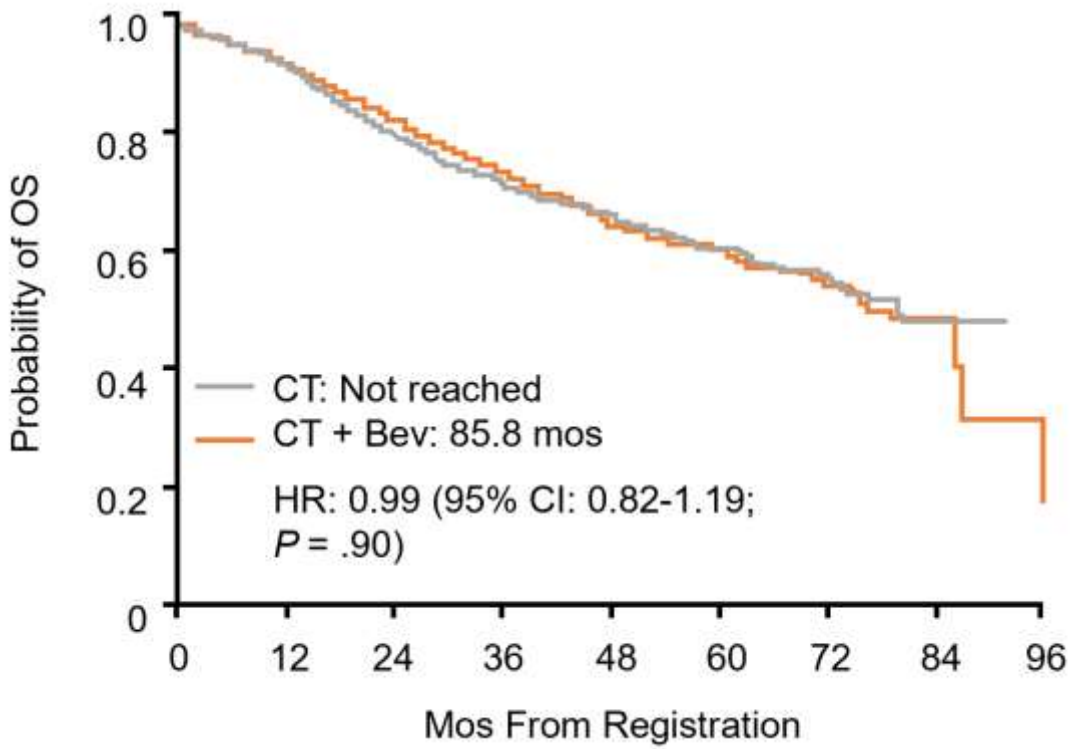
Stage IB to IIIA, resected NSCLC,
6-12 wks post-op, adequate nodal sampling,
no planned post-op RT,
acceptable organ function
(N = 1501)



Primary endpoint: OS
Secondary endpoint: DFS
Study powered for primary endpoint only not for the subset analyses

1. Pignon JP, et al. J Clin Oncol. 2008;26:3552-3559. 2. Sandler A, et al. N Engl J Med. 2006; 355:2542-2550. 3. Wakelee HA, et al. WCLC 2015. Abstract 1608. 4. Wakelee HA, et al. ASCO 2016. Abstract 8507.

Median OS by Bevacizumab Use



Median follow-up: 50.3 mos

Nonrandomized post hoc analysis performed with 475 OS events (ie, 70% of full information)
Data pooled across arms (± bevacizumab), divided by histology (nonsquamous vs squamous), and OS and DFS calculated for each chemotherapy group
Chemotherapy subsets: median follow-up, mos
- Cisplatin/vinorelbine: 54.3
- Cisplatin/docetaxel: 60.3
- Cisplatin/gemcitabine: 57.0
- Cisplatin/pemetrexed: 40.6

Wakelee HA, et al. ASCO 2016. Abstract 8507.

E1505: Overall and Chemotherapy Subset Analysis Pt Populations

***Age, race/ethnicity, other prognostic factors similar between chemotherapy groups.**

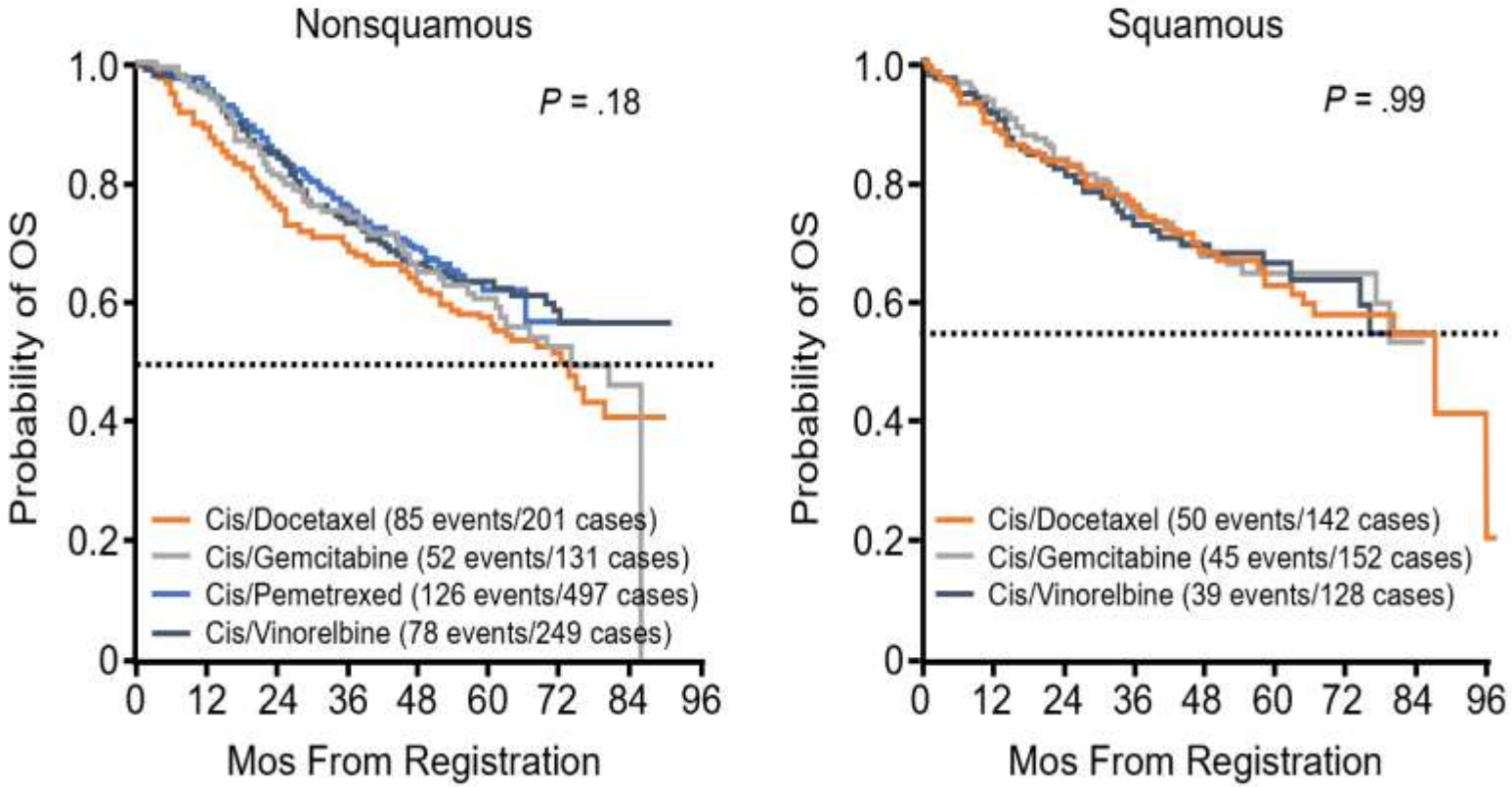
Characteristic	Overall (N = 1501)	Vinorelbine (n = 377)	Docetaxel (n = 343)	Gemcitabine (n = 283)	Pemetrexed (n = 497)
Median age, yrs (range)	61 (30-86)		NR*		
Race, %					
White	87		NR*		
Black	9				
Asian or other	4				
Male, %	50	48	55	55	44
Stage, %					
IB	26	23	26	28	28
II	44	47	40	51	40
IIIA	30	31	33	23	33
Histology, %					
Squamous	28	34	41	54	0
Adenocarcinoma	58	54	41	34	88
Large cell/other/mixed	14	12	18	12	12
Ever smoked, %	90	92	94	93	84

Grade ≥ 3 AEs, %	Squamous (n = 422)			Nonsquamous (n = 1078)			
	V (n = 127)	D (n = 140)	G (n = 149)	V (n = 241)	D (n = 199)	G (n = 132)	P (n = 485)
Anemia	12	3	15	12	3	7	4
Febrile neutropenia	**9**	6	1	**15**	7	2	0
Neutropenia	**54**	39	41	**58**	40	44	12
Thrombocytopenia	3	2	**23**	3	2	**12**	1
Fatigue	15	17	12	15	13	9	9
Diarrhea	6	9	1	5	10	2	1
Nausea	8	15	11	11	11	5	8
Vomiting	6	12	5	6	7	3	5
Dehydration	12	12	7	10	11	2	3
Hypertension	17	14	19	17	12	18	25
Thromboembolism	6	2	5	6	4	9	3
WORST DEGREE	85	80	82	83	74	83	**64**

Wakelee HA, et al. ASCO 2016. Abstract 8507.

Conclusions

- OS not significantly different between chemotherapy groups



- No differences found in OS or DFS by chemotherapy .
- Toxicity profiles of chemotherapy agents similar to known profile regardless of histology,
- Neutropenia/febrile neutropenia : vinorelbine
- Thrombocytopenia : frequently with gemcitabine
- Grade ≥ 3 toxicity lower in pemetrexed (nonsquamous) group than in other chemotherapy groups ($P < .001$)
- Bevacizumab had most severe grade ≥ 3 toxicity, including significantly increased neutropenia and hypertension

Indications for post operative Chemotherapy

According to stage :

- Stage IA : Postoperative chemotherapy not recommended .
- Stage IB : Postoperative chemotherapy recommended for high risk , margin negative disease .
- Stage II –IIIA : Post operative chemotherapy recommended .

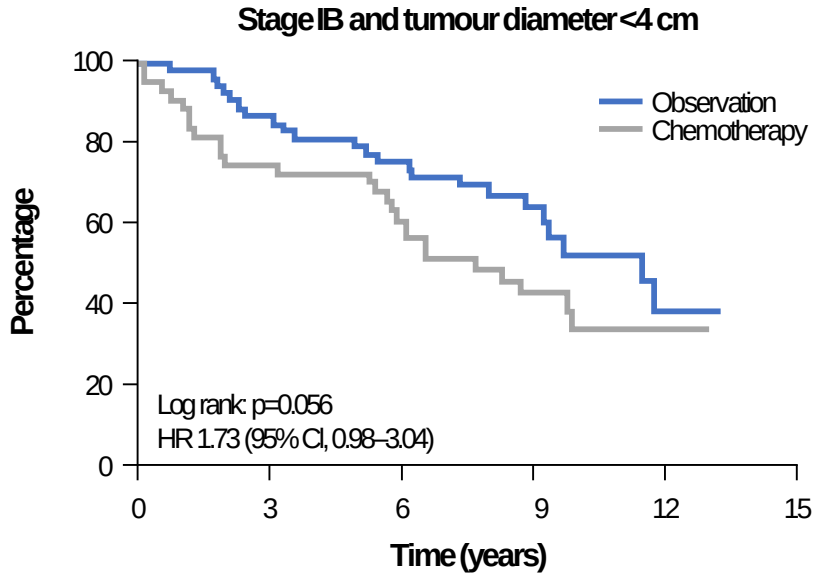
According to HPR

- pN+
- pT3-4
- +/- pT2a/b N0 if high risk features (> 4 cm tumour , high grade , LVSI , Visceral pleural involvement , or pNx.

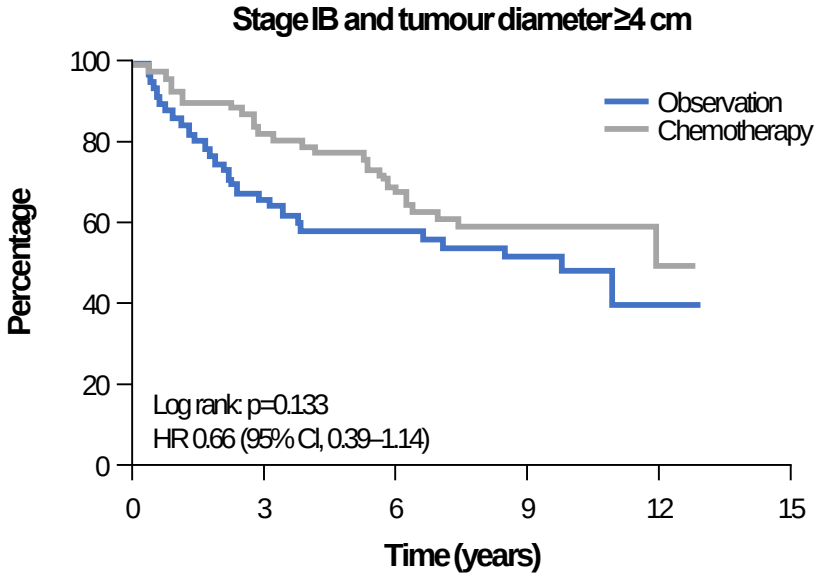
Conclusions : Adjuvant Chemotherapy in NSCLC

- Postoperative adjuvant cisplatin based chemotherapy now represents the standard of care for the management of stage II to IIIA NSCLC and improves survival.
- Doublet chemotherapy for 4-6 cycles is standard.
- Platinum combinations with vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan, and pemetrexed yield similar improvements in survival.
  - Caveat: Patients with adenocarcinoma may benefit from pemetrexed.
- Cisplatin and carboplatin yield similar improvements in outcome with different toxic effects.
- Non-platinum combinations offer no advantage to platinum-based chemotherapy, and some studies demonstrate inferiority.

Latest ESMO guidelines recommend that adjuvant chemotherapy can be considered in patients with resected Stage IB disease and a primary tumour >4 cm,[5] due to clear evidence of benefit[6]



No. at risk						
Observation	54	47	40	20	4	0
Chemotherapy	45	33	27	13	1	0



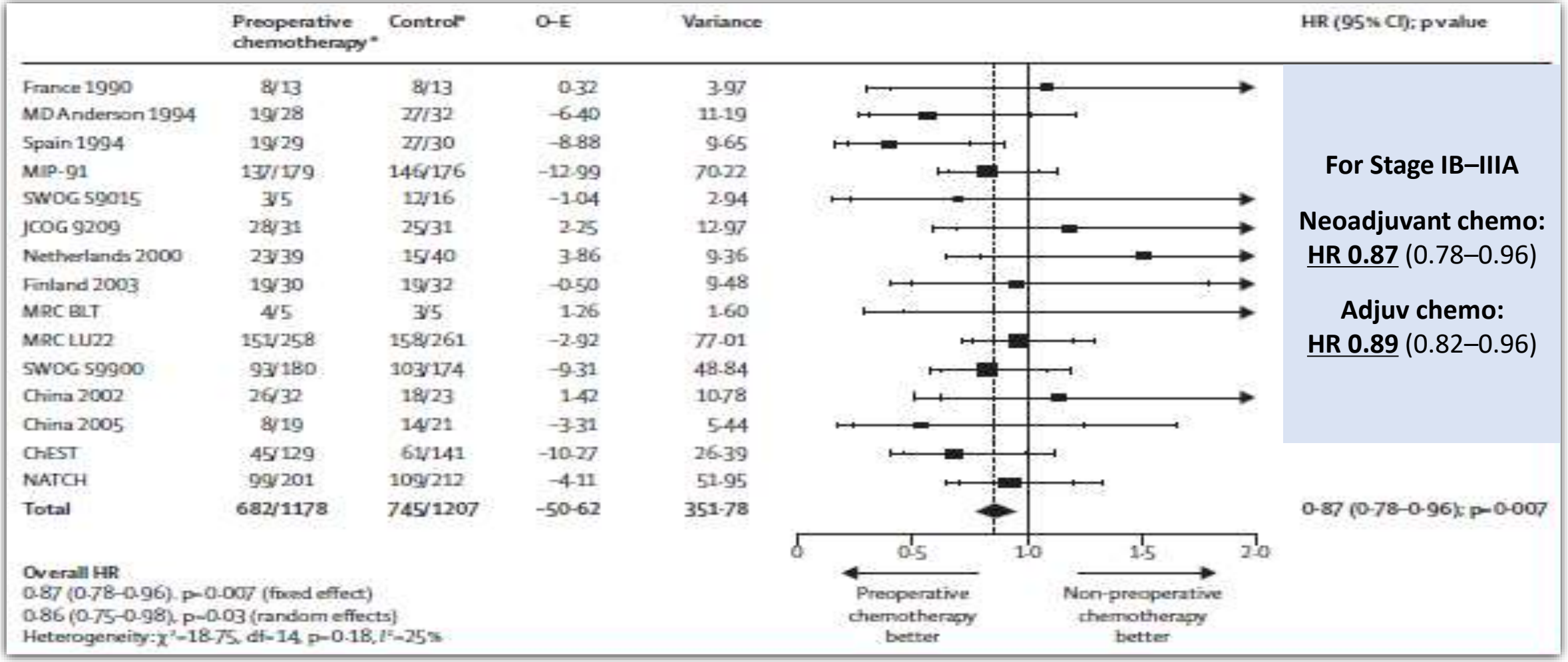
No. at risk						
Observation	54	36	29	20	1	0
Chemotherapy	66	54	43	23	5	0

However, since these guidelines were published,[5] Stage IB tumours >4 cm have been reclassified as Stage II in the 8th edition of TNM staging (2018). Therefore, adjuvant chemotherapy is now the standard of care for these patients

Adjuvant chemotherapy may remain an option for patients with Stage IB disease (8th edition of TNM staging) who are high risk due to factors other than tumour size

1. Kris MG, et al. *J Clin Oncol* 2017;35:2960–2974; 2. Winton T, et al. *N Engl J Med* 2005;352:2589–2597; 3. Pignon JP, et al. *J Clin Oncol* 2008;26:3552–3559; 4. NSCLC Meta-analyses Collaborative Group. *Lancet* 2010;375:1267–1277; 5. Postmus PE, et al. *Ann Oncol* 2017;28(Suppl 4):iv1–iv21; 6. Butts CA, et al. *J Clin Oncol* 2010;28:29–34

How well does neoadjuvant (induction) chemo work? About the same as adjuvant *Meta-analysis – efficacy*



Burdett et al, Lancet, 383:1561, 2014; Pignon et al, JCO, 26:3552, 2008

Neoadjuvant chemotherapy

Similar benefit
IB to IIIA
Absolute improvement
5% with neoadjuvant vs
5.3% with adjuvant.

- 15 randomised controlled trials : n=(2385 patients)
- Significant benefit of preoperative chemotherapy on survival
  (hazard ratio [HR] 0·87, 95% CI 0·78–0·96, p=0·007),
- 13% reduction in the relative risk of death
  (no evidence of a difference between trials; p=0·18, I^2=25%).
- Absolute survival improvement of 5% at 5 years, from 40% to 45%.

- No difference in the effect on survival by chemotherapy regimen or scheduling, number of drugs, platinum agent used, or whether postoperative radiotherapy was given.

- No clear evidence that particular types of patient defined by age, sex, performance status, histology, or clinical stage benefited more or less from preoperative chemotherapy.

- Recurrence-free survival (HR 0·85, 95% CI 0·76–0·94, p=0·002) and time to distant recurrence (0·69, 0·58–0·82, p

Burdett S et al IASLC 2011; Pignon J et al. *J Clin Oncol* 2008, 26:3552-3559.

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances
- Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[9]

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Neoadjuvant Systemic Therapy
- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for up to 3 cycles[10,*]
  - Platinum-doublet chemotherapy options include:
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - ◊ Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (non-squamous)
    - ◊ Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Adjuvant Systemic Therapy
- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

References

[*] Nivolumab in combination with platinum-doublet chemotherapy can be used for patients with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting. If an immune checkpoint inhibitor is used in the pre-operative setting, an immune checkpoint inhibitor should not be used in the adjuvant setting.

Current guidelines on neoadjuvant and adjuvant chemotherapy depend on disease stage and findings during surgery

Pathological stage	Recommended chemotherapy treatment[1,2]
Stage IA (N0, no lymph nodes)	Observation: no proven benefit of neoadjuvant or adjuvant chemotherapy
Stage IB / IIA (N0, no lymph nodes)	Multidisciplinary team discusses observation vs adjuvant chemotherapy for high-risk patients No proven benefit of neoadjuvant chemotherapy
Stage IIB (N0 / N1 lymph nodes)	Adjuvant chemotherapy recommended No proven benefit of neoadjuvant chemotherapy
Stage IIIA / IIIB (N1 / N2 lymph nodes)	Neoadjuvant chemotherapy **OR** Adjuvant chemotherapy **OR** Sequential chemotherapy + radiotherapy (N2 only)

1. Postmus PE, et al. *Ann Oncol* 2017;28(Suppl 4):iv1–iv21; 2. NCCN. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Version 3.2020. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed April 2020

Role of chemotherapy concurrently with radiation

- Unresectable stage IIIA or stage IIIB disease , chemoradiation is more efficacious than sequential chemoradiation.
- Higher rate of grade 3 or 4 esophagitis .

Concurrent with RT:

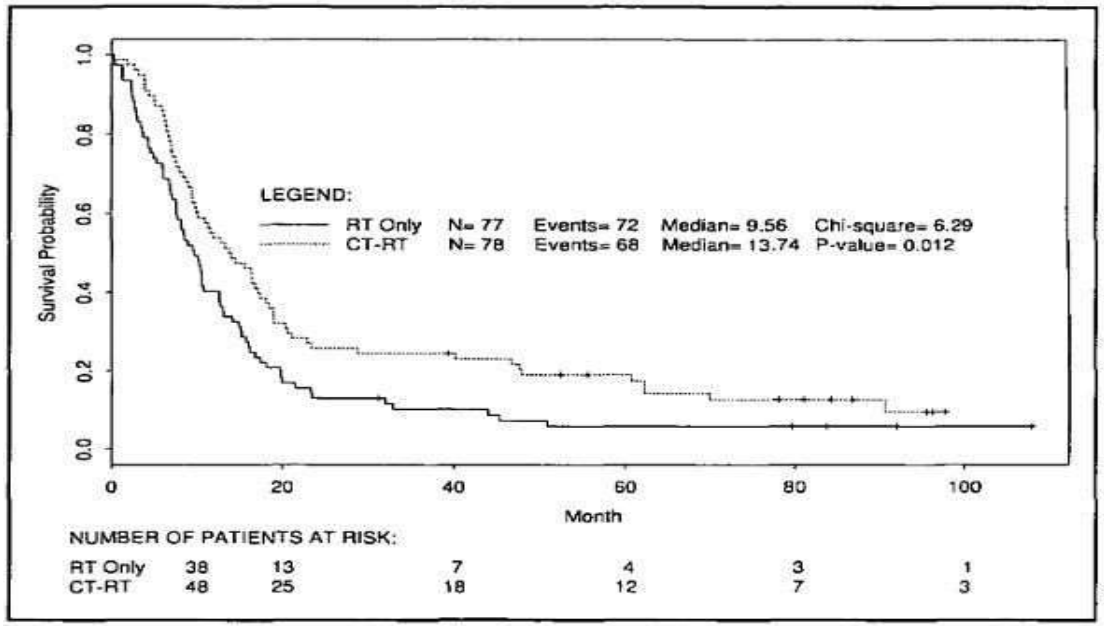
- Cisplatin + (etoposide, vinblastine or pemetrexed*)
- Carboplatin + paclitaxel (+/- 2 additional full-dose cycles)

Trial	Patients, *n*	Med. Survival, *mo*		% Survival, *y*		% Esophagitis (Gr. 3-4)	
		S	C	S	C	S	C
Furuse[15]	314	13.3	16.5	8	16(5)	4	23
RTOG-9410[16]	400	14.6	17.1	12	21(4)	5	26
GLOT[17]	212	13.9	15.6	24	35(2)	3	17
Czech[19]	102	13.2	20.6	15	42(2)	4	28
BROCAT[20]	303	14.0	19.0	—	—	0	26
LAMP[21]	178	13.8	17.4	31	33(2)	3	26

Chemo + RT vs. RT alone

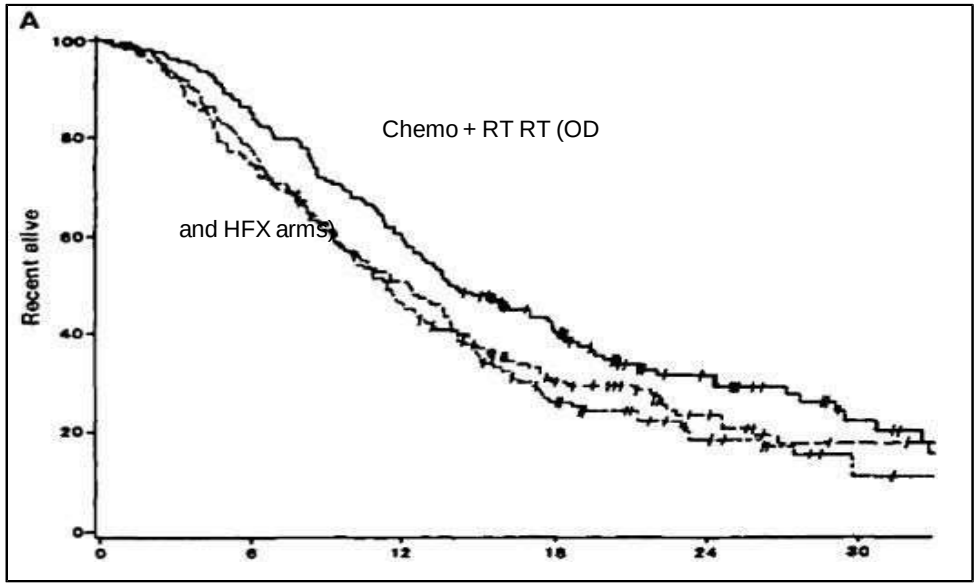
Improved Survival in Stage III Non-Small-Cell Lung Cancer: Seven-Year Follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial

*Robert O. Dillman, James Herndon, Stephen L. Seagren, Walter L. Eaton, Jr., Mark R. Green**



Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary Results of a Phase III Trial in Regionally Advanced, Unresectable Non–Small-Cell Lung Cancer

*William T. Sause, Charles Scott, Samuel Taylor, David Johnson, Robert Livingston, Ritsuko Komaki, Bahman Emami, Walter J. Curran, Roger W. Byhardt, Andrew T. Turrisi, A. Rashid Dar, James D. Cox**



JNCI 1995 and 1996
Chest 2000

Chemo: Concurrent vs. Sequential

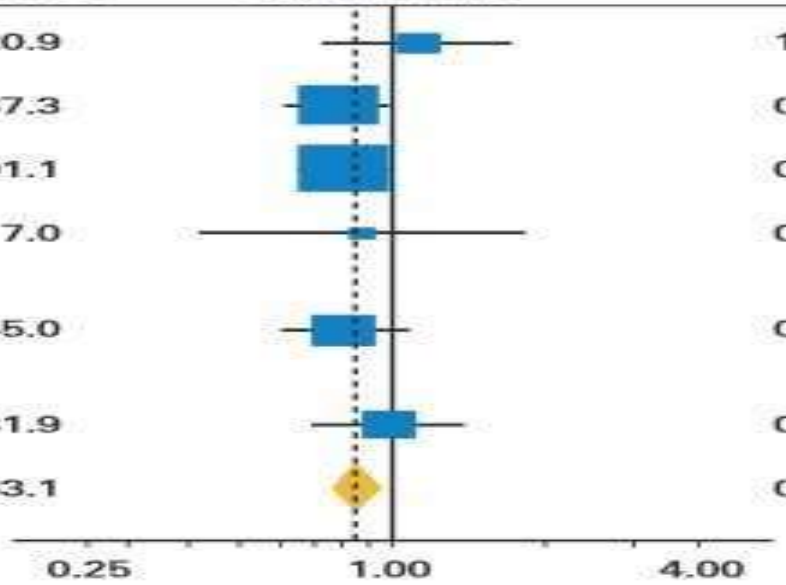
Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

A

Trial	No. Deaths / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	Hazard Ratio	HR (95% CI)
CALGB 8831	45/46	39/45	2.4	20.9		1.12 (0.73 to 1.72)
WJLCG	131/156	142/158	-16.8	67.3		0.78 (0.61 to 0.99)
RTOG 9410	180/204	189/203	-20.5	91.1		0.80 (0.65 to 0.98)
GMMA Ankara 95	15/15	15/15	-1.0	7.0		0.87 (0.41 to 1.82)
GLOT-GFPC NPC	87/102	96/103	-9.9	45.0		0.80 (0.60 to 1.07)
EORTC 08972	63/80	66/78	-0.5	31.9		0.98 (0.69 to 1.39)
Total	521/603	547/602	-46.4	263.1		0.84 (0.74 to 0.95)

Test for heterogeneity:
$\chi^2_6 = 3.24$, $P = .66$, $I^2 = 0\%$



RT + conc CT effect: Log-rank test = 8.19, $P = .004$

Auperin, JCO 2012

CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)

- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,*,†,‡]
- Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,*,†,‡] ± additional 4 cycles of pemetrexed 500 mg/m^2[†,§]
- Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[4,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Preferred (squamous)

- Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[6,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After Definitive Concurrent Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8]
(category 1 for stage III; category 2A for stage II)

Role of chemotherapy in metastatic setting

N=**2714**
16 RCT's
Supportive care and chemotherapy (1399)
Supportive care alone (1315)
Benefit of chemotherapy (HR=0.77;95%CI 0.71to 0.83, **P<0.0001**)
Relative increase in survival of 23% , absolute improvement in survival 9% at 12 months

…….people with advanced NSCLC that had chemotherapy and best supportive care lived longer than those who had best supportive care.
After 12 months, 29 out of every 100 who were given chemotherapy and best supportive care were alive compared to 20 out of every 100 who just had best supportive care.

This meta-analysis of chemotherapy in the supportive care setting demonstrates that chemotherapy improves overall survival in all patients with advanced NSCLC. Patients who are fit enough and wish to receive it should be offered chemotherapy.

Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer (Review) 2012 .The Cochrane Collaboration. Cochrane Database of Systematic Reviews

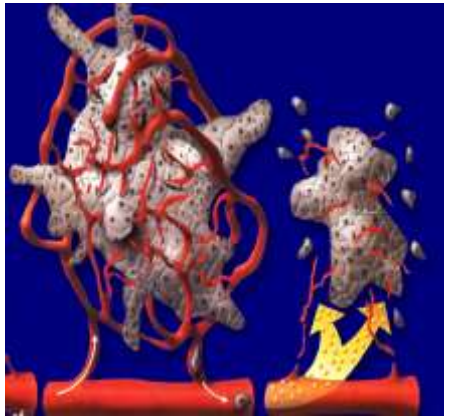
Pointbreak Trial

Carboplatin /pemetrexed/ bevacizumab

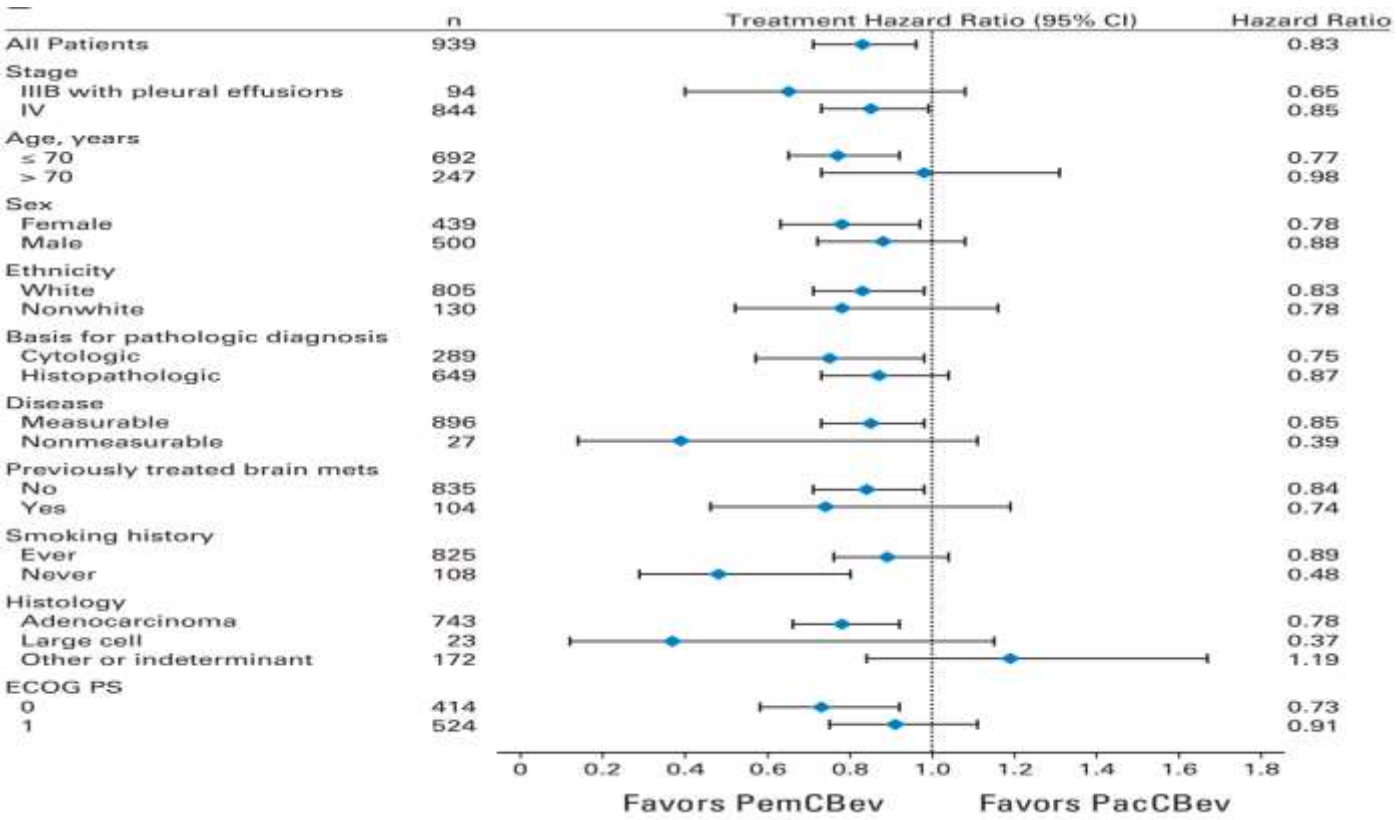
pemetrexed/ bevacizumab

Carboplatin /Paclitaxel/ bevacizumab

bevacizumab



	PemCBev (472)	PacCBev (467)
MS	12.6 mths	13.4 mths; P .949;
PFS	6.0 mths	5.6 mths; P .012;
ORR	34.1%	33.0%;
DCR	65.9%	69.8%.
G 3 /4 anemia	14.5%	2.7%,
Thrombocytopenia	23.3%	5.6%
fatigue	10.9%	5.0%
G3 /4 neutropenia	25.8%	40.6%
febrile neutropenia	1.4%	4.1% ,
sensory neuropathy	0%	4.1%
alopecia G1 /2;	6.6%	36.8%



NSCLC

E4599

- Advanced NSCLC (stage IIIB or IV)- non- squamous
  - Randomised to paclitaxel/ carboplatin or paclitaxel/carboplatin + bevacizumab
  - Excluded brain mets and haemoptysis

	Median PFS	Median OS	RR	Significant Bleeding
PC	4.5	10.3	15%	0.7%
PCB	6.2	12.3	35%	4.4%
P-value	< 0.001	0.003	< 0.001	< 0.001

AVAiL

- Advanced NSCLC (stage IIIB or IV)- non- squamous
  - Randomised to cisplatin/gemcitabine + placebo/low dose bevacizumab/ high dose bevacizumab
  - Excluded brain mets and haemoptysis
  - Confirmed outcome with less spectacular results

Reck M, et al. J Clin Oncol. 2009;27:1227-1234..

Sandler A, et al. N Engl J Med. 2006;355:2542-2550.

Minor advances with standard therapy

	Arm	ORR	OS
CALGB 9730[1]	P	17%	6.7 Mo
	PCb	30%	8.8 Mo
ECOG 1594[2]	PC	21%	7.8 Mo
	GC	22%	8.1 Mo
	DC	17%	7.4 Mo
	PCb	17%	8.1 Mo
ECOG 4599[3*]	PCb	15%	10.3 Mo
	Bevacizumab/ PCb	35%	12.3 Mo

***Nonsquamous NSCLC**

C = cisplatin; Cb = carboplatin
D = docetaxel; G = gemcitabine
P = paclitaxel

1. Lilenbaum et al., *J Clin Oncol* 2005; 23:190-196

2. Schiller et al., *New Engl J Med* 2002; 346:92-98

3. Sandler et al., *New Engl J Med* 2006; 355:2542-2550

Conclusions : Chemotherapy in Metastatic NSCLC

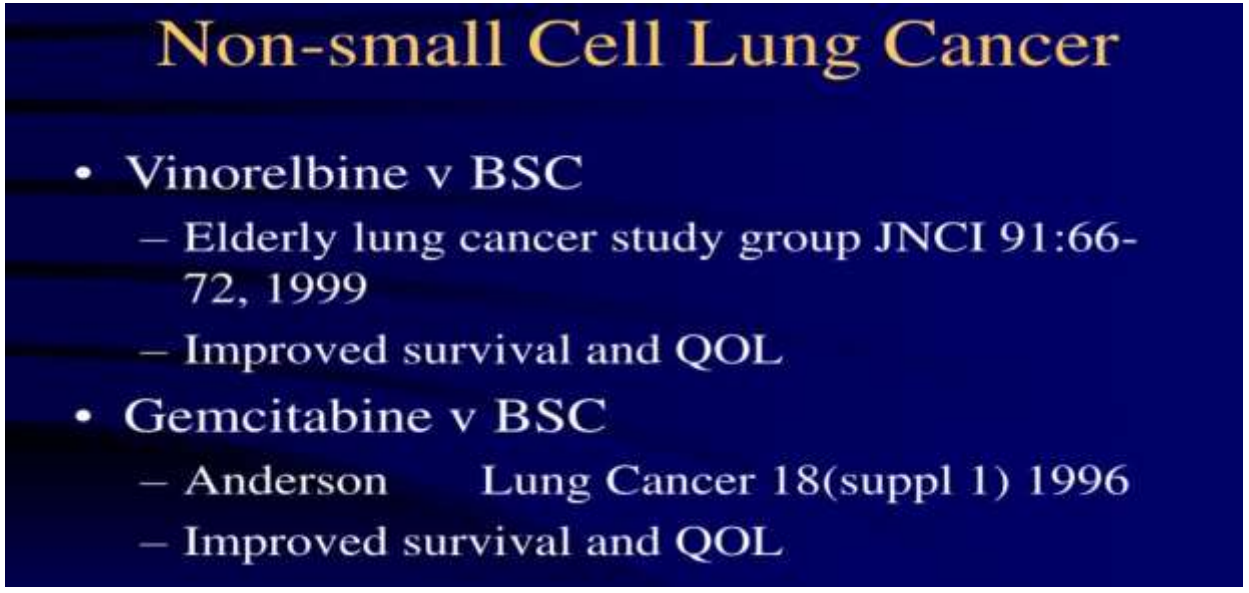
Patients with metastatic stage IV NSCLC who have a good PS benefit from chemotherapy ,usually with a platinum –based regimen, which was the only treatment option for many years before the advent of targeted therapy or immunotherapy regimens .

If patients are not eligible for the targeted therapy or immunotherapy , then chemotherapy is indicated.

Combination chemotherapy regimens produce 1 year survival rates of 30%to 40% and are more efficacious than single agents.

Chemotherapy for advanced NSCLC in the elderly population (Review)

- 51 trials :
- Non-platinum single-agent versus non-platinum combination therapy :similar effects on overall survival(hazardratio (HR) 0.92, 95%confidence interval (CI) 0.72 to 1.17; participants = 1062; five RCTs),



Platinum combination :
Improves OS (HR 0.76, 95% CI 0.69 to 0.85; participants = 1705; 13 RCTs; 1yOS (RR 0.89, 95% CI 0.82 to 0.96; participants = 813; 13 RCTs;

Improves ORR (RR 1.57, 95% CI 1.32 to 1.85; participants = 1432; 11 RCTs; compared with non-platinum therapies.

Platinum combination therapy may also improve PFS.

Small Cell Lung Cancer

- <15% of all lung cancer, poor prognosis.
- AJCC Staging is preferred (same as NSCLC staging)
  - Limited stage is M0 and extensive stage is M1
  - 66% of patients present with Stage IV (extensive stage)

- Cisplatin (or carboplatin) + etoposide for 4-6 cycles is the backbone of treatment regardless of stage.
  - 70-90% response rate.
  - Initially chemosensitive, but often develops drug resistance.

Median survival in ES-SCLC with various treatments

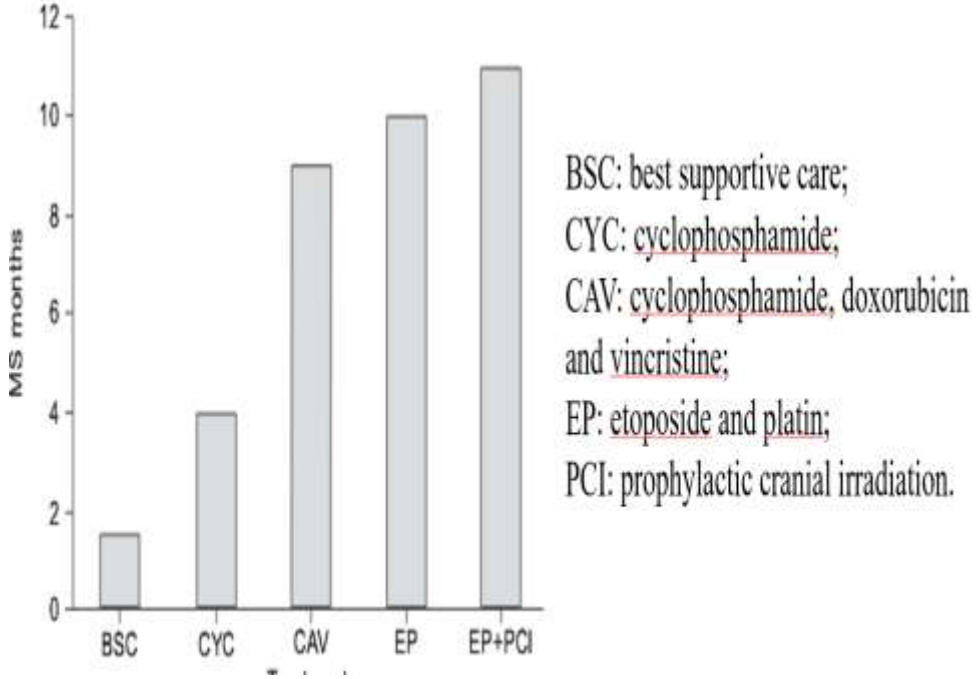


TABLE 42.1

Randomized Clinical Trials Comparing Etoposide and Cisplatin to Other Chemotherapy Regimens

Study (Ref.)	Stage	Treatment Arm	No. of Patients	Overall Response Rate (%)	Median Survival (months)	1-Year Survival (%)	2-Year Survival (%)
Fukuoka, et al.[99]	Limited and extensive	EP CAV CAV/EP alternating	97 97 94	78 55 76	9.9 9.9 11.8 ($p = 0.056$)	NR NR NR	12 10 21
Roth, et al.[100]	Extensive	EP CAV CAV/EP alternating	159 156 162	61 51 59	8.6 8.3 8.1	NR NR NR	NR NR NR
Sundstrom, et al.[101]	Limited and extensive	EP Cyclophosphate, epirubicin, vincristine	218 218	NR NR	10.2 ($p = 0.0004$) 7.8	NR NR	14 6
Skarlos, et al.[105]	Limited and extensive	EP Etoposide/carboplatin	71 72	69 78	12.5 11.8	NR NR	NR NR
Noda, et al.[108]	Extensive	EP Irinotecan/cisplatin	77 77	52 65	9.4 12.8 ($p = 0.002$)	58 38	20 5
Hanna, et al.[425]	Extensive	EP Irinotecan/cisplatin	110 221	44 48	10.2 9.3	35 35	8 8
Lara, et al.[109]	Extensive	EP Irinotecan/cisplatin	327 324	57 60	9.1 9.9	34 41	NR NR
Eckardt, et al.[115]	Extensive	EP Oral topotecan/cisplatin	395 389	69 63	9.4 9.2	31 31	NR NR
Miyamoto, et al.[130]	Limited and extensive	EP Ifosfamide with EP	45 47	78 74	12.8 13.0	53 62	15 17
Loehrer, et al.[131]	Extensive	EP Ifosfamide with EP	84 87	67 73	7.3 9.1 ($p = 0.045$)	27 36	5 13
Mavroudis, et al.[135]	Limited and extensive	EP Paclitaxel with EP	71 62	48 50	10.5 9.5	37 38	NR NR
Niell, et al.[136]	Extensive	EP Paclitaxel with EP	282 283	68 75	9.9 10.6	37 38	8 11

EP, etoposide and cisplatin; CAV, cyclophosphamide, doxorubicin, and vincristine; NR, not reported.

Evolution and evidence of targeted therapy for lung cancer.

A SPECIAL REPORT ▼ PERSONAL HEALTH

PERSONAL JOURNAL.

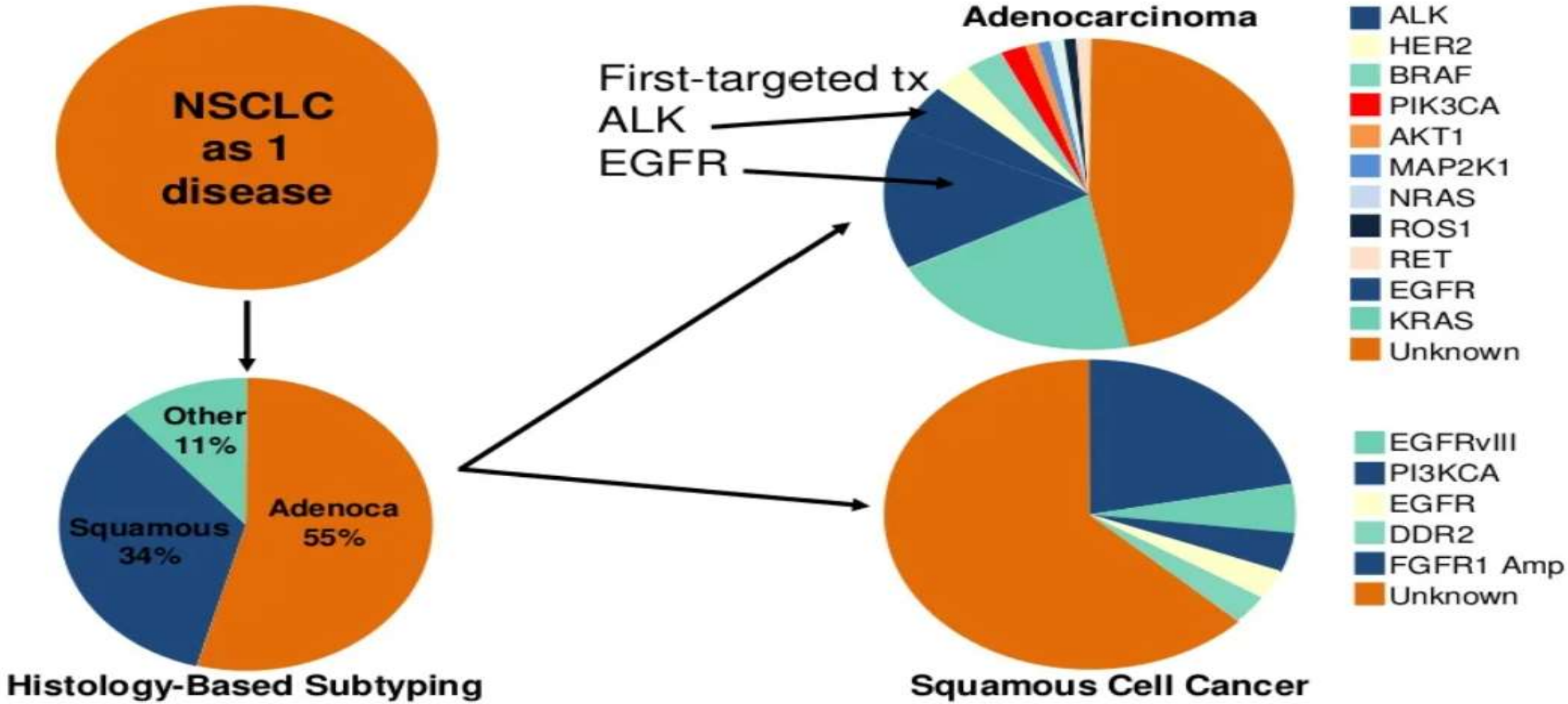
THE WALL STREET JOURNAL.

Why *Curing* Your Cancer May Not Be the Best Idea

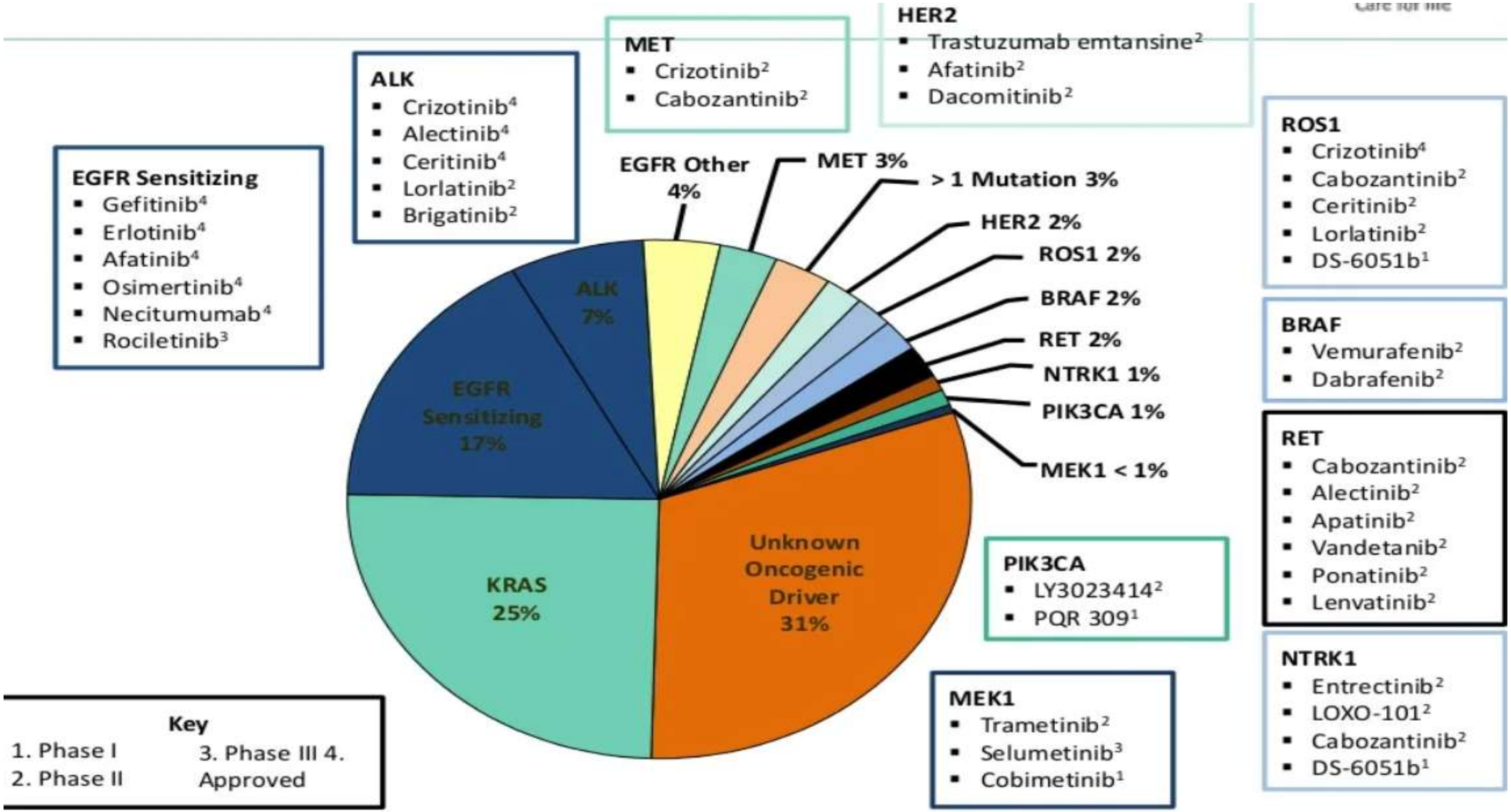
More doctors and patients are starting to view cancer as a chronic illness — something to be treated, not cured

Tara Parker-Pope Wall Street Journal 2003

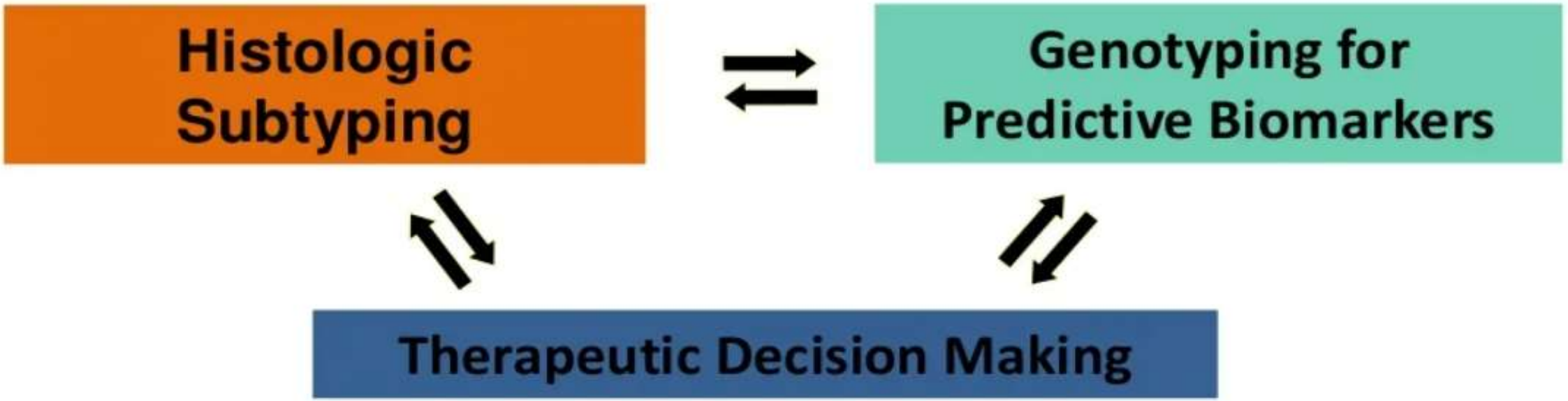
NSCLC Evolution from Single disease to many molecular defined subsets.



Targeted therapy for Lung Cancer

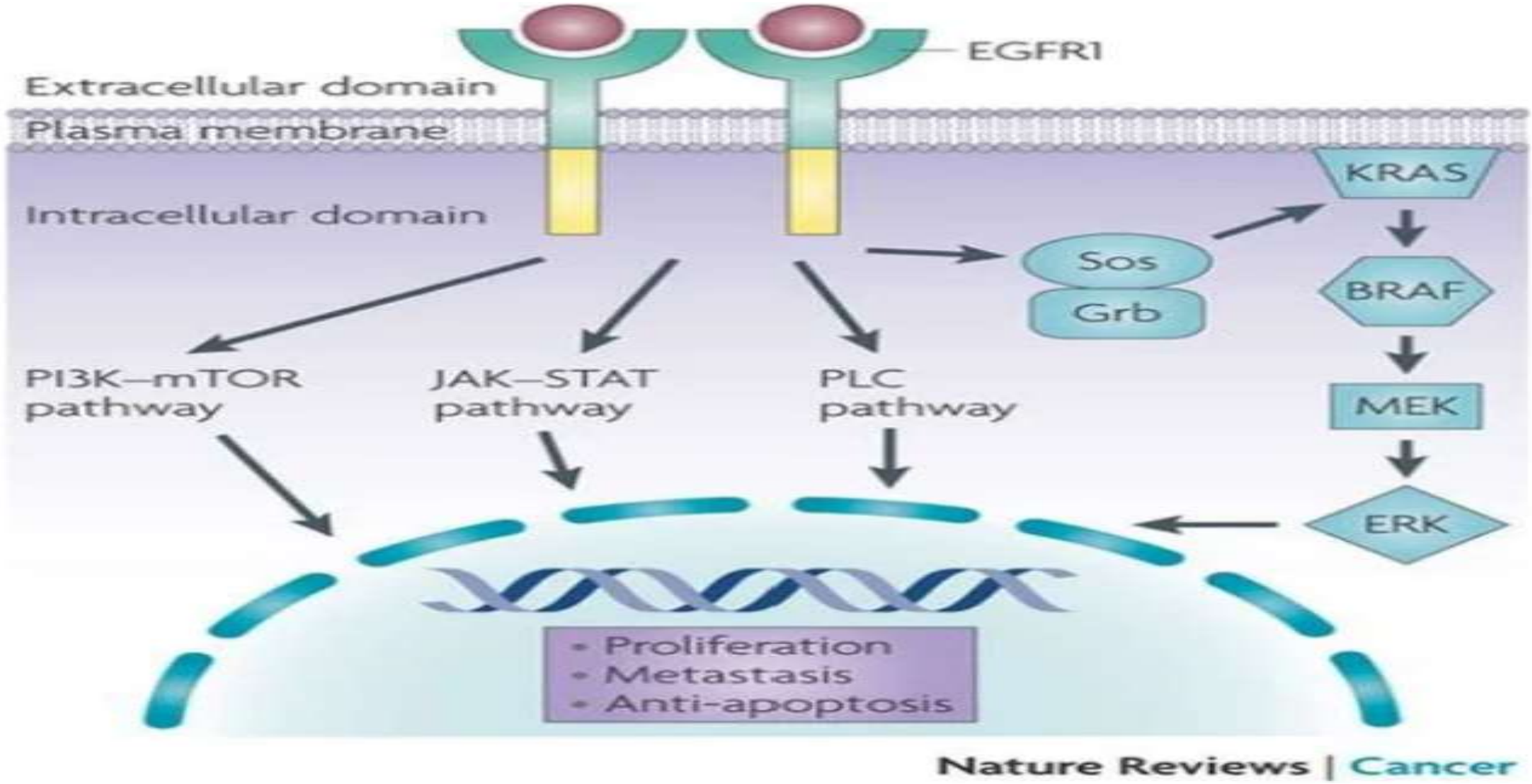


Interlinking Themes in Therapeutic decision making for Advanced NSCLC.

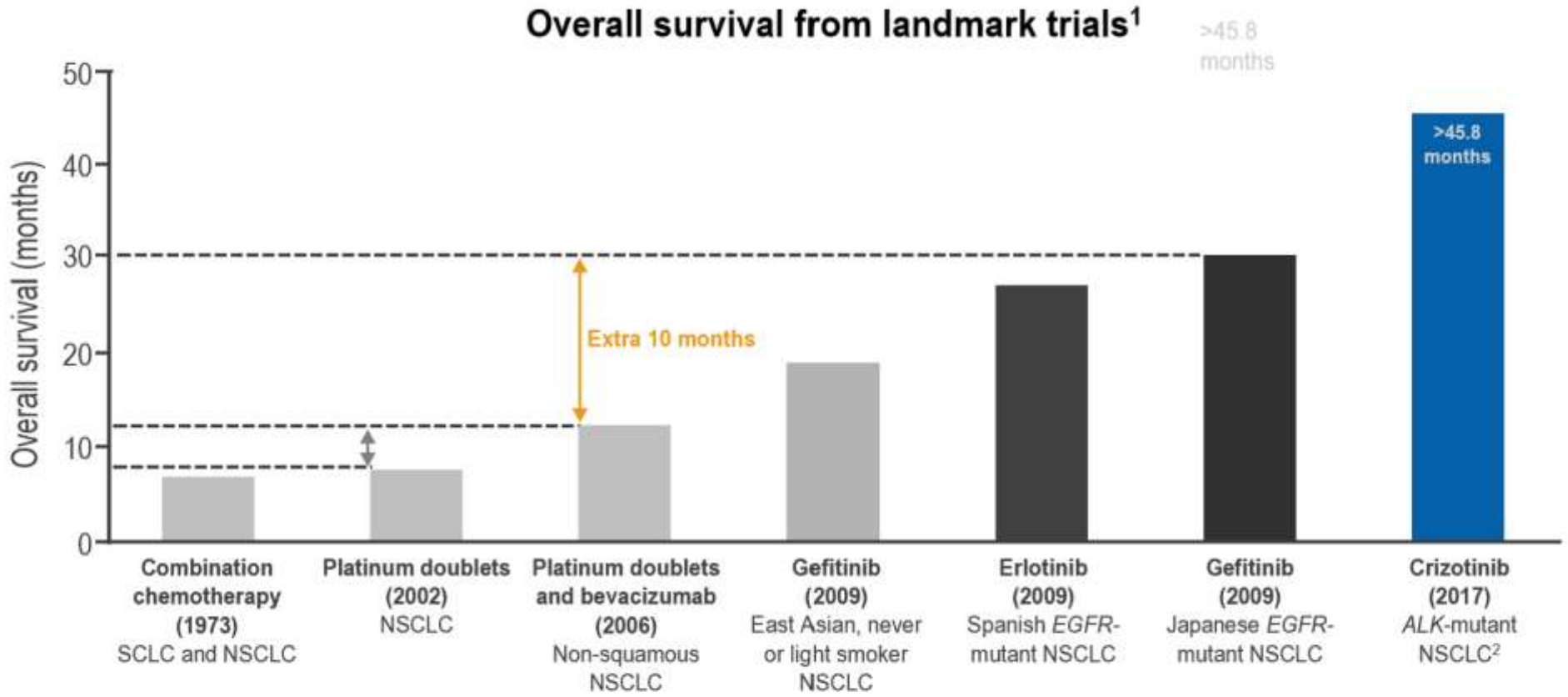


These factors are interlinked and not independent

Major Challenge : Identifying driver mutations



Targeted Therapy can modify the natural history of NSCLC.

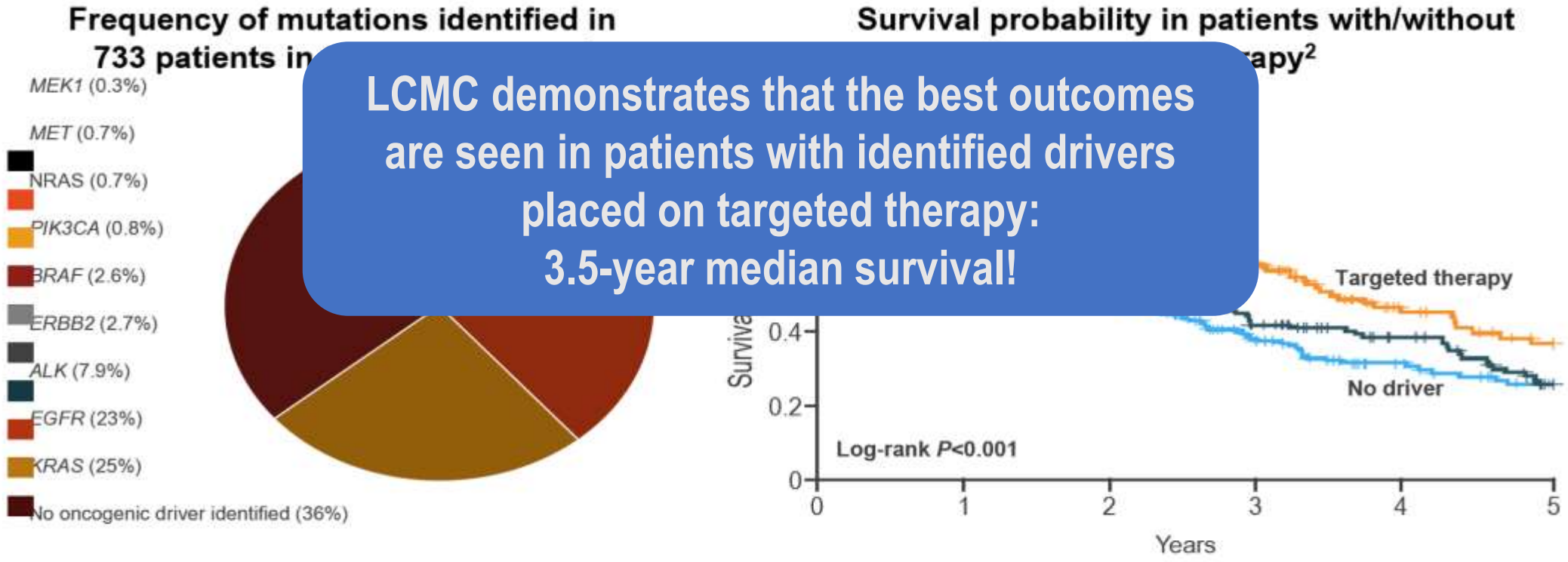


1. Adapted from Pao W & Chmielecki J. *Nat Rev Cancer* 2010;10:760–774;
2. Mok T *et al.* Presented at ESMO 2017:LBA50

SCLC, small-cell lung cancer

Survival of patients with drivers in lung cancer mutational consortium.

Targeted vs No Targeted Therapy



1. Sholl L *et al. J Thorac Oncol* 2015;10:768–777
2. Kris MG *et al. JAMA* 2014;311:1998–2006

LCMC, Lung Cancer Mutational Consortium

Tissue Sampling is key to maximize the chance of detecting underlying molecular aberrations.

Recommendations

- Pre-procedural discussion at multidisciplinary lung tumor board (surgeon, radiologist, respiratory physician) to maximize yield
- Pathologist should determine adequacy of the specimen for molecular testing[2]
- Prioritization of tissue for testing of actionable oncogenes including *ALK* and *EGFR*[2]
- Procedures for quality control and proficiency testing[3]

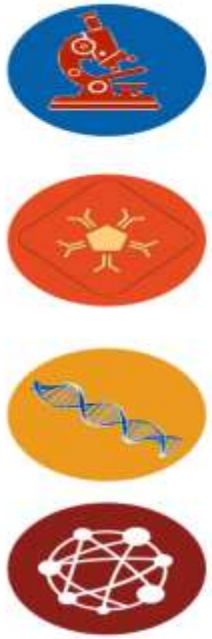
Challenges

- Biopsies may not be sufficient for mutation analysis due to low tumor content and a mixture with non-neoplastic cells[3]
- Diagnosis based on morphological criteria may not be possible with need of IHC to subtype NSCLC[1]
- Differing tissue fixatives, processing protocols and storage conditions can affect the quality of the sample[2]

1. Hiley CT *et al. Lancet* 2016;388:1002–1011; 2. Lindeman NI *et al. Arch Pathol Lab Med* 2013;137:828–860; 3. Warth A *et al. Virchows Arch* 2012;460:407–414

IHC, immunohistochemistry

A number of molecular technologies are available



FLOURESCENCE *IN SITU* HYBRIDIZATION (FISH)[1,6]
Fluorescent probes label specific gene regions causing them to fluoresce on microscopy

IMMUNOHISTOCHEMISTRY (IHC)[2,6]
Antibodies detect specific proteins expressed by cells; a chemical reaction generates a colored deposit for cells expressing the antibody, identified using microscopy

AMPLIFICATION AND SEQUENCING TECHNIQUES[3,6]

REAL TIME PCR

RT-PCR (Reverse transcriptase-polymerase chain reaction)
Target RNA is reverse transcribed to DNA amplified by PCR

NEXT-GENERATION SEQUENCING (NGS)[4,6]

Using micro- and nano-technology to run parallel

sequencing

General challenges and barriers:[5]

- Cost
- Uncertainty in the best method
- Lack of clear guidelines
- Limitations in testing accuracy
- Specialized training needed
- Highly specialist equipment requirements
- Practical limitations such as insufficient tissue

1. Vincent MD *et al. Curr Oncol* 2012;19:S33–S44; 2. Ramos-Vara JA. *Vet Pathol* 2005;42:405–426; 3. Peake I. *J Clin Pathol* 1989;42:673–676;
4. Grada A & Weinbrecht K. *J Invest Dermatol* 2013;133:e11; 5. Kerr KM. *J Thorac Oncol* 2014;9:593–595
6. Tsao MS *et al* (eds). IASLC Atlas of ALK Testing in Lung Cancer 2013. https://www.iaslc.org/publications/iaslc-atlas-alk-testing-lung-cancer. Accessed May 28, 2014

Status of liquid biopsy

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

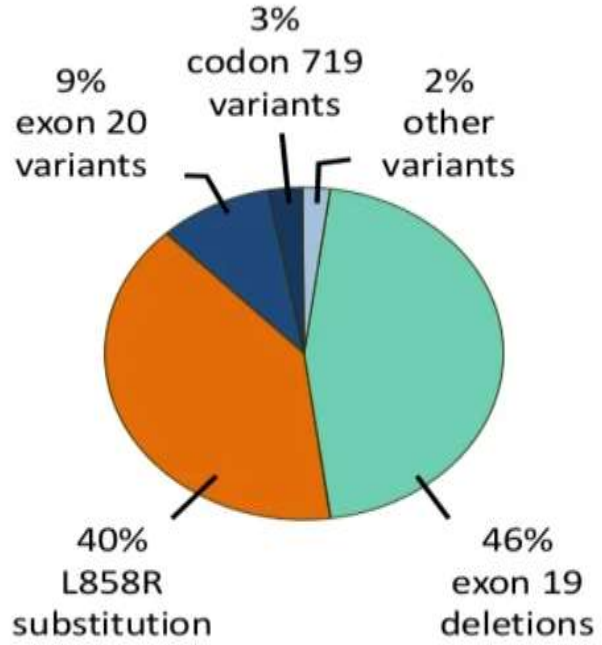
16. Recommendation.—In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify *EGFR* mutations.

Treatment based on EGFR Mutation context.

- Found in approximately 10-30% of patients with NSCLC.
- More common in never smokers , adenocarcinomas , females , Asians .
- Associated with response to first , second and third generation TKI's.
- Predominantly located in EGFR exons 18-21.

  85%of EGFR mutations are either deletions in exon 19 or a single –point mutation in exon 21 (L858R)
- The specific EGFR mutation identified is important.

  There are sensitive mutations , primary resistance mutations (often exon 20) , and acquired resistance mutations (T790)



Stewart EL, et al. Transl Lung Cancer Res. 2015;4:67-81.
Chan BA, et al. Transl Lung Cancer Res. 2015;4:36-54.

IPASS: First-line Gefitinib vs Paclitaxel/ Carboplatin in Stage IIIB/IV NSCLC

- Open-label phase III trial

Up to six 3-wk cycles

Previously untreated pts with stage IIIB/IV NSCLC, adenocarcinoma, never or ex-light smokers, WHO PS 0-2 (N = 1217)

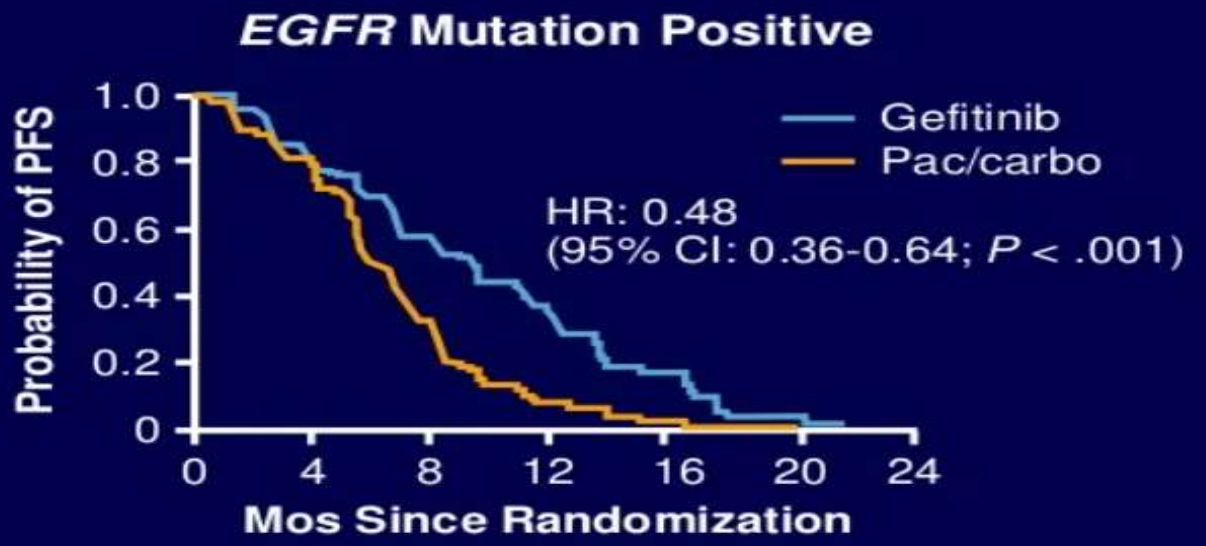
Status	Treatment	PFS	OS
EGFR +	Gefitinib	9.5 (HR 0.48)	22
EGFR+	Carboplatin/Paclitaxel	6.3	22
EGFR -	Gefinitib	1.5 (HR 2.85)	11.2
EGFR -	Carboplatin/ Paclitasel	6.5	12.7

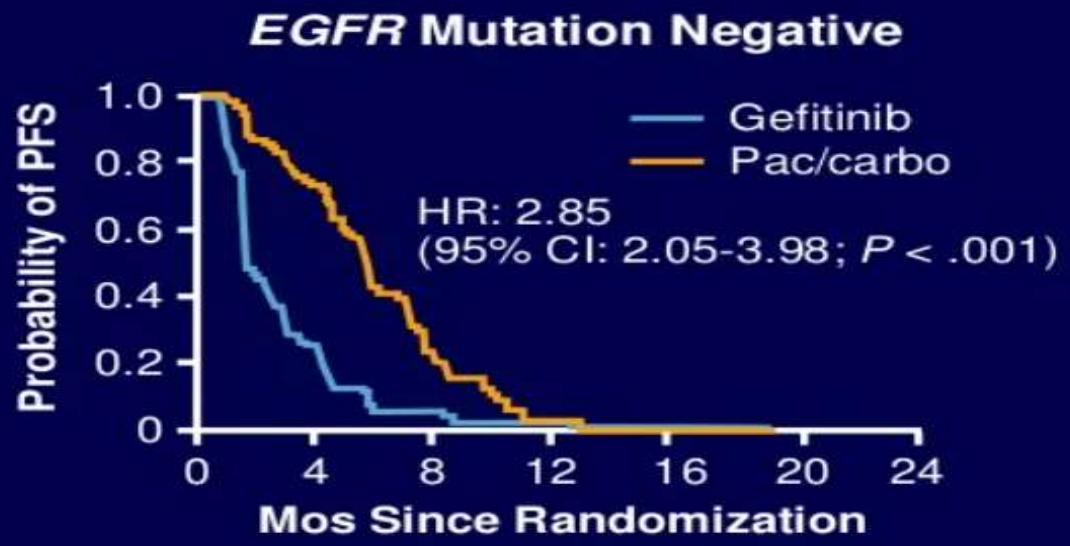
- Primary endpoint: PF
- Secondary endpoints reduction, safety
- Study conducted in Asian countries

Mok TS, et al. N Engl J Med. 2009;361:247-257.

Gefitinib vs Paclitaxel/Carboplatin in Advanced NSCLC: PFS by EGFR Status

- PFS: gefitinib superior to carboplatin/paclitaxel in ITT population
  - HR for progression/death: 0.74 (95% CI: 0.65-0.85; $P < .001$)
- ***EGFR* mutations** strongly predicted PFS (and tumor response) to first-line gefitinib vs carboplatin/paclitaxel

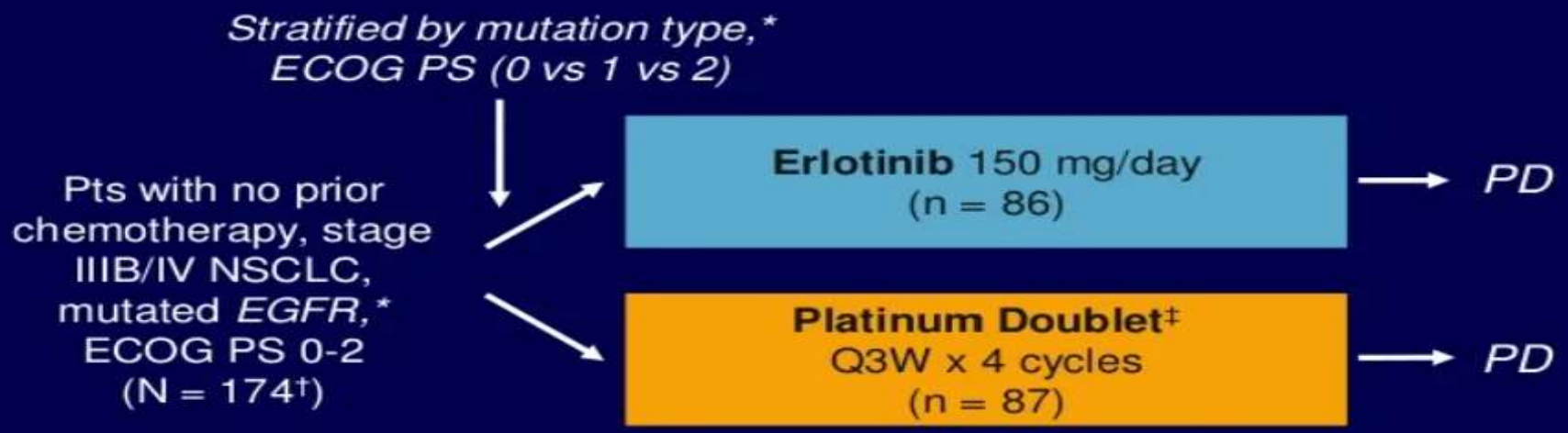




Mok TS, et al. N Engl J Med. 2009;361:947-957.

EURTAC: Erlotinib vs Chemo in *EGFR* Mutation–Positive, Stage IIIB/IV NSCLC

- Randomized, open-label phase III trial

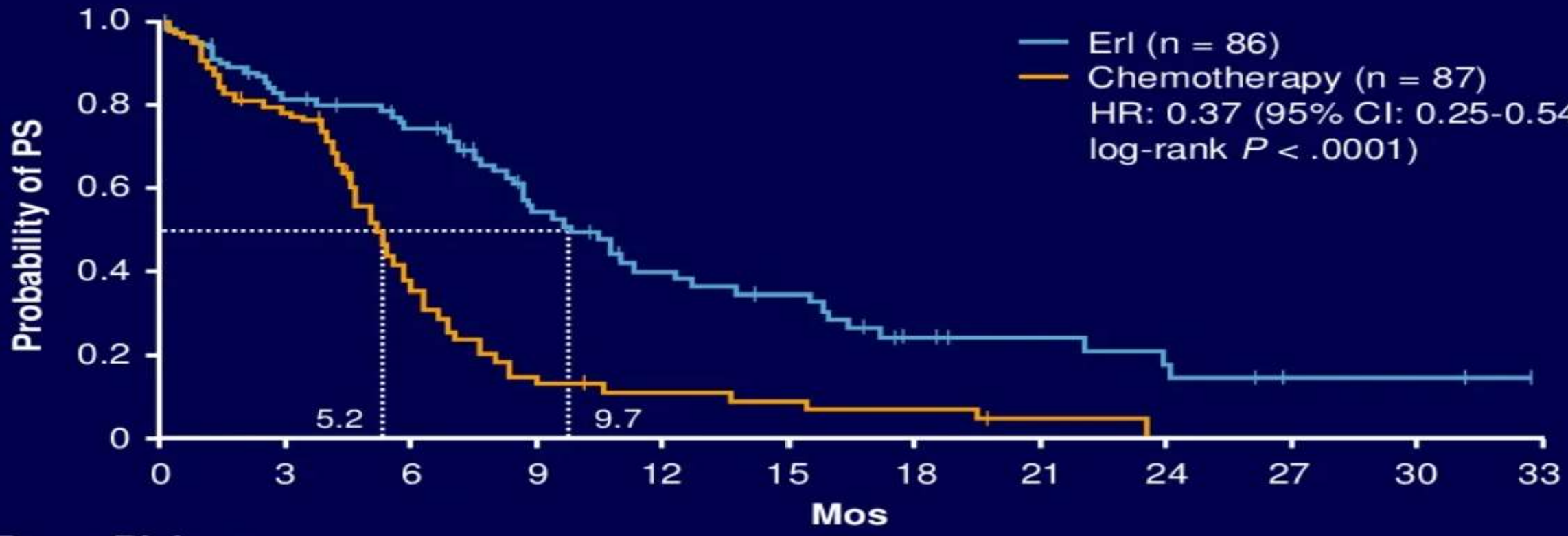


- Primary endpoint: PFS (interim analysis planned at 88 events)
- Secondary endpoints: ORR, OS, location of progression, safety, EGFR-mutation analysis, QoL

*Exon 19 deletion or exon 21 L858R mutation. †1227 pts screened; 174 pts with mutated *EGFR* enrolled; 1 pt withdrawn. ‡Cisplatin 75 mg/m² Day 1/docetaxel 75 mg/m² Day 1; cisplatin 75 mg/m² Day 1/ gemcitabine 1250 mg/m² Days 1, 8; carboplatin AUC = 6 Day 1/docetaxel 75 mg/m² Day 1; carboplatin AUC = 5 Day 1/gemcitabine 1000 mg/m² Days 1, 8.

Rosell R, et al. Lancet Oncol. 2012;13:239-246.

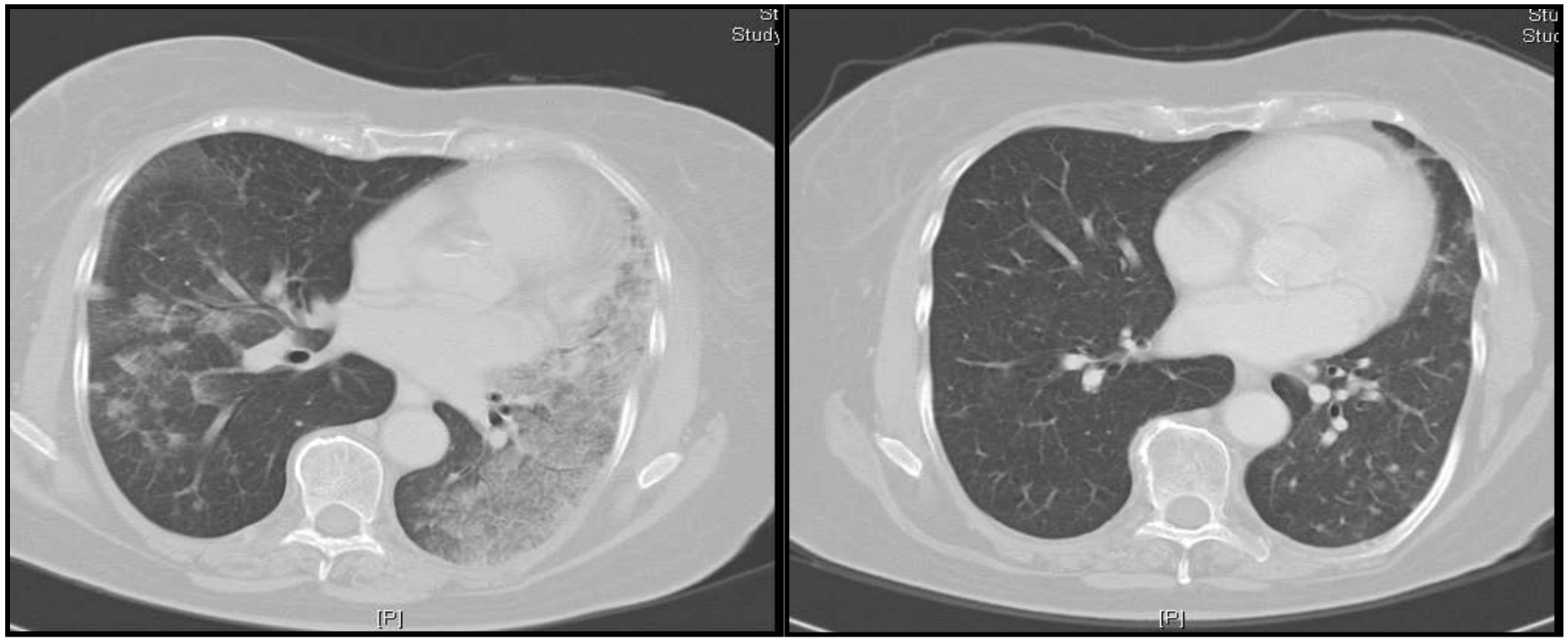
PFS in ITT Population



Pts at Risk, n

Erl	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

Rosell R, et al. Lancet Oncol. 2012;13:239-246.

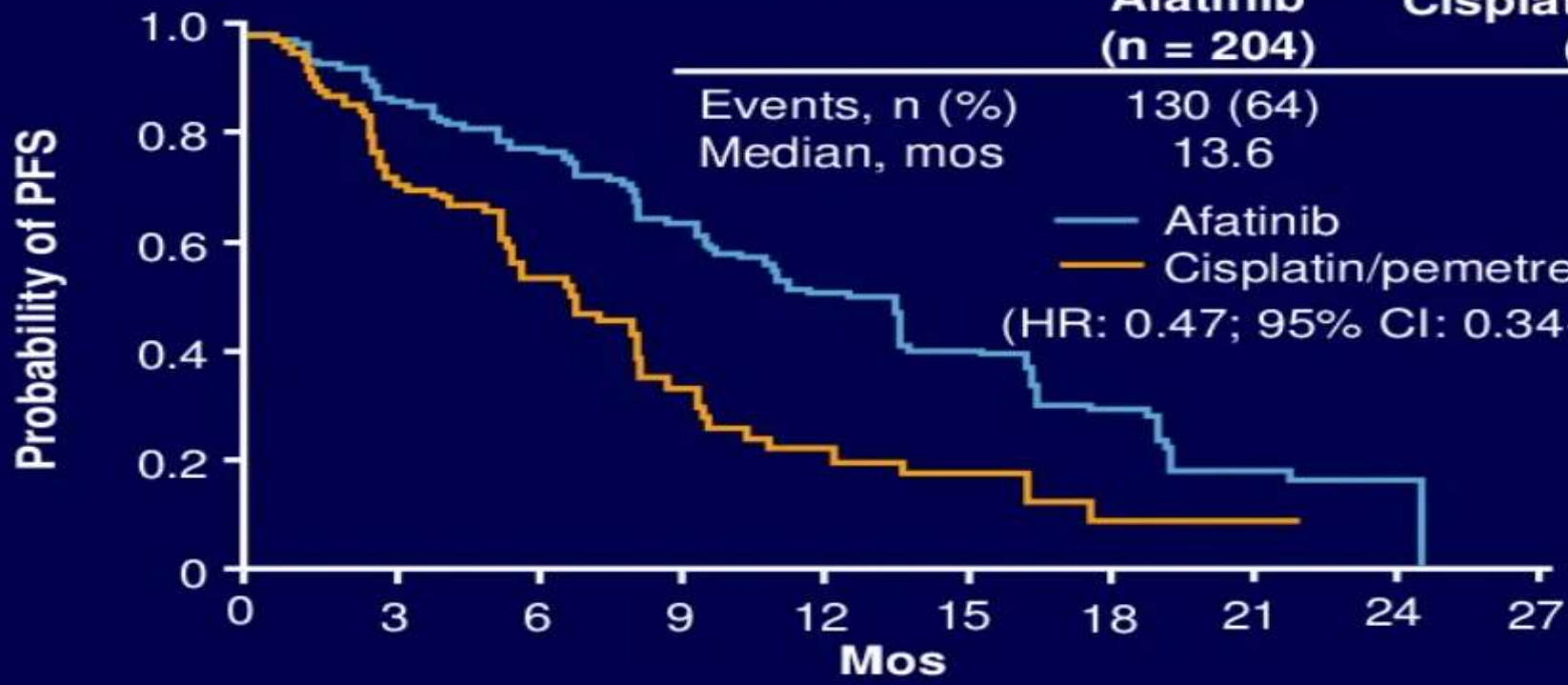

[P]
[P]

LUX-Lung 3: Afatinib vs Chemo Improves PFS in TKI-Naive *EGFR*-Mutated NSCLC

- Phase III study of afatinib vs cisplatin-pemetrexed in *EGFR*-mutant NSCLC adenocarcinoma (N = 345)

Median PFS by del(19) and L858R *EGFR* Mutation Status

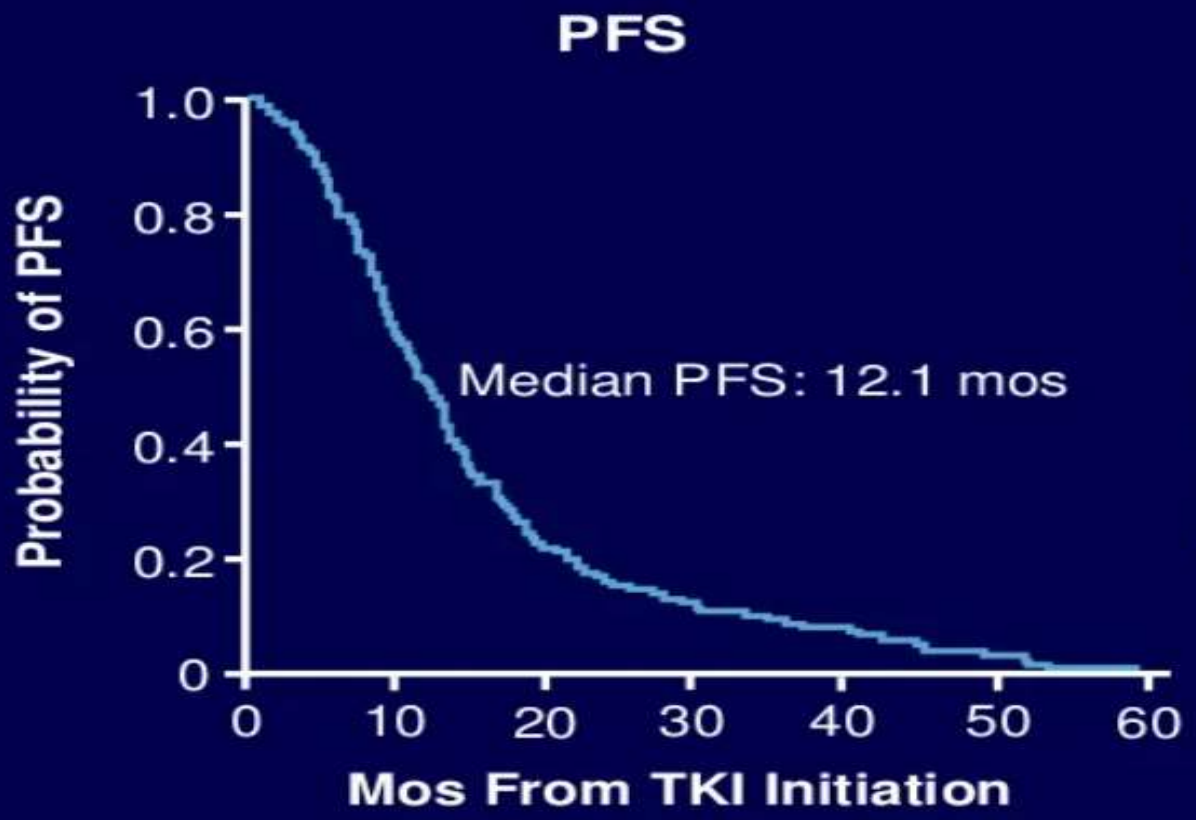
	Afatinib (n = 204)	Cisplatin/Pemetrexed (n = 104)
Events, n (%)	130 (64)	61 (59)
Median, mos	13.6	6.9

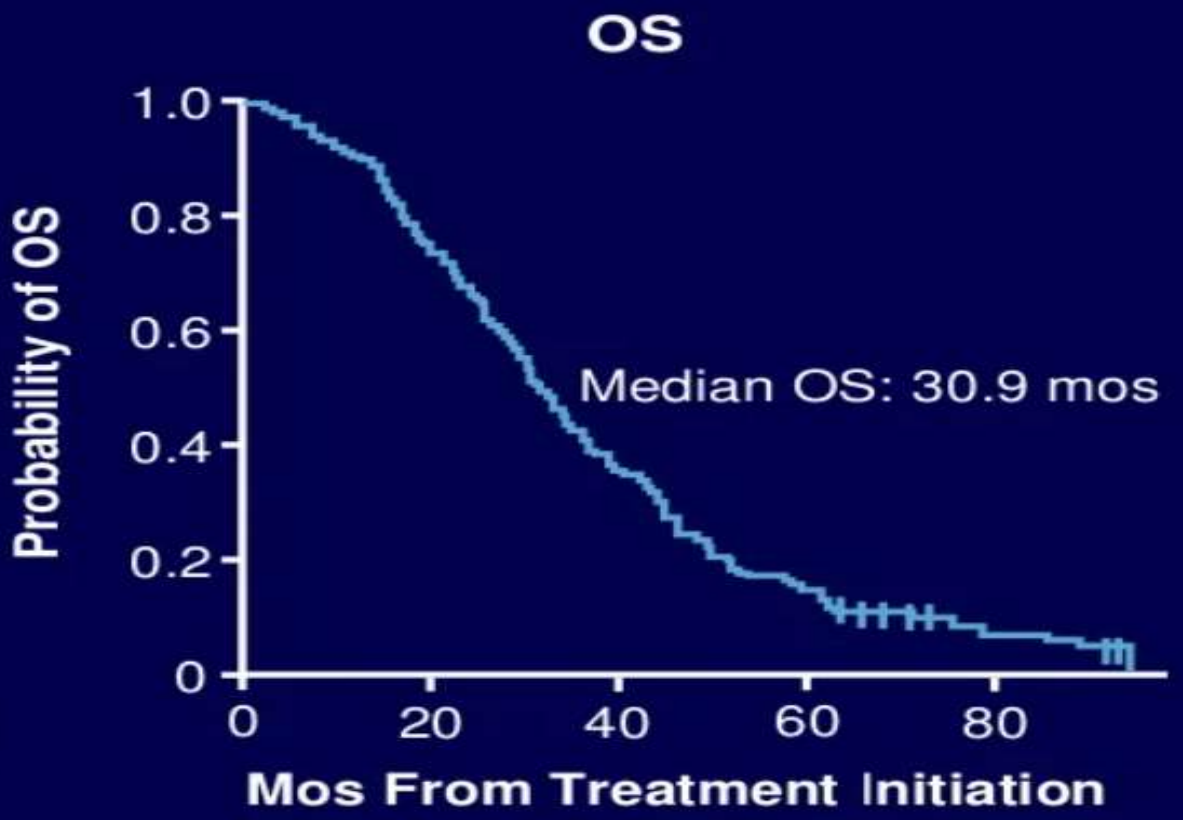


Sequist LV, et al. J Clin Oncol. 2013;31:3327-3334.

EGFR TKIs in EGFR-Mutant Metastatic Lung Adenocarcinoma: 5-Yr PFS and OS

- Pts (N = 137) treated with erlotinib or gefitnib were included

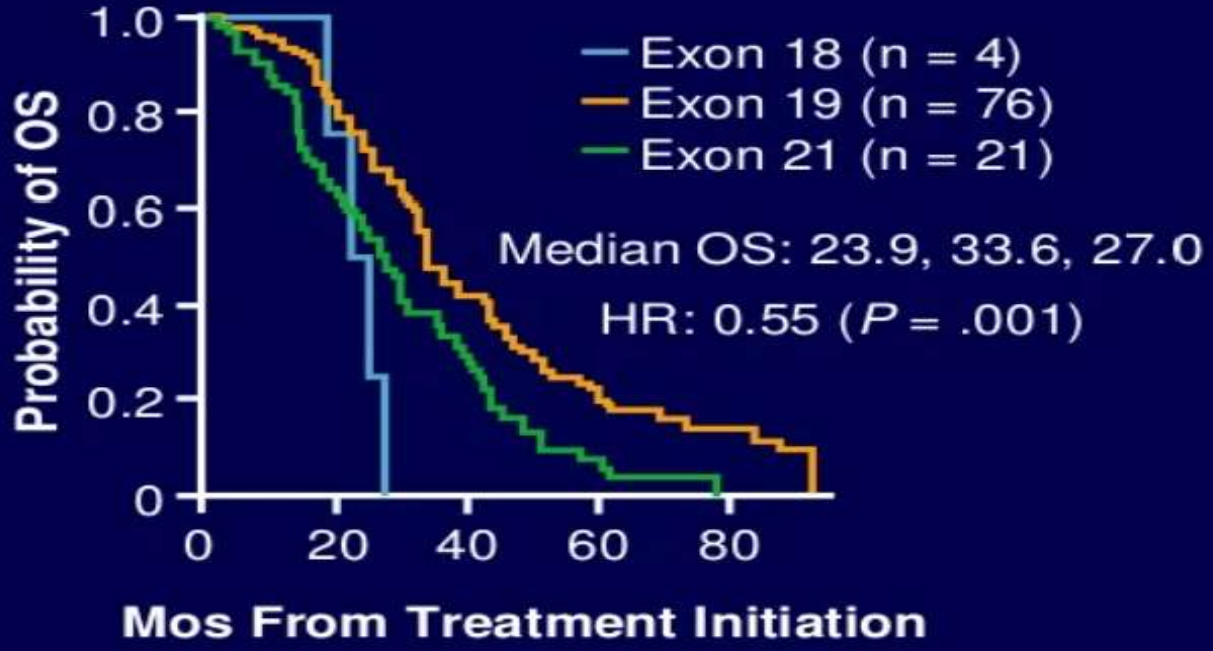


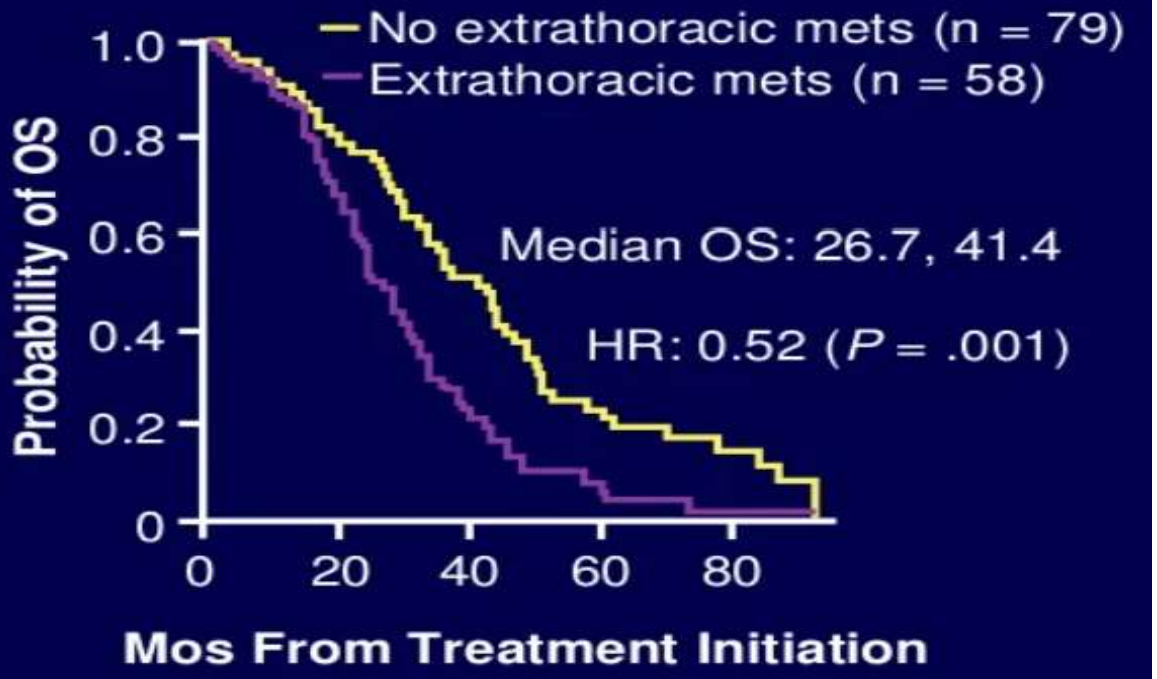


Lin JJ, et al. J Thorac Oncol. 2016;11:556-565.

5-Yr OS in *EGFR*-Mutated NSCLC Treated With Either Erlotinib or Gefitinib

- Prolonged survival associated with exon 19 vs exon 18 or 21 deletions

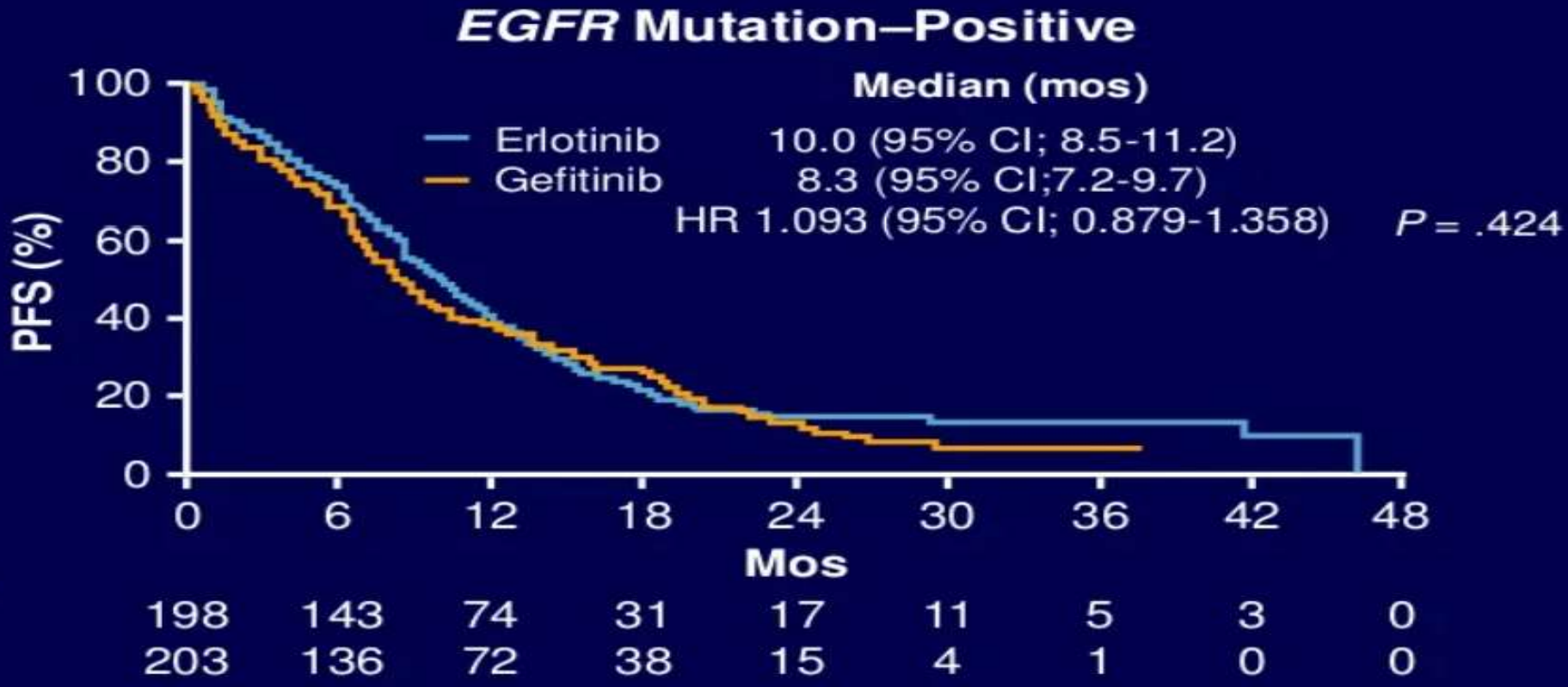




Lin JJ, et al. J Thorac Oncol. 2016;11:556-565.

Phase III WJOG 5108L Study: Erlotinib vs Gefitinib in Previously Treated NSCLC

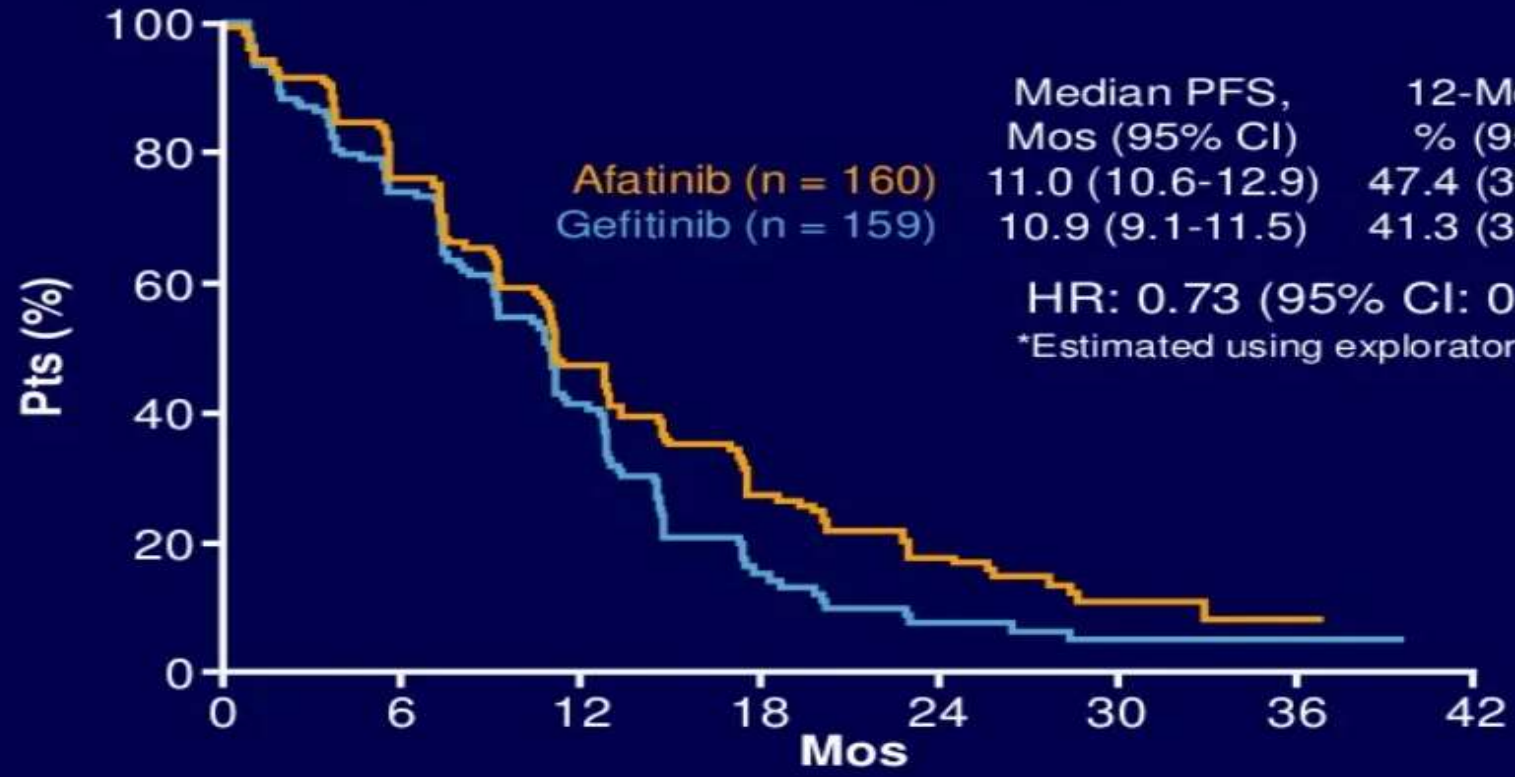
- Eligible pts had stage IIIB/IV or recurrent adenocarcinoma and previous chemotherapy; EGFR TKI naive



Urata Y, et al. J Clin Oncol. 2016;[Epub ahead of print].

LUX-Lung 7: PFS With First-line Afatinib vs Gefitinib in *EGFR*-Mutated NSCLC

- PFS significantly longer with afatinib vs gefitinib
  - Afatinib benefit observed for most subgroups except light exsmokers (smoked < 15 pack-yrs, stopped > 1 yr prior to diagnosis)



	Median PFS, Mos (95% CI)	12-Mo PFS*, % (95% CI)	24-Mo PFS*, % (95% CI)
Afatinib (n = 160)	11.0 (10.6-12.9)	47.4 (39.2-55.2)	17.6 (11.7-24.6)
Gefitinib (n = 159)	10.9 (9.1-11.5)	41.3 (33.0-49.5)	7.6 (3.5-13.8)

HR: 0.73 (95% CI: 0.57-0.95; $P = .017$)

*Estimated using exploratory Kaplan-Meier analyses.

Park K, et al. Lancet Oncol. 2016;17:577-589.

Activity of Afatinib in Populations With Specific Uncommon EGFR Mutations

Genotypes		ORR, n (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)
G719X (EXON 18) (n=18)	G719X (n=8) G719X + T790M (n=1) G719X + S768I (n=5) G719X + L861Q (n=3) G719X + T790M + L858R (n=1)	14 (78)	13.8 (6.8-NE)	26.9 (16.4-NE)
L861Q (EXON21) (n=16)	L861Q (n=12) L861Q + G719X (n=3) L861Q + Del19 (n=1)	9 (56)	8.2 (4.5-16.6)	16.9 (15.3-22.0)
S768I (EXON 20) (n=8)	S768I (n=1) S768I + G719X (n=5) S768I + L858R (n=2)	8 (100)	14.7 (2.6-NE)	NE (3.4-NE)

Note: A patient may be presented in more than 1 category.

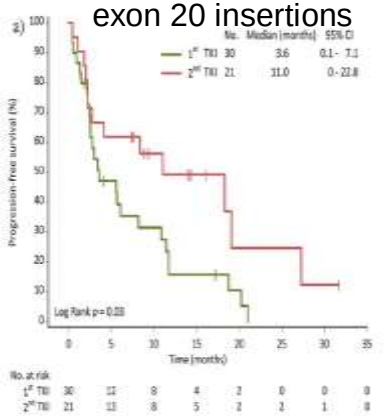
ORR = objective response rate; PFS = progression-free survival; OS = overall survival; NE = not estimable.

Yang et al. *Lancet Oncol*. 2015;16:830.

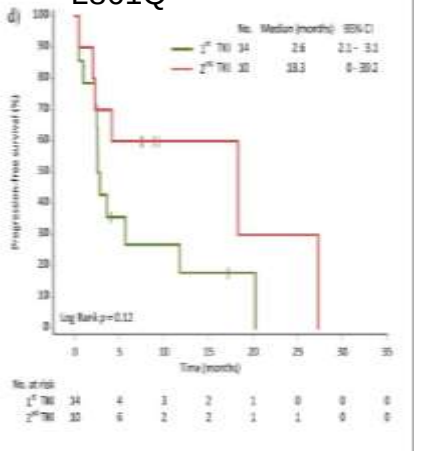
First-Line Clinical Data: Retrospective Analysis of PFS in 57 Patients Treated With Afatinib or First-Generation TKIs.

- **In all mutation groups analyzed, the afatinib group exhibited longer median PFS compared with first-generation TKIs**:
  - Entire uncommon mutations cohort, except exon 20 insertions*:
    - 11.0 mo vs 3.6 mo
  - G719X, S768I, or L861Q:
    - 18.3 mo vs 2.6 mo
  - Uncommon mutations with Del19 or L858R:
    - 11.0 mo vs 8.2 mo
  - Uncommon mutation alone or in combination with other uncommon mutations:
    - 18.3 mo vs 2.8 mo

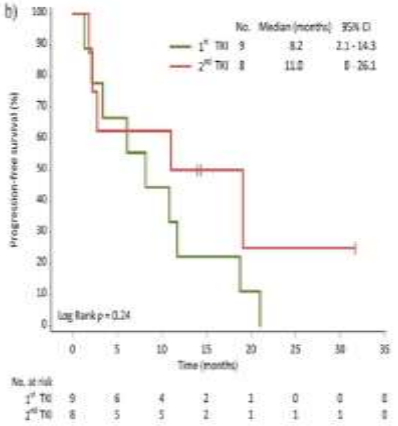
Entire uncommon mutations cohort, except exon 20 insertions



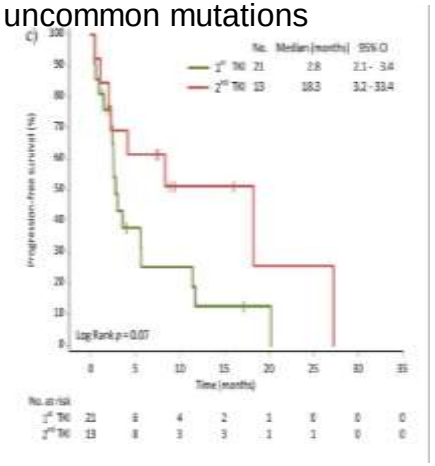
G719X, S768I, or L861Q



Uncommon mutations with Del19 or L858R



Uncommon mutation alone or in combination with other uncommon mutations



Shen et al. *Lung Cancer.* 2017;110(2017):56-62.

First Line Treatment : EGFR TKI vs Chemotherapy in EGFR Mutated NSCLC

Study	Treatment	N	Median PFS, Mos	Median OS, Mos
Maemondo[1]	Gefitinib vs carboplatin/ paclitaxel	230	10.8 vs 5.4 ($P < .001$)	30.5 vs 23.6 ($P = .31$)
Mitsudomi[2,3]	Gefitinib vs cisplatin/docetaxel	172	9.2 vs 6.3 ($P < .0001$)	35.5 vs 38.8 (HR: 1.19)
OPTIMAL[4,5]	Erlotinib vs carboplatin/gemcitabine	165	13.1 vs 4.6 ($P < .0001$)	22.8 vs 27.2 (HR: 1.19)
EURTAC[6]	Erlotinib vs platinum-based chemotherapy	174	9.7 vs 5.2 ($P < .0001$)	19.3 vs 19.5 ($P = .87$)
LUX-Lung 3[7,8]	Afatanib vs cisplatin/pemetrexed	345	11.1 vs 6.9 ($P = .001$)	28.2 vs 28.2 ($P = .39$)
LUX-Lung 6[8,9]	Afatinib vs cisplatin/gemcitabine	364	11.0 vs 5.6 ($P < .0001$)	23.1 vs 23.5 ($P = .61$)

Toxicity of EGFR TKIs in NSCLC

EGFR TKI ▪ Study	Treatment-Related AEs, %							
	Diarrhea		Rash		Paronychia		Stomatitis	
	Gr 1/2	Gr 3/4	Gr 1/2	Gr 3/4	Gr 1/2	Gr 3/4	Gr 1/2	Gr 3/4
Gefitinib								
▪ Mitsudomi	47	1.1	72	2.3	27	1.2	19	0
▪ Maemondo	38	0.9	75	5.3	NR	2.6	11	0
Erlotinib								
▪ OPTIMAL	21	1	48	2	3	0	10	1
▪ EURTAC	44	5	56	12	NR	NR	NR	NR
Afatinib								
▪ LUX-Lung 3	80	14.4	72	16.2	45	11.4	63	8.7
▪ LUX-Lung 6	81	5.4	65	14.6	32	0	45	5.4

- Gefitinib and erlotinib have comparable toxicity
- Afatinib associated with more severe toxicity than gefitinib or erlotinib

Burotto M, et al. Oncologist. 2015;20:400-410.

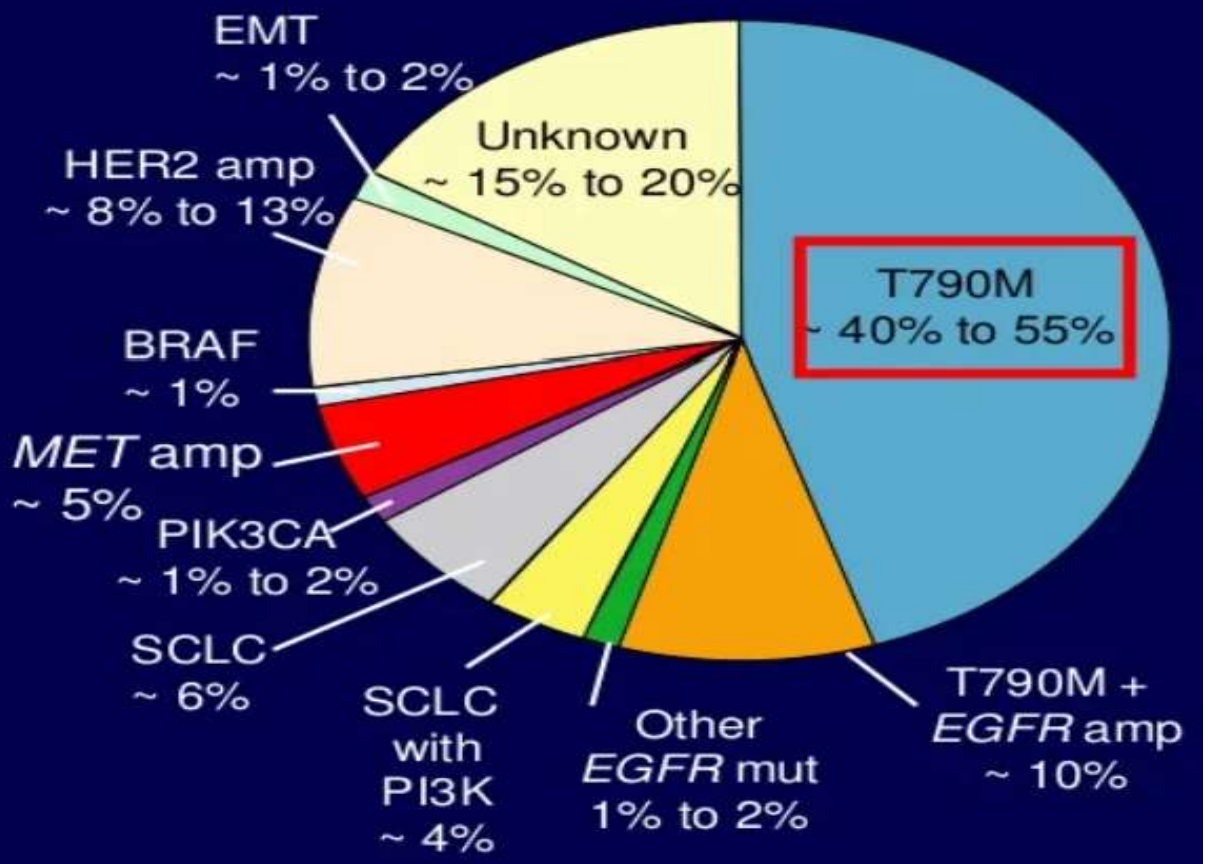
Disease Progression on EGFR TKI in NSCLC With *EGFR* Sensitizing Mutations

PD: Clinical characteristics

- Rapid global progression
- Slow growth globally
- Growth in several areas, but not all

PD: Molecular characteristics

- Unknown (other pathways)
- *EGFR* T790M (exon 20)
- *MET* amplification
- PIK3CA



Camidge DR, et al. Nat Rev Clin Oncol. 2014;11:473-481.

IMPRESS: Cis/Pem ± Gefitinib in Stage IIIb/IV NSCLC With *EGFR* Mut and PD

Phase III trial

Pts with stage IIIb/IV NSCLC, *EGFR* mutations, chemo naive, response ≥ 4 mos with first-line gefitinib, PD < 4 wks prior to randomization (N = 265)

→ **Cisplatin 75 mg/m² + Pemetrexed 500 mg/m² (≤ 6 cycles) + Gefitinib 250 mg** (n = 133)

→ **Cisplatin 75 mg/m² + Pemetrexed 500 mg/m² (≤ 6 cycles) + Placebo 250 mg** (n = 132)

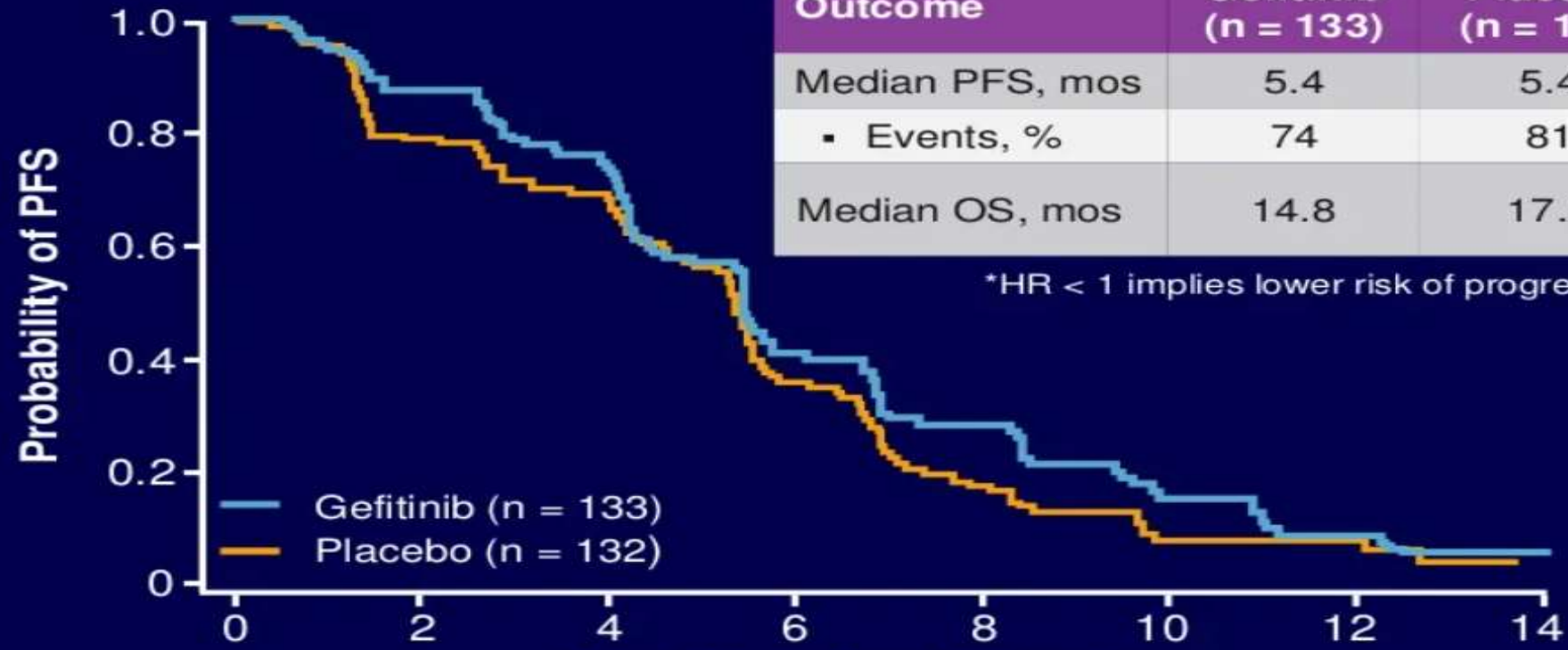
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DCR, safety/tolerability, QoL
- Exploratory endpoints: biomarkers
- Randomization did not include stratification factors; analyses adjusted for age (< vs ≥ 65 yrs) and prior gefitinib response (SD vs PR/CR)

Soria JC, et al. Lancet Oncol. 2015;16:990-998.

IMPRESS: Cis/Pem ± Gefitinib in Stage IIIb/IV NSCLC With *EGFR* Mut and PD: PFS

Outcome	Gefitinib (n = 133)	Placebo (n = 132)	HR
Median PFS, mos	5.4	5.4	0.86* (*P* = .27)
▪ Events, %	74	81	
Median OS, mos	14.8	17.2	1.62 (*P* = .03)

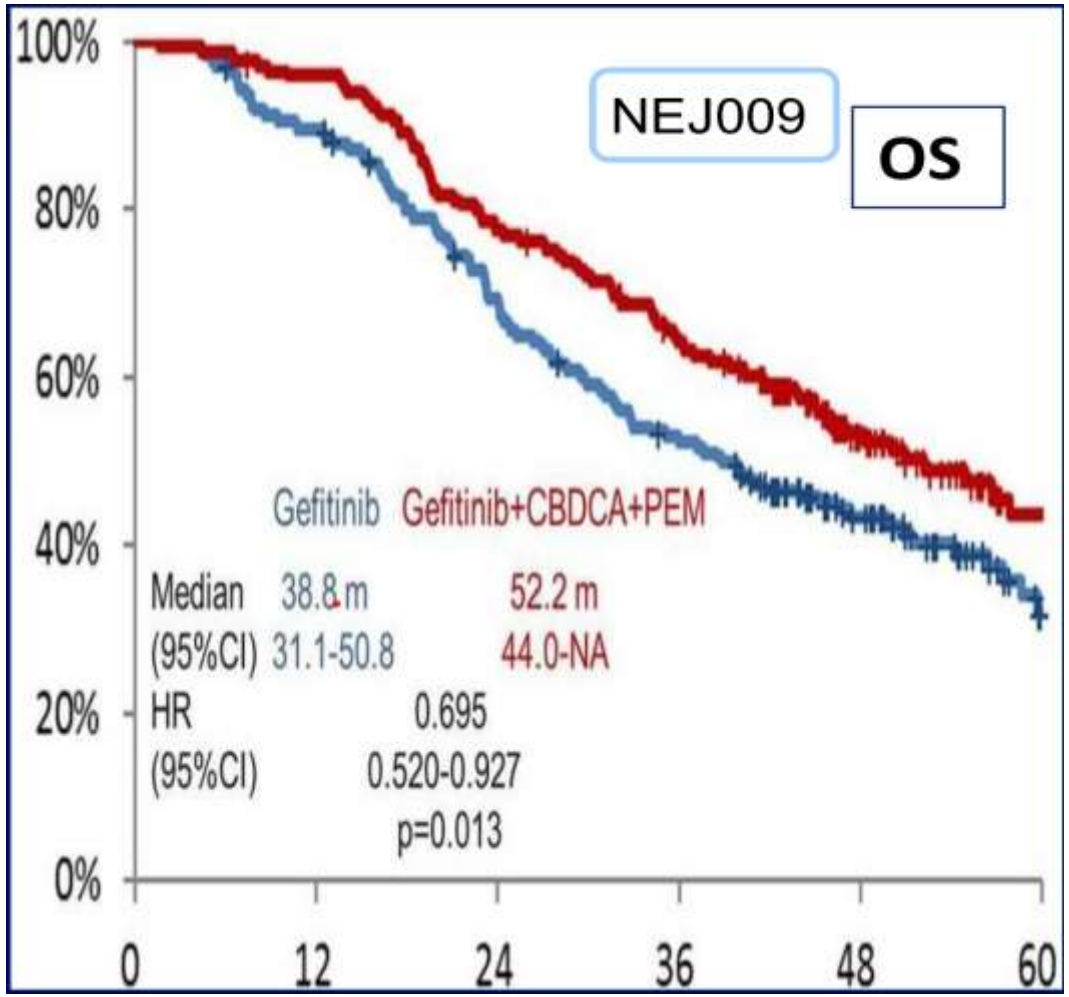
*HR < 1 implies lower risk of progression with gefitinib.

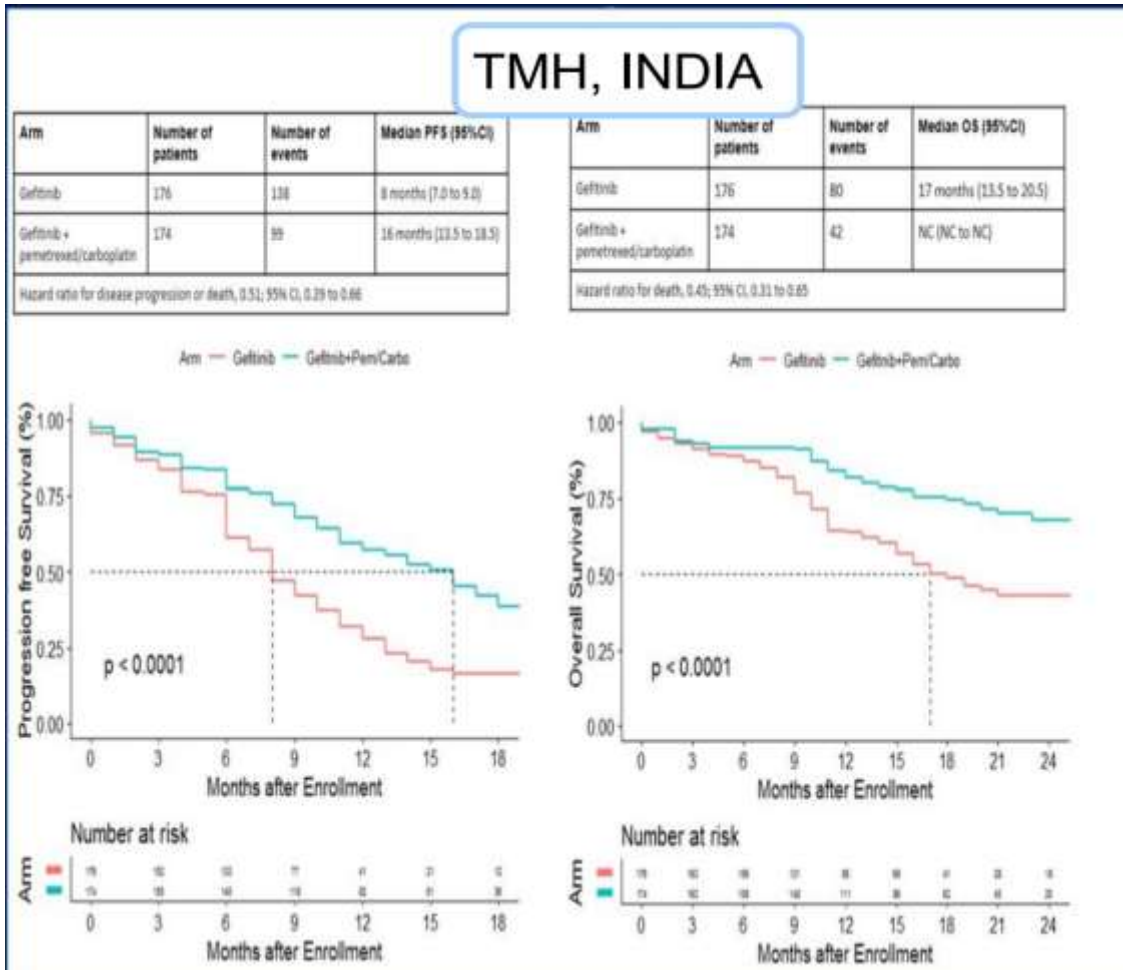


Pts at Risk, n								
Gefitinib	133	110	88	40	25	12	6	0
Placebo	132	100	85	39	17	5	4	0

Soria JC, et al. Lancet Oncol. 2015;16:990-998.

Addition of Chemotherapy to TKI





Increased QoL for first line EGFR mutated positive NSCLC.

- IPASS[1] : Gefitinib vs platinum-based doublet chemotherapy showed improvement with FACT-L
- NEJ002[2] : Gefitinib vs platinum-based doublet chemotherapy showed improvement assessed with Care Notebook.
- First Signal: Gefitinib vs platinum-based doublet chemotherapy showed improvement assessed with EORTC QoL C30 and Lung Cancer-13 questionnaires.
- OPTIMAL[4] : Erlotinib vs platinum-based doublet chemotherapy showed improvement in FACT-L and LCS scores.
- Lux-Lung-3[5] : Afatinib vs platinum-based doublet chemotherapy showed statistically significant delay in time to deterioration of cough, dyspnea; improvement in dyspnea scores, and cognitive, and physical role functions assessed by EORTC QoL C30 and Lung Cancer-13 questionnaires.

2012;17:863-870. 3. Han JY, et al. J Clin Oncol. 2012;30:1122-1128. 4. Chen G, et al. Ann Oncol. 2013;24:1615-1622. 5. Yang JC, J Clin Oncol. 2013;31:3342-3350.

Third Generation EGFR TKIs

Agent	N	RR, % T790M-	RR, % T790M+	PFS, mos	Toxicity
Osimertinib[1]	253	21	61	~ 8.2	Diarrhea
Rociletinib[2,3]	130	29 (17)	59 (45)	13.1 (6.1)	Hyperglycemia
Olmutinib[4]	62	NR	55	NR	Dyspnea/rash
EGF816[5]	53	–	60	NR	Rash
ASP8273[6]	47	~ 33	61	NR	Hyponatremia/ diarrhea

1. Jänne PA, et al. N Engl J Med. 2015;372:1689-1699. 2. Sequist LV, et al. N Engl J Med. 2015;372:1700-1709. 3. Sequist LV, et al. N Engl J Med. 2016;374:2296-2297. 4. Park K, et al. ASCO 2015. Abstract 8084. 5. Tan DS, et al. ASCO 2015. Abstract 8013. 6. Goto Y, et al. ASCO 2015. Abstract 8014.

Osimertinib (AZD9291): Novel EGFR TKI in *EGFR*-Mutated NSCLC

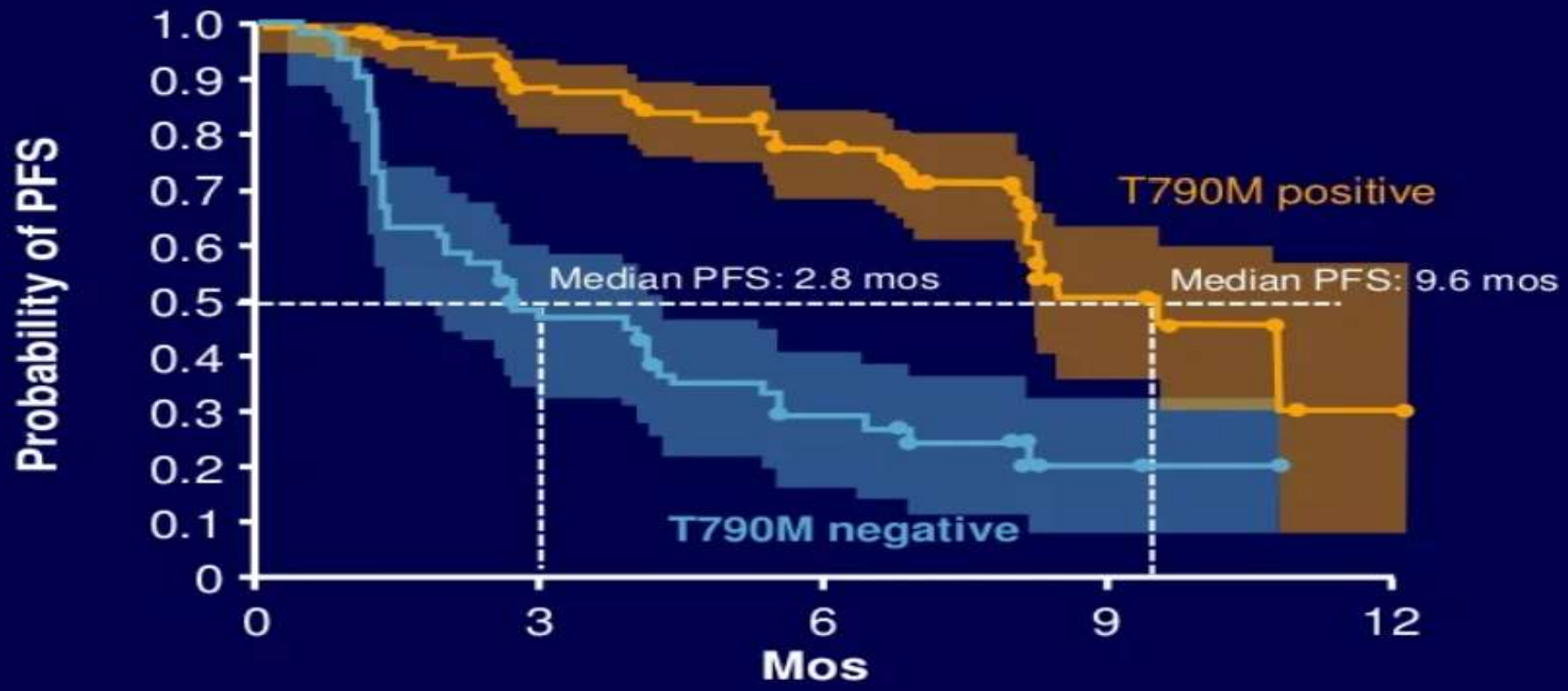
- Osimertinib FDA approved (November 2015) for advanced *EGFR* T790M–positive NSCLC after PD on prior EGFR TKI
  - Approval based on AURA and AURA2 single-arm phase II studies of osimertinib in advanced/metastatic NSCLC with *EGFR* T790M
  - Companion diagnostic test for *EGFR* mutation also approved

	AURA[1] (N = 201)	AURA2[2] (N = 210)
ORR, %	61	71 (including 2 CRs)
Disease control rate, %	--	92 at 6 wks
Median PFS, mos	Not reached	8.6
Median DOR, mos	Not reached	7.8

1. Yang JC, et al. WCLC 2015. Abstract 943.
2. Mitsudomi T, et al. WCLC 2015. Abstract 1406.

AURA: Osimertinib Efficacy by *EGFR* T790M Status

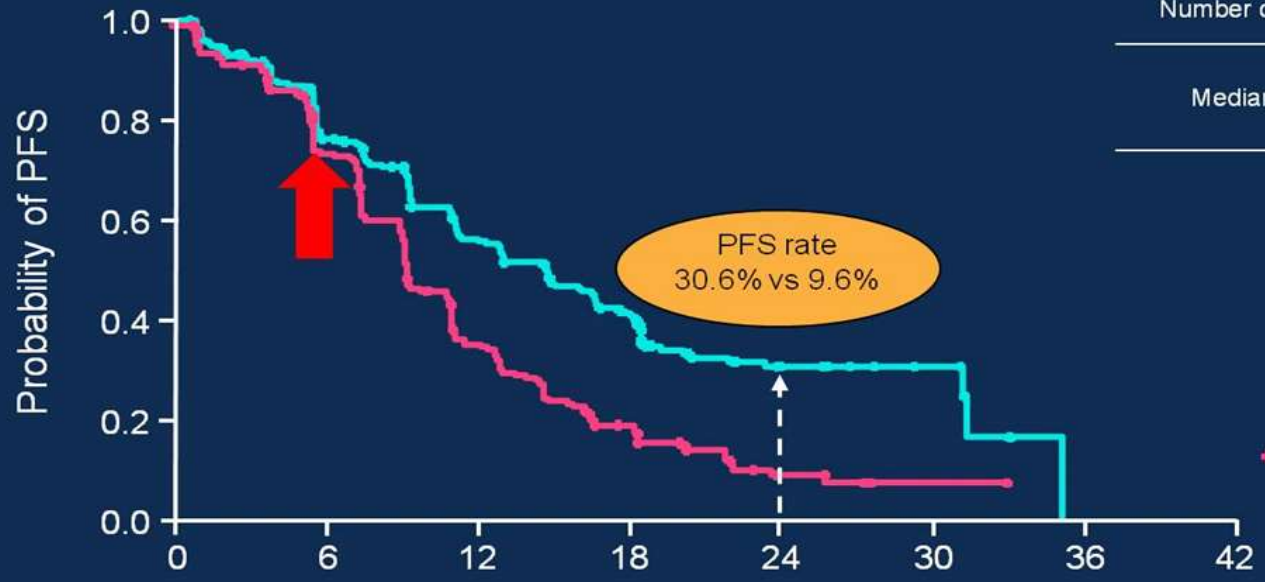
- Phase I/II trial for pts with *EGFR*-positive NSCLC with progression after previous treatment with EGFR TKIs



Jänne PA, et al. N Engl J Med. 2015;372:1689-1699.

ARCHER 1050: Dacomitinib vs Gefitinib

PFS: Blinded Independent Review
(ITT population)



	Daco (N=227)	Gef (N=225)
Number of Events, n (%)	136 (59.9%)	179 (79.6%)
Median PFS (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)	0.59 (0.47–0.74) P<0.0001	

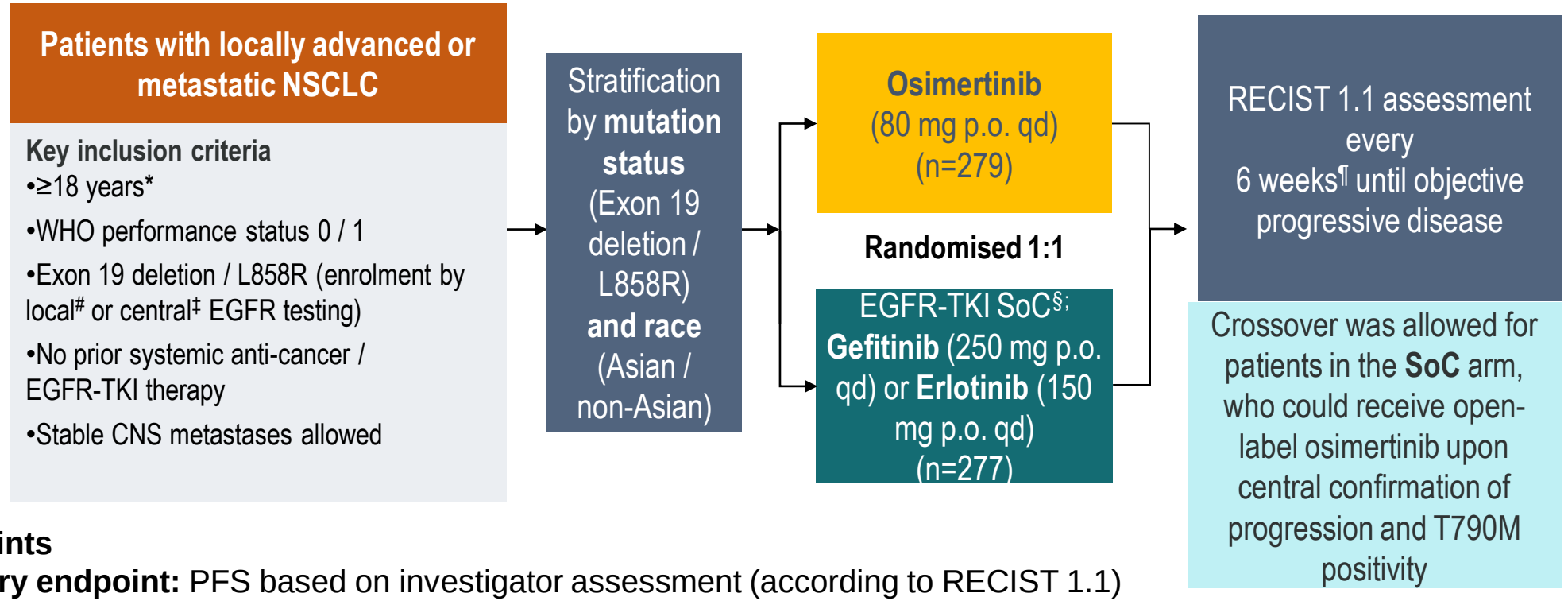
No. at risk								
Dacomitinib	227	154	106	73	20	6	0	0
Gefitinib	225	155	69	34	7	1	0	0

ARCHER 1050 vs Lux Lung 7

- Lux Lung 7 [1] & ARCHER 1050 [2]
  - PFS is significantly better than 1st Gen TKIs
  - PFS not translating into OS for Lux Lung 7 & OS advantage seen for ARCHER 1050
  - Tolerability is the concern; need to monitor patients for AEs
- Lux Lung 7 vs ARCHER 1050
  - More Asian patients in ARCHER 1050 (75%/78% in ARCHER 1050 vs 55%/59% in Lux Lung 7)
  - Patients with brain metastasis not allowed in ARCHER 1050 while asymptomatic brain mets were allowed in LL7; 16%/15% in both arms

1. Paz-Ares L, Tan E-H, O'Byrne K, Zhang L, Hirsh V, Boyer M, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017 01;28(2):270–7.
2. Wu Y-L, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. The Lancet Oncology [Internet]. 2017 Nov 1 [cited 2018 Apr 3];18(11):1454–66. Available from: http://www.sciencedirect.com/science/article/pii/S1470204517306083

FLAURA double-blind study design



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

- FLAURA data cut-off: 12 June 2017; NCT02296125
- *≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

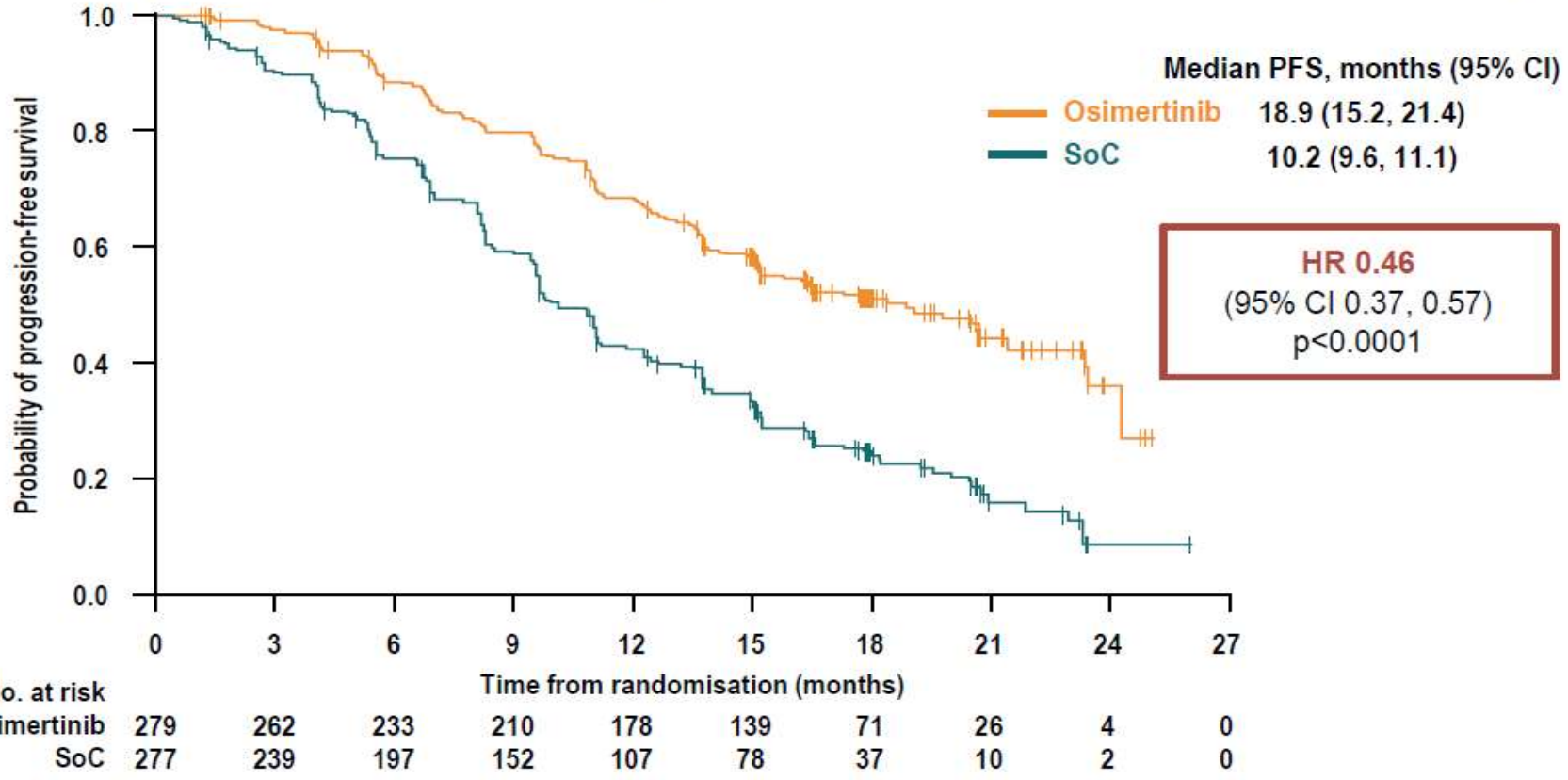
Ramalingam SS, Reungwetwattana T, Chewaskulyong B, et al. Osimertinib vs standard of care EGFR-TKI as first-line therapy in patients with EGFRm advanced NSCLC: FLAURA.[Oral presentation]. European Society for Medical Oncology Conference, Madrid, Spain, September 8-12, 2017.

PFS benefit with osimertinib

MADRID 2017 ESMO congress

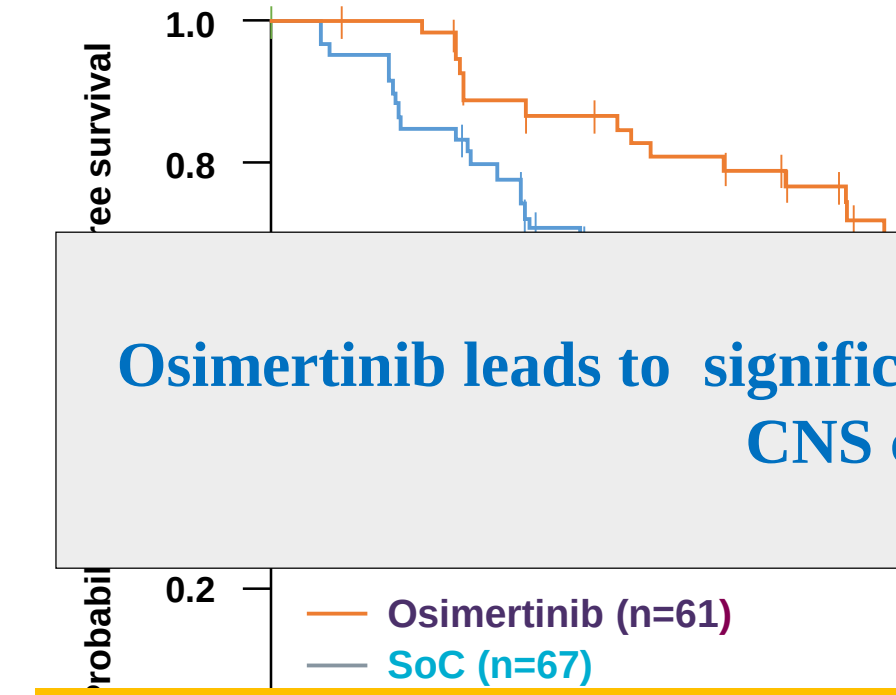
PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data;
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care; PFS, progression-free survival

FLAURA CNS PFS: Clinically Meaningful And Statistically Significant



	Osimertinib (n=61)	SoC (n=67)
Median CNS PFS, months (95% CI)	NR (16.5, NC)	13.9 (8.3, NC)
HR*		

Osimertinib leads to significant 52% reduction in risk of Progression of disease in CNS compared to 1st G EGFR TKIs

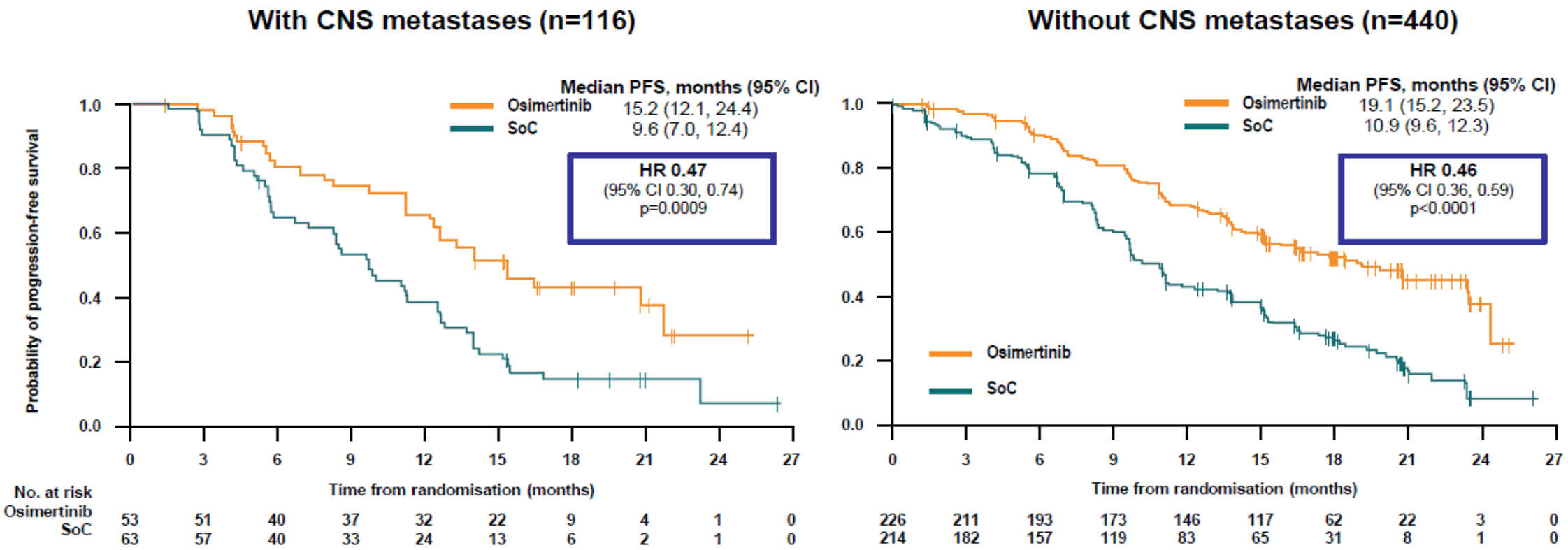
- **CNS PFS was statistically significant**

In phase 3 RCT of Dacomatinib, patients with brain metastasis were not eligible for enrollment.

Osimertinib	61	54	44	40	34	21	8	4	1	0
SoC	67	50	37	31	21	13	4	1	1	0

FLAURA data cut-off: 12 June 2017
*HR was calculated from a Cox proportional hazards model with a factor for treatment; CI was calculated using profile likelihood. HR <1 favours osimertinib.
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; NC, not calculable; NR, not reached; NS, not significant; OS, overall survival; PFS, progression-free survival; SoC, standard-of-care
Vansteenkiste ESMO Asia 2017 Abs LBA6

FLAURA: PFS in patients with and without CNS mets



CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017

Tick marks indicate censored data; *By Investigator assessment

Ramalingam et al ESMO 2017 #LBA2; Soria NE JM 2017

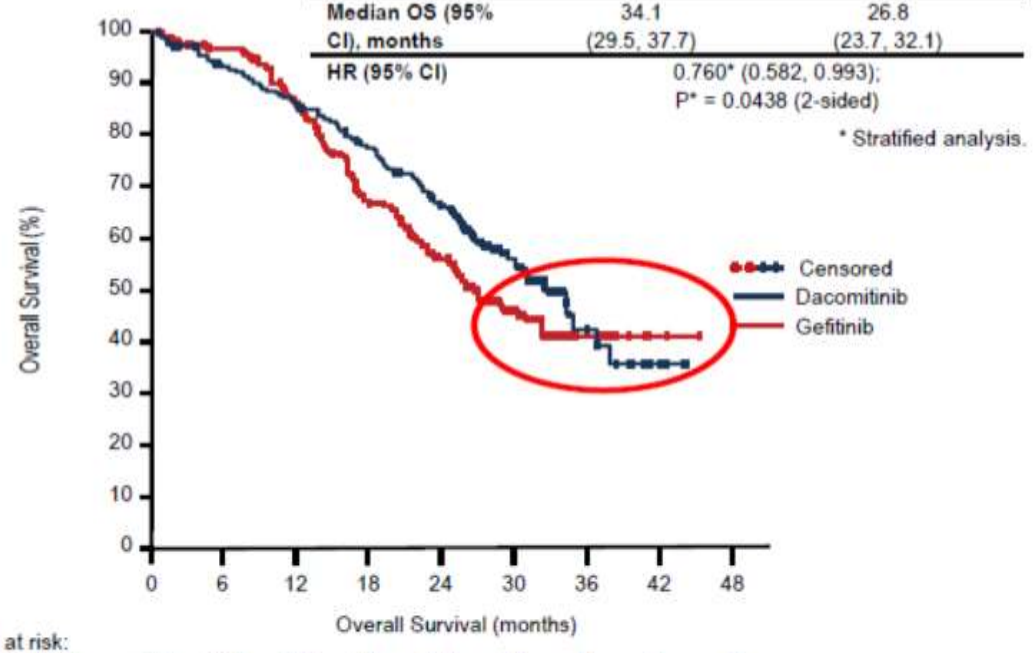
Overall survival

Overall Survival – Intention-to-Treat Population

Overall Survival (Feb. 17, 2017)

	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	103	117
Median OS (95% CI), months	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)	0.760* (0.582, 0.993); P* = 0.0438 (2-sided)	

* Stratified analysis.



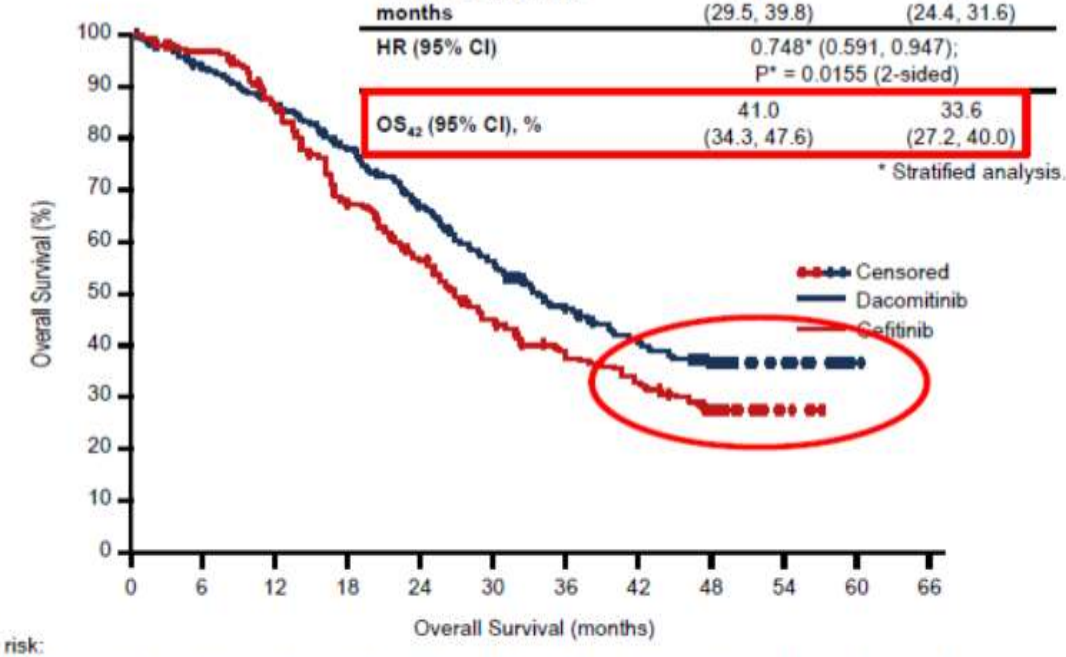
No. at risk:									
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Mok TS et al. *J Clin Oncol*. 2018;36(22):2244–2250.

Overall Survival (May 13, 2019)

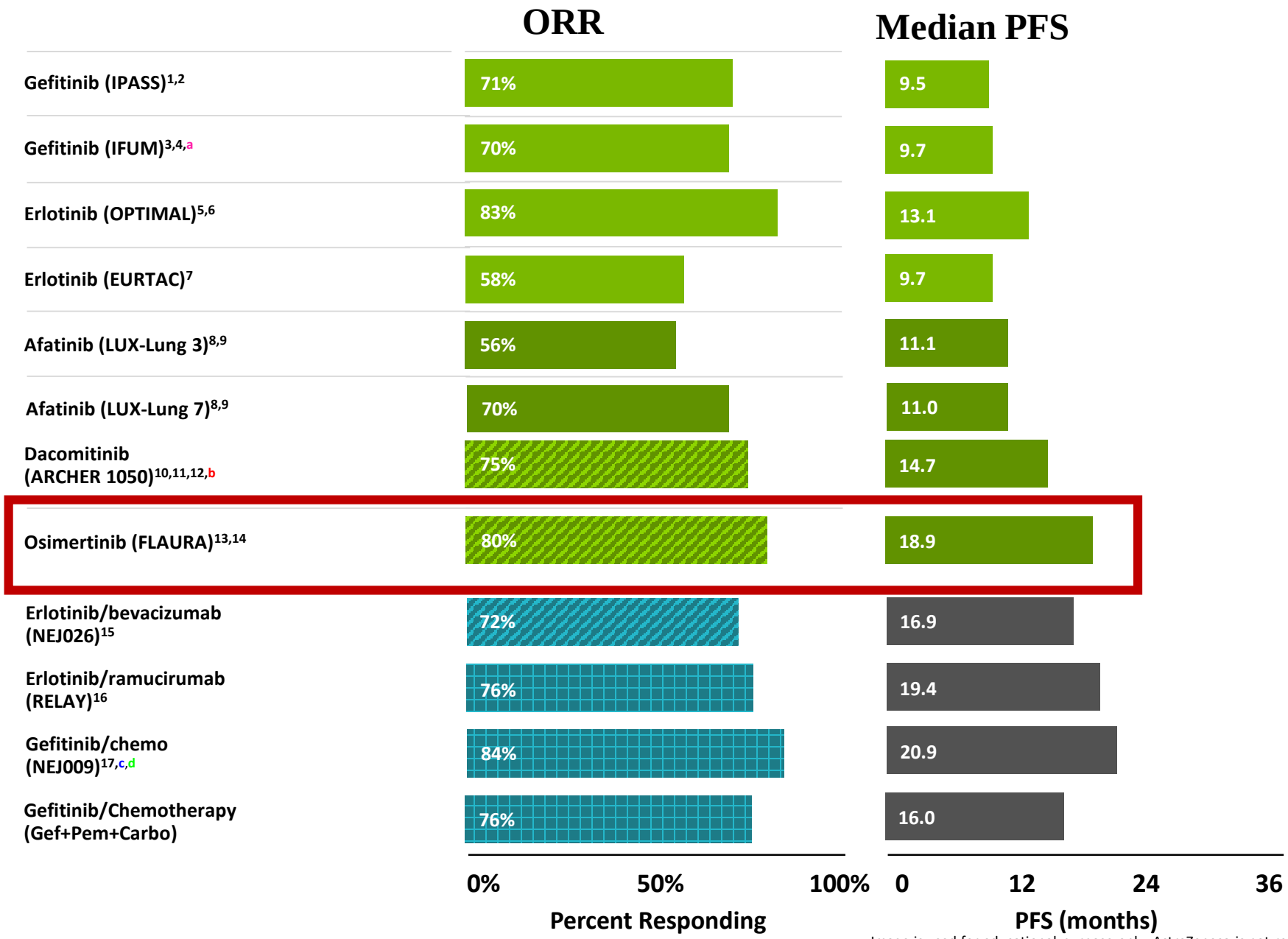
	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	133	152
Median OS (95% CI), months	34.1 (29.5, 39.8)	27.0 (24.4, 31.6)
HR (95% CI)	0.748* (0.591, 0.947); P* = 0.0155 (2-sided)	
OS_{42} (95% CI), %	41.0 (34.3, 47.6)	33.6 (27.2, 40.0)

* Stratified analysis.

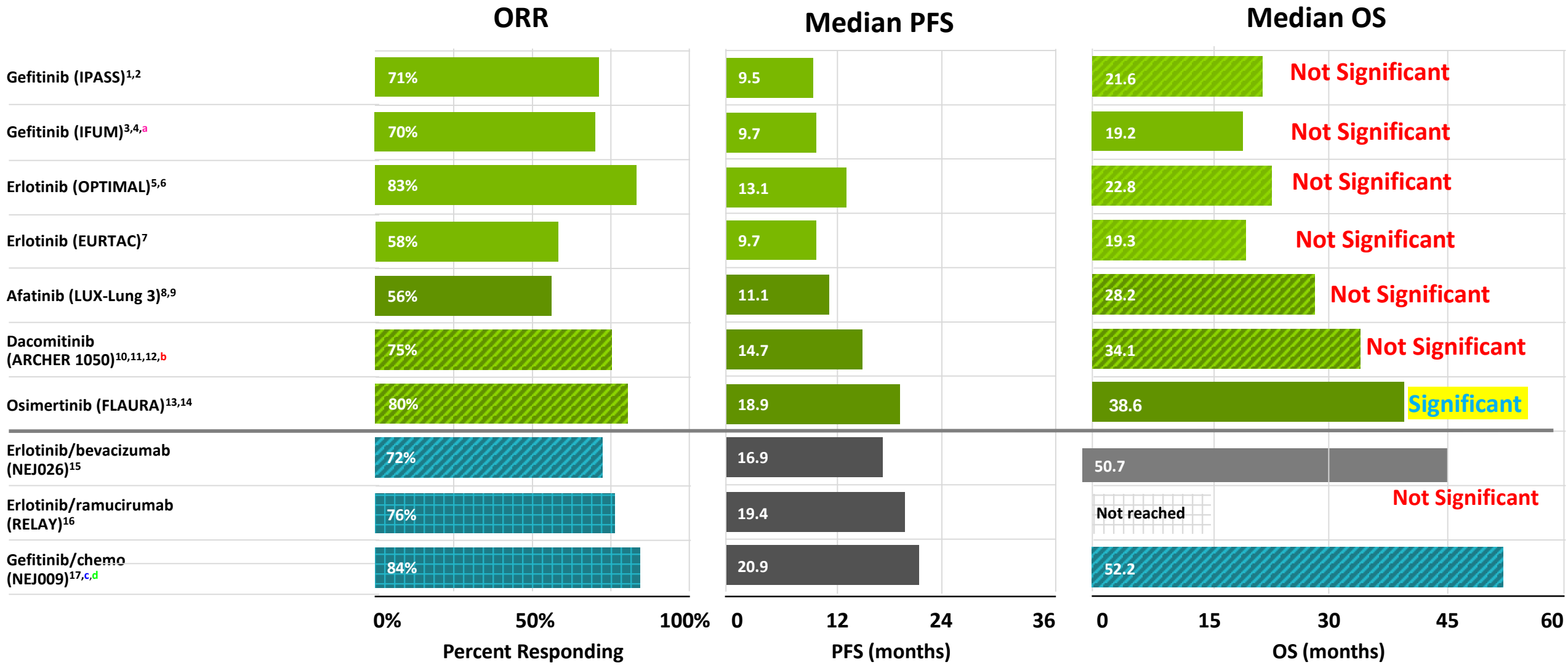


No. at risk:												
Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

PFS Summary for 1L Treatment in Metastatic *EGFR*m NSCLC



OS Outcomes for 1L Treatment in Metastatic *EGFR*m NSCLC



Osimertinib is the only EGFR TKI showed clinically meaningful and significant OVERALL SURVIVAL benefit in Stage IV EGFRm NSCLC

The data listed are from **different** clinical trials. Not for cross-trial comparison.

[a]Single-arm, Phase 4 trial;[3] [b]OS for ARCHER trial was not statistically significant due to hierarchical statistical testing and the failure of ORR to meet statistical significance;[12] [c]OS for NEJ009 was not statistically significant due to hierarchical statistical testing and the failure of the coprimary endpoint PFS2 to meet statistical significance;[17] [d]In a single-site, Phase 3 study, Noronha V et al reported similar results for ORR, PFS, and OS.[18,19]

Safety Summary for 1L Treatment in Metastatic *EGFR*m NSCLC

The second-generation EGFR-TKIs afatinib and dacomitinib have been shown to frequently cause AEs that require a dose reduction

In LUX-Lung 7, AEs leading to dose reductions were more frequent in patients receiving afatinib compared with gefitinib (**41.9% vs 1.9%,** respectively)[1]	In ARCHER 1050 there were more dose reductions in patients in the dacomitinib group compared with the gefitinib group (**66% vs 8%**)[2]	In FLAURA, the frequency of dose reduction was similar between osimertinib and SoC EGFR-TKI (**4% and 5%,** respectively)

Two-thirds of patients on dacomitinib required dose reductions.

- 1. Park K, et al. Lancet Oncol 2016;17:577-589; 2. Wu, et al. Lancet Oncol 2017;18:1454-1466.; 3. Soria, et al. N Engl J Med 2018;378:113-125

Safety Summary for 1L Treatment in Metastatic *EGFR*m NSCLC

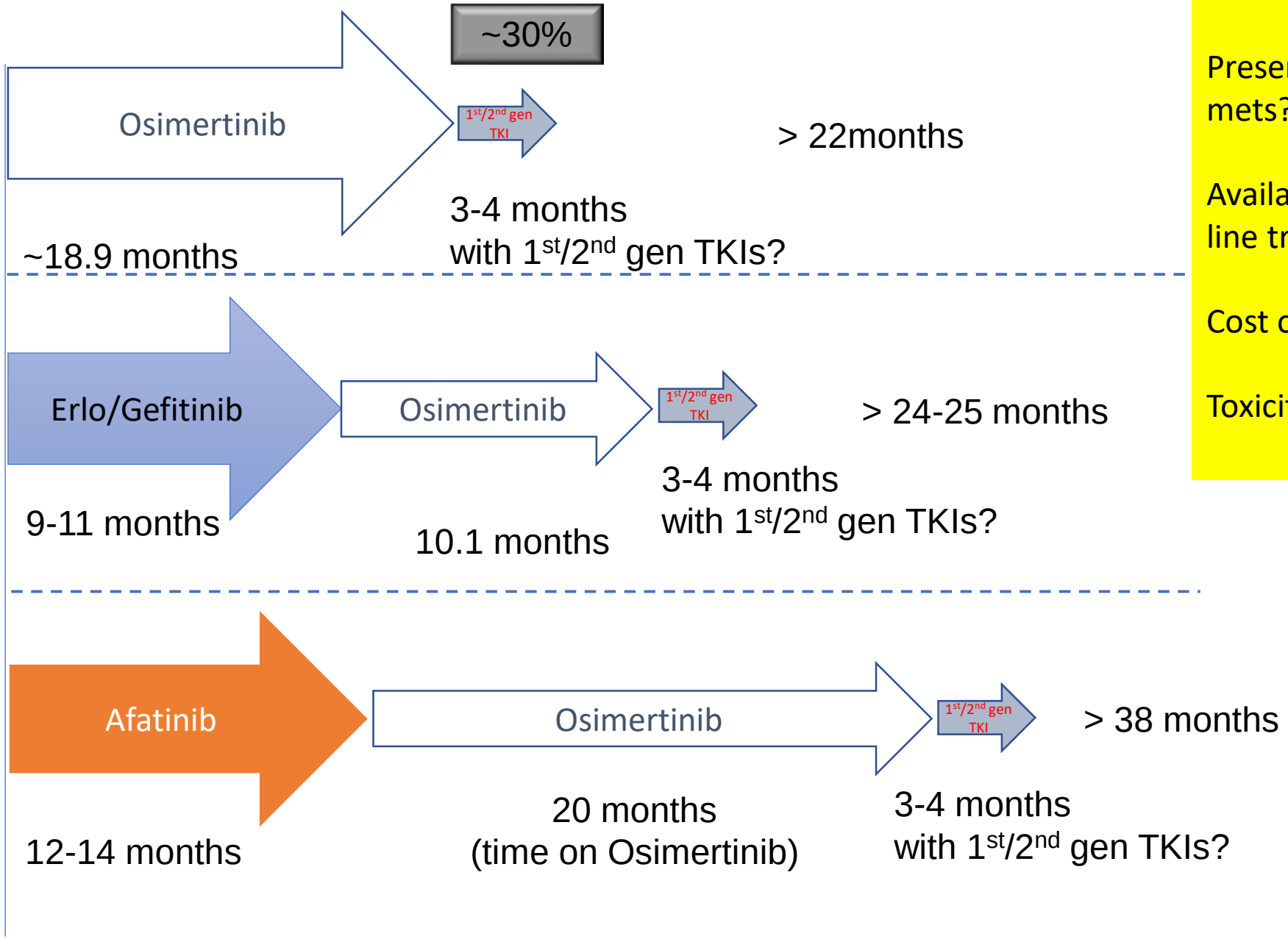
The data listed are from **different** clinical trials. Not for cross-trial comparison. Data may represent a mix of treatment-related, treatment-emergent, or all-cause/any-cause AEs, which is noted where known.

Study	Interventional Arm	N	Discontinuation due to AE	AE Grade ≥3	Rash (Grade ≥3)	Diarrhea (Grade ≥3)	Stomatitis (Grade ≥3)
IFUM[1,2]	Gefitinib	107	7.5%	15%	0%	3.7%	NR
OPTIMAL[3]	Erlotinib	83	1%	17%[a]	2%[a]	1%[a]	1%[a]
EURTAC[4]	Erlotinib	84	13%	45%[a]	13%[a]	5%[a]	NR
LUX-Lung 3[5]	Afatinib	229	8%[b]	**49%**[b]	16.2% (rash/acne)[b,c]	14.4%[b]	8.7% (stomatitis/mucositis)[b,c]
ARCHER 1050[6]	Dacomitinib	227	**10% (permanent discontinuation)** **78% (temporary discontinuation)**	**63%**[d]	4% (rash)[d] 14% (dermatitis acneiform)[d]	8.8%[d]	4%[d]
FLAURA[7,8]	Osimertinib	279	13% (permanent discontinuation)[e]	**34%**[e]	1% (rashes,acne)[a,c,f]	3%[a,f]	1%[a,f]
NEJ026[9]	Erlotinib + bevacizumab	112	19% discontinued erlotinib due to AEs; 29% discontinued bevacizumab due to AEs	88%	21%	5%	1%
RELAY[10]	Erlotinib + ramucirumab	221	13% (discontinued all study treatment)[g]	72%[g]	15% (acneiform dermatitis)[g]	7%[g]	2%[g]
NEJ009[11]	Gefitinib + chemotherapy	169	10.7%[d]	65.1%[d]	4.1%	4.1%	0.6%
CTRI/2016/08/007149[12]	Gefitinib + chemotherapy	164	16.7% discontinued pemetrexed due to AEs; 0% discontinued gefitinib due to AEs	75%	4.9%	14%	NR

1L = first-line; AE = adverse event; *EGFR*m = epidermal growth factor receptor mutation-positive; NR = not reported; NSCLC = non-small cell lung cancer.

[a]Grade 3/4;[3,4,8] [b]Treatment-related AE;[5] [c]Grouped term;[5,8] [d]All-cause/any-cause AE;[6,11] [e]Data cutoff: 12 June 2017;[7] [f]Data cutoff: 25 June 2019;[8] [g]Treatment-emergent AE.[10]

1. Douillard JY et al. *Br J Cancer*. 2014;110:55-62. 2. Study NCT01203917. ClinicalTrials.gov.website. 3. Zhou C et al. *Lancet Oncol*. 2011;12:735-742. 4. Rosell R et al. *Lancet Oncol*. 2012;13:239-246.
5. Sequist LV et al. *J Clin Oncol*. 2013;31:3327-3334. 6. Wu YL et al. Article and supplementary appendix. *Lancet Oncol*. 2017;18:1454-1466. 7. Soria JC et al. *N Engl J Med*. 2018;378:113-125.
8. Ramalingam SS et al. Presented at: ESMO Congress; September 27-October 1, 2019; Barcelona, Spain. 9. Saito H et al. *Lancet Oncol*. 2019;20:625-635.10. Nakagawa K et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL. 11. Nakamura A et al. Presented at: ASCO Annual Meeting; June 1-5, 2018; Chicago, IL. 12. Noronha V et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL.



PFS vs OS

Presence of brain mets??

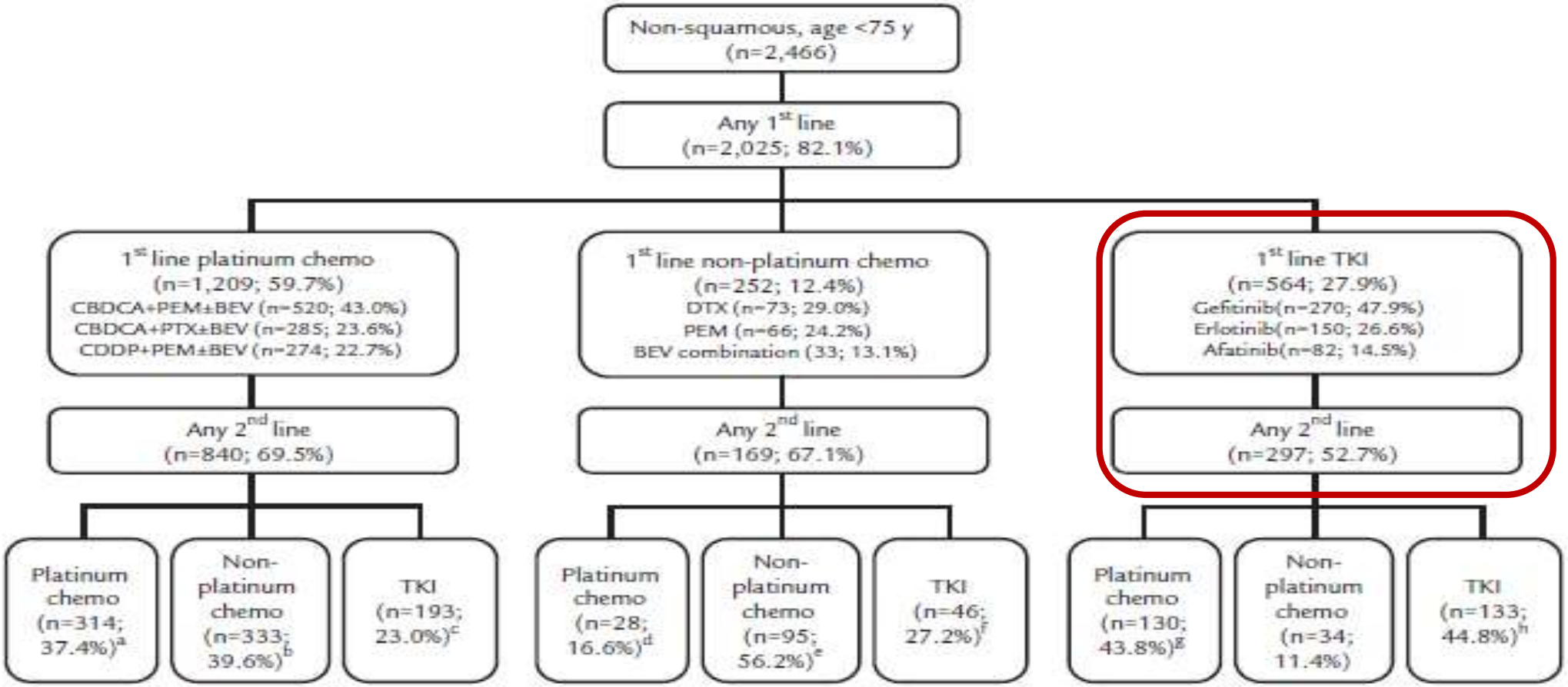
Availability of second line treatment???

Cost of treatment

Toxicity profile

1.Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*.;2014;15:213.; 3. Park K et at., *Lancet Oncol* 2016;

Real-world scenario~1/2 of patients do not receive 2L treatment after 1L TKI



Wang F, Mishina S, Takai S, Le TK, Ochi K, Funato K, et al. Systemic Treatment Patterns With Advanced or Recurrent Non–small Cell Lung Cancer in Japan: A Retrospective Hospital Administrative Database Study. Clinical Therapeutics [Internet]. 2017 Jun 1;39(6):1146–60. Available from: http://www.sciencedirect.com/science/article/pii/S014929181730245X

Summary of EGFR Mutation –Driven NSCLC

- EGFR sensitizing mutations predict higher response rate, PFS, and QoL if treated with EGFR TKI first line.
- Several approved EGFR TKIs
  - Only 2 have been compared head to head
  - Specific EGFR mutation is important to know since some predict resistance to EGFR TKIs (eg. Exon 20 insertions).
- Upon progression, postprogression biopsy is important to establish the mechanism of resistance.
  - Liquid biopsy is an option
- Osimertinib approved for pts with T790M+ disease.
  - Other third-generation EGFR TKIs are being investigated.

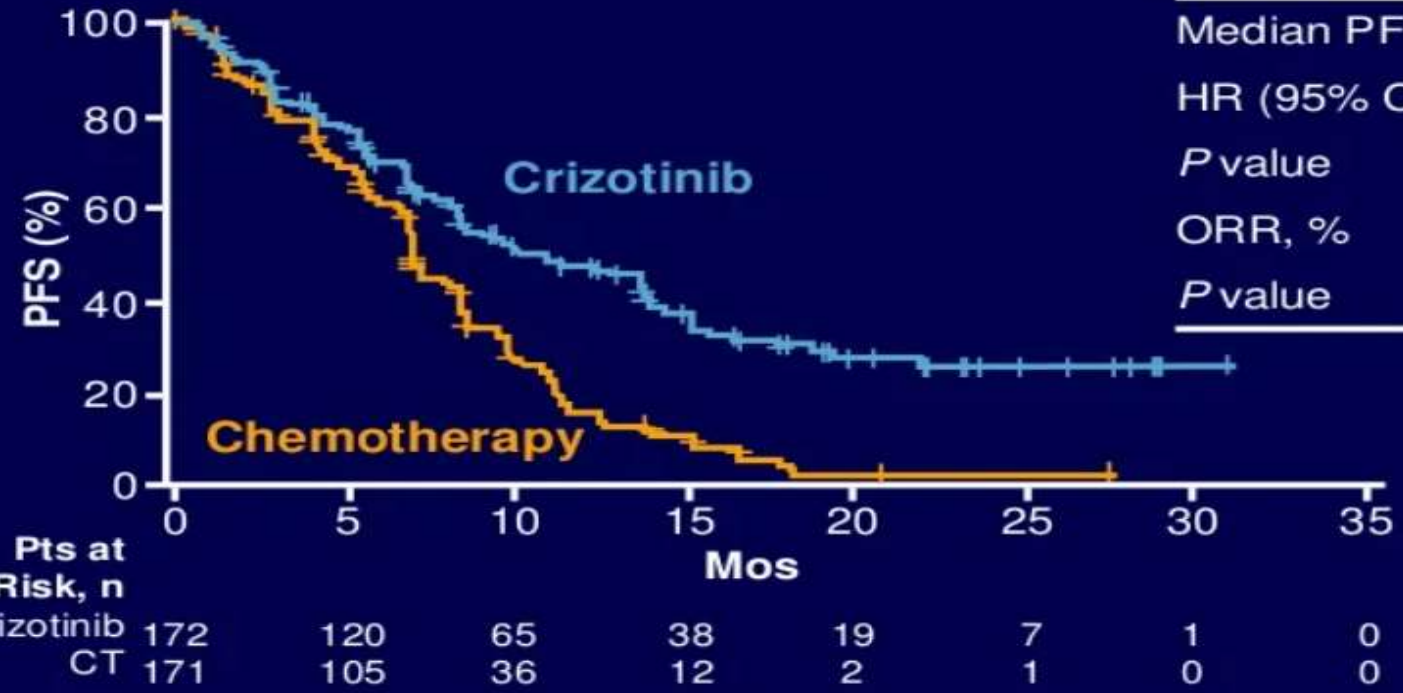
ALK Gene Rearrangement

- Most common in younger nonsmokers with adenocarcinoma, adenosquamous carcinoma, and rarely SCC
- Frequency: 4% overall, 33% in EGFR-negative never-smokers
- Several ALK variants identified in NSCLC
- Testing
  - Vysis break apart FISH (>15% cells with split signal in 50 nuclei scored); ALK IHC also approved
  - ALK next general sequencing
- 3 agents now approved for ALK-positive NSCLC (first line and/or after progression)

Shaw AT, et al. J Clin Oncol. 2009;27:4247-4253.
Soda M, et al. Nature. 2007;448:561-566.

PROFILE 1014: First-line Crizotinib vs Pemetrexed/Platinum* in Advanced NSCLC

- Phase III trial (N = 343) ALK-positive pts with nonsquamous NSCLC and no prior systemic treatment for advanced disease



	Crizotinib (n = 172)	Chemotherapy (n = 171)
Median PFS, mos	10.9	7.0
HR (95% CI)	0.45 (0.35-0.60)	
P value	< .001	
ORR, %	74	45
P value	< .001	

*Carboplatin or cisplatin.

Solomon BJ, et al. N Engl J Med. 2014;371:2167-2177.

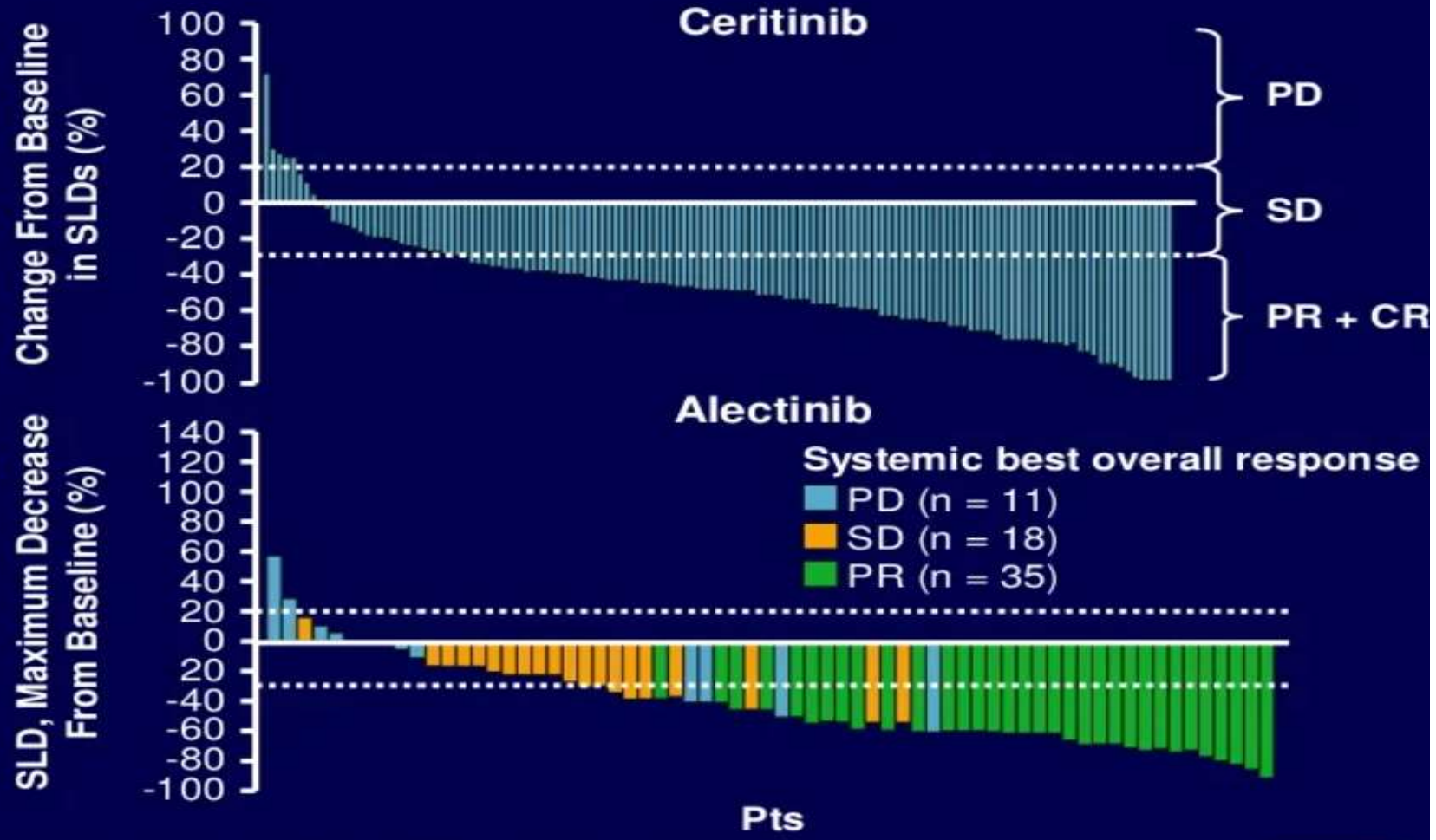
Second-Generation ALK Inhibitors

	N	Phase	Prior Cri?	ORR, %	Median PFS, Mos
Ceritinib					
▪ ASCEND-1[1]	163	I	Yes	56.0	6.9
	83	I	No	72.0	18.4
▪ ASCEND-2[2]	140	II	Yes	38.6	5.7
▪ ASCEND-3[3]	124	II	No	63.7	11.1
▪ ASCEND-5 [4]	231	III	Yes	39.1	5.4
Alectinib					
▪ Shaw[5]	87	II	Yes	48.0	8.1
▪ Ou[6]	138	II	Yes	50.0	8.9
Brigatinib[7]	222	II	Yes	45.0 (90 mg QD) 54.0 (180 mg QD)	15.6 (90 mg QD) NR (180 mg QD)

1. Kim DW, et al. Lancet Oncol. 2016;17:452-63. 2. Mok T, et al. ASCO 2015. Abstract 8059. 3. Felip E, et al. ASCO 2015. Abstract 8060. 4. Scagliotti G, et al. ESMO 2016. Abstract LBA42_PR. 5. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. 6. Ou SH, et al. J Clin Oncol. 2016;34:661-668. 7. Kim DW, et al. ASCO 2016. Abstract 9007.

Response to Ceritinib or Alectinib in Previously Treated *ALK*-Positive NSCLC

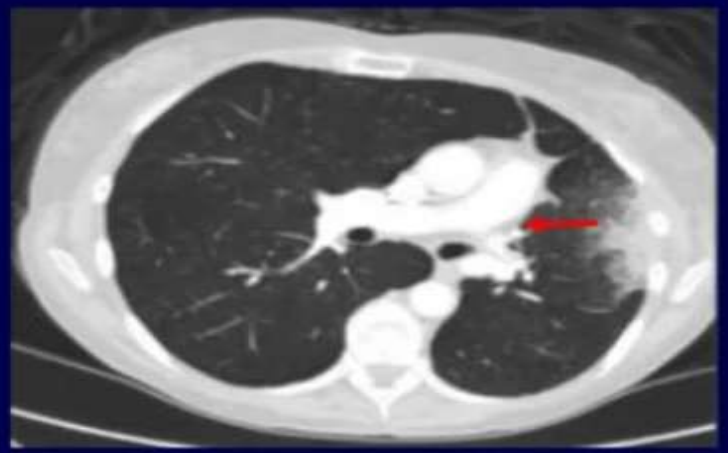
- Ceritinib (2014) and alectinib (2015) approved for pts with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib

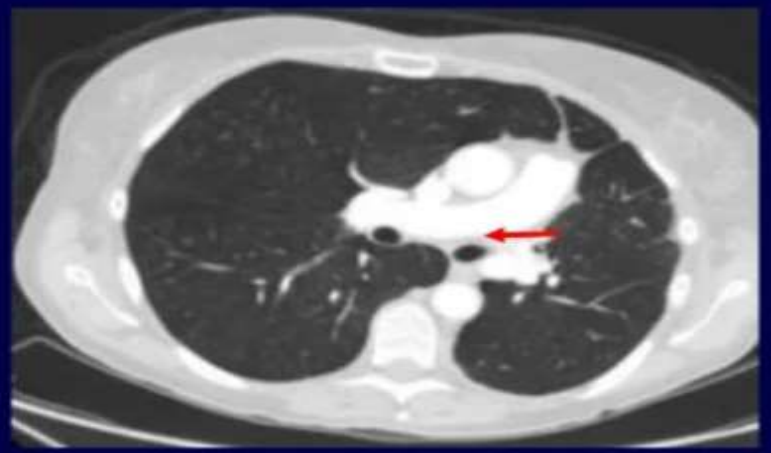


Kim DW, et al. Lancet Oncol. 2016;17:452-63. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. Ou SH, et al. J Clin Oncol. 2016;34:661-668.

Slide credit: clinicaloptions.com

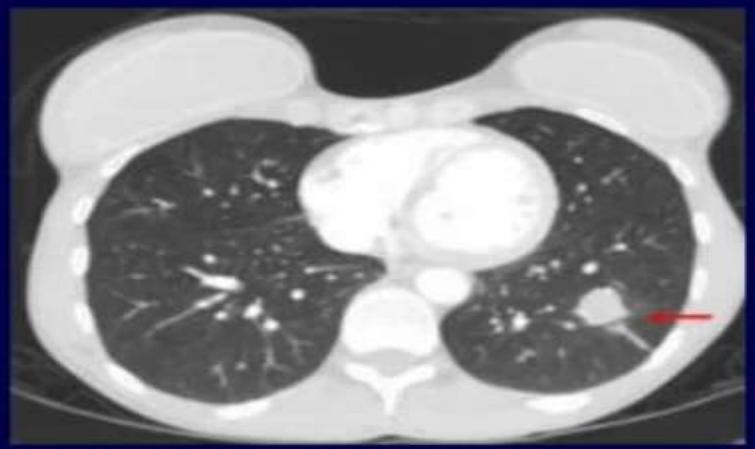
Lorlatinib Inhibits All Known Crizotinib-Resistance Mutations, Including ALK G1202R

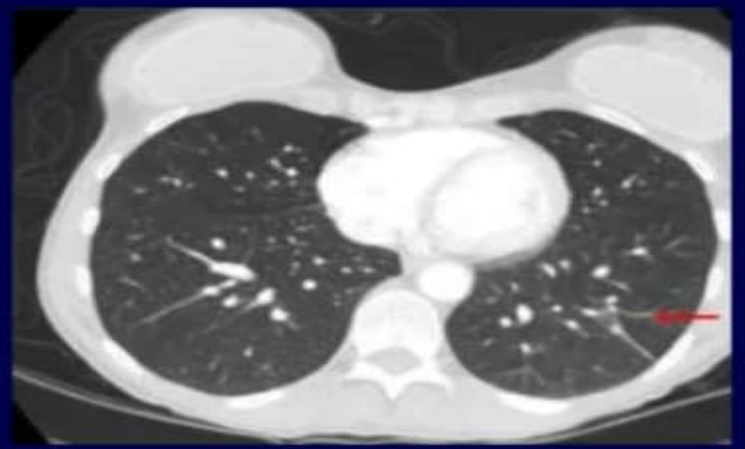




Pt 1: ALK+ NSCLC

- Previously treated with crizotinib and ceritinib
- Local molecular testing after ceritinib with ALK G1202R
- Started lorlatinib at 75 mg QD
- Dose reduced to 50 mg QD
- Ongoing at > 16 mos



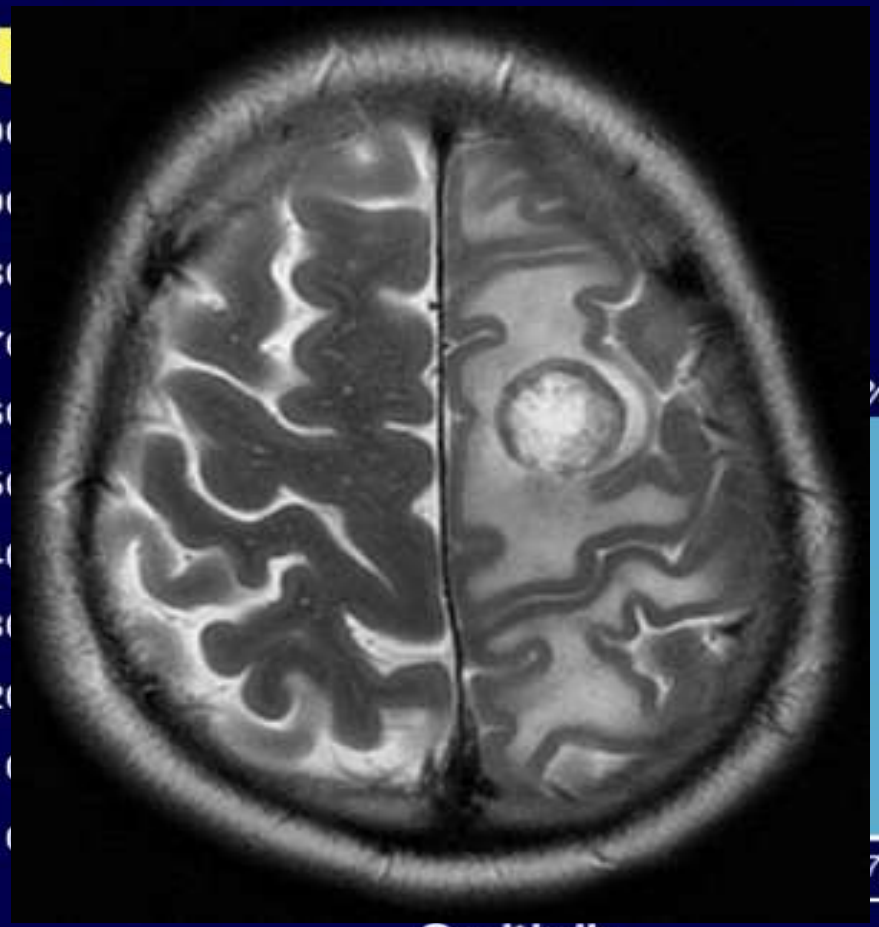


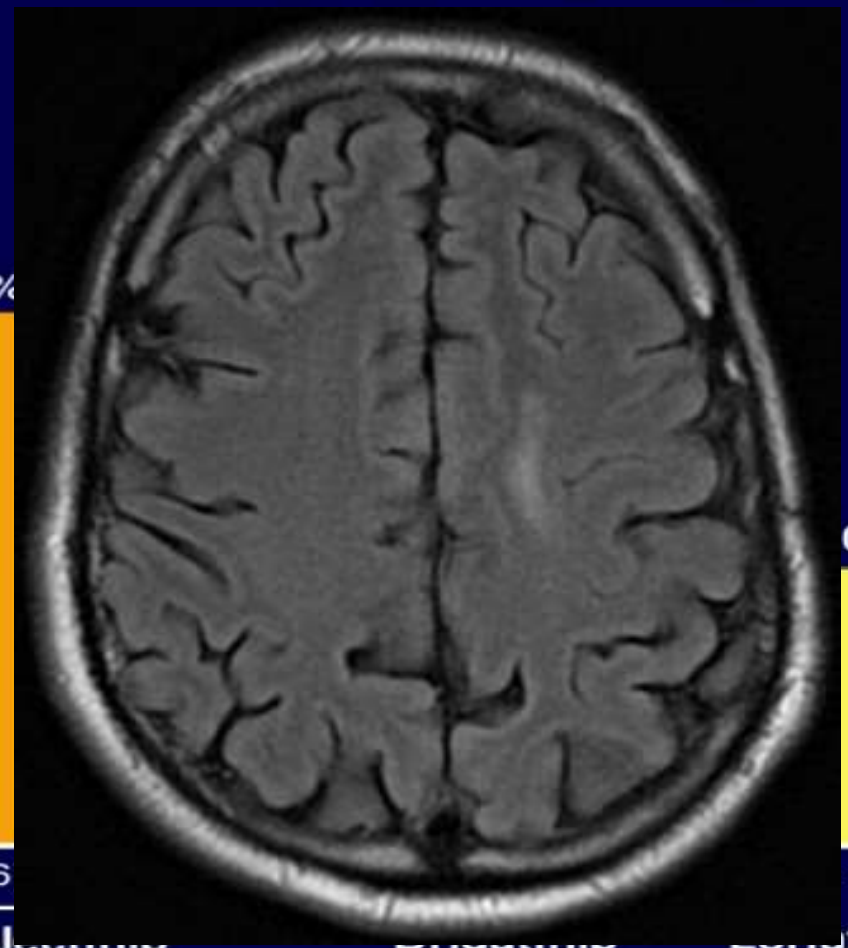
Pt 2: ALK+ NSCLC

- Previously treated with crizotinib and brigatinib
- Local molecular testing after brigatinib with ALK G1202R
- Started lorlatinib at 200 mg QD
- Dose reduced to 100 mg QD
- Ongoing at > 12 mos

Shaw AT, et al. ASCO 2015. Abstract 8018.

Second-Generation ALK Inhibitor CNS Act





Kim DW, et al. Lancet Oncol. 2016;17:452-463. Mok T, et al. ASCO 2015. Abstract 8059. Felip E, et al. ASCO 2015. Abstract 8060. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. Ou S, et al. J Clin Oncol. 2016;34:661-668. Kim DW, et al. ASCO 2016. Abstract 9007. Solomon BJ, et al. ASCO 2016. Abstract 9009.

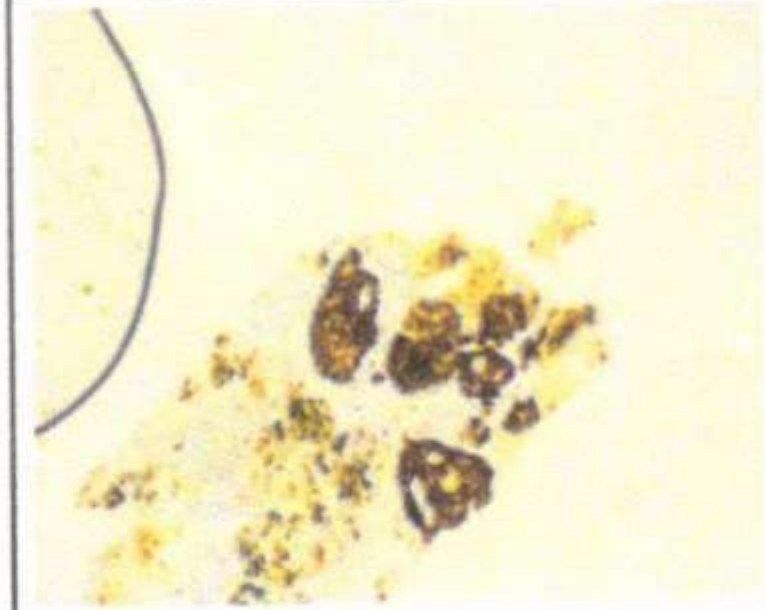
Summary of ALK Inhibitors

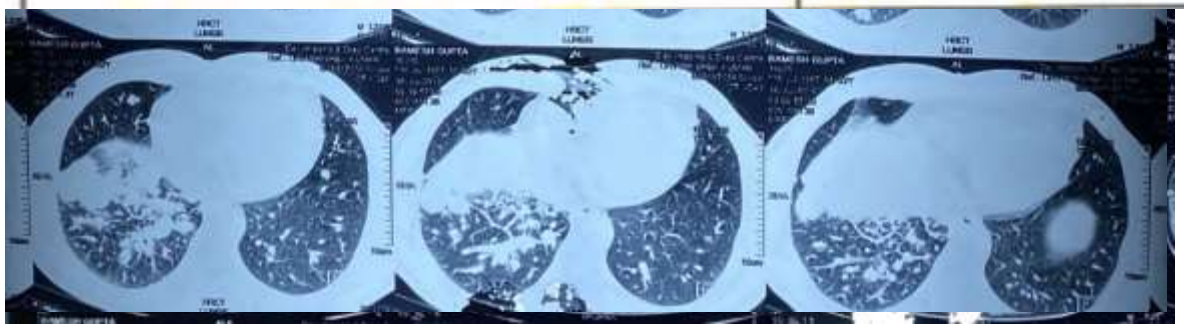
- All nonsquamous NSCLC should be tested for ALK mutations
  - Pts tend to develop brain metastases.
- Crizotinib improves response rate and PFS over chemotherapy in first-line and second-line settings.
- Second-generation ALK inhibitors ceritinib and alectinib are approved for secondary refractory disease or intolerance to crizotinib
  - Second-generation ALK inhibitors active in CNS disease.
- Alectinib demonstrated improved response rate and PFS over crizotinib as first-line therapy (J-ALEX).
- Many ALK-positive pts may derive benefit from multiple sequential ALK inhibitors.

METHODOLOGY

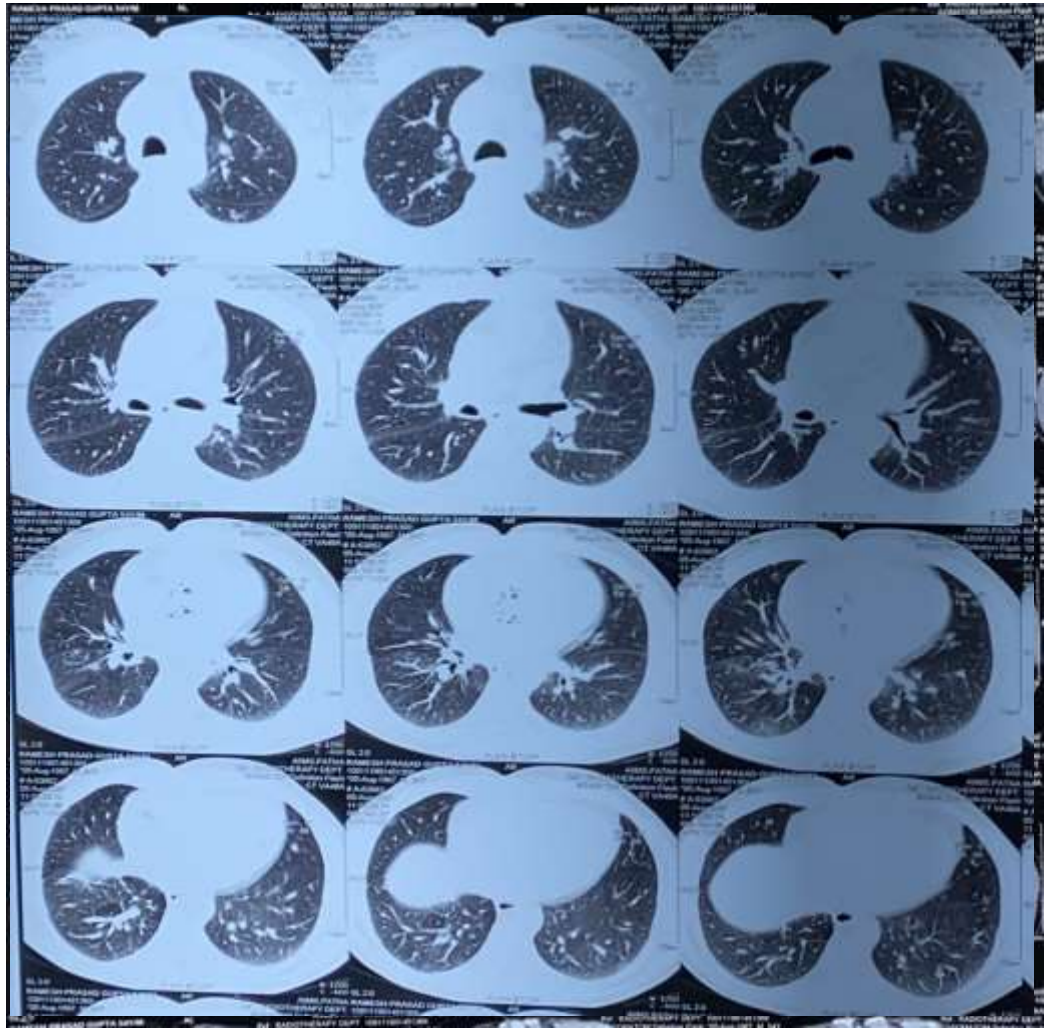
Immunohistochemistry

IMMUNOHISTOCHEMISTRY STUDIES

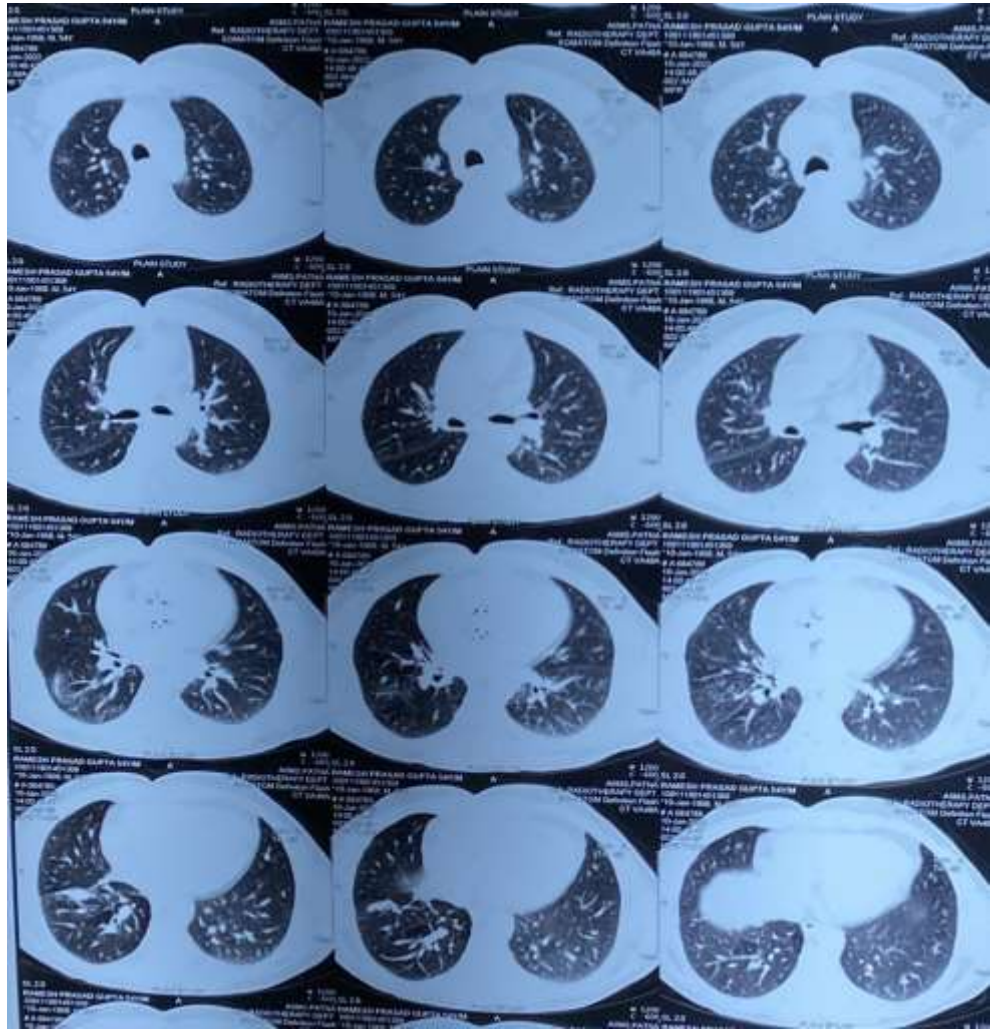
Marker(Clone)	Result	Image
ALK (D5F3)	POSITIVE	
NAPSIN A (EP 205)	POSITIVE	
P40 (Polyclonal)	NEGATIVE	



CECT Thorax
(05/08/2021)



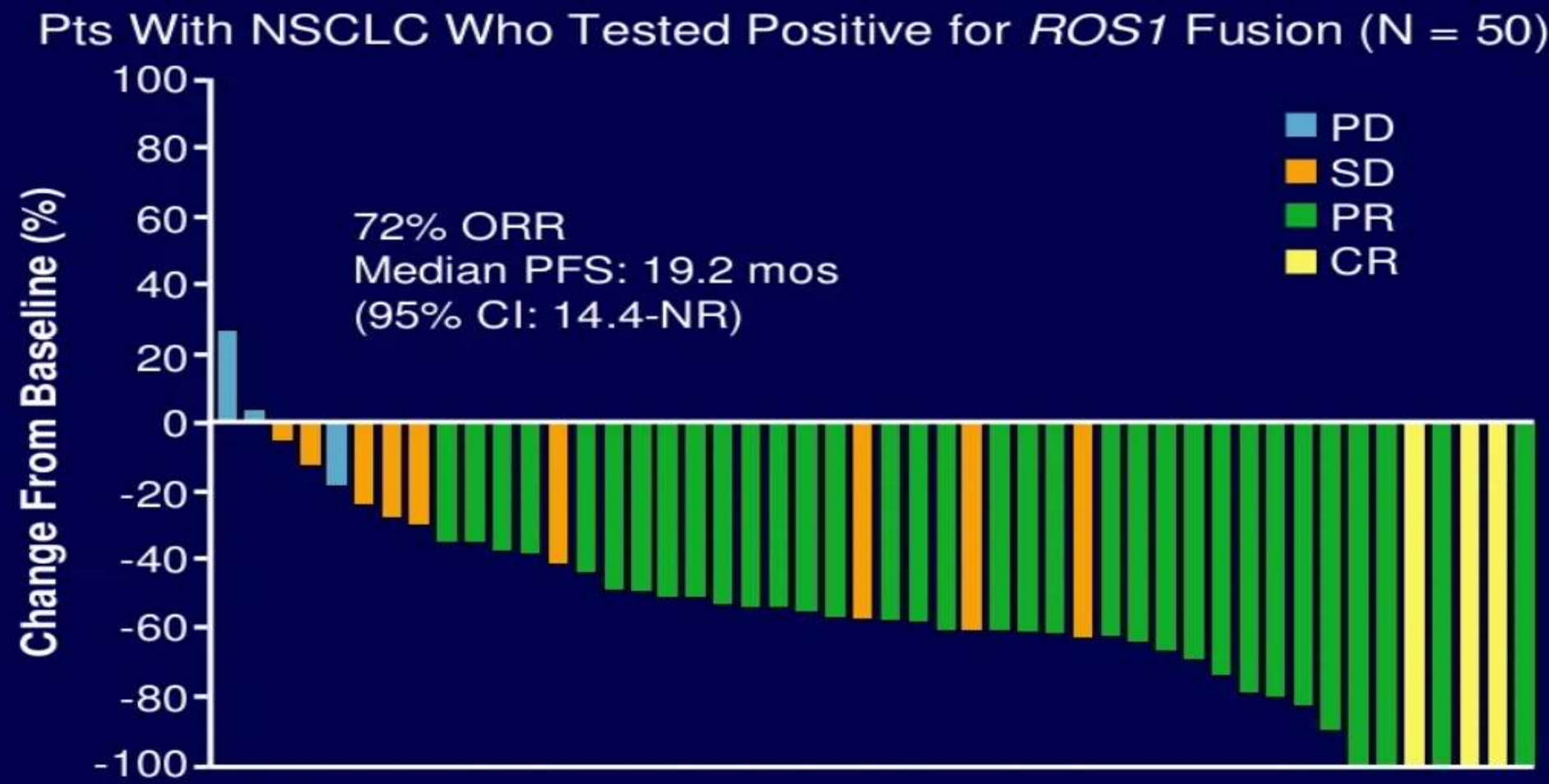
CECT Thorax
(10/01/2022)



ROS1 Fusion

- Most common in younger pts, never-smokers, adenocarcinoma, high-grade histology[1]
- Frequency: 1.2% to 1.7% overall[2]
- Several variants identified; clinical significance unknown[3]
  - FIG-, CD74-, SCL34A2-, TPM3-, SDC4-, EZR-, LRIG3, KDELR2-, and CCDC6-
- Testing: Vysis break apart FISH (>15% cells with split signal in 50 nuclei scored) [4-6]
  - ROS1 NGS, PCR, IHC (not validated)
- Crizotinib highly active; FDA approved in March 2016 for ROS1-positive NSCLC[7]

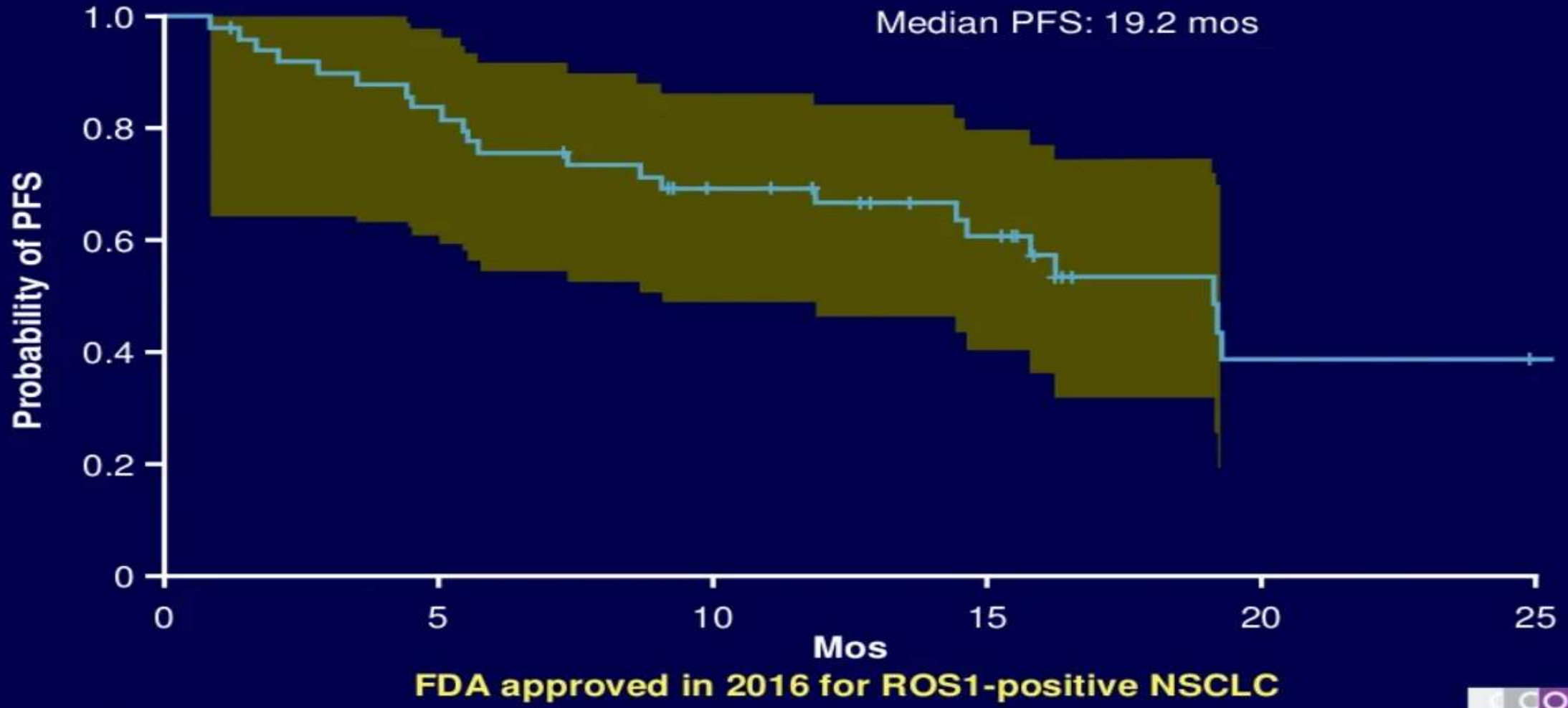
Activity of Crizotinib in Pts With *ROS1* Fusions: Best Overall Response



Shaw AT, et al. N Engl J Med. 2014;371:1963-1971.

Slide credit: clinicaloptions.com

Prolonged PFS With Crizotinib in ROS1-Positive NSCLC



FDA approved in 2016 for ROS1-positive NSCLC

Shaw AT, et al. N Engl J Med. 2014;371:1963-1971.

Slide credit: clinicaloptions.com

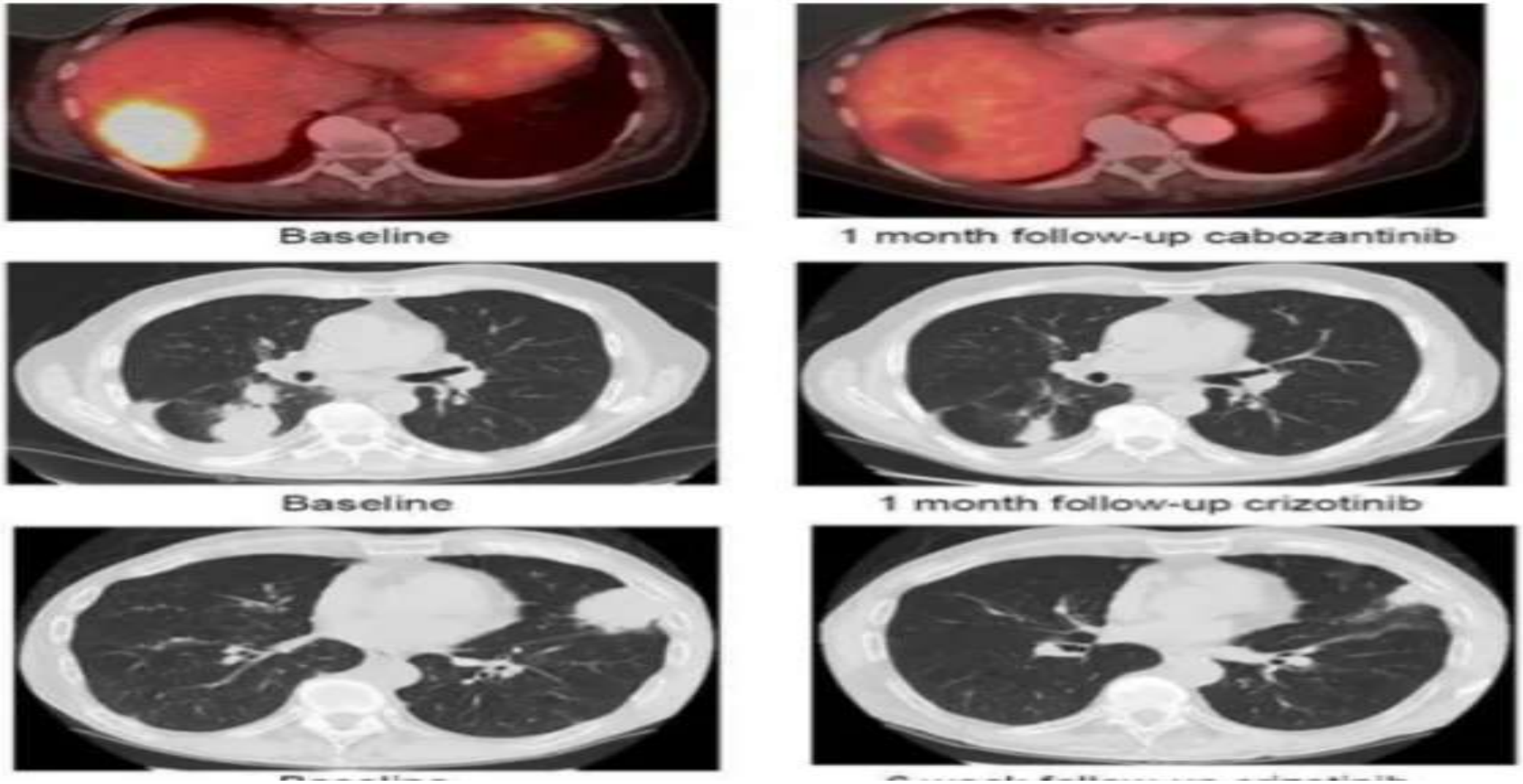
Summary ROS1 Driven Disease

- All nonsquamous NSCLC should be tested for ROS1 mutations
- Crizotinib is highly active in patients with ROS1-positive NSCLC
  - ORR of approximately 70%
  - Prolonged PFS
- Crizotinib is approved by the FDA for pts with ROS1-positive NSCLC and is the guideline recommended first-line therapy option in this setting.

MET Exon 14 Mutation in NSCLC

- Associated with advanced age (older than KRAS or EGFR mutations:
- In one series, 68% were female and 36% nonsmokers; majority had adenocarcinoma or adenocarcinoma with pleomorphic or sarcomatoid histology
- Frequency: 3% overall; 26% in sarcomatoid pulmonary carcinoma.
- Testing: PCR or NGS.
- Therapy: MET inhibitors.

Response to MET Inhibition in MET Exon 14 – Altered NSCLC.



BRAF Mutated NSCLC

More common in current and former smokers, females.

Primarily in adenocarcinoma; other histologies rarely described

Frequency: 2% to 4%.

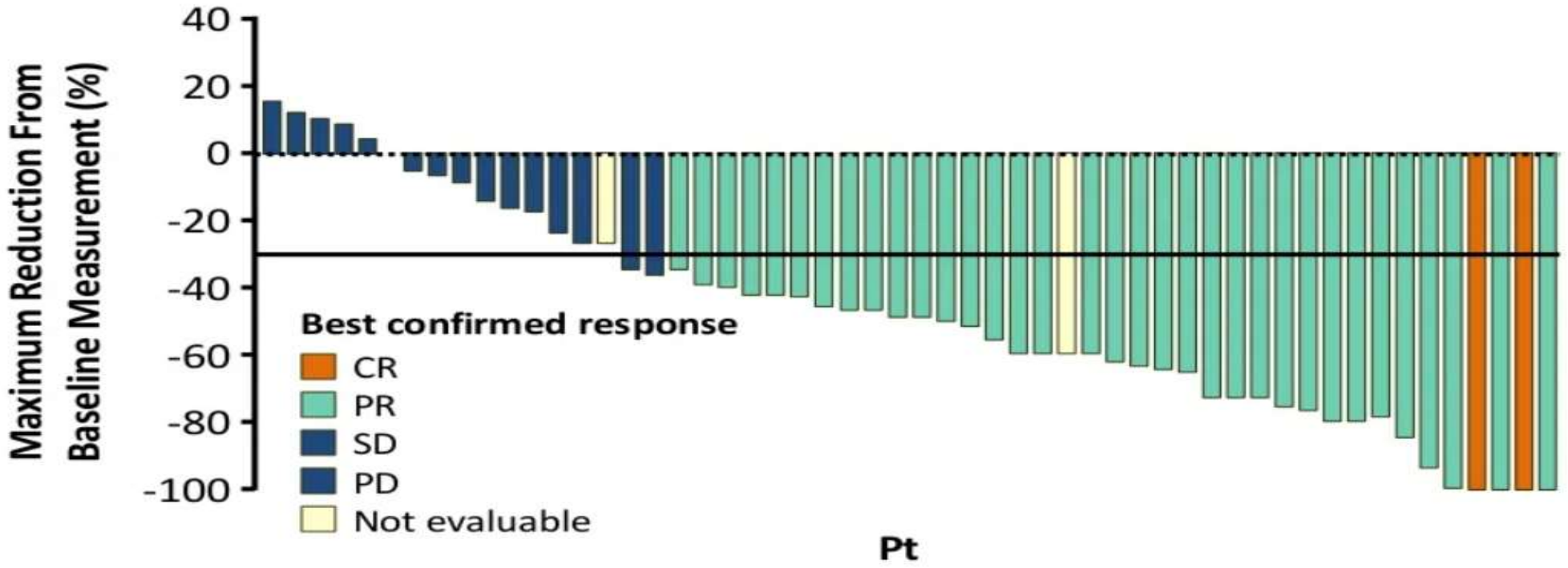
- BRAF V600E mutations account for 50% of all BRAF mutations (lower than incidence in melanoma)

Testing: PCR.

Therapy: BRAF inhibitors, single agent or in combination with a MEK inhibitor.

Dabrafenib and Trametinib best confirmed response in > second line

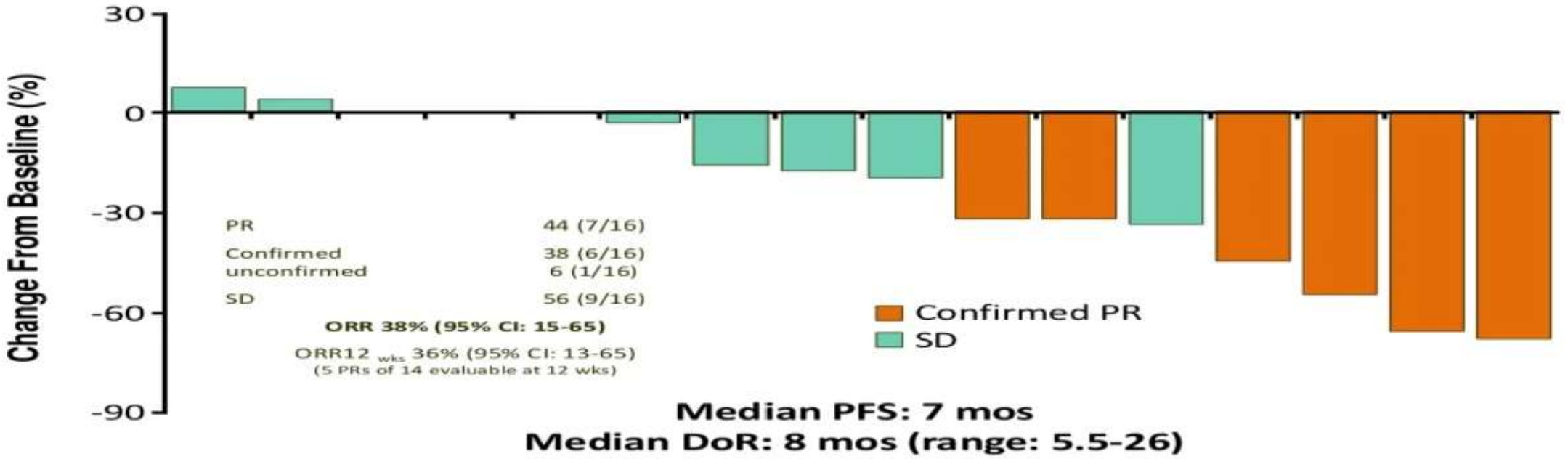
- Clinically meaningful antitumor activity with a higher ORR when compared indirectly with dabrafenib monotherapy in BRAF V600E–mutated NSCLC
  - ORR 63% and DCR 75% for dabrafenib plus trametinib
  - ORR 33% and DCR 56% for dabrafenib as monotherapy



RET fusion

- Most common in adenocarcinoma and adenosquamous carcinoma, never or former smokers, poorly differentiated tumors, earlier LN metastases[1,2]
- Frequency: 1.4% overall; increasing in nonsmokers without other mutations[2,4]
- Several variants identified in NSCLC[4]
- Testing
  - Vysis break apart FISH (>15% cells with split signal in 50 nuclei scored)
  - RET PCR (NGS)
- Multikinase inhibitors with RET activity: vandetinib, sorafenib, sunitinib, cabozantinib.

Carbozantinib in RET rearranged NSCCL : Response



Drilon AE, et al. ASCO 2015. Abstract 8007.

Neurotrophic Tyrosine Kinase (NTRK) and Tropomysin –Related Kinases A,B, C.

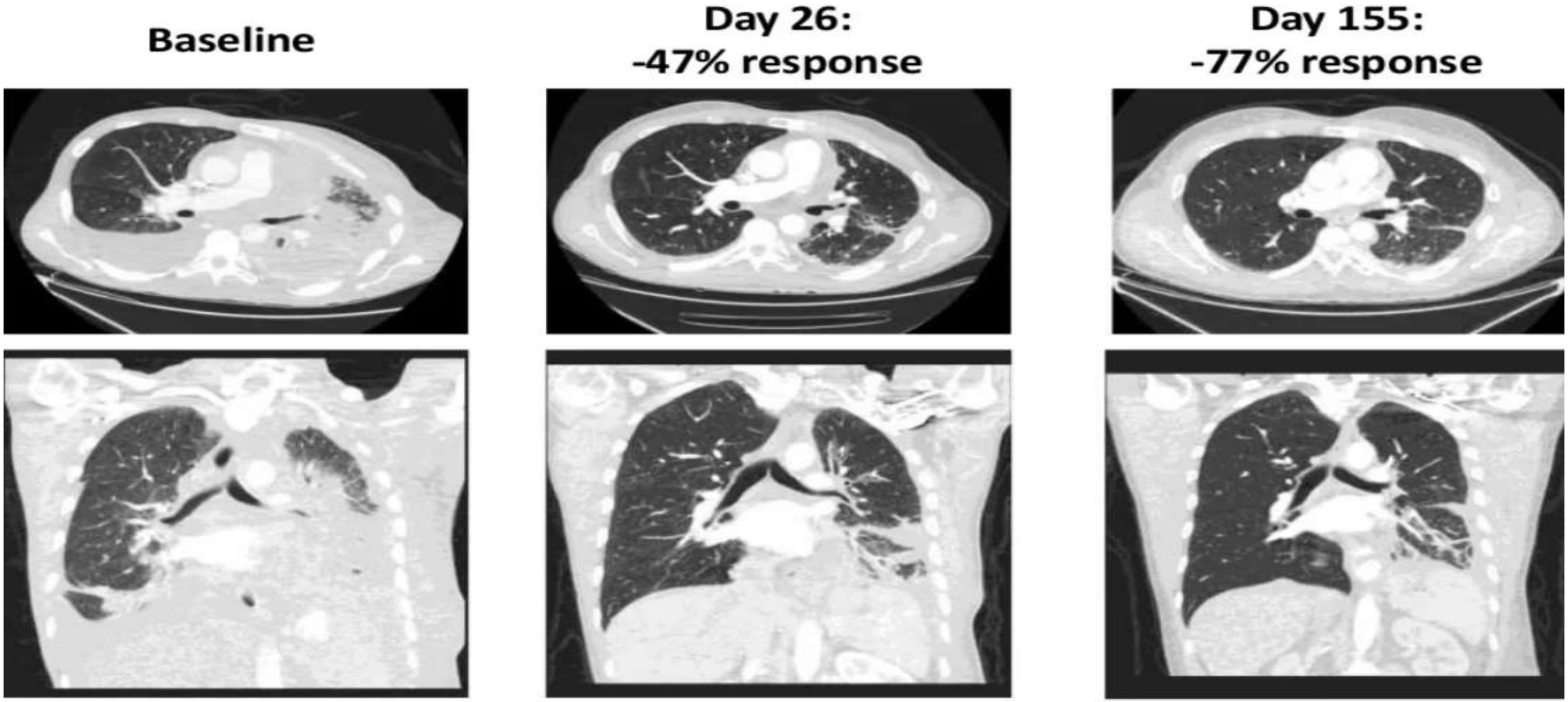
- TrkA, TrkB, and TrkC : receptor tyrosine kinases encoded by NTRK1, NTRK2, NTRK3 genes

➢ Implicated in neuronal development

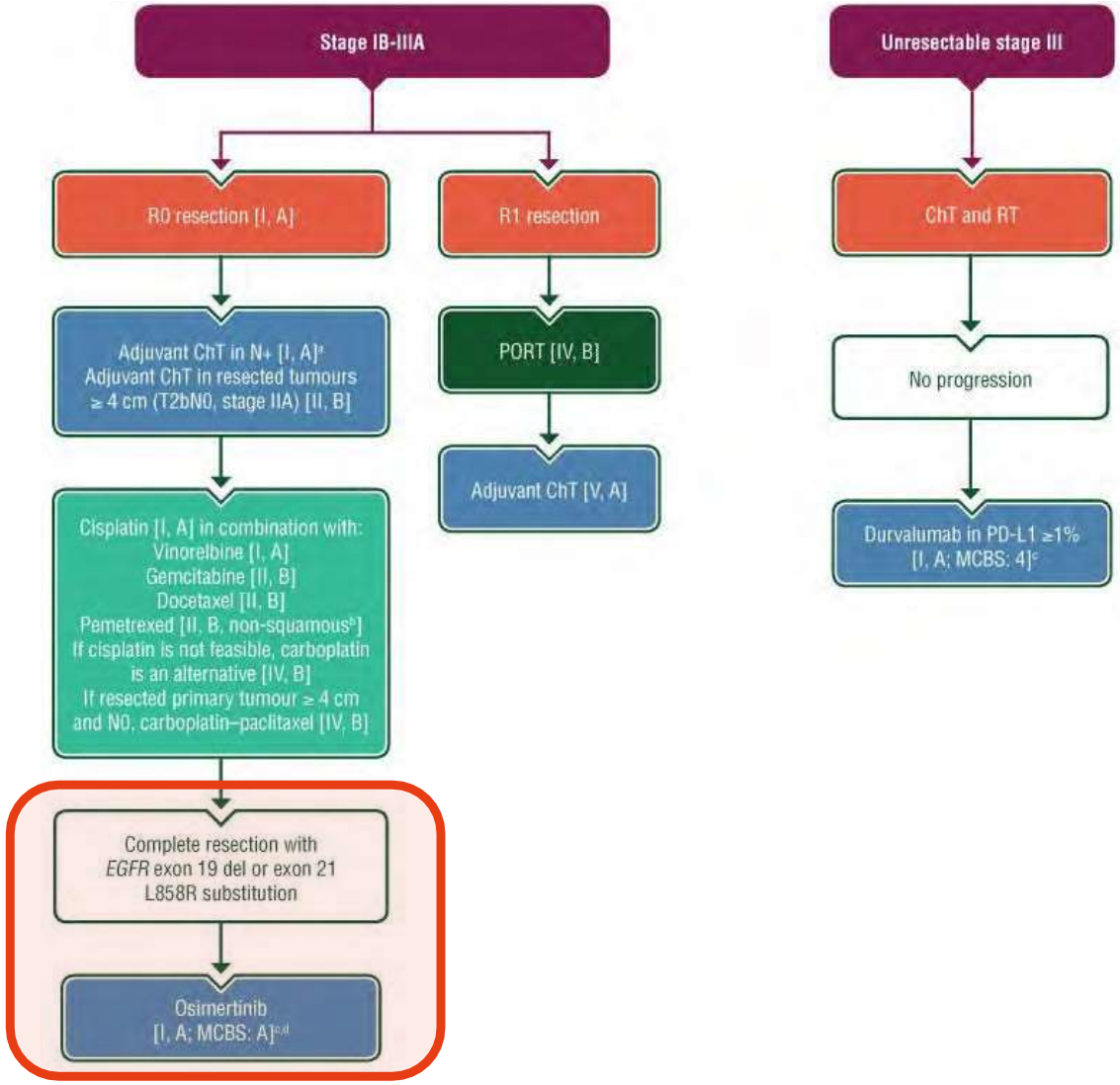
- Mutations or fusions in TK domain lead to constitutive activation

➢ Several fusions described in lung cancer primarily involving NTRK1 and NTRK2.

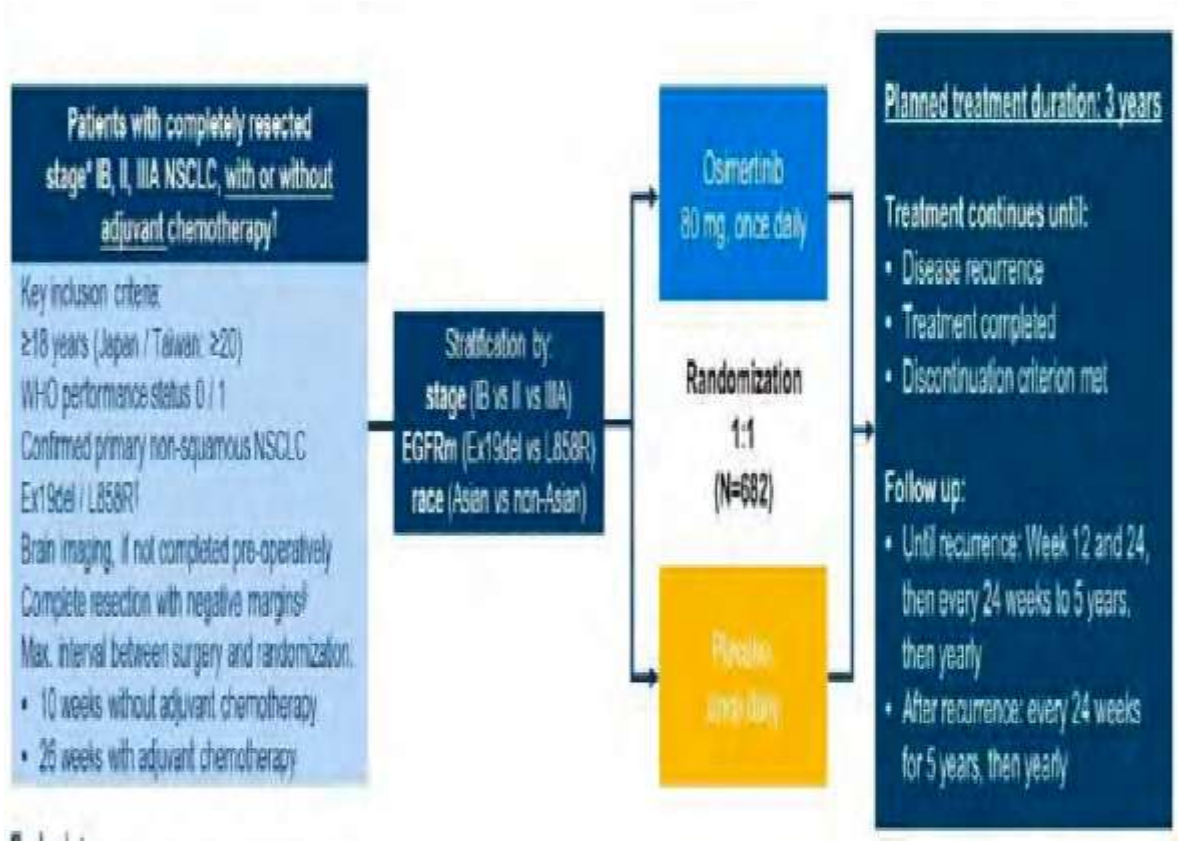
Clinical response to Entrectinib NTRK1 – Rearranged NSCLC.



EGFR mutated early NSCLC

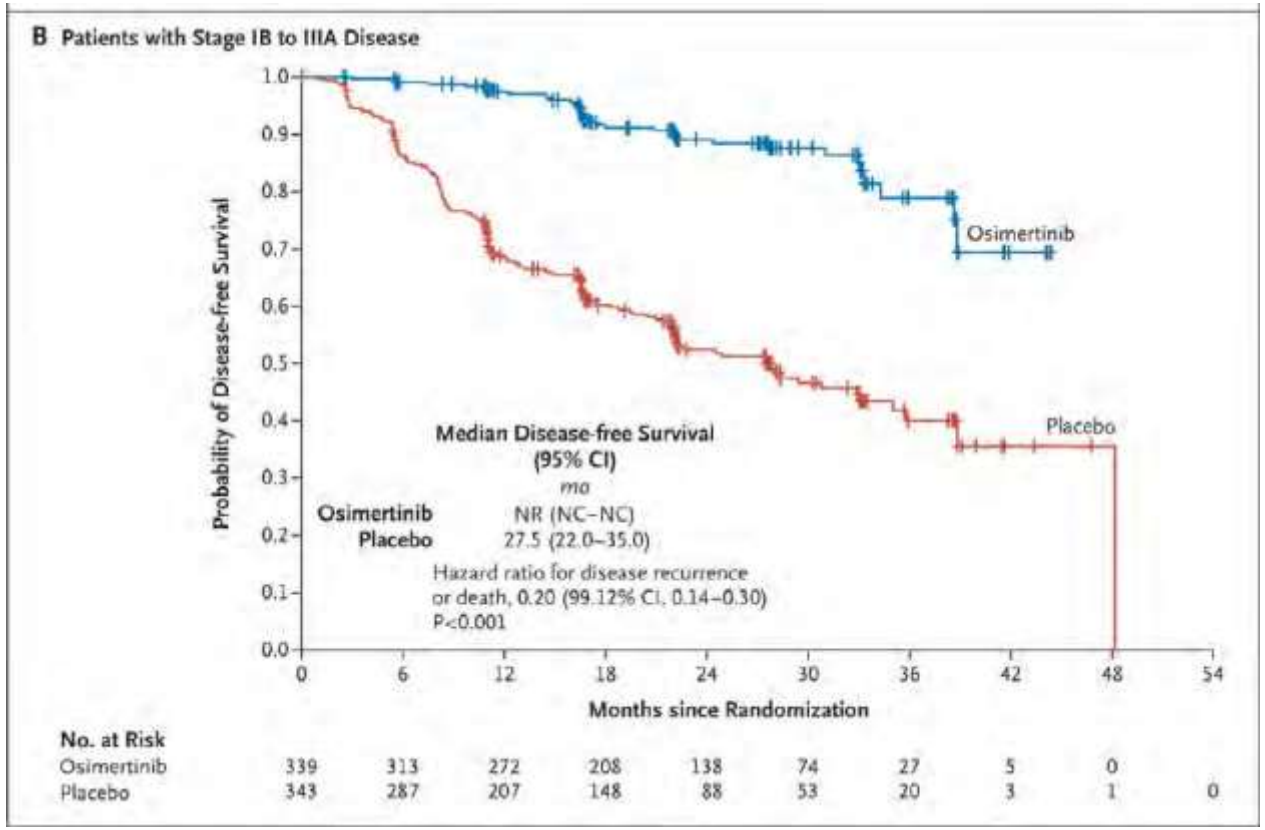


- ADAURA: Adjuvant osimertinib vs placebo

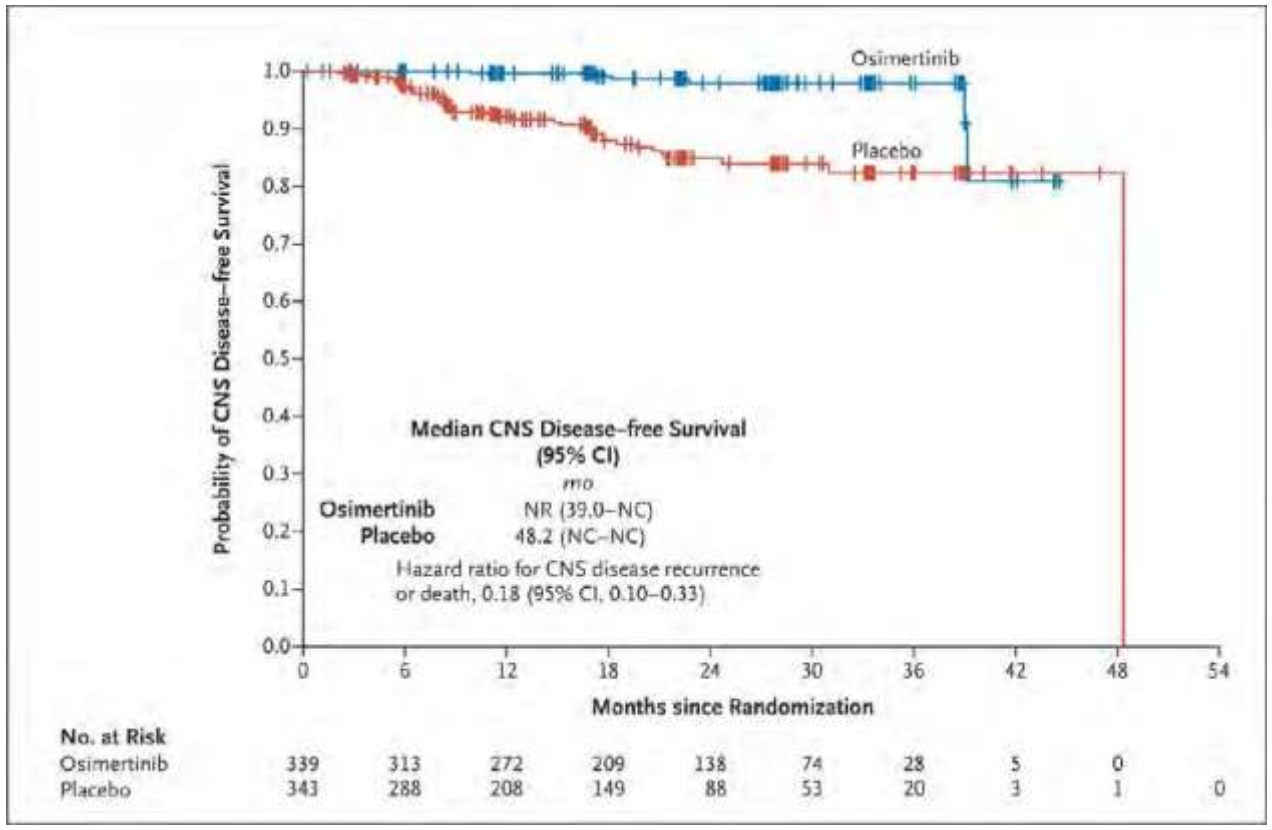


ADAURA: Adjuvant osimertinib vs placebo

Disease-free Survival

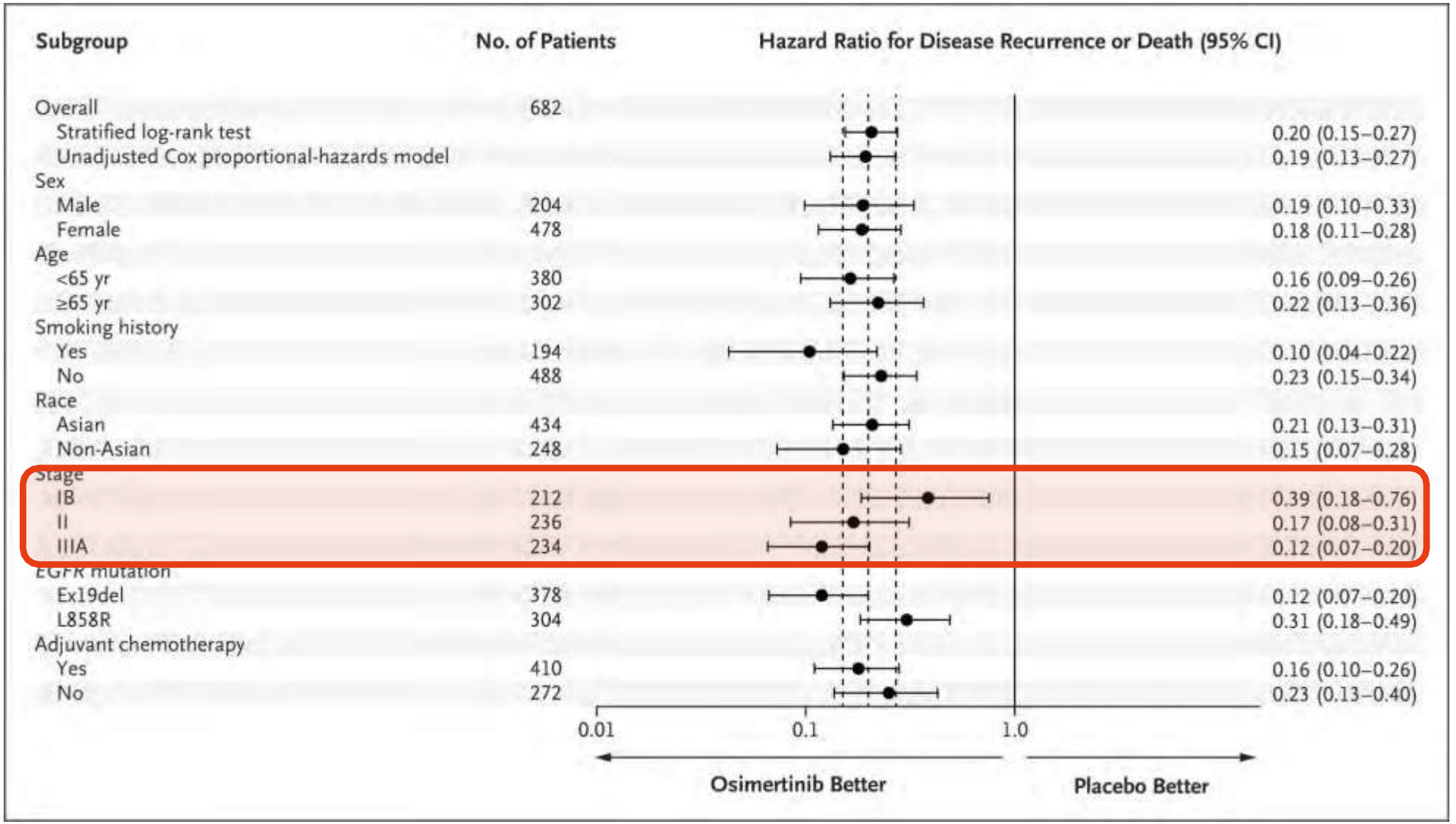


CNS disese-free survival



Wu, NEJM 2020

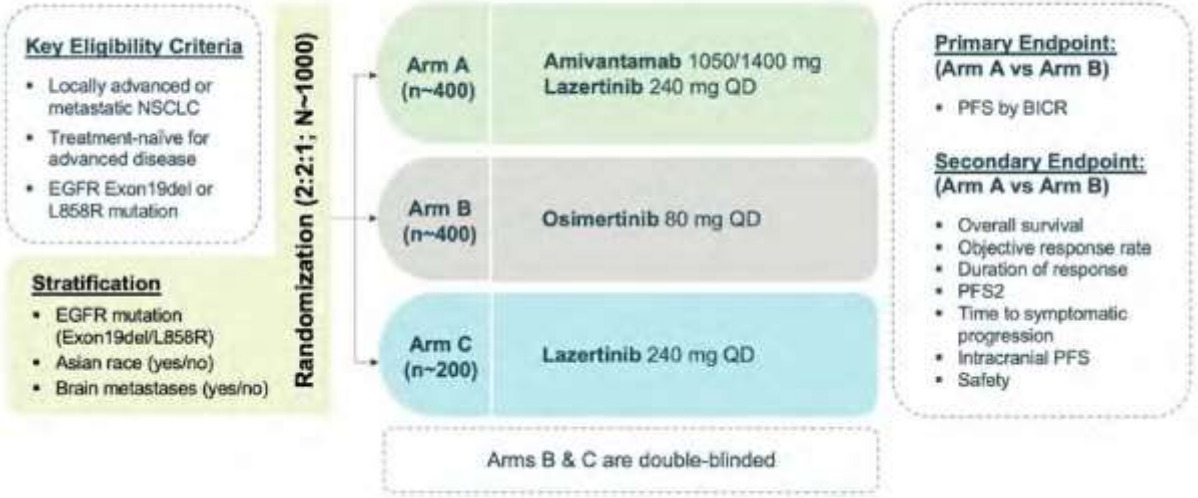
ADAURA: Adjuvant osimertinib vs placebo



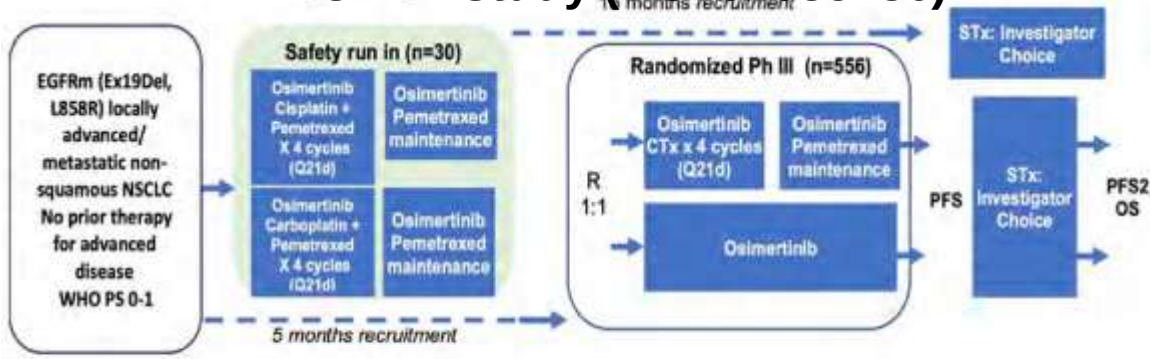
Wu, NEJM 2020

Important ongoing phase 3 trials in EGFR-mutant NSCLC

Phase 3 MARIPOSA Study (NCT04487080)



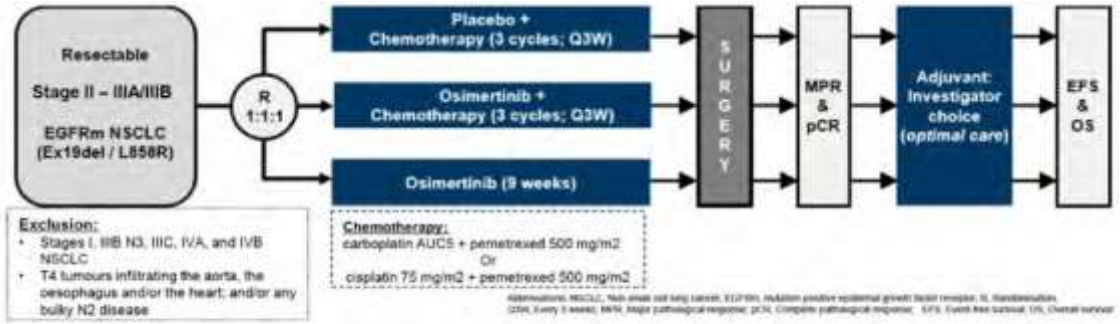
FLAURA2 study (NCT04035486)



Stratification factors:

1) Central or local method for tissue testing for potential differences in EGFR mutation detection
2) Race Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian
3) Baseline performance status based on the WHO PS.

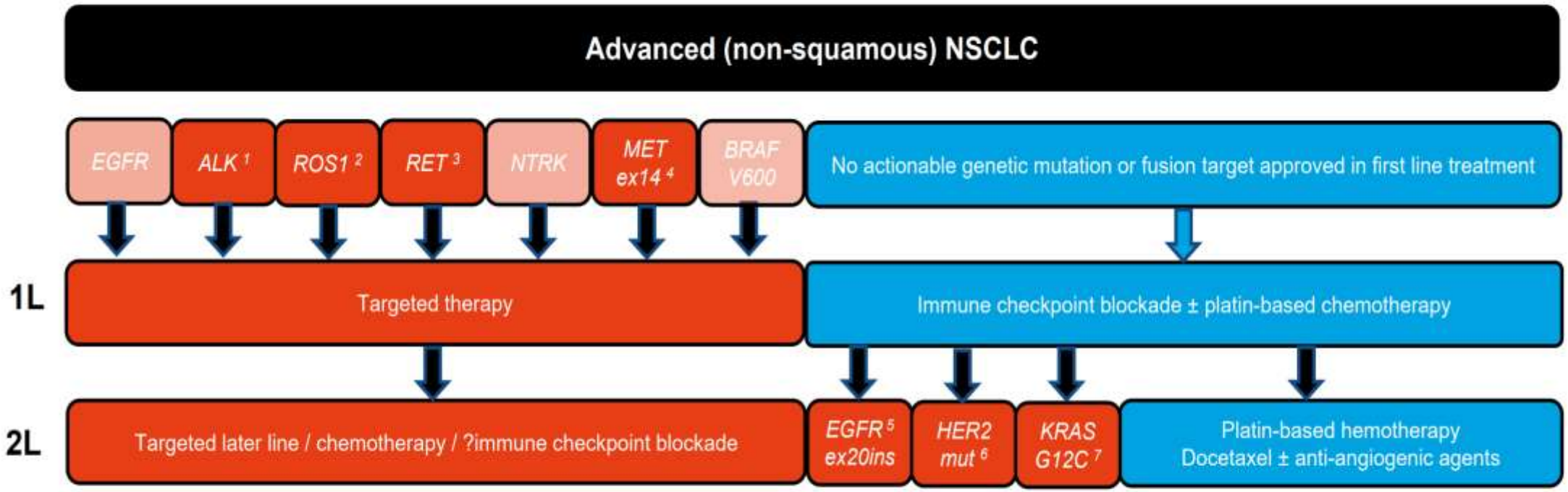
Phase 3 NeoADAURO study (NCT04351555)



Primary endpoint MPR

Secondary endpoints pCR, downstaging, EFS, OS, HRQoL, Saftery & tolerability

New treatment options in advanced NSCLC 2020 and 2021



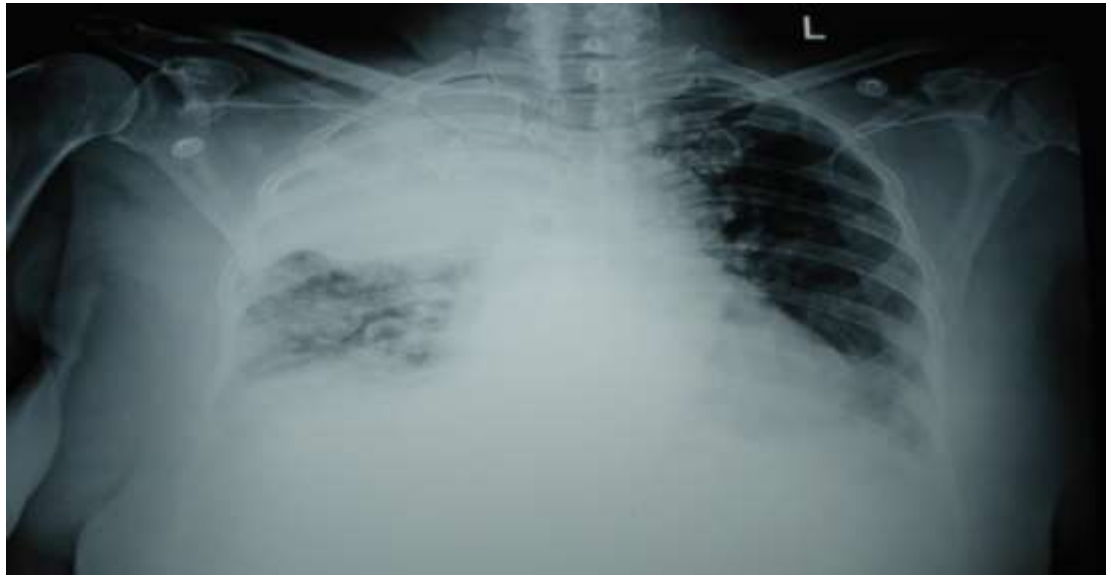
[1] Lorlatinib 1L (FDA), 2L (EMA)
[2] Entrectinib 1L (FDA), 2L (EMA)
[3] Salpercatinib 1L (FDA), 2L (EMA)
Pralsetinib 1L (FDA and EMA)
[4] Capmatinib 1L (FDA)
Tepotinib 1L (FDA)

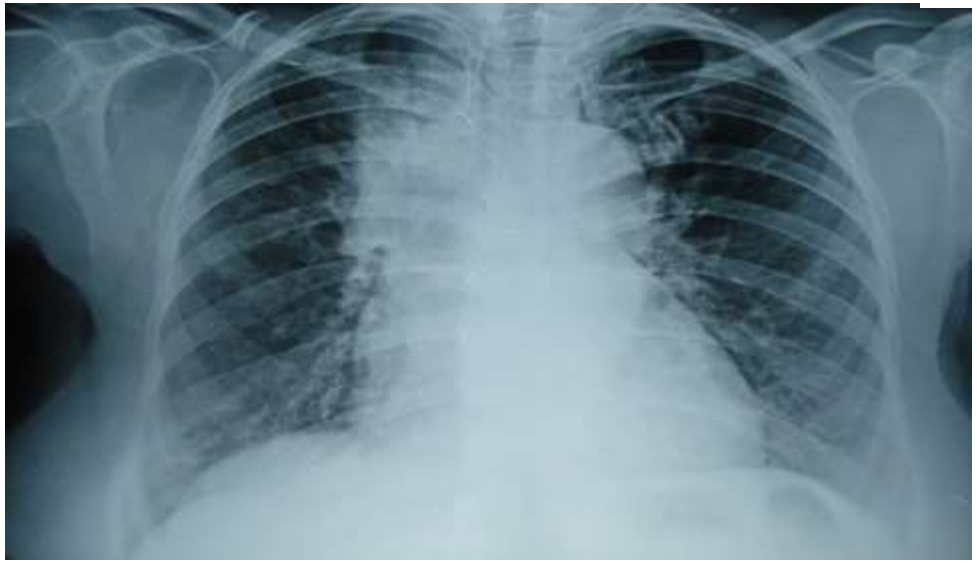
[5] Amivantamab 2L (FDA)
Mobocertinib 2L (FDA)
[6] Trastuzumab deruxtecan 2L (FDA)
[7] Sotorasib 2L (FDA)

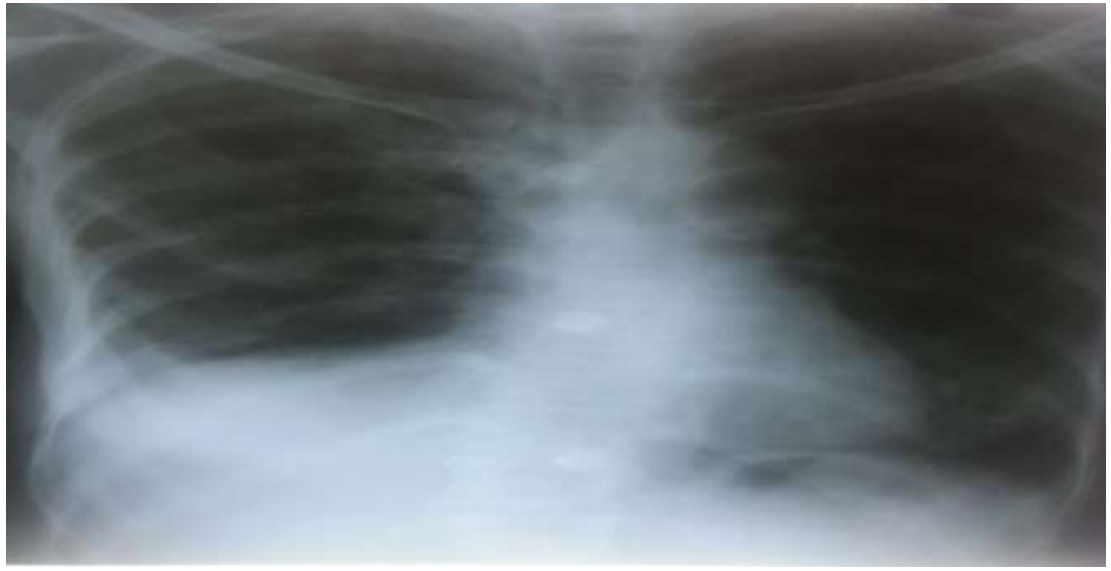
Conclusions for targeted therapy

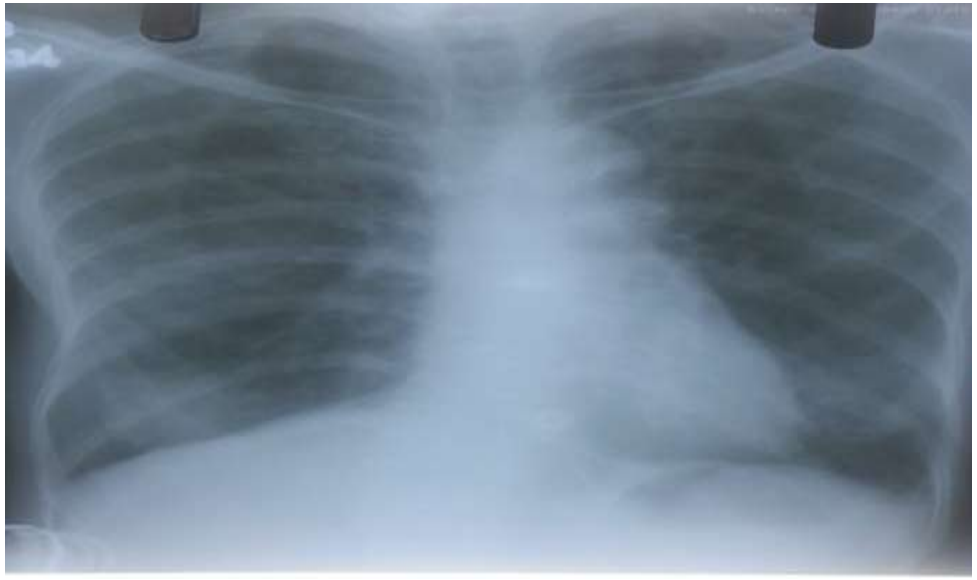
- For pts with stage IV NSCLC and adenocarcinoma component, molecular testing is the standard of care
- FDA-targeted agent approvals for treatment of metastatic NSCLC
  - ALK rearrangement: crizotinib, ceritinib, alectinib
  - EGFR mutation: afatinib, erlotinib, erlotinib, gefitinib, osimertinib
  - ROS1 rearrangement: crizotinib
- Encourage broad molecular testing for pts without ALK, EGFR, or ROS1 mutations.

Targeted Therapy





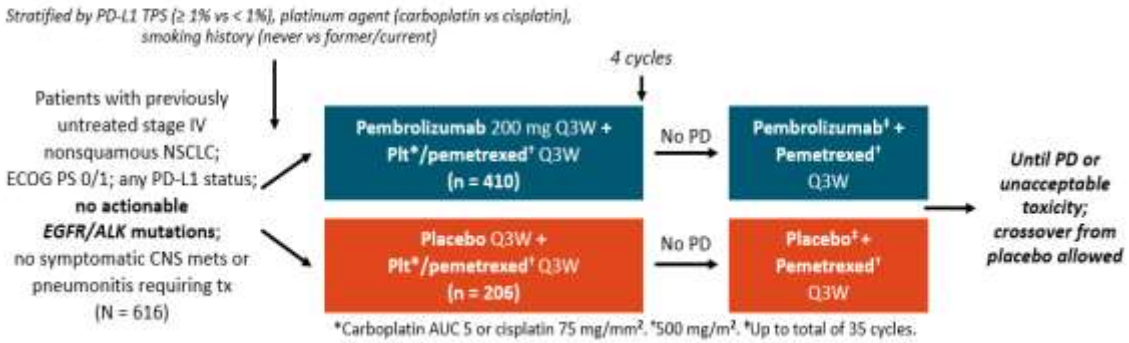




Novel Chemotherapy Regimens with Immunotherapy

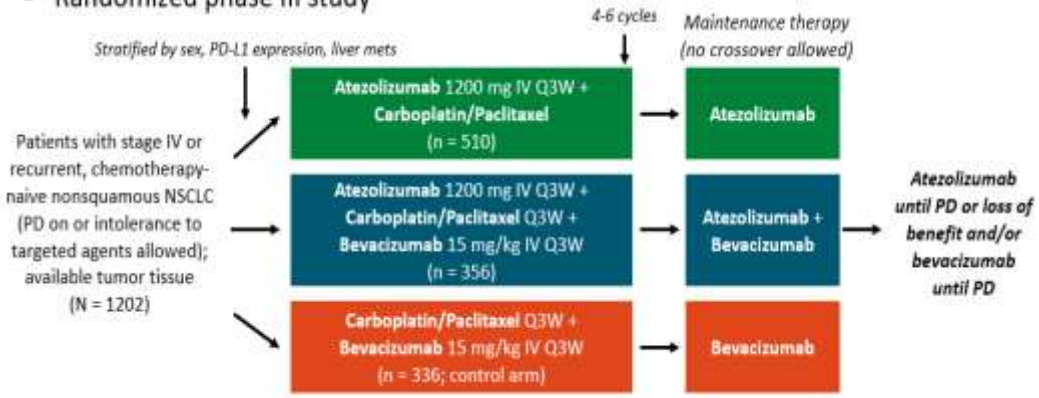
KEYNOTE-189: First-line Pembrolizumab + CT vs Placebo + CT in Stage IV Nonsquamous NSCLC

- Randomized, double-blind, international phase III study



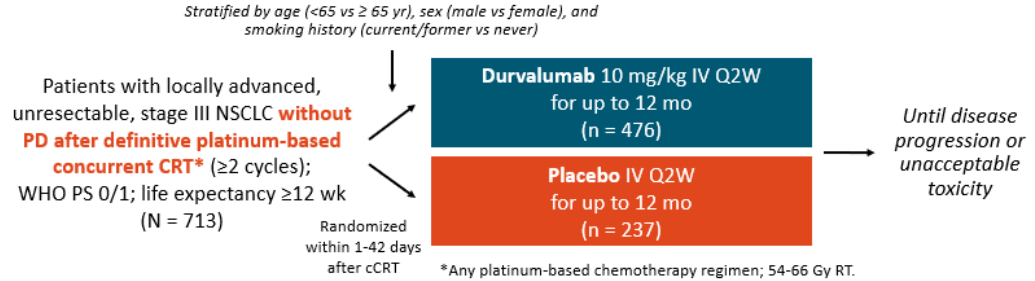
IMpower150: Addition of Atezolizumab to Carbo/Pac + Bevacizumab in Advanced NSCLC

- Randomized phase III study



PACIFIC: Consolidation Durvalumab After Concurrent CRT for Locally Advanced, Unresectable, Stage III NSCLC

- Randomized, double-blind, placebo-controlled phase III trial



Future Directions in NSCLC: Novel Approaches for the Treatment of Immune-Refractory NSCLC

ICI combination	Examples	Potential mechanism(s)
Single/dual ICI therapy	Anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-LAG3	Alternate immune checkpoints Severe T-cell exhaustion
ICI + immune stimulating agents	Anti-OX40, anti-CD137/4-1BB, anti-CD40, anti-ICOS, oncolytic viruses, TLR agonists, vaccines, NK cell activation (anti-KIR)	Lack of sufficient or suitable neo-antigens Impaired processing or presentation of tumor antigens Impaired intratumoural immune infiltration Impaired IFNγ signaling Alternate immune checkpoints
ICI + metabolic inhibitors	IDO inhibitors, adenosine receptor (A2AR) inhibitors	Metabolic/inflammatory mediators Immune suppressive cells
ICI + targeted therapies	BRAF + MEK inhibitors, VEGF inhibitors, EGFR inhibitors, PARP inhibitors, mTOR inhibitors	Impaired intratumoural immune infiltration Impaired IFNγ signaling Alternate immune checkpoints
ICI + epigenetic modifiers	Histone deacetylase inhibitors, hypomethylating agents (e.g., DNA methytransferase inhibitors)	Impaired intratumoural immune infiltration Impaired IFNγ signaling T-cell epigenetic changes
ICI + chemotherapy	Paclitaxel, dacarbazine, carboplatin/paclitaxel, carboplatin/gemcitabine	Lack of sufficient or suitable neo-antigens
ICI + radiation	Hypofractionated radiation, stereotactic body radiation	Lack of sufficient or suitable neo-antigens

Jenkins. Brit J Cancer. 2018;118:9.

Thank You

“If it were not for the great variability among individuals, medicine might as well be a science and not an art.”

Sir William Osler.