Chemotherapy and targeted therapy of non-small cell lung cancer

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17th ESO-ESMO Masterclass Clinical Oncology

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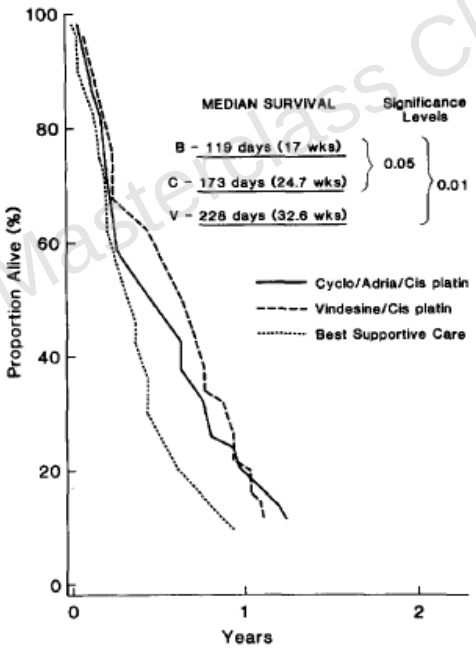
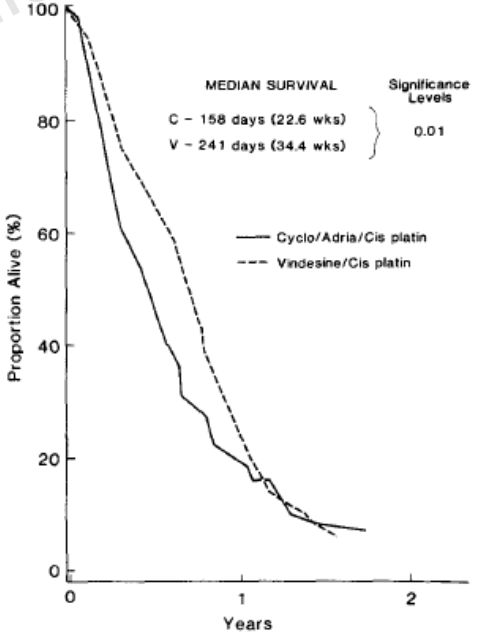
Chemotherapy can prolong survival in patients with advanced NSCLC – report of a Canadian multicenter randomized trial

		Allocated	Eligible	Evaluable for Response
RANDOMIZE	BSC	53	50	
	CAP	48	43	40
	VP	49	44	42
RANDOMIZE	CAP	52	49	45
	VP	49	47	45
TOTAL		251	233	172





Rapp, JCO 1988

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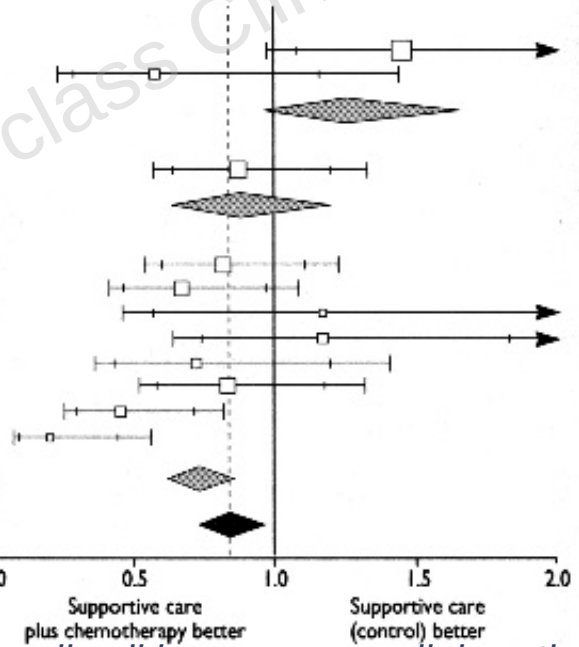
Chemotherapy of NSCLC: a meta-analysis using updated data on individual patients from 52 randomized trials

Trial	No of events/ No of patients entered: Supportive care plus chemotherapy	Supportive care	Observed – expected deaths	Variance
Long term alkylating agents:				
Oxford	120/121	62/67	16.40	43.80
Quebec	20/20	18/18	-4.38	7.99
Subtotal	140/141	80/85	12.02	51.79
Vinca alkaloids/etoposide:				
Gwent 2	96/111	67/75	-5.15	38.00
Subtotal	96/111	67/75	-5.15	38.00
Cisplatin based:				
RLW 8351	84/86	80/81	-8.06	39.94
NCIC CTG	95/97	51/53	-11.28	28.24
Southampton	17/17	15/15	1.16	7.55
NRH	44/44	40/43	2.93	18.72
UCLA	31/32	30/31	-4.83	14.53
Ancona 1	63/63	65/65	-5.72	30.95
AOI-Udine	52/52	50/50	-14.98	18.77
CEP-85	23/25	21/24	-10.52	6.61
Subtotal	409/416	352/362	-51.31	165.31
Total	645/668	499/522	-44.44	255.09



Non-small cell lung cancer collaborative group, BMJ 1995

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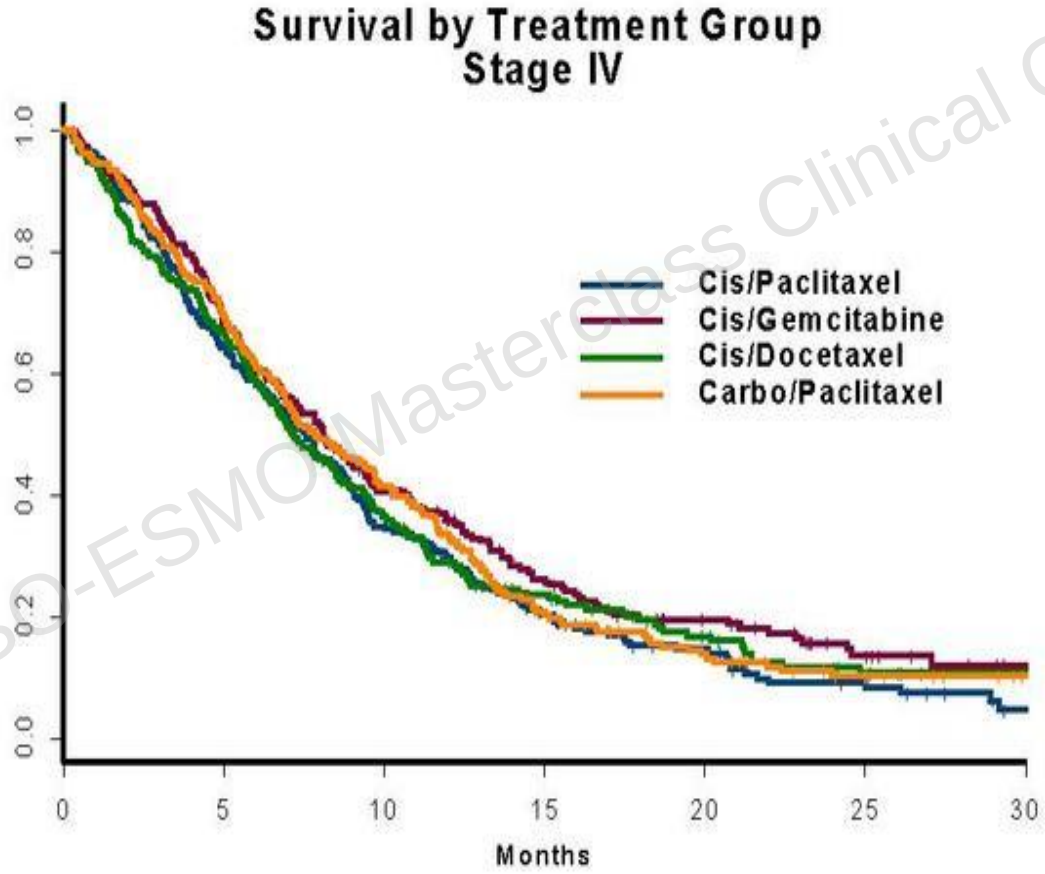
Systemic therapy of NSCLC: A pleateau had been reached



Schiller, NEJM 2001

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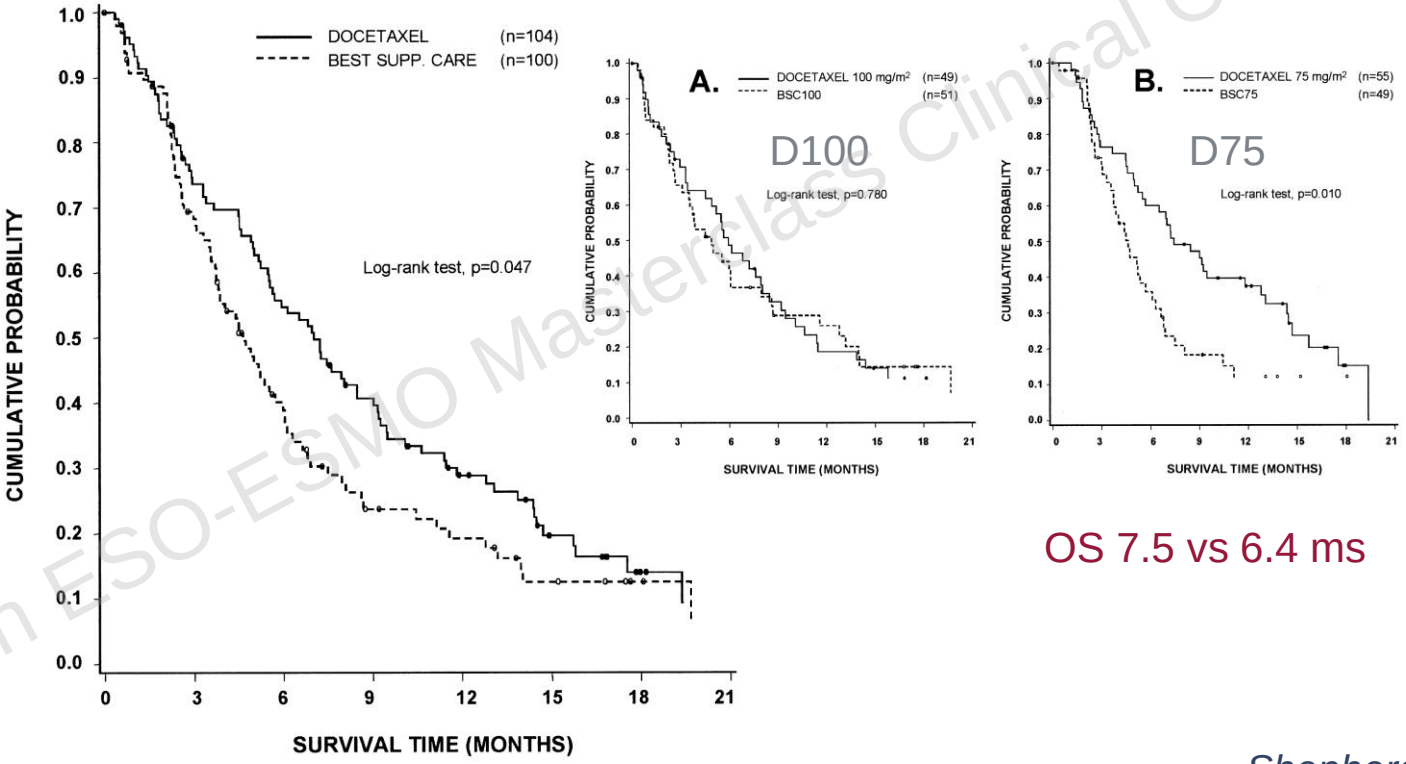
2nd line NSCLC phase III: Docetaxel vs BSC



OS 7.5 vs 6.4 ms

Shepherd, JCO 2000

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Histological classification is necessary for decision making in advanced NSCLC

- A diagnosis of “non-small cell lung cancer” is no longer acceptable as sufficient basis for treatment decisions:
  - Cisplatin superior to carboplatin in adenocarcinoma
    Ardizzoni, JNCI 2007
  - Benefit of bevacizumab added to first line chemotherapy in non-squamous cell carcinoma
    Sandler, JCO 2006; Reck; JCO 2009; Zhou, JCO 2015
  - Differential effect of pemetrexed in non-squamous vs squamous cell carcinoma and pemetrexed maintenance
    Scagliotti, JCO 2008; Paz-Ares, JCO 2013
  - Histology will help guide decision about further molecular analysis

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Pathological diagnosis

- Pathological diagnosis of all sample types should be made according to the 2015 WHO classification
- Immunohistochemistry (IHC) should be used to increase the specificity of diagnosis in the small sample setting and reduce the NSCLC-NOS (not otherwise specified) rate to fewer than 10% of cases diagnosed [IV, A]
- Minimal IHC should be used. Two markers only, p40 or p63 to predict squamous cell carcinoma and TTF1 to predict adenocarcinoma, are generally all that is required
- EGFR mutation status should be systematically analysed in advanced NSCC [I, A]
- Testing for ALK rearrangement should be systematically carried out in advanced NSCC [II, A]

Novello et al, Ann Oncol 2016

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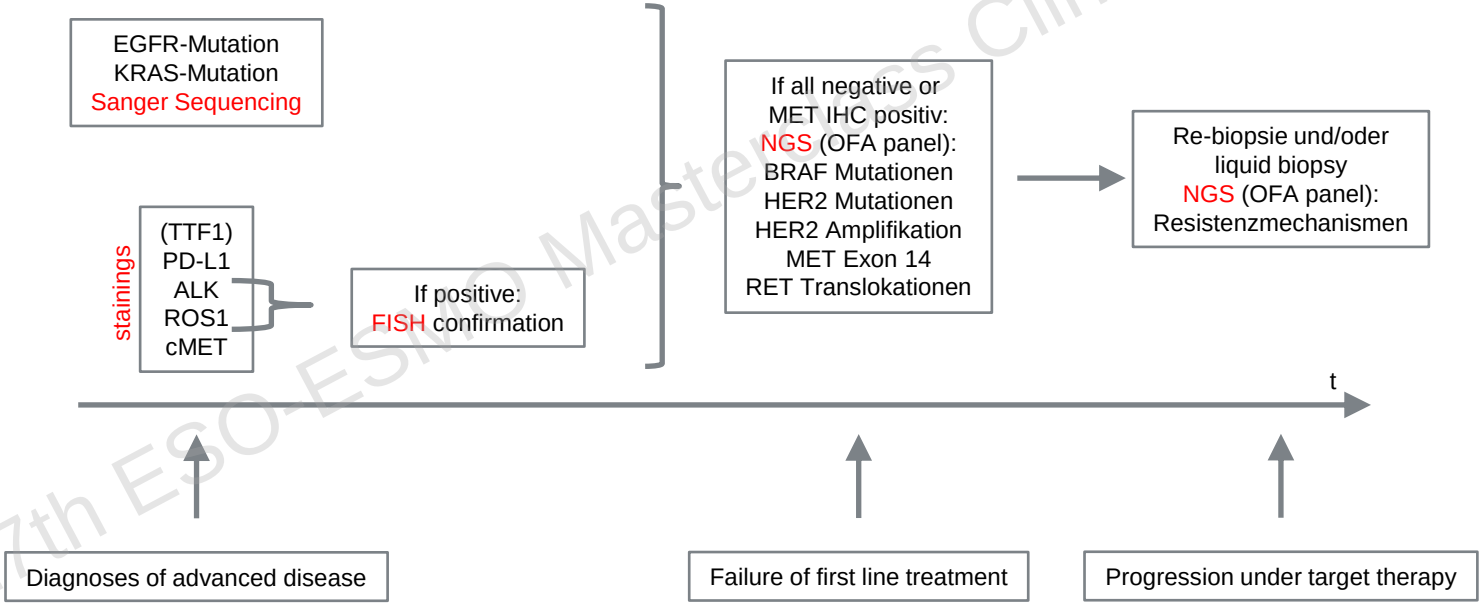
Molecular testing in non-squamous cell NSCLC at University Hospital Zürich



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What can we conclude for the first line therapy of advanced NSCLC without oncogenic driver mutation

- There is no single platinum-based doublet standard chemotherapy, however pemetrexed combinations are favoured in non-squamous cell NSCLC
- If platinum-based chemotherapy is indicated, a combination with bevacizumab is a treatment option in eligible patients with non-squamous NSCLC. In this case, carboplatin/paclitaxel is the preferred combination
- Pemetrexed maintenance therapy is an option for patients with non-squamous NSCLC without progression after first line therapy
- Immune checkpoint inhibition with pembrolizumab is becoming an option for patients with tumors with strong PD-L1 expression
- Current developments in first line immunotherapy are moving into chemotherapy7IO or IO7IO combinations

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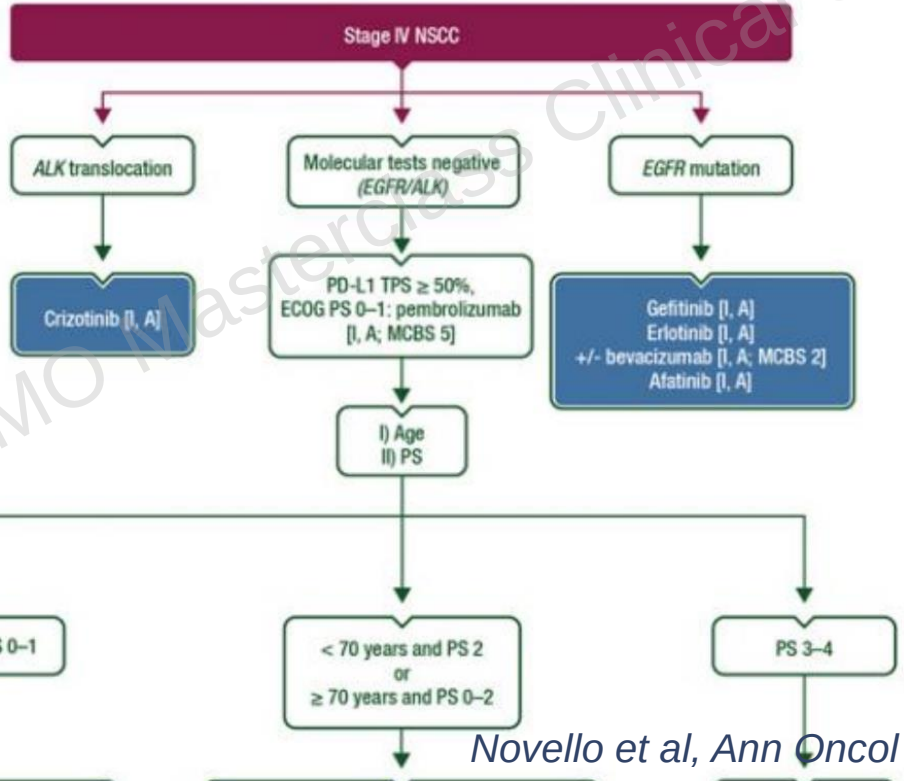
ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 1st line



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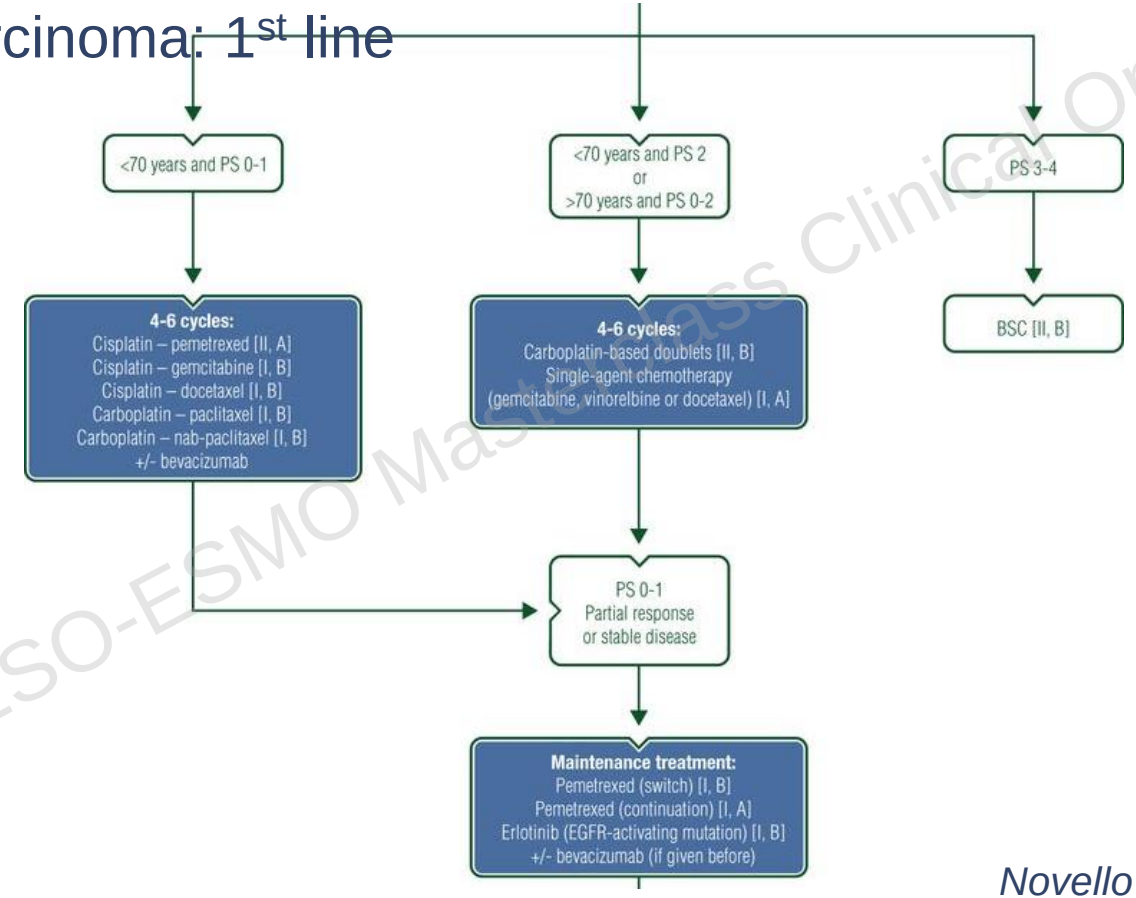
Novello et al, Ann Oncol 2016, eUpdate 2017

ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 1st line



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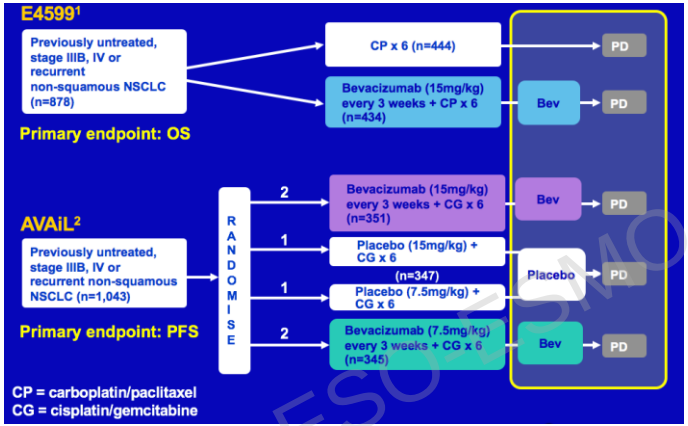
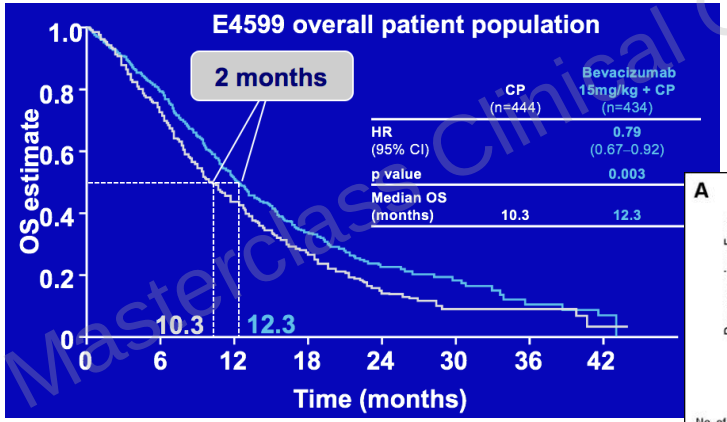
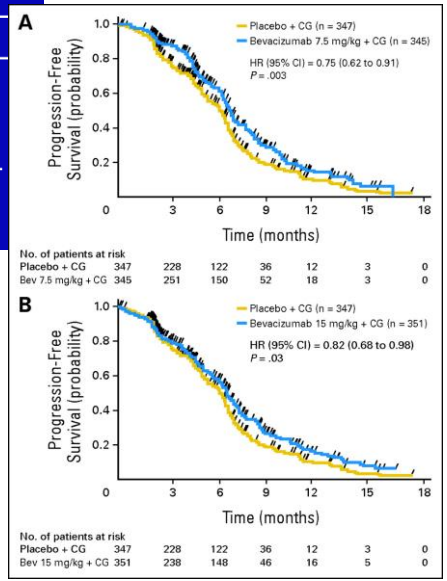
Novello et al, Ann Oncol 2016

Bevacizumab added to chemotherapy: Initial Phase III trials







Sandler, NEJM 2006; Reck, JCO 2009

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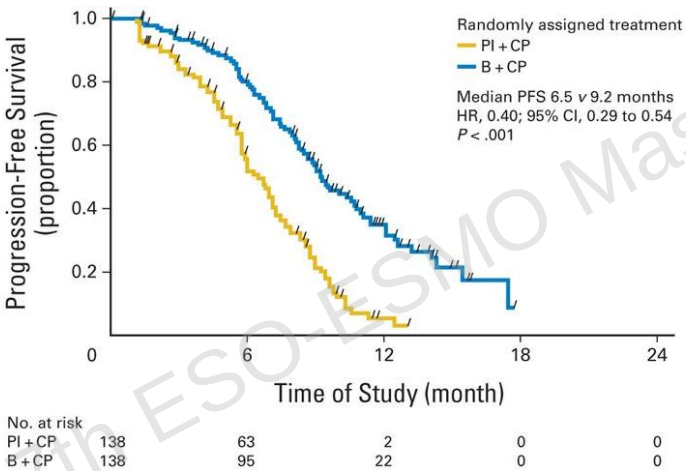
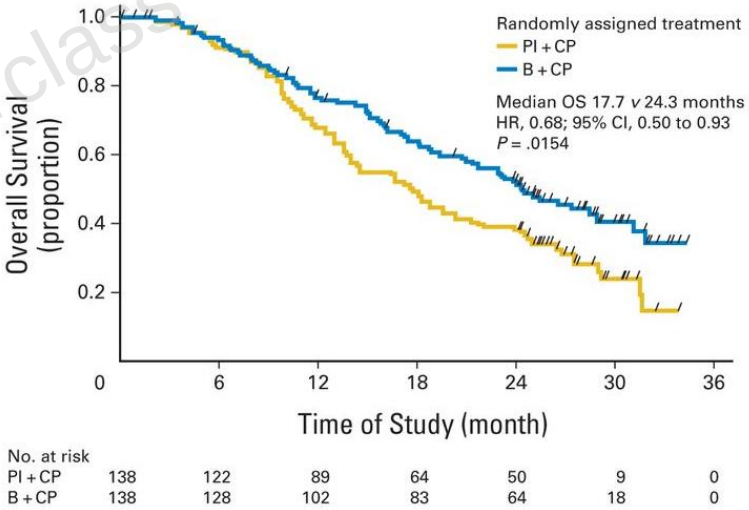
BEYOND: A randomized, double-Blind, placebo-controlled, multicenter, phase III study of 1st line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with NSCLC





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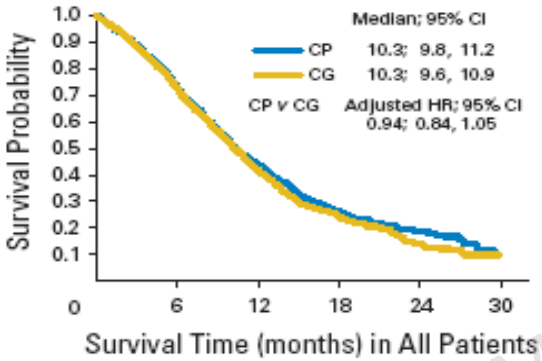
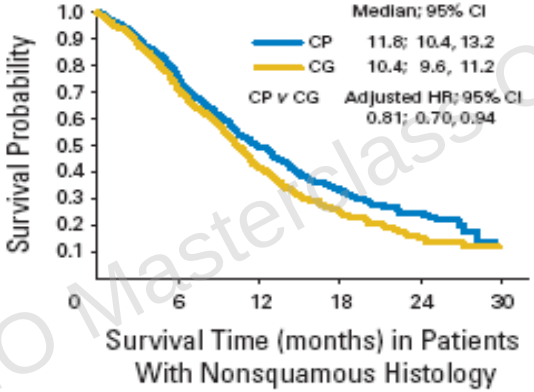
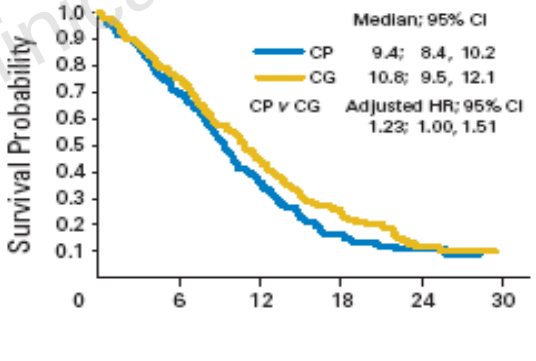
Zhou JCO 2015

Cisplatin-pemetrexed vs cisplatin-gemcitabine in advanced NSCLC







Overall no difference in PFS or survival between study arms

Cis/pem bretter than in non-squamous cell carcinoma (HR 0.81, p=0.005)

Cis/pem inferior than cis/gem in squamous cell carcinoma (HR 1.23, p=0.05)

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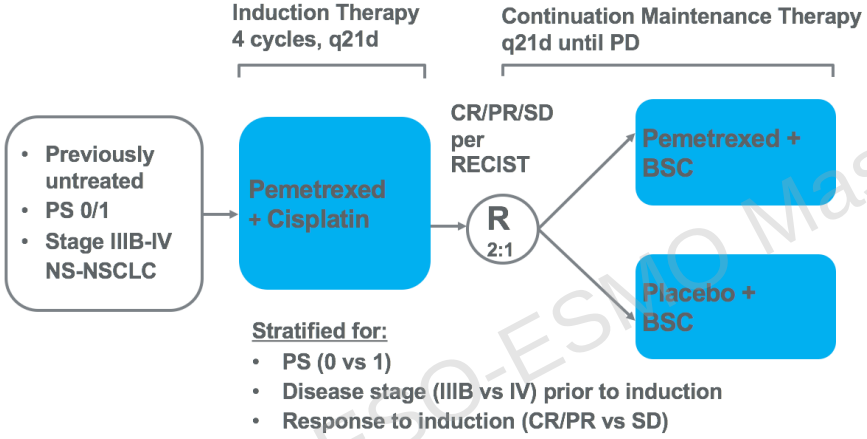
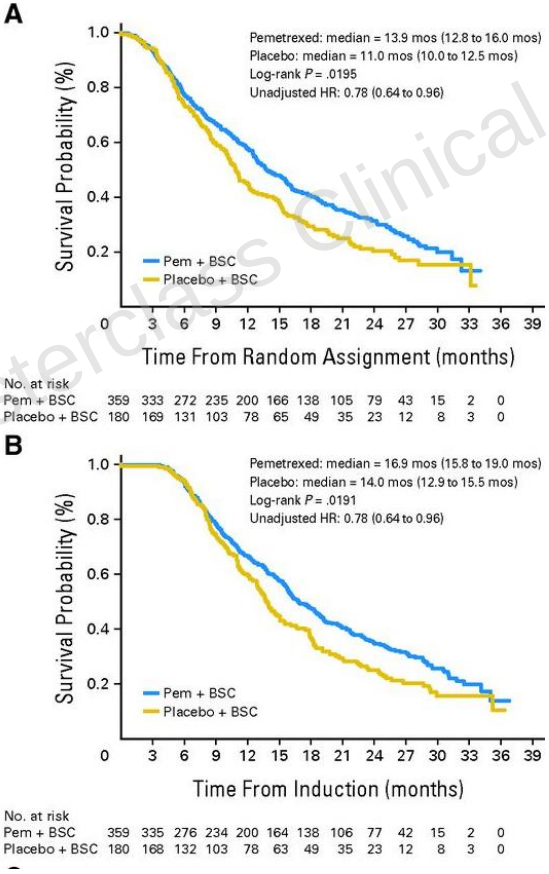
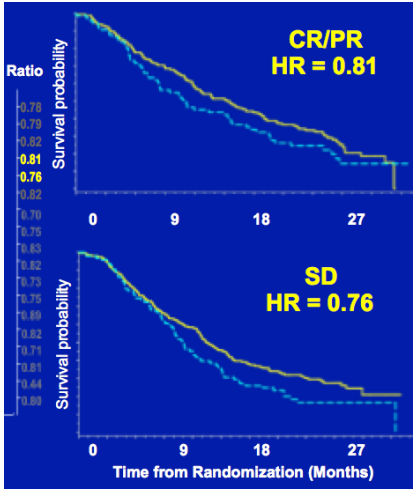
Scagliotti, JCO 2008

PARAMOUNT: Overall survival







Paz-Ares, JCO 2013

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First line systemic therapy in the elderly and frail

- In patients with PS 2, chemotherapy compared with BSC prolongs survival and improves QoL [I, B]
- Carboplatin-based combination chemotherapy should be considered in eligible PS 2 patients [II, A]
- Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel is an alternative treatment option [I, B]
- Poor PS (3–4) patients should be treated with BSC only [II, B]

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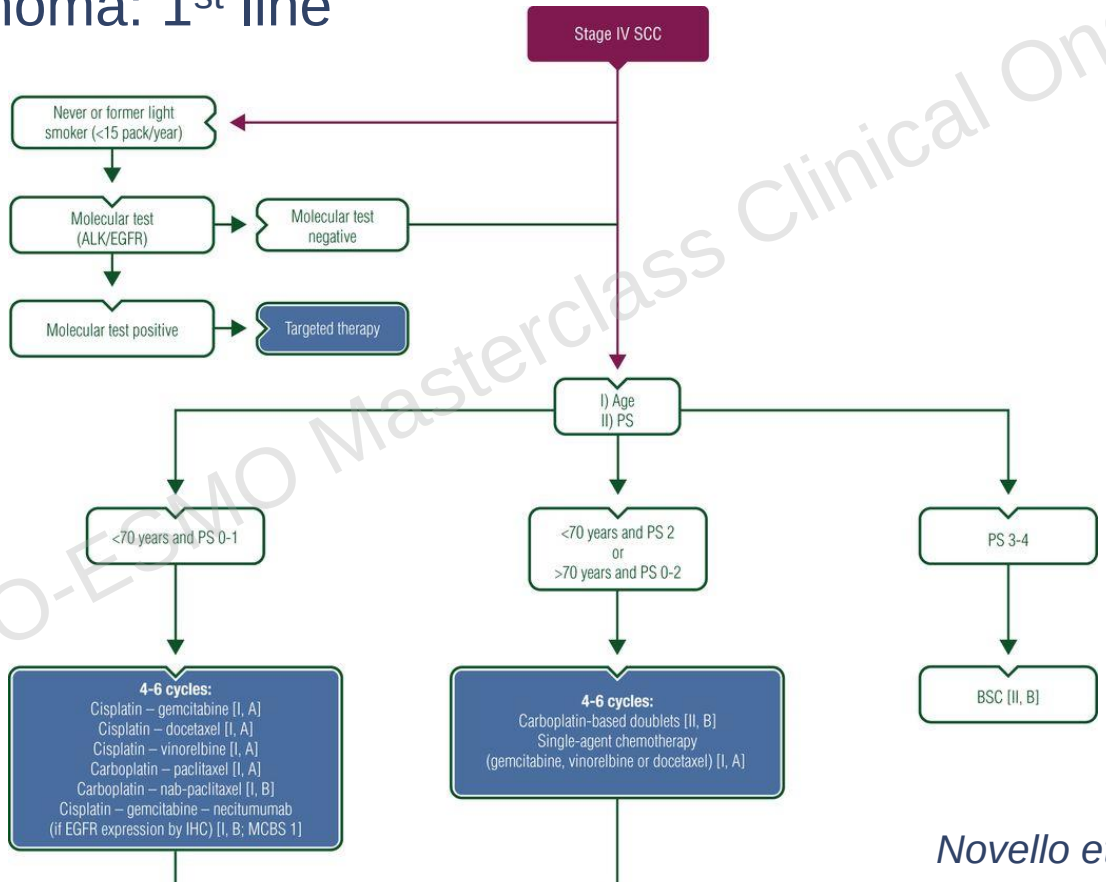
ESMO clinical practice guidelines in metastatic squamous cell carcinoma: 1st line



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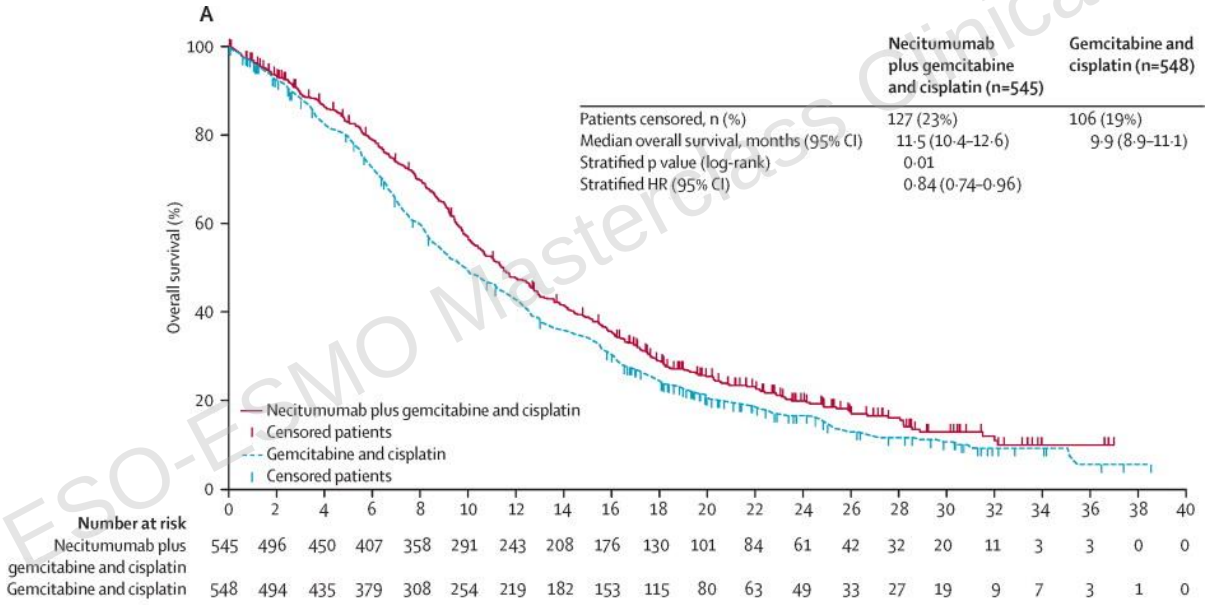
Novello et al, Ann Oncol 2016

Gemcitabine and cisplatin with or without necitumumab in squamous cell lung cancer



	Necitumumab plus gemcitabine and cisplatin (n=545)	Gemcitabine and cisplatin (n=548)
Patients censored, n (%)	127 (23%)	106 (19%)
Median overall survival, months (95% CI)	11·5 (10·4–12·6)	9·9 (8·9–11·1)
Stratified p value (log-rank)	0·01	
Stratified HR (95% CI)	0·84 (0·74–0·96)	

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Thatcher, Lancet Oncol 2015

Second and further line therapy for patients with NSCLC without oncogenic driver mutation – the shift to immumotherapy

- Docetaxel, or pemetrexed if not used in first line, used to be the standard of care
- The addition of nintedanib to docetaxel in non-squamous NSCLC and the addition of ramicirumab to docetaxel in all histologies of NSCLC is associated with small, but significant survival improvement over docetaxel alone
- Second line therapy with single agent immune checkpoint inhibitors (nivolumab, pembrolizumab or atezolizumab) provides a survival advantage over chemotherapy and is associated with fewer side effects and better quality of life

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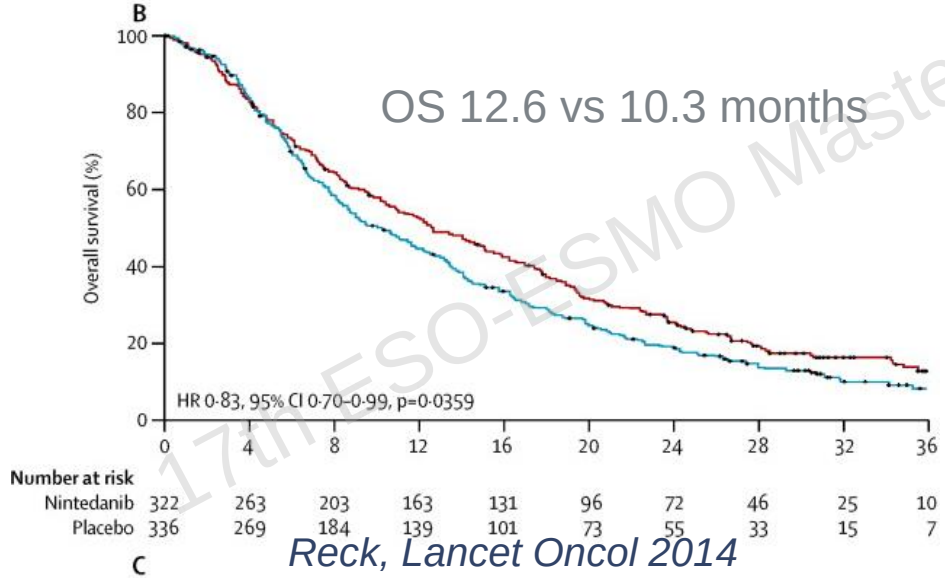
Second line chemotherapy and antiangiogenic agent in advanced NSCLC

LUME-Lung 1: Nintedanib in adenocarcinoma

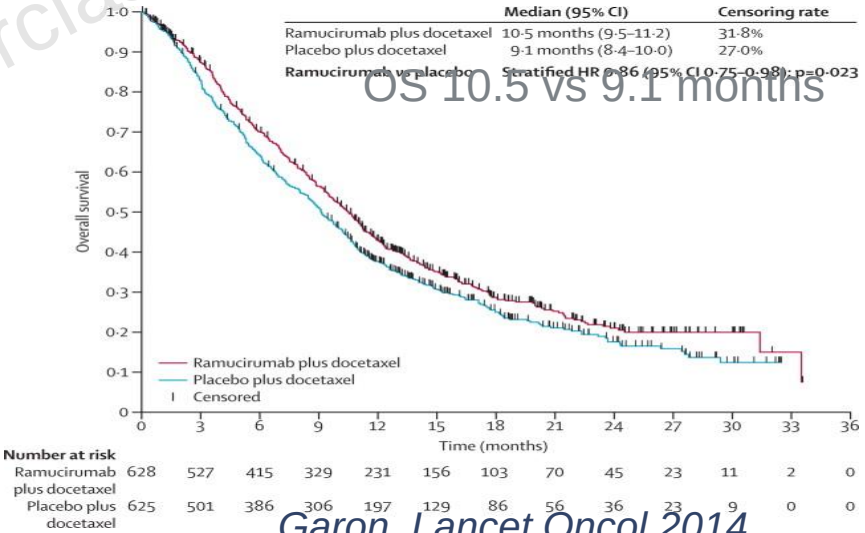
OS 12.6 vs 10.3 months



Reck, Lancet Oncol 2014

REVEL: Ramicirumab in all histologies

OS 10.5 vs 9.1 months



Garon, Lancet Oncol 2014

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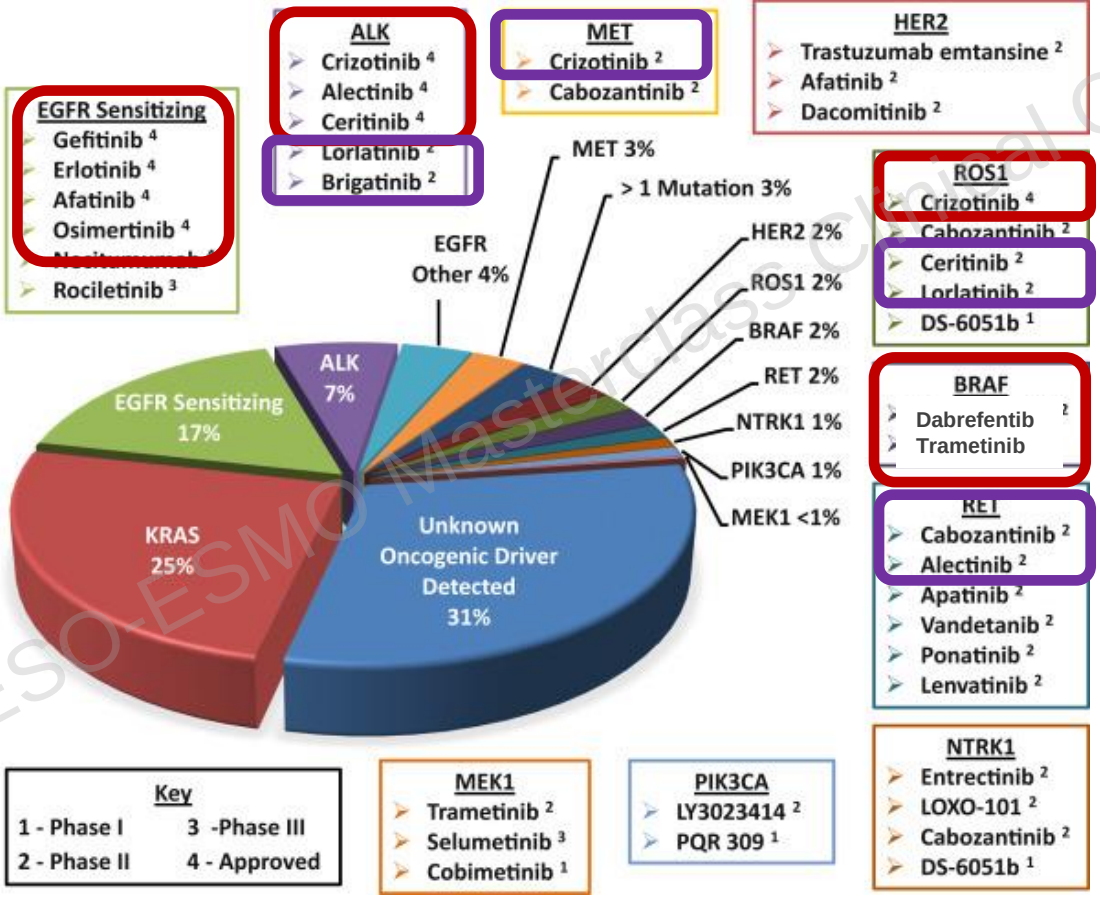
NSCLC with oncogenic driver mutations: current status



Shaw, NEJM 2014

Planchard, Lancet Oncol 2016

Tsao, JTO 2016

EMA approval in NSCLC

Available otherwise

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Where do we stand with targeted therapy in first line for patients with NSCLC with activating EGFR mutations?

- There is no clear preference between the three EGFR TKIs approved by the EMA
- The combination of erlotinib and bevacizumab has been approved by EMA based on a Japanese study and supported by the BELIEF trial
- Osimertinib has been approved for patients with acquired T790M mutation based on superior PFS as compared to platin-based combination therapy. Osimertinib had excellent activity in patients with CNS metastases
- The FLAURA randomized phase III trial has documented a superiority of osimertinib over first generation TKIs in terms of progression-free survial for patients with activating EGFR mutations

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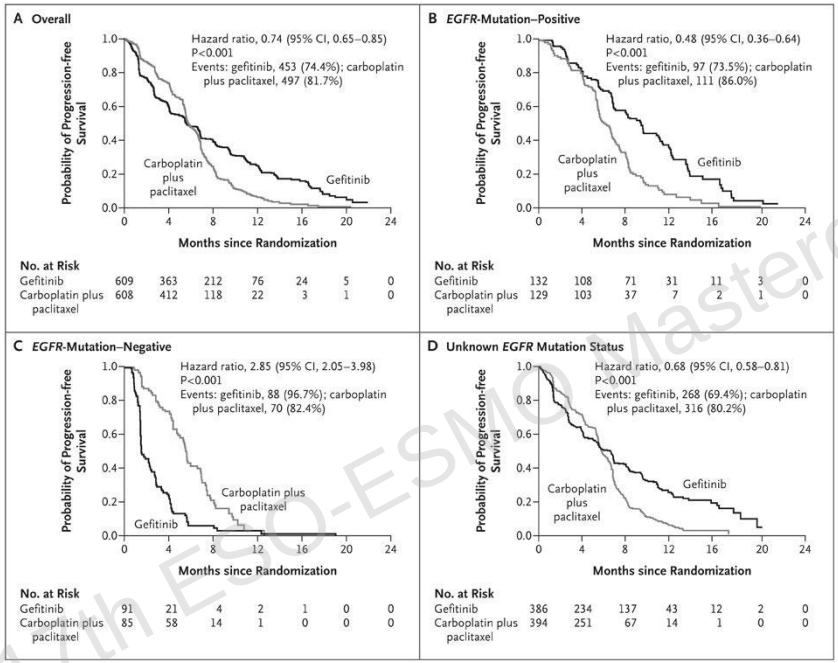
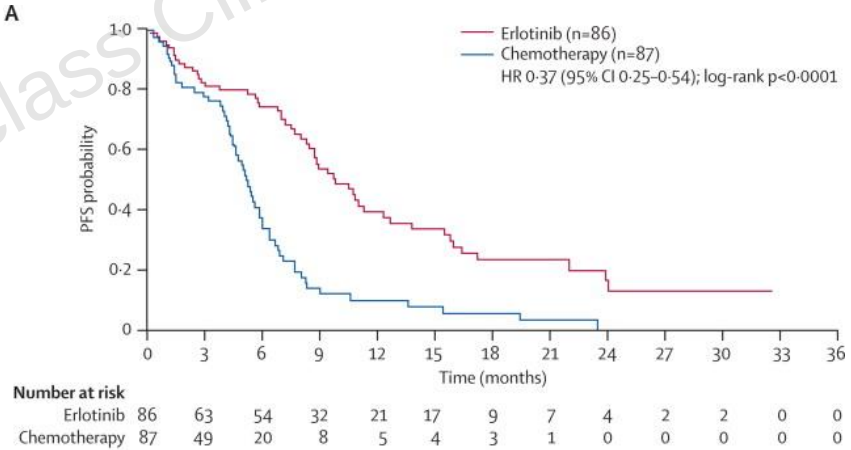
First TKI versus chemotherapy in EGFR mutated NSCLC



Mok, NEJM 2009



Rosell, Lancet Oncol 2012

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First-line TKI therapy in EGFR-mutated NSCLC: Randomized phase 3 trials of first generation EGFR TKIs

Study	N	Treatment Arm	Control Arm	Stage	mPFS	Median OS	Indication
IPASS (Mok TS, et al. *N Engl J Med*. 2009;361:947-957)	1217	Gefitinib	Carboplatin/ placitaxel	IIIB/IV	5.7 vs 5.8 mo (*EGFR*-mutated patients HR = 0.48; nonmutated patients HR = 2.84)	18.6 vs 17.3 mo (*P* = NS)	First-line
WJTOG3405 (Mitsudomi T, et al. *Lancet Oncol*. 2010;11:121-128.)	177 (*EGFR*+)	Gefitinib	Cisplatin, docetaxel	IIIB/IV	9.2 vs 6.3 mo (*P* <.001)		First-line
(Maemondo M, et al. *N Engl J Med*. 2010;362:2380-2388.)	230 (*EGFR*+)	Gefitinib	Carboplatin, paclitaxel	IIIB/IV	10.8 vs 5.4 mo (HR = 0.3, *P* <.0001)	30.5 vs 23.6 mo (*P* = NS)	First-line
OPTIMAL (Zhou C, et al. *Lancet Oncol*. 2011;12:735-742)	165 (*EGFR*+)	Erlotinib	Carboplatin/ gemcitabine	IIIB/IV	13.6 vs 4.6 mo (HR = 0.16, *P* <.0001)		First-line
EURTAC (Rosell R, et al. *Lancet Oncol*. 2012;13:239-246)	153 (*EGFR*+)	Erlotinib	Platinum-based chemotherapy	IIIB/IV	9.4 vs 5.2 mo (HR = 0.42, *P* <.0001)	22.9 vs 18.8 mo (*P* =.42)	First-line

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LUX-Lung 7: Comparison of afatinib versus gefitinib in first line treatment of EGFR-mutated NSCLC

- Stage IIIB/IV adenocarcinoma of the lung
- *EGFR* mutation (Del19 and/or L858R) in the tumor tissue*
- No prior treatment for advanced/ metastatic disease
- ECOG PS 0/1

1:1

Afatinib 40 mg once daily†

Gefitinib 250 mg once daily

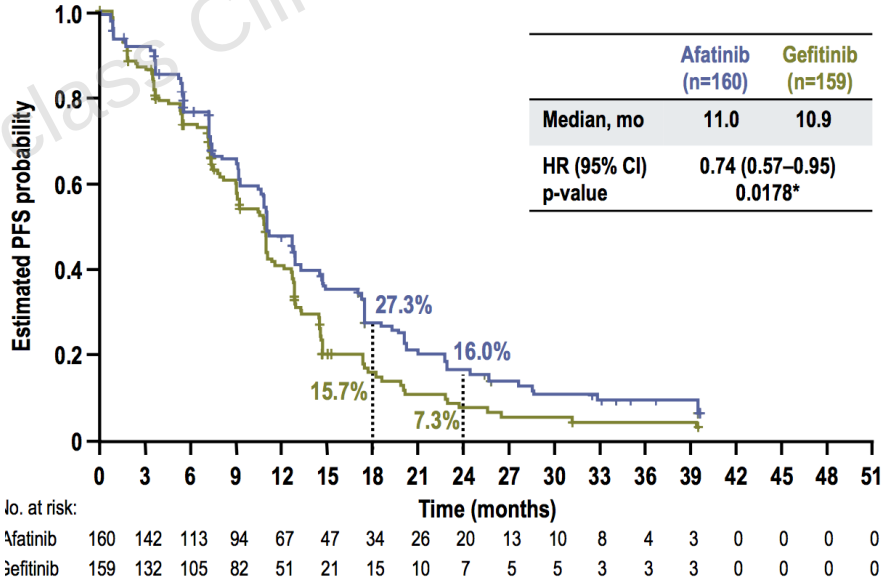
Stratified by
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Primary endpoints:
- PFS (independent)
- TTF
- OS

Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

Controlled ZNS metastases included

PFS



	Afatinib (n=160)	Gefitinib (n=159)
Median, mo	11.0	10.9
HR (95% CI)	0.74 (0.57–0.95)	
p-value	0.0178*	

Pas-Ares, ESMO 2016; Lancet Oncol 2016, Ann Oncol 2017

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LUX-Lung 7: Comparison of afatinib versus gefitinib in first line treatment of EGFR-mutated NSCLC

	Afatinib (n=160)				Gefitinib (n=159)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Total	106 (66%)	47 (29%)	3 (2%)	0	124 (78%)	26 (16%)	2 (1%)	1 (1%)
Diarrhoea	124 (78%)	19 (12%)	1 (1%)	0	95 (60%)	2 (1%)	0	0
Rash or acne*	127 (79%)	15 (9%)	0	0	124 (78%)	5 (3%)	0	0
Stomatitis†	96 (60%)	7 (4%)	0	0	38 (24%)	0	0	0
Paronychia‡	86 (54%)	3 (2%)	0	0	26 (16%)	1 (1%)	0	0
Dry skin	52 (33%)	0	0	0	59 (37%)	0	0	0
Pruritus	37 (23%)	0	0	0	36 (23%)	0	0	0
Fatigue§	24 (15%)	9 (6%)	0	0	23 (14%)	0	0	0
Decreased appetite	25 (16%)	1 (1%)	0	0	19 (12%)	0	0	0

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Park, ESMO Asia 2015 and Lancet Oncol 2016

LUX-Lung 7: Comparison of afatinib versus gefitinib in first line treatment of EGFR-mutated NSCLC

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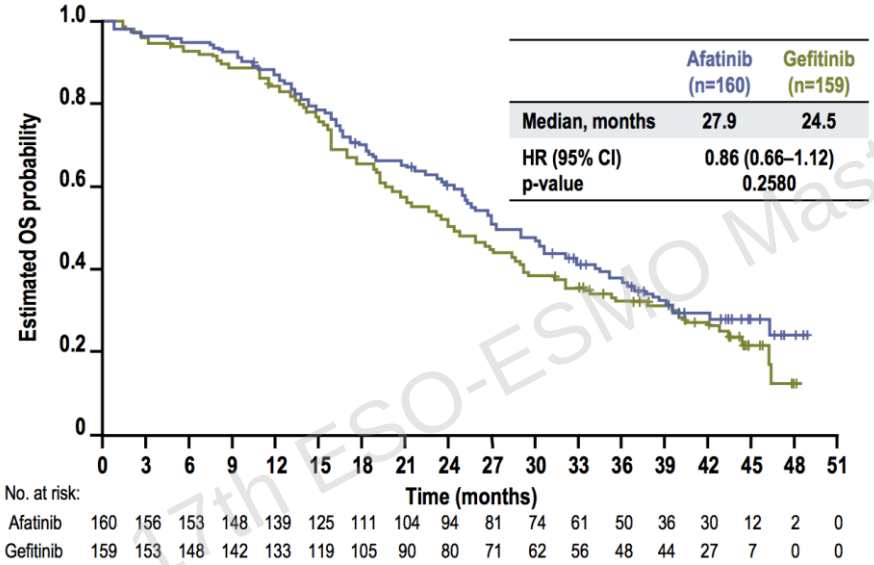

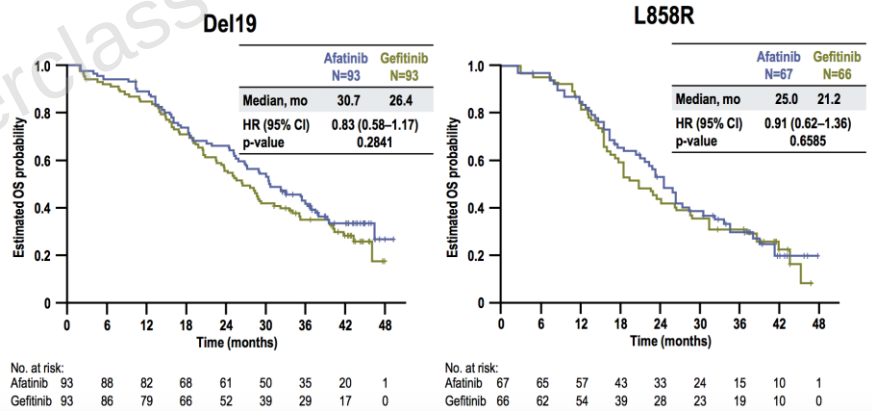

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Pas-Ares, ESMO 2016

Afatinib in uncommen EGFR mutations: Specific mutations of relative frequency

	Mutation	Objective response	Progression-free survival (months)	Overall survival (months)
Gly719Xaa (n=18)	Gly719Xaa (n=8) Gly719Xaa+Thr790Met (n=1) Gly719Xaa+Ser768Ile (n=5) Gly719Xaa+Leu861Gln (n=3) Gly719Xaa+Thr790Met+Leu858Arg (n=1)	14 (77·8%, 52·4–93·6)	13·8 (6·8–NE)	26·9 (16·4–NE)
Leu861Gln (n=16)	Leu861Gln (n=12) Leu861Gln+Gly719Xaa (n=3) Leu861Gln+Del19 (n=1)	9 (56·3%, 29·9–80·2)	8·2 (4·5–16·6)	17·1 (15·3–21·6)
Ser768Ile (n=8)	Ser768Ile (n=1) Ser768Ile+Gly719Xaa (n=5) Ser768Ile+Leu858Arg (n=2)	8 (100·0%, 63·1–100·0)	14·7 (2·6–NE)	NE (3·4–NE)

Data are n (%, 95% CI) or median (95% CI). NE=not estimable. Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

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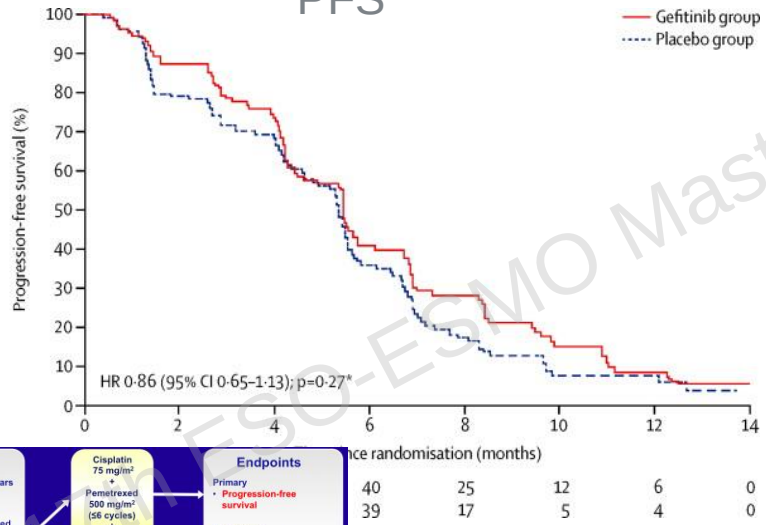
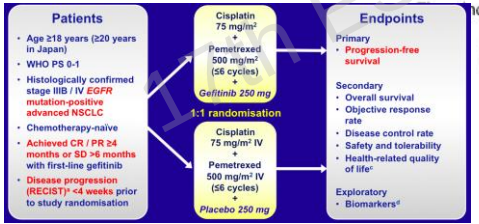
Yang, Lancet Oncology 2015

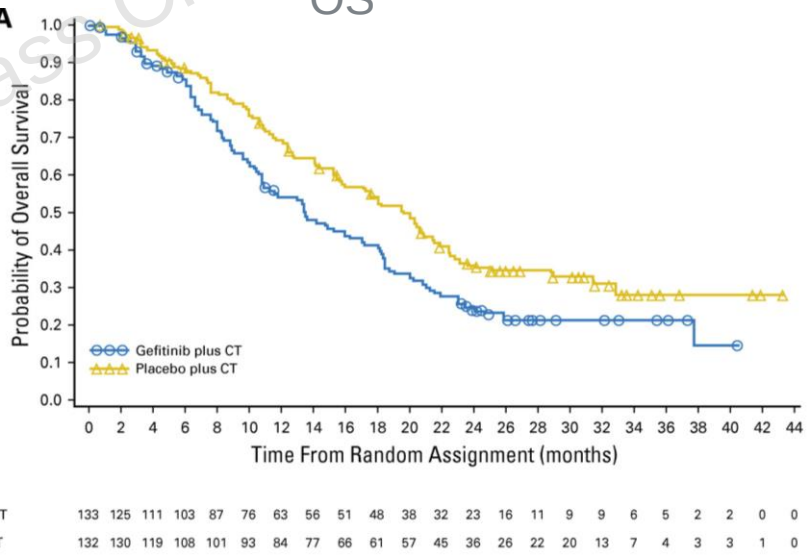
Gefitinib plus chemotherapy versus chemotherapy in EGFR mutation–positive NSCLC resistant to first-line gefitinib (IMPRESS)

PFS





OS



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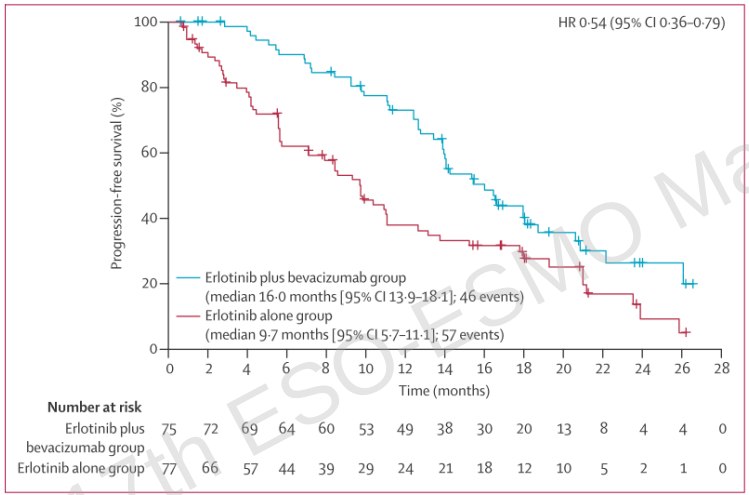
Soria, Lancet Oncol 2015; Mok, JCO 2017

EGFR-mutated advanced NSCLC: Erlotinib with bevacizumab in first-line

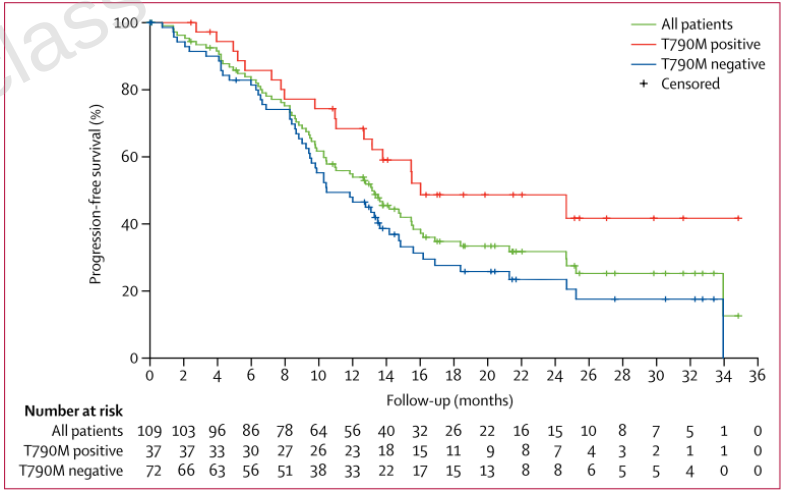
- **JO25567**: Ph2, randomized, Japanese multicenter, open-label[a]

PFS



BELIEF: Ph2, multicenter, single-arm study, stratified by pretreatment T790M status[b]

PFS



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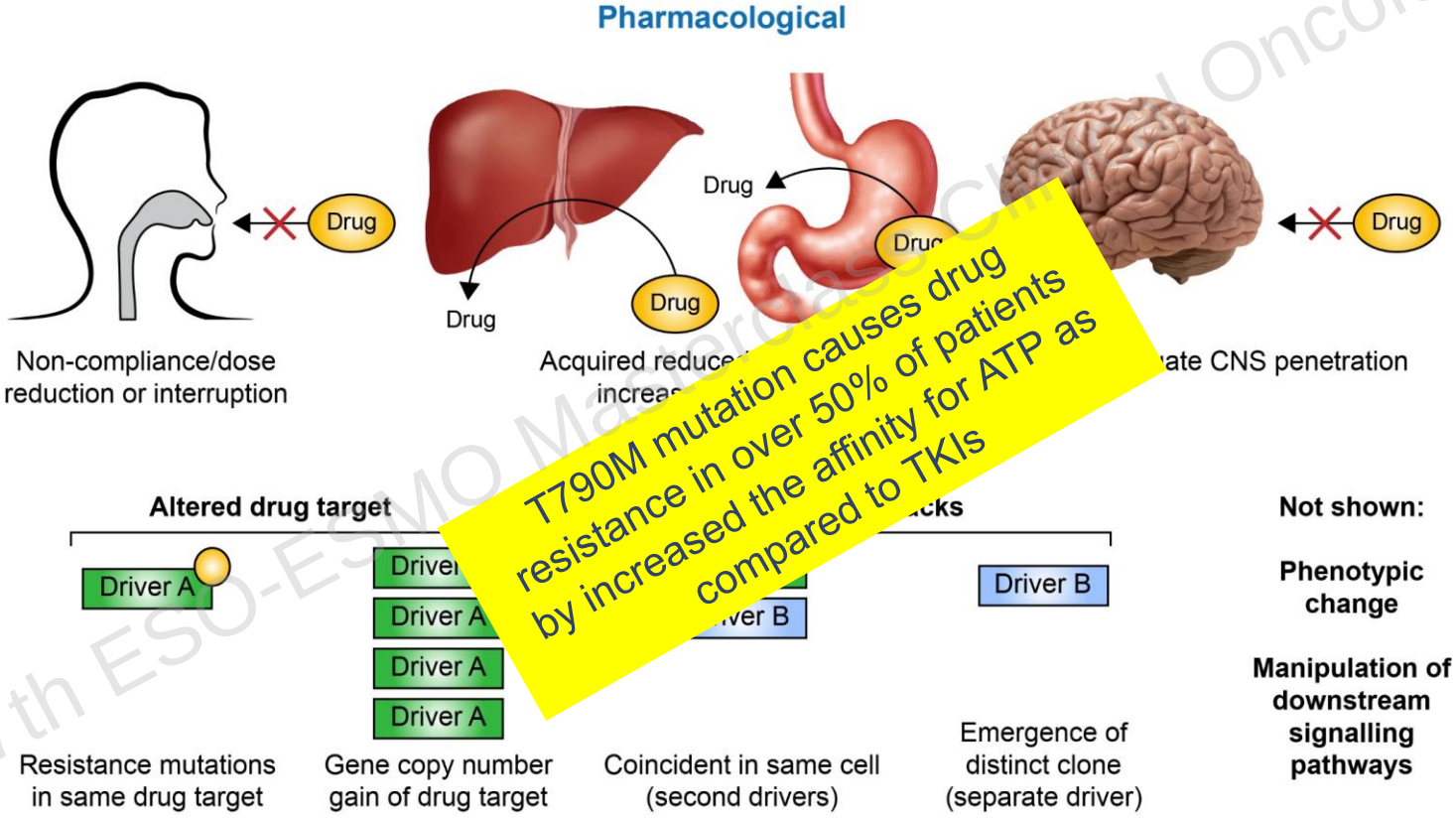
Seto, Lancet Oncol 2014; Rosell, Lancet Respir Med. 2017

Multiple reasons for acquired resistance to TKIs



Camidge Nat Rev Clin Oncol 2014

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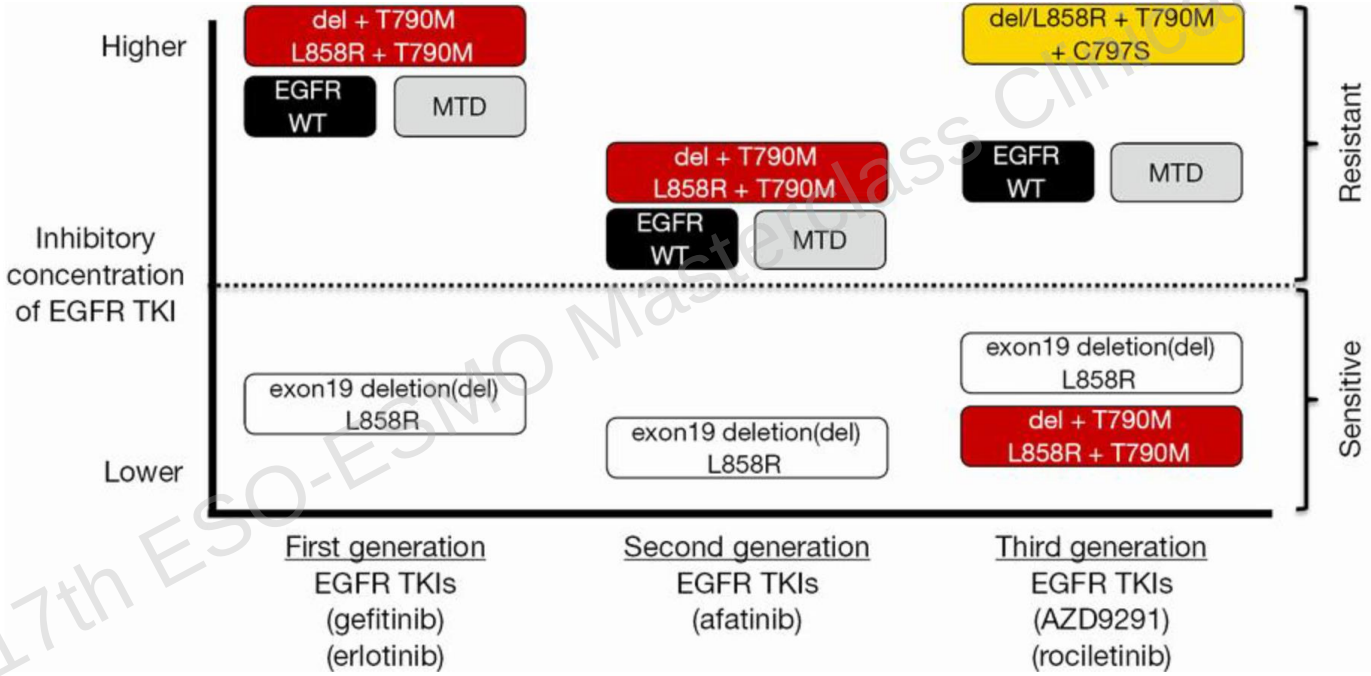
EGFR TKIs



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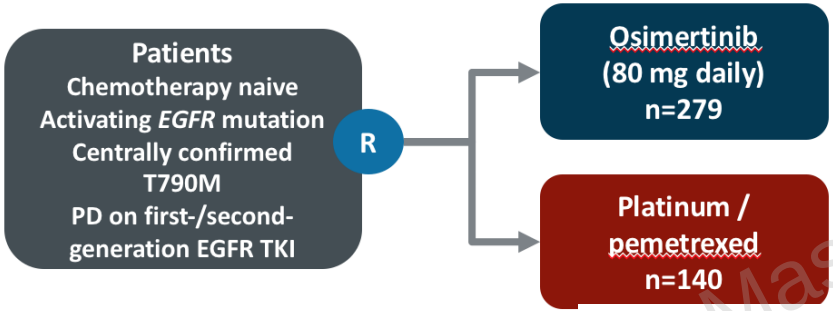
Costa, Transl Lung Cancer Res 2015

AURA3: Osimertinib or platinum-pemetrexed in EGFR TKI pretreated EGFR T790M–positive NSCLC



	Osimertinib 80 mg n=30	Chemotherapy n=16
CNS ORR (95% CI)	70% (51, 85)	31% (11, 59)
Odds ratio (95% CI)	5.13 (1.44, 20.64), *P* =.015	
Median time to response, weeks	6.1	6.1
Median Duration of Response, months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
DCR (95% CI)	93% (78, 99)	63% (35, 85)

Mok, NEJM 2017

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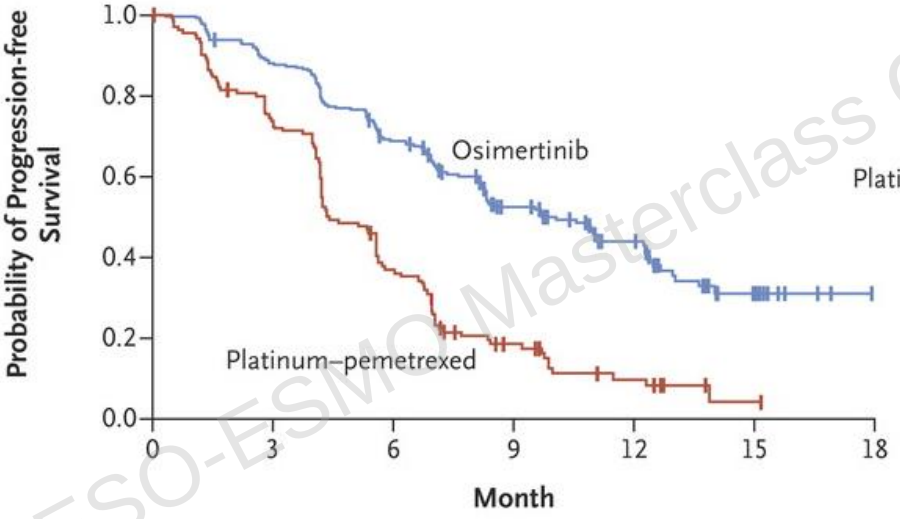
AURA3: Osimertinib or platinum-pemetrexed in EGFR TKI pretreated EGFR T790M–positive NSCLC

A Patients in Intention-to-Treat Population



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

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

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

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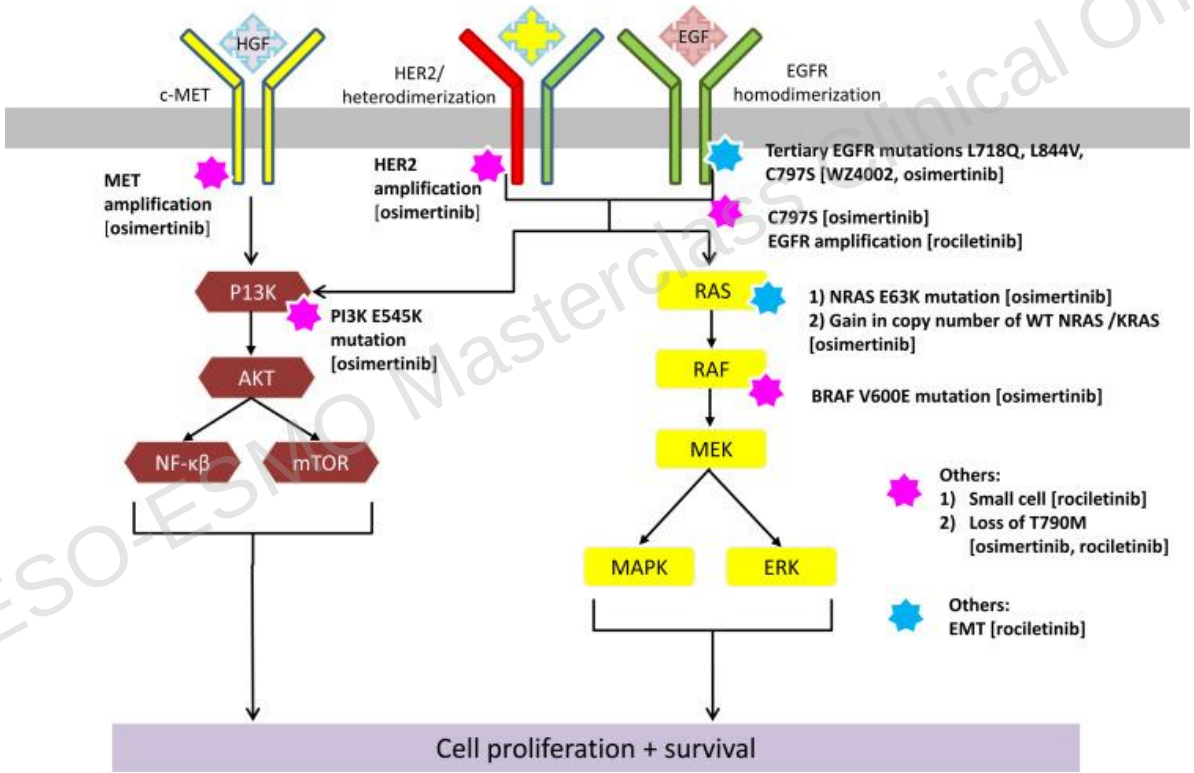
Mok, NEJM 2017

Mechanisms of resistance to third generation EGFR TKIs



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Tan, Lung Cancer 2016

Osimertinib as first-line treatment: Biomarker at progression

- 38/42 with plasma for NGS at RECIST-defined progression:
  - 19 detectable DNA
  - 9 identified with putative resistance mechanims

Baseline EGFR mutation	Post-dose plasma EGFR mutation (allelic fraction %)	Post-dose plasma resistance aberration(s) identified (allelic fraction %, copies)	Other post-dose plasma mutations identified (allelic fraction %)	Total time receiving osimertinib (months)
Ex19del*	None detected	JAK2 V617F (1.5%)	None detected	29.9+
Ex19del	Ex19del (5.2%)	EGFR C797S (3.0%)	P53 R273H (6.6%), CTNNB1 G34V (6.5%)	27.8+
L858R	L858R (16.7%)	PIK3CA E545K (1.6%)	P53 H179R (13.3%), PTEN Q171* (8.1%), NOTCH G2299G (4.6%)	26.3
Ex19del	Ex19del (34.6%)	MET CNV (3.0 copies)	RB1 R255* (64.1%), P53 pHis179fs (62.9%)	26.3
Ex19del	None detected	KRAS G12D (8.6%)	CTNNB1 S37F (3.6%)	24.9
L858R and T790M	L858R (4%) + T790M (5%)	EGFR C797S (1%)	NF2 T352M (1.5%)	14.5
Ex19del	Ex19del (7.5%)	KRAS CNV (3.7 copies), EGFR CNV (3.0 copies)	P53 H175H (15.9%), RB1 pLys427fs (9.9%)	14.3
G719S and S768I	G719S (6.9%) + S768I (5.7%)	MEK1 (MAP2K1) G128V (3.2%)	SMAD4 G358E (4.6%), PDGFRA S961C (1.1%)	5.6
L858R	None detected	HER2 ex20 ins (12.3%), HER2 E1247K (4.2%)	P53 R213* (6.3%), IDH2 R140Q (2.5%)	1.2

CNV, copy number variant; Ex19del, Exon 19 deletion; ND, none detected

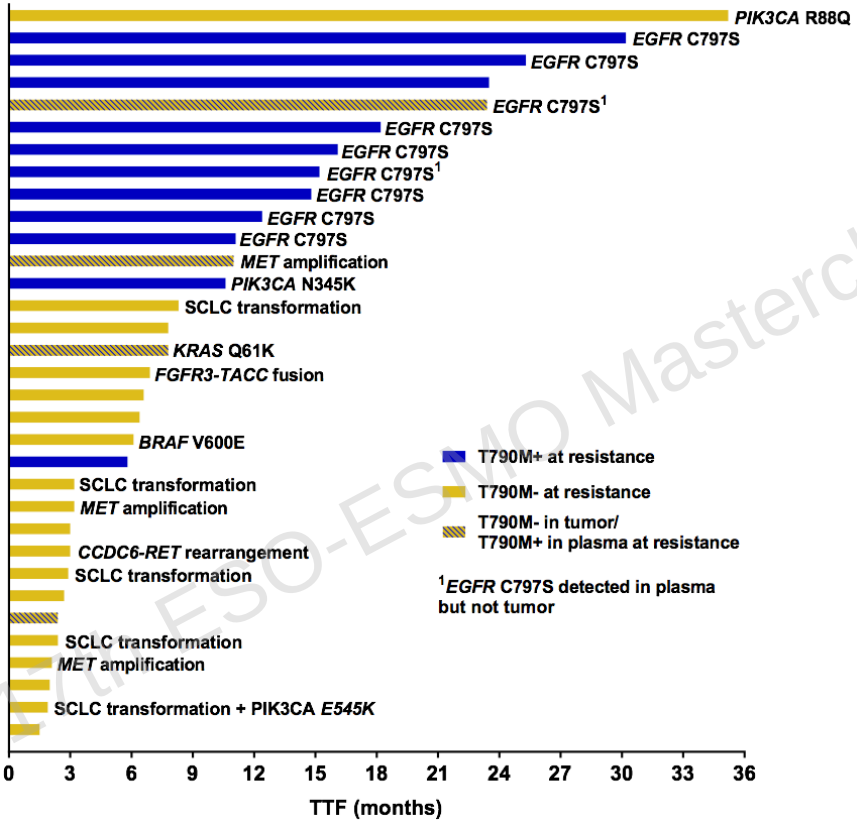
*Mutation identified by local testing

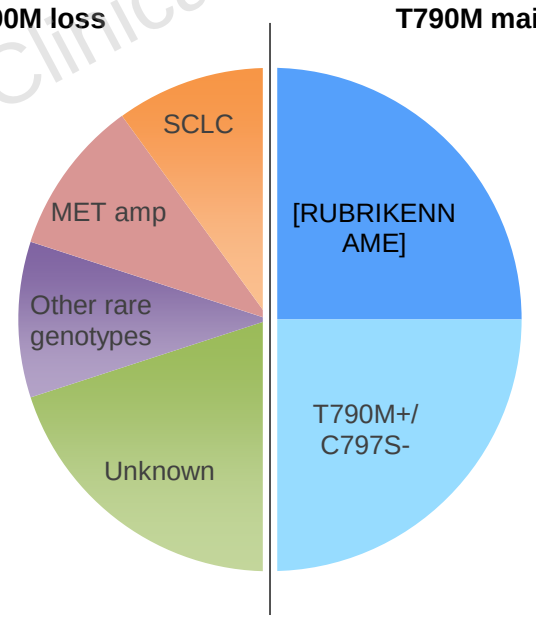
+ indicates that the patient remained on osimertinib at the time of data cutoff

Ramalingam, JCO 2017

17th ESO-ESMO Masterclass Clinical Thoracic Oncology

Osimertinib resistance mediated by loss of *EGFR* T790M is associated with early resistance and competing resistance mechanisms





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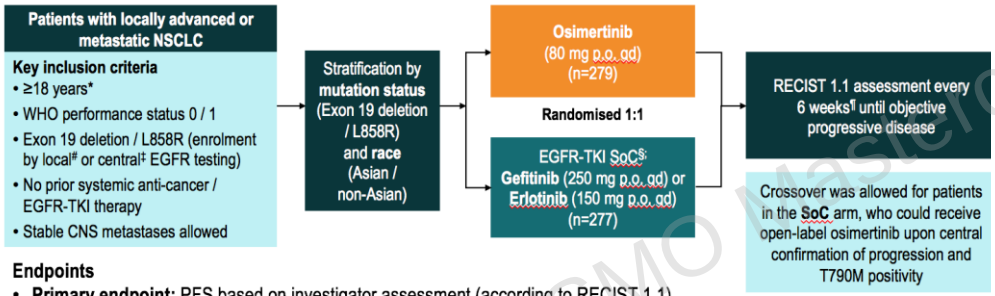
Oxnard, WCLC 2017

FLAURA: First or third generation TKI inhibitors as first line therapy for patients with EGFR mutated NSCLC



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 an 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

Characteristic, %	Osimertinib (n=279)	SoC* (n=277)
Sex: male / female	36 / 64	38 / 62
Age, median (range), years	64 (26–85)	64 (35–93)
Race: White / Asian / other#	36 / 62 / 1	36 / 62 / 1
Smoking status: never / ever	65 / 35	63 / 37
CNS metastases at study entry‡	19	23
WHO performance status§: 0 / 1	40 / 60	42 / 58
Overall disease classification¶: metastatic / advanced	95 / 5	95 / 5
Histology: adenocarcinoma / other	99 / 1	98 / 2
EGFR mutation at randomisation**: Exon 19 deletion / L858R	63 / 37	63 / 37

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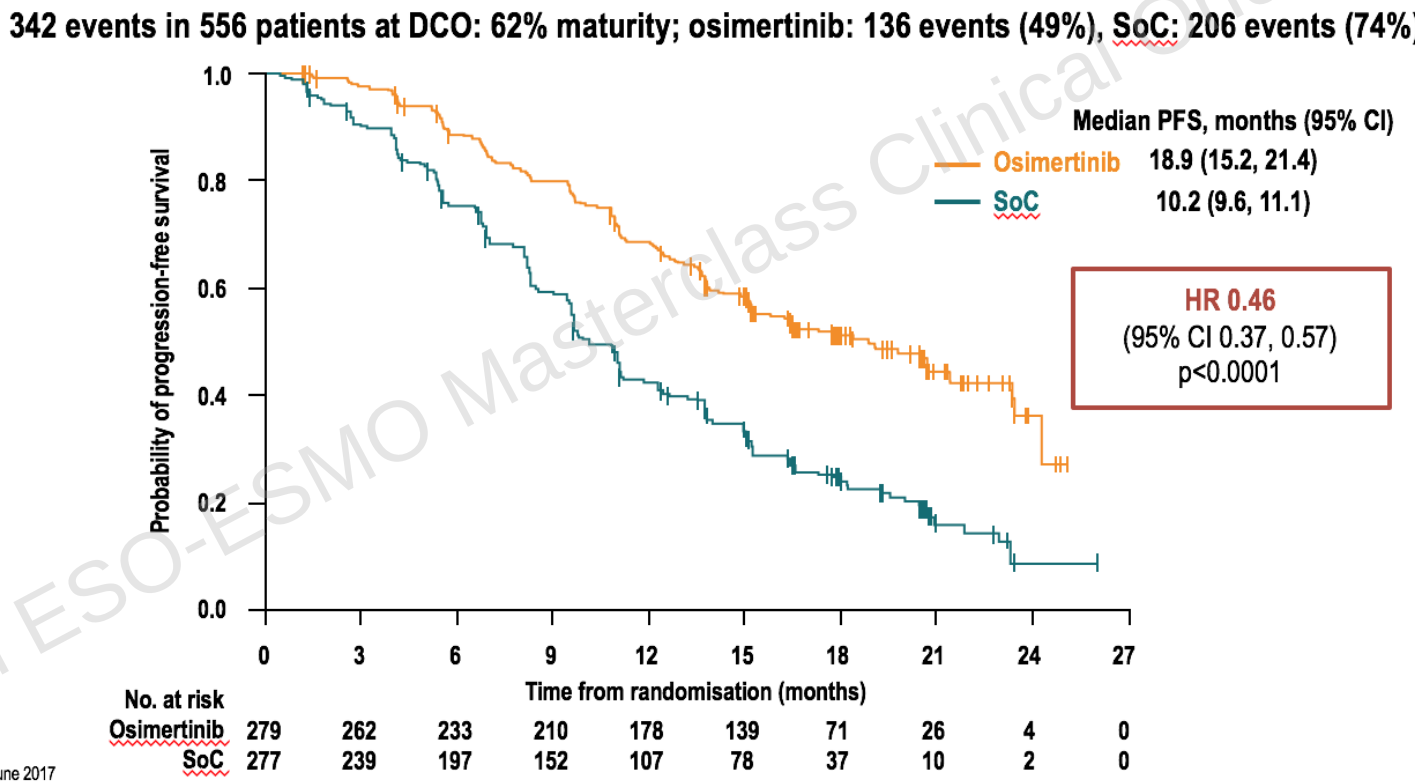
Ramalingam, ESMO 2017

FLAURA: Primary endpoint progression-free survival



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

Ramalingam, ESMO 2017; Soria NEJM 2018

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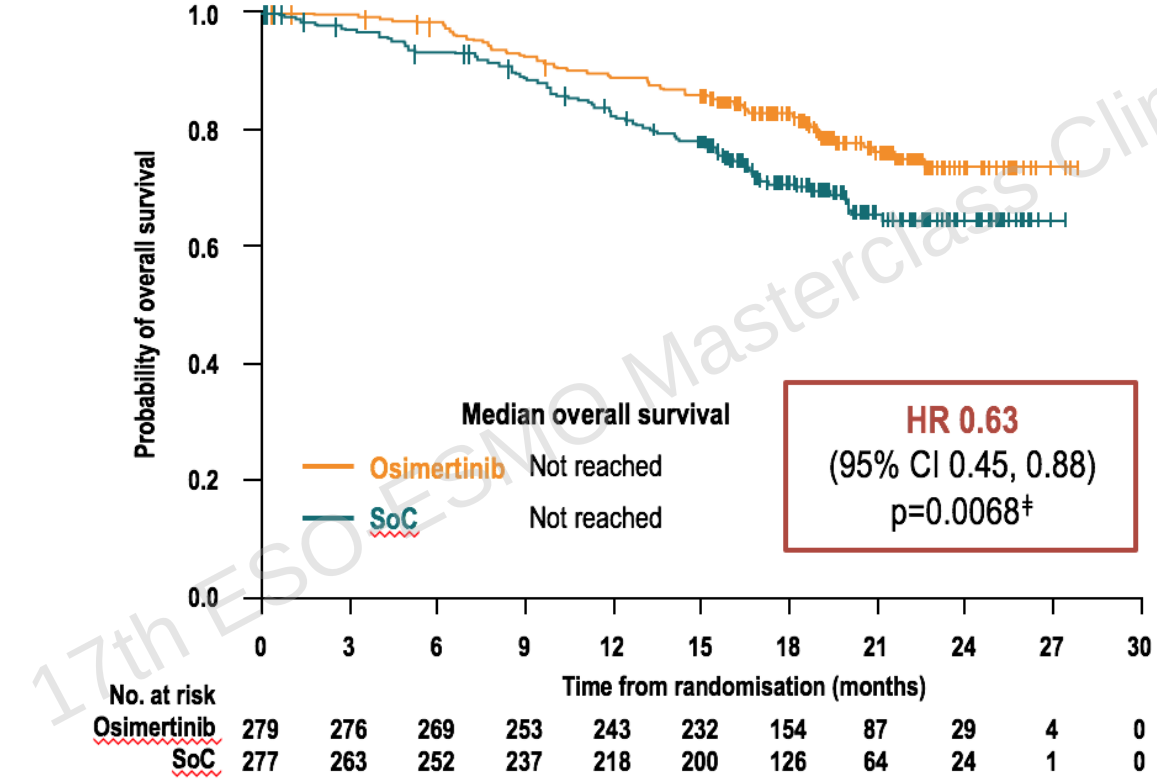
FLAURA: Overall survival – interim analysis

141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)



‡A p-value of <0.0015 was required for statistical significance at current maturity

Ramalingam, ESMO 2017

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FLAURA: CNS activity

Table S4. Reason for CNS progression, by investigator assessment (full analysis set)

Reason for progression	Known/treated CNS metastases at trial entry		No known/treated CNS metastases at trial entry	
	Osimertinib (n=53)	Standard EGFR-TKI (n=63)	Osimertinib (n=226)	Standard EGFR-TKI (n=214)
	Number (percent)			
Total number of progression events	29 (55)	53 (84)	107 (47)	153 (71)
Number of patients with progression due to death*	4 (8)	4 (6)	7 (3)	10 (5)
Number of patients with CNS progression*	10 (19)	27 (43)	7 (3)	15 (7)

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Soria, NEJM 2018

Where do we stand with targeted therapy in first line in patients with NSCLC with other oncogenic driver mutations

- Crizotinib is approved for the first line treatment of patients with ALK translocated and ROS1 translocated NSCLC
- Ceritinib, alectinib and brigatinib are approved for patients ALK translocated NSCLC progressing under critzotinib. Also there is limited access to lorlatinib in clinical studies or as compassionate use.
- The results of the J-ALEX and ALEX trial suggest alectinib to become the preferred first line therapy in ALK translocated NSCLC
- The combination of dabrafenib + trametinib has been approved by EMA for the treatment of BRAF V600 mutated NSCLC
- Other targets are under investigation

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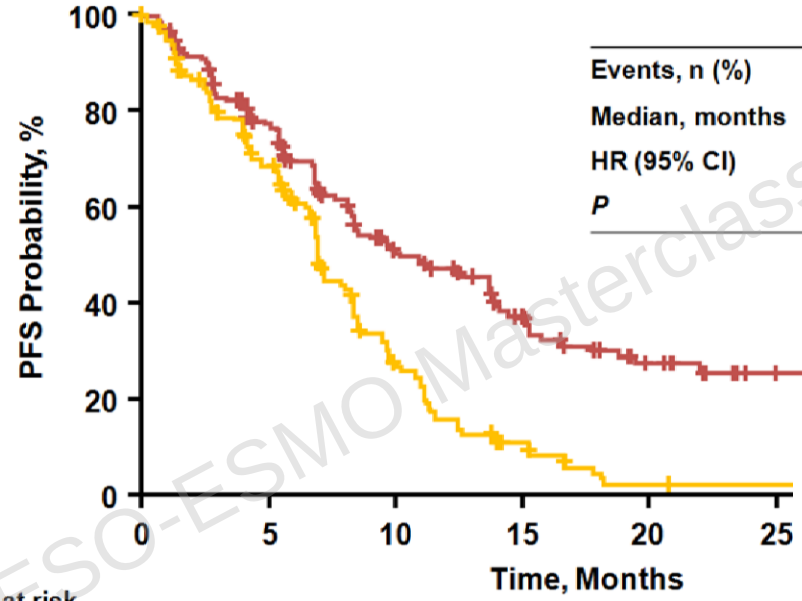
Crizotinib in fist line: PRORILFE 1014



	Crizotinib (N = 172)	Chemotherapy (N = 171)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35-0.60)	
P	<.0001	

ALK+ disease according to FISH
Locally advanced or metastatic NSCLC
No prioir platinum-based chemotherapy regimen
ECOG PS 0-2

(n=343)

R 1:1

Crizotinib 250mg BID

Pemetrexed/cisplatin OR pemetrexed/carboplatin i.v. q3w

Salomon, NEJM 2014

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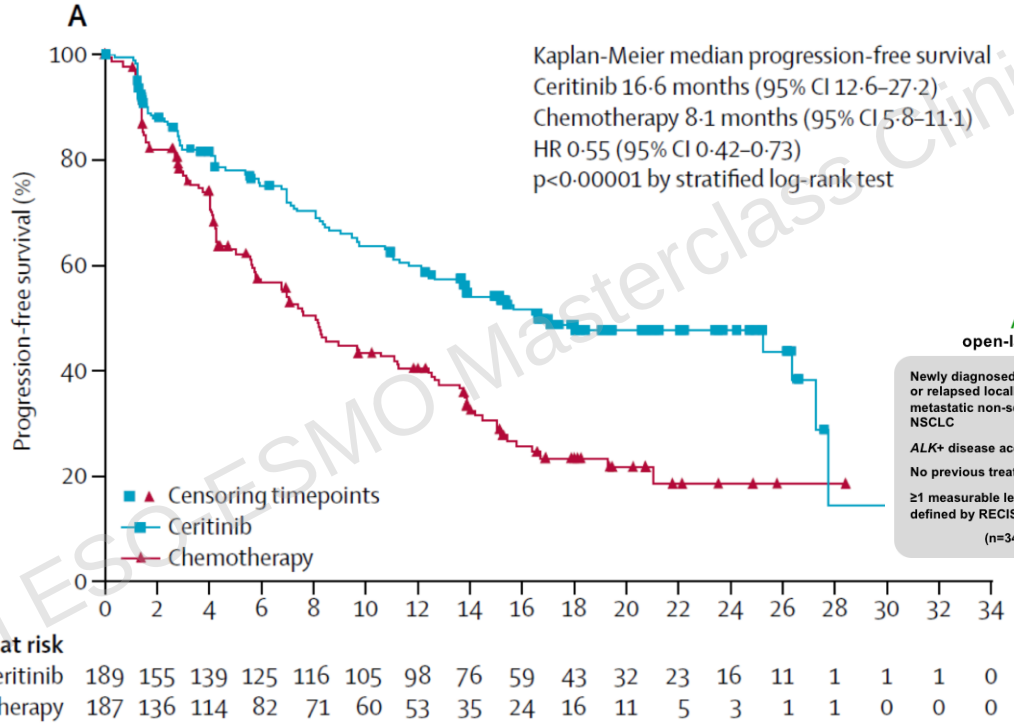
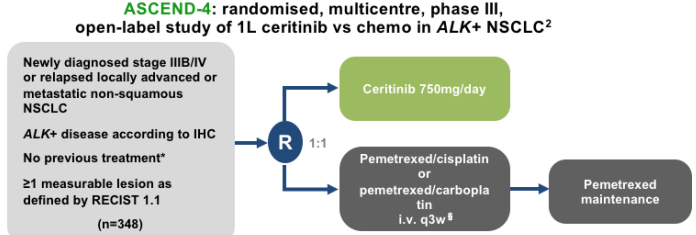
First-line ceritinib versus platinum-based chemotherapy in advanced *ALK*-rearranged NSCLC (ASCEND-4):





Median duration of follow-up: 19.7 months

Soria, et al. Lancet Oncol 2017

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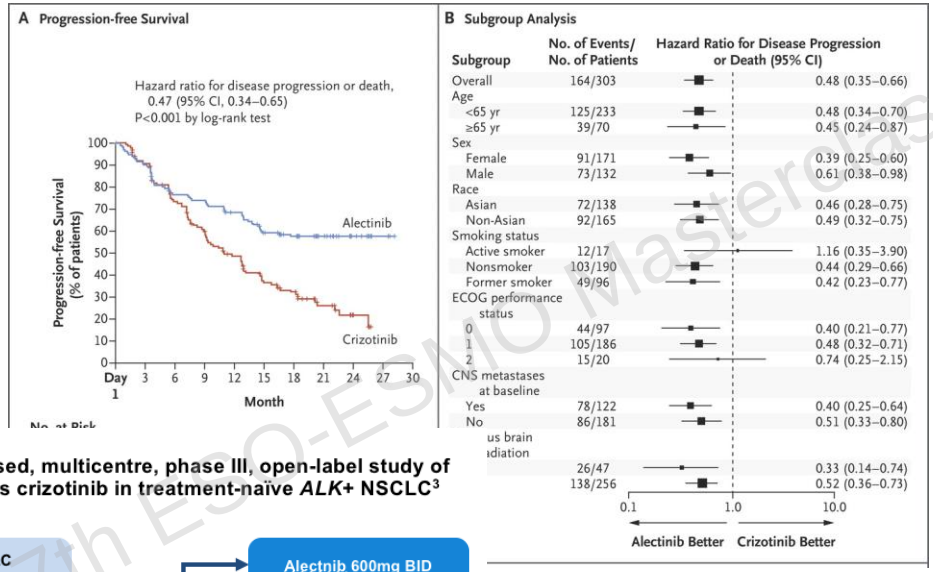
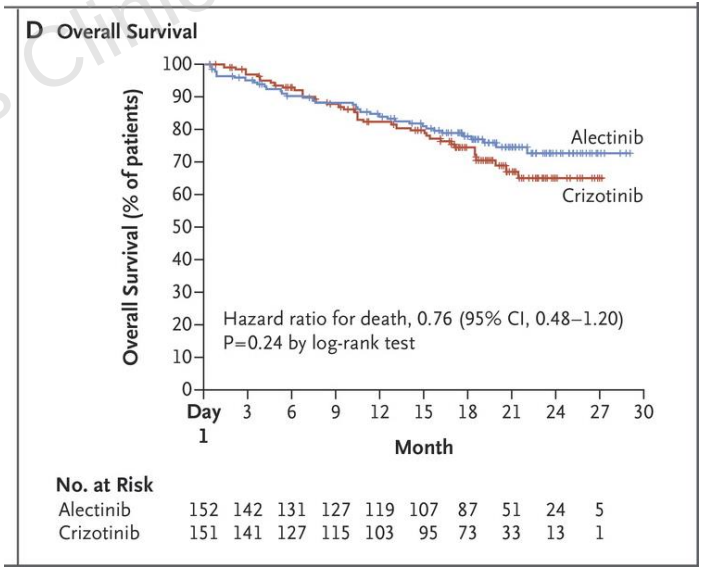
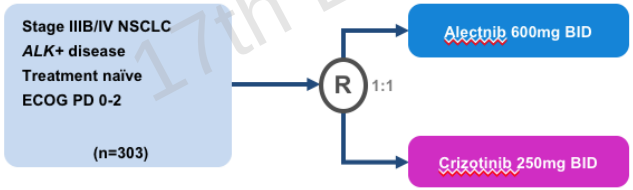
Alectinib vs crizotinib in treatment-naïve advanced *ALK*+ NSCLC: primary results of the global phase III ALEX study





ALEX: randomised, multicentre, phase III, open-label study of alectinib versus crizotinib in treatment-naïve *ALK*+ NSCLC[3]



Shaw, ASCO 2017; Peters, NEJM 2017

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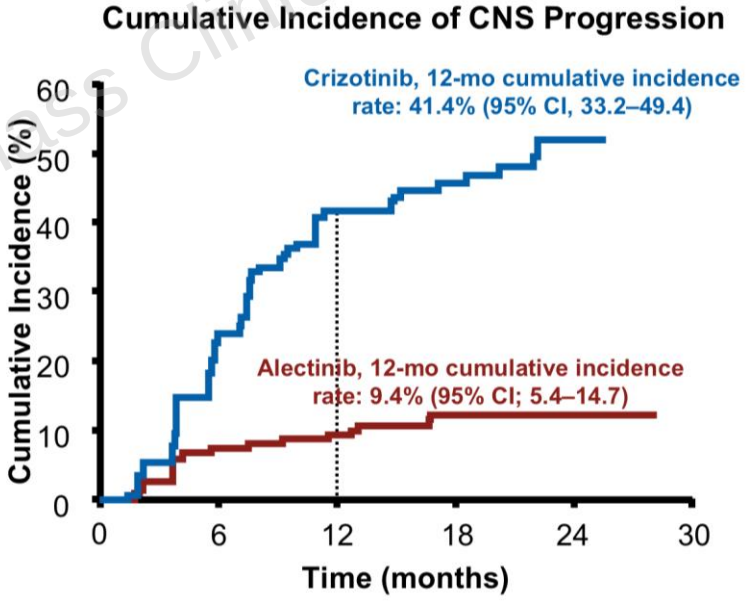
Alectinib vs crizotinib in treatment-naïve advanced *ALK*+ NSCLC: primary results of the global phase III ALEX study: CNS activity

- Competing risk of CNS progression, non-CNS progression, and death based on first event was analyzed

CNS Progression, no Previous Systemic PD	Alectinib (n = 152)	Crizotinib (n = 151)
Pts with event, n (%)	18 (12)	68 (45)
Cause-specific HR (95% CI)	0.16 (0.10–0.28)	
P value	< .0001	



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Shaw, ASCO 2017; Peters, NEJM 2017

ALK inhibitors after crizotinib failure

	Alectinib NP28673 (IRC)	Alectinib NB28761 (IRC)	Brigatinib* (180mg qd) (IRC)	Ceritinib ASCEND-1 (prior ALKi)	Ceritinib ASCEND-2
Population	n=122	n=69	n=110	N=163	N=140
ORR, %	50	51	55	56	39
DCR, %	79	80	86	74	77
mDoR, mos	11.2	13.5	13.8	8.3	9.7
mPFS, mos	8.9	8.1	15.6	6.9	5.7
Toxicity issues	Very few		Dyspnea (low grade with lead-in 90mg 7days)	GI (impacting QoL)	

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Pérol, ESMO 2016; Ahn, WCLC1017

ALK inhibitors after crizotinib failure: CNS activity

	Alectinib		Brigatinib (180mg qd)		Ceritinib		
	Measurable	Measurable and Non-measurable	Measurable	Only Non-Measurable	ASCEND-2 Measurable	ASCEND-1 Measurable and non-measurable	ASCEND-1 Measurable
	(n=60)	(n=138)	(n=18)	(n=54)	(n=20)	(n=75)	(n=28)
CNS ORR, %	**64**	**43**	**67**	**19**	**45**	**19**	**36**
CR, %	**22**	**27**	**0**	**19**	**10**	**5**	**0**
CNS DCR, %	**80**	**86**	**83**	**87**	**80**	**65**	**61**
CNS mDoR, months	**10.8**	**11.1**	**(7.4-NR)**		**-**	**6.9**	**11.1**

17th ECCO-ESMO Masterclass Clinical Oncology

Kim, ASCO 2016 and Pérol ELCC 2016