

Perugia, 5 Luglio 2019

**Evoluzione delle strategie di trattamento sequenziale
nel NSCLC con mutazione di EGFR: il punto**

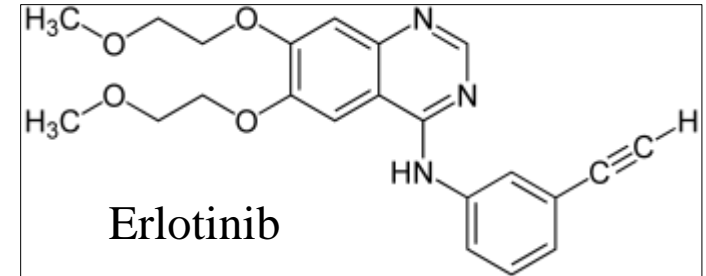
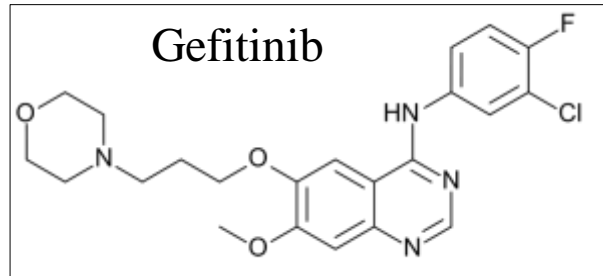
Giulia Pasquini

Azienda Ospedaliero-Universitaria Pisana
Università di Pisa

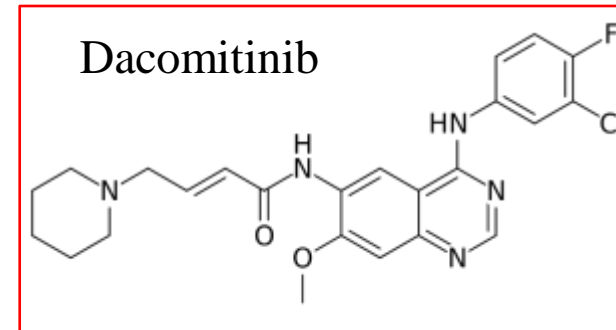
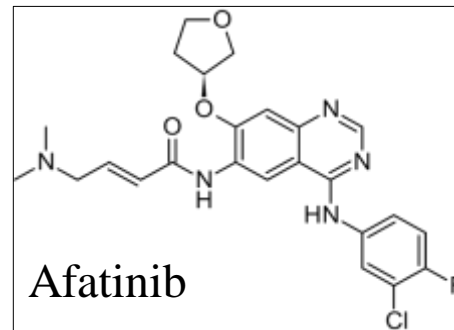


EGFR TKIs

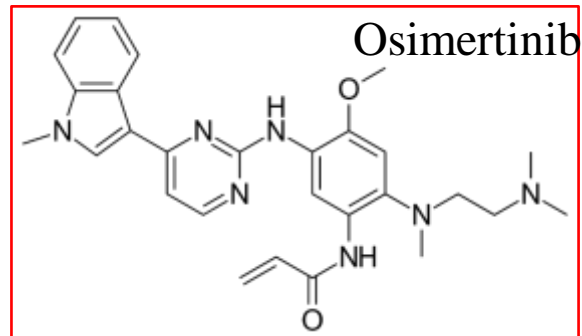
1° Generation



2° Generation



3° Generation

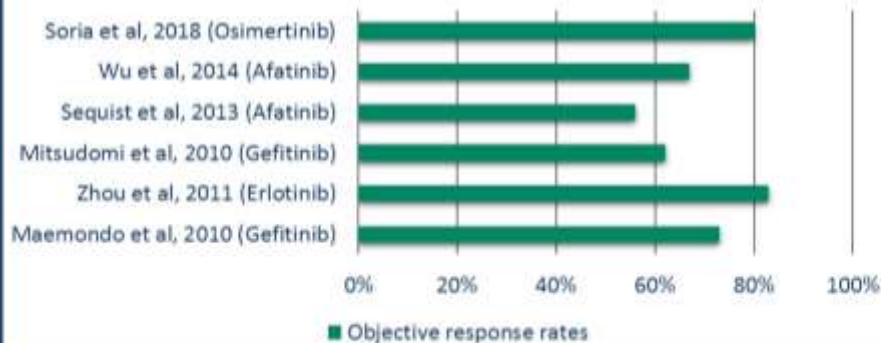


Background EGFR TKI

While targeting an oncogenic driver in NSCLC usually leads to robust initial responses, emergence of resistance is inevitable and limits clinical benefit

EGFR mutated NSCLC

OBJECTIVE RESPONSE RATE



PROGRESSION FREE SURVIVAL



EGFR TKI vs Chemotherapy

Study	Treatment	N	Median PFS, mos
Maemondo	Gefitinib vs Carboplatin / Paclitaxel	247	6.8 vs 5.4 (P < .001)
Mitsudomi	Gefitinib vs Carboplatin / Paclitaxel	180	7.2 vs 6.3 (P < .0001)
OPTIMAL	Gefitinib vs Carboplatin / Paclitaxel	171	7.0 vs 4.6 (P < .0001)
EURTAC	Gefitinib vs Carboplatin / Paclitaxel	174	9.7 vs 5.2 (P < .0001)
LUX-Lung 3	Gefitinib vs Cisplatin/pemetrexed	345	11.1 vs 6.9, (P = .001)
LUX-Lung 6	Gefitinib vs Cisplatin/Gemcitabine	364	11.0 vs 5.6, (P < .001)

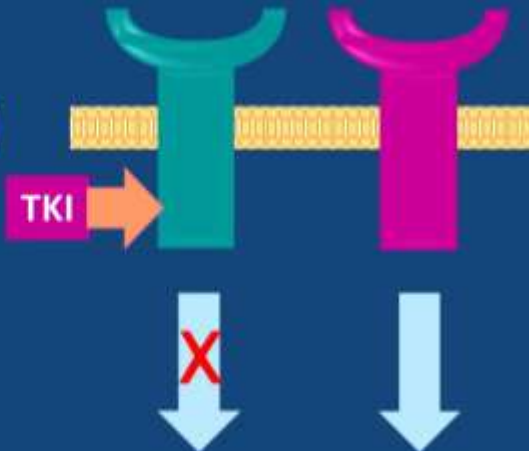
NO overall survival benefit seen in any of these studies (when reported)

Acquired resistance to TKI

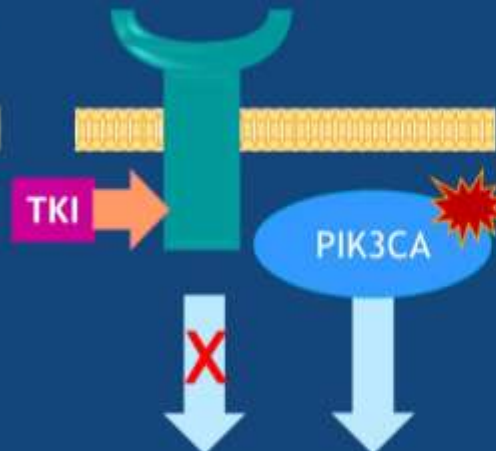
Modification of target gene



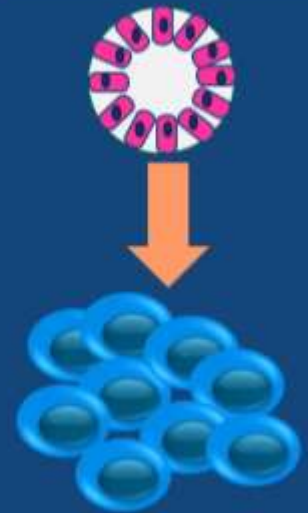
Activation of bypass pathway



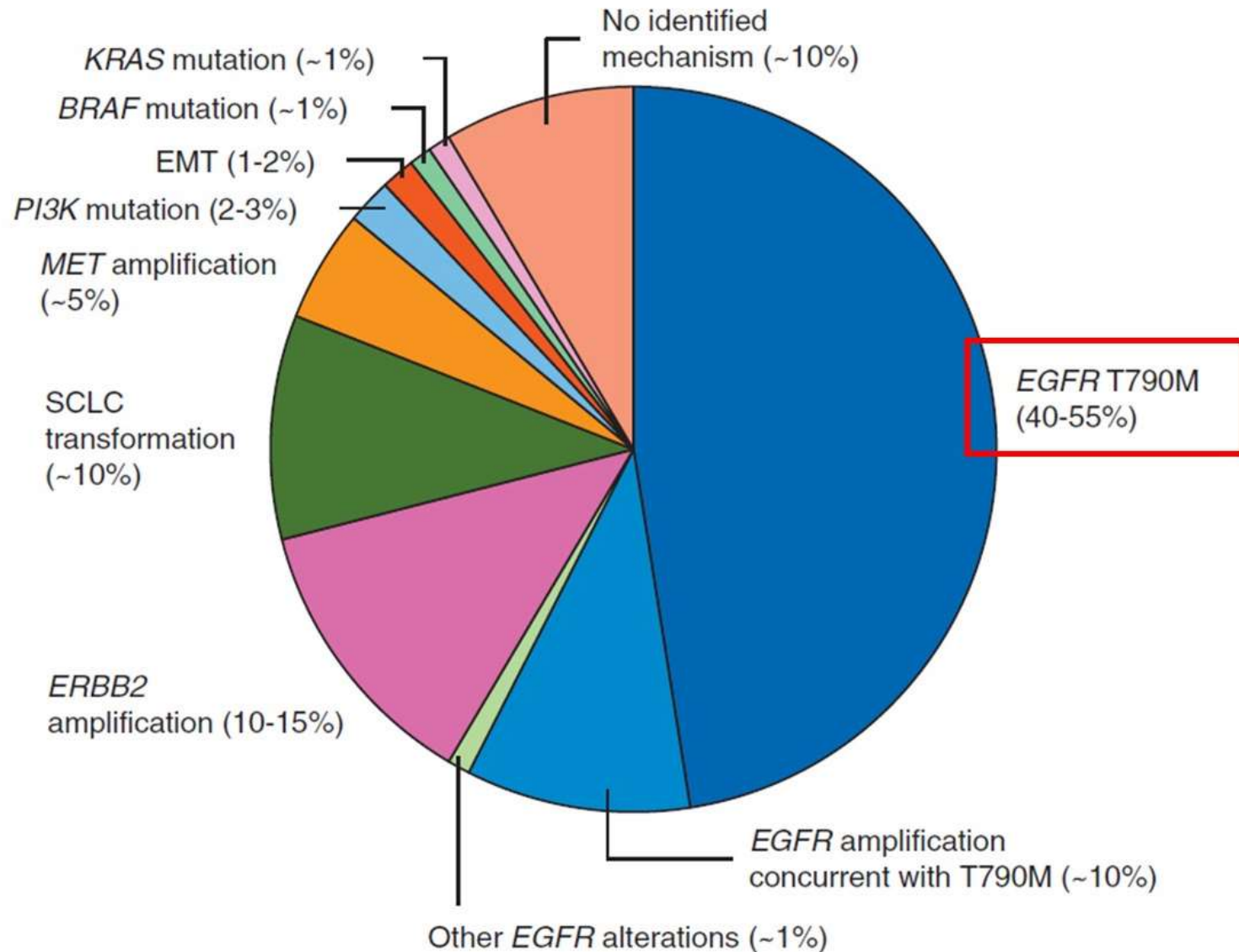
Downstream pathway activation



Histologic transformation



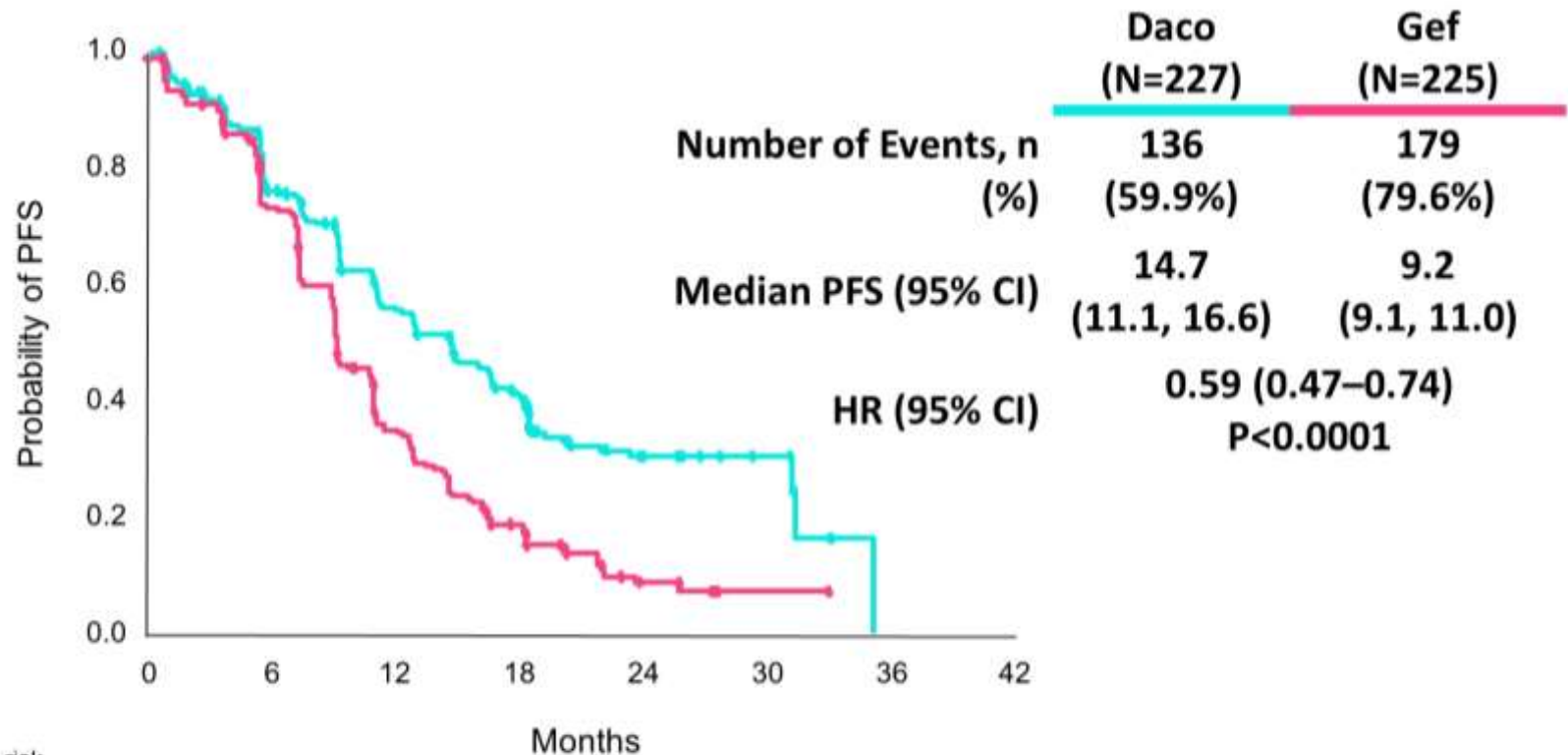
Acquired resistance to first and second generation TKIs



First line Therapy: Key Recent Trials

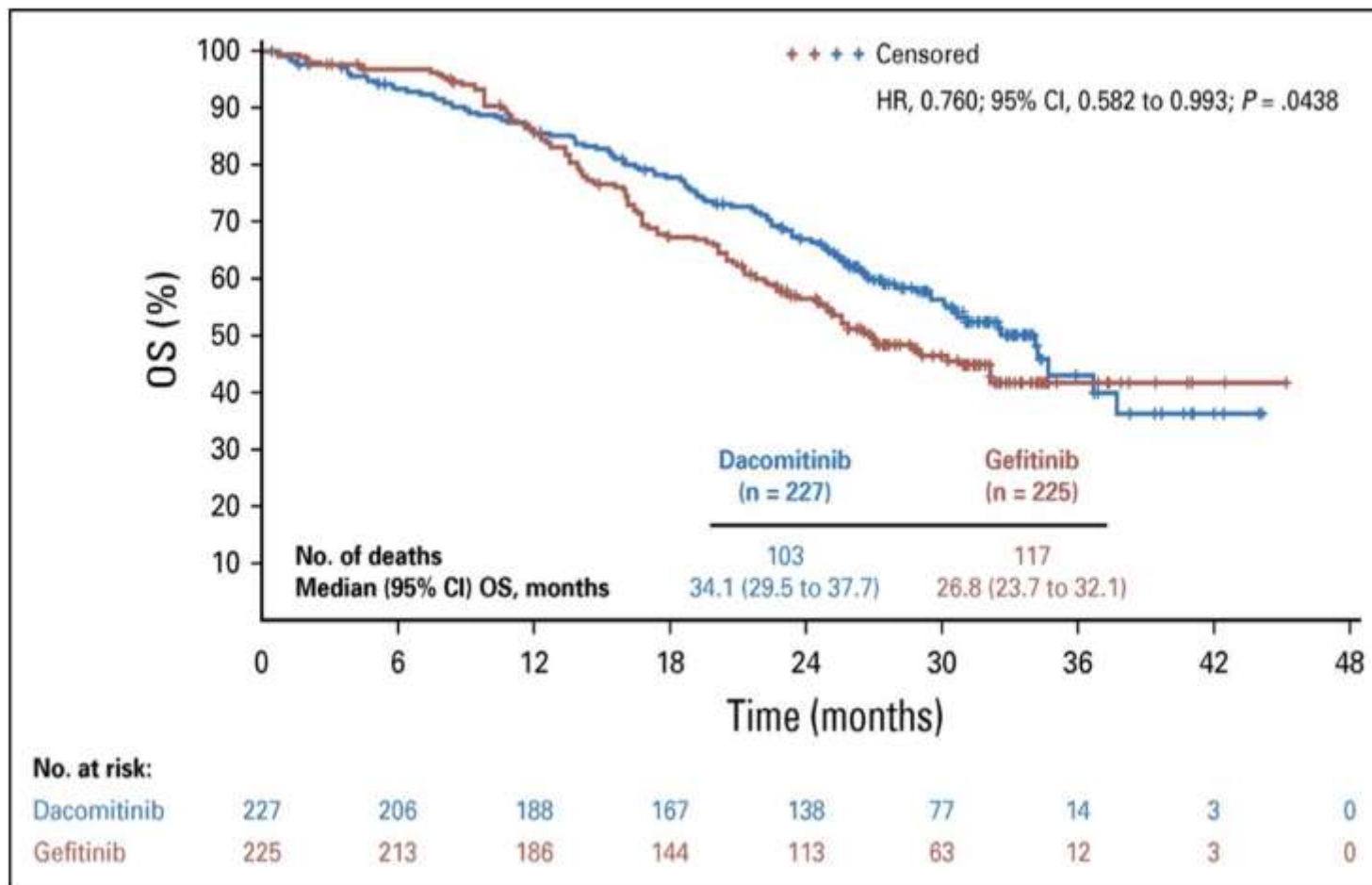
- FLAURA
 - ARCHER 1050
 - Chemo + EGFR TKI studies
 - EGFR TKI + VEGF mAb studies
- 

ARCHER-PFS (primary endpoint)



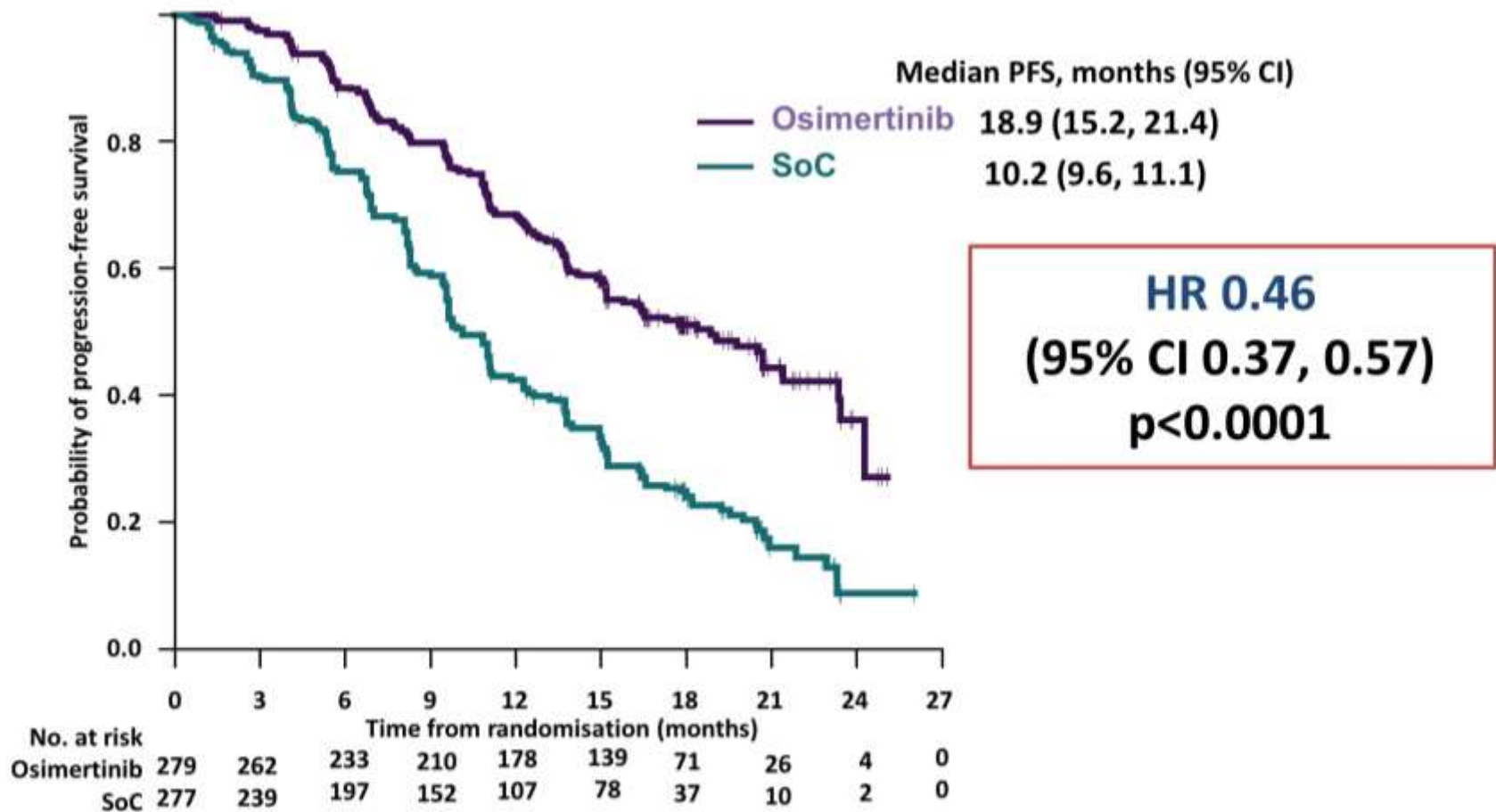
No. at risk								
Dacomitinib	227	154	106	73	20	6	0	0
Gefitinib	225	155	69	34	7	1	0	0

ARCHER-OS



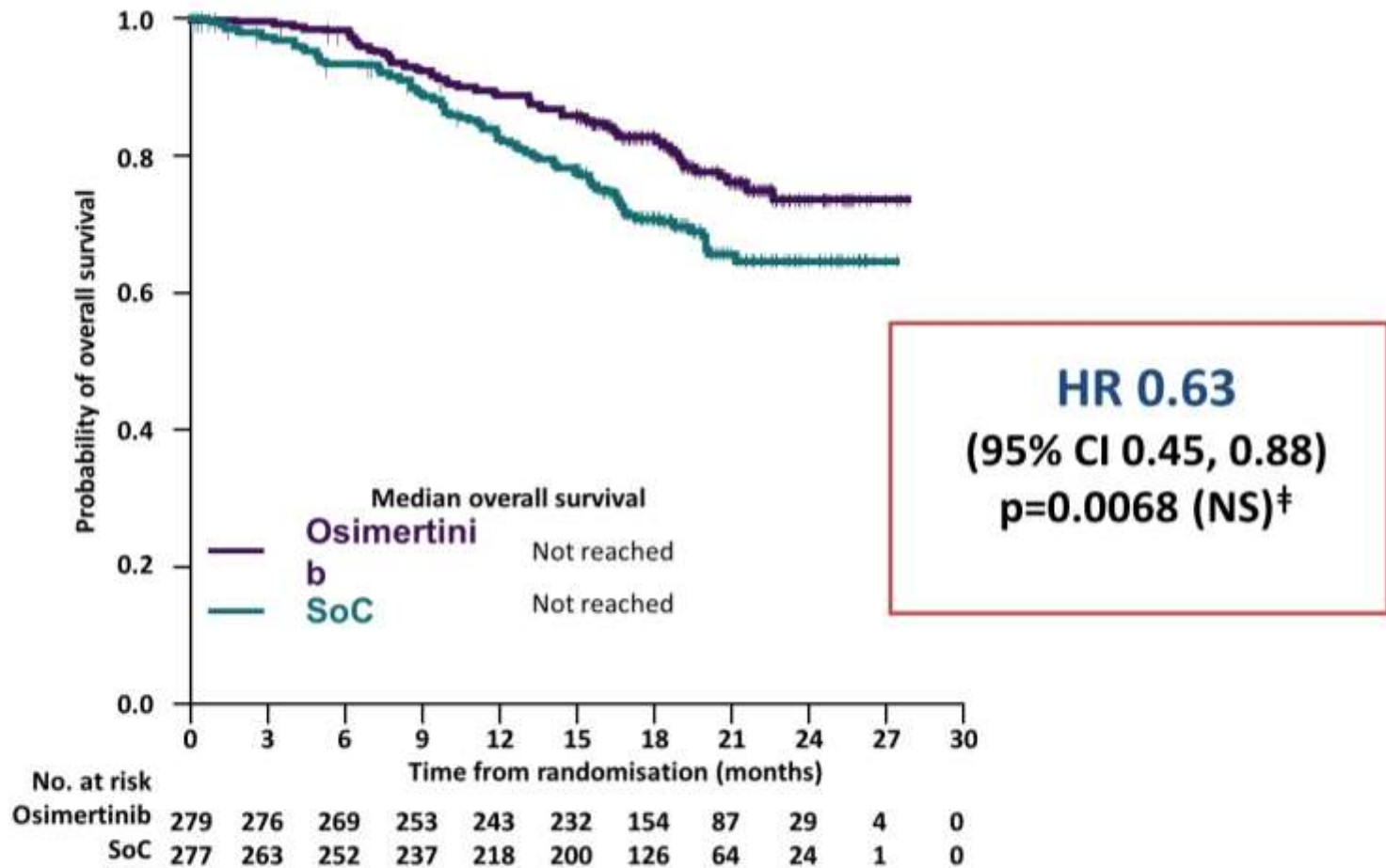
Mok et al . J Clin Oncol, 2018

FLAURA-PFS (primary endpoint)



FLAURA-OS interim analysis

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



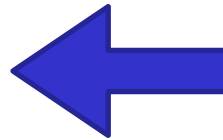
FLAURA & ARCHER 1050

	FLAURA (osimertinib)	ARCHER 1050 (dacomitinib)
Progression-Free Survival	HR 0.46 (0.37-0.47)	HR 0.59 (0.47-0.74)
Control (1 st gen TKI)	Med 10.2 mo	Med 9.2 mo
Experimental	Med 18.9 mo	Med 14.7 mo
Overall Survival		HR 0.76 (0.58-0.99)
Control (1 st gen TKI)	NA	Med 46.3 mo
Experimental		Med 56.2 mo
Experimental Arm G3+ Rash	1%	13.7%
Experimental Arm G3+ Diarrhea	2%	8.4%
Experimental Arm Dose Reduction	4%	66%
CNS metastases	Allowed if stable	Not allowed

Soria, *N Engl J Med* 2018; Wu, *Lancet Onc* 2017; Mok, *J Clin Oncol* 2018

First line Therapy: Key Recent Trials

- FLAURA
- ARCHER 1050
- Chemo + EGFR TKI studies
- EGFR TKI + VEGF mAb studies



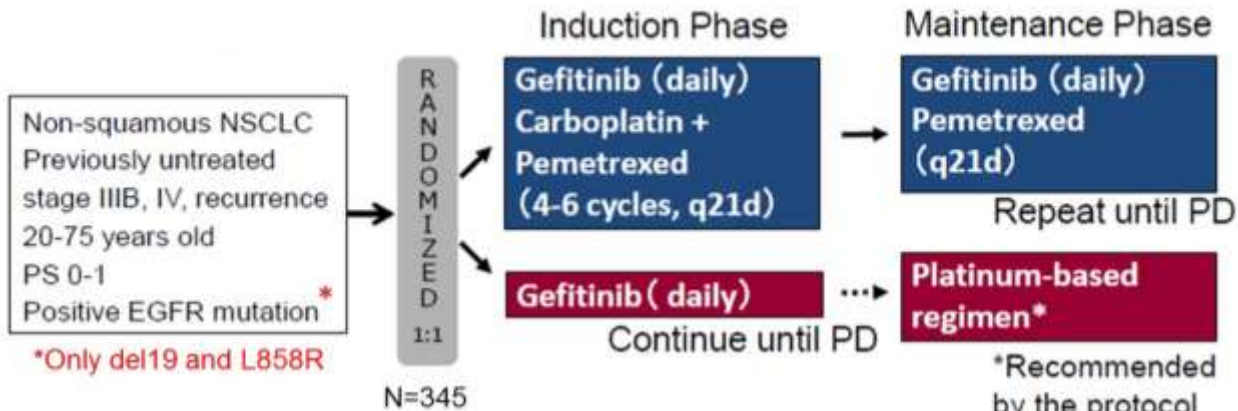
Strategy Inversion..

From tailored therapy to....combination Strategy



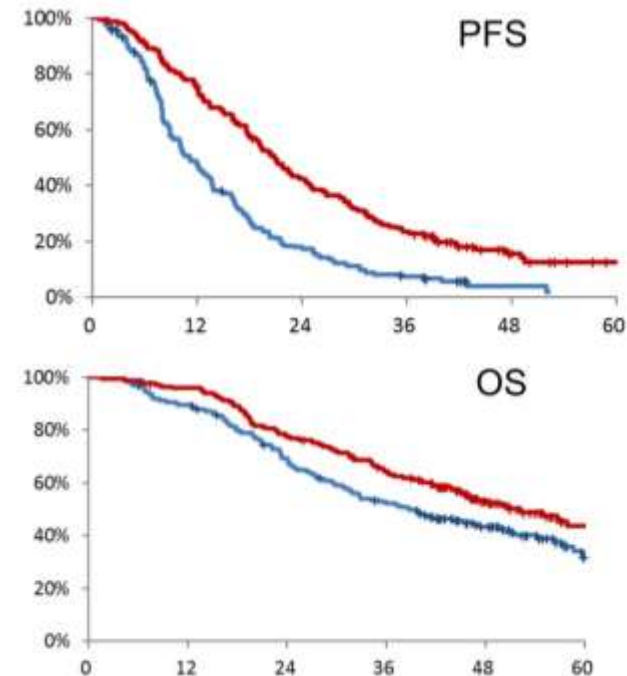
From less is more.....to more is better!

NEJ009: Upfront chemotherapy+TKI



	Gefitinib	Carbo/Pem/Gefitinib	HR (95% CI)
PFS	11.2 mo	20.9 mo	0.49 (0.39-0.63)
OS	38.8 mo	52.2. mo	0.70 (0.52-0.93)

Nakamura, ASCO 2018



Gef vs Gef+C

Gef vs Gef + C

ELIGIBILITY CRITERIA

- Age \geq 18 yrs
- Histologic/ cytologic NSCLC
- Stage IIIB not amenable to radical therapy or Stage IV
- First-line palliative intent
- Activating *EGFR* mutation (exon 19/ 21/ 18)
- ECOG PS 0 to 2
- Adequate organ function
- No h/o ILD, radiation pneumonitis that required steroids or IPF

STRATIFY

- ECOG PS (0/1 v.2)
- *EGFR* mutation (exon 19 v. other)

Randomized
1:1
Open Label

n=174

- Gefitinib 250mg daily
- Pem 500 mg/m² +
Carbo AUC 5 Q21d x 4
→ Pem 500 mg/m²
Q21d

n=176

Gefitinib 250mg
daily

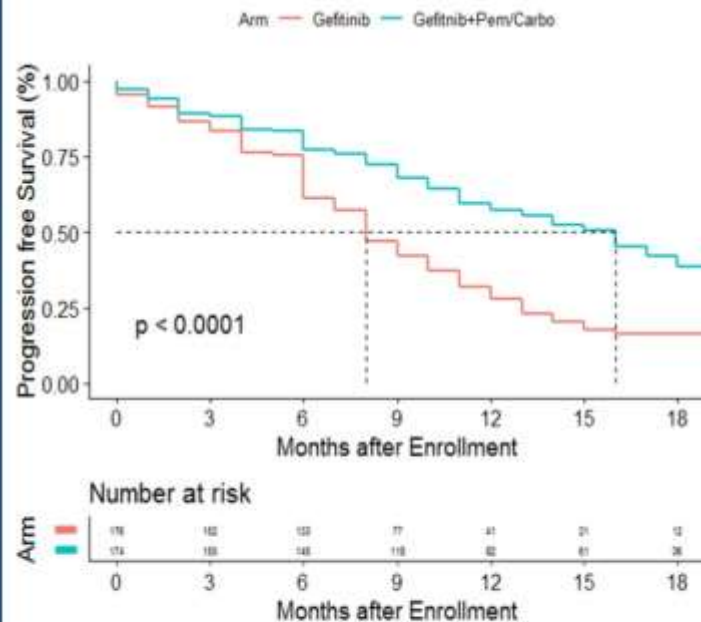
Evaluation: Clinical- Q 3 wks in Gef + C (pre-chemo), Q 2mth (gef); Radiologic-Q 2-3 mnth
Duration of Therapy: until PD, unacceptable toxicity or consent withdrawal.

Gef vs Gef+C



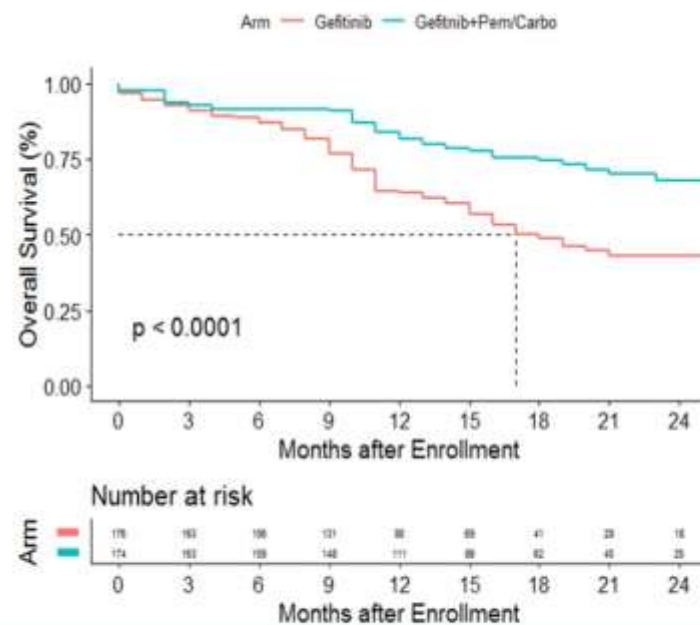
Arm	Number of patients	Number of events	Median PFS (95%CI)
Gefitinib	176	138	8 months (7.0 to 9.0)
Gefitinib + pemetrexed/carboplatin	174	99	16 months (13.5 to 18.5)

Hazard ratio for disease progression or death, 0.51; 95% CI, 0.39 to 0.66



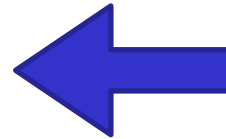
Arm	Number of patients	Number of events	Median OS (95%CI)
Gefitinib	176	80	17 months (13.5 to 20.5)
Gefitinib + pemetrexed/carboplatin	174	42	NC (NC to NC)

Hazard ratio for death, 0.45; 95% CI, 0.31 to 0.65



First line Therapy: Key Recent Trials

- FLAURA
- ARCHER 1050
- Chemo + EGFR TKI studies
- EGFR TKI + VEGF mAb studies



RCTs of Erlotinib vs Erlotinib/Bev

Trial	Setting	n	Med PFS E	Med PFS EB	PFS HR (95% CI)	OS HR (95% CI)
BETA	2 nd line	30	--	--	--	0.44 (0.11-1.67)
JO25567	1 st line	150	9.8 mo	16.4 mo	0.52 (0.35–0.76)	0.81 (0.53–1.23)
NEJ026	1 st line	214	13.3 mo	16.9 mo	0.65 (0.42-0.88)	--
Alliance	1 st line	88	13.5 mo	17.5 mo	0.81 (0.50-1.3)	1.41 (0.71-2.8)

Herbst, *Lancet* 2011; Seto, *Lancet Oncol* 2014; Saito, *Lancet Oncol* 2019;
Furuya, ASCO 2018; Stinchcombe ESMO 2018

RELAY

RELAY: Study Design^{1,2}

Key inclusion criteria

- Stage IV NSCLC
- *EGFR* mutation-positive (Ex19del or Ex 21 L858R)
- ECOG PS 0-1

Key exclusion criteria

- Known *EGFR* T790M mutation
- Prior treatment with *EGFR* TKI or chemotherapy
- Brain metastases

Phase 3^a
N=449

R
A
N
D
O
M
I
Z
E
1:1

Ramucirumab 10 mg/kg Q2W
+
Erlotinib 150 mg/day

Placebo Q2W
+
Erlotinib 150 mg/day

Treatment until
progression or
unacceptable
toxicity

Primary end point:
Progression-Free
Survival

Stratification factors

- ♦ *EGFR* status (exon 19 deletion vs. exon 21 L858R)
- ♦ Sex
- ♦ Region (East Asia vs. other)
- ♦ *EGFR* testing method (therascreen®/cobas® vs. other)

^aPhase 3 enrollment began after confirmation of dose and schedule in Phase 1b²

1. Garon EB et al. *Clin Lung Cancer* 2017; 2. Reck M et al. *Clin Lung Cancer* 2018

Clinicaltrials.gov NCT02411448

RELAY

RELAY Primary Endpoint: PFS (Investigator-Assessed)



Consistent PFS benefit by independent, blinded central review (HR 0.671, 95% CI 0.518 – 0.869; p=0.0022)

RELAY

RELAY: PFS2 and Interim OS

		RAM + ERL N=224	PBO + ERL N=225
PFS2	Events,	61	79
	Censoring rate	73%	65%
	Median, mo	NR	NR
	HR (95% CI)	0.690 (0.490, 0.972)	
Interim OS	Events	37	42
	Censoring rate	83%	81%
	Median, mo	NR	NR
	HR (95% CI)	0.832 (0.532, 1.303)	

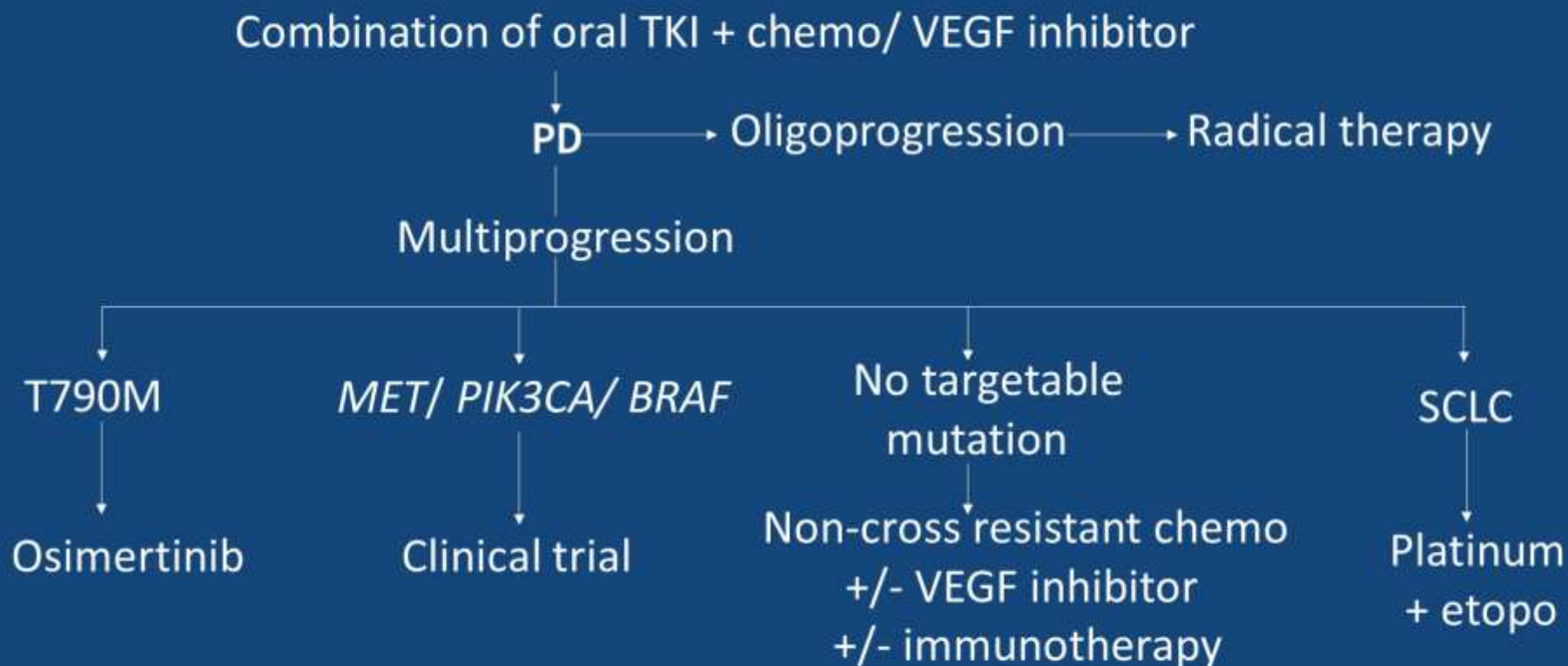
PFS2 (Investigator-assessed)



PFS2 defined as the time from randomization to 2nd disease progression (defined as objective radiological or symptomatic progression after start of additional systematic anticancer treatment), or death from any cause, whichever comes first.

Optimal sequencing..for the data available now..

Optimal sequencing...



Available sequencing..for now..



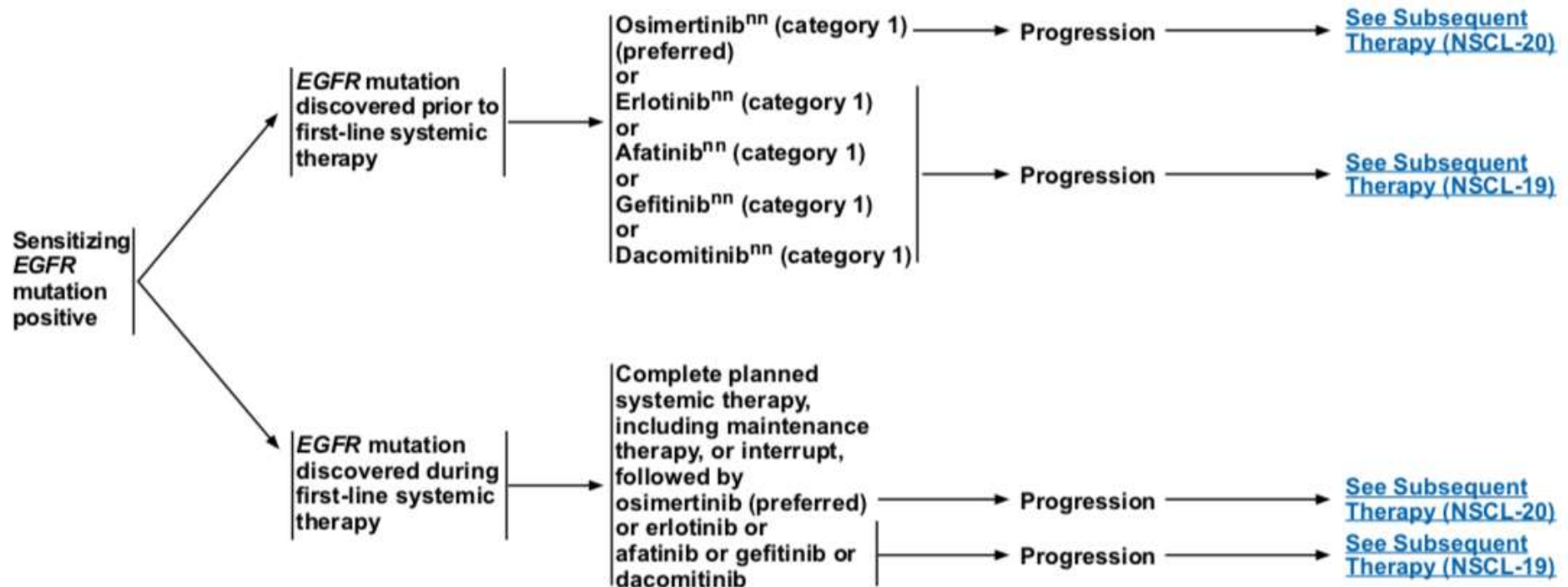
National
Comprehensive
Cancer
Network[®]

NCCN Guidelines Version 5.2019 Non-Small Cell Lung Cancer

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SENSITIZING EGFR MUTATION POSITIVE^{hh}

FIRST-LINE THERAPY^{mm}



Available sequencing..for now..



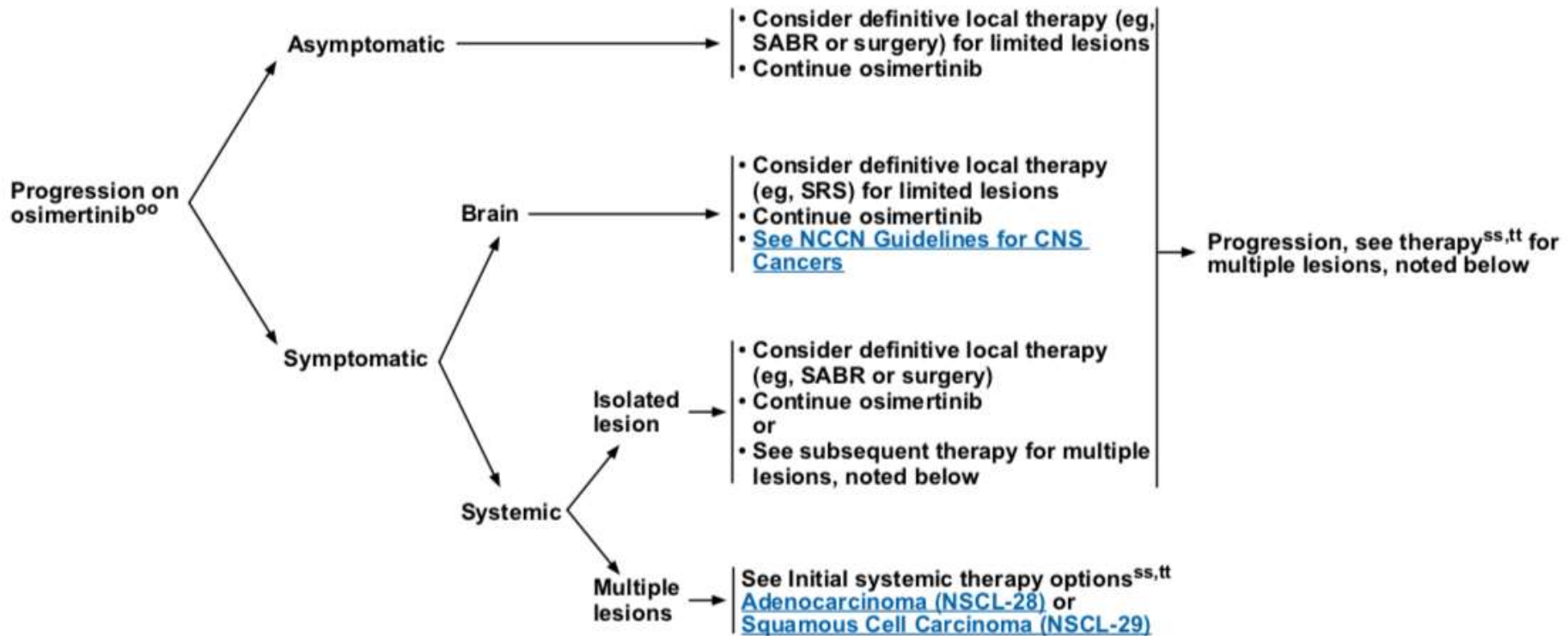
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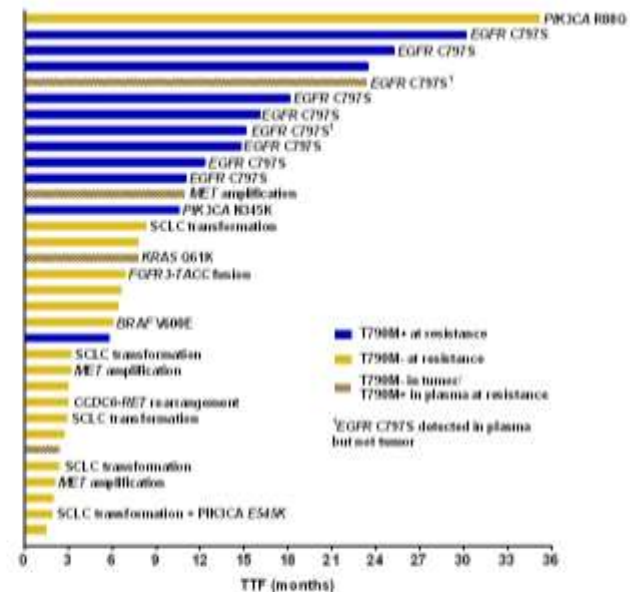
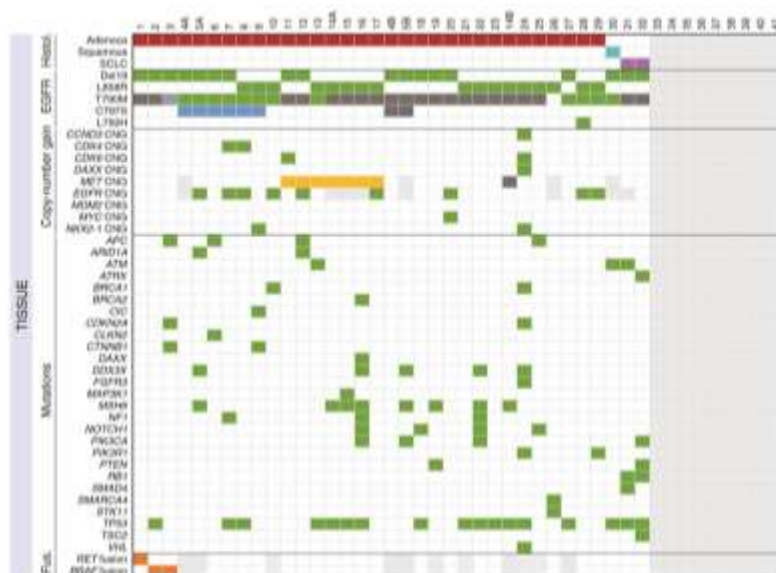
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SENSITIZING EGFR MUTATION POSITIVE^{hh}

SUBSEQUENT THERAPY^{mm}



The future: Acquired resistance to 1L Osimertinib



15-25% MET amp, 10-20% C797S, 10% SCLC, 2-3% RET translocation

Piotrowska, *Cancer Disc* 2018; Oxnard, *JAMA Onc* 2018; Ramalingam, *J Clin Oncol* 2018; Papadimitrakopoulou, *ESMO* 2018

PRESENTED AT: **2019 ASCO**
ANNUAL MEETING

#ASCO19

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PRESENTED BY: Lecia V. Sequist, MD, MPH



@LeciaSequist

Acquired resistance: ASCO 2019 and next Steps

	Abstract and Author	Session
Acquired Resistance		
U3-1402 (HER3 Ab)	9010, Janne	Clin Sci Symposium Fri 1P
JNJ-372 (Bi-specific Ab)	9009, Haura	Clin Sci Symposium Fri 1P
ABBV-399 + erlotinib in MET+	3011, Camidge	Develop Tx PD Sat 4:30P
Osi + necitumumab	9057, Riess	Posters Sunday 8A
Resistance to 1 st line osi	9028, Schoenfeld	Posters Sunday 8A

- Many new targeted compounds and combinations under study
- SAVANNAH trial (osi/savo), ORCHARD study (multiple arms) coming
- Prospective trial for SCLC transformations coming
- We rapidly need more info on chemo/IO

First line Setting: ASCO 2019 and next steps

Abstract and Author

Session

Front-Line

Carbo/pem/gefitinib
RELAY (erlot ± ramucirumab)
Osi + bevacizumab
Afatinib ± cetuximab
Gefitinib ± metformin

9001, Noronha
9000, Nakagawa
9086, Yu
9079, Cortot
9035, He

Met Orals Monday 8A
Met Orals Monday 8A
Posters Sunday 8A
Posters Sunday 8A
Posters Sunday 8A

- ECOG-ACRIN 5182 will look at 1st line osimertinib + bev
- Also important to look at chemotherapy + osimertinib

Memorial Sloan Kettering Cancer Center

A phase 1/2 study of osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancers.

Michael A. Yu, Joseph Brundage, Rachel Kim, Alex Mackay, Nina Ples, Linda Klu, Di Ma, Scott A. Hays, Robert J. Young, Maria Arellano, Maria Jankovic, Gregory J. Riely, Mark S. Riely

Abstract No. 9086

Background: EGFR tyrosine kinase inhibitors (TKIs) are the first-line treatment of choice for patients with EGFR-mutant lung cancer. EGFR TKIs are typically approved as treatment after progression on an EGFR TKI in patients with lung cancer harboring EGFR T790M. EGFR TKIs are typically approved as treatment after progression on an EGFR TKI in patients with lung cancer harboring EGFR T790M. EGFR TKIs are typically approved as treatment after progression on an EGFR TKI in patients with lung cancer harboring EGFR T790M.

Study design: This is a phase 1/2 study of osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancer. The study is designed to evaluate the safety and efficacy of osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancer. The study is designed to evaluate the safety and efficacy of osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancer.

Results: The study results show that osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancer is safe and effective. The study results show that osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancer is safe and effective. The study results show that osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancer is safe and effective.

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Osimertinib Plus Chemotherapy for EGFR-Mutant NSCLC at Progression: Safety Profile and Survival Analysis

Michael A. Yu, Joseph Brundage, Rachel Kim, Alex Mackay, Nina Ples, Linda Klu, Di Ma, Scott A. Hays, Robert J. Young, Maria Arellano, Maria Jankovic, Gregory J. Riely, Mark S. Riely

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Grazie per l'attenzione!

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