EGFR-TKI with CT: Combined or sequential in EGFR-mutant patients

Sequential combination

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P.R. China

March 28 2014 Geneva

My disclosure

- Honorarium from:
  - Eli Lilly
  - Pfizer
  - Roche
  - AstrsZeneca
  - Sanofi-Aventis

Controversy

Yi-Long Wu

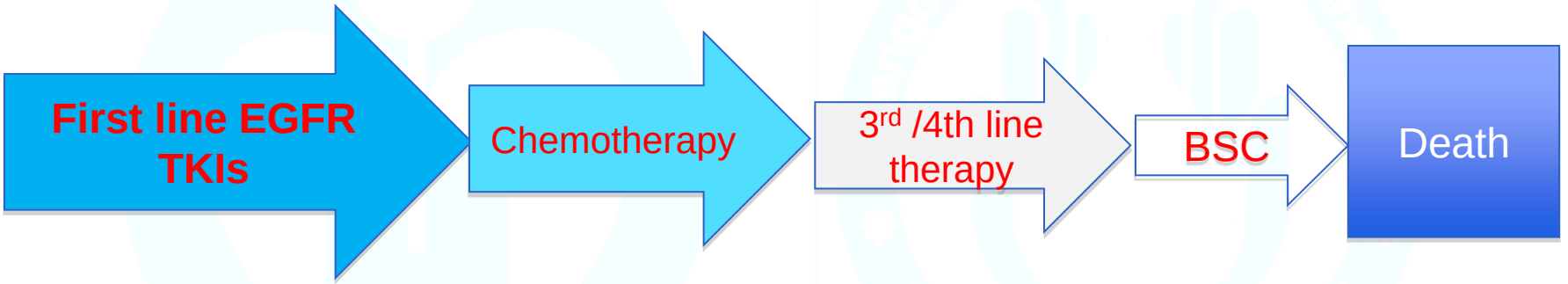
Luis Paz-Ares

Studies of EGFR-TKIs in *EGFR* sensitising mutation-positive NSCLC

Study	EGFR-TKI	n	Line	mPFS (M)	HR
IPASS[1,2]	Gefitinib	132	First	9.5	0.48
WJTOG 3405[3]	Gefitinib	86	First	9.2	0.49
NEJGSG 002[4,5]	Gefitinib	114	First	10.8	0.36
First-Signal[6]	Gefitinib	42	First	8.4	0.61
OPTIMAL[7,8]	Erlotinib	82	First	13.1	0.16
EURTAC[9]	Erlotinib	86	First	9.7	0.37
ENSURE[10]	Erlotinib	110	First	**11.0**	0.34
LUX-Lung 3[11]	Afatinib	230	First	11.1	0.58
LUX-Lung 6[12]	Afatinib	242	First	11.0	0.28

1. Mok et al. N Engl J Med 2009;361:947–957; 2. Fukuoka et al. J Clin Oncol 2011;29(21):2866–2874; 3. Mitsudomi et al. Lancet Oncol 2010;11:121–128; 4. Maemondo et al. N Engl J Med 2010;362:2380–2388; 5. Inoue et al. Ann Oncol 2013;24:54–59; 6. Han et al. JCO 2012; 7. Zhou et al. Lancet Oncol 2011;12:735–742; 8. Zhou et al. ASCO 2012 poster. Abs 7520; 9. Rosell et al. Lancet Oncol 2012;13:239–246; 10. Wu et al WCLC 2013; 11.Sequist et al. J Clin Oncol 2013 epub ahead of print; 12. Wu et al. Lancet Oncol 2014

Advanced NSCLC: EGFR mutation treatment strategy

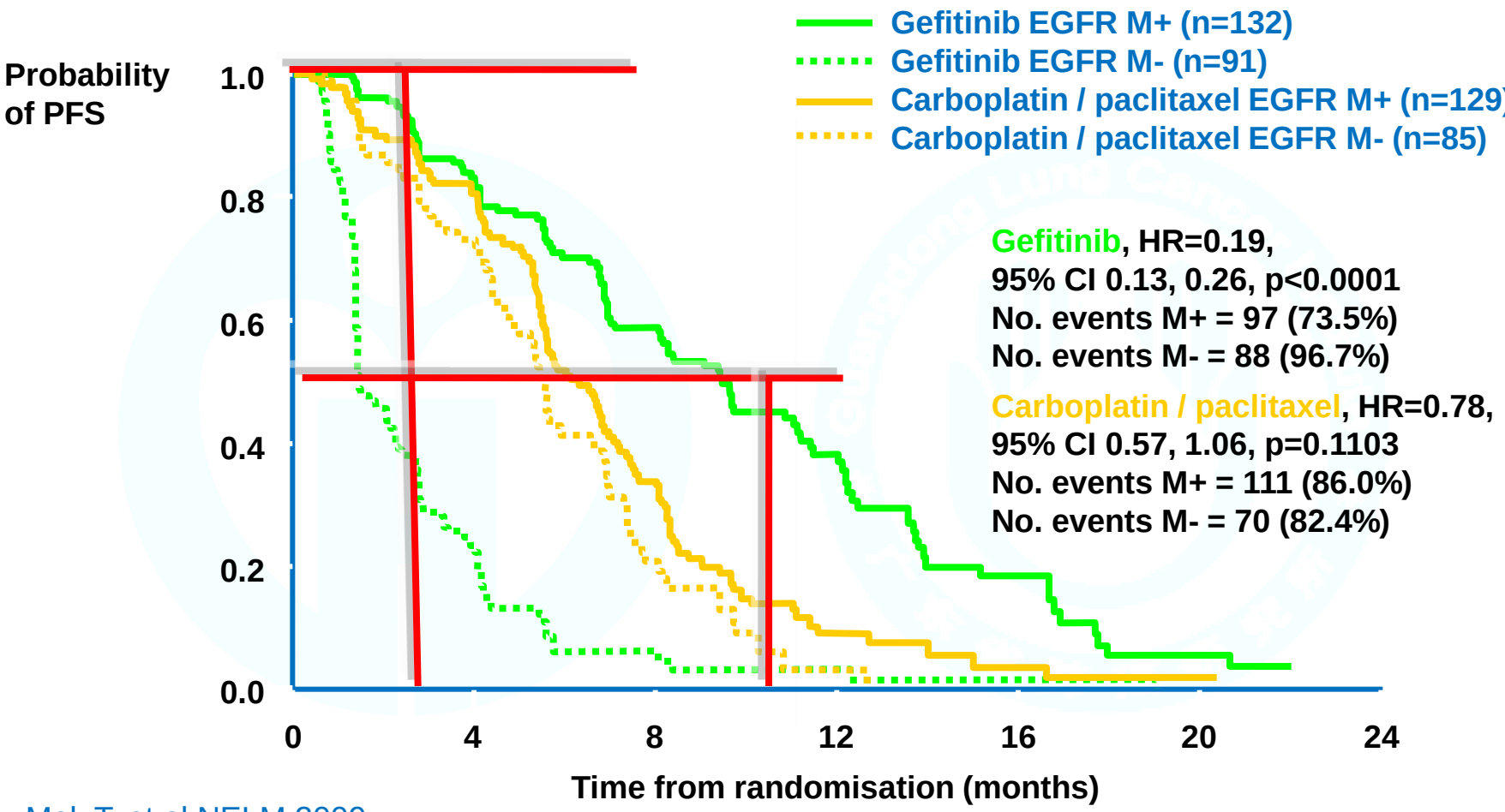


Studies of EGFR-TKIs in *EGFR* sensitising mutation-positive NSCLC

Study	EGFR-TKI	n	Line	mPFS (M)	mOS (M)
IPASS[1,2]	Gefitinib	132	First	9.5	21.6
WJTOG 3405[3]	Gefitinib	86	First	9.2	30.9
NEJGSG 002[4,5]	Gefitinib	114	First	10.8	27.7
First-Signal[6]	Gefitinib	42	First	8.4	30.6
OPTIMAL[7,8]	Erlotinib	82	First	13.1	22.7
EURTAC[9]	Erlotinib	86	First	9.7	19.3
ENSURE[10]	Erlotinib	110	First	**11.0**	**NR**
LUX-Lung 3[11]	Afatinib	230	First	11.1	NR
LUX-Lung 6[12]	Afatinib	242	First	11.0	NR

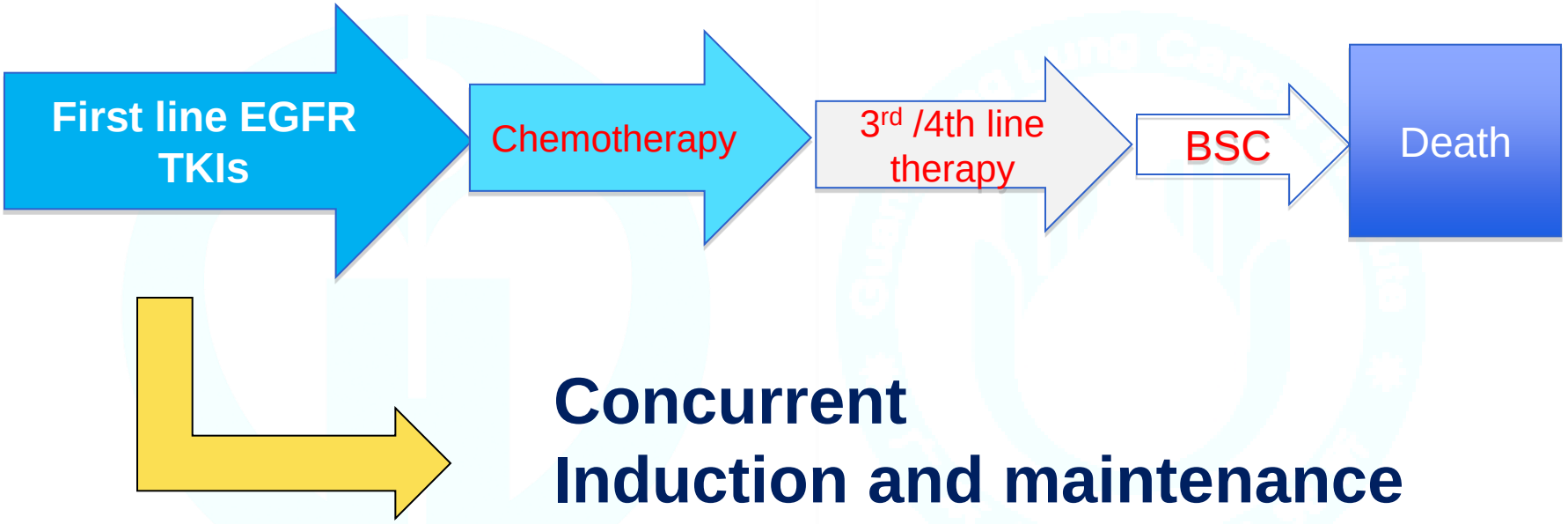
1. Mok et al. N Engl J Med 2009;361:947–957; 2. Fukuoka et al. J Clin Oncol 2011;29(21):2866–2874; 3. Mitsudomi et al. Lancet Oncol 2010;11:121–128; 4. Maemondo et al. N Engl J Med 2010;362:2380–2388; 5. Inoue et al. Ann Oncol 2013;24:54–59; 6. Han et al. JCO 2012; 7. Zhou et al. Lancet Oncol 2011;12:735–742; 8. Zhou et al. ASCO 2012 poster. Abs 7520; 9. Rosell et al. Lancet Oncol 2012;13:239–246; 10. Wu et al WCLC 2013; 11.Sequist et al. J Clin Oncol 2013 epub ahead of print; 12. Wu et al. Lancet Oncol 2014

IPASS PFS



Mok T, et al.NELM,2009

Advanced NSCLC: EGFR mutation treatment strategy



Combination with platinum doublet 4 failures

Trial	Chemo Regimen	RR (%)	TTP (months)	OS (months)
INTACT 1	GEM/CIS	47.2	6	10.9
	GEM/CIS/G250	51.2	5.8	9.9
	GEM/CIS/G500	50.3	5.5	9.9
INTACT 2	CAR/PAC	28.7	5	9.9
	CAR/PAC/G250	30.4	5.3	9.8
	CAR/PAC/G500	30	4.6	8.7
TALENT	GEM/CIS	28.2	5.6	10.1
	GEM/CIS/E150	30	5.4	9.9
TRIBUTE	CAR/PAC	19.3	4.9	10.6
	CAR/PAC/E150	21.5	5.1	10.8

Gandara DR et al, Clinical Lung Cancer 2006, 7(6): 385-388.

Maintenance treatment

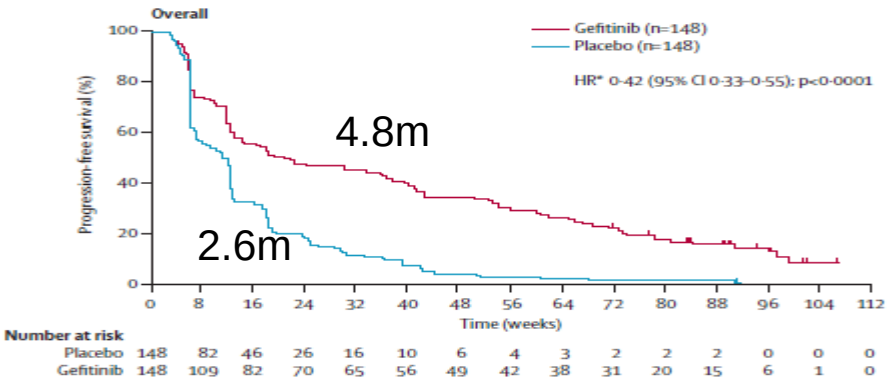
INFORM (CTONG 0804)

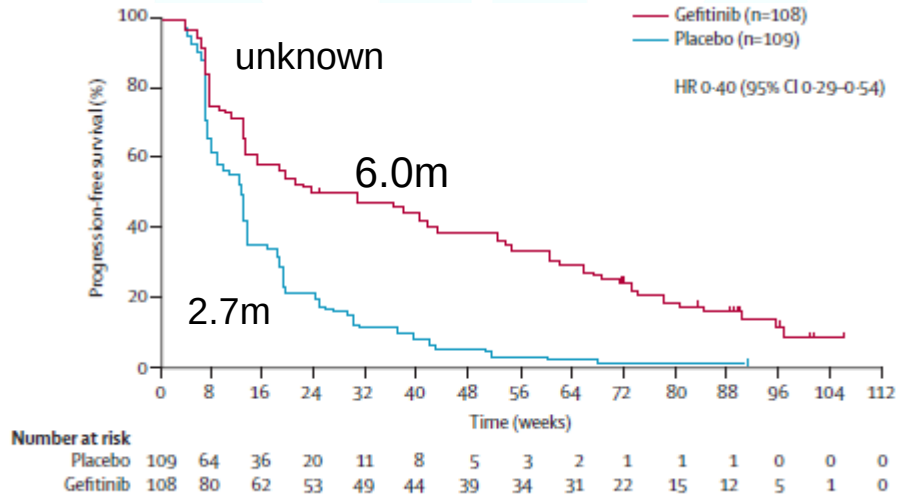
THE LANCET Oncology

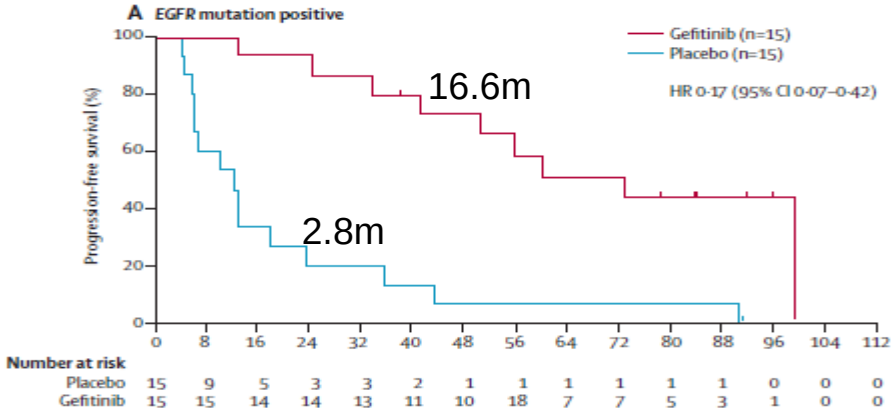
2013

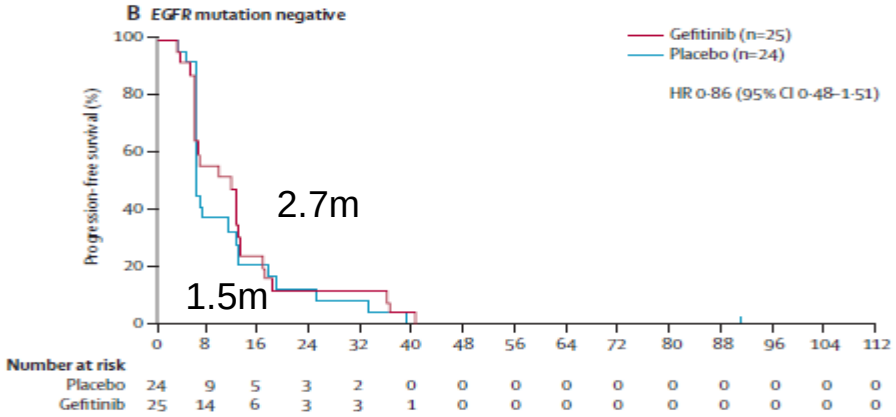
Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial

Prof Li Zhang MD [a], Shenglin Ma MD [b], Xiangqun Song MSc [c], Baohui Han MD [d], Ying Cheng MSc [e], Cheng Huang MD [f],









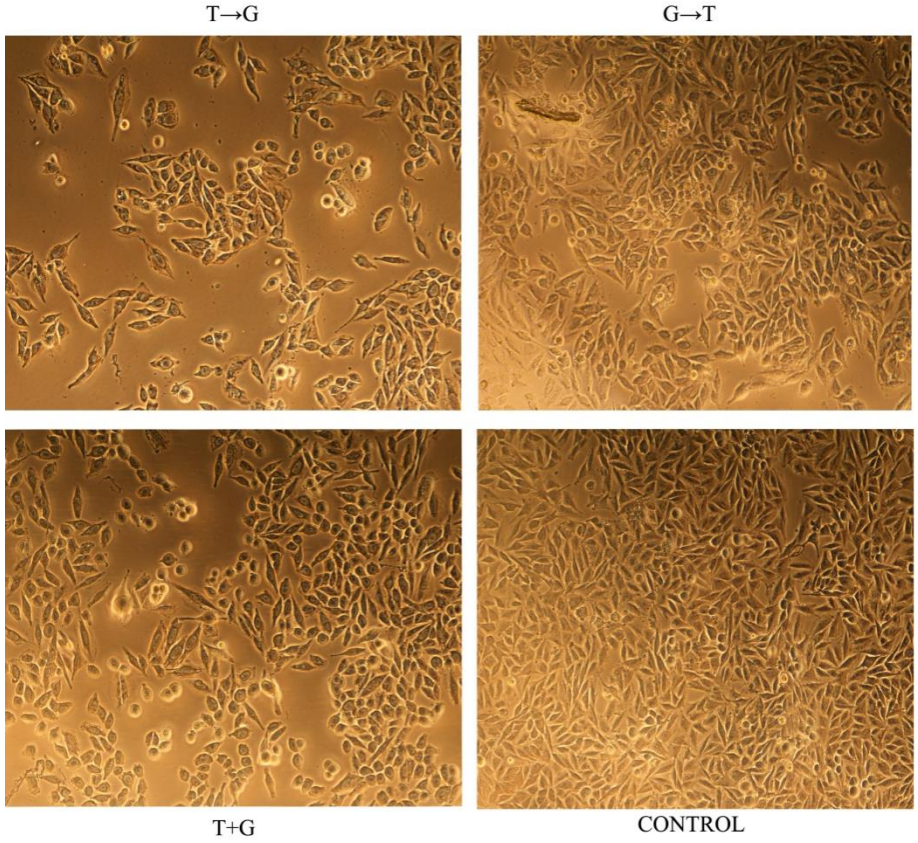
Cancer Chemother Pharmacol
DOI 10.1007/s00280-010-1347-4

ORIGINAL ARTICLE

In vitro sequence-dependent synergism between paclitaxel and gefitinib in human lung cancer cell lines

Hua Cheng · She-Juan An · Xu-Chao Zhang · Song Dong · Yi-Fang Zhang · Zhi-Hong Chen · Hua-Jun Chen · Ai-Lin Guo · Qiu-xiong Lin · Yi-Long Wu

Sequence paclitaxel and Gefitinib: T→G



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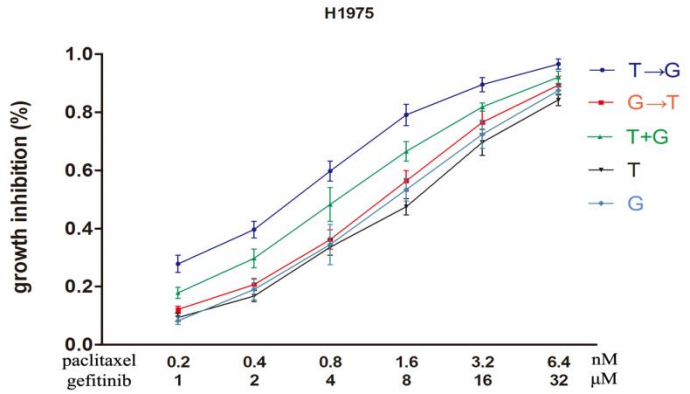

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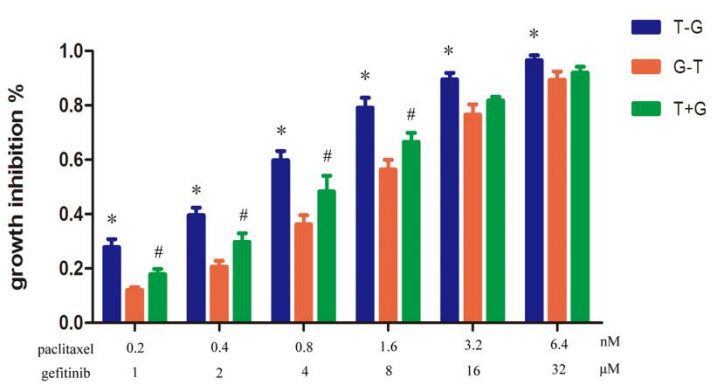


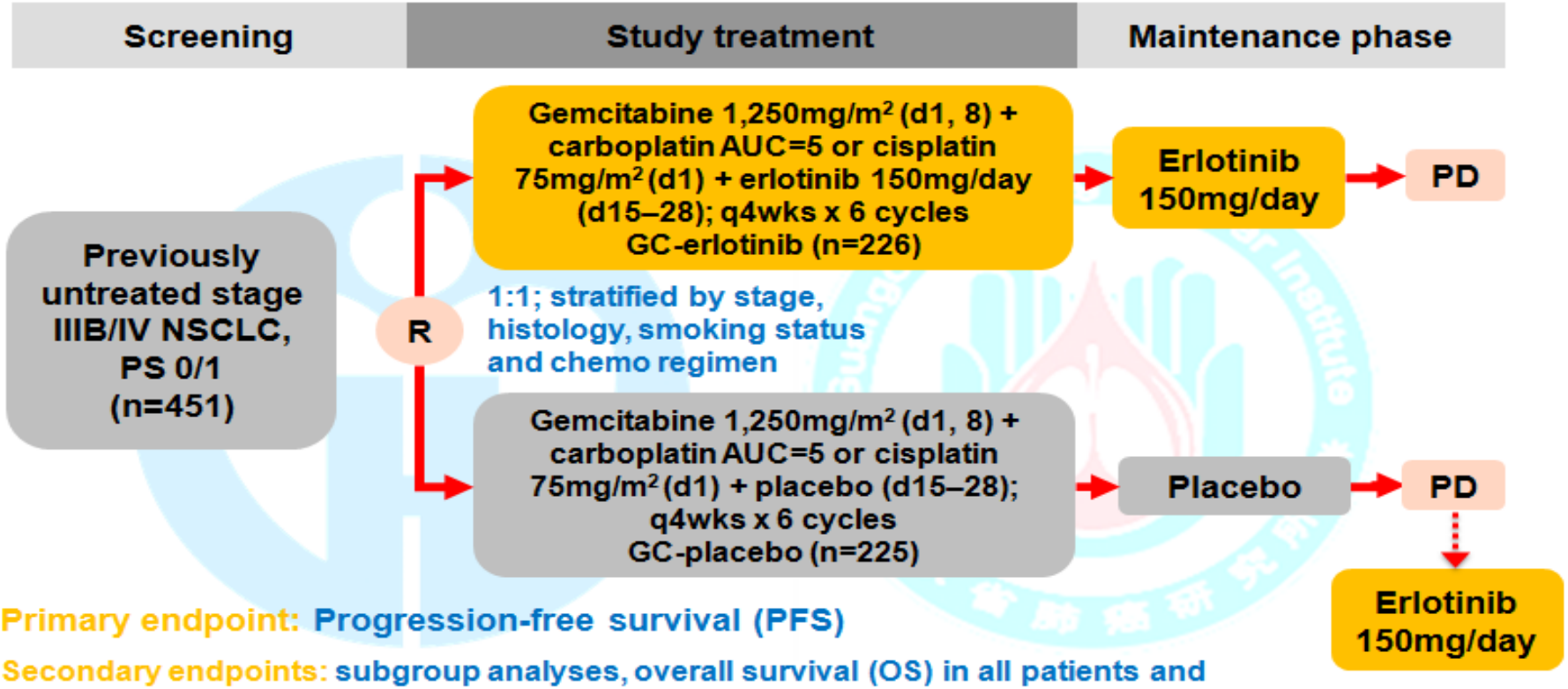
1st line treatment

FASTACT-II (CTONG0902)

THE LANCET Oncology 2013

Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial

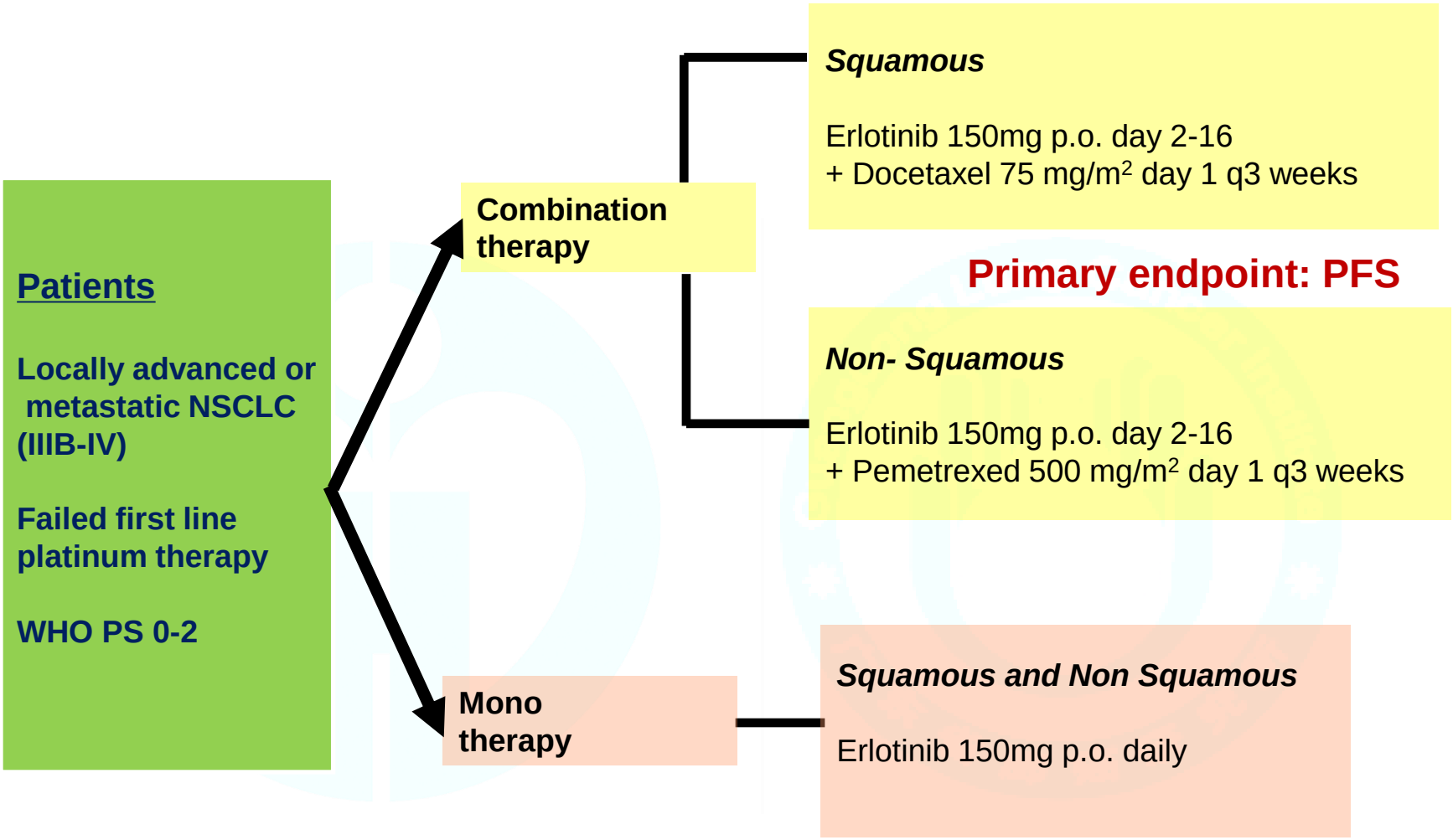
FASTACT-II (MO22201; CTONG0902) study design



Primary endpoint: Progression-free survival (PFS)

Secondary endpoints: subgroup analyses, overall survival (OS) in all patients and subgroups, objective response rate (ORR), duration of response, time to disease progression (TTP), non-progression rate (NPR) at 16 weeks, safety, quality of life (QoL)

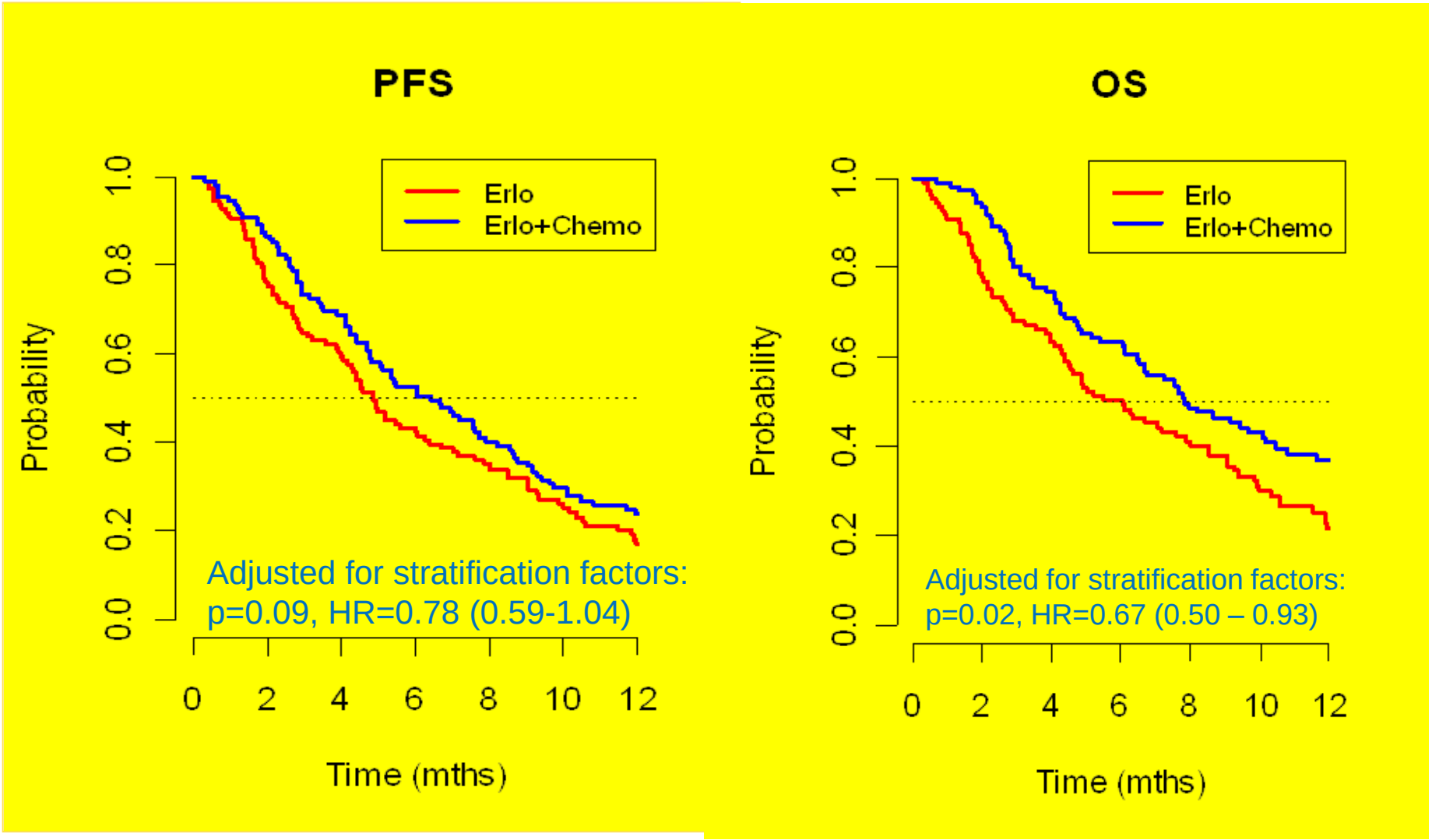
NVALT-10:Design



Chemotherapy planned 4 cycles
Erlotinib until disease progression

Aerts et al ESMO 2012

PFS and OS


PFS
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Erlo
Erlo+Chemo
Adjusted for stratification factors:
p=0.09, HR=0.78 (0.59-1.04)
0
2
4
6
8
10
12
Time (mths)
OS
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Erlo
Erlo+Chemo
Adjusted for stratification factors:
p=0.02, HR=0.67 (0.50 – 0.93)
0
2
4
6
8
10
12
Time (mths)

S103 Study Design: ESMO abstract

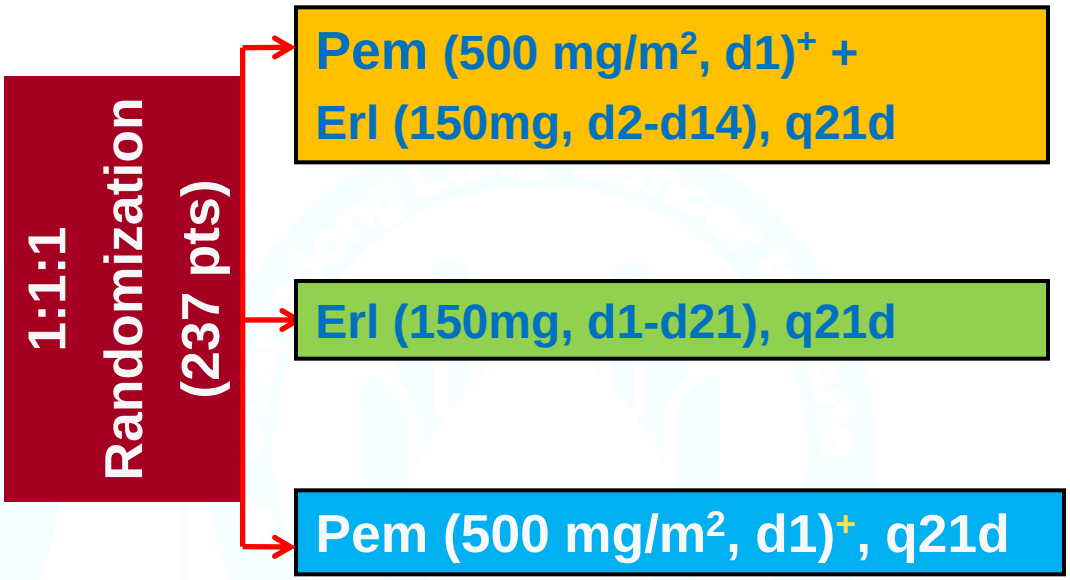
Multicenter, Open-label, Parallel, Phase II Study

Eligibility:

- Locally advanced or metastatic nonsquamous NSCLC
- Never-smokers*
- ECOG PS 0-2
- Failed one prior chemotherapy regimen

Stratification Factors:

- ECOG PS: 0-1 vs 2
- Tumor histology: Adenocarcinoma vs non-adenocarcinoma



Cycles continued until one of the criteria for discontinuation was met.

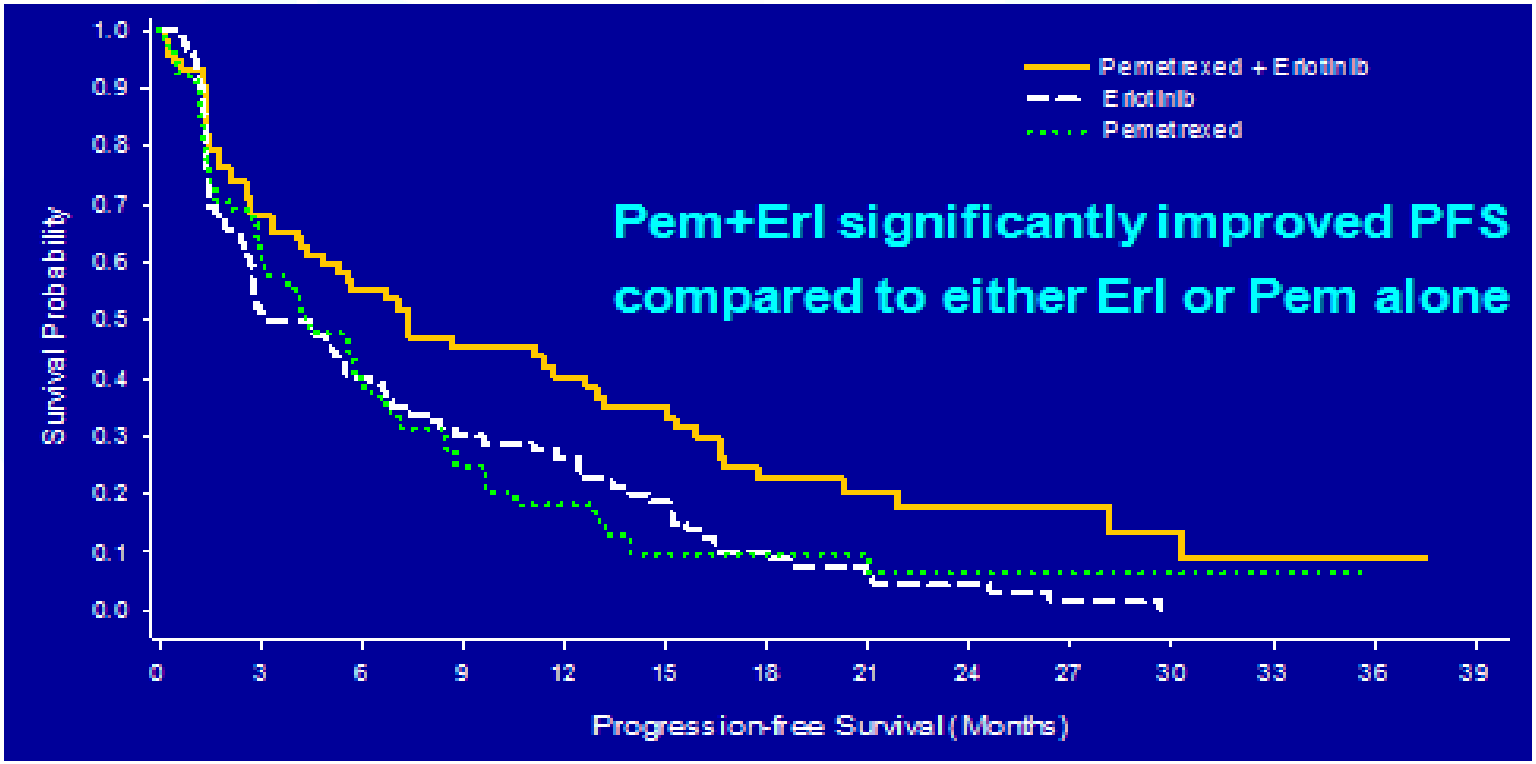
+Vitamin B_{12}, folate, and dexamethasone given in both Pem containing arms

*Patients having smoked <100 cigarettes in their lifetime

Primary Analysis: PFS (Q-ITT Population)

Global p=0.003

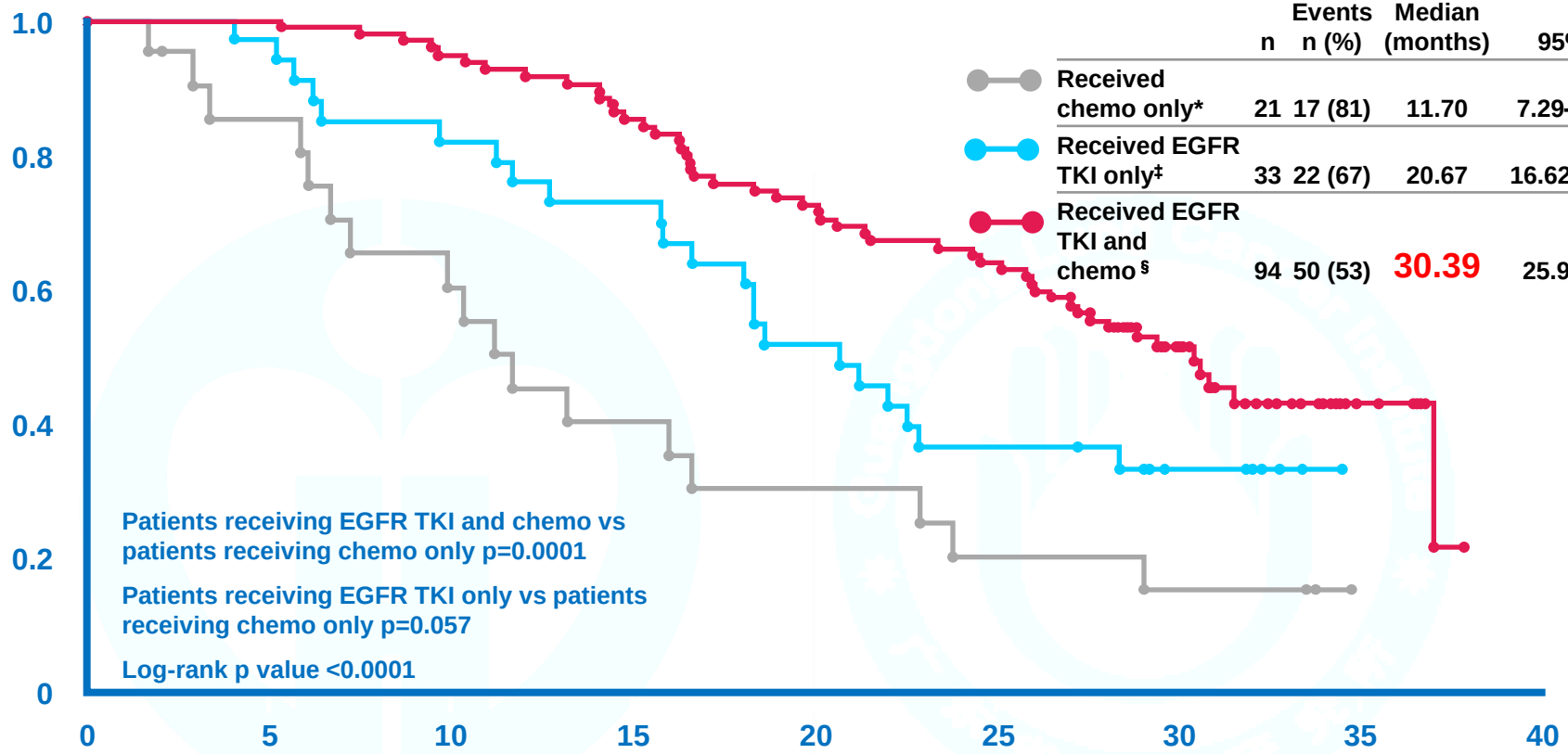
		HR(95% CI):	Median (95% CI) Months
Pem+Erl vs. Erl	p=0.002	0.57 (0.40-0.81)	7.4 (4.4-12.9)
Pem+Erl vs. Pem	p=0.005	0.58 (0.39-0.85)	3.8 (2.7-6.3)
Pem vs. Erl	p=0.959	0.99 (0.70-1.40)	4.4 (3.0-6.0)



Treatment strategies of EGFR mutation for advanced NSCLC

- **IPASS, OPTIMAL, ENSURE, LUX LUNG6 strategy**
  - **Preferred**
- **INFORM strategy**
  - **Option**
- **FASTACT2 strategy**
  - **Selected**

OPTIMAL: most benefits from TKI and chemotherapy



	n	Events n (%)	Median (months)	95% CI
Received chemo only*	21	17 (81)	11.70	7.29–22.87
Received EGFR TKI only‡	33	22 (67)	20.67	16.62–28.32
Received EGFR TKI and chemo§	94	50 (53)	30.39	25.99–NR

Patients at risk								
Patients receiving chemo only*	21	17	12	8	6	4	3	0
Patients receiving EGFR TKI only‡	33	32	27	24	17	12	7	0
Patients receiving EGFR TKI and chemo§	94	94	89	80	68	60	28	6

Zhou, et al. ASCO 2012, abstr 7520

OPEN ACCESS Freely available online

PLOS | ONE

Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis

Pu-Yun OuYang[1,2☯], Zhen Su[1,2☯], Yan-Ping Mao[1,2], Wuguo Deng[1*], Fang-Yun Xie[1,2*]

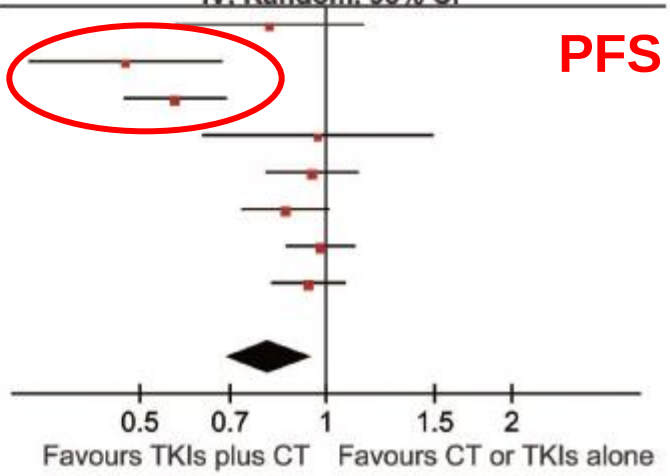
1 State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China, 2 Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CALGB 30406(2012)	-0.2107	0.1793	9.4%	0.81 [0.57, 1.15]
FASTACT(2009)	-0.7472	0.1844	9.2%	0.47 [0.33, 0.68]
FASTACT-II(2013)	-0.563	0.098	13.8%	0.57 [0.47, 0.69]
Hirsch et al.(2011)	-0.0305	0.2202	7.7%	0.97 [0.63, 1.49]
INTACT 1(2004)	-0.0513	0.0877	14.4%	0.95 [0.80, 1.13]
INTACT 2 (2004)	-0.1508	0.0836	14.6%	0.86 [0.73, 1.01]
TALENT(2007)	-0.0202	0.0666	15.5%	0.98 [0.86, 1.12]
TRIBUTE(2005)	-0.0651	0.0705	15.3%	0.94 [0.82, 1.08]
Total (95% CI)			**100.0%**	**0.81 [0.69, 0.95]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 35.17$, df = 7 ($P < 0.0001$); $I^2 = 80\%$

Test for overall effect: $Z = 2.58$ ($P = 0.010$)

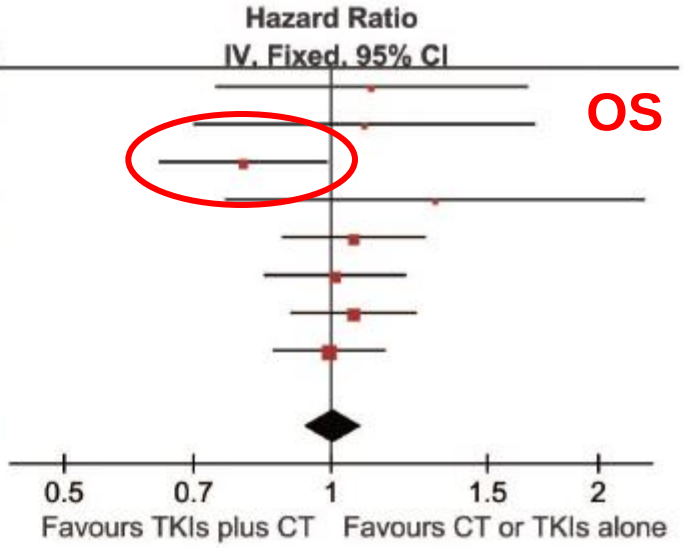


B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CALGB 30406(2012)	0.1044	0.2069	3.4%	1.11 [0.74, 1.67]
FASTACT(2009)	0.0862	0.2259	2.9%	1.09 [0.70, 1.70]
FASTACT-II(2013)	-0.2282	0.1113	11.8%	0.80 [0.64, 0.99]
Hirsch et al.(2011)	0.27	0.2778	1.9%	1.31 [0.76, 2.26]
INTACT 1(2004)	0.0583	0.095	16.2%	1.06 [0.88, 1.28]
INTACT 2 (2004)	0.01	0.094	16.5%	1.01 [0.84, 1.21]
TALENT(2007)	0.0583	0.0835	20.9%	1.06 [0.90, 1.25]
TRIBUTE(2005)	-0.005	0.0744	26.4%	1.00 [0.86, 1.15]
Total (95% CI)			**100.0%**	**1.01 [0.93, 1.08]**

Heterogeneity: $Chi^2 = 6.40$, df = 7 ($P = 0.49$); $I^2 = 0\%$

Test for overall effect: $Z = 0.16$ ($P = 0.87$)



4 strategies for EGFR M in 1st setting

IPASS
SATURN、INFORM
FAST-ACT
Chemo first

	PFS	OS
IPASS OPTIMAL	9.5 13.1	21.6 30.4
SATURN INFORN	56 weeks 16.6	
FAST-ACT	16.8	31.4
Chemo	6.3	21.9

Which is the best?

For PFS: IPASS strategy

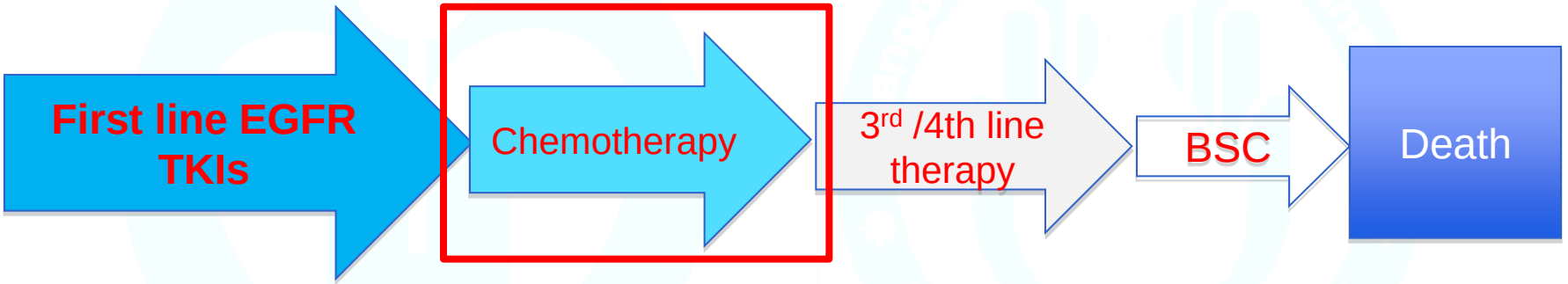
For OS: my suggestion

Luis Role: NO !

1. **Chemo**
2. **FAST-ACT**
3. **INFORM**
4. **IPASS**
5. **OPTIMAL**
6. **SATURN**

alphabetical rule !!

Advanced NSCLC: EGFR mutation treatment strategy



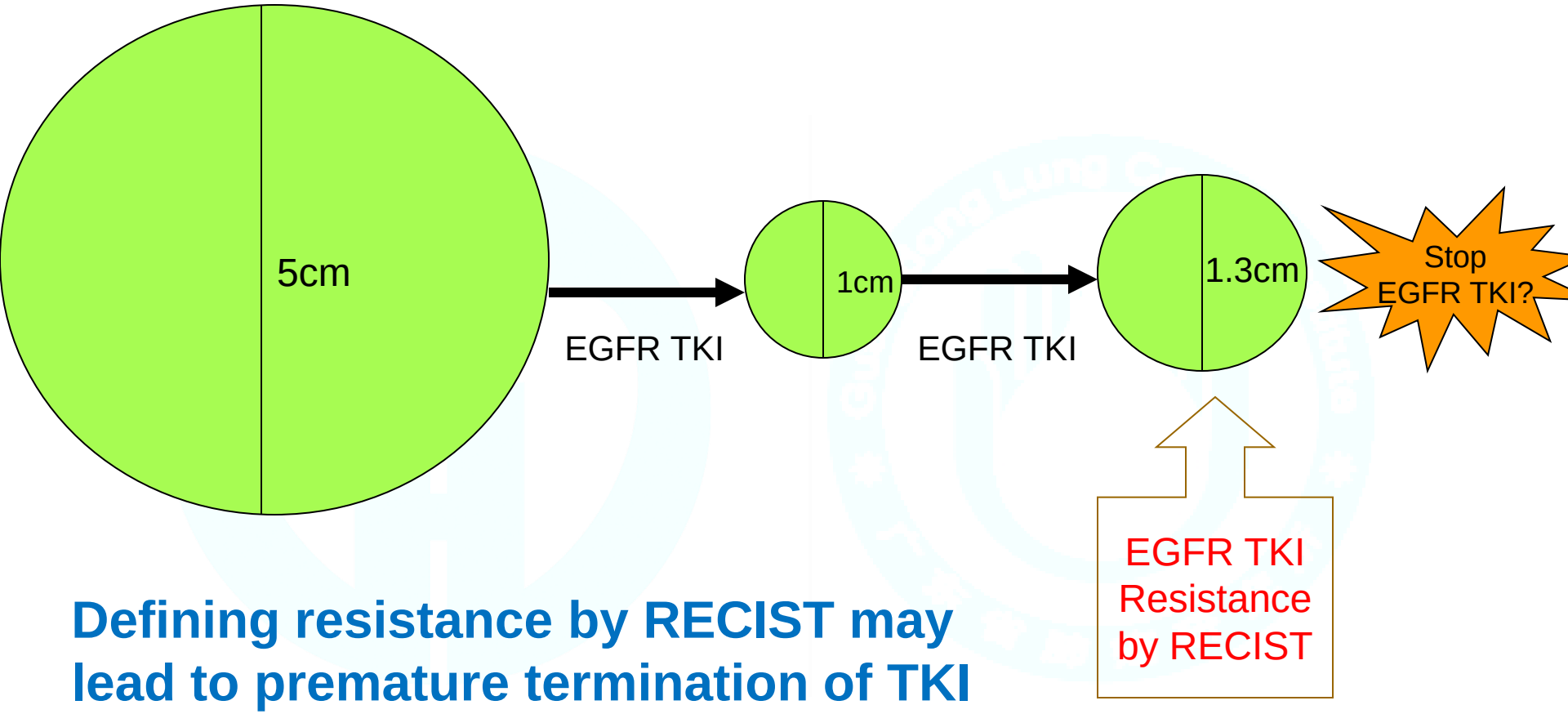
Acquired Resistant: Clinical Perspectives

- How do we define progressive disease?
- EGFR-TKI continuation in combination with or sequential chemotherapy
- When should we switch from monotherapy to combination?

How do we define progressive disease?

- RECIST & JACKMAN criteria
- China criteria

Problem with RECIST Criteria as definition of resistance



Defining resistance by RECIST may lead to premature termination of TKI

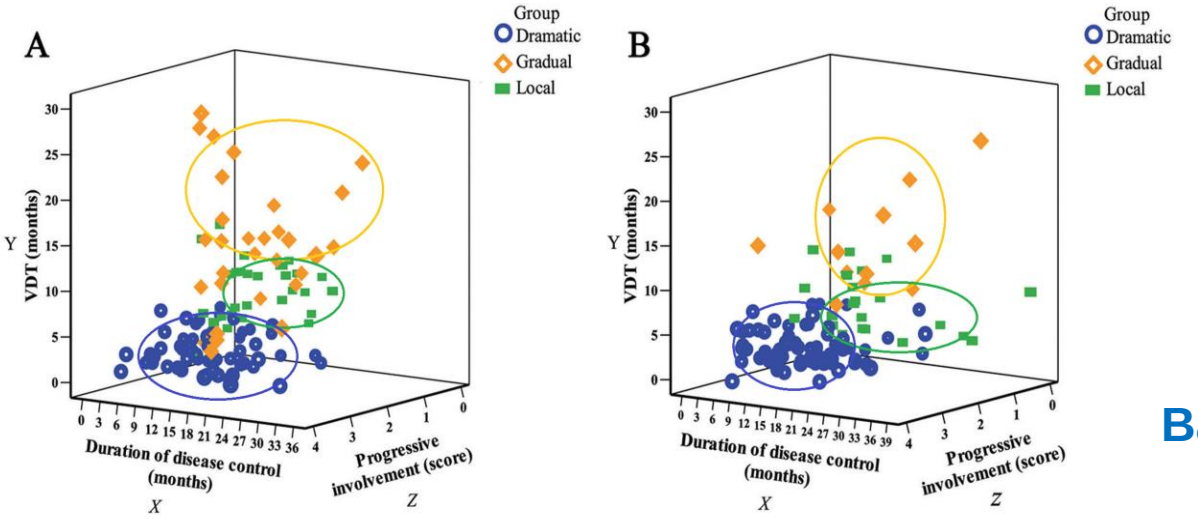
Slide from Mok

Contents lists available at SciVerse ScienceDirect

Lung Cancer

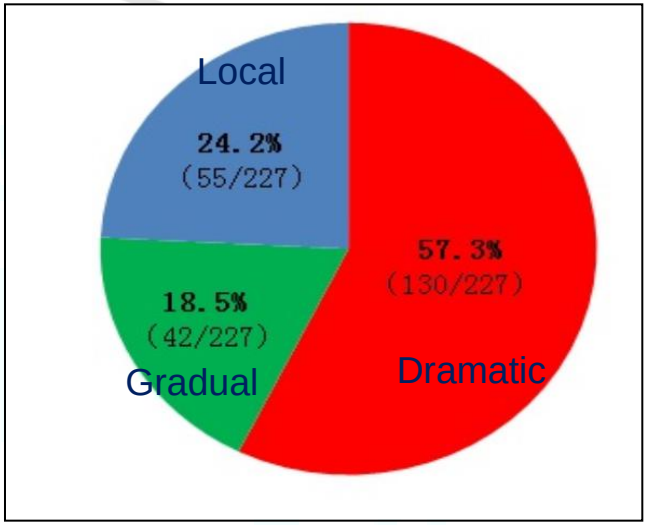
journal homepage: www.elsevier.com/locate/lungcan

Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer



120 trials Pts, training set

107 non-trial Pts validating set



Based on Clinical factors:

- **Tumor burden**
  - **Target lesions**
  - **non-target lesions**
- **EGFR TKI exposure time**
- **Symptom**

Yang JJ, Chen HJ, Wu YL ,et al. Lung Cancer 2013

EGFR TKI failure in NSCLC

Dramatic progression
Disease control ≥3 months;
Compared with previous assessment, rapid increment of tumor burden;
Symptom deterioration.

Gradual progression
Disease control ≥6 months;
Compared with previous assessment, minor increment of tumor burden;
Symptom benefit.

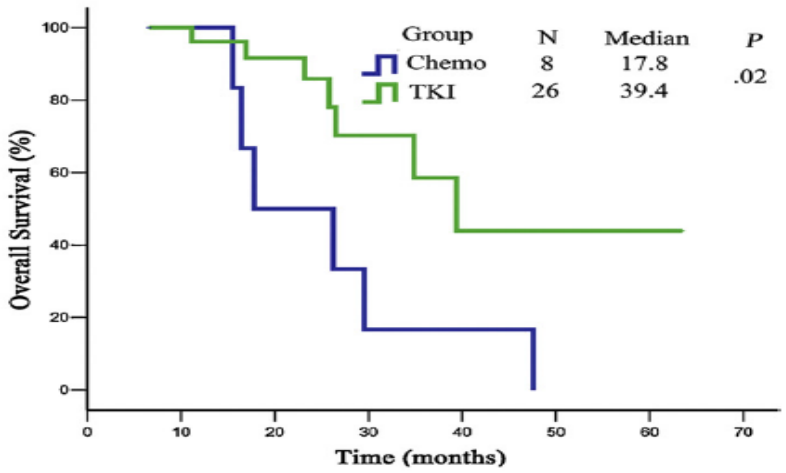
Local progression
Disease control ≥3 months;
Solitary extracranial progression or intracranial progression;
Symptom benefit.

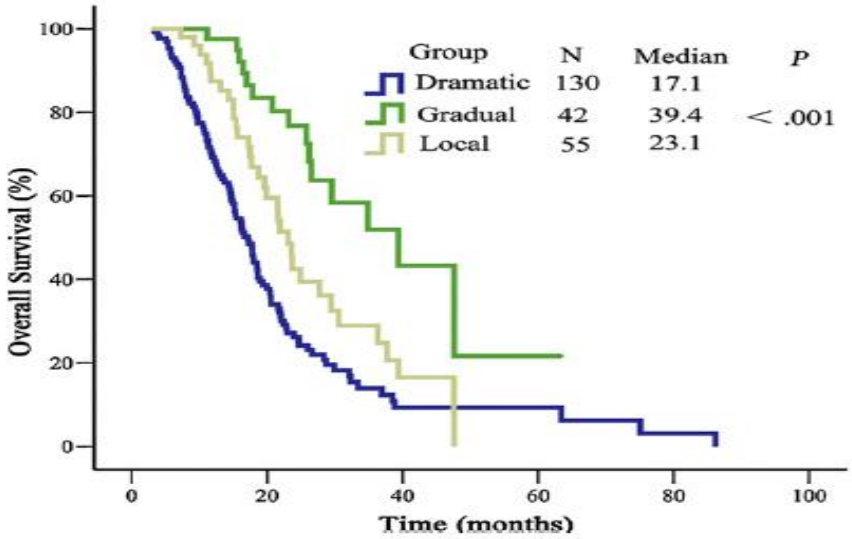
Chemotherapy

Continuation of TKIs

Continuation of TKIs plus local intervention

D





广东省肺癌研究所

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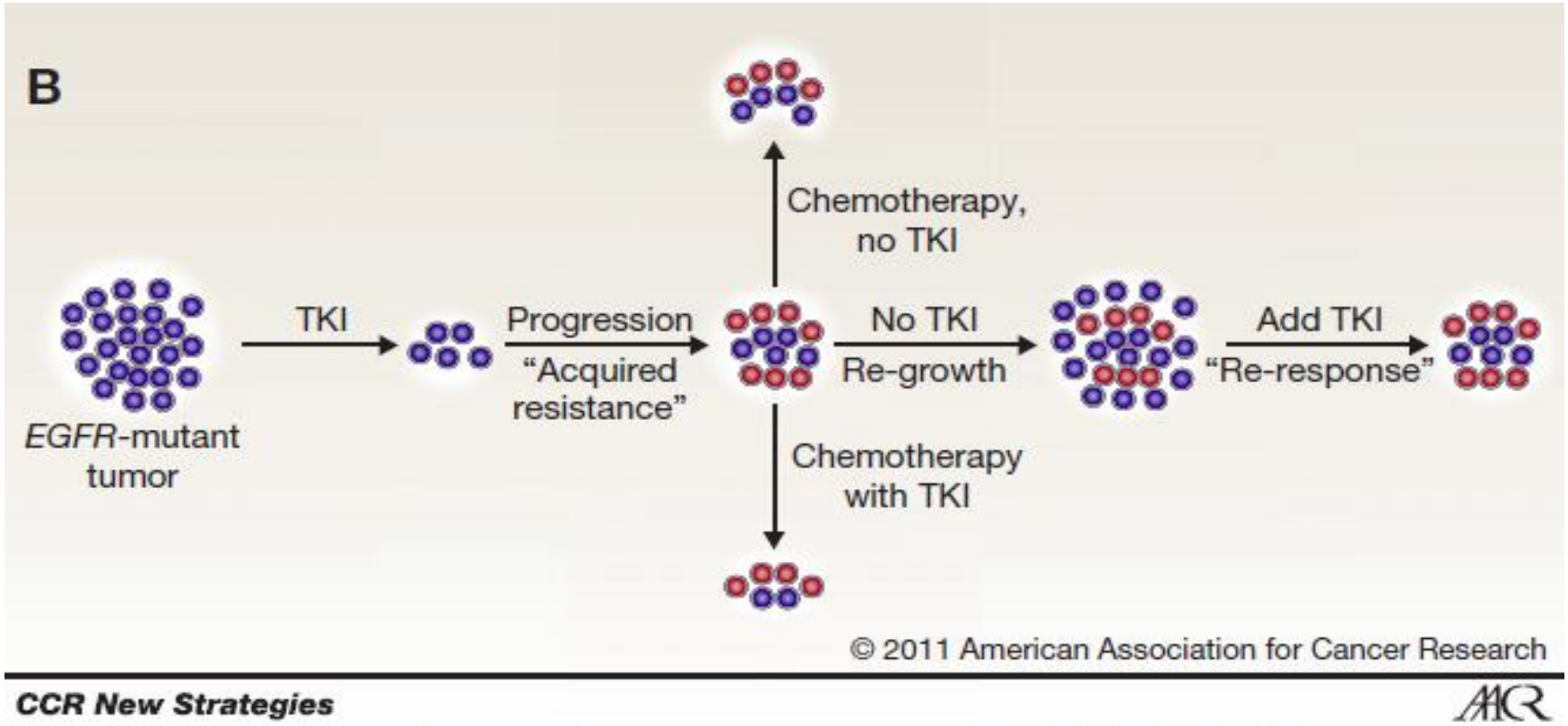
广东省人民医院 Guangdong General Hospital

Yang JJ, Chen HJ, Wu YL ,et al. Lung Cancer 2013

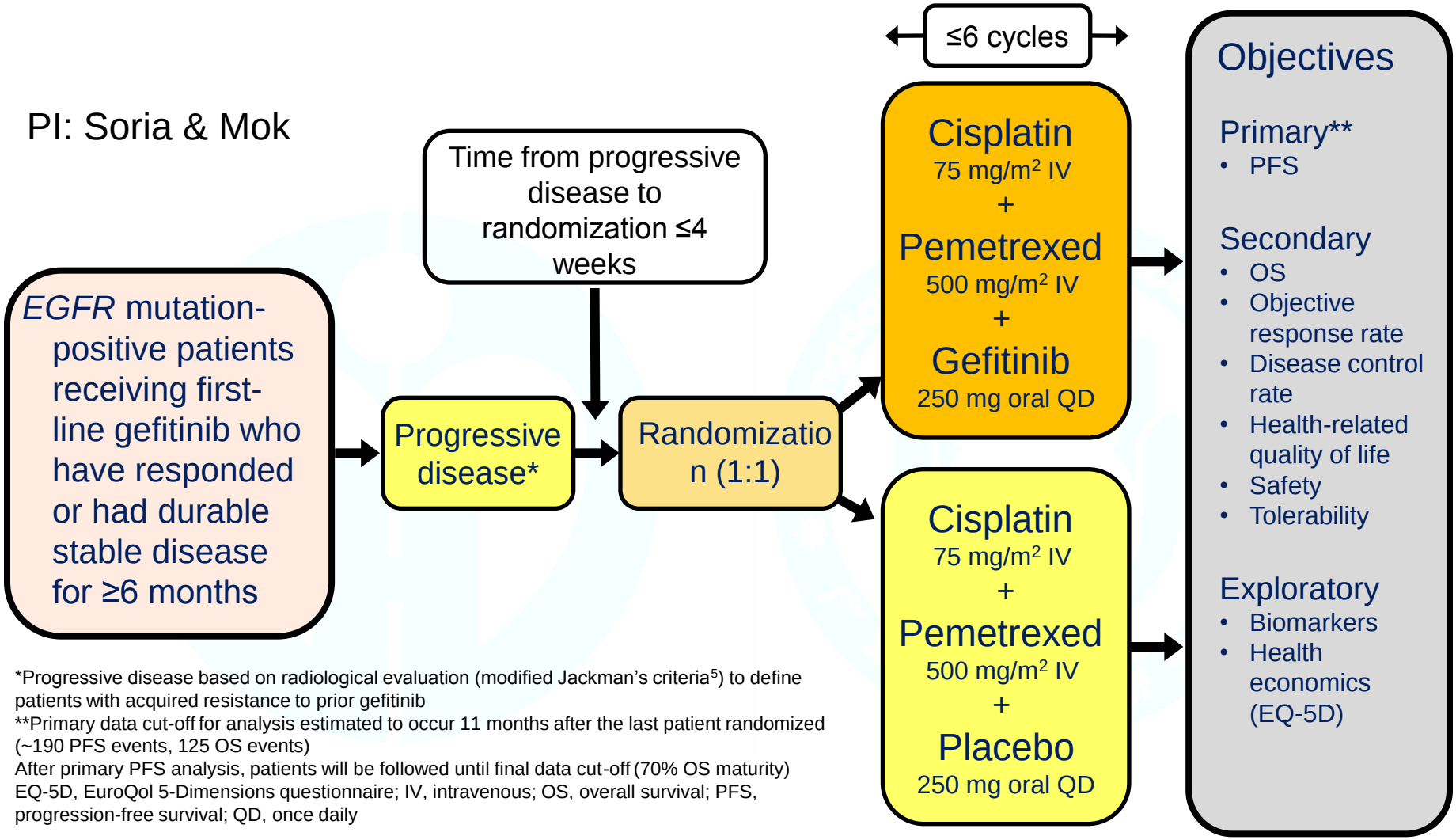
EGFR-TKI continuation in combination with or sequential chemotherapy



Standard chemotherapy regimens may target EGFR-TKI-resistant tumor cells, while EGFR-TKI continuation may prevent repopulation by cells with residual EGFR-TKI sensitivity

Iressa Mutation Positive Multicenter Treatment Beyond ProgRESsion Study (IMPRESS; NCT01544179)

PI: Soria & Mok



*Progressive disease based on radiological evaluation (modified Jackman's criteria[5]) to define patients with acquired resistance to prior gefitinib
**Primary data cut-off for analysis estimated to occur 11 months after the last patient randomized (~190 PFS events, 125 OS events)
After primary PFS analysis, patients will be followed until final data cut-off (70% OS maturity)
EQ-5D, EuroQol 5-Dimensions questionnaire; IV, intravenous; OS, overall survival; PFS, progression-free survival; QD, once daily

Wu et al. JSMO 2012

PREFER: Post pRogression Erlotinib For Erlotinib Resistance

N = 180

- Stage IV/recurrent NSCLC
- EGFR activating mutation
- Progression on 1st-line erlotinib (Tarceva)
- ECOG PS 0-2

R

Chemotherapy x 4 cycles + Erlotinib (Tarceva) → **Maintenance chemotherapy + Erlotinib (Tarceva)** → **PD**

Stratification

- EGFR mutation type (exon 19 del vs. exon 21 L858R)
- ECOG PS (0 vs. 1 vs. 2)

Chemotherapy x 4 cycles → **Maintenance chemotherapy** → **PD**

???

Chemotherapy:

Carboplatin (AUC 5 or 6) + pemetrexed 500 mg/m² q 21 days

Continue EGFR TKI?? → **PD** → **Re-treatment EGFR TKI?** → **PD**

Erlotinib (Tarceva):

Given daily at 150 mg or at previously tolerated dose

Primary endpoint

- Progression free survival

Secondary endpoints

- Objective response rate
- Non-progression rate at 12 weeks
- Overall survival
- Safety
- Exploratory biomarkers

RE-treatment with EGFR TKI

Table 4 Tumor response to 2nd EGFR-TKI vs. chemotherapy

Characteristics	2nd TKI group	Control group	P
OS from 1st gefitinib			
Median	21.5	12.3	0.07
95% CI	14.6 - 28.4	9.4 - 15.2	
Response to 2nd TKI or chemotherapy			
PR	1	0	
SD	7	1	
PD	3	4	
PFS to 2nd TKI or chemotherapy			
Median	3.4	2	0.1
95% CI	2 - 5.2	1.5 - 2.4	
OS from 2nd TKI or chemotherapy			
Median	7.3	2.2	0.12
95% CI	2.7 - 13	2.2 - 2.8	

DCR: 73% (8/11)

Watanabe et al. BMC Cancer 2011, 11:1

Re-treatment with same EGFR TKI

Author	Cases	DCR of 1st gefitinib		DCR of 2nd gefitib	
Yokouchi et al (2007)	9	9		8	
Yoshimoto et al (2007)	1	1		1	
Yano et al (2005)	3	3		2	
Hashimoto et al (2006)	1	1		0	
Kurata et al (2004)	1	1		1	
Watanabe et al (2011)	11	11		8	
Oh et al (2012)	23	23		15	
Sum	**49**	**49**	**100%**	**35**	**71.4%**

Re-treatment with different EGFR TKI

Author	No. of patients	Response to gefitinib CR/PR/SD	Response to gefitinib PD	Response to erlotinib CR/PR/SD	Response to erlotinib PD	DCR (%)
cases	**1st gefitinib**			**2nd erlotinib**		
152	113	74.3%		53		34.9%
Sim SH et al.	16	11	5	4	12	25
Chang JW et al.	1	1	0	1	0	100

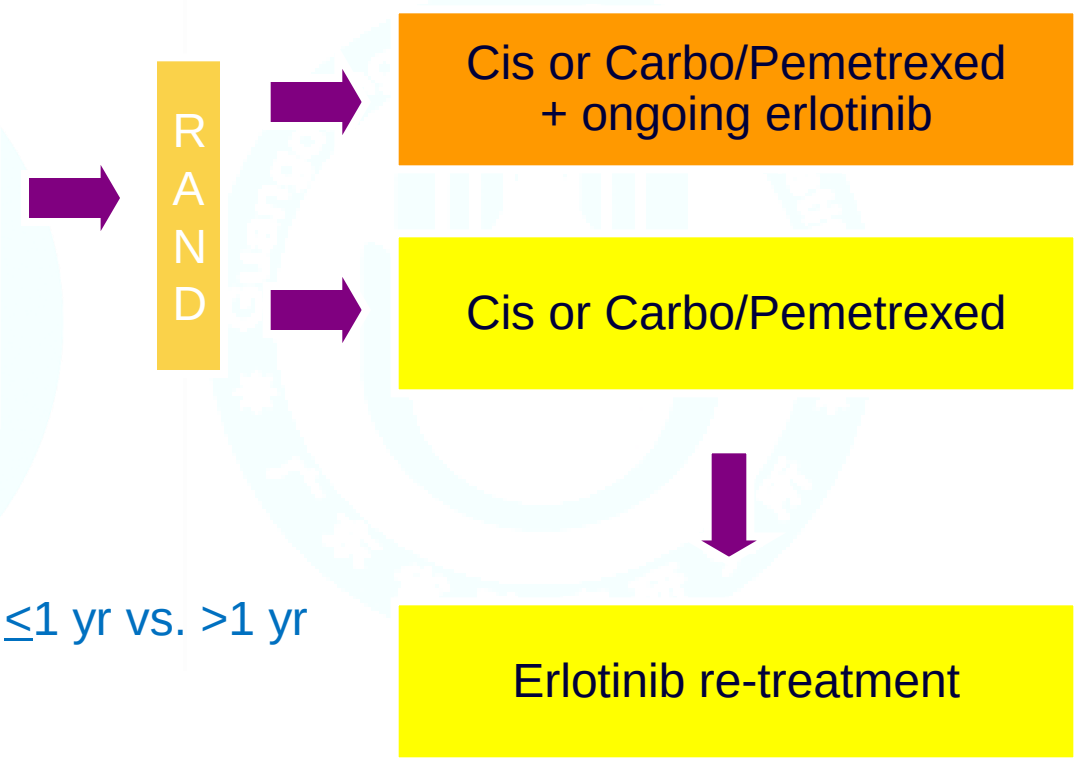
Patients who showed SD during 1st gefitinib treatment had better survival with 2nd EGFR-TKI; Those who had PD to 1st gefitinib rarely responded to 2nd EGFR-TKI.

Watanabe et al. BMC Cancer 2011

Chemotherapy +/- Ongoing EGFR TKI for Acquired Resistance, with Retreatment

PI: Leora Horn (Vanderbilt)

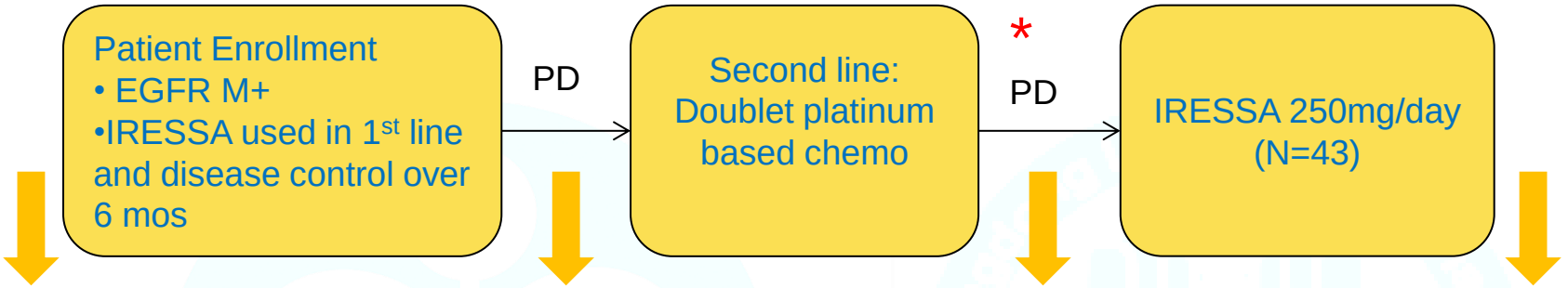
Advanced NSCLC
Activating EGFR TKI
Resp to EGFR TKI>4 mo
No prior chemotherapy
PS 0/1
N= 120



Stratification by:

- EGFR mut'n exon 19 vs. exon 21
- Time to progression on EGFR TKI ≤1 yr vs. >1 yr
- PS 0 vs. 1

CTONG1304 Study Design



Test 1:
EGFR mutation test
T790M+/-
plasma essential
biopsy optional

Test 2:
EGFR mutation test
T790M+/-
plasma essential
biopsy optional

Test 3:
EGFR mutation test
T790M+/-
plasma essential
biopsy optional

Test 4:
EGFR mutation test
T790M+/-
plasma essential
biopsy optional

Primary End point: DCR
Secondary Endpoints: ORR, PFS, OS, QoL
Exploratory Endpoint: EGFR mutation status, T790M mutation status

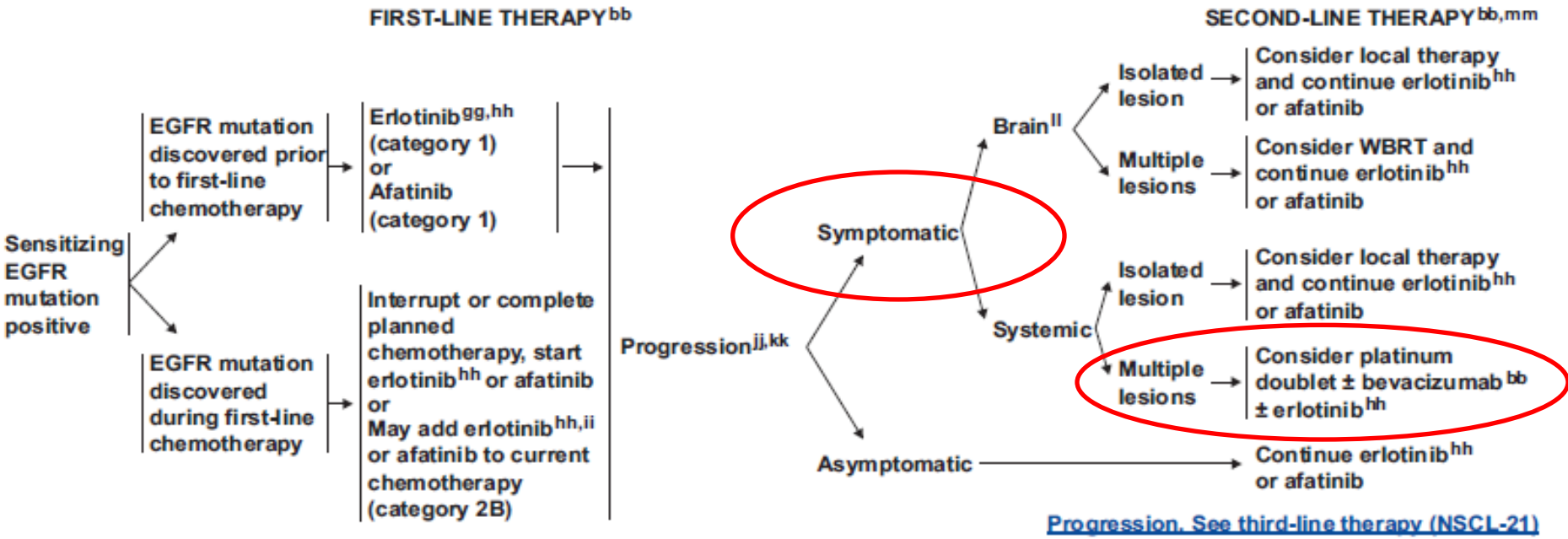
*sign informed consent form

When should we switch from monotherapy to combination?

NCCN criteria

China criteria

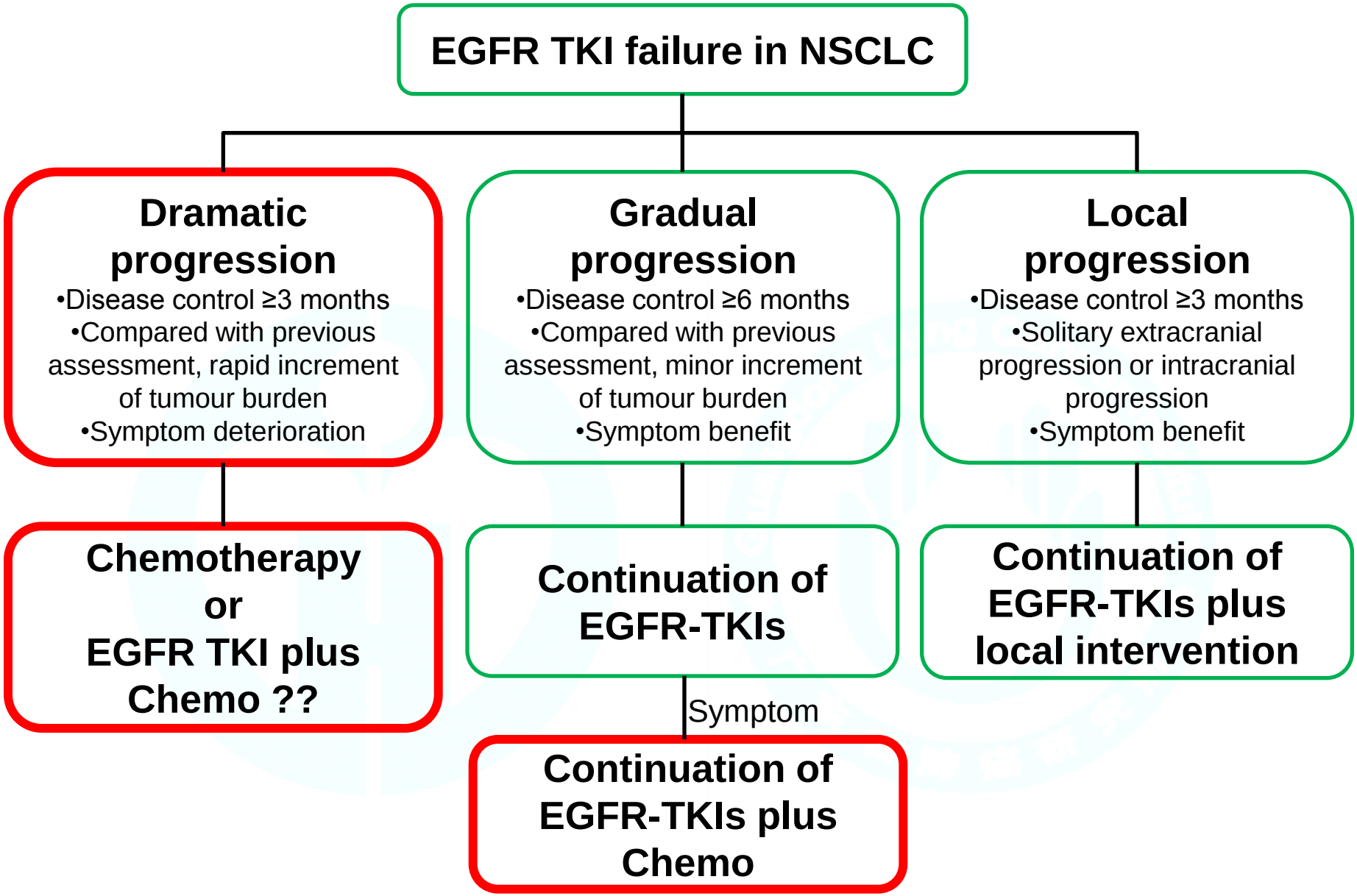
ADENOCARCINOMA, LARGE CELL, NSCLC NOS: SENSITIZING EGFR MUTATION POSITIVE[a]



Progression, See third-line therapy (NSCL-21)

[a] See Principles of Pathologic Review (NSCL-A).
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[gg] For performance status 0-4.
[hh] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[ii] Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012;30:2063-2069.
[jj] Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will transform to SCLC at progression.
[kk] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[ll] Consider pulse erlotinib for carcinomatosis meningitis.
[mm] Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.


EGFR TKI failure in NSCLC
Dramatic progression
•Disease control ≥3 months
•Compared with previous assessment, rapid increment of tumour burden
•Symptom deterioration
Gradual progression
•Disease control ≥6 months
•Compared with previous assessment, minor increment of tumour burden
•Symptom benefit
Local progression
•Disease control ≥3 months
•Solitary extracranial progression or intracranial progression
•Symptom benefit
Chemotherapy or EGFR TKI plus Chemo ??
Continuation of EGFR-TKIs
Continuation of EGFR-TKIs plus local intervention
Symptom
Continuation of EGFR-TKIs plus Chemo

In summary

Either 1st line or 2nd line or beyond, targeted sequential chemotherapy is always preferred

The question is

Does FASTACT strategy belong to sequential or combined?

One thing is:

FASTACT is only used special circumstances

Hi, Luis, Do you agree?

The Winners of the Australian National Goanna Pulling Championship

Thanks!

谢谢