广东省肺癌研究所
Guangdong Lung Cancer Institute

VIENNA 2012 ESMO congress

ESMO-CSCO Joint symposium

Lung Cancer: Chinese Thoracic Oncology Group (CTONG)

Yi-Long Wu

Guangdong Lung Cancer Institute,

Guangdong General Hospital & Guangdong Academy of Medical Sciences

PR China

广东省医学科学院 Guangdong Academy of Medical Sciences

广东省人民醫院 Guangdong General Hospital

ESMO Congress:

Invited Speaker Disclosure Form

Conducting research sponsored by Roche, Boehringer-ingelheim;

Received the honorarium from Roche, AstraZeneca, Pfizer, Merck, Eli Lilly, Novartis.

Outline

- **Regulatory Environment in China**
- **Chinese Thoracic Oncology Group trials**
- **Near future: biomarker-driven clinical trial in China**

Regulatory Environment

- State Food & Drug Administration (SFDA)
  - Became part of MOH since Mar 2008
  - National regulatory authority of drug and medical device
  - In charge of comprehensive supervision on food safety management
- General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ)
  - Drafts rules and regulations on certification and accreditation, safety and quality licensing, hygiene registration and qualification assessment
  - Conducts mandatory safety registration, certification and inspection for certain devices (CCC mark)

SFDA

- All imported medical products must be registered with SFDA prior to selling in China
- Products made outside China need to go to central SFDA for approval
- Registration is valid for 4 years
- Registration cannot be transferred

Criteria for application of IND

- An IND is required for a clinical study if it is intended to support a:
  - New indication
  - Change in the approved route of administration or dosage level
  - Change in the approved patient population (e.g. pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
  - Significant change in the promotion of an approved drug

The categories of IND

- *Sponsor-initiated*.
  - filed by pharmaceutical companies studying new drugs or new uses for existing drugs.
- *Investigator-initiated*,
  - used when a physician wishes to perform a clinical trial to study an unapproved drug treatment, for example a new indication for an existing drug.
- *Emergency Use IND*
  - To authorize use of an experimental drug in an emergency situation that does not allow time for submission of IND

Registered the time limit for examination and approval

Registration Type	department / Working days	受理中心	CDE(IND /NDA)	DDR/SFDA
New	New chemicals application	30	90/150	20#
	Special approval	30	80/120	20#
	Generic application	30	160	20#
	Supplementary application	30	40	20#
supplement	New chemicals application	0	30/50	20#
	Special approval	0	20/30	20#
	Generic application	0	53	20#
	Supplementary application	0	13	20#

Pharmaceutical Industry in China

- $40 billions market in 2004
- Average annual growth rate of about 16%
- Foreign companies account for 10 to 20% of sales, and the rest by domestic companies
- About 1.5% of the global drug market

International Pharmaceuticals in China

Company	Investments (2007 estimation)
Pfizer	Dalian GMP manufacturing facilities ($500 millions)
Novartis	Manufacturing facilities in Beijing and Changsu. (100 millions)
Astrazeneca	Manufacturing facilities in Wuxi ($170 millions) and R & D facilities in Shanghai
Roche	R & D center in China with 50 scientist and growing

Chinese Generic Companies Dominate the Industry

- **About 80% of drugs sold in China are generics**
- **China's Drug Administration Law**
  - Drugs that have never been manufactured in China are new drugs
- **Imported medicines are prohibited or restricted from China's social medical insurance**
- **Domestic company market share: 65%**
- **Foreign company market share: 35%**

Source: VOI Consulting, Inc.

The Drug Approvals Made in Accordance with the Newly Revised Provisions on Drug Registration

Registration Type	Approval for domestic production				Approval for Importation
	New Drugs	Changed Dosage Forms	Generics	Total	
Chemical Drugs	175	17	356	548	100
TCMs	72	8	12	92	1
Biological Products		38		38	13
Total		678			114
Total		792			

From Zhang, SFDA 2010

Approval INDs clinical trials in China

(2010. 12. 31）

- **Approval for domestic production：**
  - 37 Chemicals: 5 from phase 1 to phase 2
- **Approval for Importation：**
  - International clinical trials: 152，approval 123 (81%)，related 35 new chemicals including 24 TKIs

Outline

- Regulatory Environment in China
- **Chinese Thoracic Oncology Group trials**
- Near future: biomarker-driven clinical trial in China

中国胸部肿瘤研究协作组
Chinese Thoracic Oncology Group (CTONG)

- **CTONG Committee**
  - Chairman：Prof. Yi-long Wu
  - Vice-chairman：Prof. L Zhang，S Lu，C-c Zhou
  - Secretary General：Prof. Qing Zhou
- **C-TONG Members**
  - From 20 clinical cancer centers or hospitals
- **Established in 2007**

中国胸部肿瘤研究协作组
Chinese Thoracic Oncology Group (CTONG)

20 sites

Vision and Mission of C-TONG

- Design and develop multi-center clinical trials in the field of chest tumor, especially for lung cancer
- Provide a high level of evidence for clinical practice of thoracic tumor
- Promote standardization, modernization and internationalization of clinical and research work in thoracic tumor area
- Improve the level of diagnosis and treatment of chest tumor in China, as well as international status

Key Scopes of CTONG

- Phase I-IV clinical trials
- Translational research
- Tissue bank
- Database of patient data
- Education Programe
  - Website
  - Annual meeting

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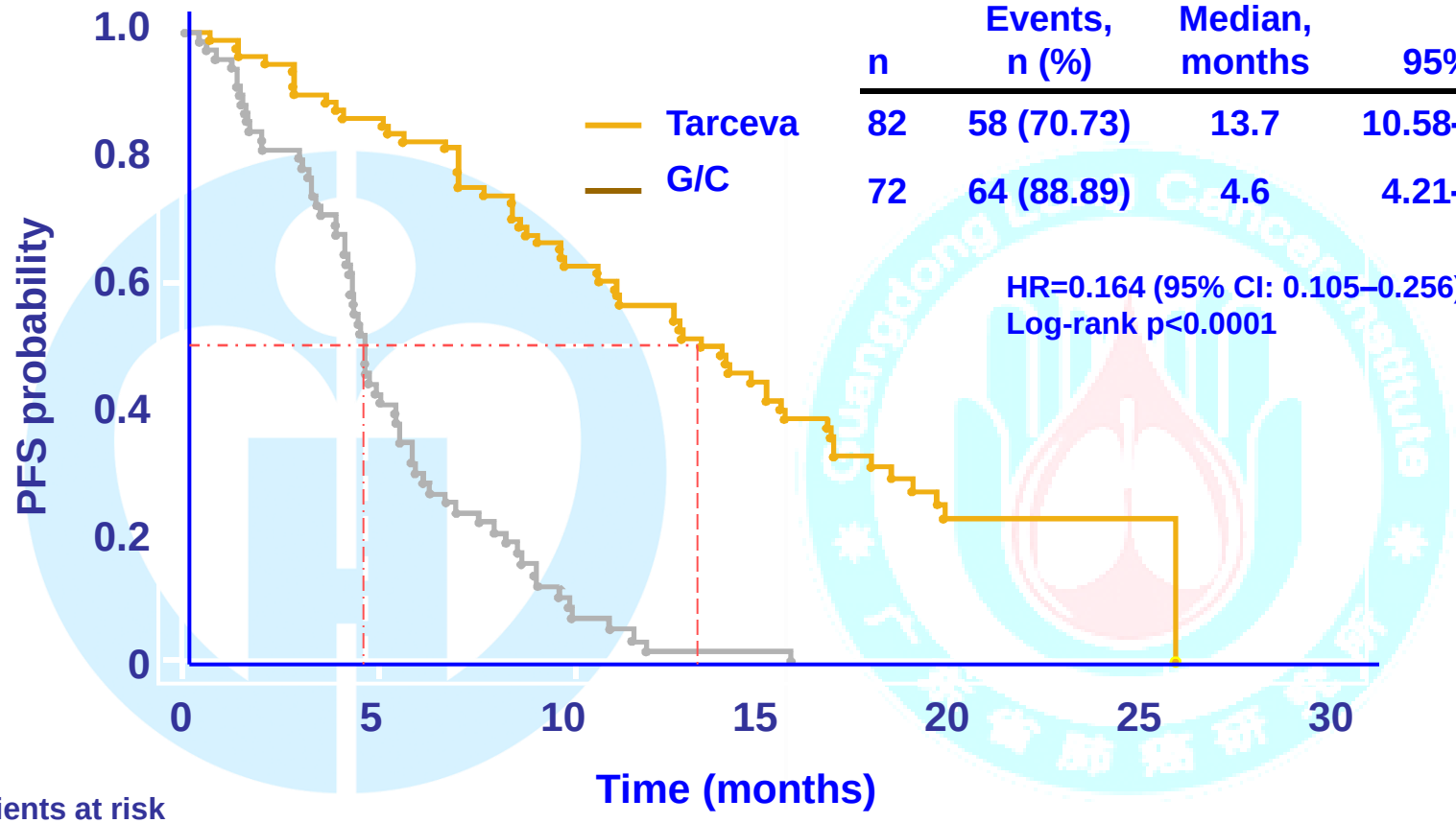
Chinese Thoracic Oncology Group (C-TONG) Study List

Study number	NCT number	Investigational drug	Study title	status
C-TONG 0801	NCT00765687	Bisphospohnates	Screening Non Small Cell Lung Cancer With Bone Metastasis and Efficacy and Safety Research of Receiving Bisphosphonates (BLEST)	Ongoing, but not recruiting
C-TONG 0802	NCT00874419	Erlotinib	Erlotinib Versus Gemcitabine/Carboplatin in Chemo-naive Stage IIIB/IV Non-Small Cell Lung Cancer Patients With Epidermal Growth Factor Receptor (EGFR) Exon 19 or 21 Mutation(Optimal)	Ongoing, but not recruiting
C-TONG 0803	NCT00663689	Erlotinib	Efficacy of Erlotinib for Brain Metastasis of Non-Small Cell Lung Cancer	Ongoing, but not recruiting
C-TONG 0804	NCT00770588	Gefitinib	Assess the Efficacy, Safety and Tolerability of Gefitinib (Iressa® 250mg) as Maintenance Therapy in Locally Advanced or Metastatic (Stage IIIB/IV) Non Small Cell Lung Cancer (NSCLC) (INFORM)	Completed
C-TONG 0805	NCT00922584	Sorafenib	Sorafenib Treatment in Non-Small Cell Lung Cancer After Failure of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor	Recruiting
C-TONG 0806	NCT00891579	Pemetrexed Gefitinib	Study of Pemetrexed Versus Gefitinib in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer Who Have Previously Received Platinum-Based Chemotherapy Without Epidermal Growth Factor Receptor (EGFR) Mutations	Recruiting
C-TONG 0807	NCT00816868	Erlotinib/ Carpecitabine	A Study of TX Regimen as First-Line Treatment in Elderly Patients With Stage IIIB/IV Adenocarcinoma Non-Small Cell Lung Cancer	Ongoing, but not recruiting
C-TONG 0901	NCT01024413	Erlotinib/ Gefitinib	Erlotinib Versus Gefitinib in Advanced Non Small Cell Lung Cance With exon21 Mutation：A Randomized Trial	Recruiting

Chinese Thoracic Oncology Group (C-TONG) Study List

Study number	NCT number	Investigational drug	Study title	status
C-TONG 0902	NCT00883779	Erlotinib	A Study of Tarceva (Erlotinib) or Placebo in Combination With Platinum-Based Therapy as First Line Treatment in Patients With Advanced or Recurrent Non-Small Cell Lung Cancer	Ongoing, but not recruiting
C-TONG 0904	NCT01038661	Docetaxel	Tax First-line Chemotherapy With Different Doses and Then Maintenance Therapy (TFINE)	Recruiting
C-TONG 1001	NCT01319669	rhTPO	Clinical Trial on the Prevention of Thrombocytopenia After First-line Chemotherapy	Recruiting
C-TONG 1002	NCT01236716	Nab-Paclitaxel/ Gemcitabine	Nab-Paclitaxel Treatment in Advanced Squamous Cell Carcinoma of Lung	Not yet opening
C-TONG 1003	NCT01175096	Rad001 (Afinitor)	Safety and Tolerability Profile of RAD001 Daily in Chinese Patients With Advanced Pulmonary Neuroendocrine Tumor	Ongoing, but not recruiting
C-TONG 1101	NCT01297101	Erlotinib	A single arm, one center, phase II study of sequential administration of erlotinib in combination with Gemcitabine/Cisplatin as neoadjuvant treatment in patients with stage IIIA NSCLC	Recruiting
C-TONG 1102		Gefitinib	Iressa vs chemo as intermittent treatment in advanced NSCLC	Not yet opening
C-TONG 1103		Ertlotinib	Erlotinib vs chemo as neoadjuvant in IIIA-N2 NSCLC with EGFR Mutation in exon 19 or 21	Recruiting

OPTIMAL (CTONG 0802) : Primary endpoint PFS



	n	Events, n (%)	Median, months	95% CI
Tarceva	82	58 (70.73)	13.7	10.58–15.28
G/C	72	64 (88.89)	4.6	4.21–5.42

HR=0.164 (95% CI: 0.105–0.256)
Log-rank p<0.0001

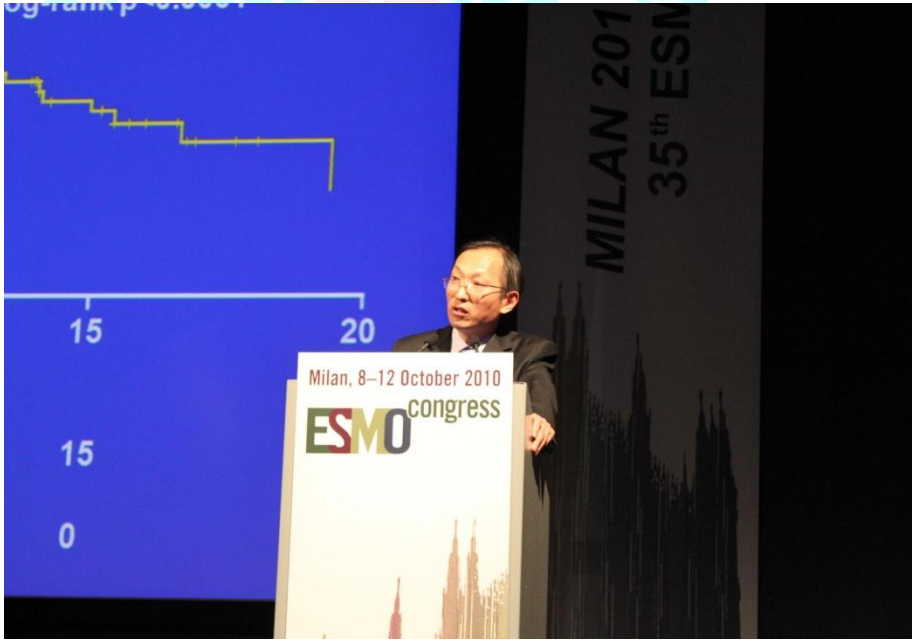
Patients at risk

Tarceva	82	70	51	29	8	2	0
G/C	72	26	4	1	0	0	0

Zhou, et al. Lancet Oncol 2011

OPTIMAL (CTONG 0802)

- The first phase III study compare Tarceva vs chemo in 1L mutation NSCLC, supported by Roche
- **Oral Presentation in ESMO 2010** and WCLC 2011, Poster in ASCO 2010, and Poster Discussion in ASCO 2011, 2012
- Manuscript has been published by **Lancet Oncology** (2011)
- Support global Tarceva 1L mutation indication as filling **dossier**



CTONG0803: Second-line erlotinib in NSCLC patients with brain metastases: efficacy outcomes

PFS

	Patients, n	Events, n	Mean, months*	95% CI	Median, months	95% CI
Overall	48	26	11.47	8.97–13.97	10.13	7.64–12.63
Brain metastases, n						
≤3	23	12	12.45	8.92–15.98	10.20	3.32–17.08
>3	25	14	9.71	7.13–12.28	8.27	6.20–10.34
***EGFR* mutation status**						
Wild type	15	14	8.11	5.06–11.17	8.20	3.19–13.21
Positive	7	2	17.43	10.85–24.02	NR	–
Unknown	26	10	12.06	9.54–14.58	15.33	2.83–27.83

- Six-month and 1-year OS rates: 87% and 74%, respectively
- More than half of the patients (52.1%) had partial response, 2 patients (4.2%) had complete response, for an ORR of 56.3%

***Estimation is limited to the longest survival time if it is censored; NR = not reached**

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CTONG 0803

- Phase II study of erlotinib as 2nd-line treatment in NSCLC patients with asymptomatic brain metastases, supported by Roche
- **Mini-Oral Presentation in WCLC 2011,** Poster in ASCO 2011
- Manuscript has been accepted by Ann Oncol (2012)

A phase II study (CTONG0803) of erlotinib as 2nd-line treatment in advanced non-small-cell lung cancer (NSCLC) patients (pts) with asymptomatic brain metastases (BM) after 1st-line chemotherapy (CT)
NCT00663689

Yi-long Wu, Caicun Zhou, Ying Cheng, Shun Lu, Gongyan Chen, Cheng Huang, Yi-Sheng Huang, Hong-Hong Yan, Jin-Ji Yang, on behalf of the CTONG0803 investigators
P.R. China

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CTONG1201: An Open label, randomized, parallel group, multicentre, Phase III study to assess efficacy, safety and tolerability of Icotinib versus whole brain irradiation in sensitive EGFR mutant patients with advanced (stage IIIB or IV) non-small cell lung cancer (NSCLC)

Brain Metastasis Treated with Radiotherapy And Iconitib for Non-small cell lung Cancer (BRAIN)

广东省医学科学院 Guangdong Academy of Medical Sciences
广东省人民医院 Guangdong General Hospital

BRAIN: study design

- Stage IIIB/IV NSCLC
- *EGFR* Mut+ (exon 19 deletion or exon 21 L858R mutation)
- BM lesions ≥3 at 1 > 1cm
- ECOG PS 0–1

N=170

R 1:1

Icotinib 250mg/tid/day → WBI

Whole brain irradiation with 30GY/3GY*10 ± Chemo → **Icotinib 250mg/tid /day**

PD

Primary endpoint
- Intra-cranial Progression-free survival (iPFS)

Secondary endpoints
- PFS, Overall survival (OS), objective response rate (ORR), time to disease progression, duration of response, safety, HRQoL (FACT-L, LCSS), exploratory biomarker analyses

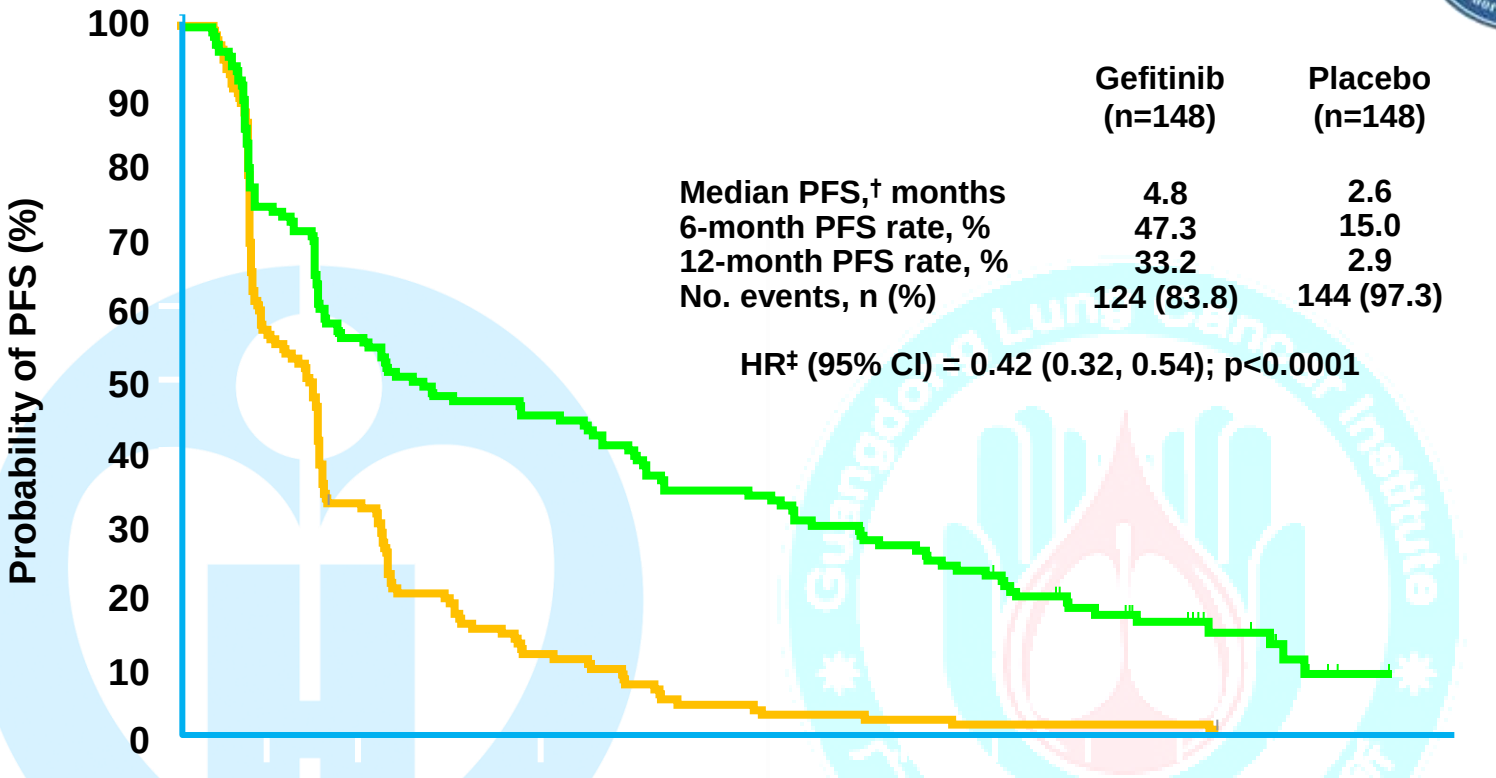
Stratification factors
- Mutation type (19 *vs* 21)
- 1st line *vs* 2nd line
- Asymptomatic *vs* symptomatic

Efficacy assessment
- Every 6 weeks

ECOG = Eastern Cooperative Oncology Group; PS = performance status; HRQoL = health-related quality of life; FACT-L = Functional Assessment of Cancer Therapy-Lung; LCSS = lung cancer symptom scale

PI: YL WU

CTONG 0804: INFORM



	Gefitinib (n=148)	Placebo (n=148)
Median PFS,† months	4.8	2.6
6-month PFS rate, %	47.3	15.0
12-month PFS rate, %	33.2	2.9
No. events, n (%)	124 (83.8)	144 (97.3)

HR‡ (95% CI) = 0.42 (0.32, 0.54); p<0.0001

Patients at risk :

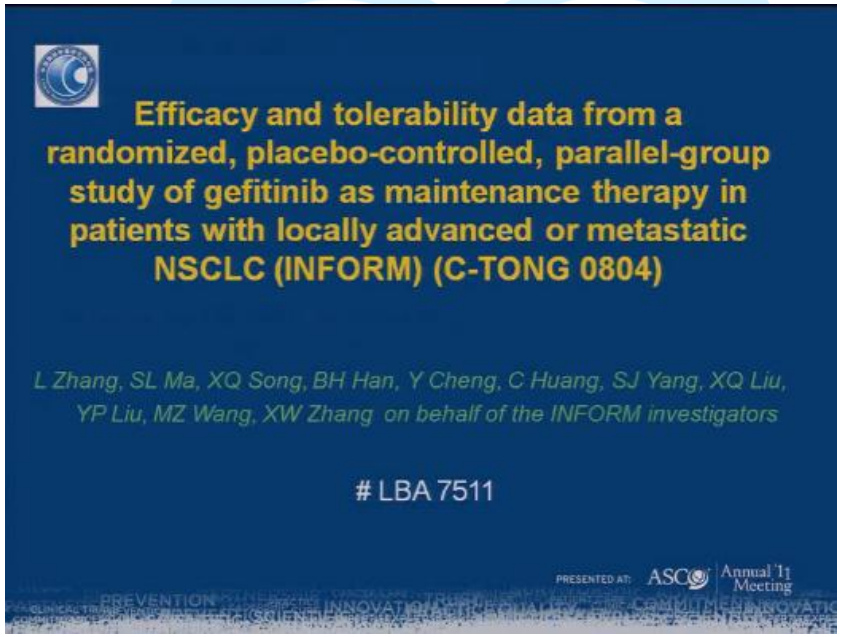
Placebo	148	82	46	26	16	10	6	4	3	2	2	2	0	0	0
Gefitinib	148	109	82	70	65	56	49	42	38	31	20	15	6	1	0

†Estimated using the Kaplan-Meier method
‡Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib

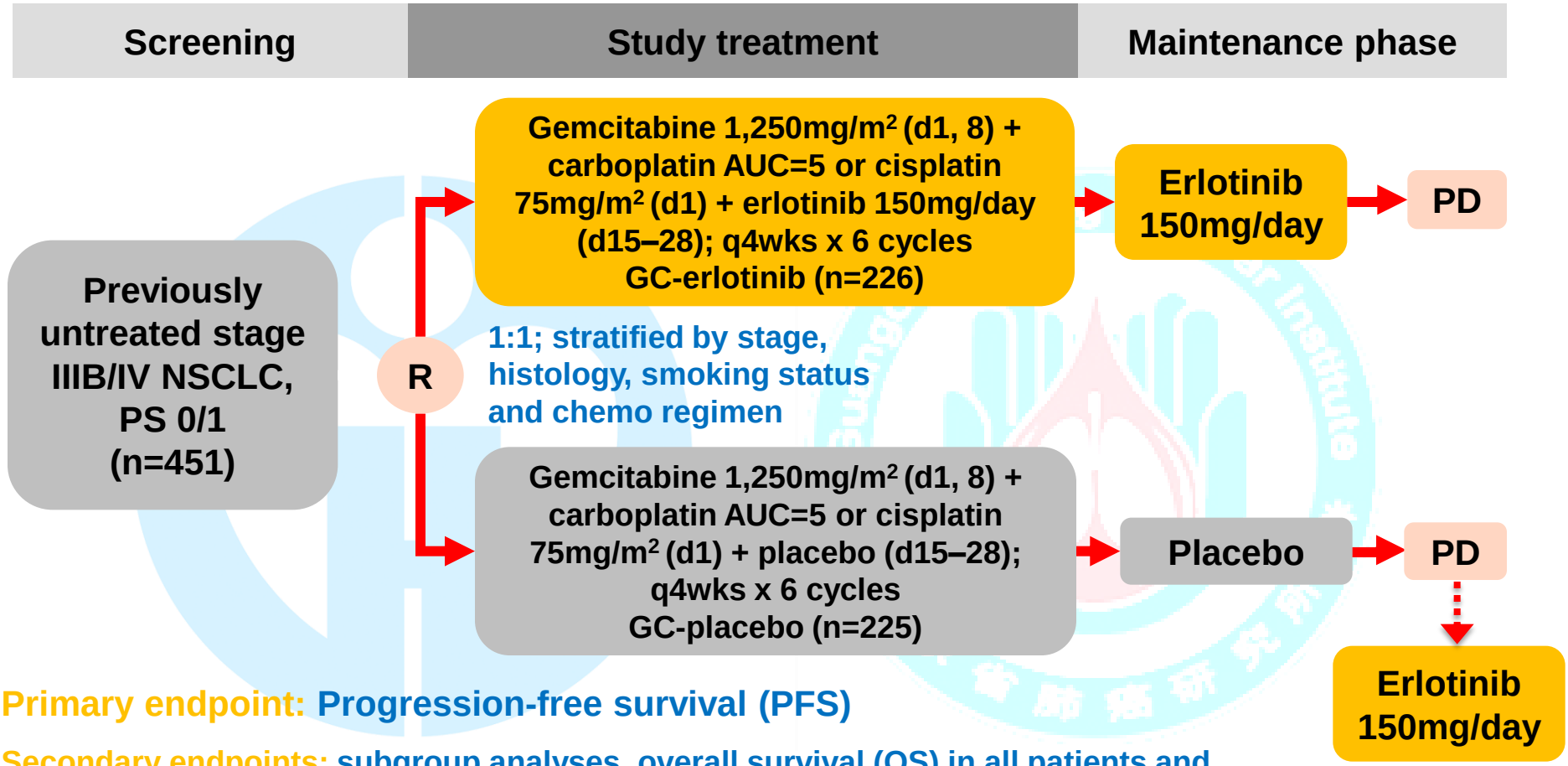
Zhang et al Lancet Oncology 2012

INFORM (C-TONG 0804)

- Phase III, randomized, placebo-controlled study of gefitinib as 1L maintenance therapy in patients with locally advanced or metastatic NSCLC, supported by AZ
- Oral Presentation in ASCO 2011
- Manuscript has been published by Lancet Oncol (2012)



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)

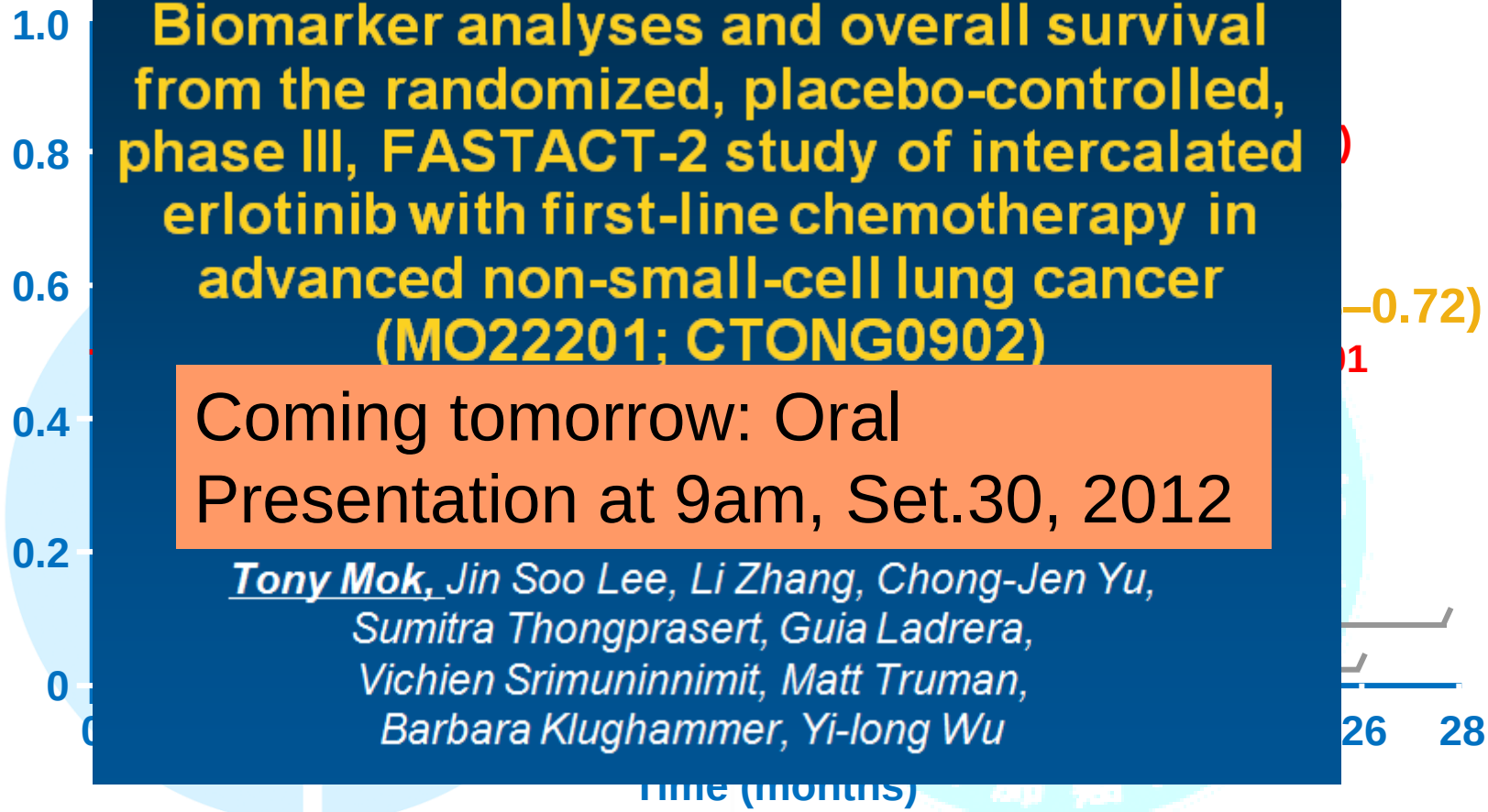
Mok, Wu et al. ASCO 2012

PFS according to IRC

Biomarker analyses and overall survival from the randomized, placebo-controlled, phase III, FASTACT-2 study of intercalated erlotinib with first-line chemotherapy in advanced non-small-cell lung cancer (MO22201; CTONG0902)

Coming tomorrow: Oral Presentation at 9am, Set.30, 2012

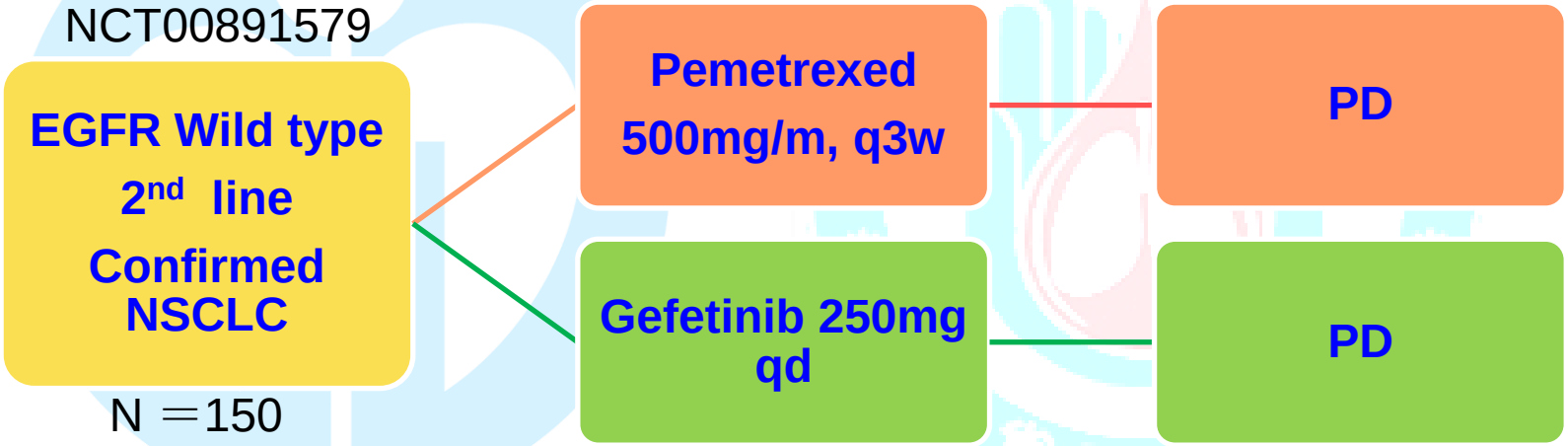
Tony Mok, *Jin Soo Lee, Li Zhang, Chong-Jen Yu, Sumitra Thongprasert, Guia Ladrera, Vichien Srimuninnimit, Matt Truman, Barbara Klughammer, Yi-long Wu*



Erlotinib	226	200	177	151	14	93	76	59	43	29	14	3	1	1	0
Placebo	225	200	179	134	79	51	35	19	12	7	3	1	1	1	0

Mok, Wu et al. ASCO 2012

Phase 2 Randomized, Controlled, Open-label Study of Pemetrexed versus Gefitinib in Patients with Locally Advanced or Metastatic Non Small Cell Lung Cancer who have Previously Received Platinum-Based Chemotherapy without EGFR Mutations (CTONG0806)



Primary endpoint: PFS
Second endpoint: OS, RR, QoL

Outline

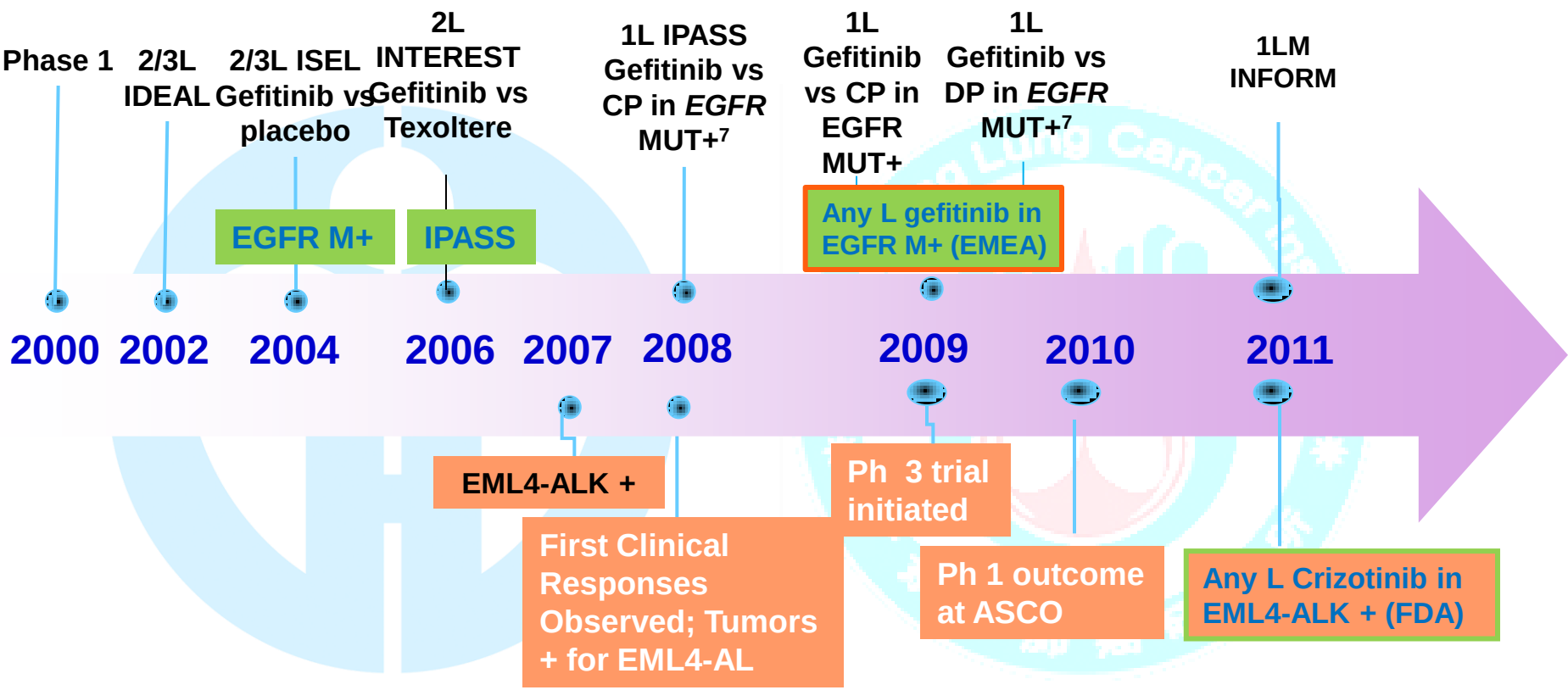
- Regulatory Environment in China
- Chinese Thoracic Oncology Group trials
- **Near future: biomarker-driven clinical trial in China**

EGFR 时代： 30%的EGFR突变

Studies of EGFR TKIs in *EGFR* Act Mut+ NSCLC

Study	EGFR TKI	n	Line	Median PFS (months)
IPASS	Gefitinib	132	First	9.5
WJTOG 3405	Gefitinib	86	First	9.2
NEJSG 002	Gefitinib	114	First	10.8
OPTIMAL	Erlotinib	82	First	13.1
EURTAC	Erlotinib	87	First	9.7
ENSURE	Erlotinib	210	First	Closed
LUX-LUNG-3	Afatinib	160/345	First	13.6
LUX-LUNG-6	Afatinib	364	First	Closed

Gefitinib and Crizotinib: 5 years and 4 years

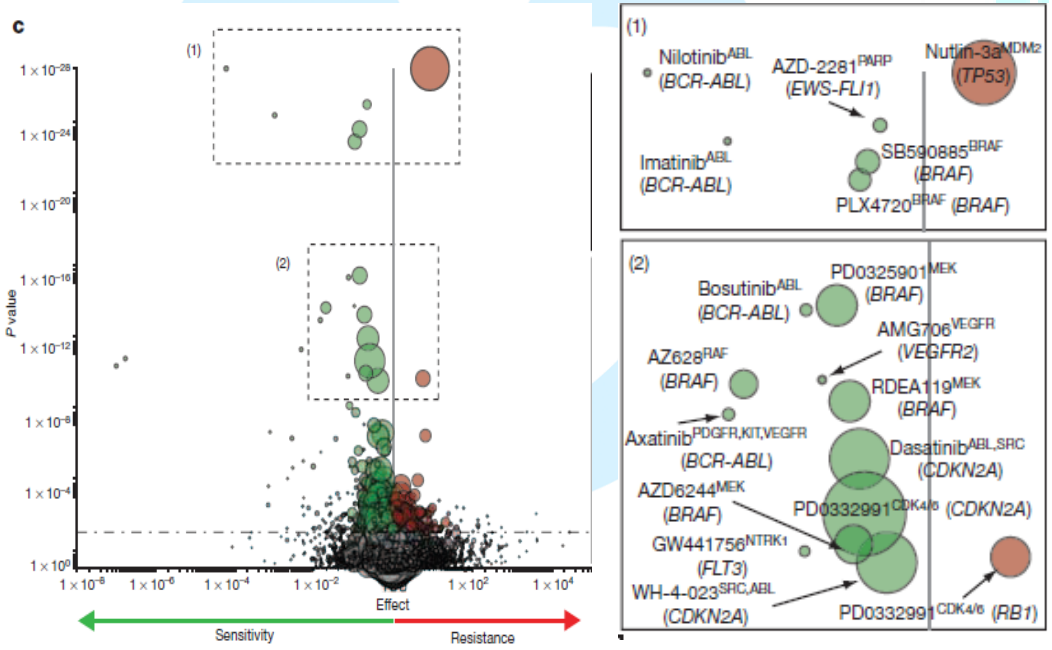


1.Fokuoka 2002; Kris 2002. 2. Thatcher Lancet 2005; 3. Kim 2007; 4 Mok, et al. NEJM 2008;
5. Mitsdomi 2009; 6. NEJ002 2009 ; 7. Zhou, et al.2010; 8.Bang ASCO 2010

Sensitivity to most drugs tested was associated with a mutation in at least one cancer gene (118/130, 91%)

ARTICLE nature International weekly journal of science
doi:10.1038/nature11005

Systematic identification of genomic markers of drug sensitivity in cancer cells



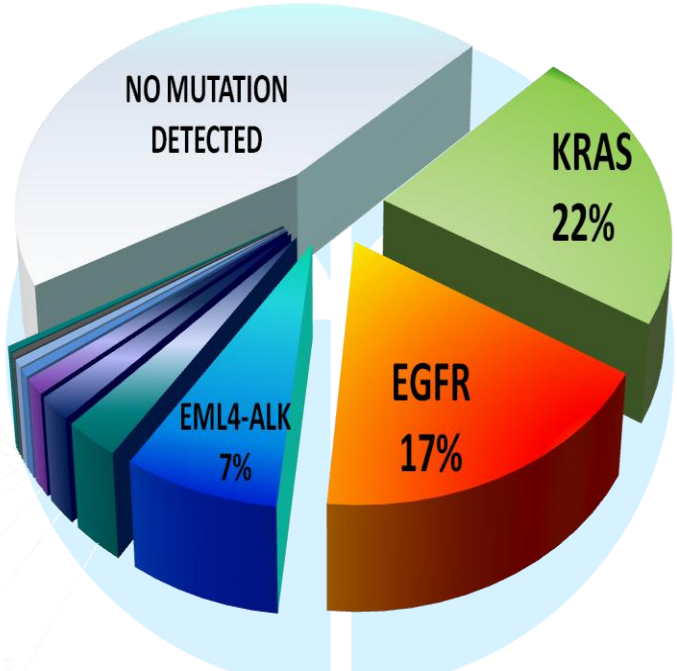
A range of 275–507 cell lines screened per drug (mean 368 cell lines per drug)

Garnett MJ, et al. Nature 2012; 483:570-577.

Driver genes in NSCLC

Lung Cancer Mutation Consortium

Adeno=516



Mutation found in 54% (280/516) of tumors completely tested.

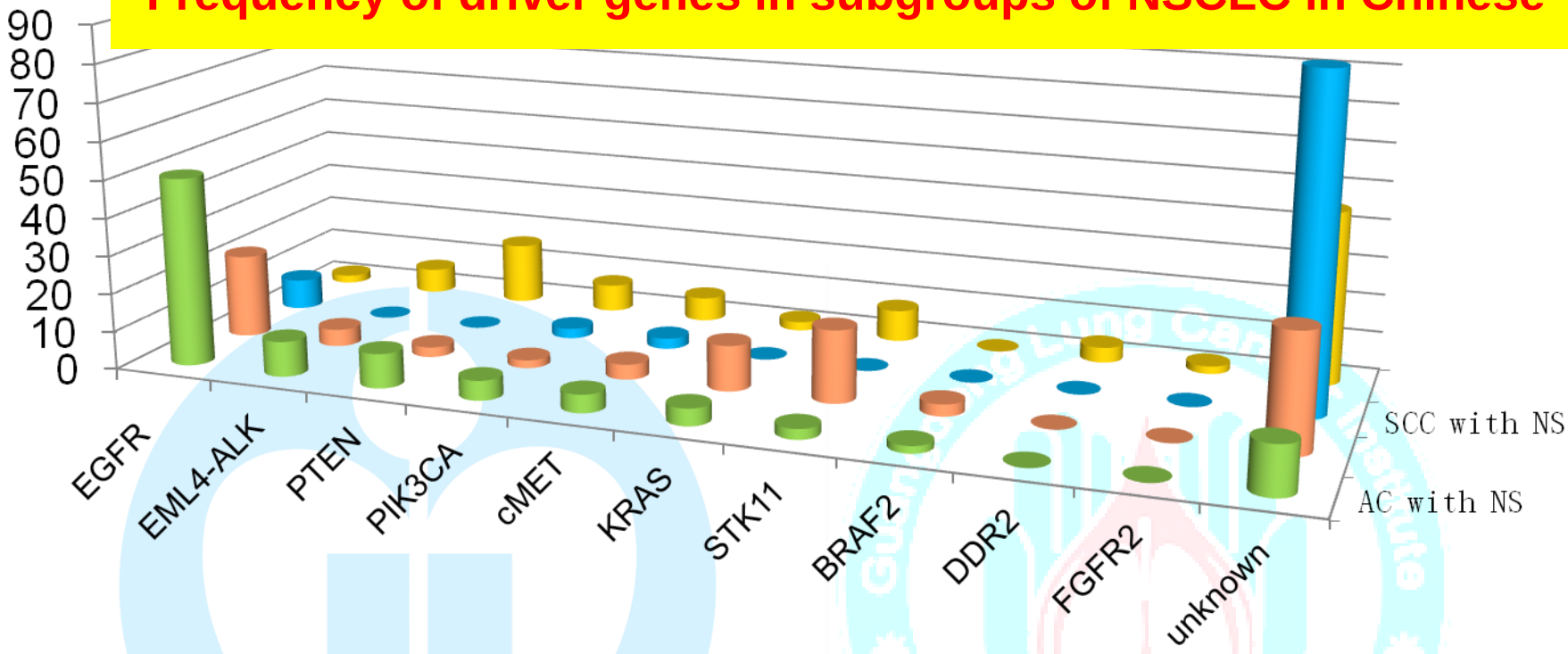
Kris et al. ASCO 2011

The Cancer Genome Atlas (TCGA) Project SCC 178 cases

Gene	Event Type	Frequency
CDKN2A	Deletion/Mutation/ Methylation	72%
PI3KCA	Mutation	16%
PTEN	Mutation/Deletion	15%
FGFR1	Amplification	15%
EGFR	Amplification	9%
PDGFRA	Amplification/Mut ation	9%
CCND1	Amplification	8%
DDR2	Mutation	4%
BRAF	Mutation	4%
ERBB2	Amplification	4%
FGFR2	Mutation	3%

Govindan et al. ASCO 2012

Frequency of driver genes in subgroups of NSCLC in Chinese



	EGFR	EML4-ALK	PTEN	PIK3CA	cMET	KRAS	STK11	BRAF2	DDR2	FGFR2	unknown
AC with NS	49.8	9.3	9.1	5.2	4.8	4.5	2.7	1.9	0	0	12.7
AC with S	22	4.5	2.6	2.1	4	12	19	3.1	0	0	30.7
SCC with NS	8	0	0	2.6	2.8	0	0	0	0	0	86.6
SCC with S	2.1	6.5	16.1	7.2	6.3	2.3	8.3	0	4	2	45.2

An SJ, Wu YL. PLoS One June 2012

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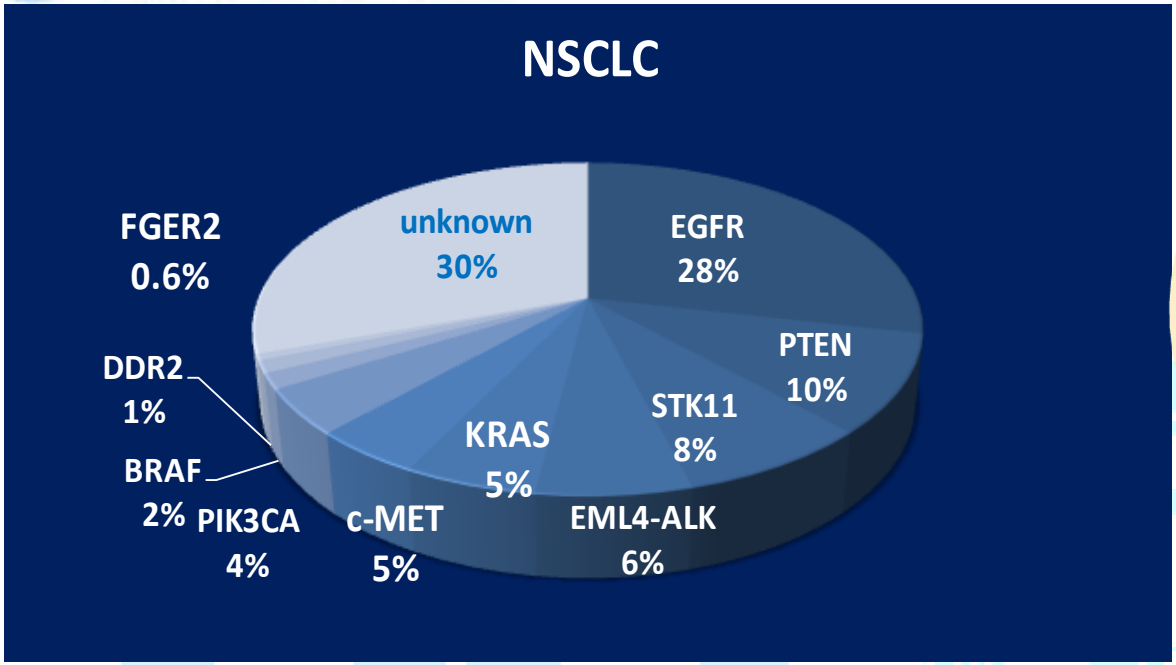
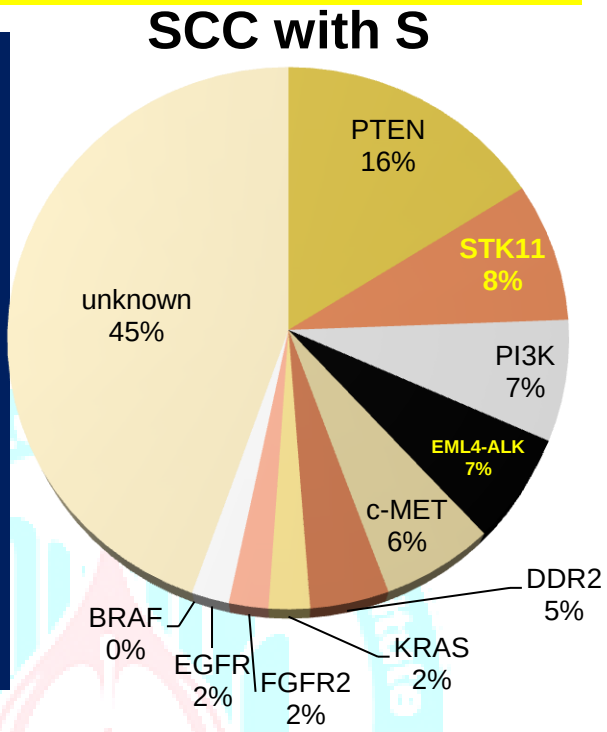
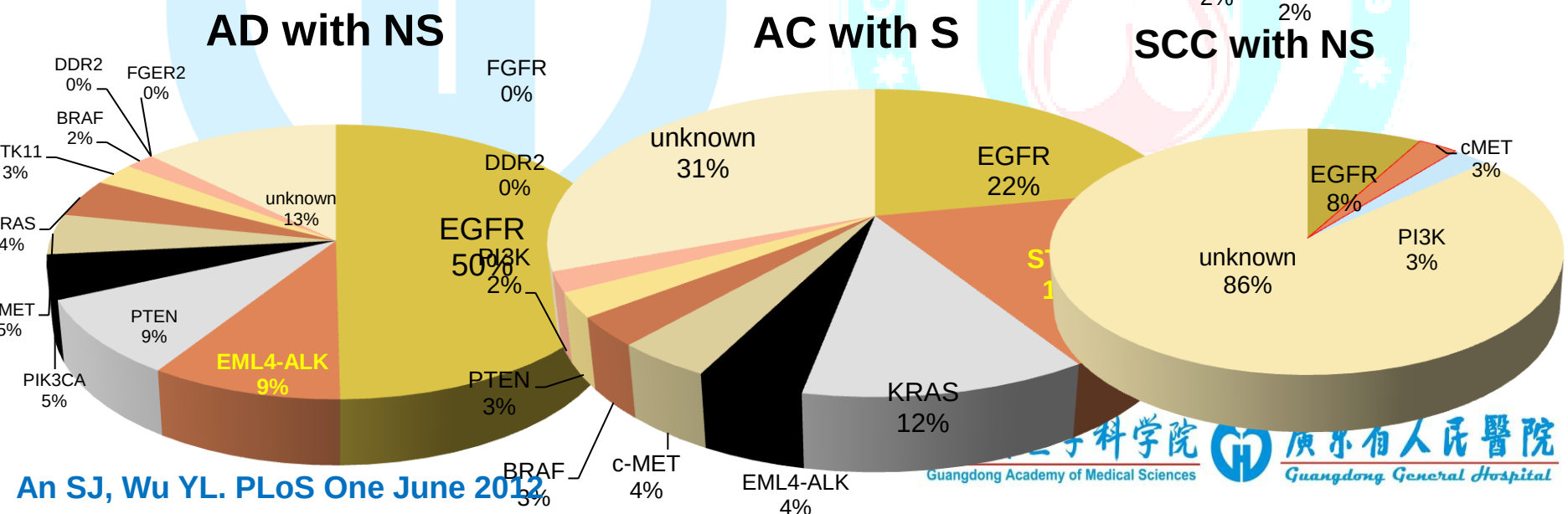
Frequency of driver genes subgroups of NSCLC





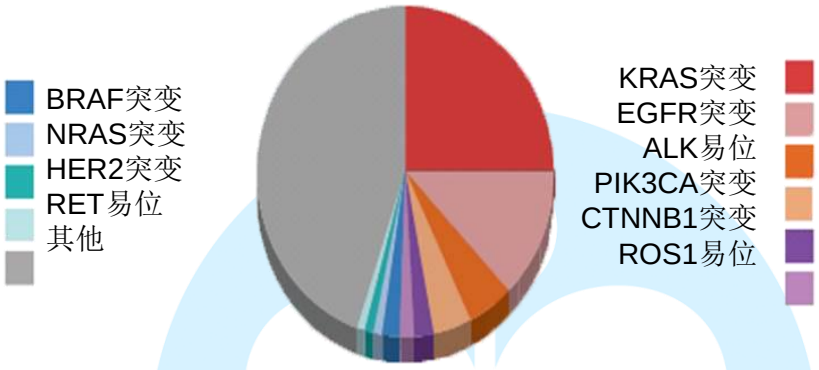


An SJ, Wu YL. PLoS One June 2012

Guangdong Academy of Medical Sciences
Guangdong General Hospital

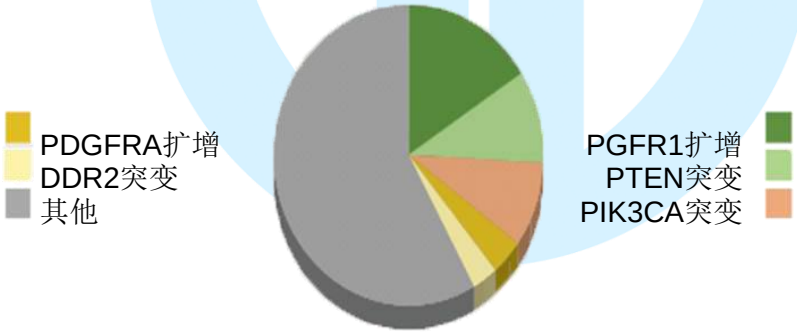
Near future：personalized treatment

Lung adenocarcinoma



*mutations in TP53 and STK11/LKB1 are common occurrence, not included in pie chart due to high overlap with other mutations

Lung squamous Ca



*mutations in TP53 are a common occurrence, not included in pie chart due to high overlap with other mutations

EGFR	厄洛替尼 (获批)	PDGFRA	MEDI575
	吉非替尼 (获批)		IMC-3G3
	PF299804	PI3K	BKM120
	阿法替尼 (BIBW2992)		PX-866
ALK	克唑替尼 (获批)		GDC-0941
	LDK378		SAR245408
	AP26113	PI3K/ MTOR	GDC-0980
	AF802		BEZ235
ROS1	Crizotinib		SAR245409
HER2	PF299804	MEK	MEK162
	阿法替尼 (BIBW2992)		GDC-0973
FGFR	BGJ398		GSK1120212
	FP1039 (HGS1036)		MSC1936369B
	Ponatinib (AP24534)	STAT3	OPB51602
FGFR/ PDGFRA/ VEGFR	BIBF1120	AKT	MK2206
	帕唑帕尼		
	Lenvatinib (E7080)		
	Brivanib (BMS-582,664)		
	多韦替尼 (TKI258)		

Heist RS, et al. Cancer Cell 2012; 21:448.

广东省肺癌研究所
Guangdong Lung Cancer Institute

Expert Opinion

1. National collaborative clinical

Clinical trials and biomarker research on lung cancer in China

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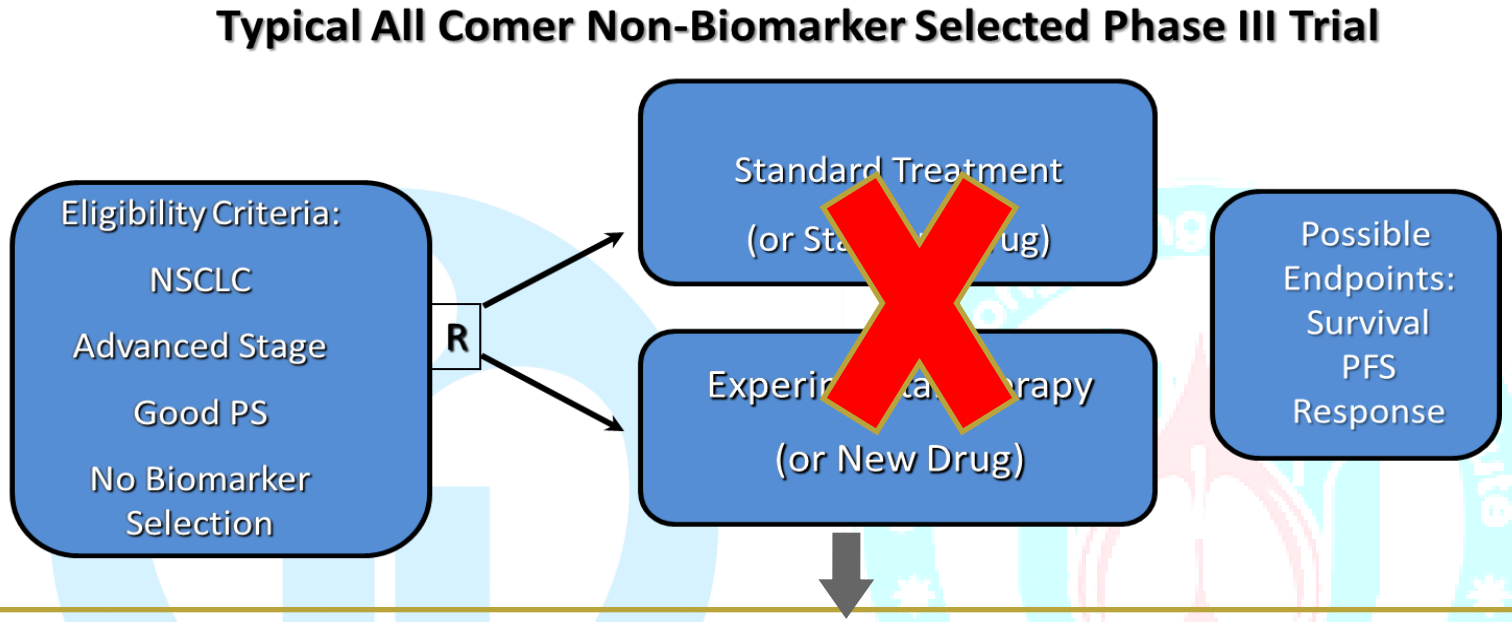
Article highlights.

- The Chinese national collaborative clinical trial group is still at an early stage. Many challenges must be overcome in order to perform useful trials.
- Chinese investigators are focused on trials driven by biomarkers. Huge numbers of patients in China can be enrolled in these trials.
- The rate of lung adenocarcinoma driver mutations in China is higher than that in the USA.
- Biomarkers from serum or single nucleotide polymorphism (SNP) identification as surrogate markers for EGFR mutation still require further investigation.
- Current challenges of biomarker-driven clinical trials include the limitations of biomarker validation methodologies, design and performance of clinical trials and regulatory hurdles.

Expert Opin. Ther. Targets [Early Online]

广东省医学科学院 Guangdong Academy of Medical Sciences
广东省人民醫院 Guangdong General Hospital

Clinical Trial Design for Targeted Agents



Biomarker-driven Clinical Trial Designs

- **All-Comer's Design (Biomarker as secondary)**
- **Overall Population-Focused Hybrid Design**
- **Subgroup-focused Hybrid Design**
- **Targeted Design (Discrete Hypothesis Hybrid)**

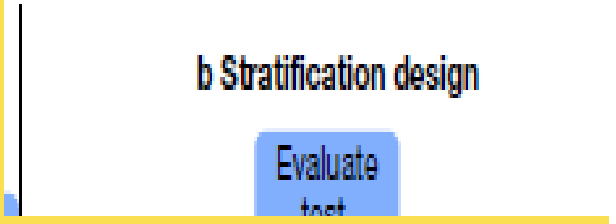
from Redman, Gandara et al: Clin Cancer Res (in press)

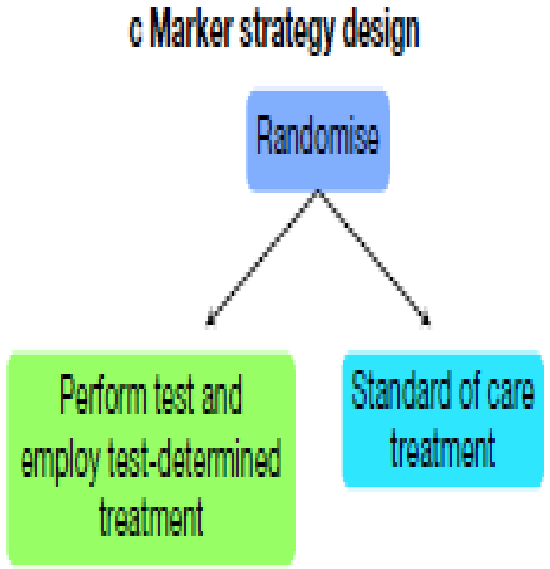
Innovational clinical trials design

When a predictive test has been developed but there are no compelling biological or Phase II data that test-negative patients do not be from the new trea It is to evaluate th treatment overall a the subsets deter by the prespecifie

s appropriate when: as a modest lected patients xicity:

The marker strategy design is inefficient in settings where many patients may receive the same treatment regardless of which group they are randomised. A very large number of patients may have to be randomised. It may confound marker effects with treatment effects

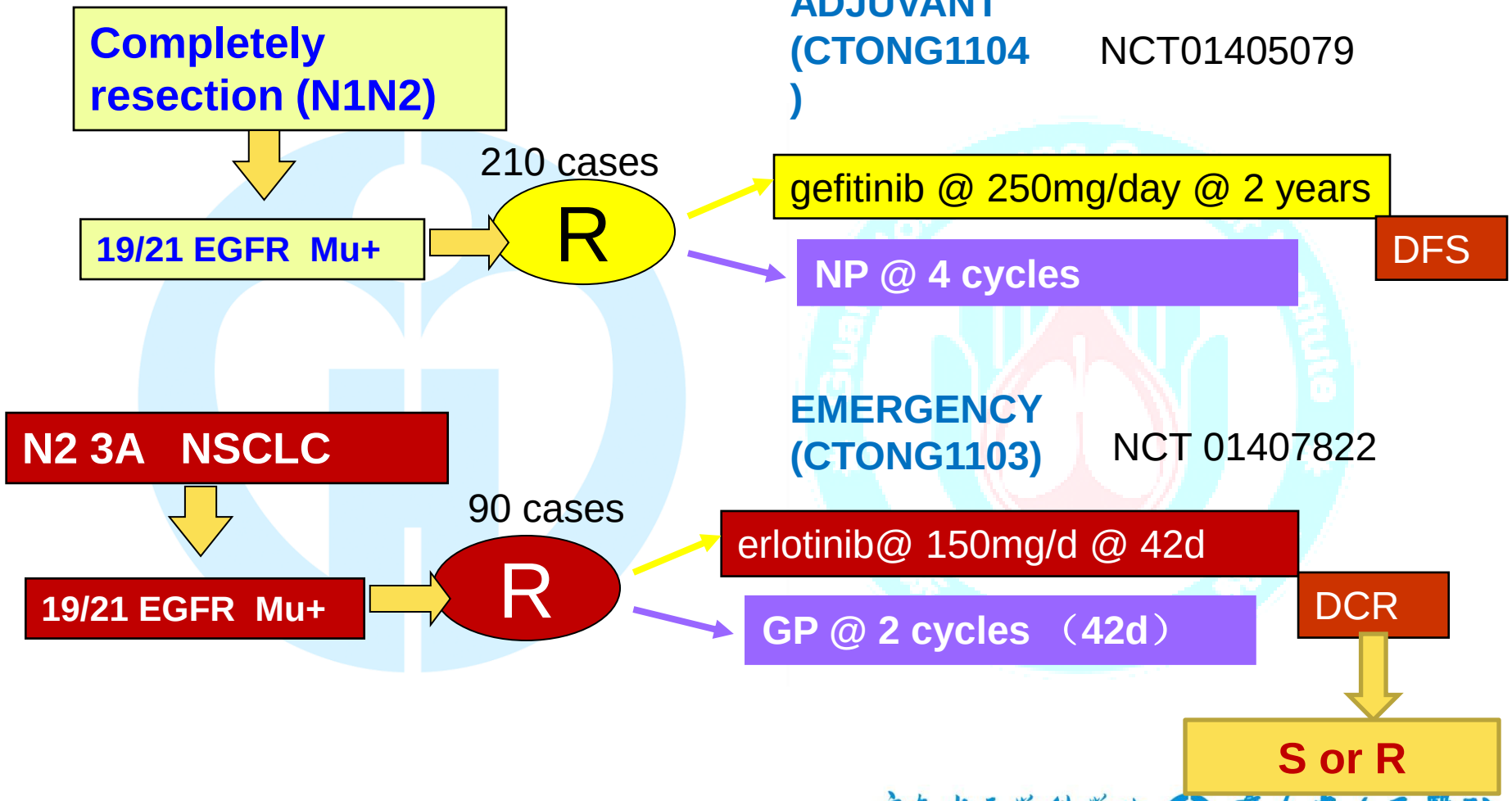




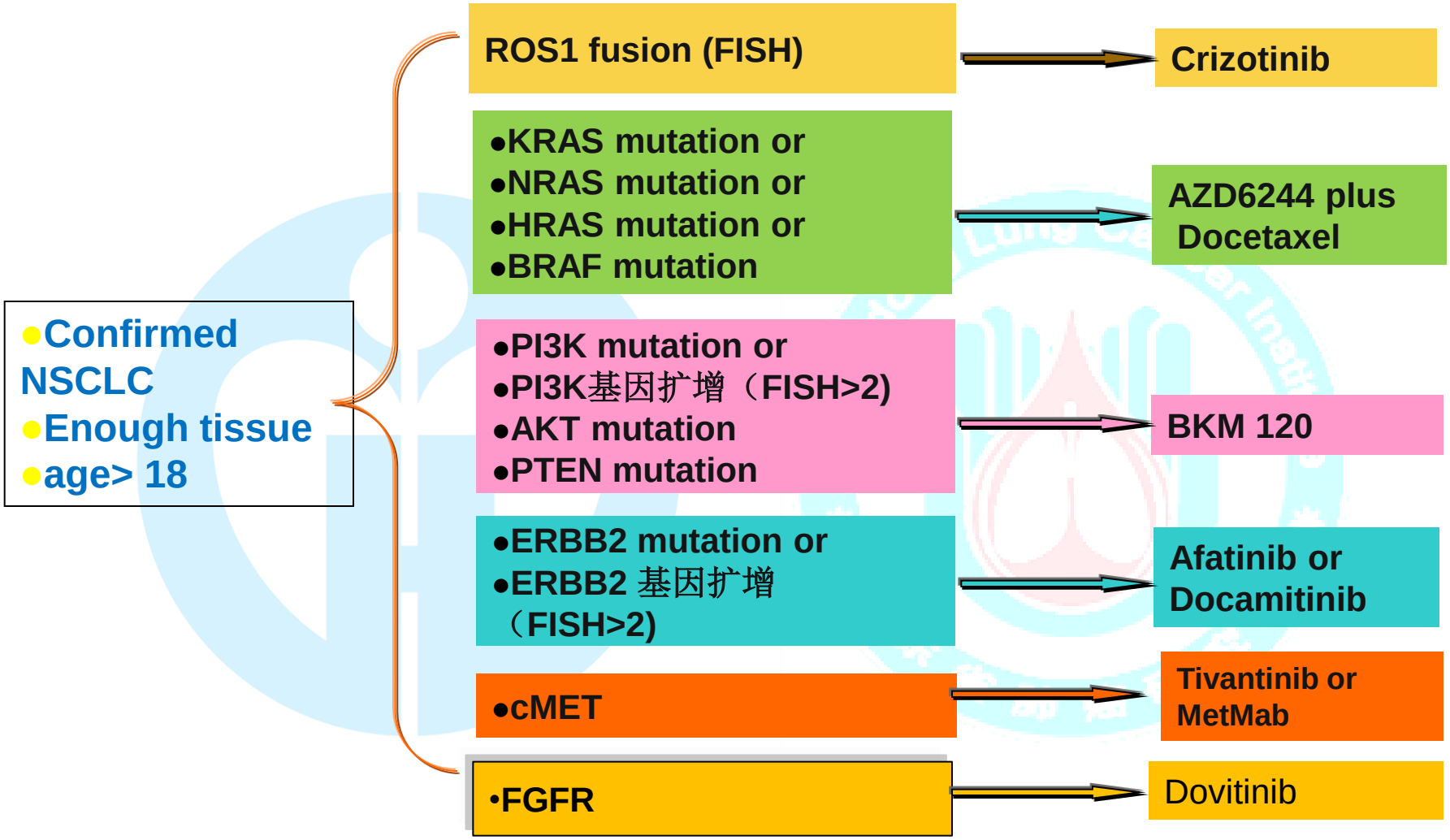
Three desig clinical trials biomarker classifiers

Expert Reviews in Molecular Medicine，2010

Biomarker-driven adjuvant and neo-adjuvant trials



Biomarker-driven trial



Summary

- INDTs and IITs at the early stage in China
- CTONG play an important role in INDTs and IITs
- Biomarker-driven clinical trial will be direction in future

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Thank You

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