

帝京がんセンター化学療法室セミナー
2009.9.2

EGFR-TKI 治療の最適化を目指して

光富徹哉
愛知県がんセンター胸部外科



63, 234

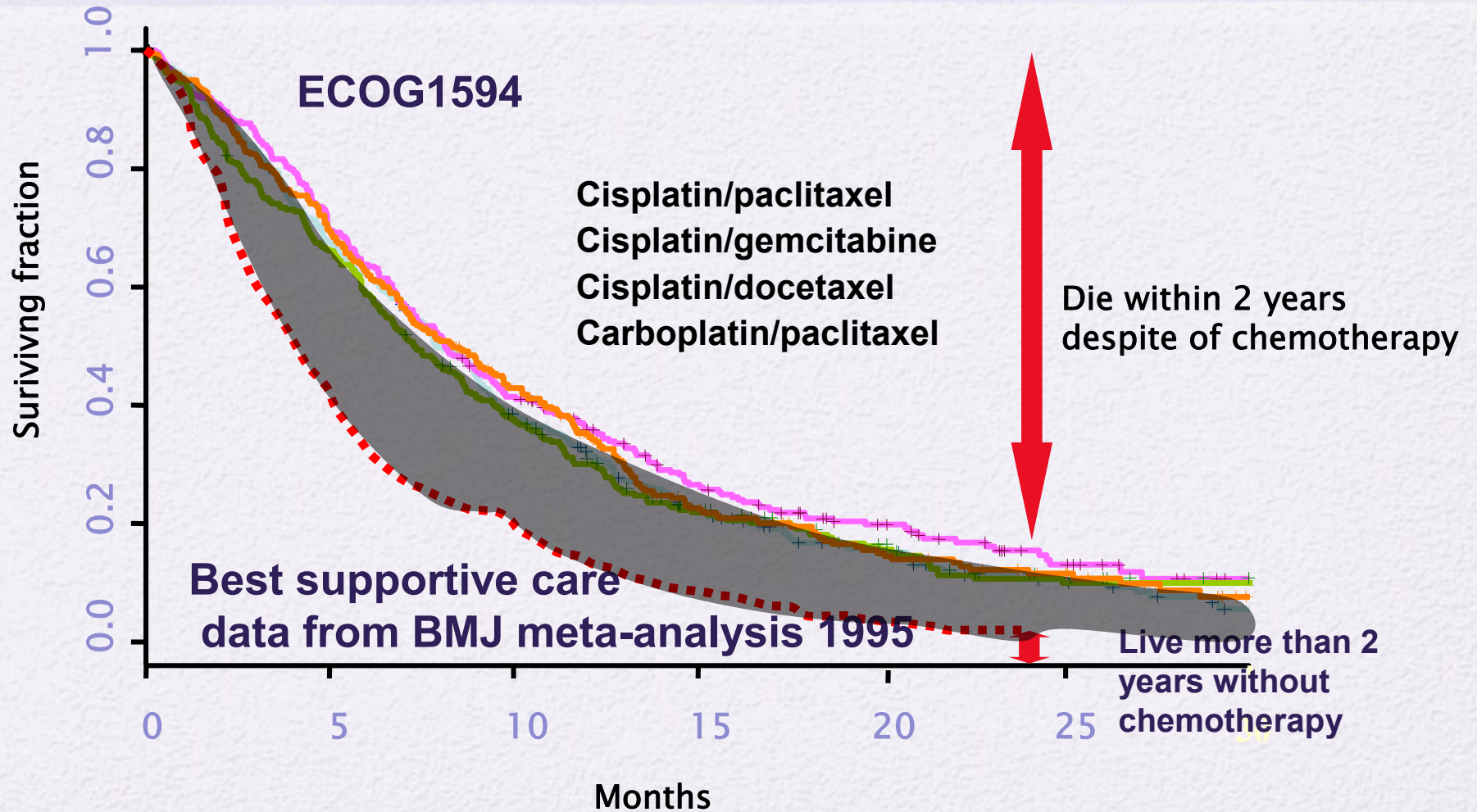
2004 59922/320,358
2005 62058/325,885

2006

肺がん

- 日本人がん死亡原因の第一位、2006年には63,234名が死亡
- 非喫煙者(40%<)、女性(40%<)、腺癌(80%<)が増加
- 化学療法や手術による治療成績の改善は限界?
 - 全ステージの5年生存率 15%
- 早期に全身化
- 予後や治療反応性に関してのheterogeneityが大きい
- 分子標的治療に期待...EGFR Tyrosine kinase inhibitor (TKI, Ab), angiogenesis inhibitor

NSCLC patients have heterogenous prognosis
Not all patients are benefited from chemotherapy





分子標的薬

■従来の抗癌剤

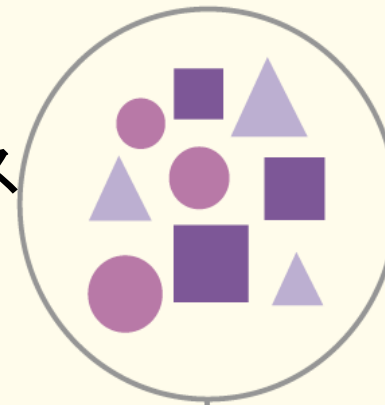
- 細胞株での増殖抑制効果でスクリーニング
- あとから作用機序の解明

■分子標的薬

- 標的分子の同定
- 分子機能を阻害する薬物をスクリーニング
- 腫瘍縮小効果を確認

✳ 従来の抗癌剤

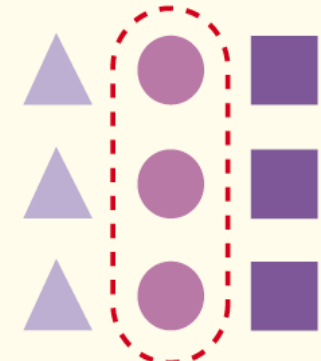
🎯 分子標的薬



腫瘍縮小効果の確認

作用機序の解明

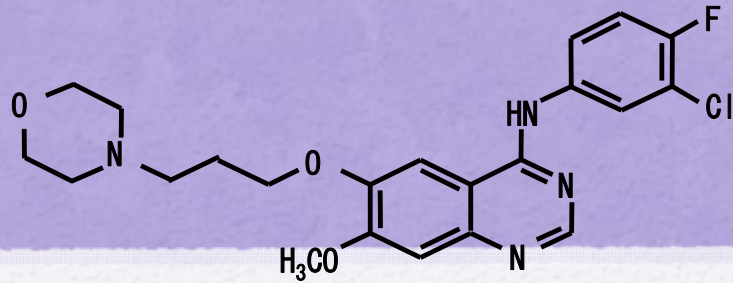
標的分子の選定



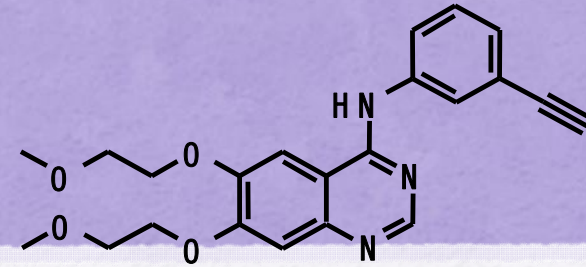
腫瘍縮小効果の確認

肺癌の分子標的治療薬

標的	阻害機序	薬物
EGFR	TK 阻害	ゲフィチニブ(イレッサ)、エルロチニブ(タルセバ)
	抗体	セツキシマブ(アービタックス)、パニツズマブ、マツズマブ
EGFR+HER2...	TK 阻害	BIBW2992, PF00299804
VEGF	抗体	ベバシズマブ(アバスチン)
VEGFR+EGFR	TK 阻害	vandetanib(zactima)
VEGFR+KIT+RAF...	TK 阻害	ソラフェニブ(ネクサバール)
VEGFR+KIT+PDGFR...	TK 阻害	スニチニブ(スーテント), axitinib, AZD2171(cediranib)
IGF1R	抗体	CP751,871
MET	TK 阻害	ARQ197, XL184
mTOR		CCI-779, RAD009
HSP90		17-AAG, 17-DMAG, CNF1010
Vascular disrupting		ASA-404(DMXAA)



ゲフィチニブ (イレッサ)

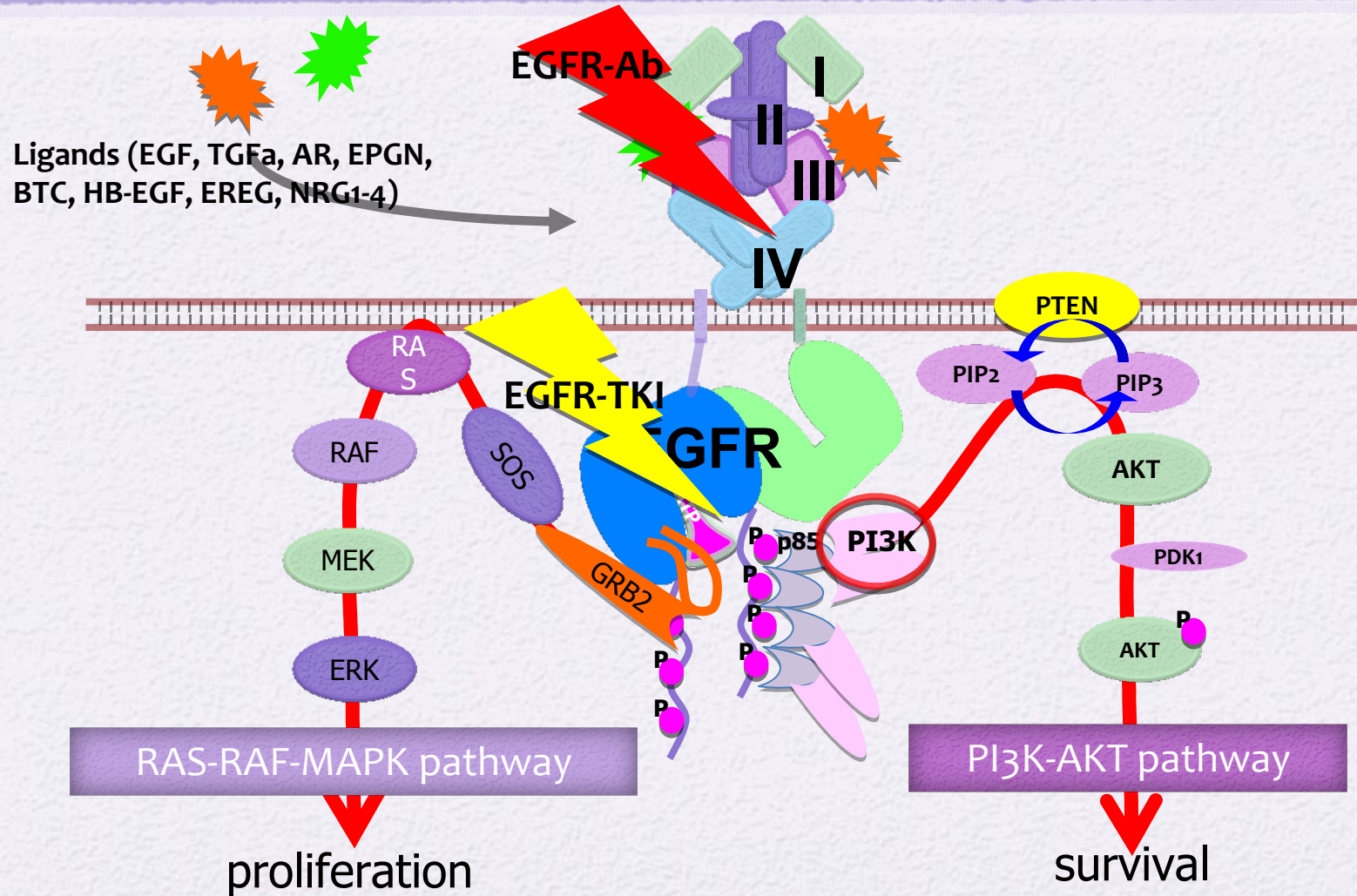


エルロチニブ (タルセバ)

肺癌の分子標的薬

- 上皮成長因子受容体(EGFR)のチロシンキナーゼ阻害剤
- 非喫煙者、女性、東洋人の肺腺癌患者にしばしば劇的な効果
- 6%に副作用として致死的な間質性肺炎
- 後にEGFR遺伝子に突然変異のある肺癌（日本人の肺癌の約40%）に効果が高い(奏効率80%)

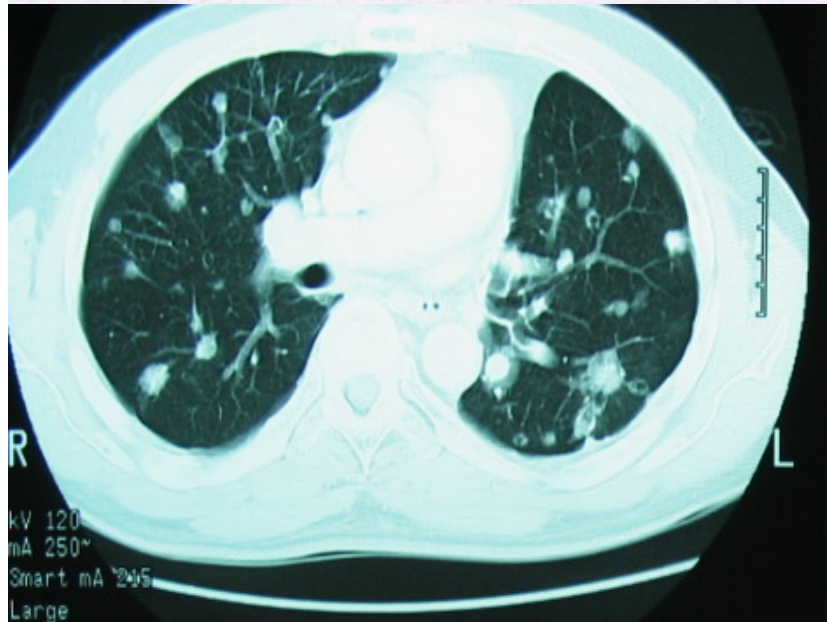
EGFR pathway



45才男性、肺腺癌

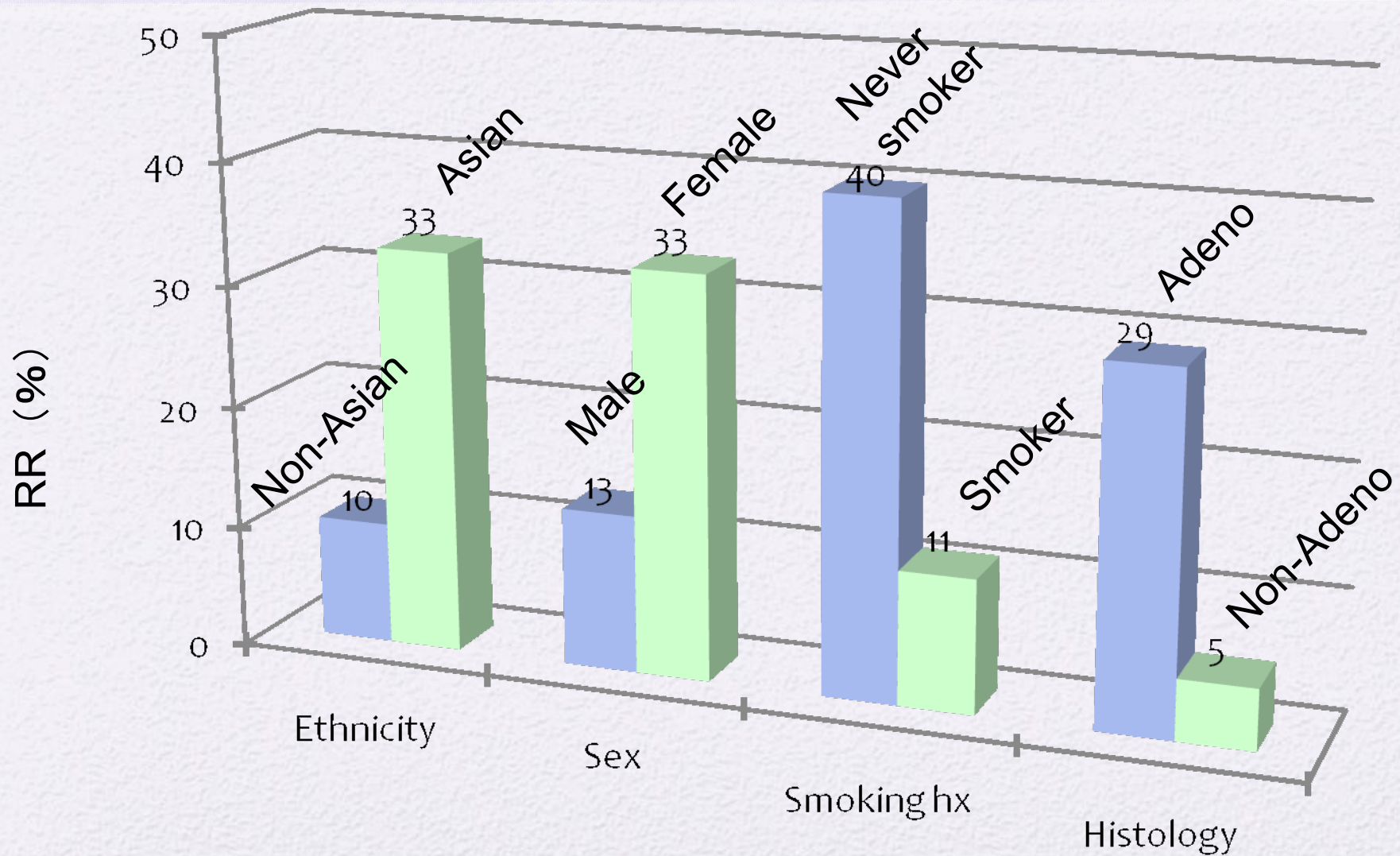


イレッサ



臨床背景別にみたEGFR-TKIの奏効率

(compiled from the literature N=1974)



2004 EGFR遺伝子の突然変異の発見

Lynch et al., NEJM, Paez et al., Science

■ 肺癌特異的

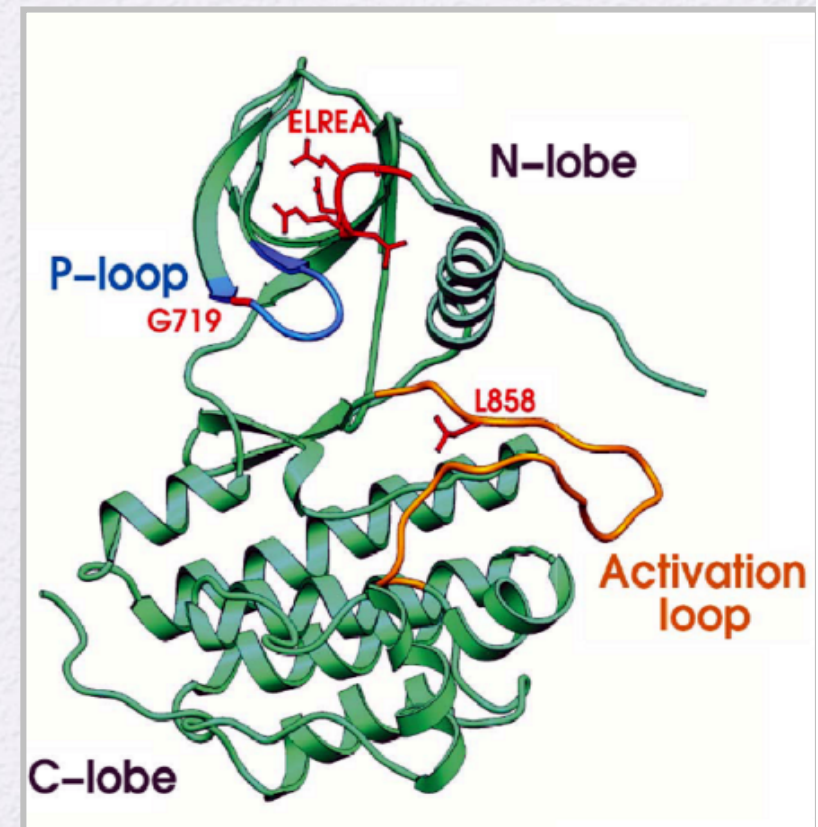
■ 特定の臨床背景と関連

- Adeno, Non smokers, Asians, Females

■ チロシンキナーゼドメインにおこる

- Exon 19 deletion
- L858R
- G719, Exon 20 insertion, others

■ EGFR-TKIの奏効と相関



EGFR突然変異は肺癌特異的

Lynch 2004	Gazdar 2004	Lee 2005	Barber 2005
乳癌	0/141	0/31	0/93
頭頸部癌	0/65		
膵癌	0/54		
肝癌			0/73
胃癌		0/54	0/185
前立腺癌	0/25	0/24	
大腸癌	0/21	0/56	0/98
腎癌	0/15		
脳腫瘍	0/4		0/59
胆嚢癌		0/50	
膀胱癌		0/28	
成人白血病			0/88
肺癌	2/25	146/591	4/10

非肺癌 1/1368

肺の腺癌におけるEGFR遺伝子の突然変異

740

*

750

*

760

*

860

*

正常

• • • KIPVAIKELREATSPKANKEILD • • • FGLAKLLG • •

欠失型突然変異 (エクソン19)

50%

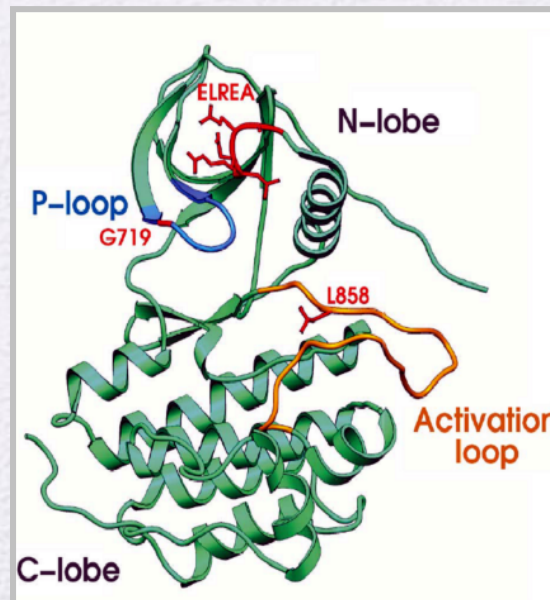
• • • KIPVAIK-----TSPKANKEILD • • • FGLAKLLG • •

点突然変異 (コドン858)

40%

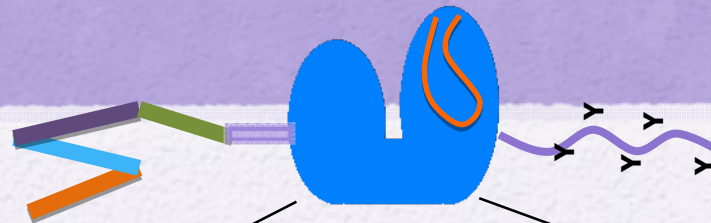
• • • KIPVAIKELREATSPKANKEILD • • • FG**R**AKLLG • •

その他の突然変異10%

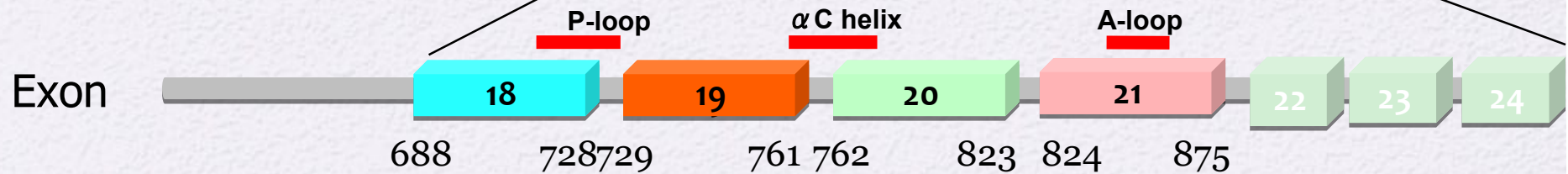


EGFR変異の分布とその頻度

Reviewed by Mitsudomi et al.,
Cancer Science, 2007



Kinase domain



↑ **G719**
↑ **Deletion**
↑ **Insertion**
↑ **L858R**
 others

Incidence (N=569) 3.2% 48.2% 3.7% 42.7% 2.2%

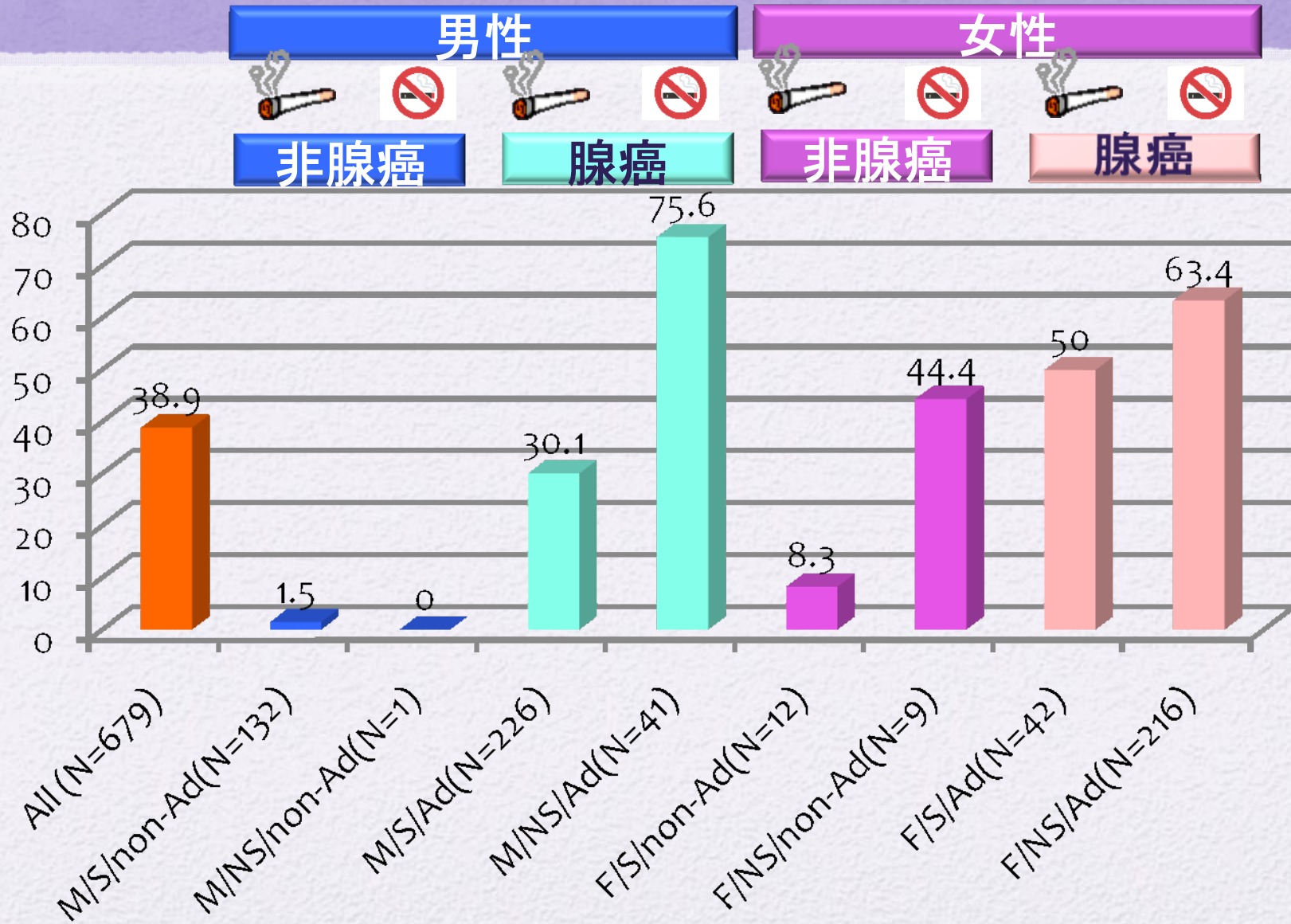
臨床背景別にみたEGFR変異

(compiled from the literature N=2880, Mitsudomi et al., Cancer science)

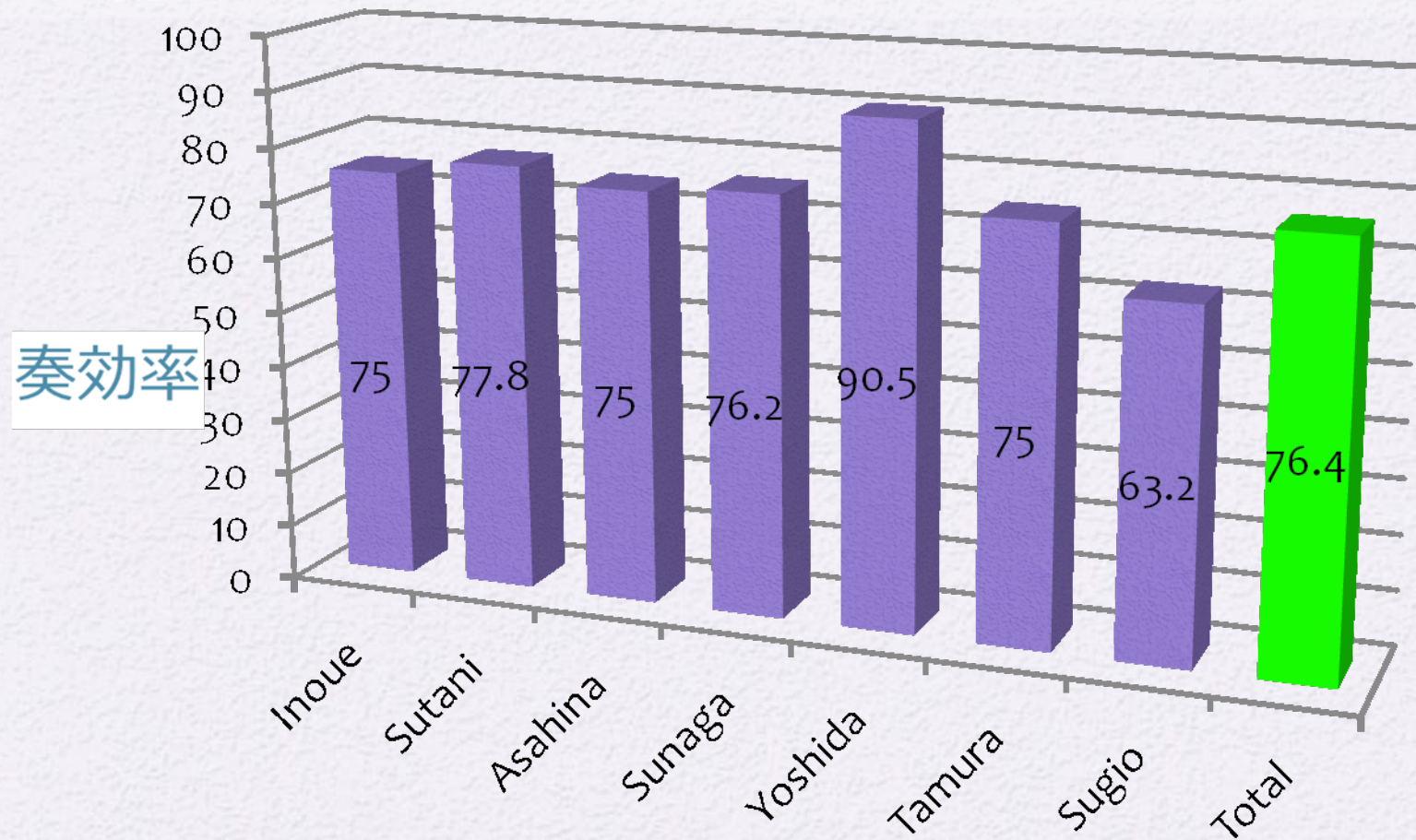


Clinical background からはEGFR変異を予測するのは困難

Onozato et al., N=679 at ACC

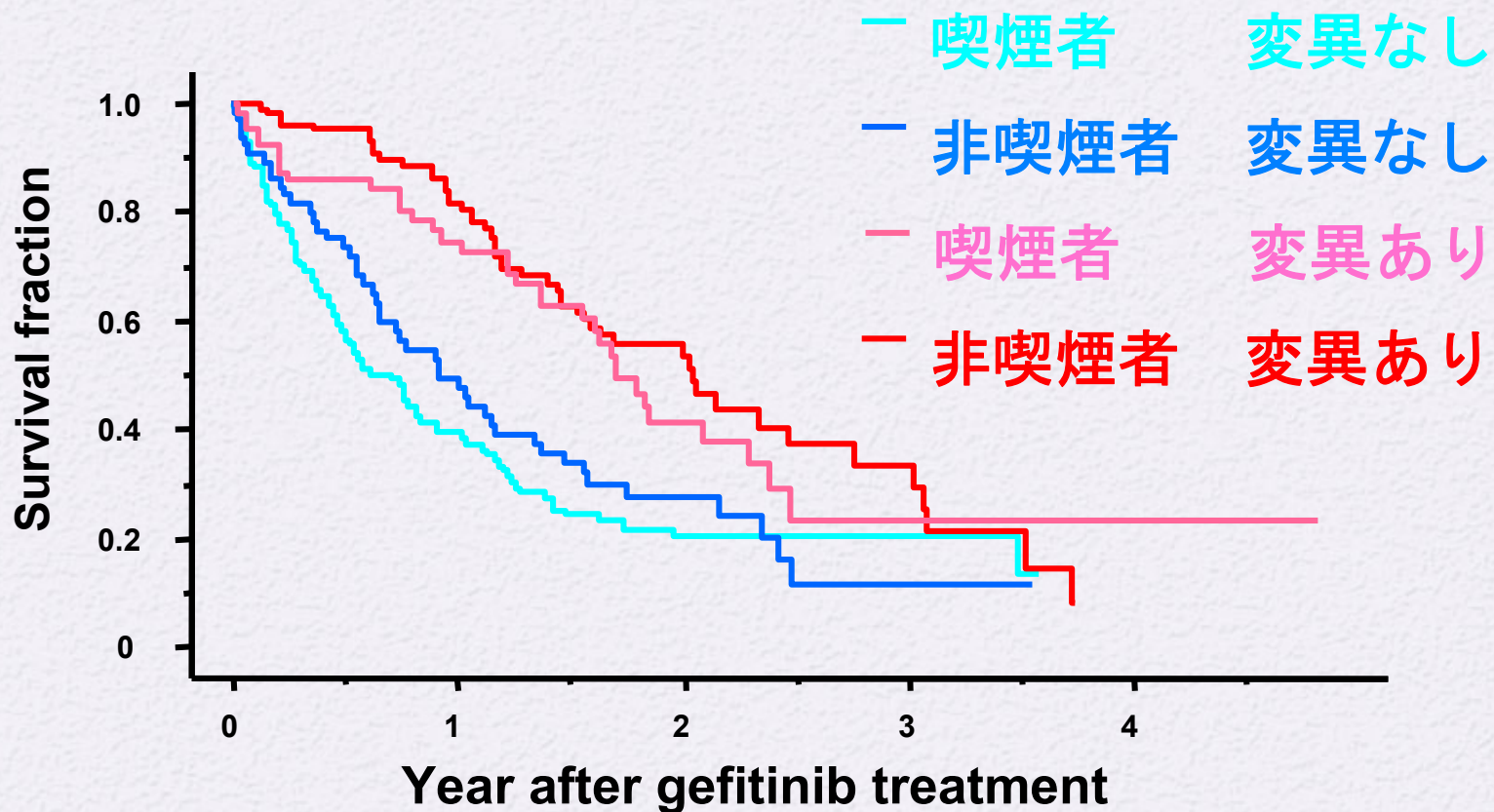


I-CAMP: EGFR変異陽性肺癌患者の ゲフィチニブ治療の統合解析



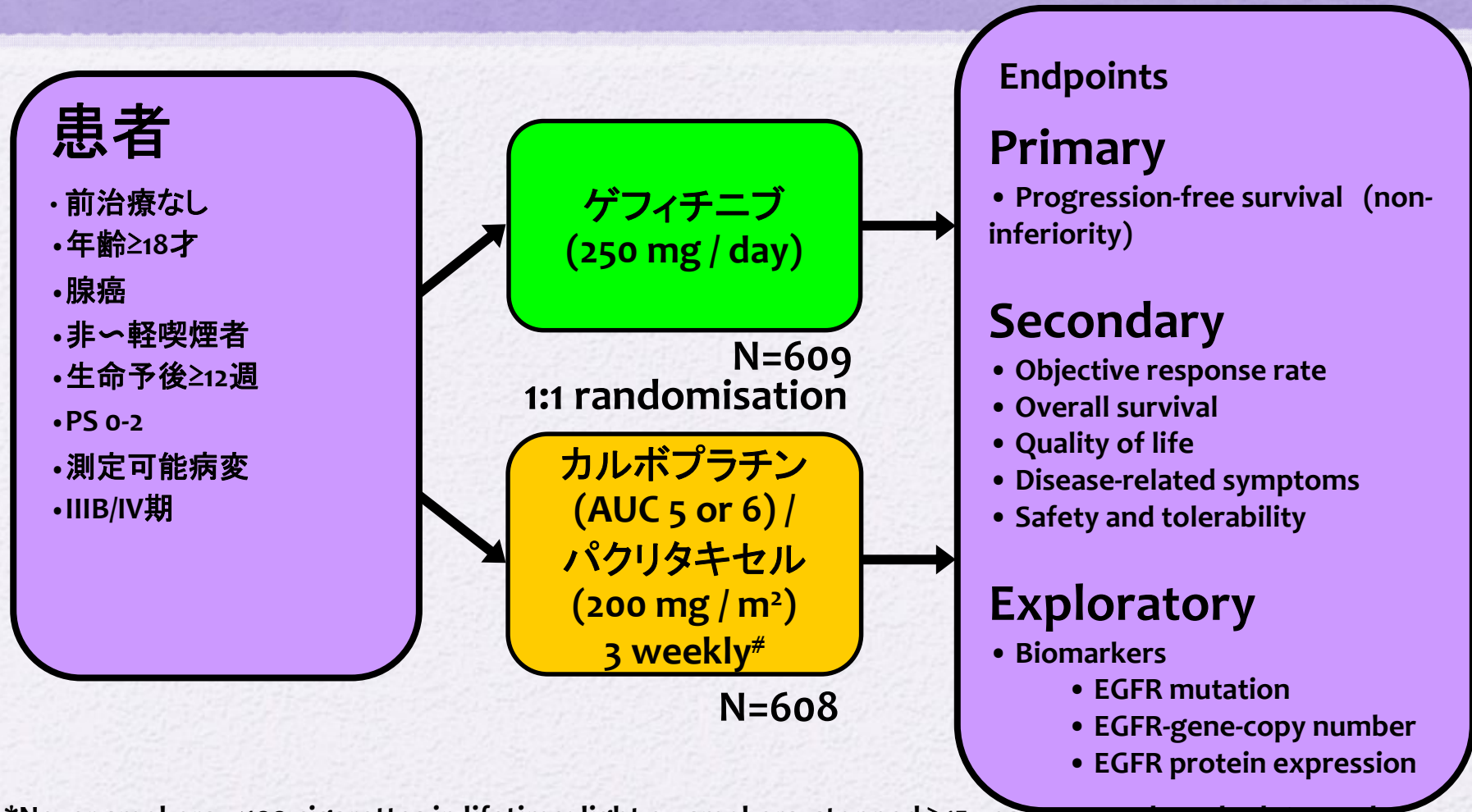
Morita et al., ASCO 2008, Yoshida et al., ESMO 2008

ゲフィチニブ治療を受けた腺癌における喫煙習慣とEGFR変異別にみた生存期間



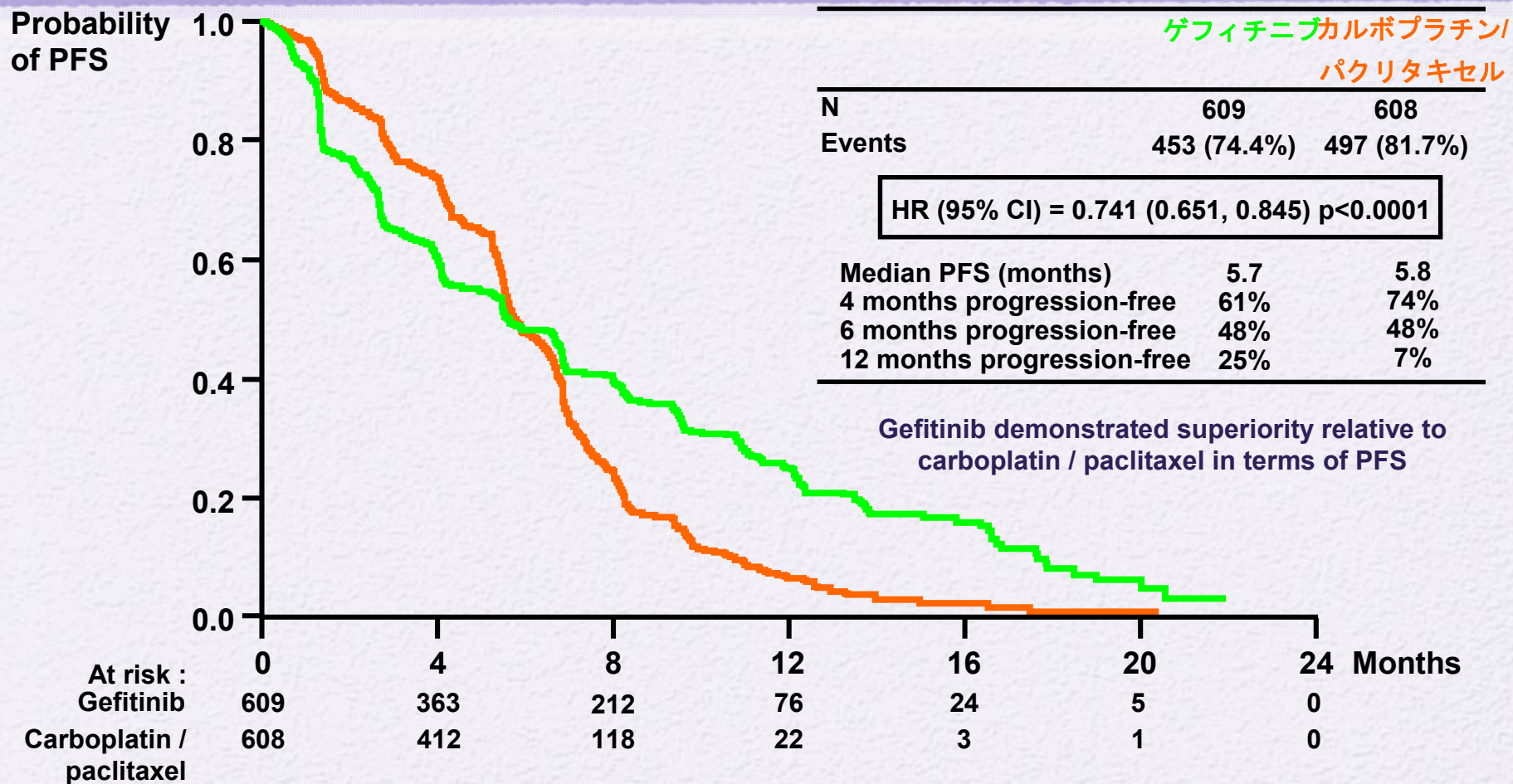
岡山大、国立がんセ、愛知県がんセのプールデータ (N=352)
岡山大学 豊岡伸一先生より

IPASS: 臨床的背景で選択した進行非小細胞肺癌における
ゲフィチニブ対カルボプラチン+パクリタキセルの第三相試験
Mok et al., ESMO 2009



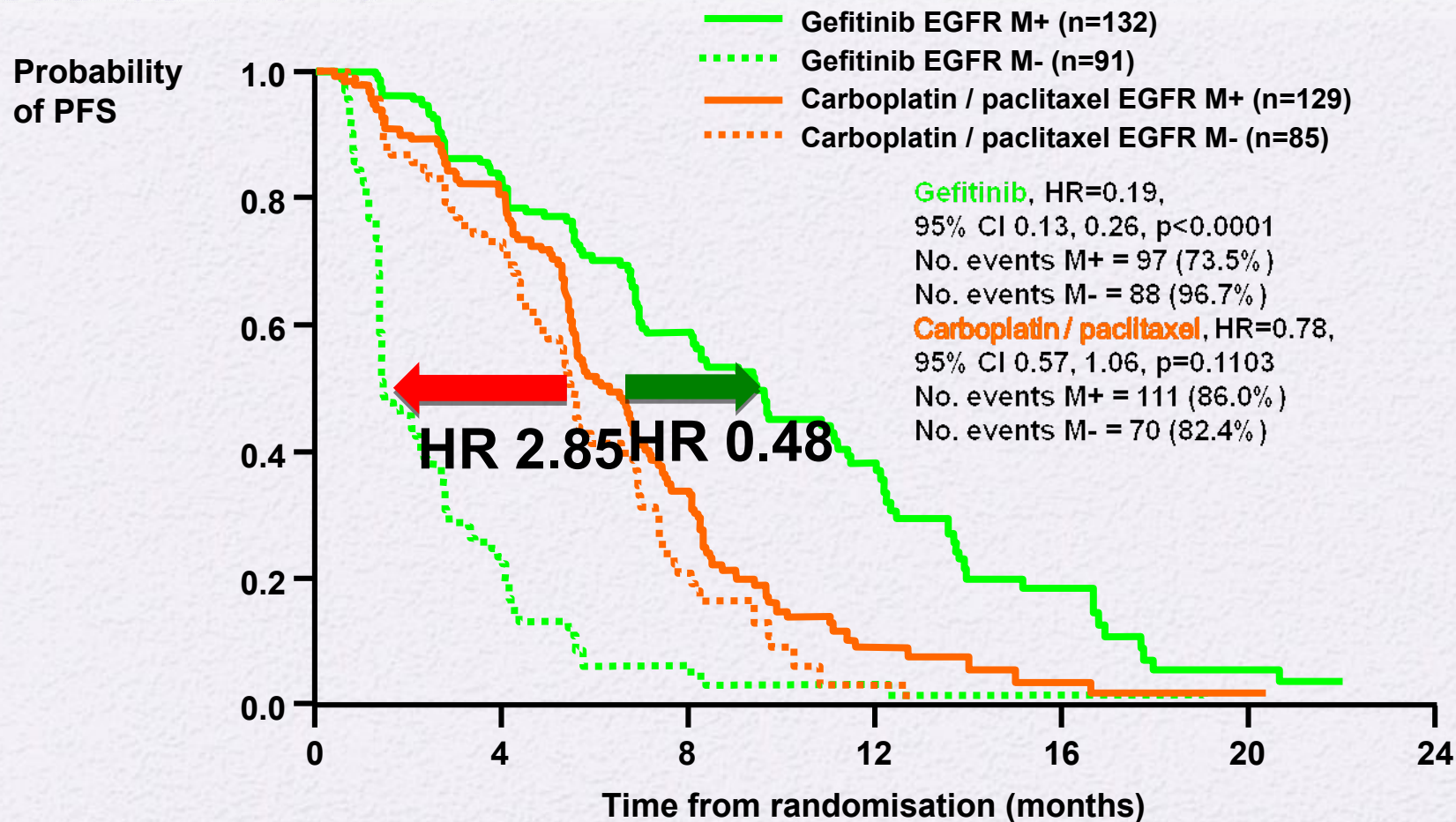
*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥ 15 years ago and smoked ≤ 10 pack years; [#]limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression

IPASS: 無増悪生存期間 (PFS)



Primary Cox analysis with covariates
 HR <1 implies a lower risk of progression on gefitinib

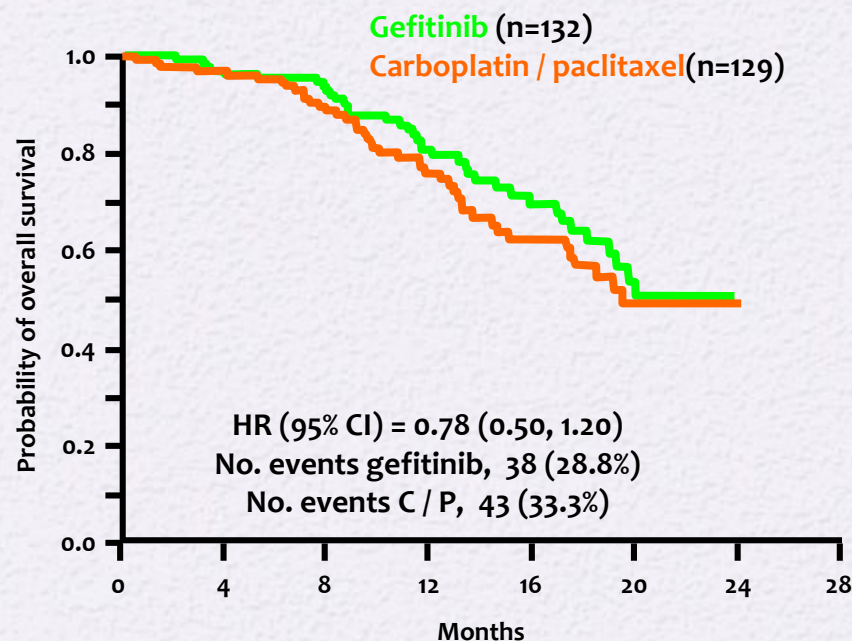
EGFR変異別、治療アーム別にみた無病生存期間



Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M- group
 M+, mutation positive; M-, mutation negative

IPASS: EGFR変異別に見た全生存期間

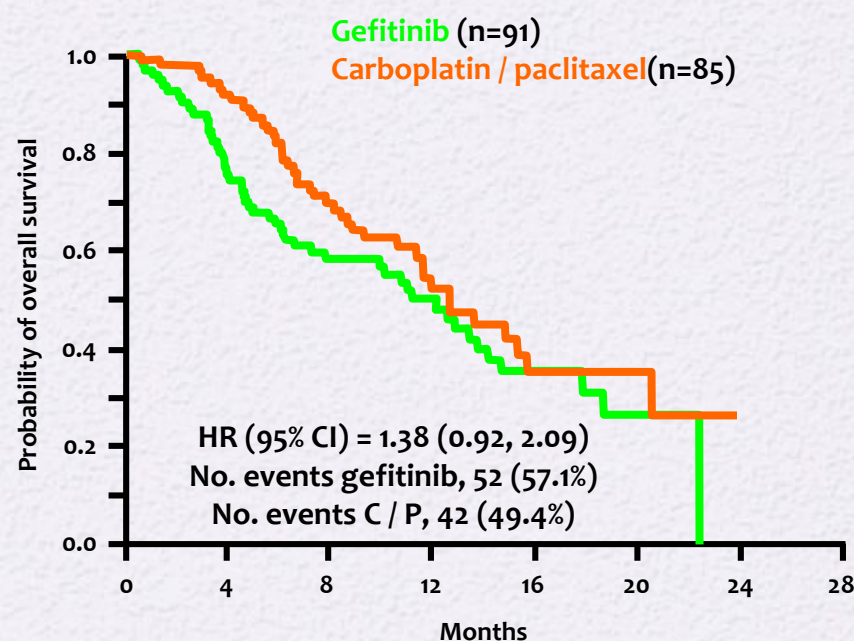
EGFR mutation positive



Patients at risk:

Gefitinib	132	126	114	73	41	17	0	0
C / P	129	123	105	67	38	15	1	0

EGFR mutation negative



Gefitinib	91	69	44	25	13	5	0	0
C / P	85	75	55	24	9	4	0	0

Cox analysis with covariates

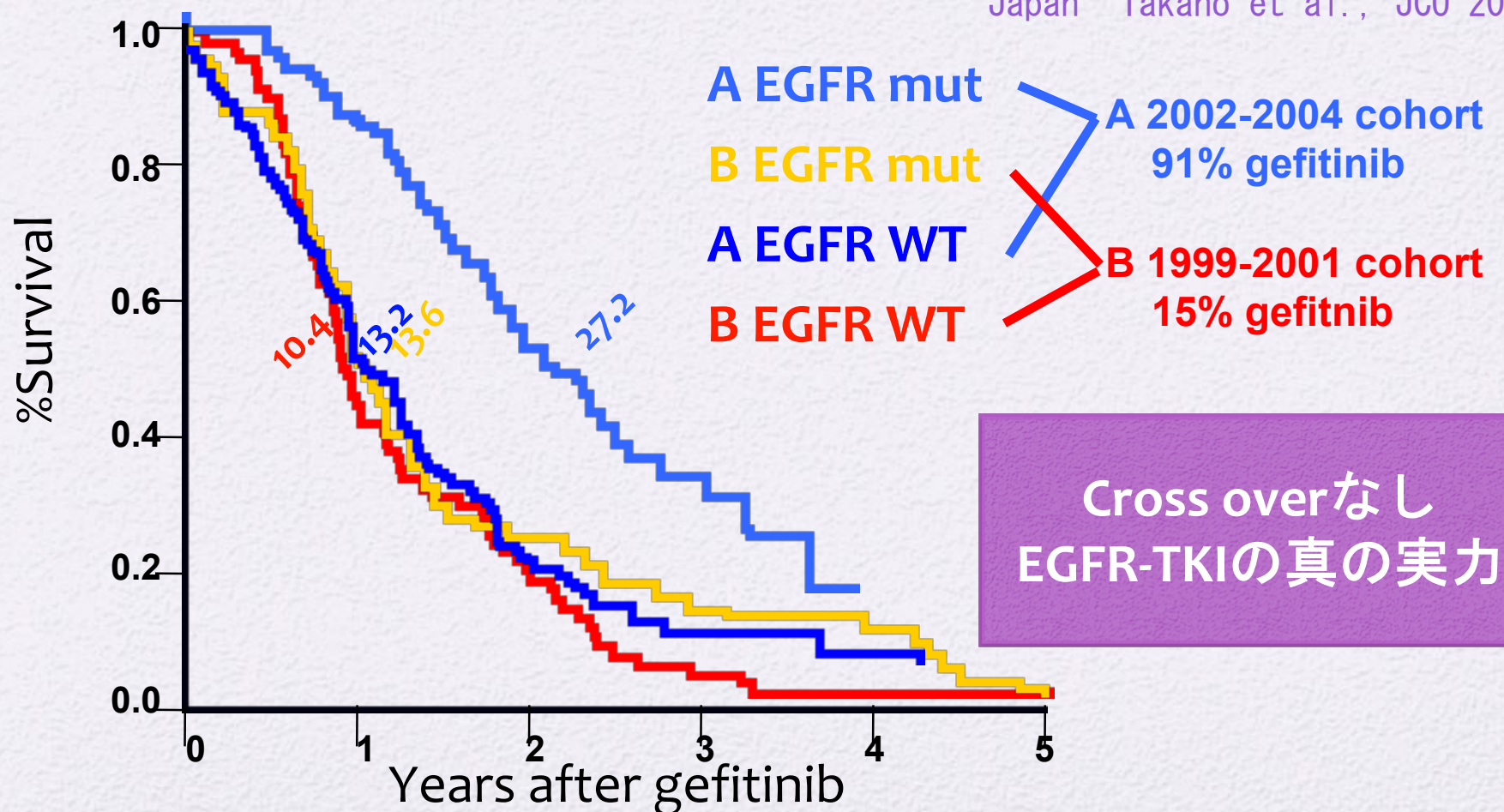
HR <1 implies a lower risk of death on gefitinib

ITT population

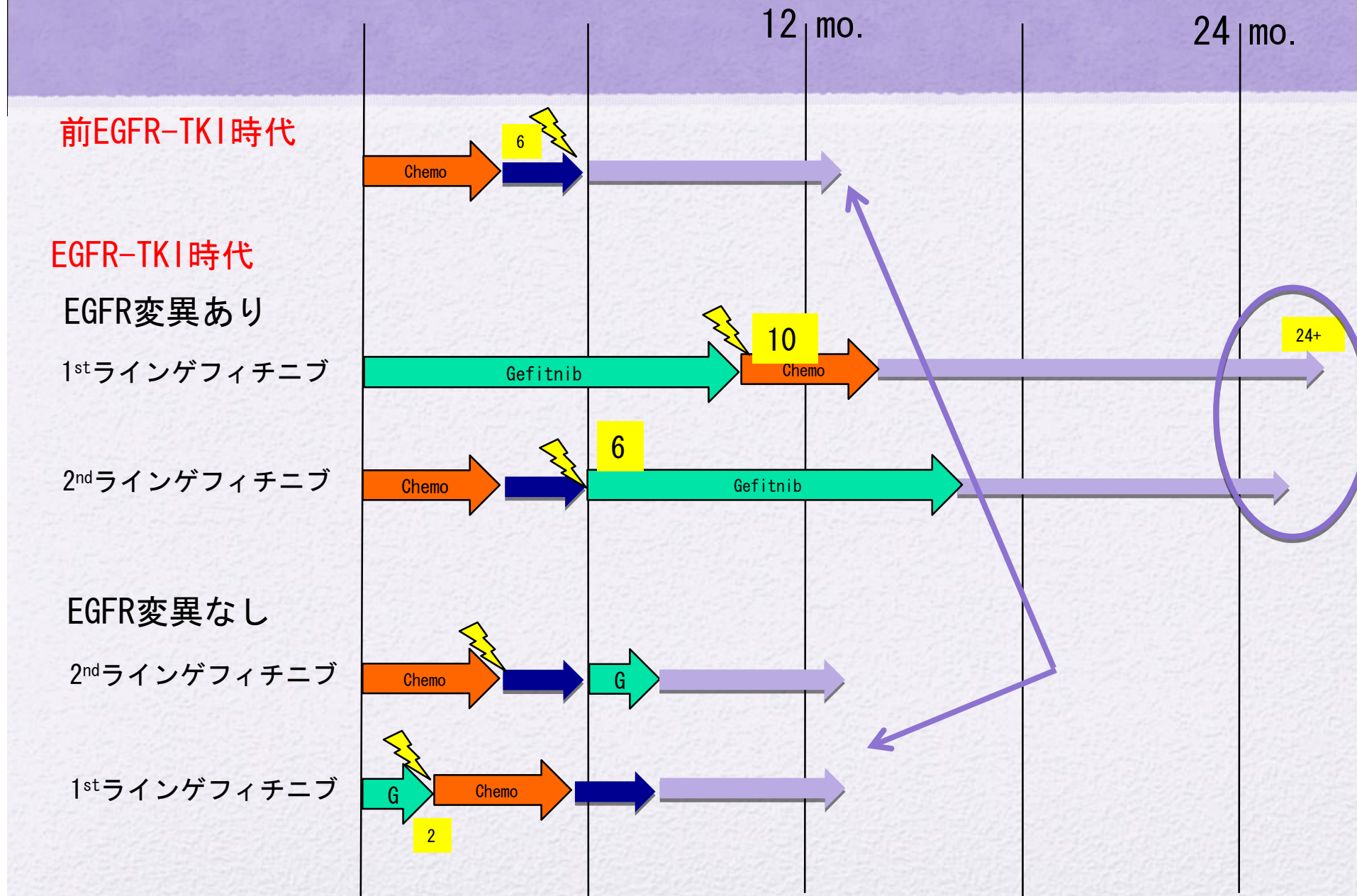
Post-hoc analysis of overall survival (follow-up ongoing) by EGFR mutation status

進行肺腺癌においてEGFR変異はゲフィチニブ治療の生存期間を予測する






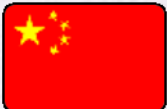
A historical comparison of patients treated before and after gefitinib approval in Japan Takano et al., JCO 2008



EGFR-TKI と非小細胞肺癌の予後

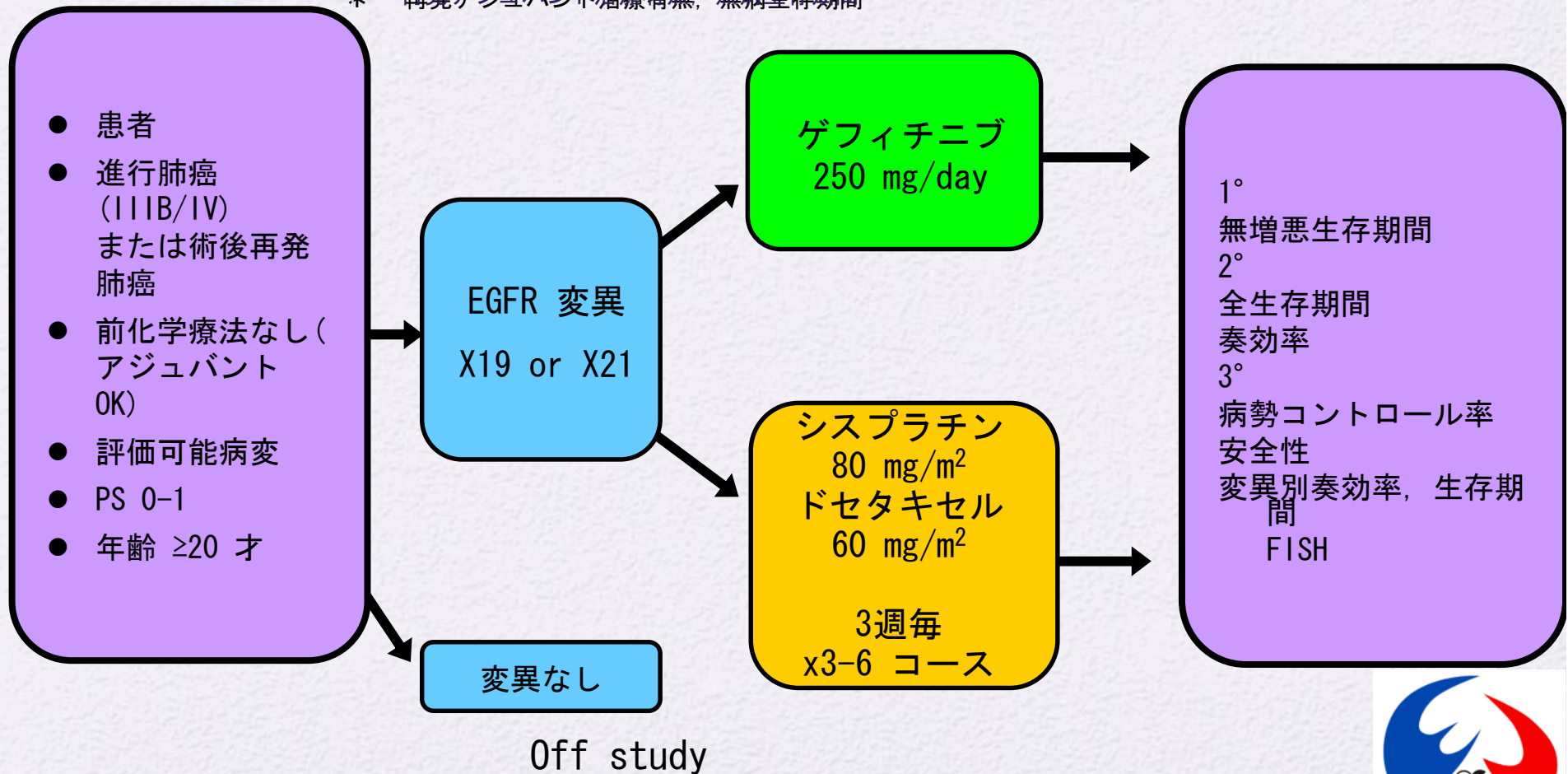


進行中のEGFR変異陽性患者を対象とした ゲフィチニブと化学療法の比較試験

	Group	Study	EGFR mutation	N	Primary endpoint	TKI	Control
		3405	X19, L858R	200 (HR=0.56)	PFS	G	CDDP+D OC
	NEJ	002	X19, L858R, G719X, L861Q	320 (HR=0.69)	PFS	G	CBDCA+P AC
	 <small>Grupo Español de Cáncer de Pulmón Spanish Lung Cancer Group</small>	EURTARC	X19, L858R	130	PFS	E	Pt doublet
	China C.Zhou	ML20981	EGFR mutation	150	PFS	E	CBDCA+ GEM

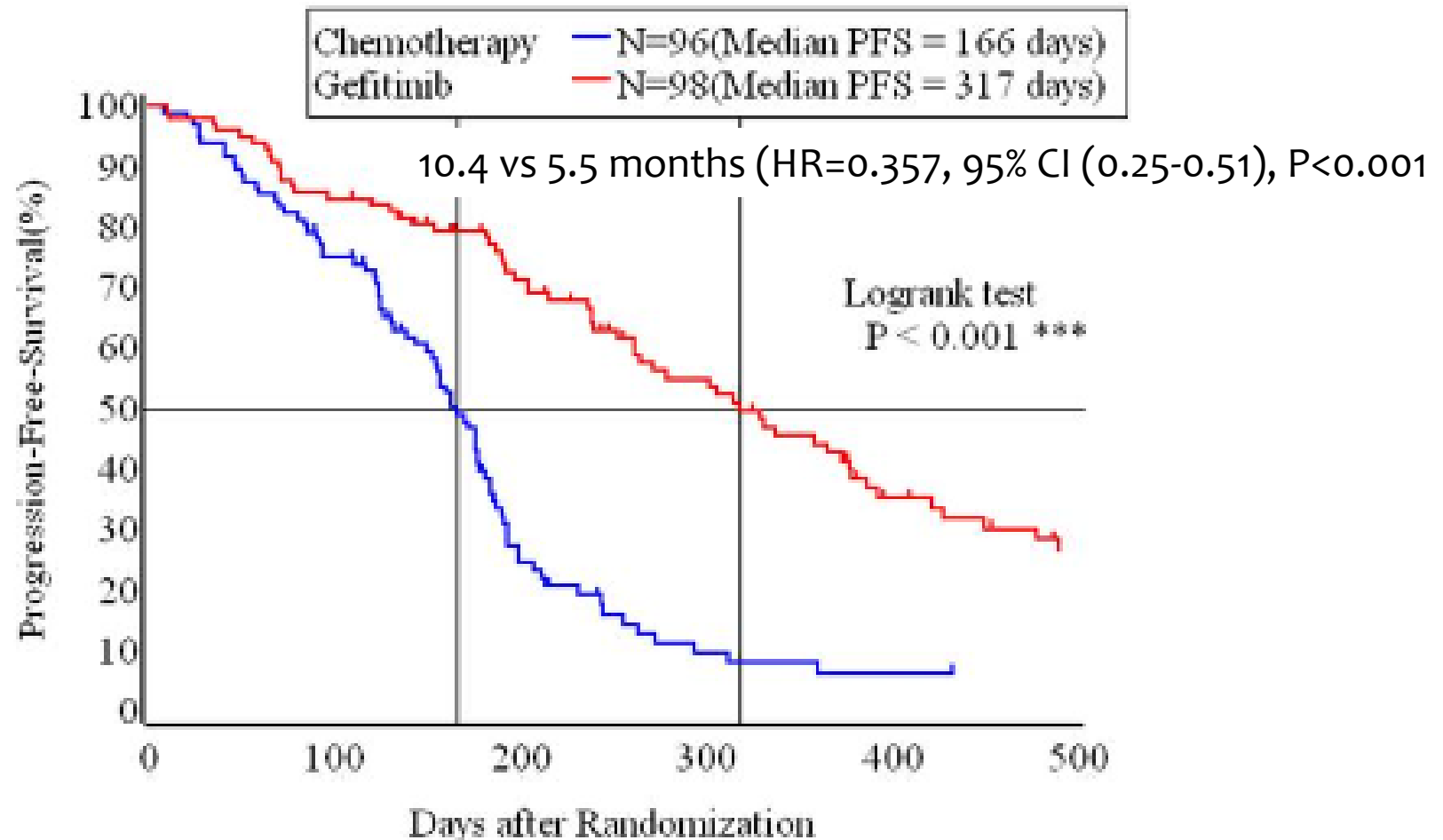
WJTOG3405

- * EGFR変異を有する患者200 名
- * 割り付け調整因子
 - * IIIB/IV 施設, 病期, 性
 - * 再発アジュバント治療有無, 無病生存期間



Progression free survival (NEJ study 002)

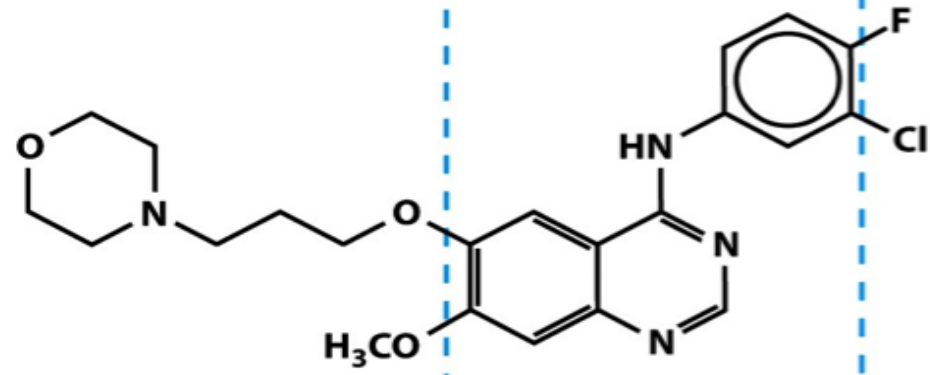
Kobayashi et al., ASCO 2009



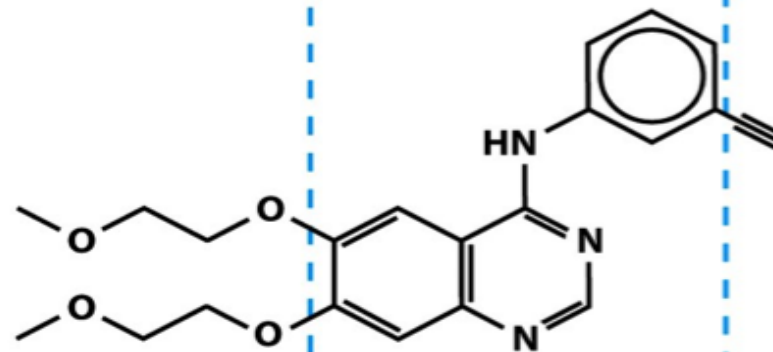
- Four patients treated by CBDCA+TXL were excluded in this analysis. These patients had no CT examination after starting chemotherapy due to no starting chemotherapy by complicating empyema and early cessation of chemotherapy (allergy of paclitaxel, early death and changing hospital).

[*North East Japan \(NEJ\) Gefitinib Study Group*](#)

ゲフィチニブとエルロチニブの違い



Iressa



Tarceva

anilinoquinazoline
skeleton

150mg エルロチニブで得られるAUCはを得るためにはゲフィチニブは700mg以上必要

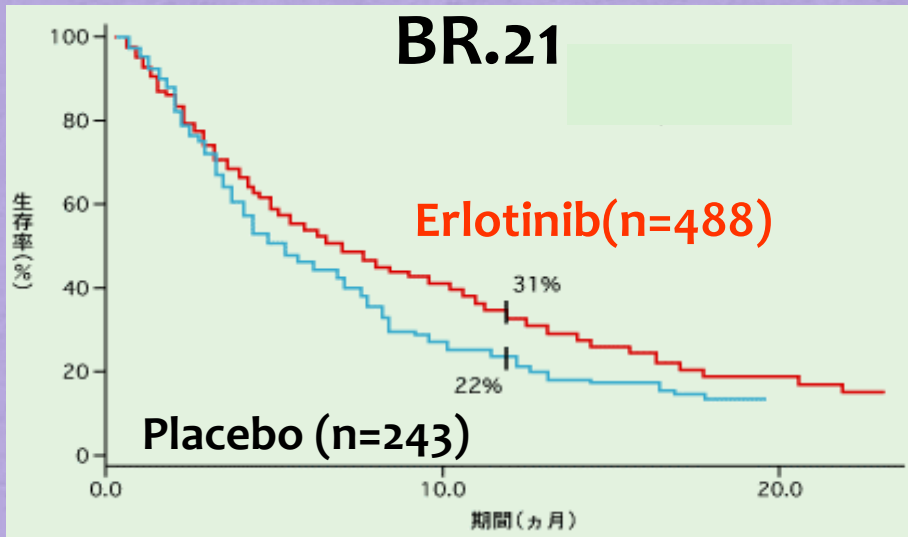


- Tarceva is administered at the maximum tolerated dose
- For gefitinib to achieve equivalent drug concentrations to Tarceva, patients would need to take >3 times the recommended dose

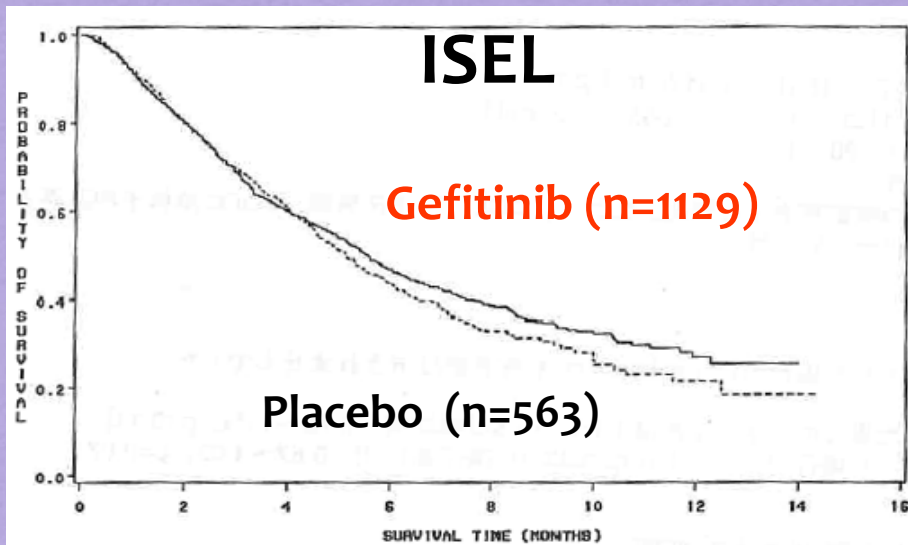
¹Hidalgo M, et al. J ClinOncol 2001;19:3267-79

²Ranson M, et al. J ClinOncol 2002;20:2240-50

化学療法不応例に対するEGFR TKI vs BSCの臨床試験



Shepherd et al., NEJM, 2005



Thatcher et al., Lancet, 2005

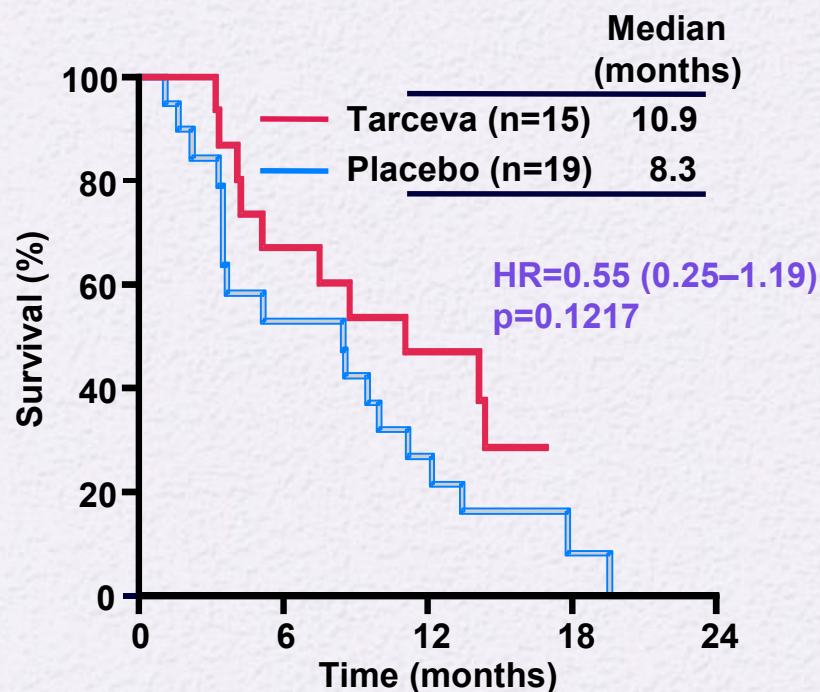
	BR21	ISEL
TKI	Erlotinib	Gefitinib
N	731	1692
RR	8.9%	8.0%
MST	6.7 M 4.7 M	5.6 M 5.1 M
HR	0.71	0.89
P	<0.0001	P=0.087
COX	-	P=0.0299

ISELとBR. 21のHazard ratioの比較



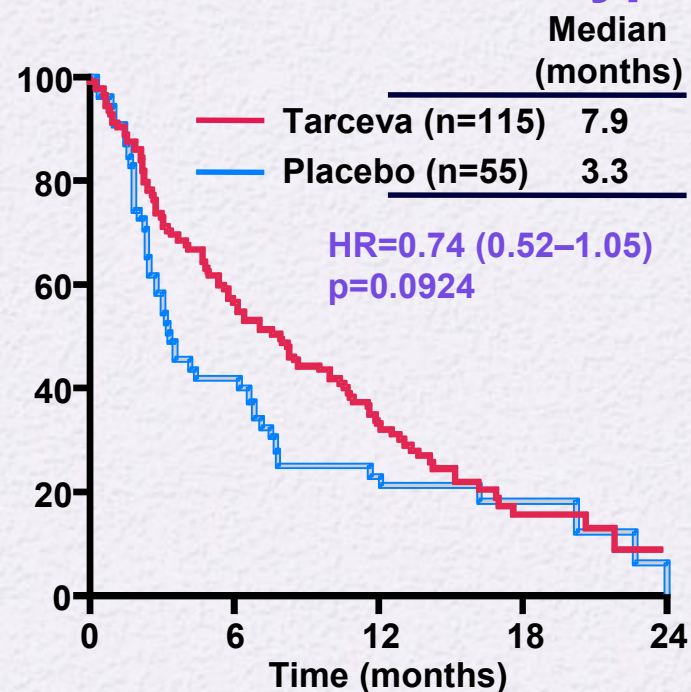
Tarcevaは変異型, 野生型EGFRの どちらの肺癌にも有効

Exon 19 or 21 mutations



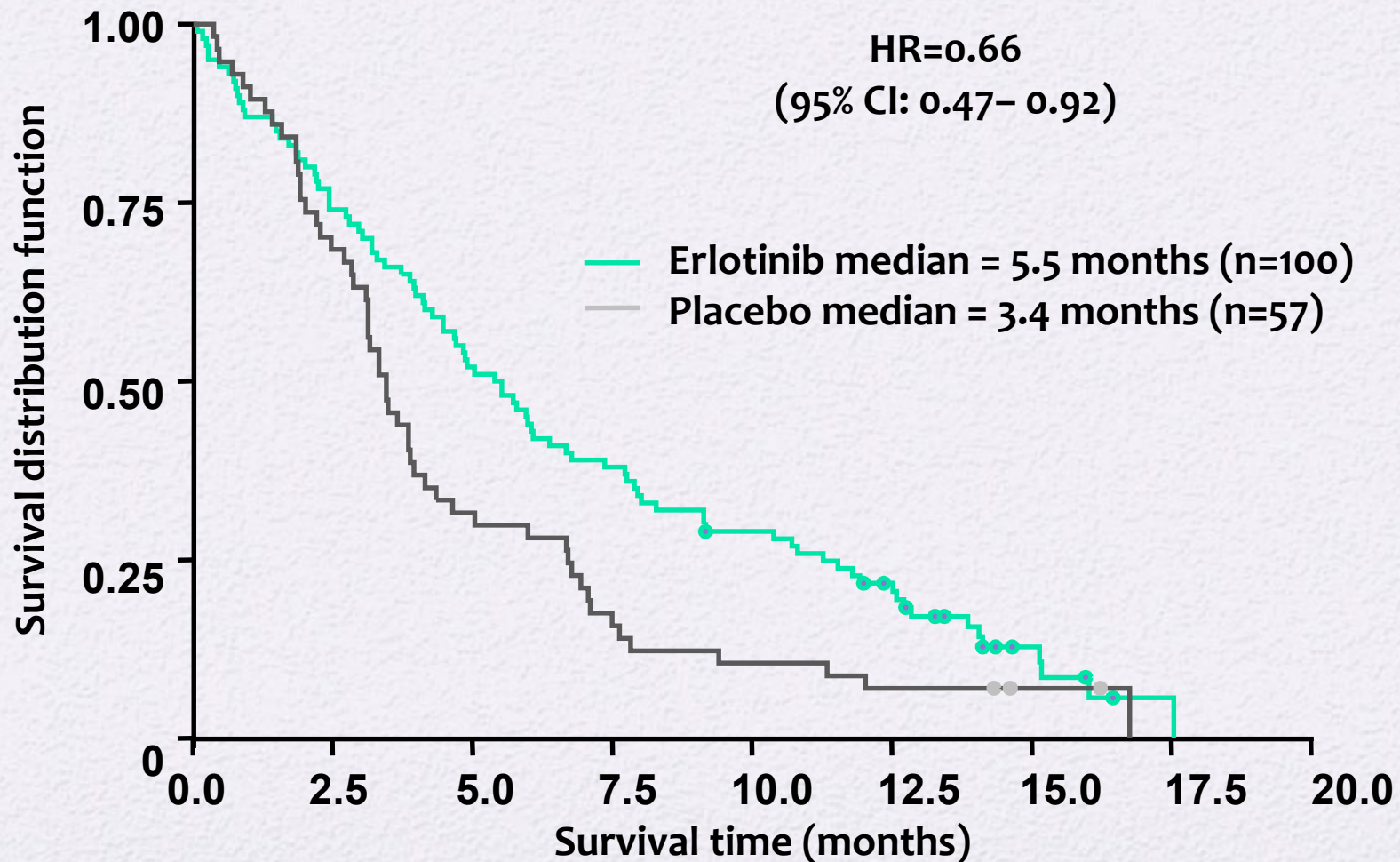
Improved survival with Tarceva in patients with mutations (not significant – small patient numbers)

EGFR wild-type

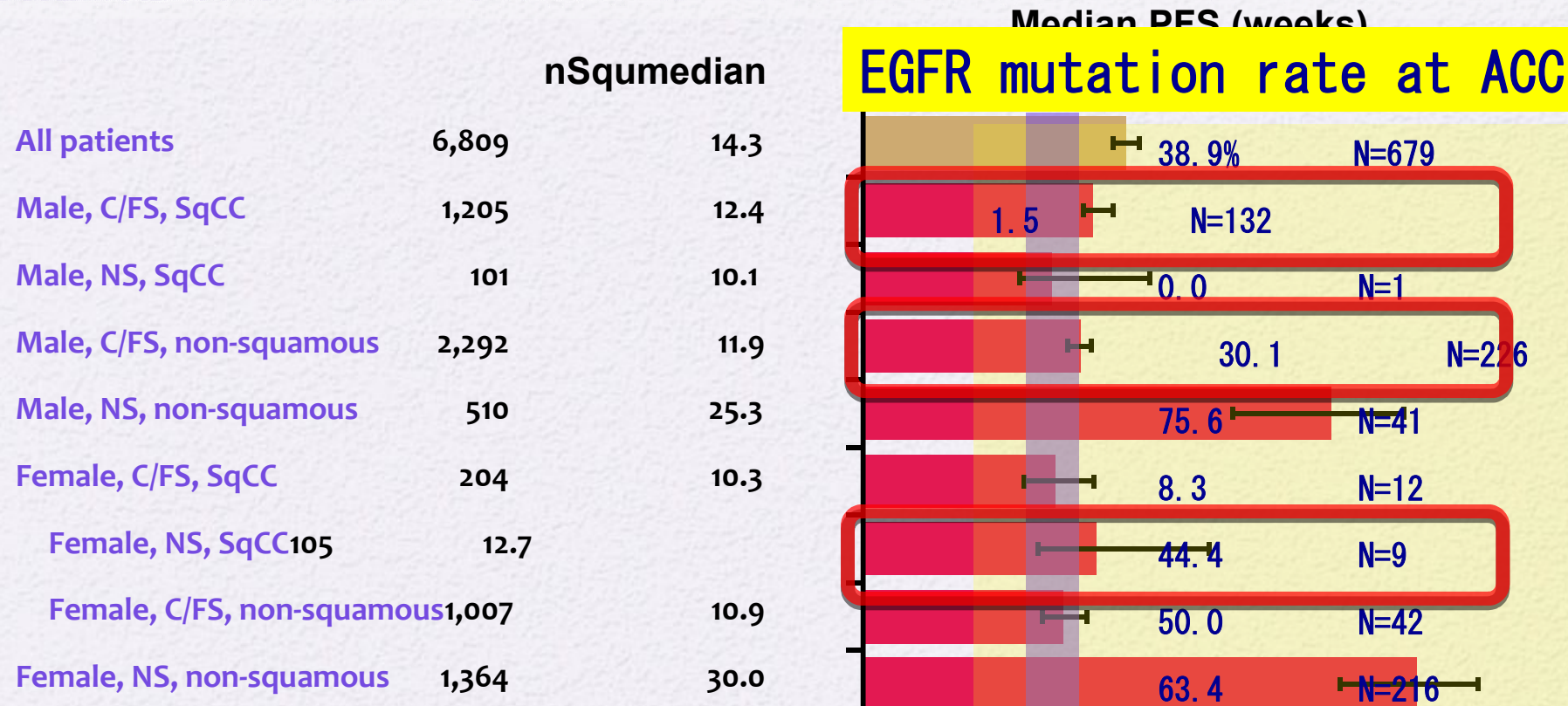


Clear trend towards improved survival with Tarceva in patients with wild-type EGFR

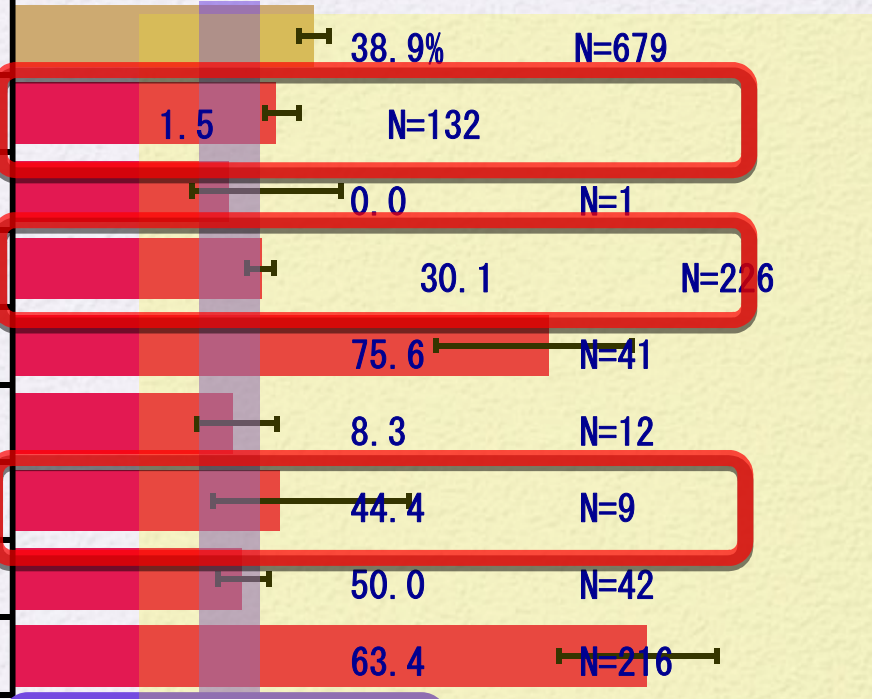
BR.21: survival benefit apparent in male smokers with squamous-cell carcinoma



Efficacy observed across patient subgroups¹ in TRUST study



Median DFS (weeks) EGFR mutation rate at ACC



Docetaxel second-line
 V15-32 (2.0 months)²
 INTEREST (2.7 months)³

C/FS = current/former smoker
 NS = never smoker
 SqCC = squamous-cell carcinoma

1. Bosquée L, et al. Ann Oncol 2008;19(Suppl. 8):99 (Abstract 261P)
2. Maruyama R, et al. J Clin Oncol 2008;26:4244-52
3. Douillard JY, et al. J Thorac Oncol 2007;2(Suppl. 4):S305 (Abstract PRS-02)

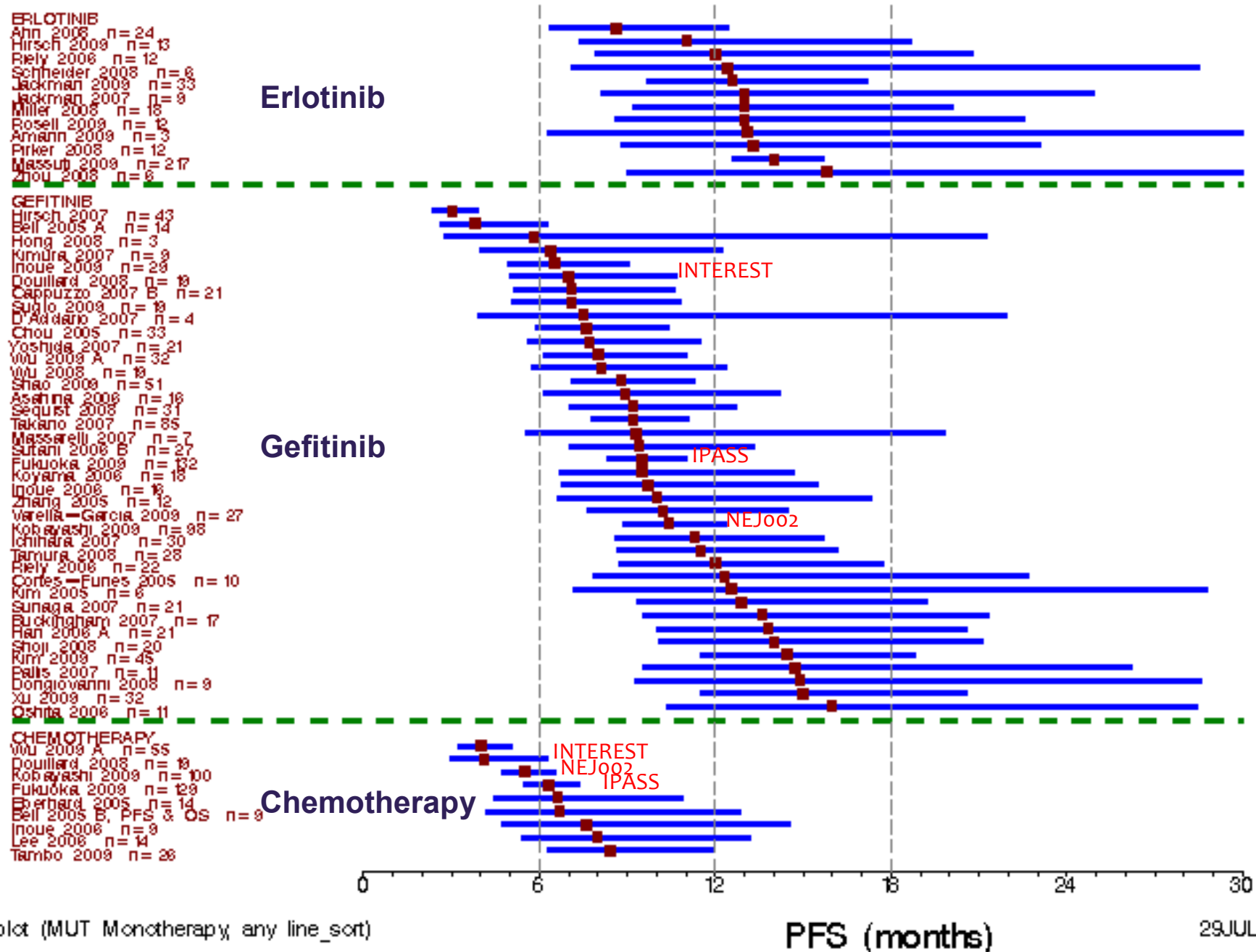


Pooled analysis of clinical outcomes in studies of patients with EGFR mutations treated with either an EGFR TKI or chemotherapy

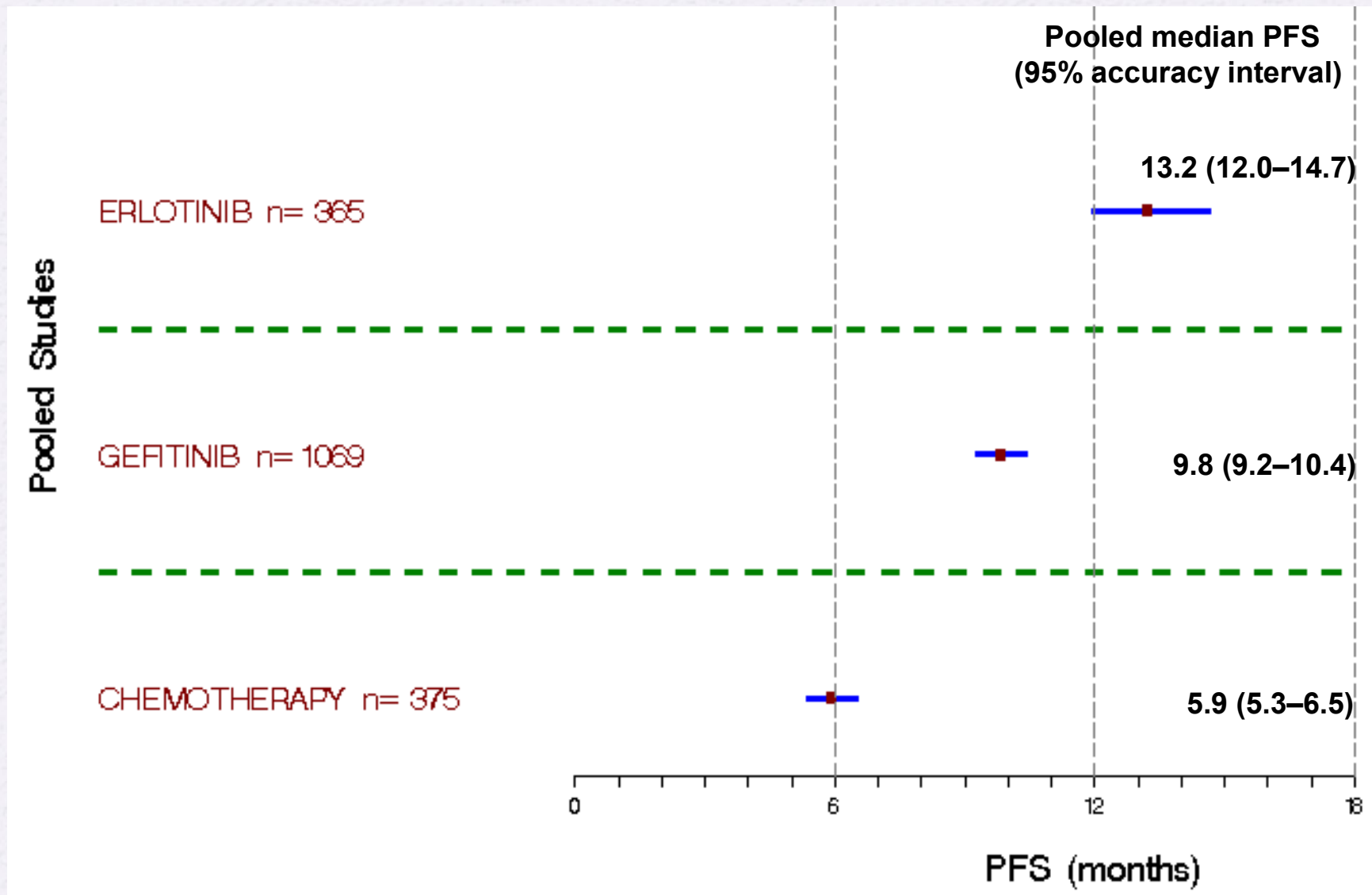
Luis Paz-Ares¹, Denis Soulières², Barbara Klughammer³, Ivan Melezínek⁴, Joachim Moecks⁵, Tony Mok⁶

¹Hospital Universitario Virgen del Rocío, Seville, Spain; ²Centre Hospitalier de l'Université de Montréal, Montréal, Canada; ³F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁴Roche Products Ltd, Welwyn Garden City, UK; ⁵BIOMCON GmbH, Mannheim, Germany; ⁶The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

Median PFS from individual studies (any line of therapy)



Pooled analysis (any line of therapy)



forestplot (pooled MUT_mono_anyline, alpha=0.05)

29JUL09

**Permutation test for estimated pooled median PFS (1,000 iterations)
EGFR TKI vs chemotherapy p=0.000 (two-sided)**

EGFRを有する癌性髄膜症患者における 高用量のゲフィチニブ治療

Modified from Jackman et al., JCO 20;24(27), 4517-20, 2006

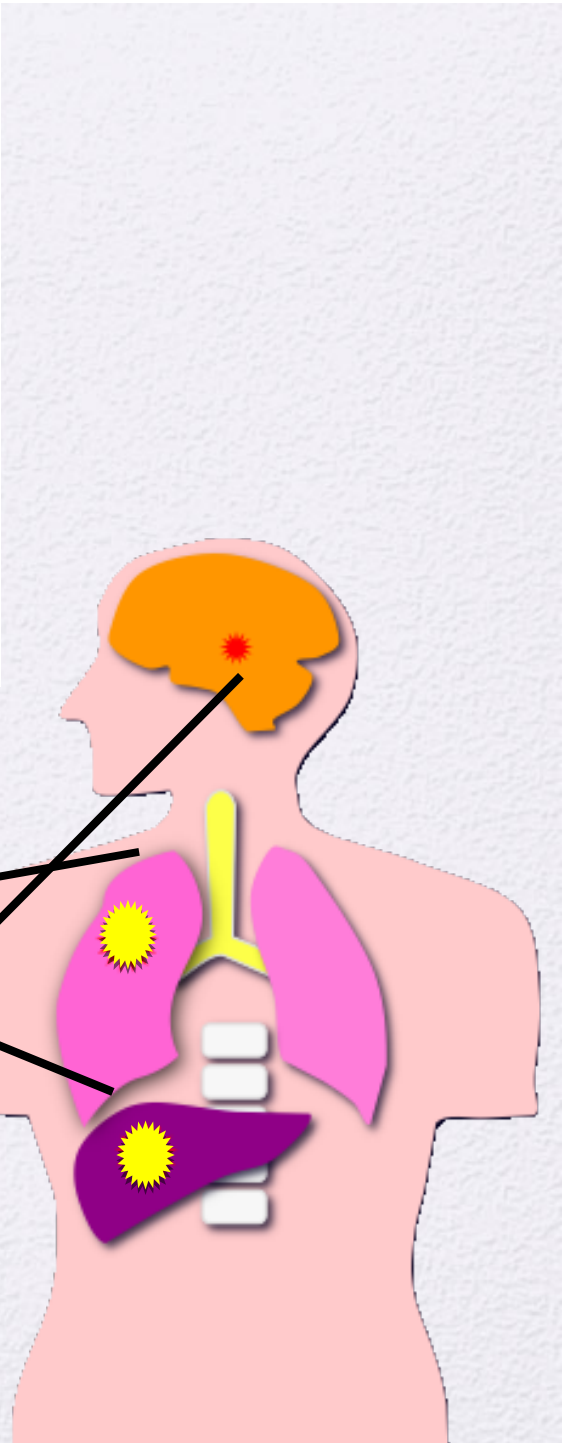
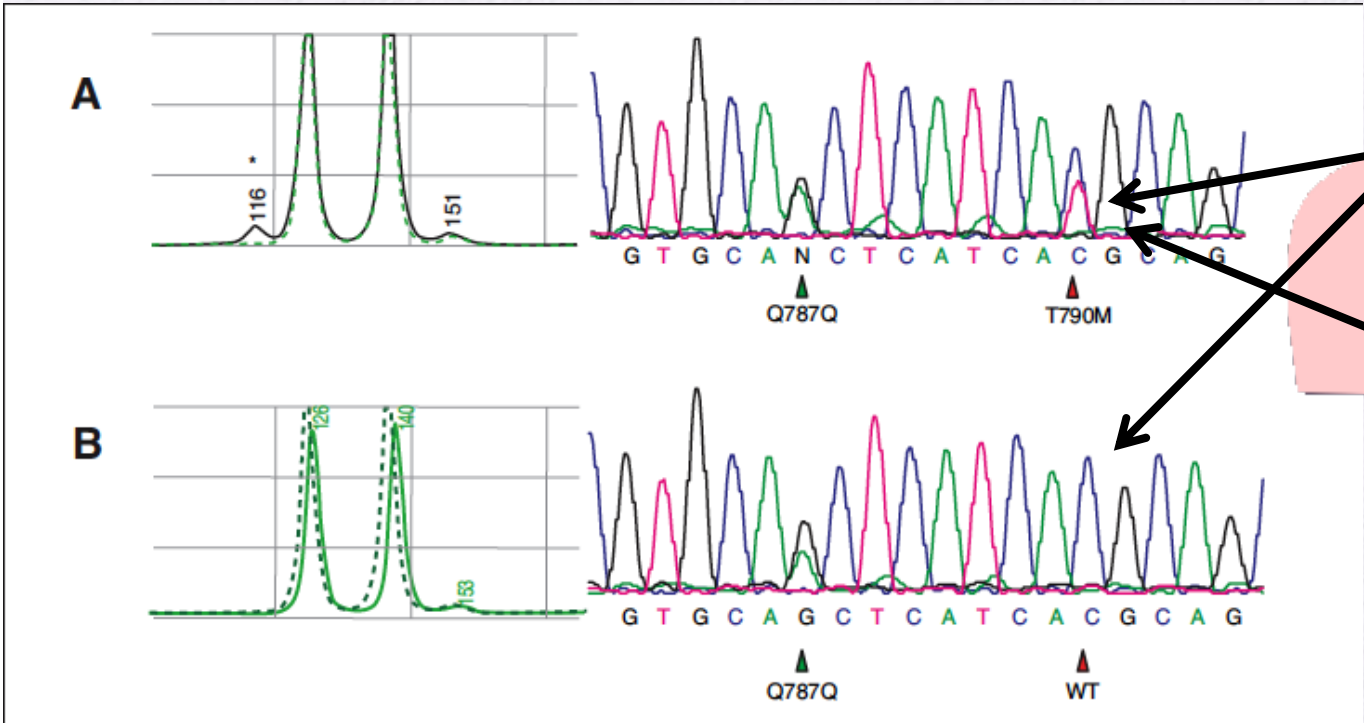
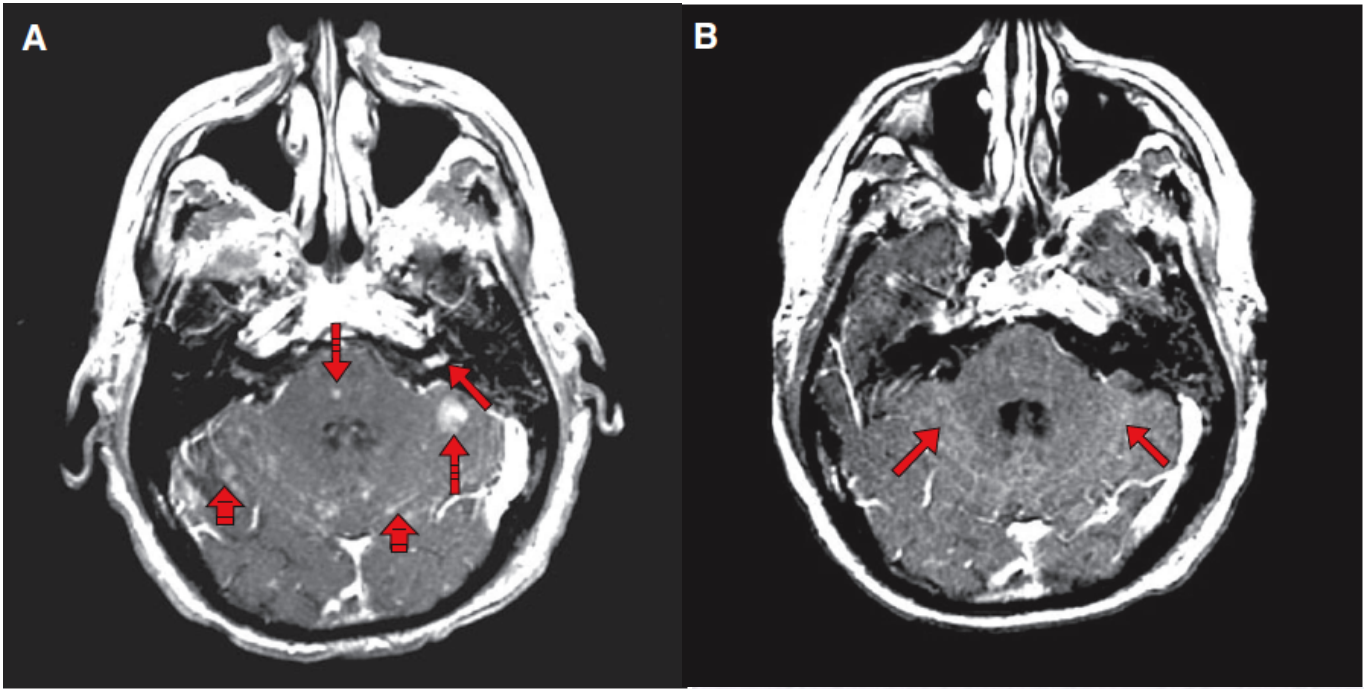
Date	Gefitinib Dose(mg)	Gefitinib concentration, CSF(nM)	CSF Cytology Result	ALT/AST (mg/dl)
Sep.5,2004	500	6.2	-	18/15
Sep.21,2004	500	18	+	19/15
Oct.13,2004	750	32	+	30/20
Nov.23,2004	750	NA	+	32/20
Dec.15,2004	1,000	42	-	81/57
Jan.7,2005	1,000	42	-	122/47
Feb.16,2005	1,250	39	NA	43/35

**Serum
3730nM**

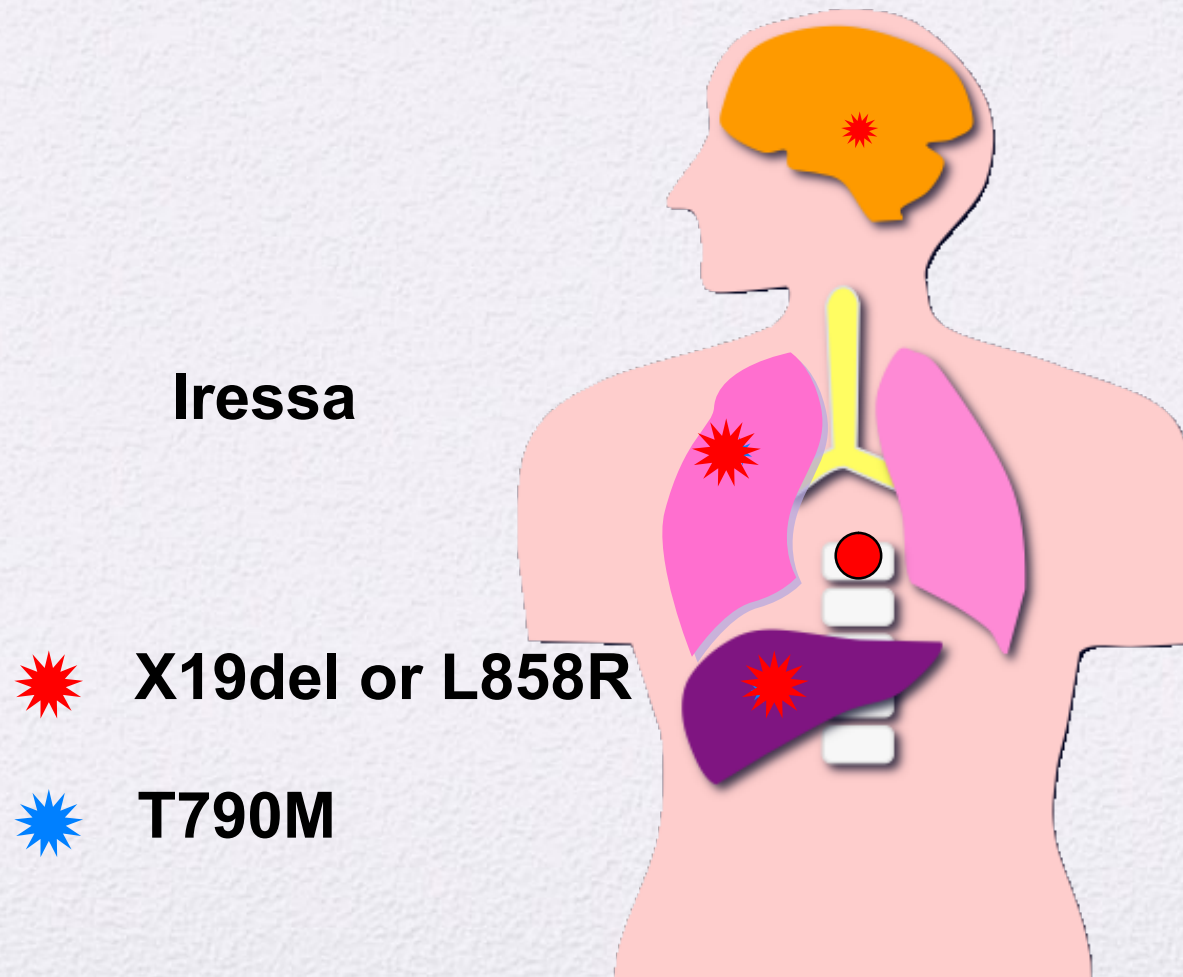
EGFR X19 del.



•Lung,liver& intestine **T790M(+)**
•CNS **T790M(-)**



EGFR mutationを有してIressaに奏効後、
CNSが増悪した症例



EGFR mutationを有してIressaに奏効後、
CNSが増悪した症例に対するTarcevaの効果

Tarceva

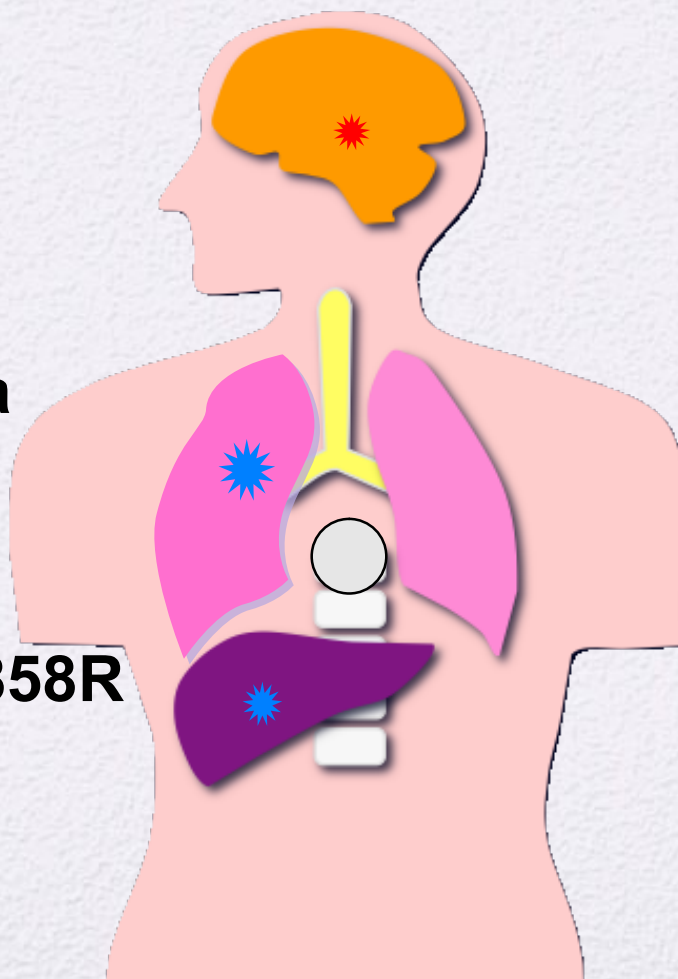
Iressa



X19del or L858R



T790M



日本肺癌学会総会 平成20年11月

ゲフィチニブが抵抗性となった後に エルロチニブを投与し有効であった 肺腺癌中枢神経転移5症例の検討

愛知県がんセンター 胸部外科¹、呼吸器内科²、遺伝子病理診断部³

片山 達也¹、清水 淳市²、須田 健一¹、福本 紘一¹、小野里 良一¹

小林 零¹、福井 高幸¹、伊藤 志門¹、波戸岡 俊三¹、篠田 雅幸¹、樋田 豊
明²、谷田部 恭³、光富 徹哉¹

症 例

症例	年齢	性別	組織型	EGFR変異	G投与時の病変部位
1	81	M	腺癌	X19 del.	脳、骨
2	63	F	腺癌	X19 del.	縦隔LN、肺、皮下
3	58	F	腺癌	L858R	脳、肺
4	60	F	腺癌	X19 del.	脳、骨
5	64	M	腺癌	NA	脳、肺
6	60	F	腺癌	L858R	肺、骨
7	61	F	腺癌	X19 del.	縦隔LN、骨

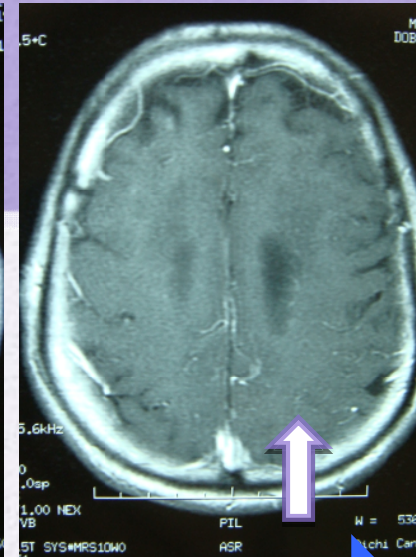
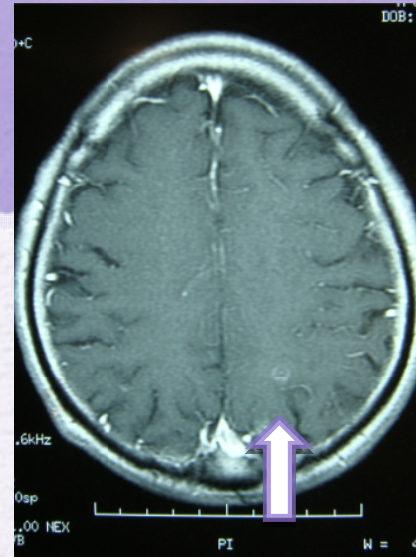
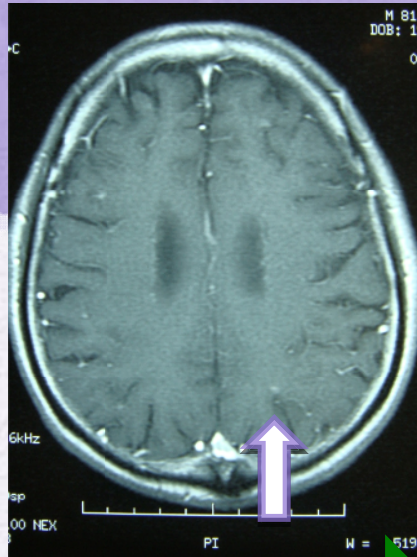
ゲフィチニブ内服後の経過

症例	G服用期間	脳外病変	中枢神経病変	中枢神経症状	投与間隔 G→E	PS
1	275日	骨 (CR)	脳転移増悪 髄膜炎	記憶力低下 歩行障害	35日	4
2	516日	縦隔LN、肺 皮下 (PR)	多発脳転移出現	意識障害	2日	3
3	113日	肺 (SD)	脳転移増悪 髄膜炎	頭痛 姿勢保持困難	47日	4
4	1211日	肺 (SD)	髄膜炎へ移行	失神発作 複視	5日	1
5	192日	肺 (PR)	脳転移巣再増悪	意識障害 歩行障害	2日	3
6	242日	肺, 骨 (NA)	多発脳転移出現	記憶障害 歩行障害	8日	4
7	382日	縦隔LN、骨 (CR)	髄膜炎へ移行	頭痛、吐き気	1日	3

A

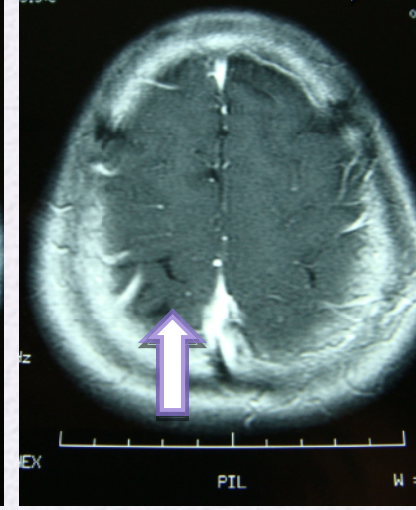
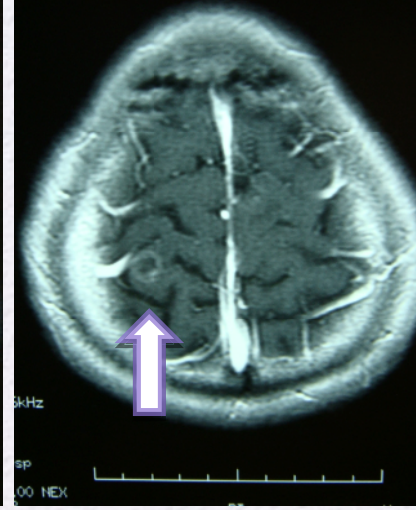
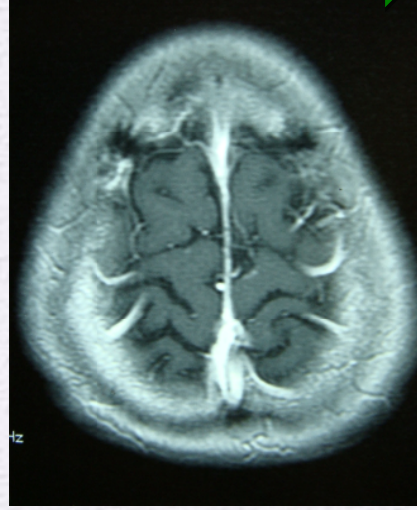
B

C



Iressa →

→ **Tarceva**



Nov. 2007

Jan. 2008

May. 2008

エルロチニブ内服後の経過

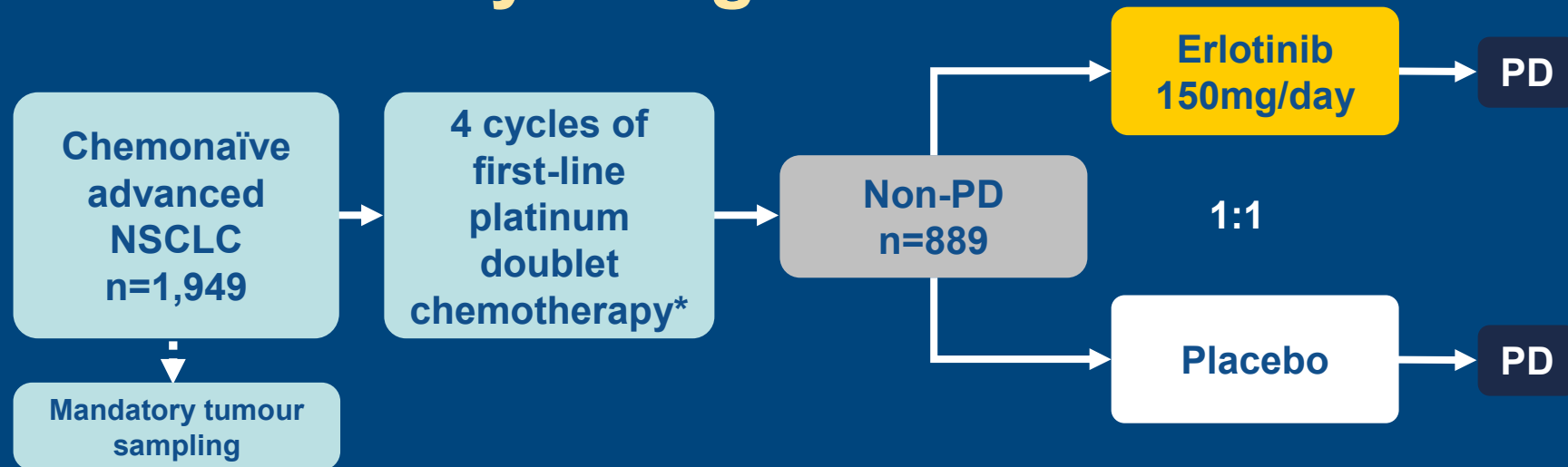
症例	E服用期間	脳転移巣への効果	症状	PS	CEA	有害事象
1	178日	腫瘍縮小	意識障害改善	4→4	43.6 →11.5	皮疹 FN
2	247日	変化なし	意識障害改善	3→1	451.0 →7.1	皮疹
3	60日	変化なし	頭痛、 レベル改善	4→3	67.0 →47.6	-
4	530日	腫瘍縮小	複視が改善	1→1	3429.5 →1294.5	皮疹 下痢
5	88日	腫瘍縮小	ADL改善	4→2	NA	皮疹
6	15日	変化なし	悪化	4→4	17.4 →9.5	-
7	23日	NA	悪化	3→4	136.7 →110.8	-

SATURN: a double-blind, randomized, phase III study of maintenance erlotinib versus placebo following non-progression with 1st-line platinum-based chemotherapy in patients with advanced NSCLC

Federico Cappuzzo¹, Tudor Ciuleanu², Lilia Stelmakh³, Saulius Cicenas⁴, Aleksandra Szczesna⁵, Erzsebet Juhasz⁶, Emilio Esteban Gonzalez⁷, Olivier Molinier⁸, Gaelle Klingelschmitt⁹, Giuseppe Giaccone¹⁰, on behalf of the SATURN investigators

¹Istituto Clinico Humanitas IRCCS, Rozzano (Milan), Italy; ²Institute of Oncology Ion Chiricuta, Cluj-Napoca, Romania; ³Pavlov State Medical University, St Petersburg, Russian Federation; ⁴Institute of Oncology, Vilnius University, Vilnius, Lithuania; ⁵Mazowieckie Centrum Leczenia Chorob Pluc I Gruzlic, Otwock, Poland; ⁶Koranyi National Institute for Pulmonology, Budapest, Hungary; ⁷Hospital Universitario Central de Asturias, Oviedo, Spain; ⁸Centre Hospitalier Le Mans, Le Mans, France; ⁹F. Hoffmann-La Roche Ltd, Basel, Switzerland; ¹⁰CCR, National Cancer Institute, NIH, Bethesda, MD

SATURN study design



Stratification factors:

- EGFR IHC (positive vs negative vs indeterminate)
- Stage (IIIB vs IV)
- ECOG PS (0 vs 1)
- CT regimen (cis/gem vs carbo/doc vs others)
- Smoking history (current vs former vs never)
- Region

Co-primary endpoints:

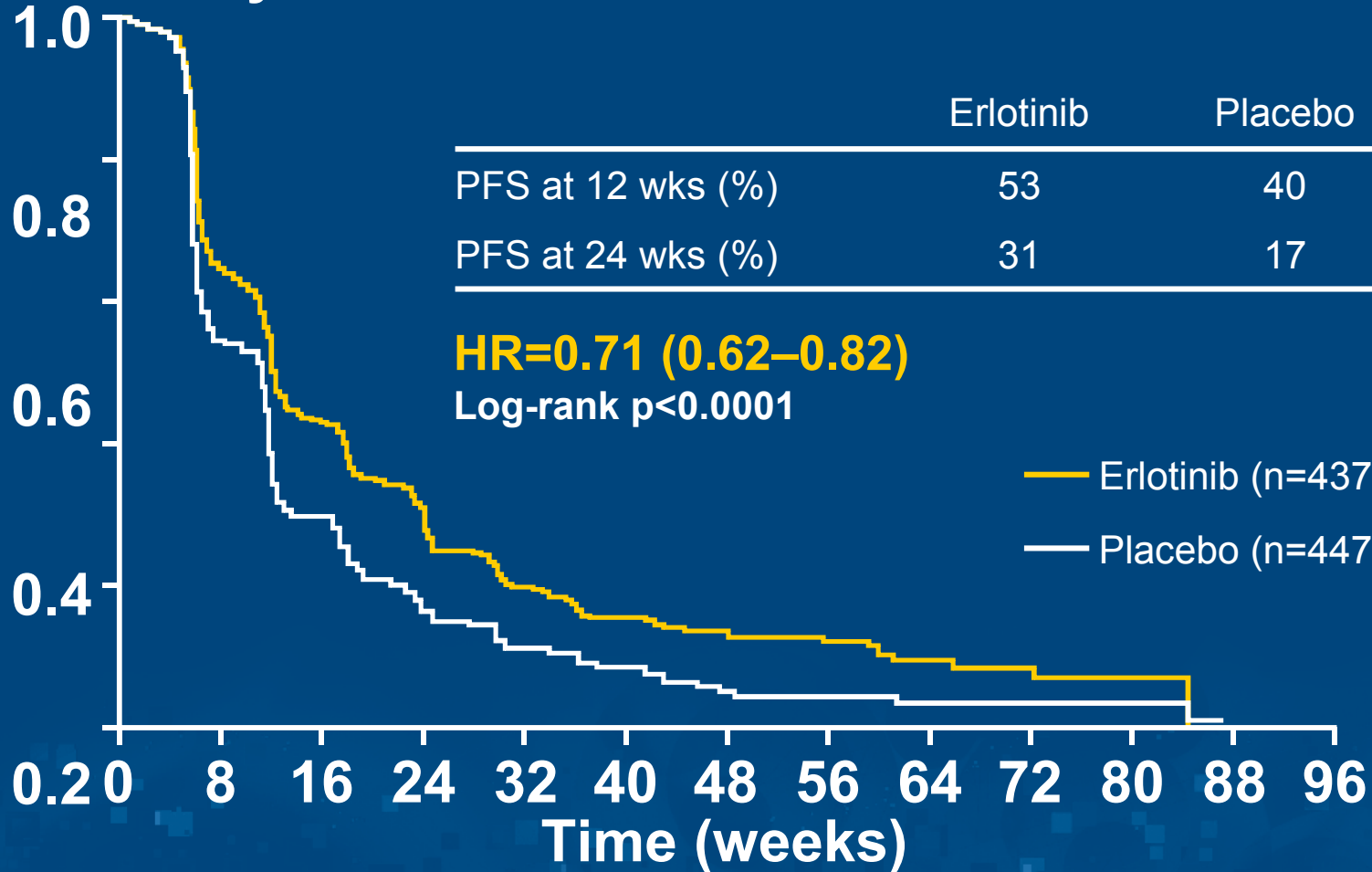
- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

Secondary endpoints:

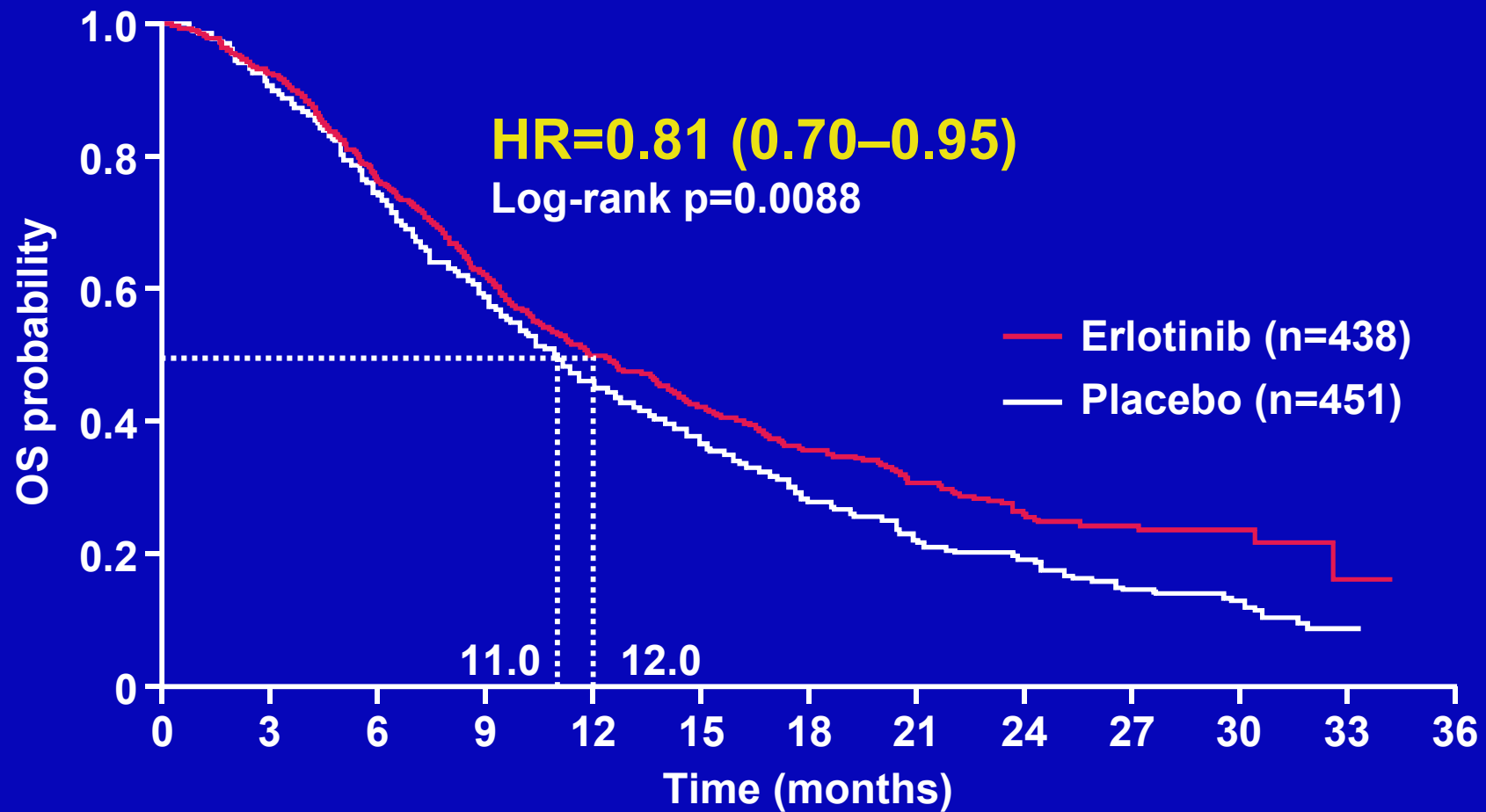
- OS in all patients and those with EGFR IHC+ tumours, OS and PFS in EGFR IHC- tumours; biomarker analyses; safety; time to symptom progression; QoL

PFS*: all patients (ITT)

PFS probability



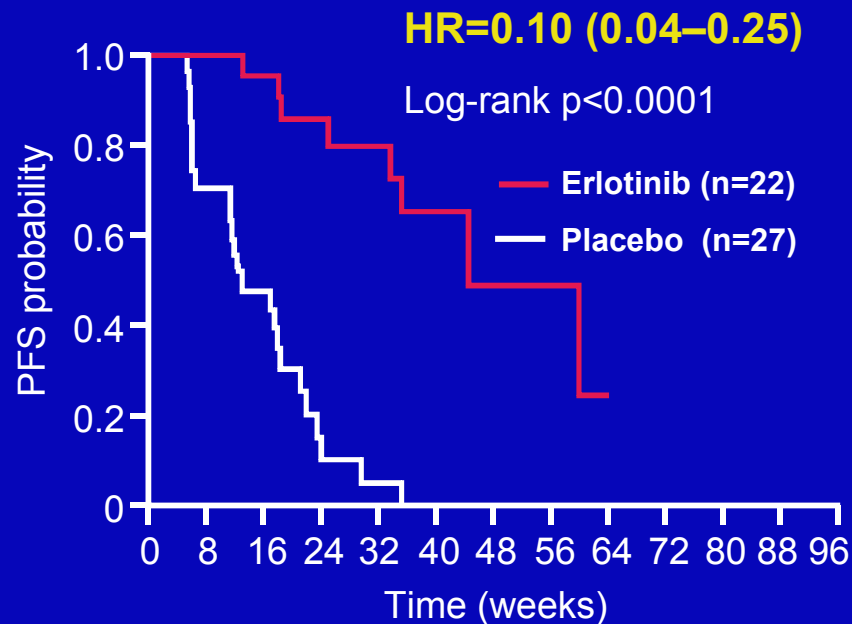
OS*: all patients (ITT)



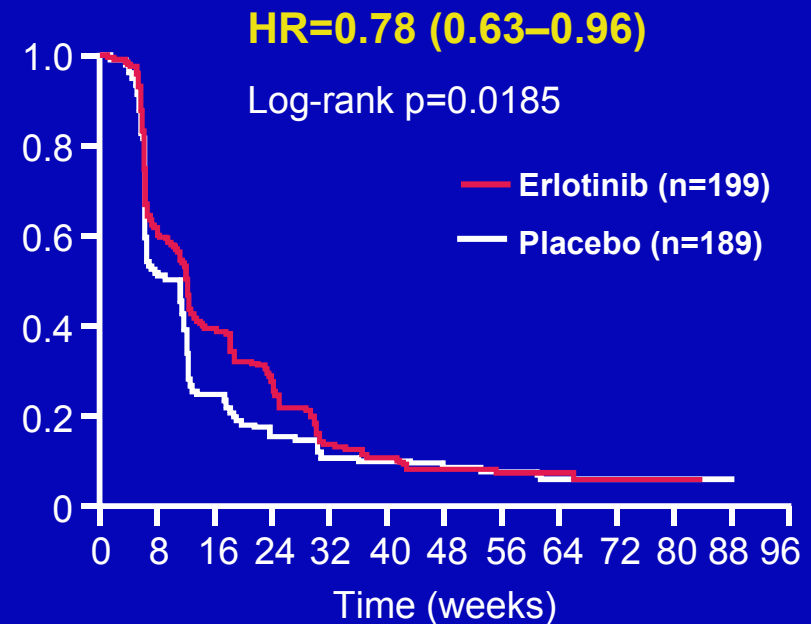
*OS is measured from time of randomisation into the maintenance phase;
ITT = intent-to-treat population

Largest benefit with erlotinib in patients with *EGFR* mutated tumours

EGFR mutation+

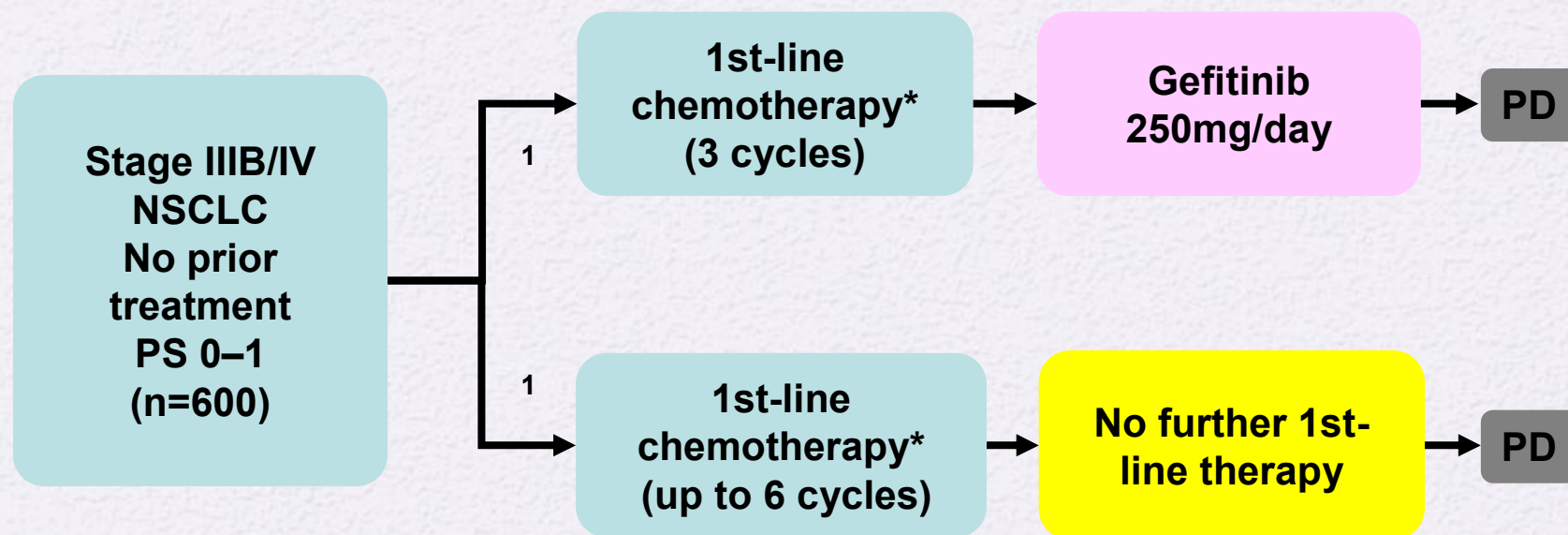


EGFR wild-type



Interaction p<0.001

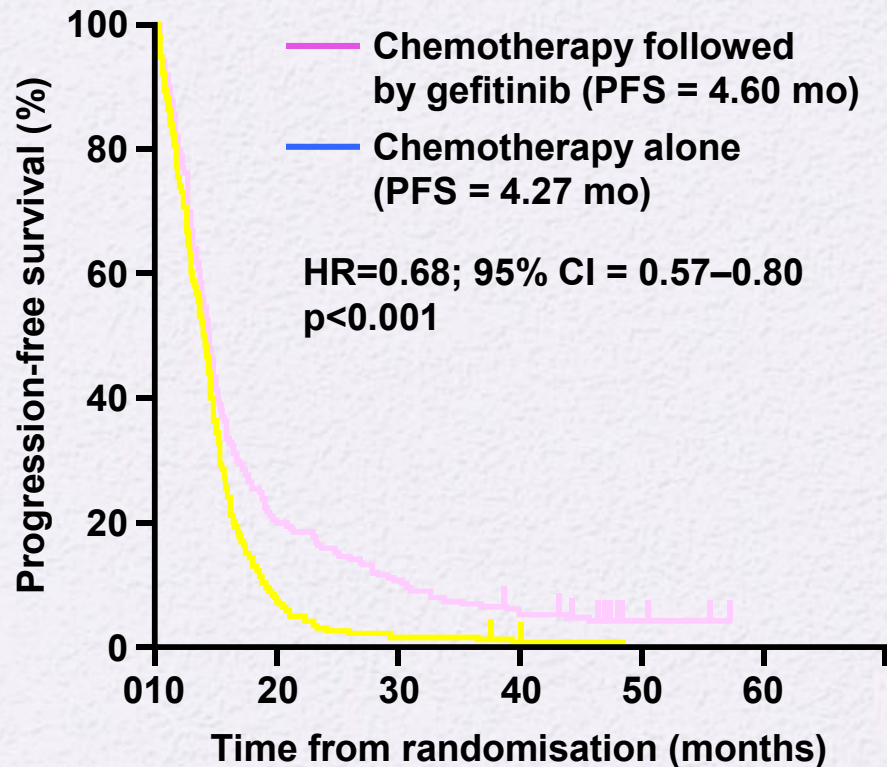
Immediate sequential use of EGFR TKI: WJTOG0203 (Japan) study design



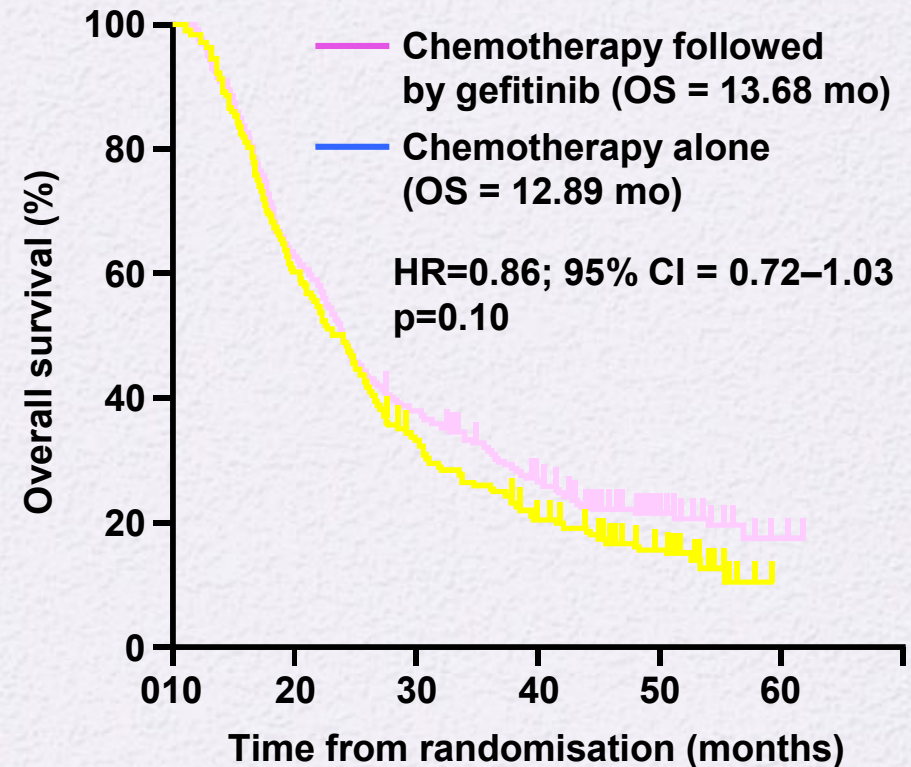
*carboplatin + paclitaxel; cisplatin + irinotecan; cisplatin + vinorelbine; cisplatin + gemcitabine; cisplatin + docetaxel

Gefitinib as immediate sequential therapy

Progression-free survival



Overall survival



■ Maintenance gefitinib

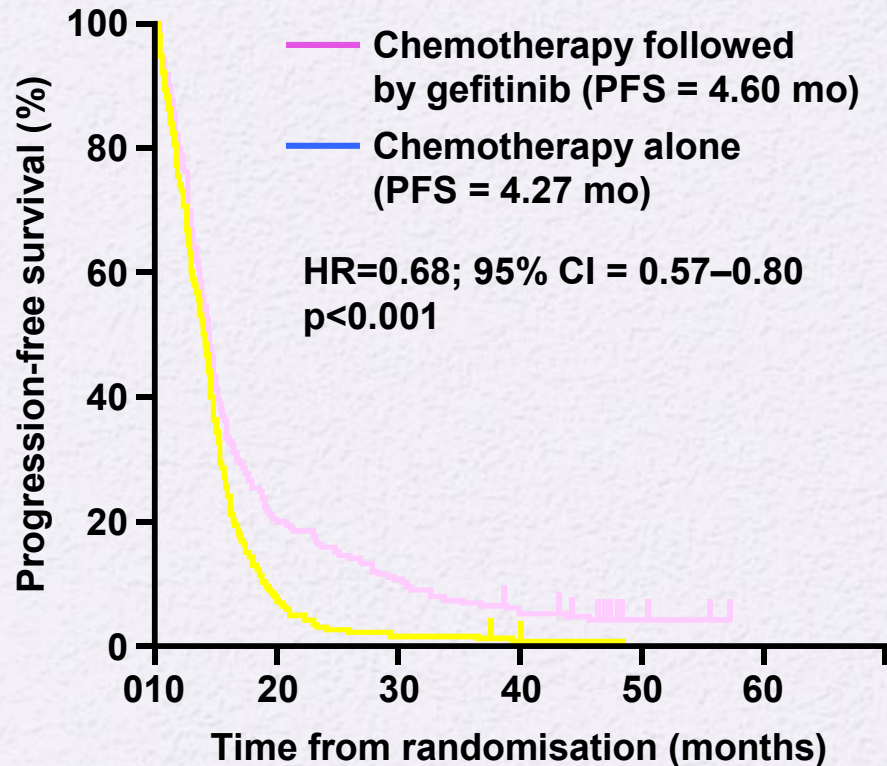
■ prolonged PFS

■ failed to improve OS (primary endpoint)

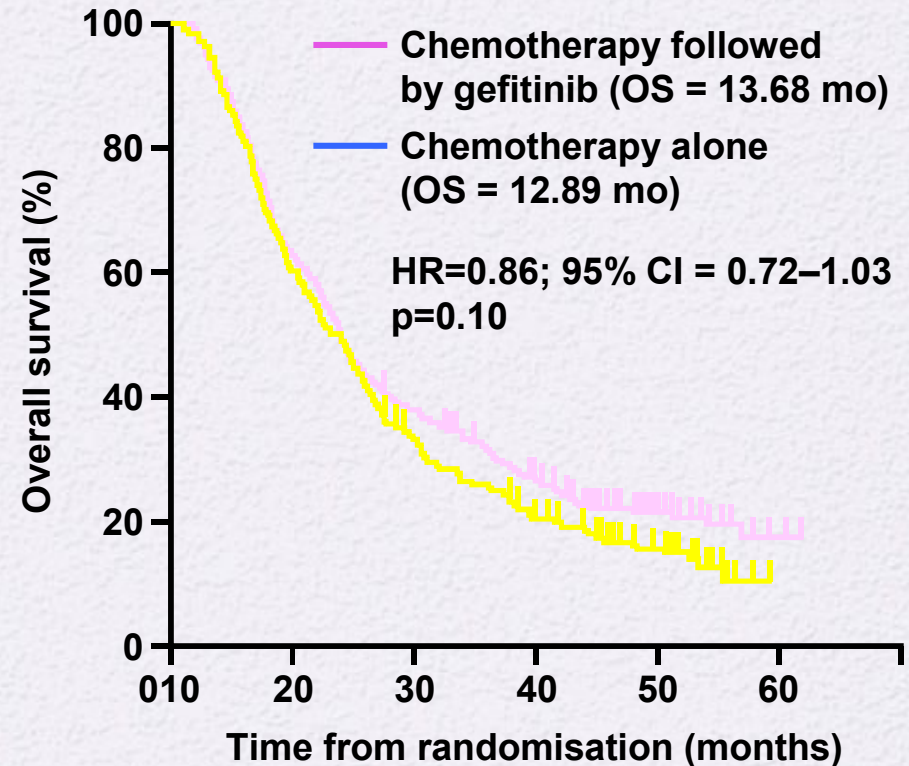
Hida, T et al. J Clin Oncol
2008;26(Suppl. 15 Pt I): 427s
Abs. LBA8012

Gefitinib as immediate sequential therapy

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Overall survival



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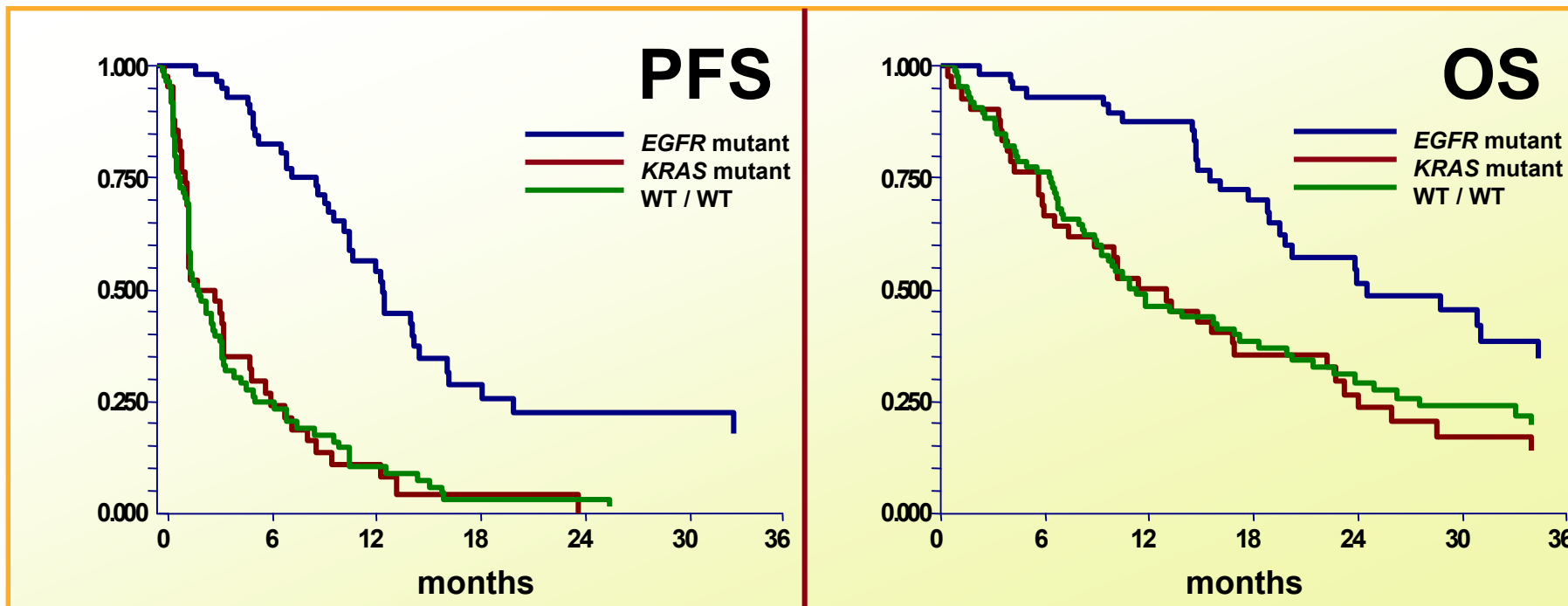
Results of EGFR-TKI maintenance trials

Trial	Line	Experimental	Control	N	PFS	OS
SWOG 0023	1st	PE/RT->DOC->G	PE/RT->DOC->Placebo	243	Exp 8m, Cont 12m P=0.17	Exp 23m, Cont 35m P=0.013
WJTOG 0203	1st	Pt doublet->G	Pt doublet	600	HR 0.68 P<0.001	HR 0.86 P=0.10
FASTACT	1st	Pt+Gem+E->E	Pt+Gem+placebo	152	HR 0.47 P=0.0002	HR 1.09 P=0.42
BeTA	2nd	E+Bev	E+placebo	636	HR 0.62 P<0.0001	HR 0.97 P=0.8573
SATURN	1st	Pt doublet->E	Pt doublet->placebo	194 9	HR 0.71 P<0.0001	
ATLAS	1st	CTx+Bev-->E+Bev	CTx+Bev-->Placebo+Bev	1150	HR 0.722 P=0.0012	

K-ras mutations as a negative predictive biomarker for EGFR-TKI

Author	Journal	TKI	Response rate	
			Mutation	Wild-type
Pao	2005 ProsMed	Gefitinib	0/5	12/19
		Erlotinib	0/4	9/31
Endoh	2006 JTO	Gefitinib	0/6	24/46
Giaccone	2006 CCR	Erlotinib	0/10	4/15
Han	2006 CCR	Gefitinib	0/9	16/60
Jackman	2007 JCO	Erlotinib	0/6	5/35
Cappuzzo	2007 JCO	Gefitinib	0/1	
Massrelli	2007 CCR	G or E	0/16	7/54
Hirsch	2007 Ann Oncol	Gefitinib	2/36	19/102
Zandwijk	2007 Ann Oncol	Gefitinib	0/3	3/12
Miller	2008 JCO	Erlotinib	0/18	20/62
Sugio	Unpublished	Gefitinib	0/4	15/27
Total			2/118 (1.7%)	134/463 (28.8%)

Impact of EGFR and KRAS Jackman et al., WC



	<i>EGFR sensitizing / KRAS wild-type</i>	<i>EGFR wild-type / KRAS positive</i>	<i>EGFR wild-type / KRAS wild-type</i>	P
N	59	42	85	
Response	68% (40/59)	0 (0/42)	5% (4/85)	< .0001
PFS, months	13.0	2.3	2.3	< .0001
OS, months	24.5	11.4	11.3	.0005

TRUST study

Effect of EGFR and KRAS mutation

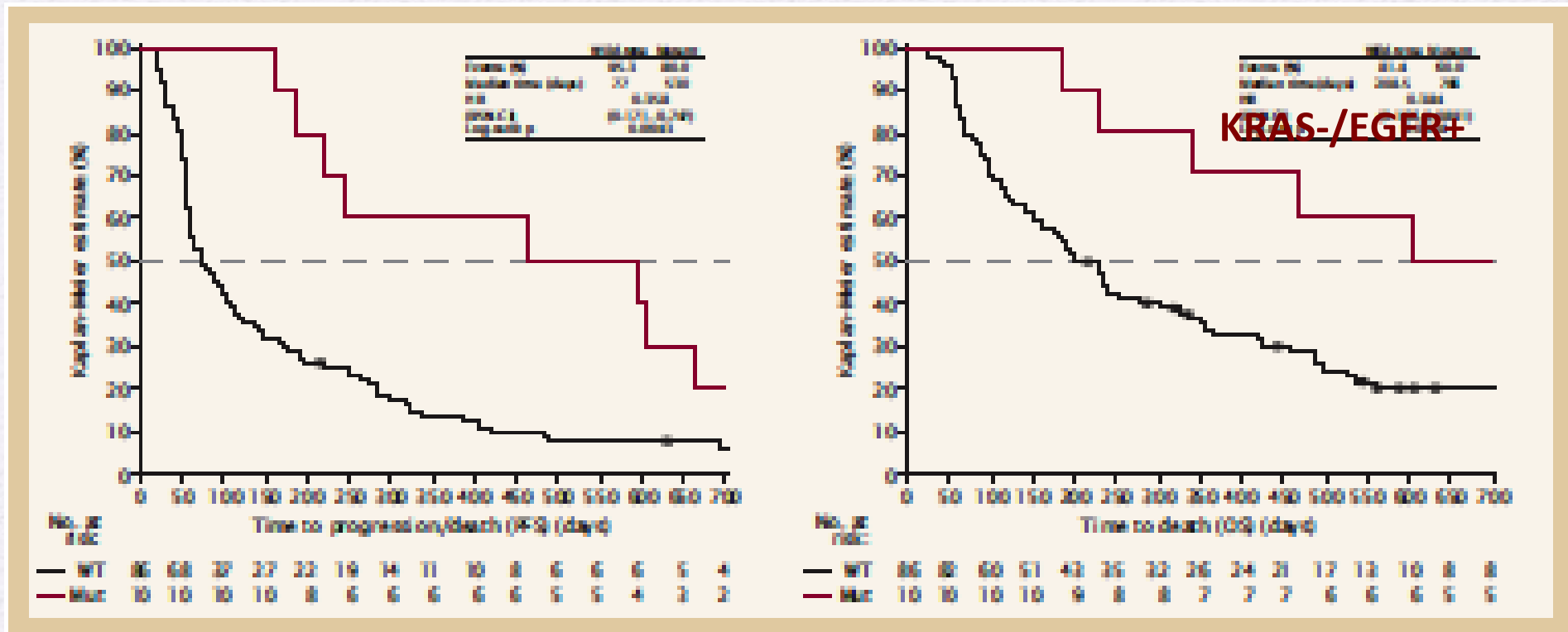
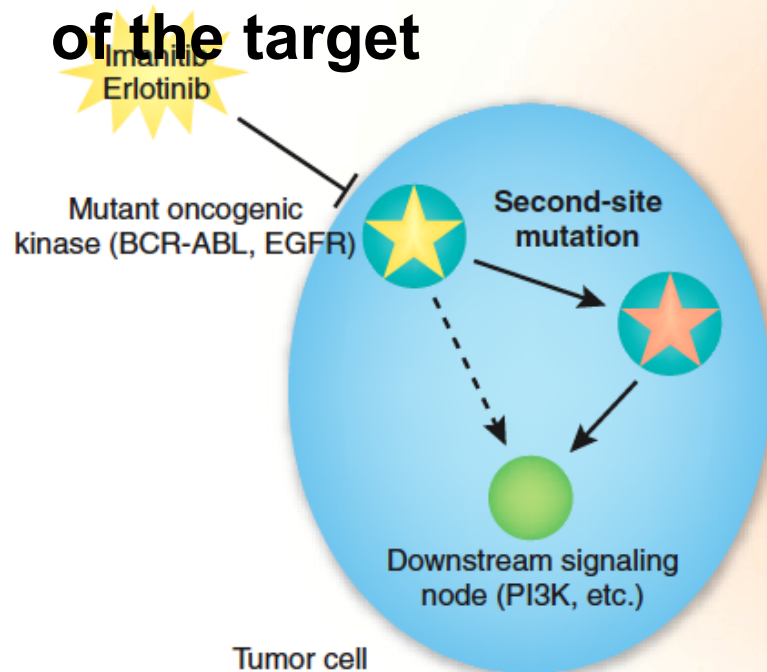


Figure 4. EGFR mutation status relative to PFS and OS in KRAS wild-type patients.

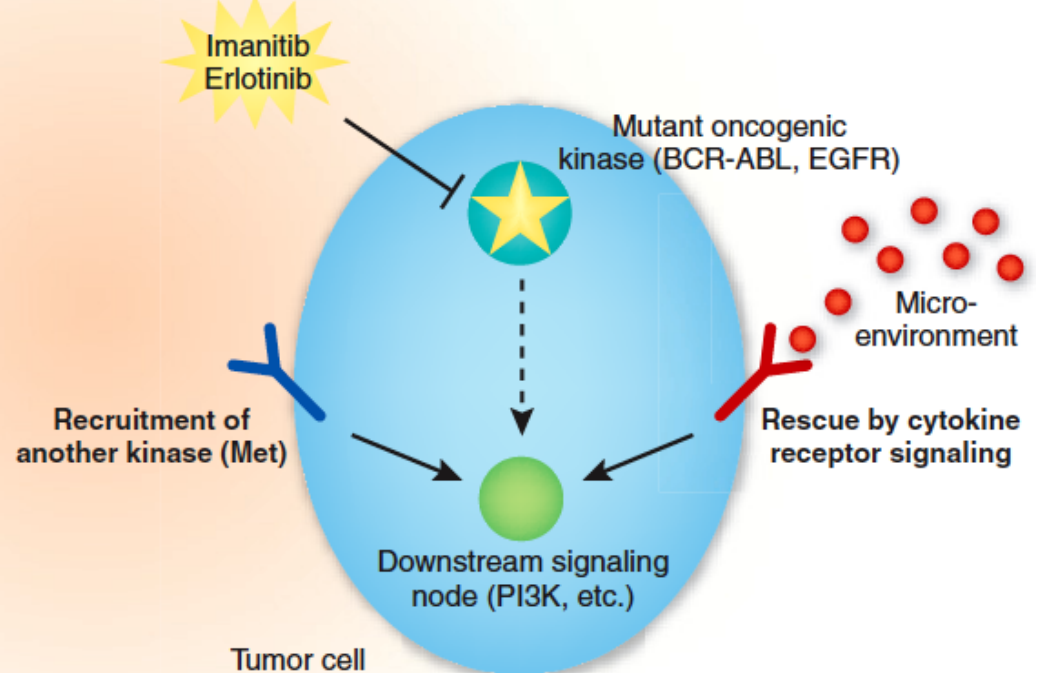
Mechanisms for acquired resistance in targeted therapy of cancer

Sawyers, Nature Med, 2007

A: secondary mutation of the target



B: Bypassing the inhibited path



Lung cancer vs. EGFR-TKI

T790M ~50%<

D761Y, L747S, T854A ~rare

MET amplification ~20%

IGF1R activation ?

Mechanisms for acquired resistance of EGFR- TKIs

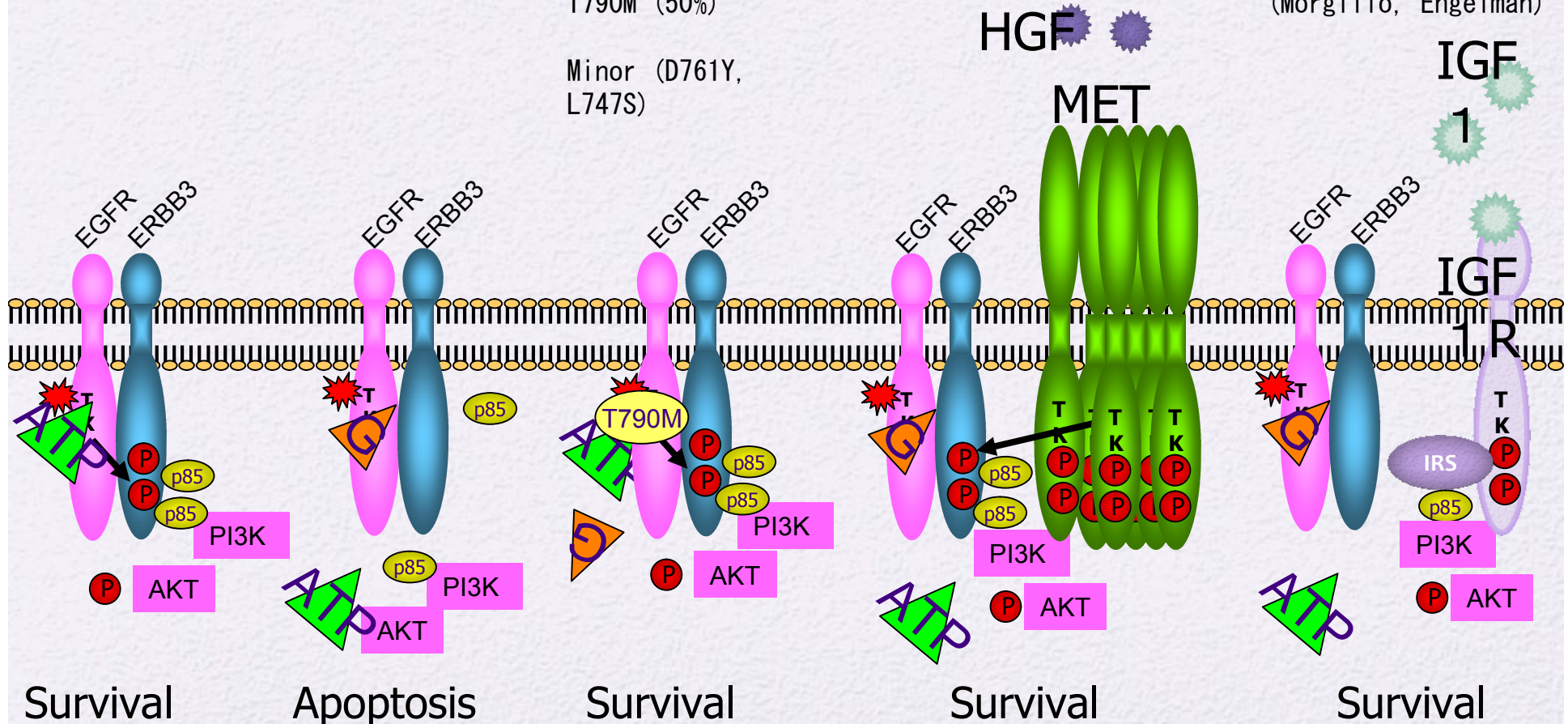
A
Activating
mutation of
the EGFR gene

B
Gefitinib
treated

C
Secondary
mutation of the
EGFR gene
T790M (50%)

D
MET activation
Amplification (Engelman)
HGF mediated ? (Yano)

E
IGF1R activation by
down regulation of
IGFBP
(Morgillo, Engelman)



Circumvention of acquired resistance of EGFR-TKI

- T790M
 - New generation of the EGFR-TKI (irreversible)
- Recruitment of other kinases
 - Cocktail therapy (EGFR TKI + MET or IGF1R inhibitor)
- Other approaches
 - Inhibition of PI3K, HSP90, mTOR



EGFR-TKIの有害事象としての 間質性肺障害

ILD incidence (mortality)

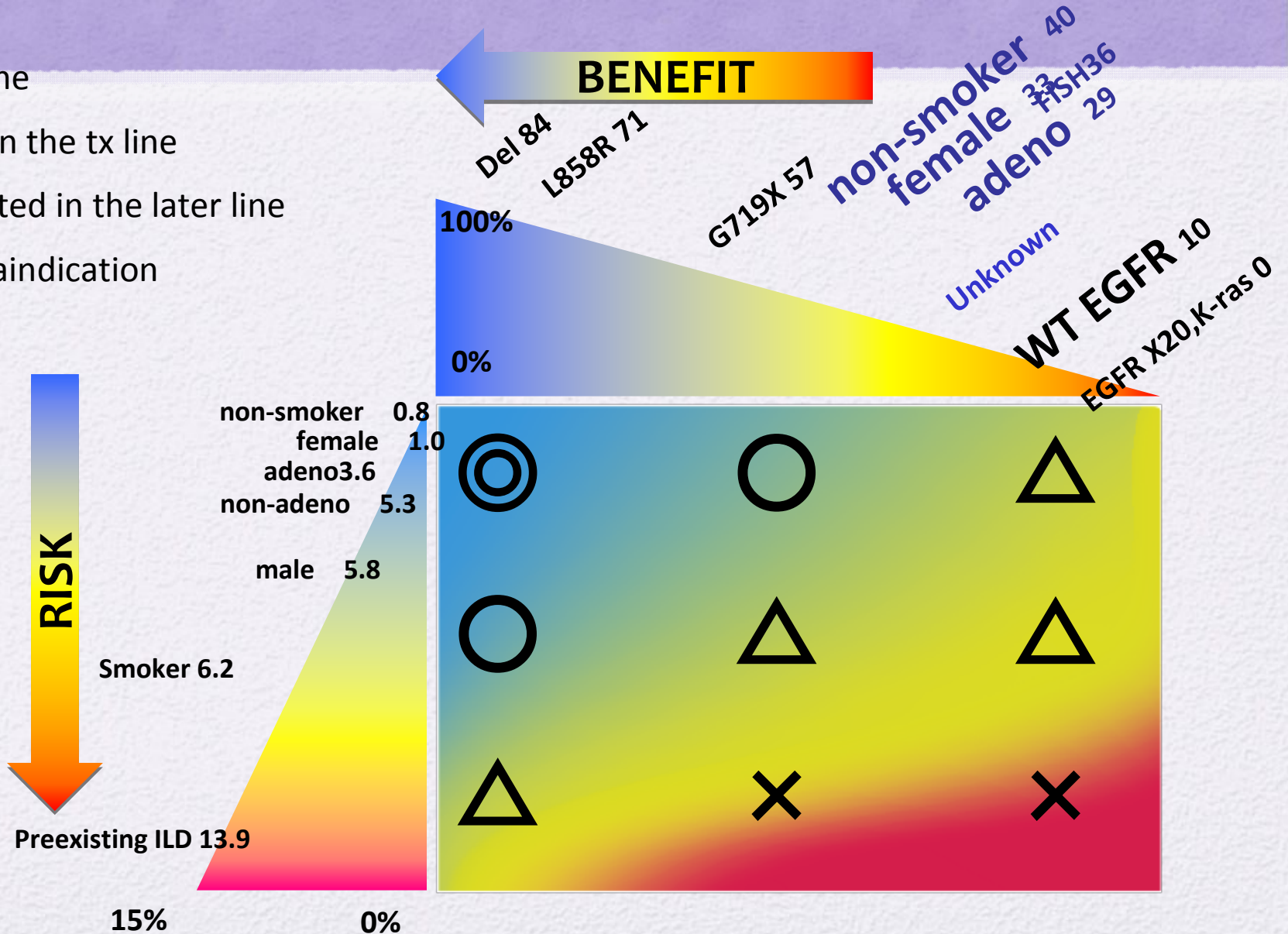
EGFR mutation frequency

Gender	Smoking Status	ILD incidence (mortality)	EGFR mutation frequency
Male	Former / current	5.9%(2.8%)	26%
	Never	6.6(3.0)	
Female	Former / current	1.8(1.8)	18%
	Never	1.0% (0.2%)	94%
	Never	3.3(0.8)	59%
	Never	0.4(0.0)	50%
			61%

*ILD data from WJTOG, EGFR mutation data from ACC

臨床プラクティスにおけるEGFR-TKIの使用

- ◎ first line
- early in the tx line
- △ indicated in the later line
- × contraindication



愛知県がんセンター中央病院 呼吸器グループ '09

■ 胸部外科

■ 光富徹哉、波戸岡俊三、安部哲也、伊藤志門、福井高幸

■ 片山達也、斉藤卓也、福本紘一、丹羽幸子、厚田幸子、小野里良一、
須田健一、富澤健二

■ 遺伝子病理診断部

■ 谷田部恭

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■ 樋田豊明、吉田公秀、堀尾芳嗣、清水淳一、小川紫都、朴 将哲