Gefitinib as a first line treatment in advanced non small cell lung cancer: Potential benefit in Asian population

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Scope of Talk

1. Overview of NSCLC treatment
2. Gefitinib: Mechanism of action and Pharmacokinetic
3. Gefitinib as 2nd or 3rd line therapy
4. Gefitinib as 1st line therapy in Asian population
5. Take home massages

Background

- Non-small-cell lung cancer (NSCLC): 80%[1]
  - Adenocarcinoma (40%)
  - Squamous-cell carcinoma (30%)
  - Large cell carcinoma (10%)
- 75% with metastatic disease at diagnosis[2]
- Therapeutic option:
  - Chemotherapy alone
- Goal:
  - To slow down the progression
  - To relieve the symptoms
  - To increase the overall survival

1. Hirsch FR, et al. J Clin Oncol. 2006;24:5034-5042.
2. Kim ES, et al. Lancet. 2008;372:1809-1818.

Platinum-based in 1st line therapy

- A meta-analysis (1995 and 2008)[1,2]
  - Platinum-based: improve OS vs. BSC in advanced NSCLC
- Survival were similar among platinum-based doublets:[3-5]
  - Paclitaxel, Docetaxel, Vinorelbine, Gemcitabine
- ECOG 4599 and AVAIL: results[6,7]
  - Bevacizumab: *non-squamous NSCLC*
- Scagliotti and colleagues[8]
  - Pemetrexed: *non-squamous NSCLC*

1. Non Small Cell Lung Cancer Collaborative Group. BMJ. 1995;311(7010):899–909.
2. NSCLC Meta-Analyses Collaborative Group. J Clin Oncol. 2008;26(28):4617–4625.
3. Waters JS, O'Brien MER. Br J Cancer. 2002;87(5):481–490.
4. Scagliotti GV, De Marinis F, Rinaldi M, et al. J Clin Oncol. 2002;20(21):4285–4291.
5. Schiller JH, Harrington D, Belani CP, et al. N Engl J Med. 2002;346(2):92–98.
6. Sandler A, Gray R, Perry MC, et al. N Engl J Med. 2006;355(24):2542–2550.
7. Reck M, Von Pawel J, Zatloukal P, et al. J Clin Oncol. 2009;27(14):1227–1234.
8. Scagliotti GV, Parikh P, von Pawel J, et al. J Clin Oncol. 2008;26(21):3543–3551

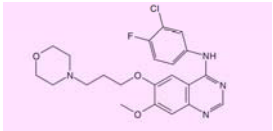
2nd line therapy

- 2nd line therapy:
  - Docetaxel and pemetrexed[1]
- EGFR has been found in 40–80% of NSCLC[2]
  - Gefitinib or erlotinib for EGFR mutation[3]

1. Gridelli C, Ardizzoni A, Ciardiello F, et al. J Thorac Oncol. 2008;3(4):430–440.
2. Bunn PA Jr, Franklin W. Semin Oncol. 2002;29 Suppl 14:S38–S44.
3. Azzoli CG, Baker S Jr, Temin S, et al. J Clin Oncol. 2009;27(36):6251–6266.

Gefitinib

- Orally administered low MW anilinoquinazoline
- Dosages regimen:
  - 250 mg/day
- Pharmacokinetic studies:
  - Absorbed slowly
  - Tmax: 3-7 hours
  - Half-life: 28 hours
  - Metabolized: CYP4503A4



Chemical structure of gefitinib (ZD1839) [4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline]

1. Albanell JR, Rojo F, Averbuch S, et al. J Clin Oncol. 2002;20(1):110–124.
2. Nakagawa K, Tamura T, Negoro S, et al. Ann Oncol. 2003;14(6):922–930.

Gefitinib: Safety and tolerability

- Generally well tolerated (elderly, poor PS)
- Most common side effects:
  - Skin rash and diarrhea
- Less common:
  - Nausea, vomiting and anorexia
  - Elevation of AST/ALT
- Interstitial lung disease (ILD)
  - Rare and potentially life threatening
  - Japan (1.6%-3.5%), other parts of the world (0.3%)

1. Takano T, Ohe Y, Kusumoto M, et al. Lung Cancer. 2004;45(1):93–104.
2. Ando M, Okamoto I, Yamamoto N, et al. J Clin Oncol. 2006;24(16):2549–2556.

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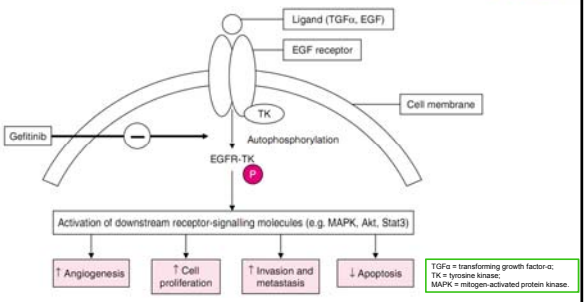
Gefitinib: Mechanism of action



1. Albanell J, Rojo F, Baselga J. Semin Oncol 2001;28 (5 Suppl. 16): 56-66
2. Arteaga CL, Johnson DH. Curr Opin Oncol 2001;13 (6): 491-8

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Gefitinib: The story so far

- **1994** • Discovery of Gefitinib
- **1998** • Favourable tolerability and unprecedented responses in phase I trials
- **2000** • IRESSA Dose Evaluation in Advanced Lung Cancer (**IDEAL I, II**)
  • IRESSA NSCLC Trial Assessing Combination Treatment (**INTACT I, II**)
- **2003** • **IDEAL I, II** were published
  • US FDA approval (**IDEAL II**)
- **2004** • **INTACT I, II**: Failed to demonstrate a survival advantage
- **2005** • **ISEL**: Non-significant survival advantage in overall population
  • But subgroups show benefit: ***Asian origin*** and ***never smoke***

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Gefitinib: The story so far

- **2005** • Gefitinib approved for use in 36 countries worldwide
  • Established therapy for pre-treated advanced NSCLC in the **pan-Asian region**
- **2006** • **SIGN:** Gefitinib equivalence in 2nd line advanced NSCLC vs docetaxel
- **2008** • **V-15-32 (Japan), INTEREST and ISTANA (Korea 2010):**
  • Proves Gefitinib has equivalent efficacy to docetaxel in 2nd line NSCLC
- **2009** • **Meta-analysis:** SIGN, V-15-32 (Japan), INTEREST and ISTANA (Korea)
  • **IPASS, First-SIGNAL:** Superior Gefitinib efficacy over CMT (EGFR mutation+)
  • **WJTOG3405, NEJ002:** Superior Gefitinib efficacy over CMT (planned EGFR mutation)

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Gefitinib: Phase II trial

- **IDEAL-1 and IDEAL-2**
  - IDEAL-1: Europe, Japan, South Africa, Australia (210)
  - IDEAL-2: US (221)
- Aim: evaluate the activity of gefitinib in vary dose
- Population: pretreated advanced NSCLC
- Results: Gefitinib 250 mg/d
  - Response rates of 12% and 18%
  - Median survival time: 7.0 and 7.6 months
  - The toxicity profile was not severe

IDEAL: IRESSA Dose Evaluation in Advanced Lung Cancer

1. Fukuoka M, Yano S, Giaccone G, et al. J Clin Oncol. 2003;21(12): 2237–2246.
2. Kris MG, Natale RB, Herbst RS, et al. JAMA. 2003;290(16):2149–2158.

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Gefitinib as 2nd or 3rd line therapy

From these trials emerged the first evidence about the major efficacy of gefitinib in some specific subgroups of patients:

- Female gender
- Adenocarcinoma histological subtype
- Asian ethnicity

Gefitinib received accelerated FDA approval in May 2003 as a 3rd line therapy in NSCLC based on the IDEAL-2 study.

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Gefitinib vs. CMT as a 1st line

- **INTACT 1 & 2 Trial**
- Randomized, controlled phase III trials
- Advanced NSCLC, first-line treatment
- Identical trial designs in Europe and U.S.
- Randomized 2:1 to gefitinib (250, 500 mg), placebo
  - Cisplatin/gemcitabine ± gefitinib (INTACT 1)
  - Carboplatin/paclitaxel ± gefitinib (INTACT 2)
- Over 1000 pts enrolled in each trial
- Results:
  - NO DIFFERENCE in OS, TTP, RR

INTACT: Iressa NSCLC Trial Assessing Combination Treatment

1. Giaccone et al, JCO 2004; 22:777-84
2. Herbst et al, JCO 2004; 22:785-94

Gefitinib vs. BSC

- **ISEL (IRESSA Survival evaluation in Lung Cancer)** trial[1]
- **Aim:** Impact on survival of gefitinib (250 mg/d) vs. BSC

	Gefitinib (n=1100)	BSC (n=560)	P Value
Median survival (mo.)	5.6	5.1	0.11
1 yr survival (%)	27	22	
Subgroup analysis: adenocarcinoma			
Median survival (mo.)	6.3	5.4	0.07
1 yr survival (%)	31	17	

- Significantly higher RR and longer TTT failure
- Subgroup analysis: longer survival time
  - Never-smokers (P = 0.012)
  - Asian origin (P = 0.01)

1. Thatcher N, Chang A, Parikh P, et al. Lancet. 2005;(366):1527–1537

Gefitinib vs. CMT as 2nd line

- **SIGN** (2nd line indication of gefitinib in NSCLC) trial[1]
- Phase II open-label randomized study
  - Gefitinib 250 mg/d (n=60 patients)
  - Docetaxel 75 mg/m² every 3 weeks (n=73 patients)
- Primary objective:
  - Symptom improvement
- **The results:**
  - Similar efficacy
    - Symptom improvement rates, RR, Median PFS, Median OS
    - QOLs improvement rates (33.8% and 26%, gefitinib vs docetaxel)
  - Favorable tolerability

1. Cufer T, Vrdoljak E, Gaafar R, et al. Anticancer Drugs. 2006;17(4):401–409

Gefitinib vs. CMT as 2nd line

	Number of patients	RR (%)	P	PFS (months)	HR [95% CI]	P	OS (months)	HR [95% CI]	P
INTEREST trial (n = 1,433) [1]									
Gefitinib 250 mg	733	9.1	0.33	2.2	1.04	0.47	7.6	1.020	–
Docetaxel 75 mg/m²	733	7.6		2.7	[0.93–1.18]		8.0	[0.905–1.150]	
V-15-32 trial (n = 489) [2]									
Gefitinib 250 mg	245	22.5	0.009	2.0	0.81	0.77	11.5	1.12	0.330
Docetaxel 60 mg/m²	244	12.8		2.0	[0.65–1.02]		14.0	[0.89–1.40]*	
ISTANA trial (n = 161) [3]									
Gefitinib 250 mg	82	28.1	0.0007	3.3	0.729	0.0441	14.1	0.870	0.437
Docetaxel 60 mg/m²	79	7.6		3.4	[0.533–0.998]**		12.2	[0.613–1.236]	

Notes: *95.24% CI. **90% CI.
Abbreviations: RR, response rate; TTF, time to treatment failure; HR, hazard ratio; CI, confidence interval; OS, overall survival; NR, not reached; –, data not available; PFS, progression-free survival.

The results of three phase III trials comparing gefitinib vs. docetaxel in this setting have been published. The primary endpoints were the ***non-inferiority*** *of gefitinib in comparison with docetaxel.*[1-3]

1. Kim ES, Hirsch V, Mok T, et al. Lancet. 2008;(372):1809–1818.
2. Maruyama R, Nishiwaki Y, Tamura T, et al. J Clin Oncol. 2008;26(26):4244–4252.
3. Lee DH, Park K, Kim JH, et al. Clin Cancer Res. 2010;16(4):1307–1314.

2nd line: Meta-analysis

- Meta-analysis: 4 previously reported
  - SIGN, INTEREST, V-15-32, and ISTANA trials
  - Gefitinib vs. docetaxel in unselected pretreated patients
- Results: Gefitinib showed similar
  - OS (HR, 1.03, 95% CI, 0.93–1.13, P=0.5773)
  - PFS (HR, 0.96, 95% CI, 0.87–1.05, P=0.3784)
  - Increase RR (13.6% vs. 9%, OR, 1.65, P = 0.0007)

1. Shepherd FA, Douillard J, Fukuoka M et al. J Clin Oncol. 2009;27 Suppl:S15.

Gefitinib: Phase III studies

1. Mok T, Wu YL, Thongprasert S, et al. N Engl J Med. 2009;361(10):947–957.
2. Lee JS, Park K, Kim SW, et al. J Thor Oncol. 2009;4 Suppl:PRS.4.
3. Mitsudomi T, Morita S, Yatabe Y, et al. Lancet Oncol. Epub 2009 Dec 21.
4. Kobayashi K, Inoue A, Maemondo M, et al. J Clin Oncol. 2009;27 Suppl:S15.

IPASS: Study design

Patients

- ❑ Chemonaïve
- ❑ Age ≥18 years
- ❑ Adenocarcinoma histology
- ❑ Never or light ex-smokers*
- ❑ Life expectancy ≥12 weeks
- ❑ PS 0-2
- ❑ Measurable stage IIIB/IV disease

Gefitinib (250 mg/d)

1:1 randomisation

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg/m²) 3 weekly#

Primary
- ❑ Progression-free survival (non-inferiority)

Secondary
- ❑Objective response rate
- ❑Overall survival
- ❑Quality of life
- ❑Disease-related symptoms
- ❑Safety and tolerability

Exploratory: Biomarkers
- ❑ EGFR mutation
- ❑ EGFR-gene-copy number
- ❑ EGFR protein expression endpoints

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped≥15 yrs ago and smoked ≤10 pack yrs; #limited to a maximum of 6 cycles Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

1. Mok T, Wu YL, Thongprasert S, et al. N Engl J Med. 2009;361(10):947–957.

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Demographic and Baseline Characteristics

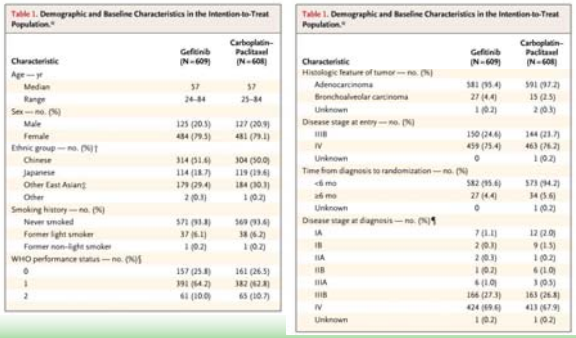

Table 1. Demographic and Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Gefitinib (N = 609)	Carboplatin–Paclitaxel (N = 608)
Age — yr		
Median	57	57
Range	24–84	25–84
Sex — no. (%)		
Male	125 (20.5)	127 (20.9)
Female	484 (79.5)	481 (79.1)
Ethnic group — no. (%) †		
Chinese	314 (51.6)	304 (50.0)
Japanese	114 (18.7)	119 (19.6)
Other East Asian‡	179 (29.4)	184 (30.3)
Other	2 (0.3)	1 (0.2)
Smoking history — no. (%)		
Never smoked	571 (93.8)	569 (93.6)
Former light smoker	37 (6.1)	38 (6.2)
Former non-light smoker	1 (0.2)	1 (0.2)
WHO performance status — no. (%)§		
0	157 (25.8)	161 (26.5)
1	391 (64.2)	382 (62.8)
2	61 (10.0)	65 (10.7)

Table 1. Demographic and Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Gefitinib (N = 609)	Carboplatin–Paclitaxel (N = 608)
Histologic feature of tumor — no. (%)		
Adenocarcinoma	581 (95.4)	591 (97.2)
Bronchoalveolar carcinoma	27 (4.4)	15 (2.5)
Unknown	1 (0.2)	2 (0.3)
Disease stage at entry — no. (%)		
IIIB	150 (24.6)	144 (23.7)
IV	459 (75.4)	463 (76.2)
Unknown	0	1 (0.2)
Time from diagnosis to randomization — no. (%)		
<6 mo	582 (95.6)	573 (94.2)
≥6 mo	27 (4.4)	34 (5.6)
Unknown	0	1 (0.2)
Disease stage at diagnosis — no. (%)¶		
IA	7 (1.1)	12 (2.0)
IB	2 (0.3)	9 (1.5)
IIA	2 (0.3)	1 (0.2)
IIB	1 (0.2)	6 (1.0)
IIIA	6 (1.0)	3 (0.5)
IIIB	166 (27.3)	163 (26.8)
IV	424 (69.6)	413 (67.9)
Unknown	1 (0.2)	1 (0.2)

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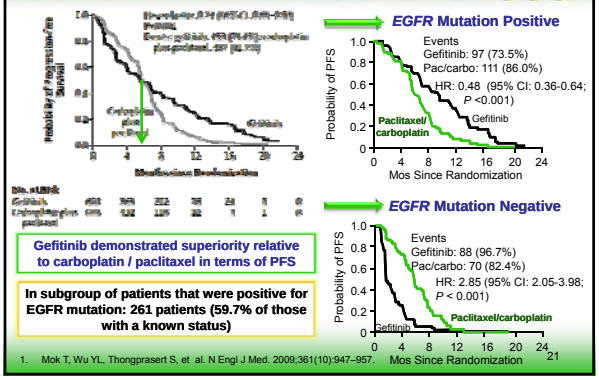
IPASS: Progress Free Survival



Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

In subgroup of patients that were positive for EGFR mutation: 261 patients (59.7% of those with a known status)

1. Mok T, Wu YL, Thongprasert S, et al. N Engl J Med. 2009;361(10):947–957.

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IPASS: Other outcomes

- OS similar between arms in preliminary analysis
  - Median OS: 18.6 mo with gefitinib vs 17.3 mo with PC
  - Gefitinib-treated *EGFR* mutation–positive subgroup
    - HR: 0.78 (95% CI: 0.50-1.20)
  - Gefitinib-treated *EGFR* mutation–negative subgroup
    - HR: 1.38 (95% CI: 0.92-2.09)
- Ongoing analysis of OS
- Response rate to both gefitinib and PC better in EGFR mutation-positive vs. EGFR mutation-negative patients

1. Mok T, Wu YL, Thongprasert S, et al. N Engl J Med. 2009;361(10):947–957.

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IPASS: QOL

- 1151 patients (gefitinib: 590, PC: 561)
- Better outcome:
  - Total score and TOI improvements
  - LCS improvement was similar for both treatments
- Total score, TOI and LCS
  - EGFR M⁺: Favoured gefitinib
  - EGFR M⁻: Favoured carboplatin/paclitaxel
  - Unknown: QoL improvements were similar overall population
- Time to worsening for FACT-L
  - Overall: Longer with gefitinib vs. PC (median 8.3 vs 2.5 months)
  - EGFR M⁺: Longer with gefitinib vs. PC (15.6 vs 3.0 months)
  - EGFR M⁻: Similar (median 1.4 months for both arms)

1. Mok T, Wu YL, Thongprasert S, et al. N Engl J Med. 2009;361(10):947–957.

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First-SIGNAL* Trial

- Compare: 309 patients (F: 89%)
  - Gefitinib 250 mg/d: until disease progression
  - Cis-Gem: maximum of 6 cycles
- The primary endpoint was OS
- Results:

	Gefitinib	PC	HR (95% CI)	P value
No. of pts	159	150	-	-
RR (%)	53.5	45.3	-	0.153
PFS (mo)	6.1	6.6	0.813 [0.641-1.031]	0.044
OS (mo)	21.3	23.3	1.003 [0.749-1.343]	0.428

* First-line single agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung trial

1. Lee JS, Park K, Kim SW, et al. [abstract]. J Thor Oncol. 2009;4 Suppl:PRS.4.

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First-SIGNAL* Trial

- Results based on mutation status:
  - Overall EGFR mutation rate: 43.8% (42/96 patients)
- RR:
  - Mutation$^+$: RR: G 84.6% vs CMT 37.5% (P=0.002)
  - Mutation$^-$: RR: G 29.9% vs CMT 51.9% (P=0.051)
- OS: no difference by mutation status
- PFS: some difference in PFS in mutation$^+$
  - 8.5 vs 6.7 months; HR, 0.613 (P = 0.0849)

1. Lee JS, Park K, Kim SW, et al. [abstract]. J Thor Oncol. 2009;4 Suppl:PRS.4.

Two phase III Japanese studies have been performed specifically in patients EGFR mutated to compare the efficacy of gefitinib versus chemotherapy in the first-line treatment of NSCLC (WJTOG3405 and NEJ002 trials)

WJTOG3405* Trial

- 172 EGFR mutated patients:
  - Gefitinib vs cisplatin-docetaxel
- The primary endpoint was PFS
- Results:
  - Median PFS
    - 9.2 mo (G) and 6.3 mo (CMT) (HR, 0.489,P=0.0001)
  - RR
    - 62.1% (G) and 32.2% (CMT) (P=0.0001)
  - OS:
    - 30.9 mo (G) and not reached (CMT) (p=0.211)

The WJTOG3405 trial results confirm once more gefitinib to be superior to chemotherapy in terms of RR and PFS in patients with EGFR mutations

*** WJTOG3405: west Japan Thoracic Oncology Group3405**

1. Mitsudomi T, Morita S, Yatabe Y, et al. Lancet Oncol 2010; 11: 121–28

NEJ002 Trial[1]

- Compare Gefitinib (n=98) vs Carboplatin-paclitaxel (n=96)
- Population: Advanced NSCLC EGFR mutation
- Interim analysis:
  - Median PFS: 10.4 mo (G) vs 5.5 mo (CMT) (HR, 0.357, P=0.001)
  - Median OS: 28 mo (G) vs 23.6 mo (CMT) (P=0.354)
  - RR: 74.5% (G) vs 29% (CMT) (P=0.001)
- Update 2010[2]: 230 were enrolled
  - Median PFS: 10.8 mo (G) vs 5.4 mo (CMT) (HR, 0.30, P<0.001)
  - Median OS: 30.5 mo (G) vs 23.6 mo (CMT) (P=0.31)
  - RR: 73.7% (G) vs 30.7% (CMT) (P<0.001)

1. Kobayashi K, Inoue A, Maemondo M, et al. [abstract]. J Clin Oncol. 2009;27 Suppl:S15
2. Maemondo M, et al. N Engl J Med. 2010;362:2380-88.

Gefitinib's 1st line in EGFR mutation positive patients

Trials	Trial phase	Prior CMT	Median PFS (mo)		p-value (HR 95% CI)
			Gefitinib	*Platinum doublet*	
NEJ002[1]	III	No CMT	10.4	5.5	p<0.001 (HR 0.357: 0.252-0.507)
Update2010[2]	III	No CMT	10.8	5.4	p<0.001
WJTOG3405[3]	III	No CMT	9.2	6.3	p<0.0001 (HR 0.489: 0.336-0.710)
IPASS (EGFR M$^+$)[4]	III	No CMT	9.5	6.3	p<0.001 (HR 0.48: 0.36-0.64)
First-SIGNAL (EGFR M$^+$)[5]	III	No CMT	8.4	6.7	p<0.084 (HR 0.613: 0.308-1.221)

1. Kobayashi K, Inoue A, Maemondo M, et al. J Clin Oncol. 2009;27 Suppl:S15.
2. Maemondo M, Inoue A, Kobayashi K, et al. N Engl J Med 2010;362:2380-88.
3. Mitsudomi T, Morita S, Yatabe Y, et al. Lancet Oncol 2010; 11: 121–28
4. Mok T, Wu YL, Thongprasert S, et al. N Engl J Med. 2009;361(10):947–957.
5. Lee JS, Park K, Kim SW, et al. J Thor Oncol. 2009;4 Suppl:PRS.4.

Conclusions:

- **IPASS, First-SIGNAL, WJTOG3405 and NEJ002**
  - Mutations of EGFR TK binding domain:
    - Response rate
    - Progression-free survival
- **Mutation analysis:**
  - Recommended in those patients who present at least one of the clinical or pathological features
- EGFR mutation positive:
  - Up-front treatment with gefitinib should be considered

Take home messages

1st line setting

- Adenocarcinoma:
  - If tissue available:
    - EGFR test → Mutation+ → TKI first line (IPASS/WJTOG3405/NEJ002)
  - If tissue available:
    - Clinical parameter → Asian, Non-smoking → TKI first line / Monitor carefully (IPASS)
    - Smoker → Doublet CMT +/- Bevacizumab
- Squamous cell carcinoma → Doublet CMT

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Take home messages

2nd and 3rd setting

- Considered TKI if not received at 1st line
- Considered 2nd line CMT if clinical parameter not support response to TKI

- ***Future perspectives: Need Research on***
  - TKI resistance
  - Other mutation

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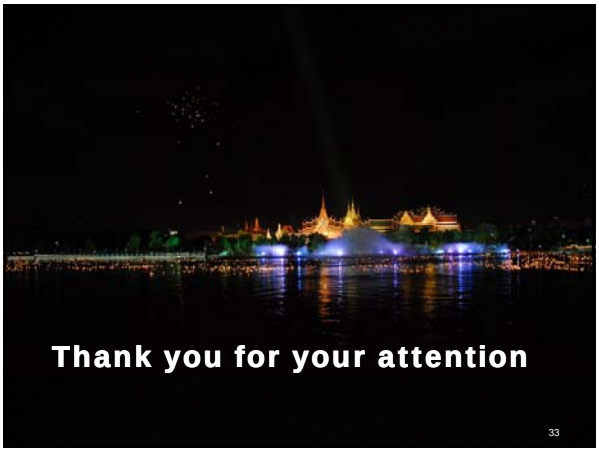

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