다기관 임상연구 사례발표

Treatment of HER2 Positive NSCLC

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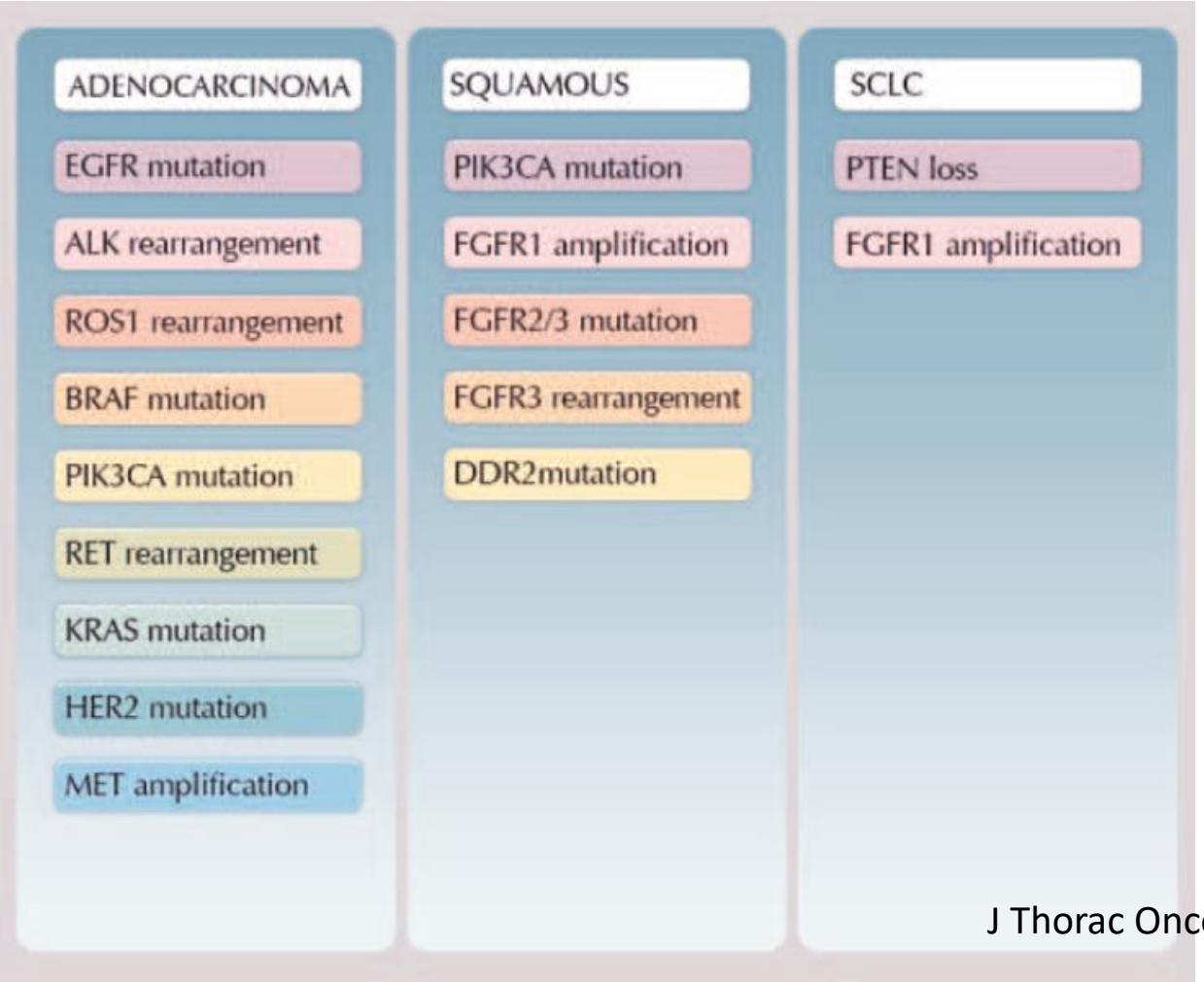
Potential targetable oncogenes by histology



J Thorac Oncol 2015;10:S1–S63

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; DDR2, discoidin domain receptor tyrosine kinase 2; FGFR1, fibroblast growth factor receptor 1; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, MET proto-oncogene; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homology deleted on chromosome 10; RET, ret proto-oncogene; SCLC, small-cell lung cancer

HER2/Neu or ErbB-2

- *HER2* (human epidermal growth factor receptor-2)
  - Named because it has a similar structure to human EGFR, or HER1
- *Neu*
  - Named because it was derived from a rodent glioblastoma cell line, a type of neural tumor
- *ErbB-2*
  - Named for its similarity to *ErbB* (avian erythroblastosis oncogene B), the oncogene later found to code for EGFR

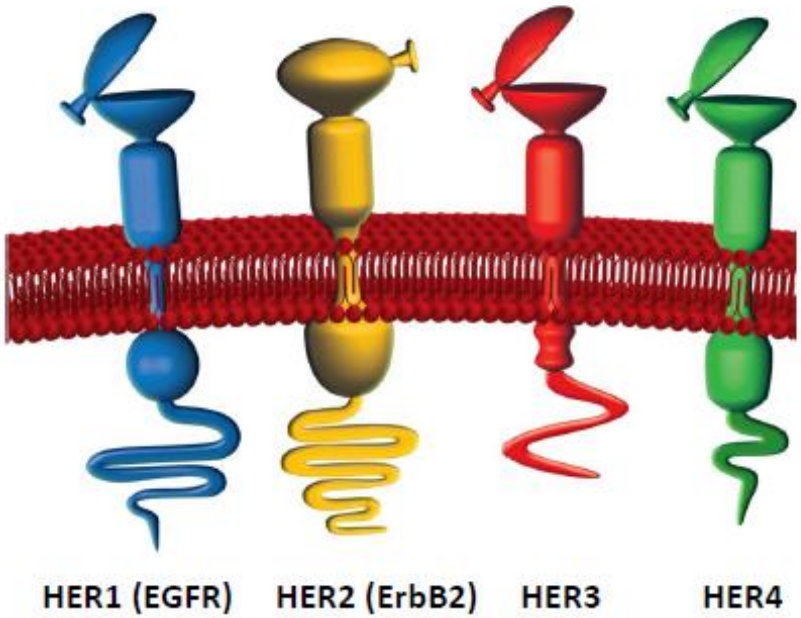
- Gene cloning showed that *HER2, Neu*, and *ErbB-2* are all encoded by the same orthologs
- *ERBB2*, a known proto-oncogene, is located at the long arm of human chromosome 17 (17q12)

HER tyrosine kinase families

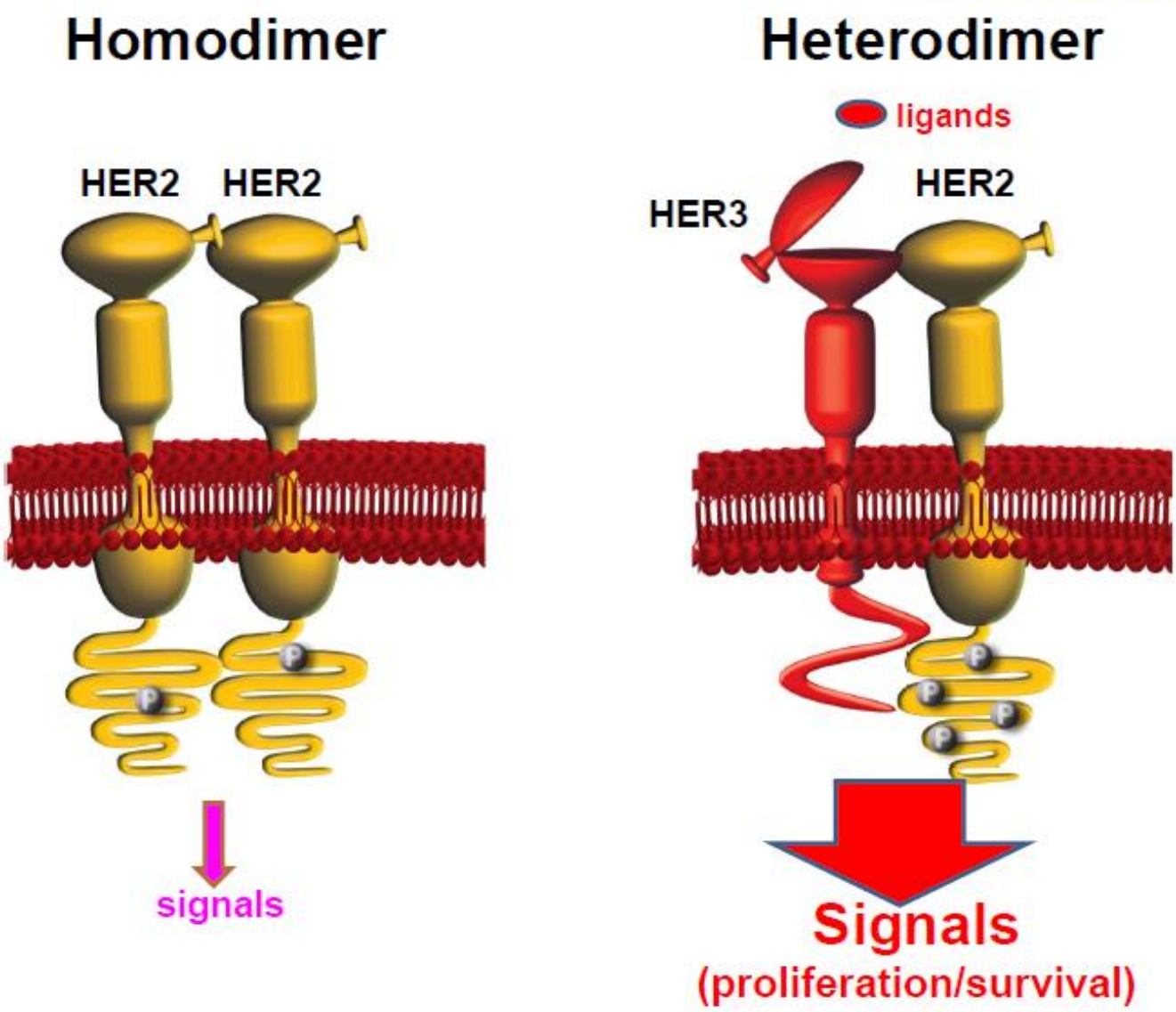
Family of 4 type I receptor tyrosine kinase

Important in human growth & development

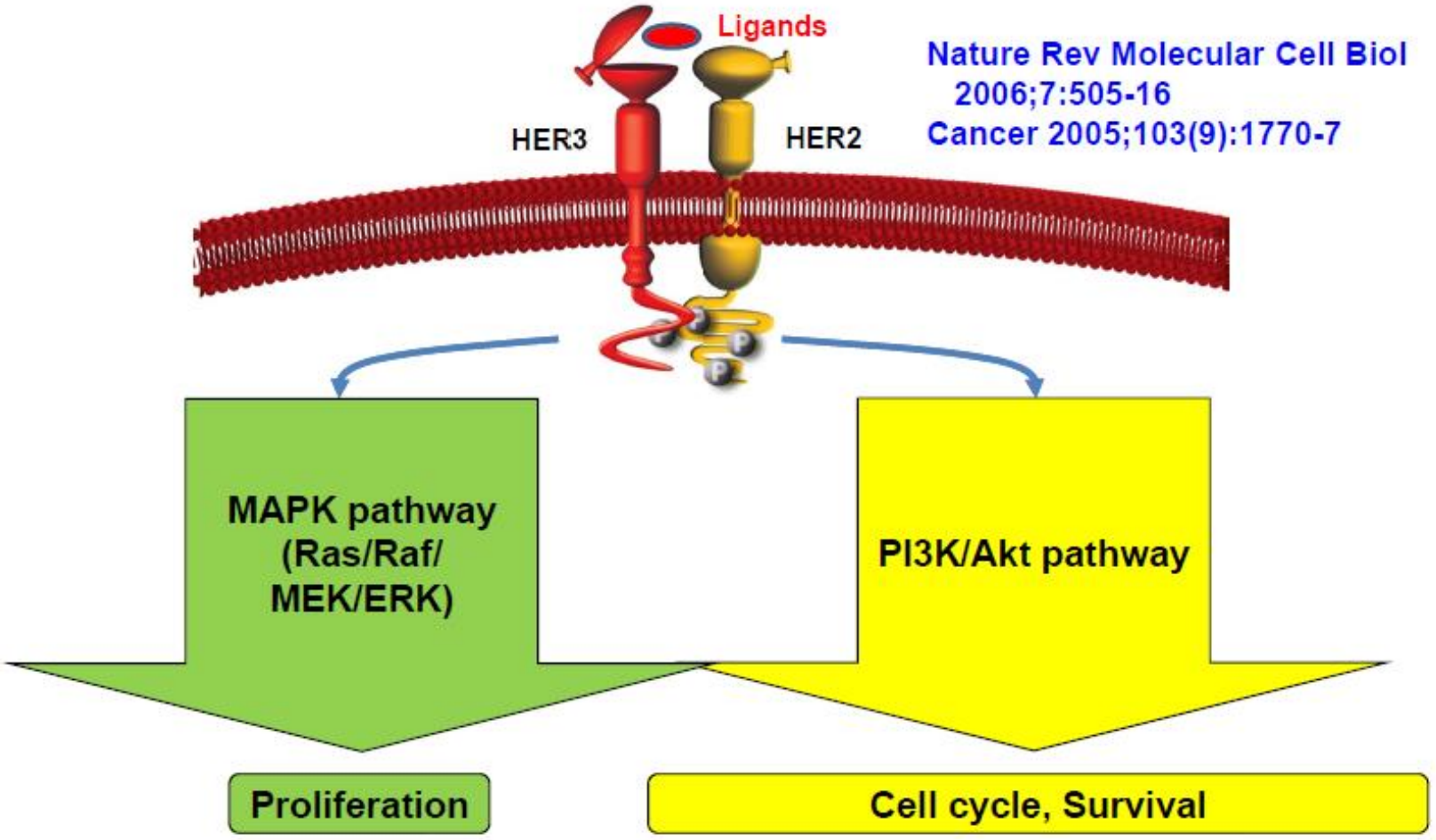
Similar structures, but
- HER2 lacks ligand binding domain
- HER3 lacks functional intracellular tyrosine kinase domain



EMBO 14:4267-75, 1995

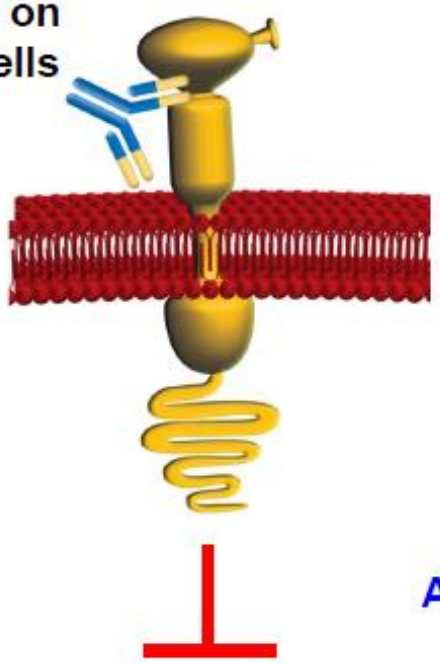


HER2 receptor signal through two main pathways : MAPK & PI3K/Akt



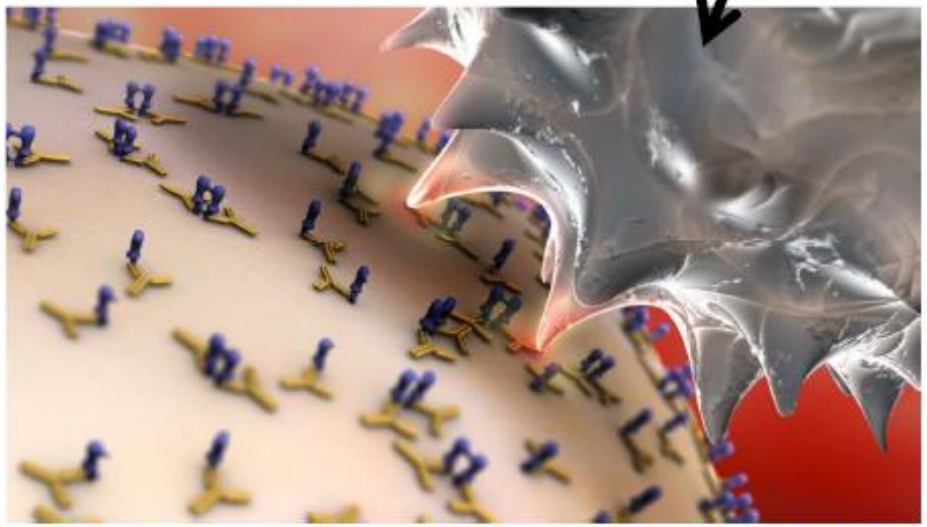
Trastuzumab binds to the extracellular domain for anti-tumor effect

Trastuzumab binds to HER2 on tumor cells



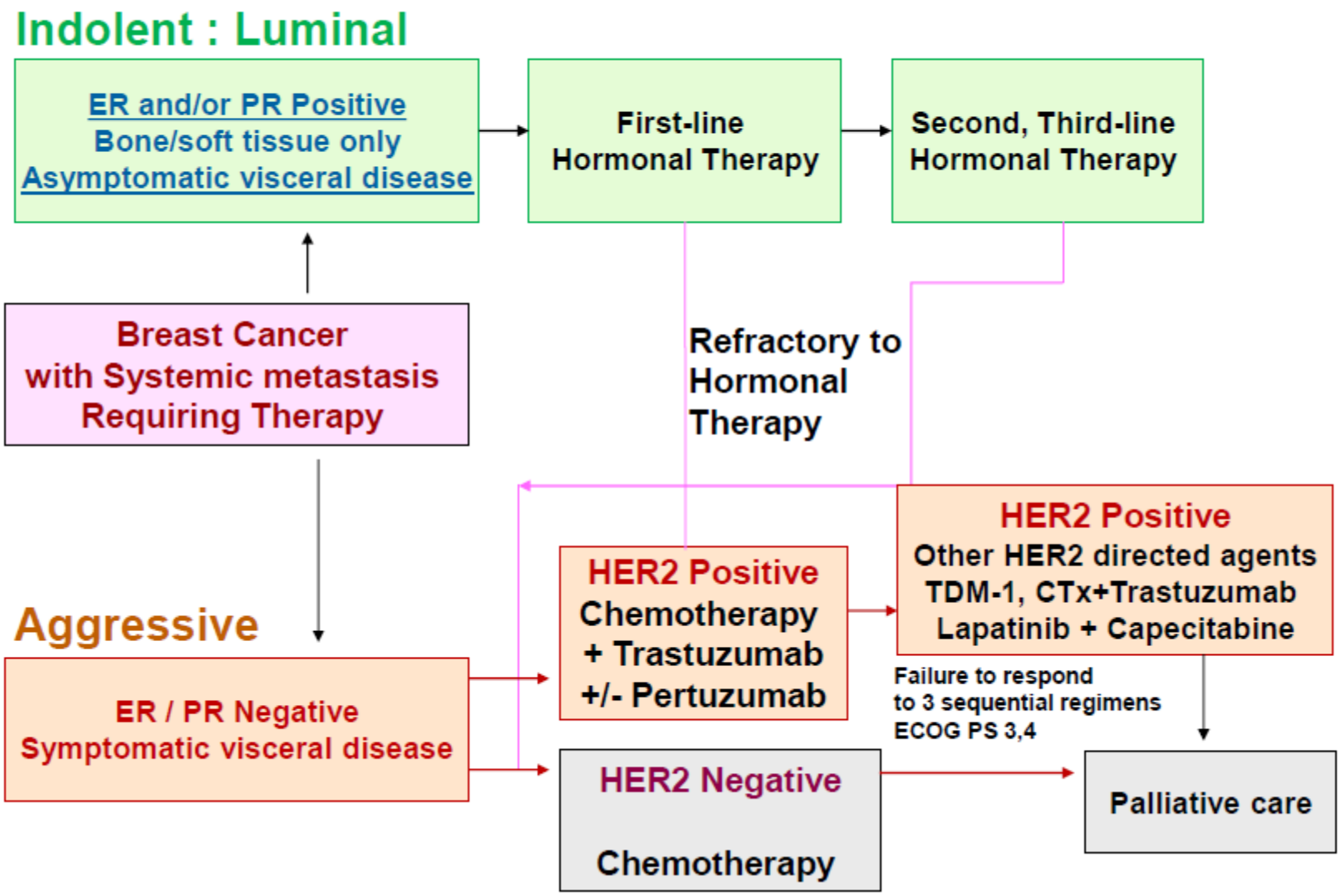
Inhibition of intracellular signaling

Immune Cell

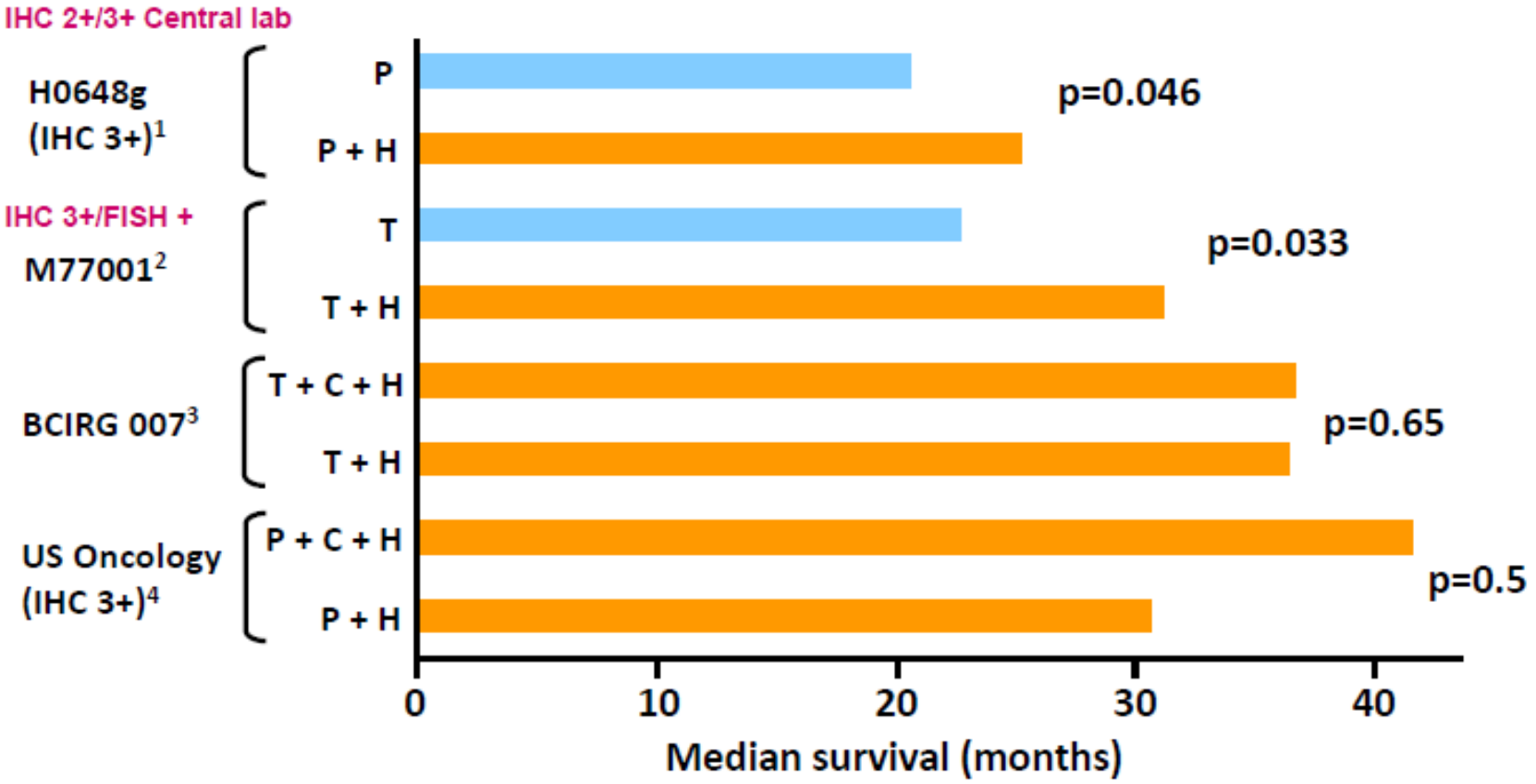


Antibody dependent cellular cytotoxicity (ADCC)

Changing treatment paradigm



Trastuzumab provides proven OS benefit in first-line HER2-positive MBC



IHC, immunohistochemistry;
P, paclitaxel (Taxol); H, trastuzumab (Herceptin);
T, docetaxel (Taxotere); C, carboplatin

1. Slamon et al. NEJM 2001; 2. Marty et al. JCO 2005;
3. Pegram et al. JCO 2007; 4. Robert et al. JCO 2006

HER2 pathway in NSCLC

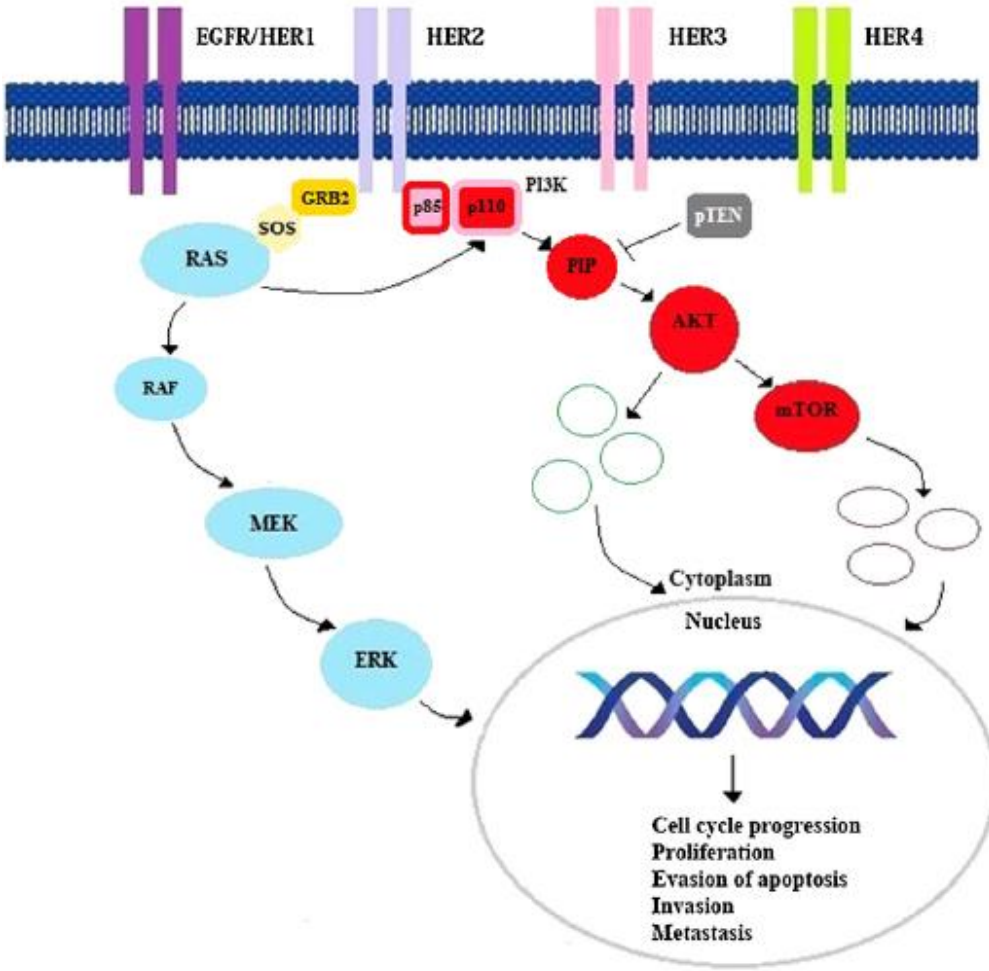
- Oncogenic activation of HER2 is observed in a variety of malignancies including breast, stomach, lung, bladder, ovarian, and pancreatic cancer

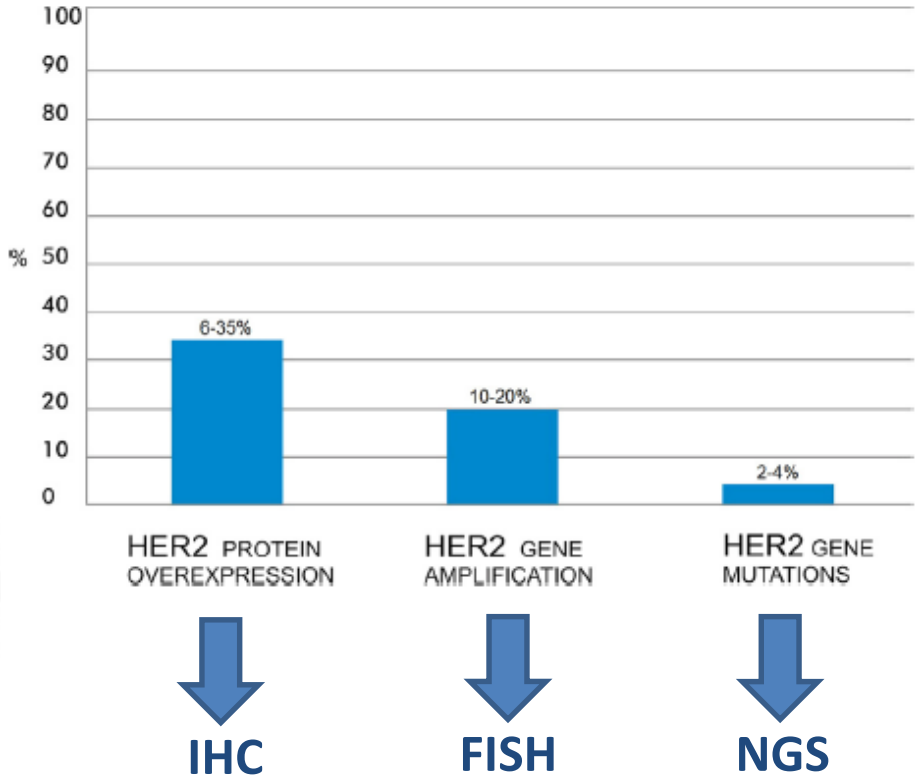
- In NSCLC, HER2 (+) confers relative resistance to conventional chemotherapy → emerging as a key target for molecular Tx
- Heterodimers between EGFR & HER2 are the most stable

  → resulting in augmentation of EGFR signaling by HER2

  & HER2 also mediates sensitivity of EGFR-mutant lung tumors to anti-EGFR therapy

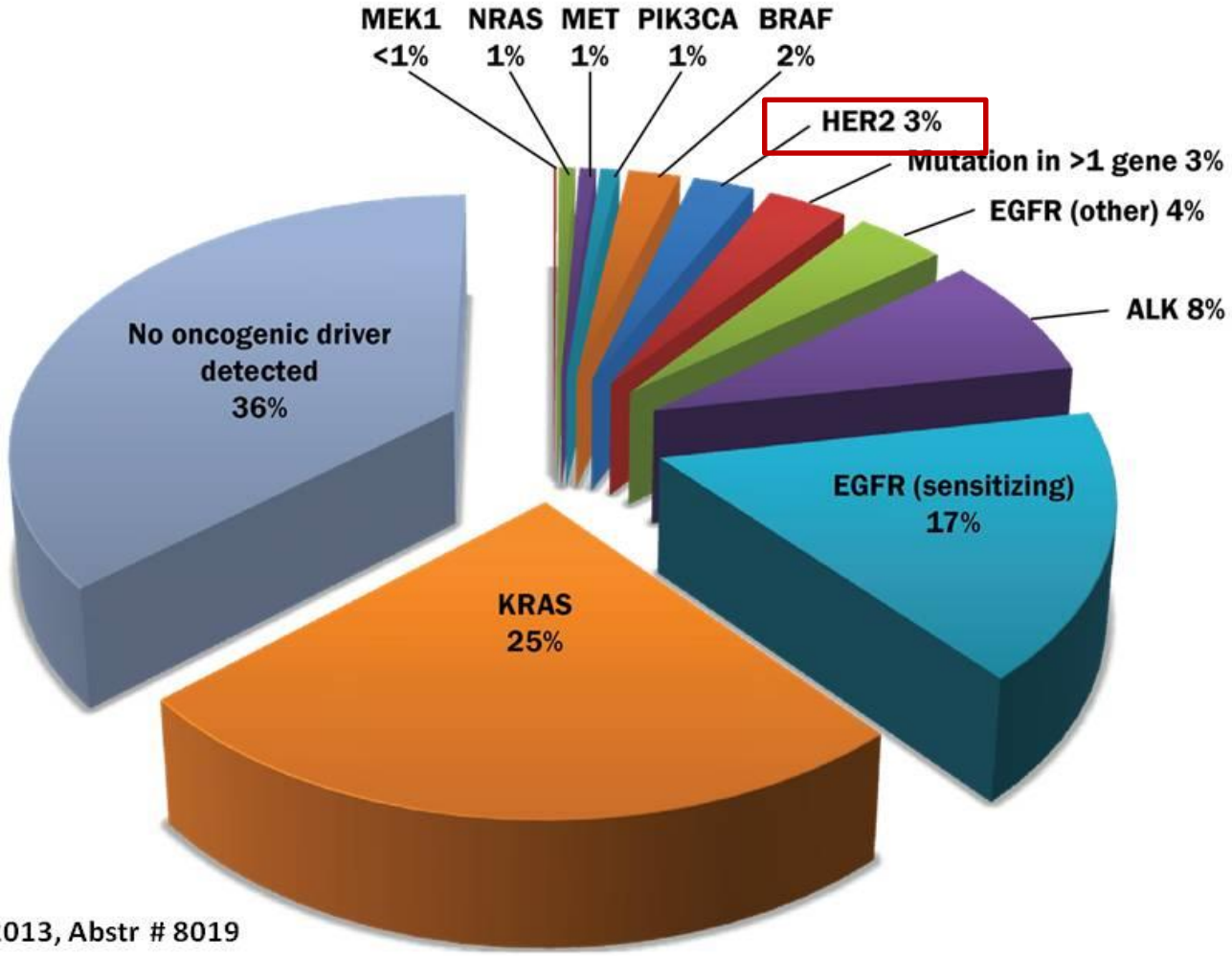
Cancer Discov 2012;2(10): 922–33





Lung Cancer (2015), http://dx.doi.org/10.1016/j.lungcan.2014.12.018

Lung Cancer Mutation Consortium: Incidence of Driver Mutations



ASCO 2013, Abstr # 8019

HER2 mutation

- HER2 mutations are typically observed with ADC histology, in never-smokers, and women

Lancet Oncol 2011;12:175–80

- Usually mutually exclusive with EGFR, KRAS, and ALK mutations in NSCLC
- In a selected population of EGFR/KRAS/ALK mutation negative patients, the incidence can reach up to **6%**

Clin Cancer Res 2012;18:4910–8

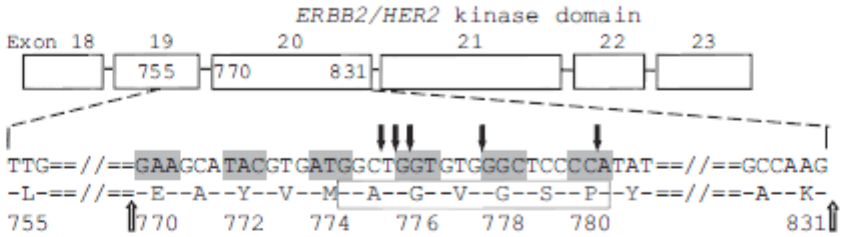
Study group	Total (No.)	HER2 mutation (No.)	%
Tomizawa K et al. (Lung Cancer 2011)	504	13	2.58
Li C et al. (J Thor Oncol 2012)	224	8	3.57
Sun Y et al. (J Clin Oncol 2010)	52*	2	3.85
Arcila M et al. (Clin Cancer Res 2012)	560	25	4.46
Zhang Y et al. (Clin Cancer Res 2012)	349**	16	4.58
Cardarella S et al. (J Thor Oncol 2012)	276	13	4.71
Li C et al. (PLos One 2011)	202*	12	**5.94**

*Inclusion of adenocarcinoma samples of never-smokers only,
**Inclusion of adenocarcinoma samples of female never-smokers only

Transl Lung Cancer Res **2**(2): 122-127.

A

Schematic organization of *ERBB2* kinase domain



Wild-type sequence, exon 20

B

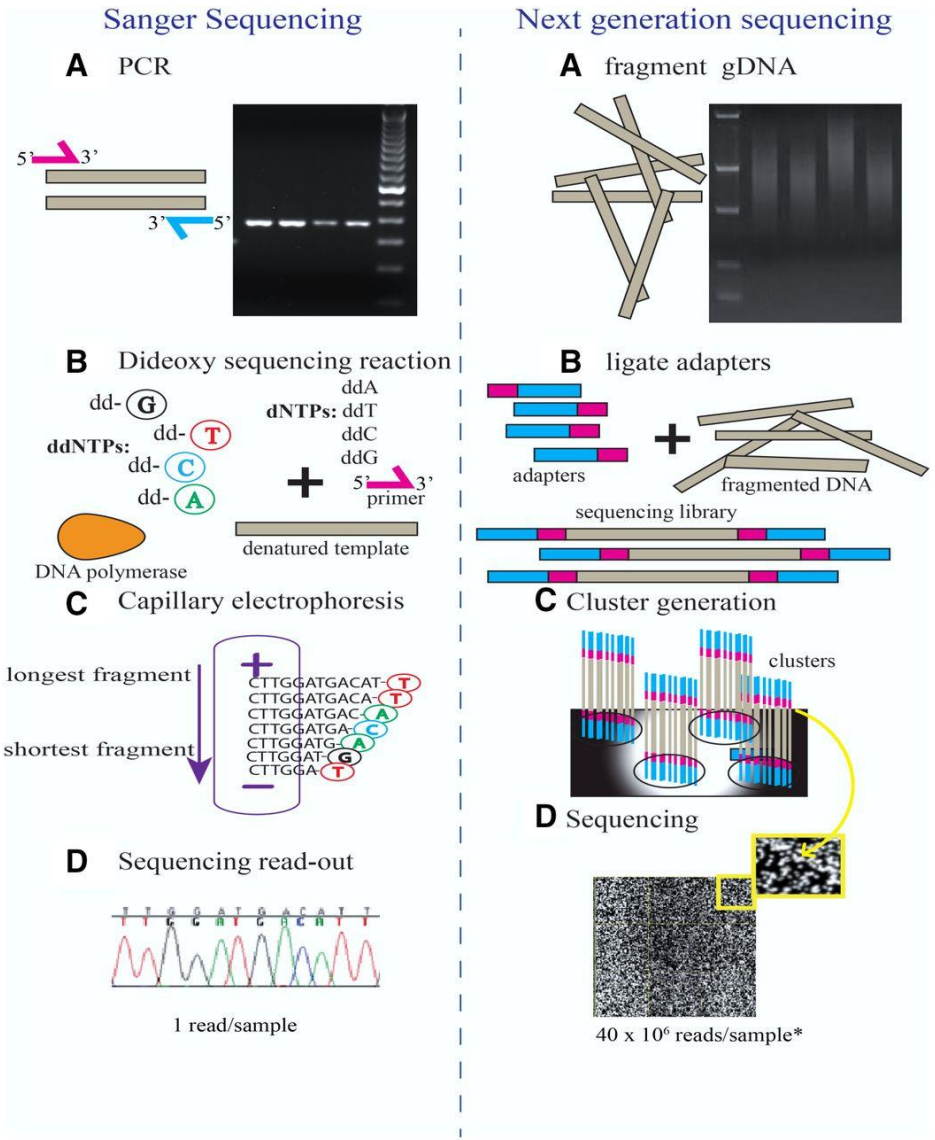
Spectrum of *ERBB2/HER2* mutations

Mut size	Total Cases (n = 25)	Nucleotide sequence*	CDS mutation (inserted sequence)	Amino acid mutation
12-bp ins	19 (76%)	TTG==//==GAAGCATACGTGATGGC**ATACGTGATGGC**TGGTGTGGGCTCCCCATAT -L-==//==-E--A--Y--V--M--A--**Y--V--M--A**--G--V--G--S--P--Y	c.2324_2325ins12 (ATACGTGATGGC duplication*)	p.Ala775_Gly776insTyrValMetAla
12-bp ins	1 (4%)	TTG==//==GAAGCATACGTGATGGCT**TACGTGATGGCT**GGTGTGGGCTCCCCATAT -L-==//==-E--A--Y--V--M--A--**Y--V--M--A**--G--V--G--S--P--Y	c.2325_2326ins12 (TACGTGATGGCT duplication)	p.Ala775_Gly776insTyrValMetAla
3-bp ins	2 (8%)	TTG==//==GAAGCATACGTGATGGCTG**TGT**GTGTGGGCTCCCCATAT -L-==//==-E--A--Y--V--M--A--**V--C**--V--G--S--P--Y	c.2326_2327ins3 (TGT insertion)	p.Gly776>ValCys
9-bp ins	1 (4%)	TTG==//==GAAGCATACGTGATGGCTGGTGTGGGCTCCCC**TGGCTCCCC**ATAT -L-==//==-E--A--Y--V--M--A--G--V--G--S--P--**G--S--P**--Y	c.2339_2340ins9 (TGGTCTCCC insertion)	p.Pro780_Tyr781insGlySerPro
Subs+ 6-bp ins	1 (4%)	TTG==//==GAAGCATACGTGATGGCTTGTGTG**TGTGGG**GGCTCCCCATAT -L-==//==-E--A--Y--V--M--A--**C--V--C--G**--G--S--P--Y-	c.2326G>T and c.2331_2332ins6 (TGTGGG duplication)	p.Gly776Cys and p.Val777_Gly778insCysGly
Subs	1 (4%)	TCG==//==GAAGCATACGTGATGGCTGGTGTGGGCTCCCCATAT -**S**-==//==-E--A--Y--V--M--A--G--V--G--S--P--Y-	c.2264T>C (Substitution)	p.Leu755Ser

Clin Cancer Res 2012;18(18): 4910–8

NGS for HER2 mutation

- NGS is emerging as an important method for identification of HER2 gene mutations in NSCLC
  - The value of performing NGS in place of or in addition to IHC and FISH in lung ADC remains to be validated

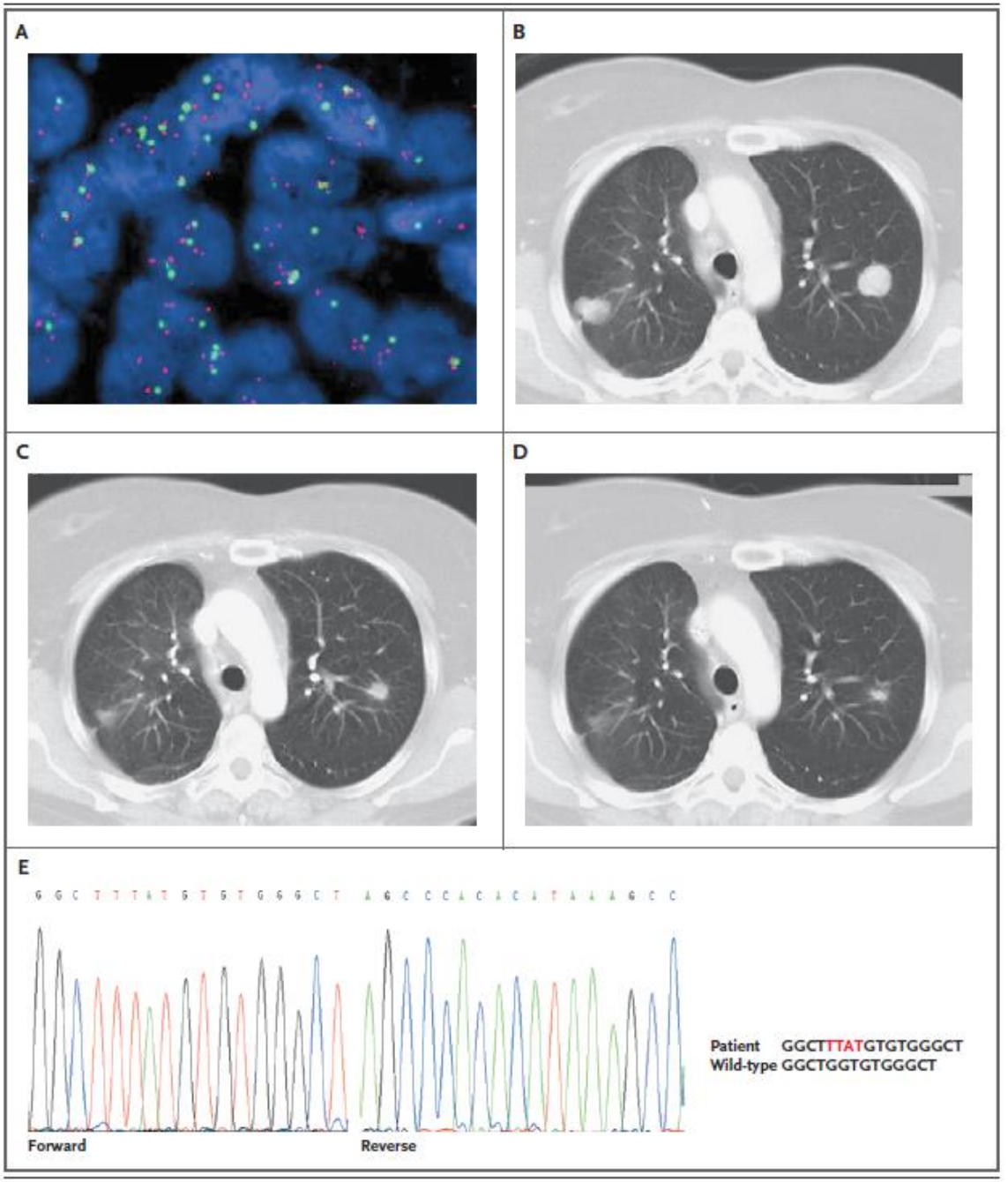


Jaya Punetha, and Eric P. Hoffman Circ Cardiovasc Genet. 2013;6:427-434

The NEW ENGLAND JOURNAL of MEDICINE

HER2 Mutation and Response to Trastuzumab Therapy in Non–Small-Cell Lung Cancer

TO THE EDITOR: Trastuzumab is a monoclonal antibody against HER2, a member of the epidermal growth factor receptor (EGFR) family, that improves the outcome of HER2-positive breast cancer.[1] Preclinical data have demonstrated that trastuzumab is effective in non–small-cell lung cancer, with additive or synergistic effects with various cytotoxic agents. However, trials of trastuzumab or other HER2-targeted agents, such as pertuzumab, failed to demonstrate clinical benefit in non–small-cell lung cancer when administered as monotherapy or



therapy.[2]

In these studies, HER2 immunohistochemical ar not optimal.[3] Moreover, tumors had *HER2* gene were treated with trastuzu trastuzumab.[2] Recently, *HER2* were reported in offering the potential for altered protein.[4] Here, v

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N Engl J Med 2006 Jun 15;354(24):2619-21

Case report

Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu☆,☆☆

J. De Grève[a,*], E. Teugels[a], C. Geers[a], L. Decoster[a], D. Galdermans[b], J. De Mey[a], H. Everaert[a], I. Umelo[a], P. In't Veld[a], D. Schallier[a]

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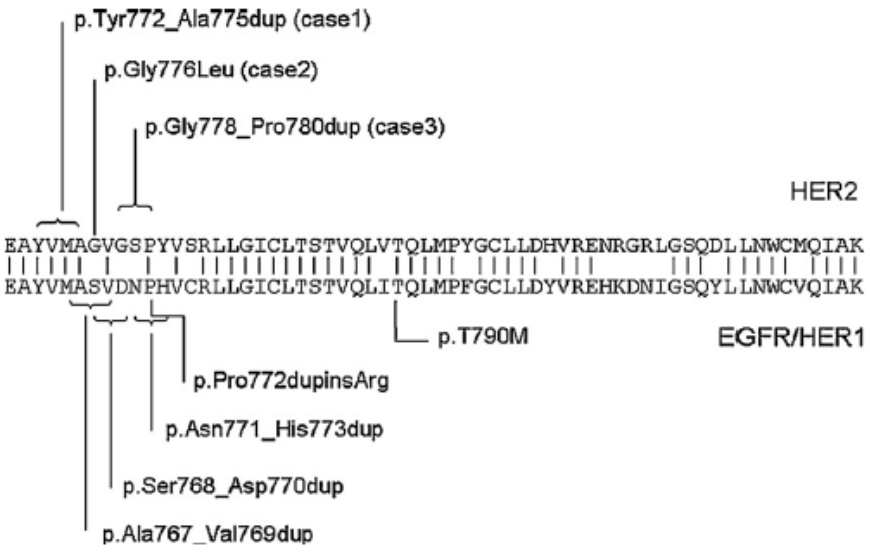
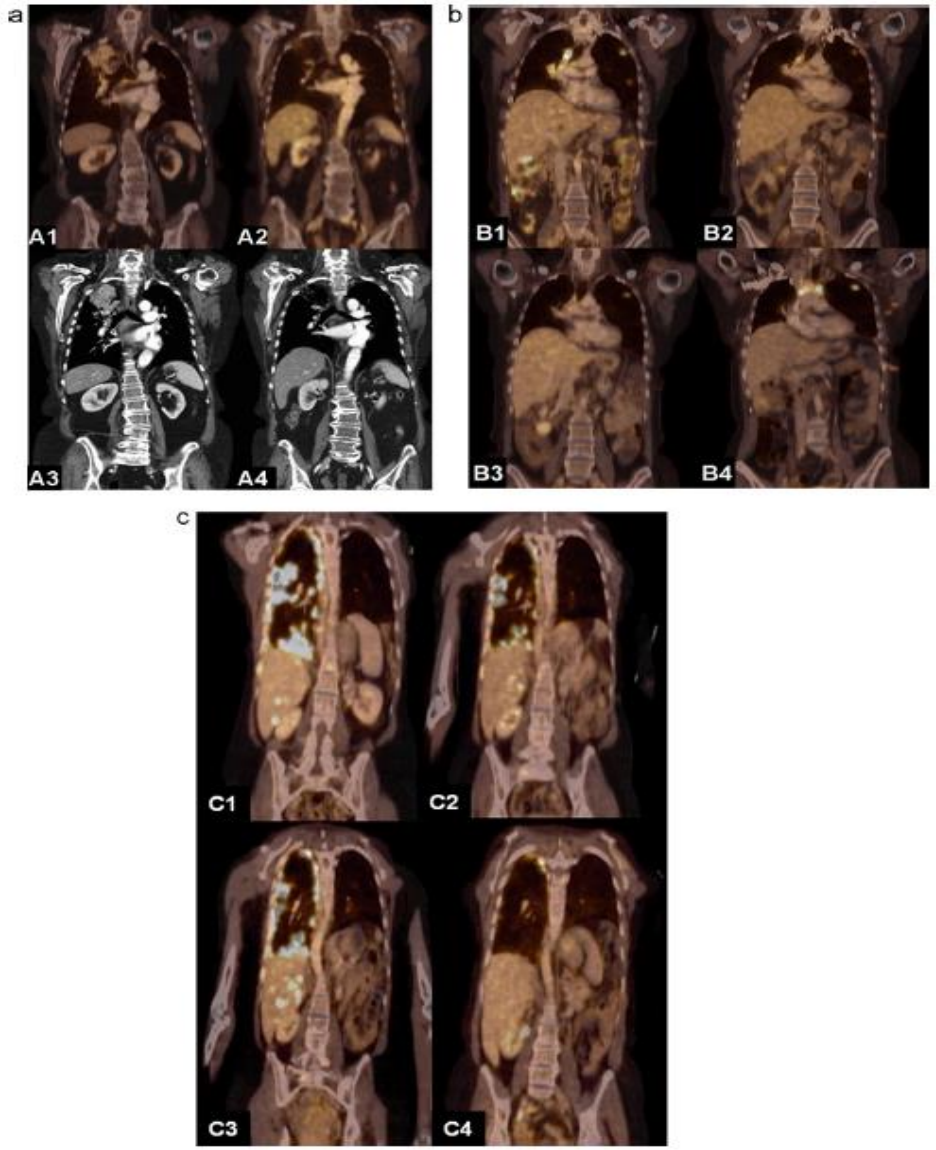


Fig. 1. Examples of HER2 exon 20 mutations.



Lung Cancer 2012;76:123– 127

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lung Cancer That Harbors an *HER2* Mutation: Epidemiologic Characteristics and Therapeutic Perspectives

Julien Mazières, Solange Peters, Benoit Lepage, Alexis B. Cortot, Fabrice Barlesi, Michéle Beau-Faller, Benjamin Besse, Hélène Blons, Audrey Mansuet-Lupo, Thierry Urban, Denis Moro-Sibilot, Eric Dansin, Christos Chouaid, Marie Wislez, Joachim Diebold, Enriqueta Felip, Isabelle Rouquette, Julie D. Milia, and Oliver Gautschi

ABSTRACT

Purpose

HER2 mutations are identified in approximately 2%of non–small-cell lung cancers (NSCLC). There are few data available that describe the clinical course of patients with *HER2*-mutated NSCLC.

Patients and Methods

We retrospectively identified 65 NSCLC, diagnosed with a *HER2* in-frame insertion in exon 20. We collected clinicopathologic characteristics, patients' outcomes, and treatments.

Results

HER2 mutation was identified in 65 (1.7%) of 3,800 patients tested and was almost an exclusive driver, except for one single case with a concomitant *KRAS* mutation. Our population presented

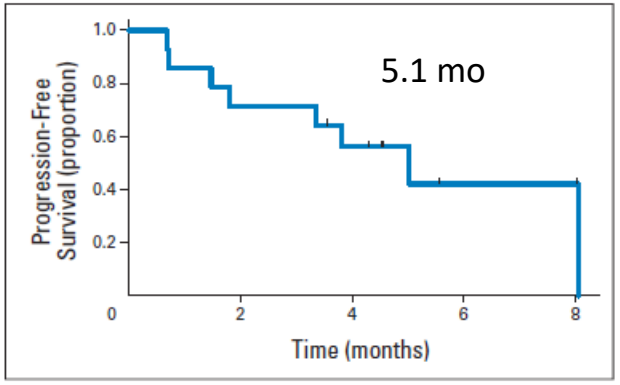
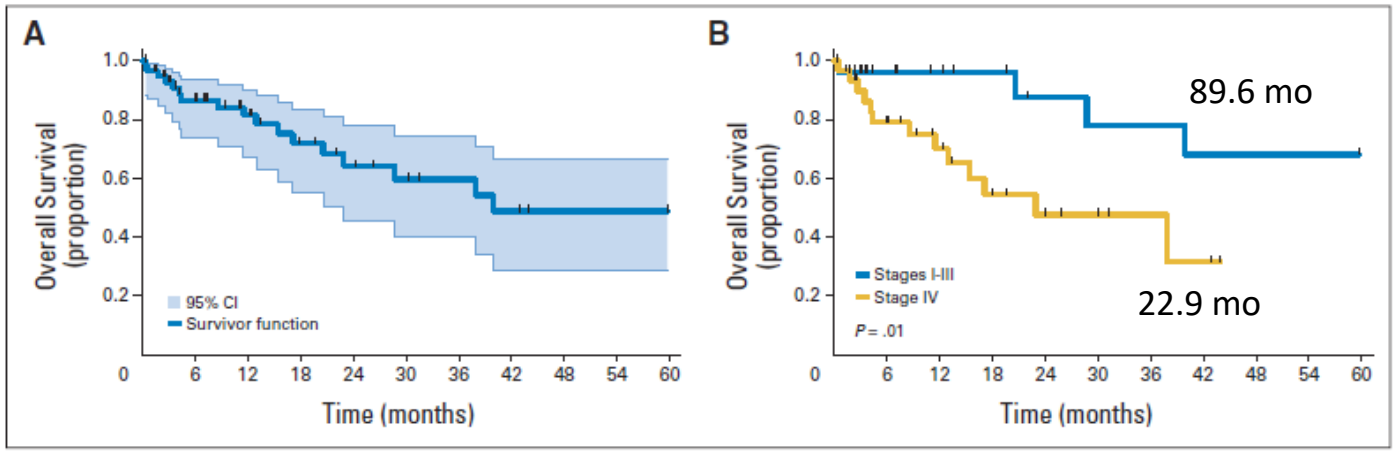


Fig 3. Progression-free survival of stage IV patients treated with anti–human epidermal growth factor receptor 2 (HER2) targeted drugs (n = 15). Only first-line HER2-targeted treatments were analyzed.



J Clin Oncol 2013 Jun 1;31(16):1997-2003

Table 2. Stage IV Patients Treated With Anti-*HER2*–Specific Treatments

Patient	First-Line Treatment		Second-Line Treatment		Third-Line Treatment		Fourth-Line Treatment	
	Treatment	Best Disease Response	Treatment	Best Disease Response	Treatment	Best Disease Response	Treatment	Best Disease Response
11	VIN-HER	PR						
15	CAR-PAC-TRAS	SD						
19	TXT-MASA	PD						
24	VIN-TRAS	PR						
26	CAR-PAC-TRAS	PR						
27	VIN-TRAS	PR						
28	VIN-TRAS	SD						
30	LAP	PD						
31	NVB-HER	PR						
32	LAP	PD	TRAS-VIN	PR	AFA	SD	CAR-TRAS	SD
37	VIN-TRAS	PD						
41	DOC-TRAS	PR						
43	VIN-TRAS	PR	AFA	PR				
44	VIN-TRAS	PR	AFA	SD				
45	VIN-TRAS	SD	PAC-TRAS	SD				
47	TRAS	PR						

- Trastuzumab-based tx (n=15)
  - DCR = 93%
- Afatinib (n=3)
  - DCR = 100%

NOTE. Conventional treatment: CAR, PAC, VIN, and DOC. HER2-specific treatments: TRAS, LAP, AFA, and MASA.

Abbreviations: AFA, afatinib; CAR, carboplatin; DOC, docetaxel; HER2, human epidermal growth factor receptor 2; LAP, lapatinib; MASA, masatinib; NE, not evaluated; NVB, Navelbine (VIN; Pierre Fabre, Castres, France); PAC, paclitaxel; PD, progressive disease; PR, partial response; SD, stable disease; TRAS, trastuzumab; TXT, Taxotere (DOC; sanofi-aventis, Paris, France); VIN, vinorelbine.

J Clin Oncol 2013 Jun 1;31(16):1997-2003

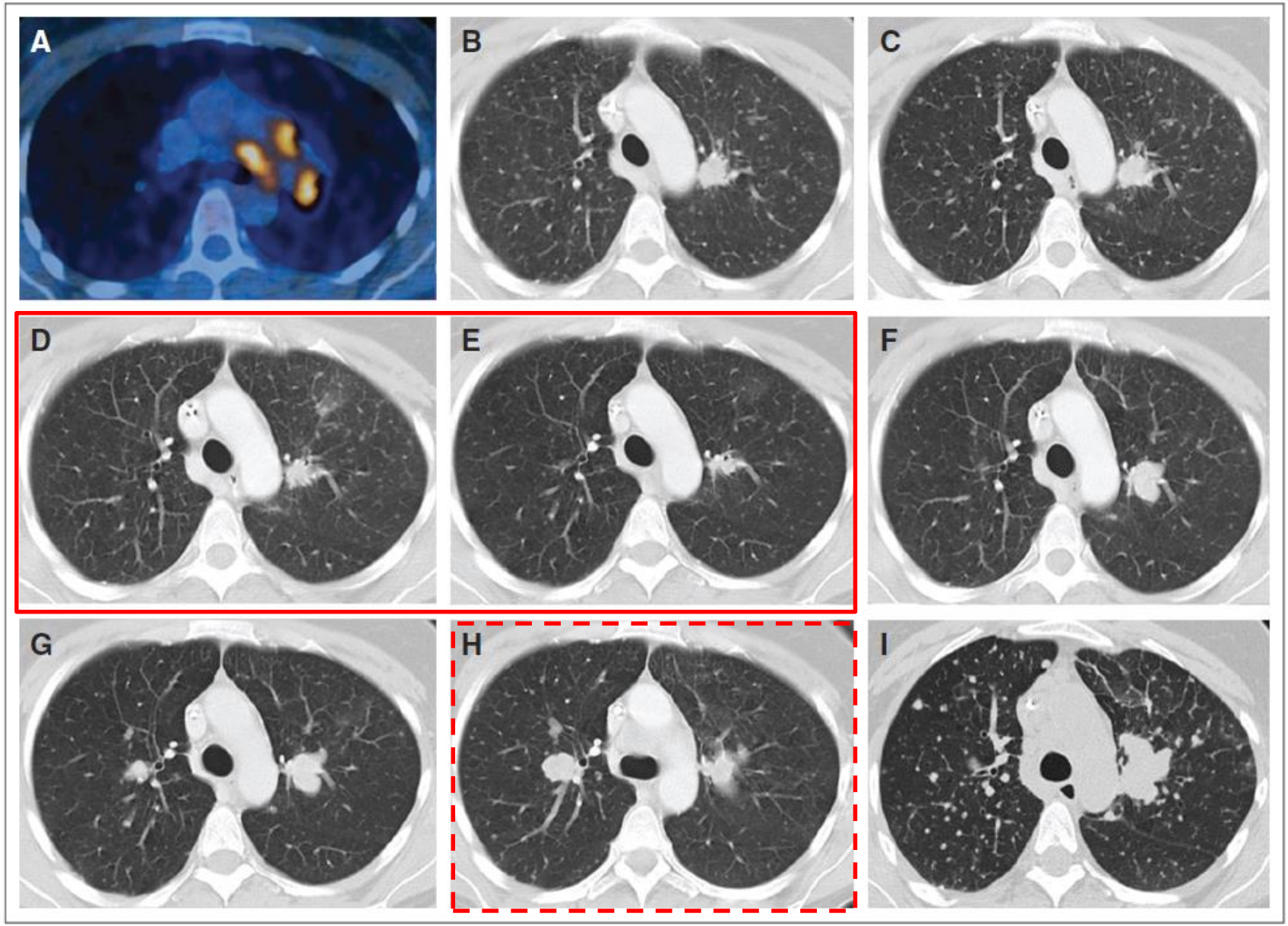


Fig 4. Example of tumor response (patient No. 32). (A) Positron emission tomography–computed tomography scan at initial diagnosis. (B) No response to chemotherapy (platinum, gemcitabine, and bevacizumab, followed by pemetrexed). (C) No response to lapatinib. (D and E) Good partial remission with trastuzumab and vinorelbine. (F) Local progression with trastuzumab maintenance therapy. (G) No response to afatinib. (H) Mixed response to trastuzumab and carboplatin. (I) Disseminated progression, switch to nab (nanoparticle albumin-bound) –paclitaxel and trastuzumab.

J Clin Oncol 2013 Jun 1;31(16):1997-2003

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2017
Non-Small Cell Lung Cancer

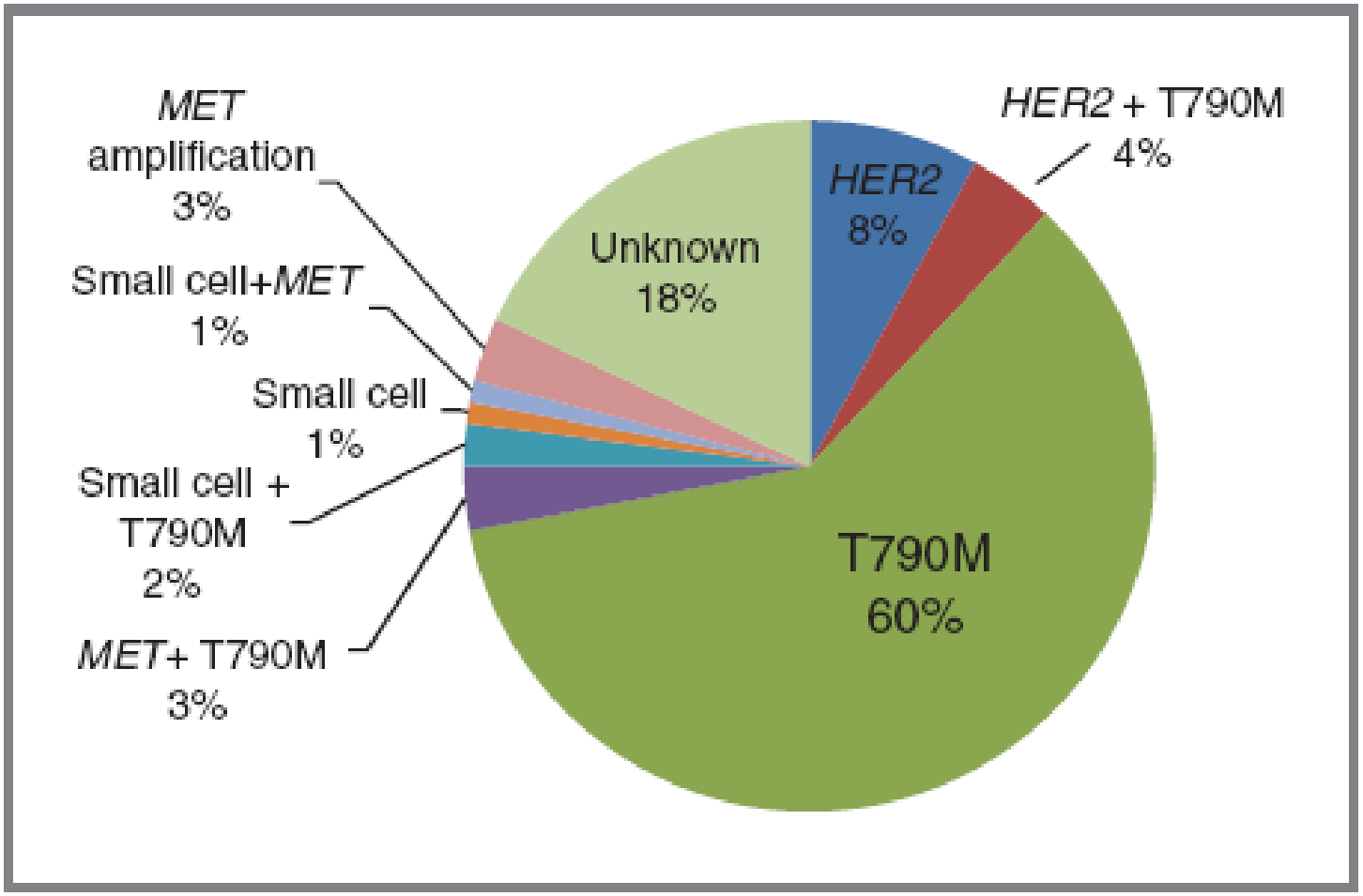
NCCN Guidelines Index
Table of Contents
Discussion

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF* V600E mutation *Non-V600E mutations have variable kinase activity and response to these agents.	vemurafenib[1,2] dabrafenib[2,3] dabrafenib + trametinib[4]
High-level ***MET*** amplification or MET exon 14 skipping mutation	crizotinib[5-9]
RET rearrangements	cabozantinib[10,11] vandetanib[12]
HER2 mutations	trastuzumab[13] (category 2B) afatinib[14] (category 2B)

13. N Engl J Med 2006 Jun 15;354(24):2619-21
14. J Clin Oncol 2013 Jun 1;31(16):1997-2003

Acquired resistance in 1st generation EGFR-TKI



Yu et al. Clin Cancer Res 2013

HER2 amplification with acquired resistance to 1st-generation EGFR TKIs

- HER2 amplification has also been described as an acquired mechanism of resistance to EGFR-TKIs in up to 12% of EGFR-mutant NSCLC tumors, occurring independently of the T790M mutation

Cancer Discov 2012;2:922–33

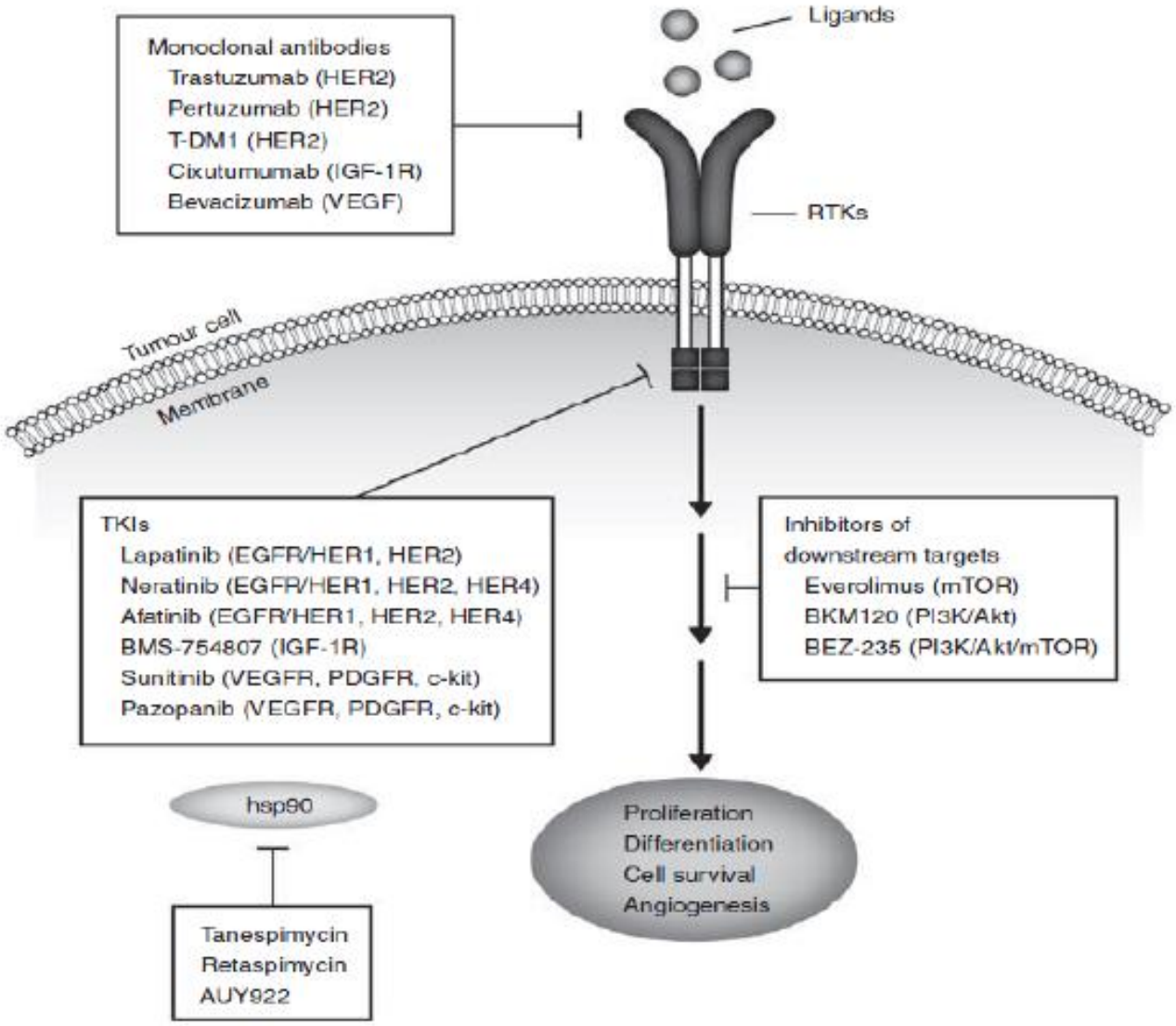
- In this scenario,
  - **Dual EGFR blockade** by afatinib + cetuximab
    - Induce responses in some patients negative for the T790M mutation

Cancer Discov 2014;4:1036–45

  - **Dual inhibition of EGFR and HER2** by afatinib, dacomitinib, lapatinib or neratinib
    - Results with afatinib in HER2(+) NSCLC have been promising

Lung Cancer 2012;76:123–7

Targeted agents for HER2+ BC



British Journal of Cancer (2012) 106(1), 6 – 13

SUMMARY

- HER2 (+) has been well-studied in breast cancer, but its importance is still being **explored in NSCLC**
  - Laboratory methods (IHC, FISH, NGS) should be validated
  - **HER2 mutations** & the clinical demonstration of activity of anti-HER2 agents have renewed interest on the role of HER2 pathway
  - It may be plausible to conclude that HER2 (+) in NSCLC confers a favorable prognosis due to availability of the **HER2 targeted therapies**

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International Journal of Cancer

Antitumor activity of HM781-36B, a highly effective pan-HER inhibitor in erlotinib-resistant NSCLC and other EGFR-dependent cancer models

Mi Young Cha[1,2], Kwang-Ok Lee[1], Mira Kim[1], Ji Yeon Song[1], Kyu Hang Lee[1], Jongmin Park[2], Yun Jung Chae[1], Young Hoon Kim[1], Kwee Hyun Suh[1], Gwan Sun Lee[1], Seung Bum Park[2,3] and Maeng Sup Kim[1]

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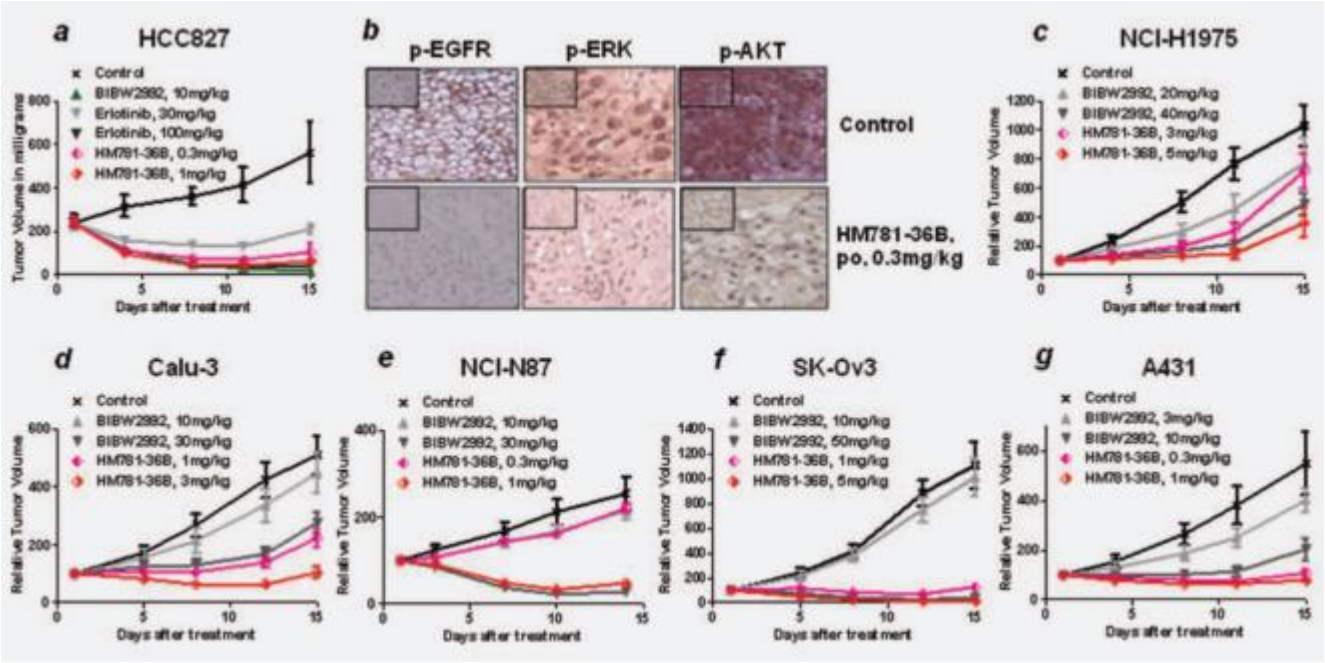


Int J Cancer 2012;130:2445–2454.

pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2017;49(1):10-19

https://doi.org/10.4143/crt.2016.058

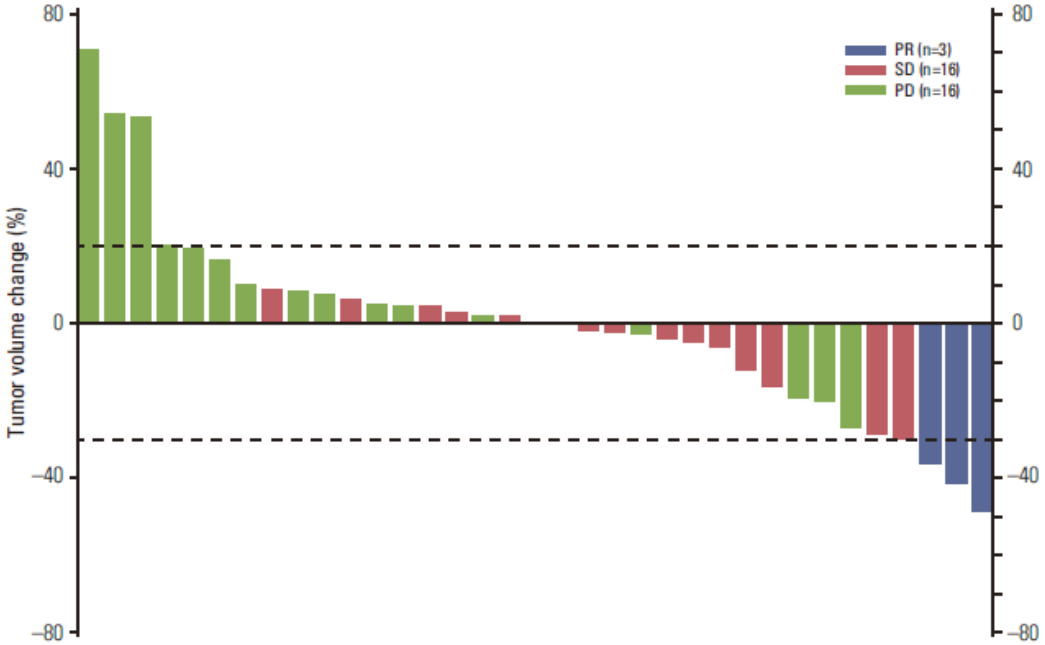
Original Article

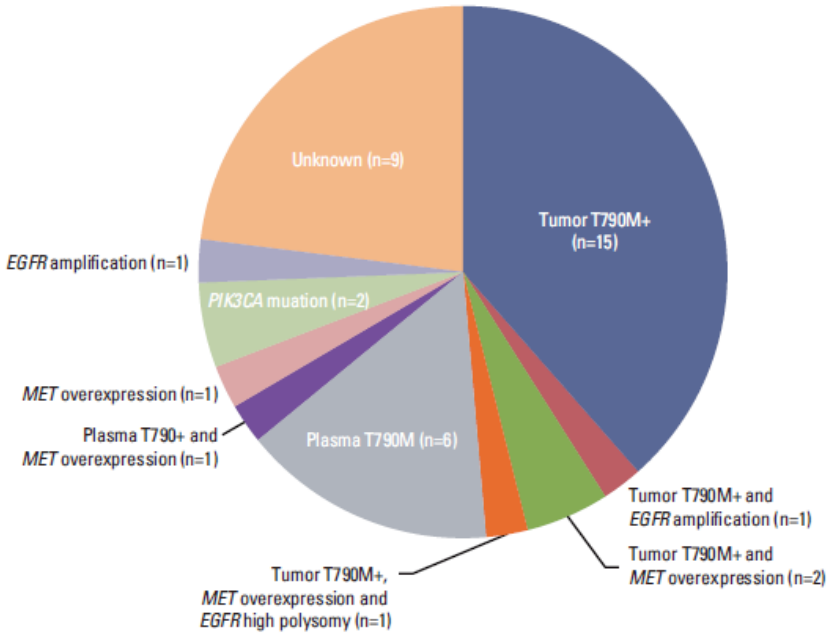
Open Access

A Phase II Study of Poziotinib in Patients with Epidermal Growth Factor Receptor (*EGFR*)-Mutant Lung Adenocarcinoma Who Have Acquired Resistance to EGFR–Tyrosine Kinase Inhibitors

Table 2. Response to treatment with poziotinib by independent review

Variable	Total (n=39)
PFS events, n (%)	34 (87)
Estimated PFS, median (95% CI, mo)	2.7 (1.8-3.7)
PFS events at week 16, n (%)	24 (62)
Estimated PFS at week 16 (95% CI, %)	35 (20-51)
Deaths, n (%)	20 (51)
Estimated OS, median (95% CI, mo)	15.0 (9.5-NE)
Best response, n (%)	
CR	0
PR	3 (8)
SD	17 (44)
PD	18 (46)
Not evaluable	1 (3)
ORR (95% CI, %)	8 (2-21)
DCR (95% CI, %)	51 (35-68)
Estimated duration of response, median (95% CI, mo)	4.5 (3.7-4.6)
Estimated duration of disease control, median (95% CI, mo)	3.7 (1.8-3.8)





Conclusion

In this explorative phase II study poziotinib provided modest clinical benefit in patients with advanced or metastatic lung adenocarcinoma having progressed on erlotinib or gefitinib. This study provided **no** obvious clinical evidence showing that poziotinib may overcome AR secondary to *EGFR* T790M mutation.

Table 3. TEAEs by CTCAE grade reported in ≥ 5% of patients

Preferred term	Any grade	Grade 1	Grade 2	Grade 3
No. of patients	39 (100)	39 (100)	39 (100)	39 (100)
Total with adverse events	39 (100)	39 (100)	37 (95)	37 (95)
Diarrhoea	36 (92)	30 (77)	17 (44)	4 (10)
Rash	30 (77)	14 (36)	17 (44)	23 (59)
Pruritus	25 (64)	10 (26)	17 (44)	2 (5)
Stomatitis	23 (59)	11 (28)	13 (33)	7 (18)
Paronychia	21 (54)	8 (21)	13 (33)	2 (5)
Decreased appetite	19 (49)	12 (31)	8 (21)	5 (13)
Mucosal inflammation	18 (46)	8 (21)	9 (23)	10 (26)
Dry skin	15 (38)	8 (21)	7 (18)	1 (3)
Fatigue	12 (31)	7 (18)	7 (18)	1 (3)
Dyspepsia	8 (21)	6 (15)	2 (5)	0
Hypokalaemia	7 (18)	2 (5)	2 (5)	4 (10)
Alopecia	6 (15)	6 (15)	0	0
Dermatitis acneiform	5 (13)	2 (5)	0	4 (10)

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Rank	Status	Study
1	Terminated	NOV120101 (Poziotinib) for 1st Line Monotherapy in Patients With Lung Adenocarcinoma **Conditions:** Adenocarcinoma of Lung Stage IIIB; Adenocarcinoma of Lung Stage IV **Intervention:** Drug: NOV120101 (Poziotinib)
2	Recruiting	Study of Poziotinib in Patients With HER2-Positive Metastatic Breast Cancer **Condition:** Breast Cancer **Intervention:** Drug: Poziotinib
3	Recruiting	A Phase II, Single-Arm Trial of Poziotinib as Salvage Treatment in Patients With Metastatic Breast Cancer Who Has HER2 or EGFR Mutation or Activated AR or EGFR Pathway **Condition:** Metastatic Breast Cancer **Intervention:** Drug: Poziotinib
4	Active, not recruiting	Poziotinib in Patients With HER2+ Recurrent Stage IV BC Who Have Received at Least 2 Prior HER2-directed Regimens **Condition:** Metastatic Breast Cancer **Intervention:** Drug: NOV120101 (Poziotinib)
5	Completed	Clinical Trial to Determine the MTD of HM781-36B in Patients With Advanced Solid Tumors **Condition:** Advanced Solid Malignancies **Intervention:** Drug: HM781-36B tablets
6	Recruiting	Poziotinib in Stage IV Lung Adenocarcinoma With HER2 Mutation (KASTT001) **Conditions:** HER2 Gene Mutation; Adenocarcinoma Lung Stage IV **Intervention:** Drug: Poziotinib
7	Completed	A Phase I-II Study of HM781-36B Combined With Paclitaxel and Trastuzumab in HER-2 Positive Advanced Gastric Cancer **Condition:** HER-2 Positive Advanced Gastric Cancer **Interventions:** Drug: HM781-36B(Poziotinib); Drug: Paclitaxel; Drug: Trastuzumab
8	Completed	NOV120101 Phase 2 Study in NSCLC Patients With Aquired Resistance to 1st Generation EGFR Tyrosine Kinase Inhibitors **Condition:** Increased Drug Resistance **Intervention:** Drug: NOV120101 (Poziotinib)
9	Completed	Phase I Study to Determine the Maximum Tolerated Dose and to Assess the Safety and Pharmacokinetic Profile

Poziotinib in Stage IV Lung Adenocarcinoma With HER2 Mutation (KASTT001)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2016 by Korean Association for the Study of Targeted Therapy

Sponsor:
Korean Association for the Study of Targeted Therapy

Collaborators:
Konkuk University Medical Center
Kyungpook National University
Kosin University Gospel Hospital
Chonnam National University Hospital
Chungnam National University Hospital

Information provided by (Responsible Party):
Korean Association for the Study of Targeted Therapy

ClinicalTrials.gov Identifier:
NCT02979821

First received: November 24, 2016
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Last verified: November 2016
History of Changes

[임상시험 계획서 요약]

임상시험 제목	HER2 돌연변이가 확인된 4기 폐선암 환자를 대상으로 Pan-HER 저해제 (HM781-36B, Poziotinib)의 효과를 평가하기 위한 2상 연구
임상시험 단계	제 2상
임상시험용 의약품	시험약: 포지오티닙 (Poziotinib)
목 적	HER2의 돌연변이가 확인된 4기 진행성 폐선암 환자를 대상으로 항암요법으로서의 Poziotinib의 유효성 및 안전성을 평가한다.
시험 설계	전향적, 공개, 단일군, 다기관 치료적 탐색 임상시험
대상질환	HER2 돌연변이가 확인된 4기 폐선암
시험대상자수	폐암의 항암치료에 대한 반응률이 일반적으로 50%로 알려져 있고, HER2 mutation이 있는 환자에서 poziotinib에 대한 반응률이 70%로 나올 경우 일반 항암치료의 반응률 50%와 비교하여 유효성이 좋다는 전제하에, single stage phase II design에 근거하여 유의수준 5%와 검정력 80%하에서 43명의 환자가 필요하다. 이에 탈락률 10%를 고려해서 47명의 환자를 모집하도록 한다.

유전자 검사

- Central HER2 mutation 검사는 두 기관에서 시행
  - ❖ 1차 검사(스크리닝)
    - 마크로젠에서 Sequencing을 통해 양성/음성 확인
    - DNA 200 ng
  - ❖ 2차 검사
    - Sequencing(+) 대상으로 시선바이오에서 NGS technique으로 HER2 mutation 확진
    - DNA 100 ng

시험대상자의 선정/제외 기준	**선정기준** (대상환자들은 다음의 모든 기준에 적합해야 한다) 1) 4 기 폐선암 환자 2) NGS technique 진단에 의한 HER2(EXON 20 mutation) 양성인 환자 - Confirmed EGFR/ALK negative patients with remnant tumor DNA EGFR 돌연변이(EXON18 G719A/S , EXON19 deletion, EXON21 L858R) 음성인 환자 및 ALK 전위 음성인 환자 (ALK test; 면역염색 or FISH, both acceptable) - NGS technique 진단에 의해 이미 HER2(EXON 20 mutation) 양성이 확인된 환자는 재검사 없이 참여가 가능하다. 3) 최소 1 회 이상의 화학요법을 받은 환자 (not EGFR-TKI) 단, 마지막 항암치료로부터 최소 2 주가 경과되고, 이전 화학요법에 대한 독성이 grade 1 이하로 회복된 경우 4) ECOG 수행도; 0-2 5) RECIST 기준에 따라 반응 평가 가능한 병변이 있는 환자 (최소한 하나 이상의 측정 가능한 병변이 있어야 함) 6) 적절한 골수, 신장, 간기능을 유지하고 있는 환자 (1) Neutophil count: > 1,500/uL (2) Platelet count: > 100,000/uL (3) Hb: > 9.0g/dL (4) AST/ALT : < 2.0 x upper normal limit (5) Bilirubin: < 1.25 x upper normal limit (6) Serum creatinine : < upper normal limit

제외기준 (다음 조건의 어느 하나라도 해당되는 환자는 본 임상시험에 참여할 수 없다.)

1) 예측 잔여생존기간이 3개월 미만
2) 수술 및/또는 방사선으로 아직 명확하게 치료되지 않은 CNS 전이가 있거나 척수압박이 있는 경우 (단, 수술 및/또는 방사선 치료를 받은 이후 임상적으로 안정된 상태인 경우, 뇌전이가 있더라도 증상이 없는 경우로 연구자가 적합하다고 판정한 경우 연구에 참여 가능)
3) 시험자가 판단하였을 때, 중증 또는 조절되지 않는 전신 질환의 증거가 있는 경우 (예, 불안정한 또는 uncompensated 호흡기, 심장, 간 또는 신장 질환)
4) 이전에 EGFR 저해제 및 pan-HER 저해제로 치료 받은 경우
5) 임부 및 수유부
6) 임상시험기간 및 투여 종료 후 최소 2 개월 이상 금욕하거나 적절한 피임법을 사용 할 의사가 없는 가임 여성 및 남성
7) 기존의 간질성 폐질환을 동반한 환자
8) 폐선암 외 악성 종양의 병력이 있는 환자(단, 효과적으로 치료된 비흑색종 피부암, 자궁경부의 상피내암종, 유방 관상피내암 및 기타 악성 종양 환자로서 3 년 이상 관 해 상태를 유지하여 완치된 것으로 시험자가 판단한 경우는 제외한다.)
9) 안정시 좌심실 구출률(LVEF)이 각 기관 기준의 정상하한치 미만인 환자 (단, 시험기 관의 정상치가 설정되어 있지 않은 경우에는 50%를 기준으로 한다.)
10) 본 임상시험용의약품 투여 4 주 이내에 전신마취 혹은 호흡 보조장치를 필요로 하 는 대수술을 받은 환자

시험기간	식품의약품안전처 승인일로부터 36개월
평가 항목 및 평가 방법	1. 유효성 평가 1.1 일차 유효성 평가 변수 완전 반응(CR)와 부분 반응(PR) 비율을 포함한 객관적 반응률(Objective response rate, ORR) 1.2 이차 유효성 평가 변수 시험약 투여 이후 질병진행까지의 기간(Time to progression, TTP) 2. 안전성 평가 이상반응(NCI-CTCAE ver4.0 기준), 활력징후, 신체검사, 실험실적 검사
통계분석	**1. 일차 유효성 평가에 대한 분석** 객관적 반응률(ORR)에 대하여 시험대상자의 빈도와 비율을 계산하고, 95%의 신뢰구간을 산출한다. **2. 이차 유효성 평가에 대한 분석** 시험약 투여 이후 질병진행까지의 기간(TTP)은 Kaplan-Meier method를 이용하여 중앙 생존기간(median survival time)과 그에 대한 95% 신뢰구간을 제시한다.

▪ 임상시험 흐름도

임상시험기간	Screening	Treatment period (21일)		End of treatment	FU
		Cycle 1[1] (이후 홀수 주기)	Cycle 2 (이후 짝수 주기)		
Day	(Day -28)	D1 ± 3일	D1 ± 3일		± 7일
시험대상자 동의서	V				
인구통계자료/ 환자 기초정보	V				
스크리닝 번호 부여	V				
등록번호 부여		V[2]			
활력징후	V	V	V	V	
체중	V	V	V	V	
임신 검사[3]	V				
신체검사/ECOG 평가	V	V	V	V	
항암제(시험약) 배부/반납		V	V	V[4]	
실험실적 검사[5]	V	V	V	V	
MUGA or 심초음파[6]	v				
심전도[7]	V	V		V	
선행 및 병용약물검사[8]	V				
X-ray	V[9]		V	V	
종양 평가	V	V[10]		V	V[11]
DNA 검사를 위한 검체 수집	V				
이상반응조사		V	V	V	V[13]

조기종료 근거 및 기준

- 현재까지 알려진 HER2 mutation의 발현율은 폐선암에서 1-4% 이나 국내에서는 HER2 mutation의 발현율이 얼마나 되는지에 대한 연구 결과는 아직 없는 상태이다.
- 그러나 국외에서는 EGFR mutation과 ALK translocation이 모두 음성인 환자에게서 HER2 mutation이 최고 6%까지 발현되는 것으로 보고 되었다.

- HER2 mutation의 국내 및 국외 발현율을 고려하고 불필요한 선별검사를 최소화하기 위해, EGFR mutation과 ALK translocation이 모두 음성인 환자 100명 중에서 **HER2 mutation 발현율이 5%**를 넘지 않으면 본 연구를 중지할 수 있다.
- 또한, HM-PHI-102 1상 연구 결과를 토대로 등록된 10명의 환자에게서 **3명 미만으로 DCR**을 보일 경우에도 연구를 중지할 수 있다.

시험약 재투여시 용량 감량 기준		용량 감량		
이상약물반응 유형 및 단계		**1차 발현**	**2차 발현**	**3차 발현**
설사	적절한 지사제 투여 및 수분 보충에도 불구하고 CTCAE 3등급의 설사가 있는 경우	12 mg (시험자 판단에 따라 8 mg 으로 감량 가능)	8 mg	8 mg (2주 투여 1주 휴약)
	적절한 지사제 투여 및 수분 보충에도 불구하고 2일(48시간) 이상 연속적으로 CTCAE 2등급의 설사가 있는 경우	12 mg	8 mg	8 mg (시험자 판단에 의해 2주 투여 1주 휴약 가능)
오심 및/또는 구토	적절한 항구토 치료 및 수분 보충에도 불구하고 CTCAE 3등급의 오심 및/또는 구토가 있는 경우	12 mg (시험자 판단에 따라 8 mg 으로 감량 가능)	8 mg	8 mg (2주 투여 1주 휴약)
	적절한 항구토 치료 및 수분 보충에도 불구하고 2일(48시간) 이상 연속적으로 CTCAE 2등급의 오심 및/또는 구토가 있는 경우	12 mg	8 mg	8 mg (시험자 판단에 의해 2주 투여 1주 휴약 가능)
전신 항생제를 포함한 최적의 보존적 요법에도 불구하고 CTCAE 3등급의 발진이 있는 경우		12 mg	8 mg	8 mg (시험자 판단에 의해 2주 투여 1주 휴약 가능)
간질성 폐질환 또는 폐렴 (pneumoniti)	진단	시험약 투여 영구 중단		
위에 제시된 경우를 제외한 CTCAE 3등급의 모든 이상약물반응		12 mg (시험자 판단에 따라 8 mg 으로 감량 가능)	8 mg	8 mg (2주 투여 1주 휴약)

HER2 Mutation Test

Sites	D-sequencing (n)	NGS (n)	HER2 Positive (n)	%
서울아산병원	294	66	15	5.1%
화순전남대병원	25	15	7	**28.0%**
부산대병원	28	14	3	10.7%
강남성모병원	50	28	4	8.0%
Total	**407**	**129**	**29**	**7.1%**

Mutation types (in Ex 20)	아산병원	화순전남대병원	부산대	강남성모	Total
c.2324_2325 InsYVMA	3	2	1	2	**8**
c.2324_2327 InsTG-T			1		**1**
c.2325_2329 InsGT-T	2				**2**
c.2326_2327 InsTGT	9	3		1	**13**
c.2339_2340 InsGSP				1	**1**
p.N813D (A>G)		1			**1**
p.V773M (G>A)	1				**1**
p.E812K (G>A)		**1**			**1**
p.R814H(G>A), p.Q828R(A>G)			1		**1**
Total	15	7	3	4	29

Demographics of HER2(+) NSCLC

Characteristics (N = 29)	No. (%)
Age, median (range, years)	57 (25 – 86)
Sex	
Female	17 (58.6)
Male	12 (41.4)
Smoking status	
Never	20 (70.0)
Ex / current smoker	3 (10.3)/ 6 (20.7)
< 20 pack-years	2 (6.9)
≥ 20 pack-years	7 (24.1)
Histology	
ADC	29 (100)
Coexisting alterations	
EGFR mutation	0
ALK rearrangement (IHC/FISH/NA)	2 (6.9) / 0 / 3 (10.3)
Stage	
IA / IB	6 (20.7) / 1 (3.4)
IIA / IIB	1 (3.4) / 0
IIIA / IIIB	2 (6.9) / 3 (10.3)
IV	16 (55.2)

Site Enrollment Status

2017-02-09 현재

Site No.	Site Name	PI	Screened #	S/F #	Enrolled #	Ongoing #	EOT #	
							PD	Others*
01	건국대학교병원	이계영 교수님	2	0	**2**	0	2	0
04	화순전남대학교병원	김영철 교수님	8	3	**4**	0	1	3
Actual N / Planned N : 6/47 (13%)			**10**	**3**	**6**	**0**	**3**	**3**

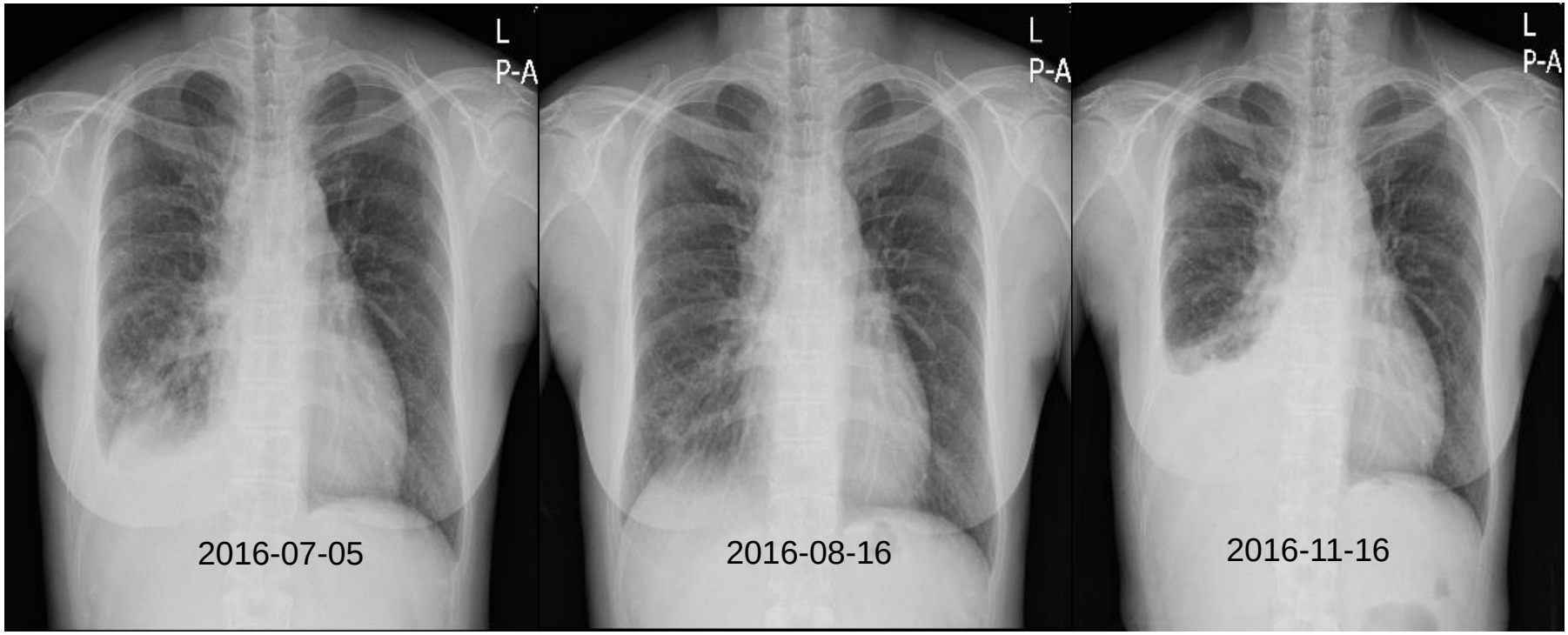
*** EOT_Others: SAE, UK, IP non-compliance, AE, Lost to FU**

Demographics

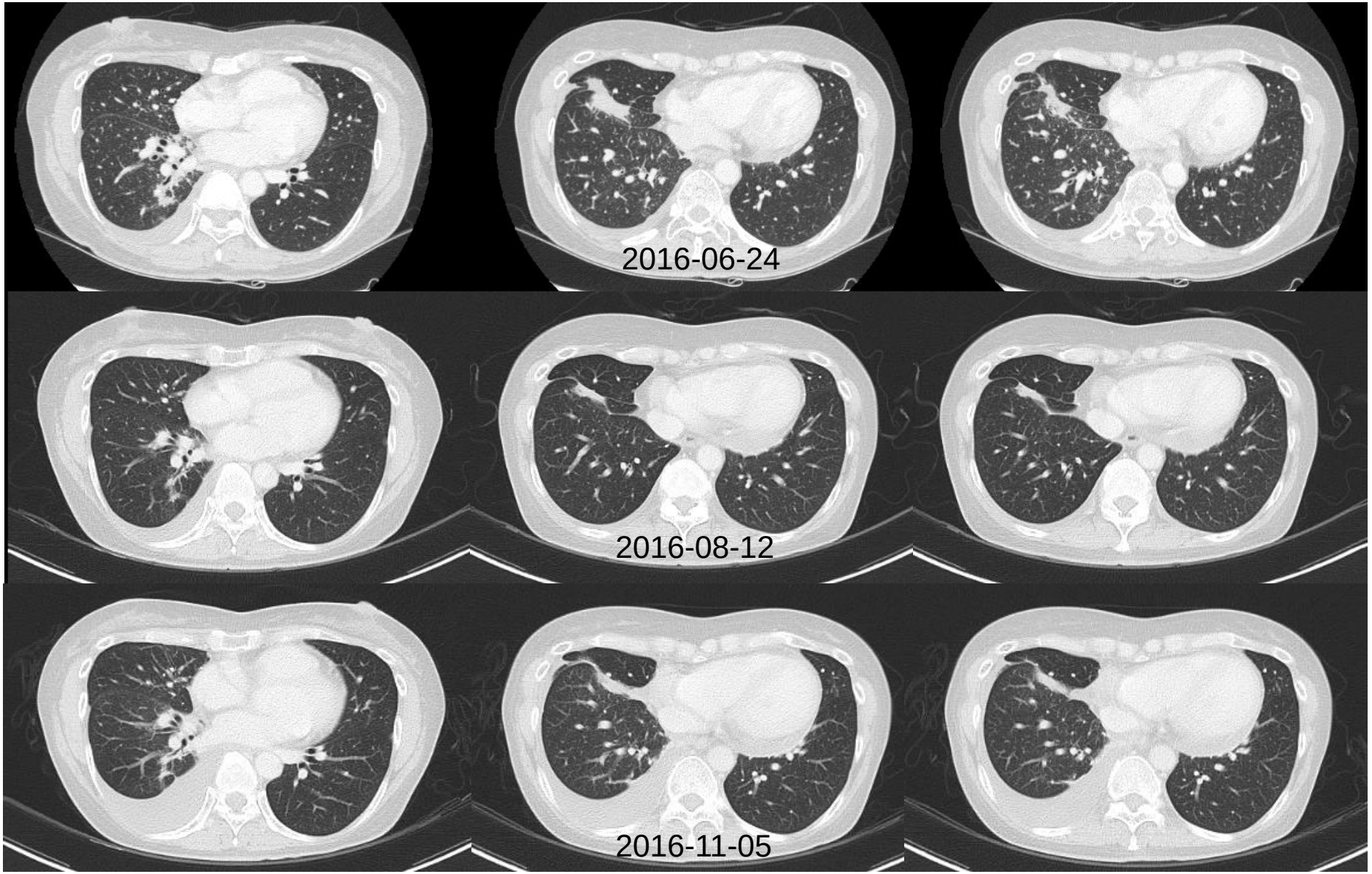
Characteristics (N = 6)	No. (%)
Age, median (range, yr)	60 (47 – 67)
Sex	
Female	6 (100)
Male	0
Smoking status	
Never	6 (100)
Smoker	0
ECOG PS	
0	1 (16.7)
1	4 (66.7)
2	1 (16.7)
Previous treatment (*response*)	
AP (*1SD, 1PD*) → **D** (*PR*)	2 (33.4)
CCRT with EP (*SD*) → **A** (*SD*) → **G** (*SD*)	1 (16.7)
AP (*SD*)	1 (16.7)
A (*SD*)	1 (16.7)
GC (*PD*)	1 (16.7)

47 YO Female

- 2014.8.18 ADC cT2N2M0, EGFR(-), ALK(-), K-ras(-), HER2 c.2336 Ins TGT
- Neoadjuvant CCRT
- Alimta: 2016.3.14. SD, 2016.6.30. PD
- Poziotinib 12 mg: 2016.7.5 ~



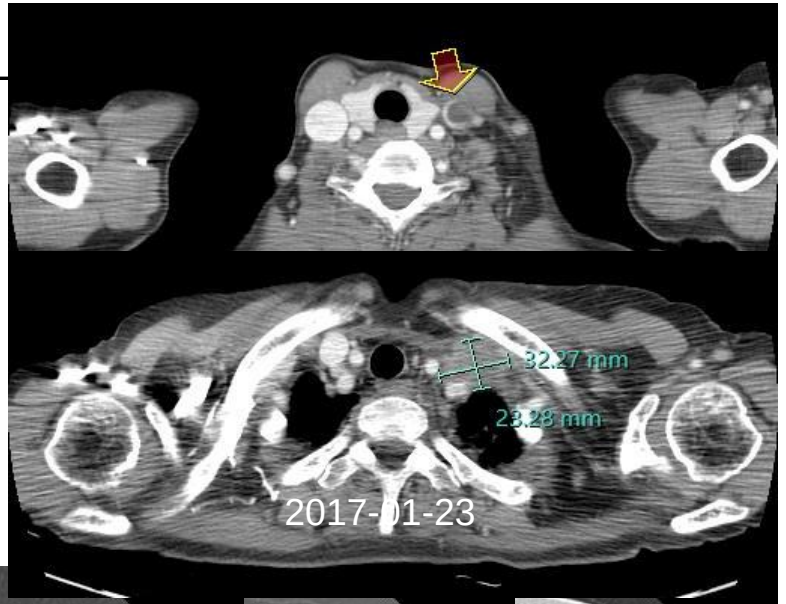
47 YO Female

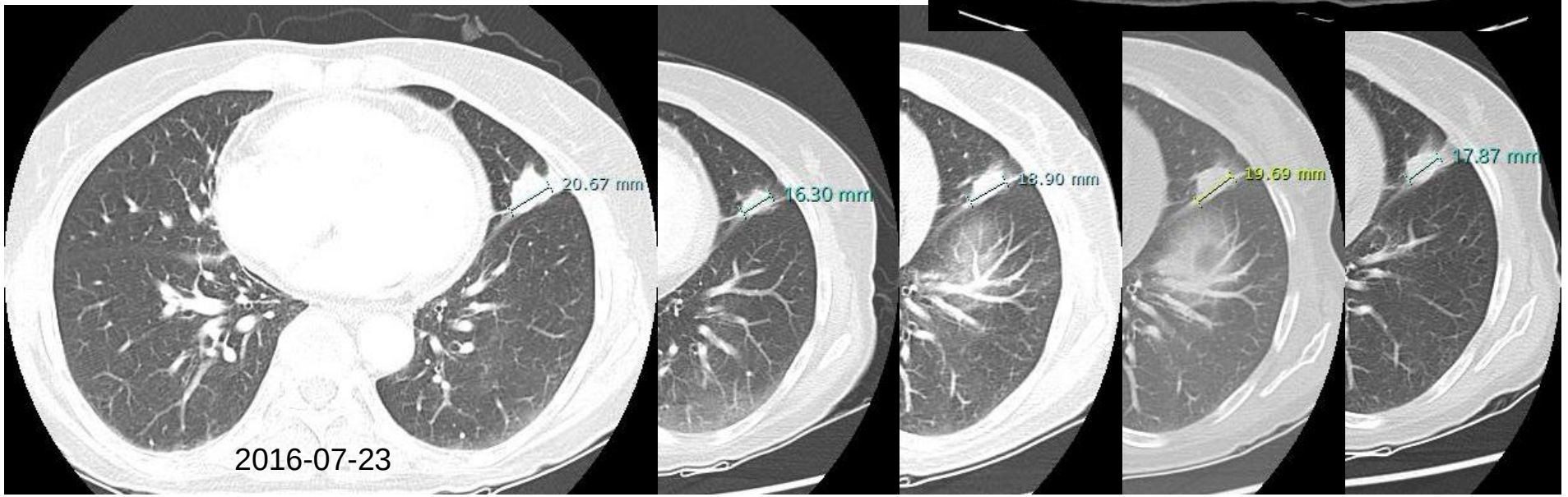


58 YO Female

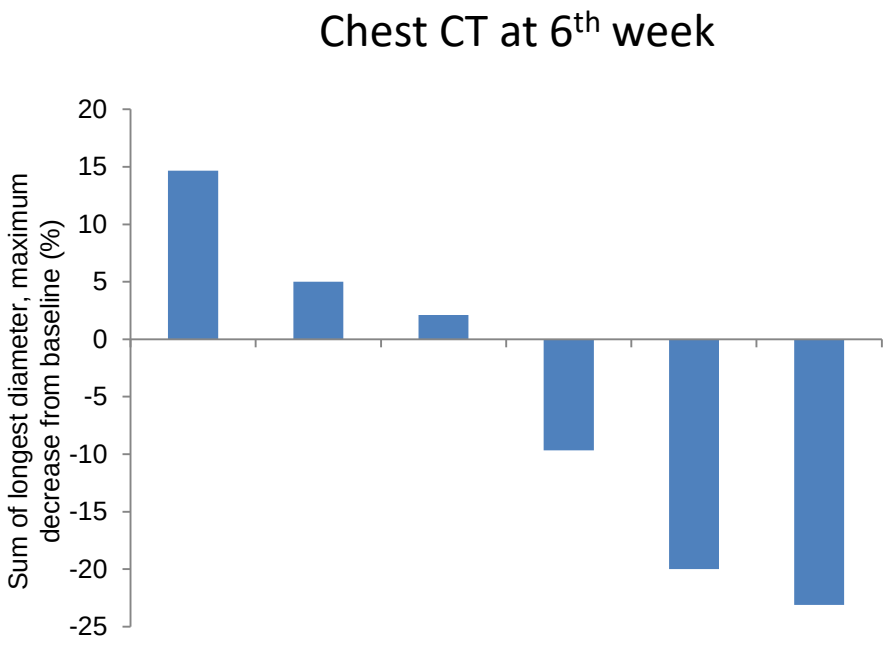
- ADC,LUL(2015.2.12) IV(T1aN3M1b) - both cervical L
- ✓ EGFR PNA: wild, ALK IHC (1+), ALK FISH(-)
- ✓ HER2 Exon 20 Ins YVMA mutation

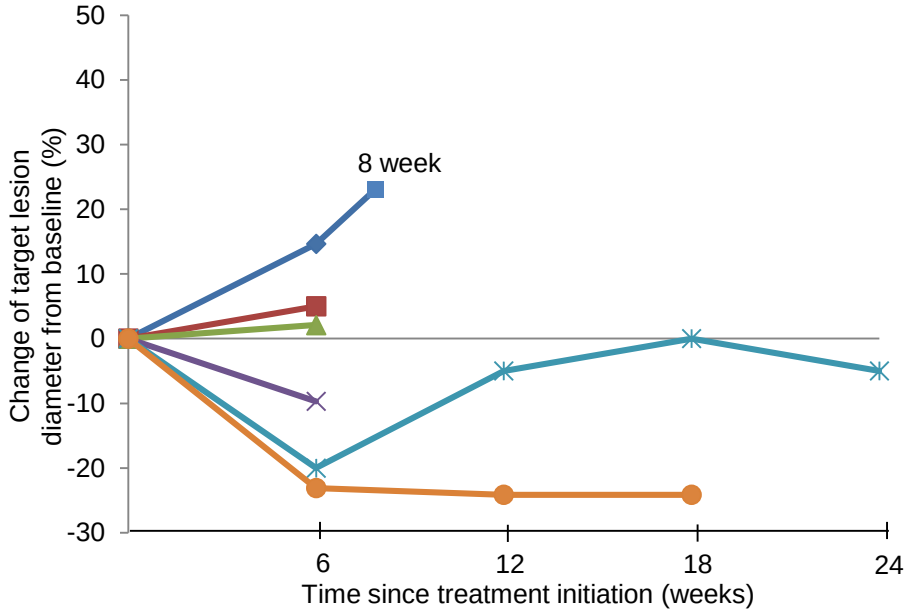
- 1AP4 : 2015.3.5 ~ 5.7, mA5-10: 2015.6.4 ~ 10.29
- 2Avelumab(Doce4): 2015.12.31 ~ 2016.3.3
- 3Poziotinib <u>12mg</u>: 2016.8.8 ~ 8.16,
  <u>8mg d/t diarrhea</u>: 8.25 ~ 2017.1.25





Response Evaluation





Response & Survival

By RECIST v1.1

Best response (N = 6)	n (%)
CR	0
PR	0
SD	2 (33.3)
PD	4 (66.7)
Disease control rate	**33.3%**

Survival analysis	days
Median TTP	58.5
Median PFS	60.5
Median OS	88.5

HER2 E812K mutation

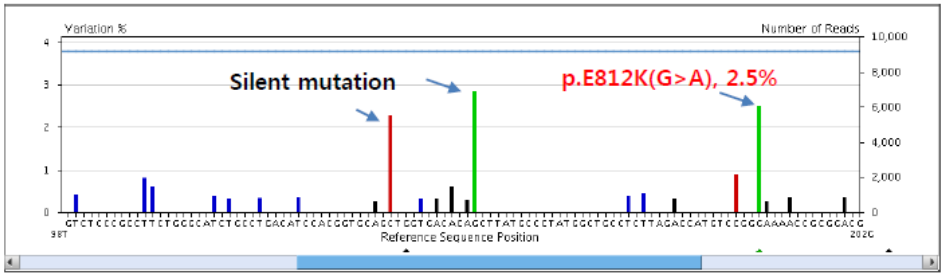
H9618

p.L796L(C>T) : 2.29% | **p.Q799Q(G>A) : 2.85%** | **p.E812K(G>A) : 2.5%**

Silent mutation

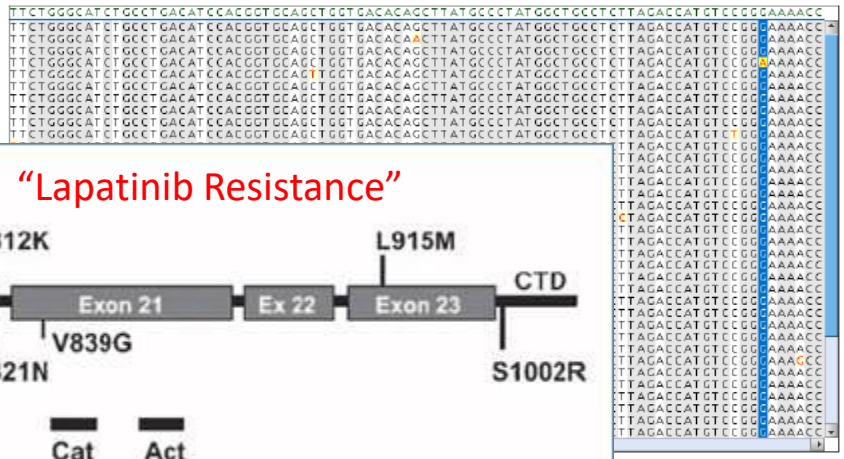
```
2308 GAA GCA TAC GTG ATG GCT GGT GTG GGC TCC CCA TAT GTC TCC CGC CTT CTG GGC ATC TGC CTG ACA TCC ACG GTG CAG TTG
 770  E   A   Y   V   M   A   G   V   G   S   P   Y   V   S   R   L   L   G   I   C   L   T   S   T   V   Q   L
2389 GTG ACA CAA CTT ATG CCC TAT GGC TGC CTC TTA GAC CAT GTC CGG AAA AAC CGC GGA CGC CTG GGC TCC CAG GAC CTG CTG
 797  V   T   Q   L   M   P   Y   G   C   L   L   D   H   V   R   K   N   R   G   R   L   G   S   Q   D   L   L
2470 AAC TGG TGT ATG CAG ATT GCC AAG G
 824  N   W   C   M   Q   I   A   K
```

Plot Snapshot to Image



Reference

NGS sequence

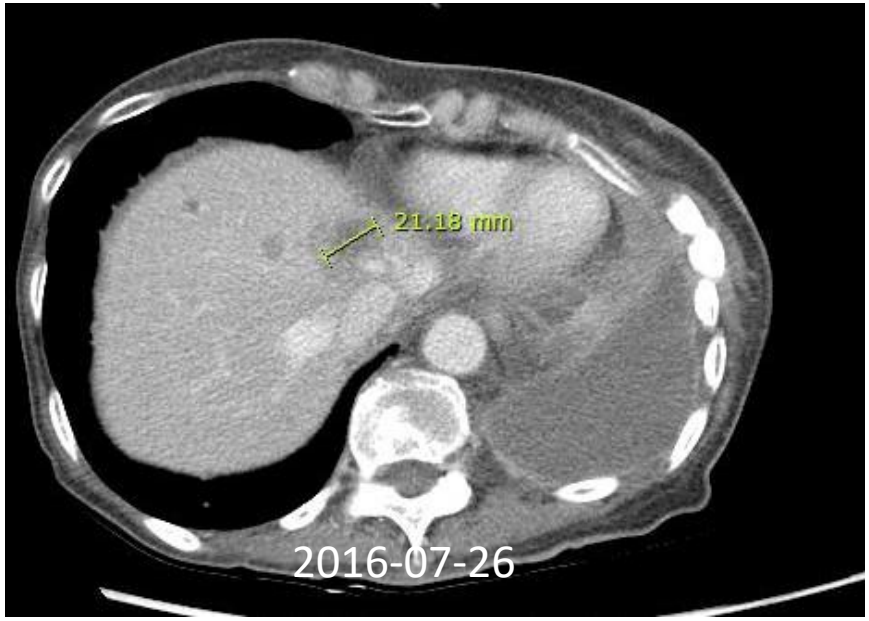


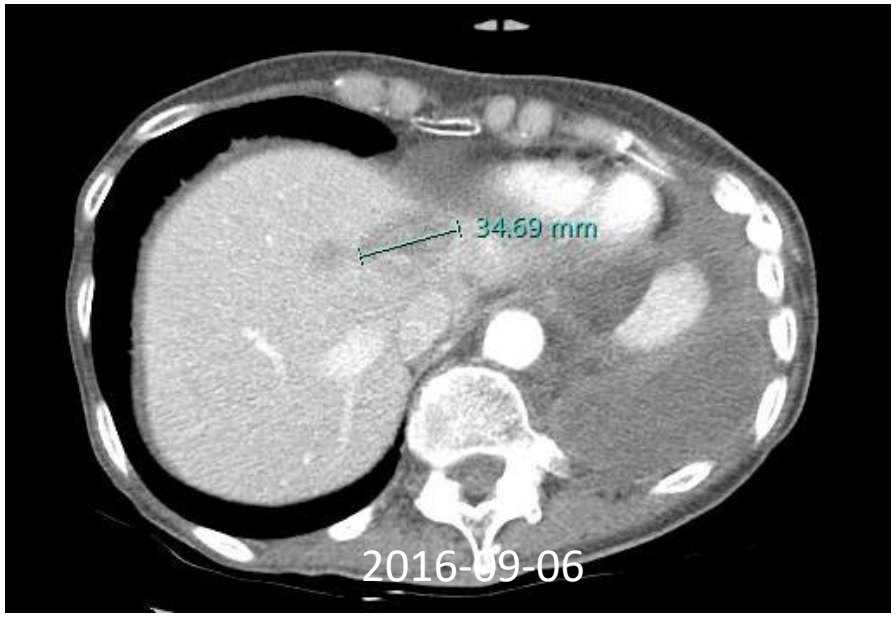
Clin Cancer Res 2008;14(8):2465-2475

61 YO Female

ADC,LLL(2014.5.13) pIIIA(pT2aN2M0) -> IV; pleura, liver mets
EGFR PNA: wild, ALK FISH(-), HER2 seq(-), NGS: E812K mutation
- VATS LLL lobectomy c MLND: 2014.6.3
- ATC4: 2014.07.04 ~ 09.12
- 1CCRT(EP2) for pleural mets: 2015.2.9 ~ 3.20, 27fx
- 2A6: 2015.10.23 ~ 2016.2.15
- 3G2 : 2016.4.4 ~ 5.9
- 4Poziotinib 12 mg: 2016.7.27 ~ 8.12, 8 mg d/t diarrhea: 2016.8.25 ~ 9.6

*E0010402
- Response = PD
- TTP = 57 days
- EOT by diarrhea



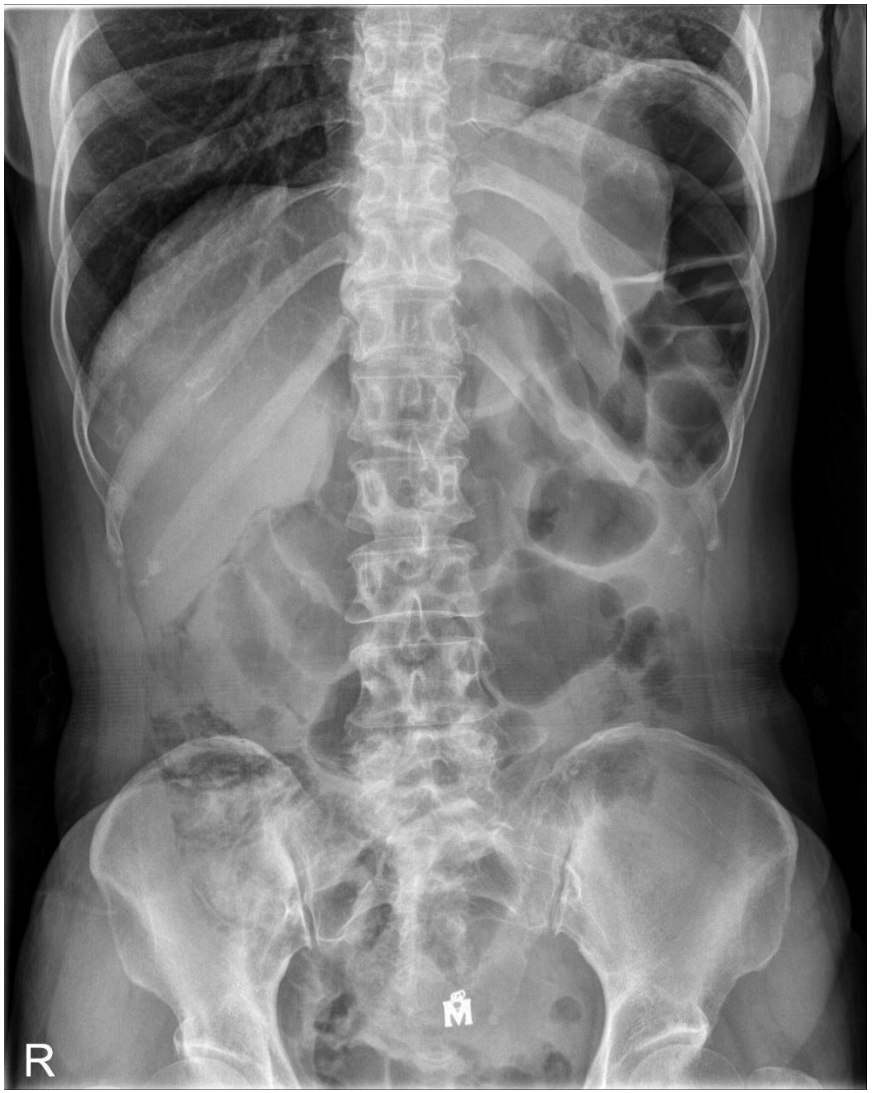


Safety

No.	Site Name	Subject No	Report date	SAE term	Relationship to IP	Outcome	Dose modification	Study 종료
1	건국대학교병원	E0010101	2016-04-04	**Oral mucositis**	Possibly Related	Recovered	PZT 8mg	No
2	건국대학교병원	E0010101	2016-05-30	Pneumonia	Probably not related	Recovered	-	**Yes**
3	**화순전남대학교병원**	**E0010401**	**2016-06-27**	**Colitis**	**Definitely not related**	**Recovered**	**-**	**No**
4	화순전남대학교병원	E0010402	2016-07-11	Herpes zoster	Definitely not related	Recovered	-	No
5	화순전남대학교병원	E0010402	2016-08-16	**Diarrhea**	Probably Related	Recovered	**PZT 8mg 2주 투여 1주 휴약**	**Yes**
6	화순전남대학교병원	E0010403	2016-08-16	**Diarrhea**	Probably Related	Recovered	PZT 8mg	No
7	화순전남대학교병원	E0010404	2016-11-07	**Nausea**	Probably Related	Recovered	PZT 8mg	No
8	화순전남대학교병원	E0010404	2016-11-25	**Pneumatosis intestinalis**	Possibly related	Recovered		**Yes**
9	건국대학교병원	E0010102	-	**Diarrhea Skin toxicity**	Possibly related	Recovered	PZT 8mg	No

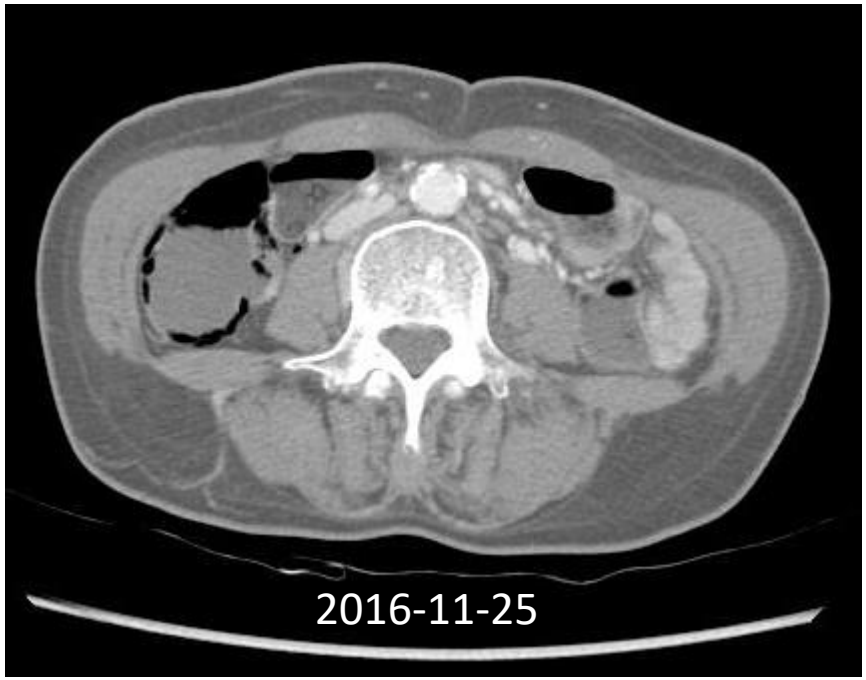
SAE 아님

55 YO Female



*<u>Poziotinib 12 mg</u> start on 2016-10-14

- Diarrhea (Gr. 2)
- Paused d/t nausea (Gr. 3)
- <u>8 mg</u> restart from 2016-11-8



Rt. hemicolectomy
d/t pneumatosis intestinalis (Gr. 4)

KASTT Korean Association for the Study of Targeted Therapy

Newsletter vol.04

KASTT001

Protocol No. PZT1401

[국문] HER2 돌연변이가 확인된 4 기 폐선암 환자를 대상으로 Pan-HER 저해제 (HM781-36B, Poziotinib) 의 효과를 평가하기 위한 2 상 연구

[영문] A phase II study to assess efficacy of pan-HER inhibitor (HM781-36B, Poziotinib) instage IV lung adenocarcinoma with HER2 mutation

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KASTT001 연구에 참여해 주시는 연구자 및 연구담당자 선생님들께

안녕하세요 표적치료연구회 CRA이혜영입니다.

KASTT001_PZT1401 HER2 연구를 위해 각 기관에서 보여 주시는 많은 관심과 도움에 감사 드리며, 지난 8월 이후 그 간의 연구진행현황에 대한 업데이트를 전달 드립니다.

➢ Study Progress

총 5개 참여기관 중 건국대학교병원 및 화순전남대학교병원, 현재 총 2개 기관이 오픈, 대상자 등록 중인 상태입니다.

칠곡경북대학교병원 및 고신대학교복음병원에서는 IRB 승인 최종 확인되었고, 충남대학교병원은 IRB 신규접수 진행중이었으나 2016년 09월 28일에 스크리닝 중단 공지되어 현재 연구 개시 보류 중입니다.

현재 치료 진행중인 참여 환자를 제외하고 추가적인 환자 등록은 불가능한 상태입니다. **이전 HER2 screening 시 양성 확인되었으나 PD소견 없어 poziotinib 투약 받지 못한 환자는 PD확인될 경우 연구 참여가 가능합니다.** 중간분석 완료 후 추후 진행 관련 사항에 대하여 재공지 예정입니다.

original article

Annals of Oncology 00: 1–6, 2015
doi:10.1093/annonc/mdv573

Lung cancer patients with *HER2* mutations treated with chemotherapy and *HER2*-targeted drugs: results from the European EUHER2 cohort

J. Mazières[1*], F. Barlesi[2], T. Filleron[3], B. Besse[4], I. Monnet[5], M. Beau-Faller[6], S. Peters[7], E. Dansin[8], M. Früh[9], M. Pless[10], R. Rosell[11], M. Wislez[12], P. Fournel[13], V. Westeel[14], F. Cappuzzo[15], A. Cortot[16], D. Moro-Sibilot[17], J. Milia[1] & O. Gautschi[18]

Table 1. Clinical and biological characteristics of patients with an *HER2* mutation ($n = 101$)

	Number	Value
Age at initial diagnosis, years ($n = 101$)		
Median		61
Range		30–87 years
Gender		
Male	38	37.6%
Female	63	62.4%
Tobacco use		
Never	61	60.4%
Former	36	35.6%
Current	4	4%
Median pack-years consumption (current and former)		15 (3–48)
Range		
Tumor stage		
I	4	4%
II	2	2%
III	14	13.9%
IV	81	80.2%
Metastatic sites of stage IV		
Lung	22	22%
Brain	6	6%
Bone	10	10%
Multiple organs	33	33%
Other	7	7%
None	15	15%
Unknown	8	8%
Concomitant mutations		
EGFR mutations	5	5%
ALK translocation	1	1%
ROS translocation	1	1%

Annals of Oncology 2016;27:281–286.

Table 2. Overall response rate (ORR), disease control (DC), progression-free survival (PFS, weeks), and overall survival (OS, weeks) according to drug type

Treatment	*n*	ORR	DC	PFS median (95% CI)	OS median (95% CI)
First-line: without HER2-targeting treatment	93	43.5%	70.7%	6 (5; 7.1)	24 (19.1; 36.4)
Second-line: without HER2-targeting treatment	52	10%	36%	4.3 (3.1; 5)	19.4 (9.6; 24.7)
EGFR-TKI[a]	26	7.6%	26.8%	2.99 (1.87; 4.47)	20.14 (7.14; 32.95)
Trastuzumab combination, T-DM1[a]	58	50.9%	75.5%	4.8 (3.4; 6.5)	13.3 (8.1; 15)
Neratinib, lapatinib, and afatinib[a]	29	7.4%	55.5%	3.4 (2.4; 4)	6.5 (4.7; 30.6)

[a]If the same drug has been given more than one time, the results presented here are from their first administration.

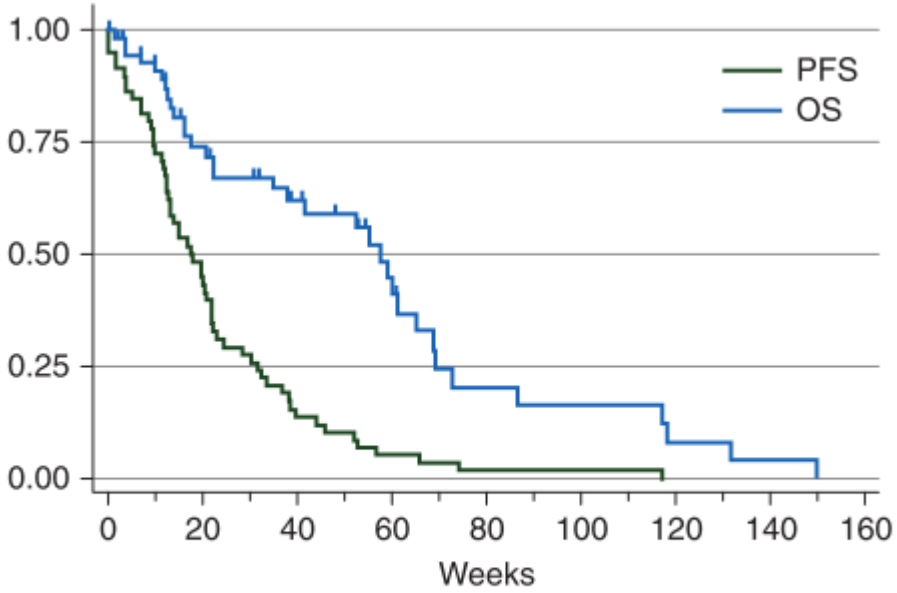


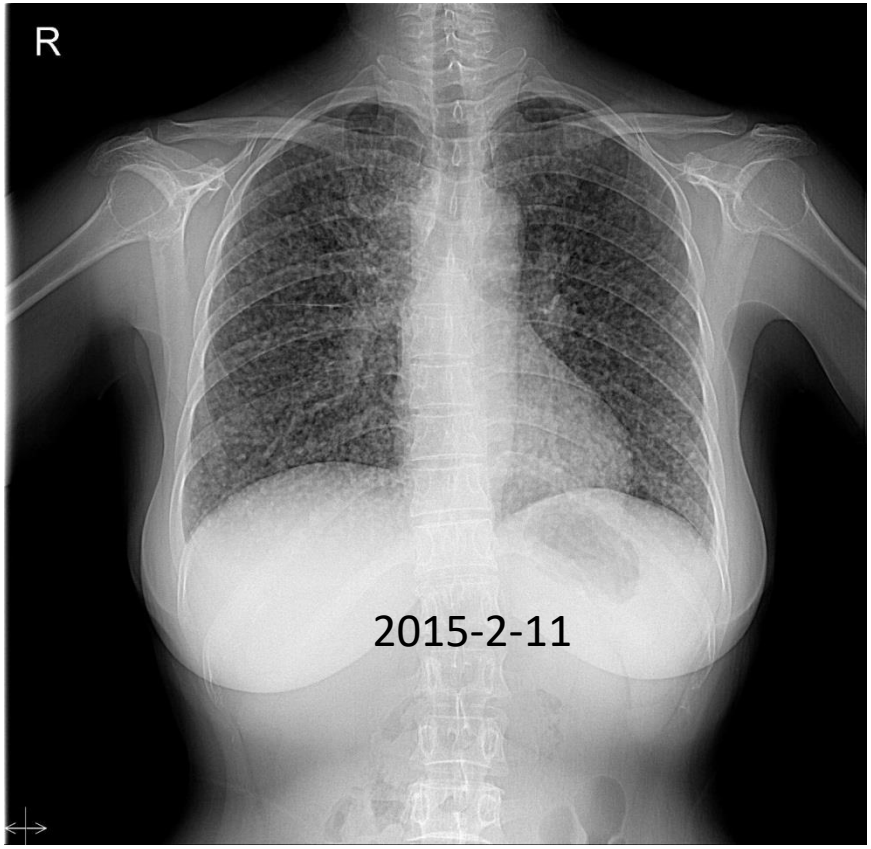
Figure 2. Progression-free survival and overall survival of patients treated with trastuzumab-based combination.

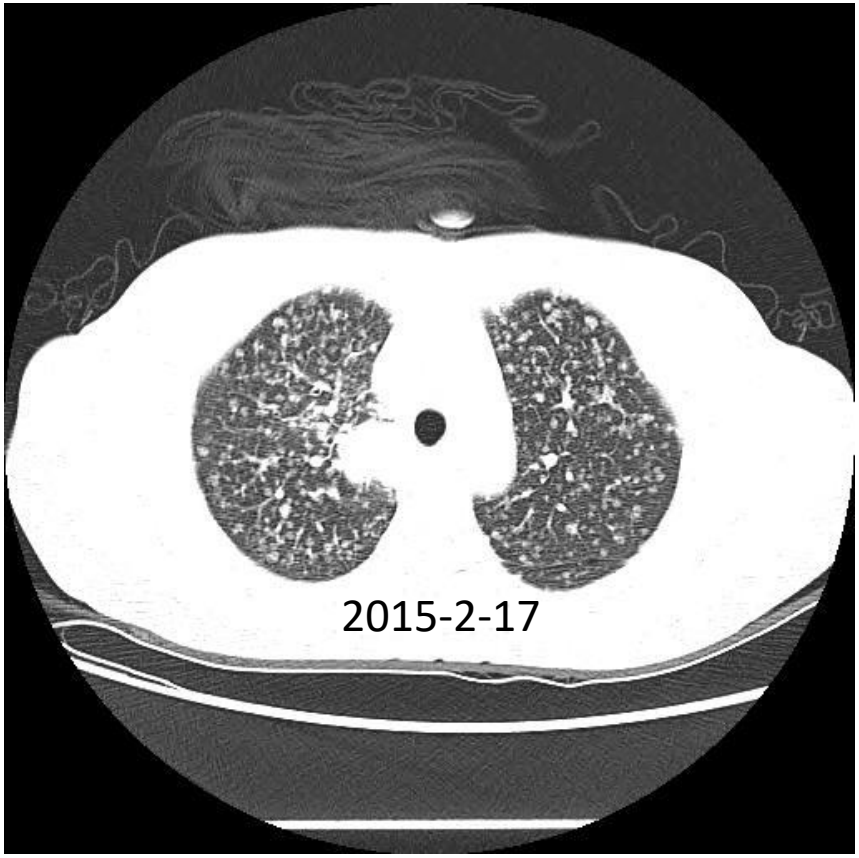
❖ <u>For afatinib</u>

- ORR = 18.2%
- DCR = 63.7%
- PFS = 3.9 months

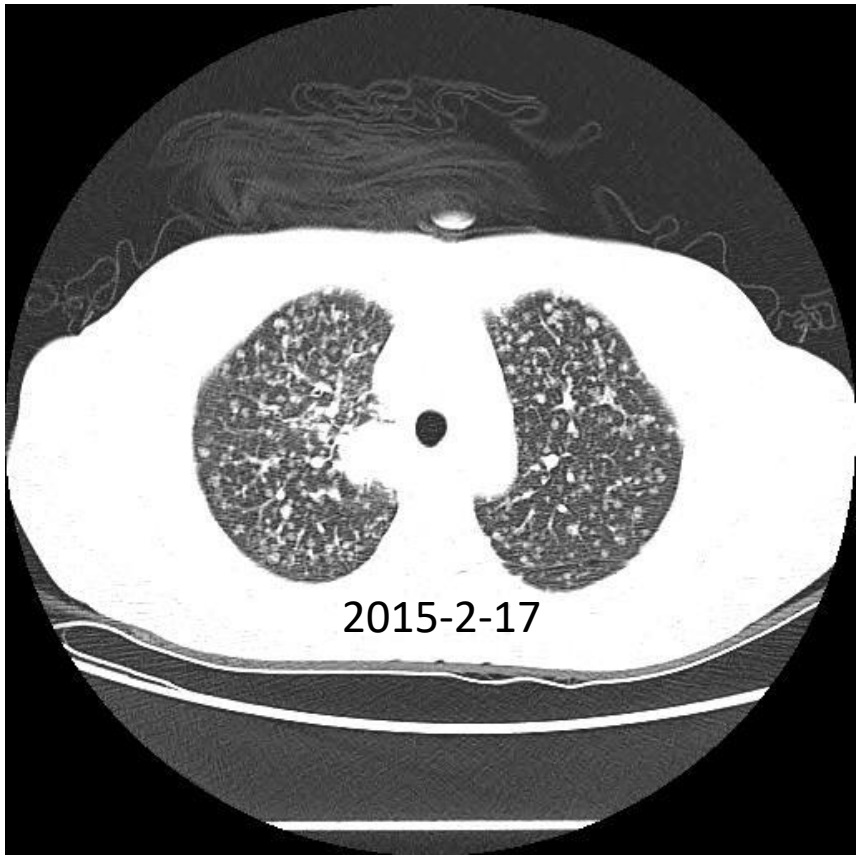
Annals of Oncology 2016;27:281–286.

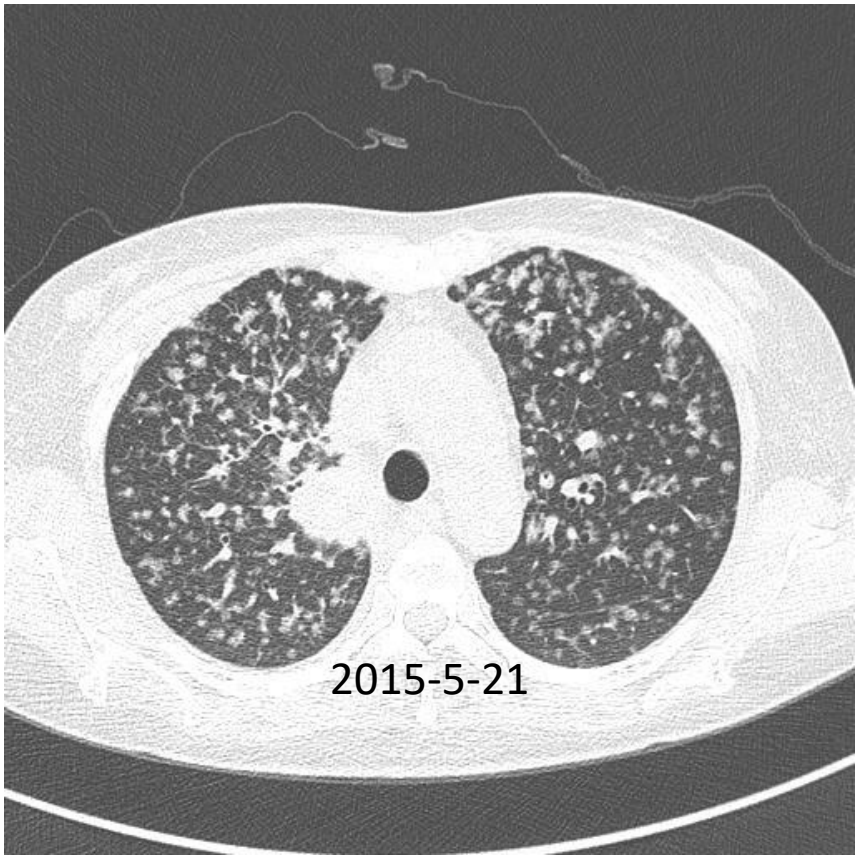
ADC,RUL(2015.2.26) IV(T4N3M1b) - lung to lung, T12, Lt femur, Rt frontal mets
EGFR PNA: wild , ALK IHC(1+)



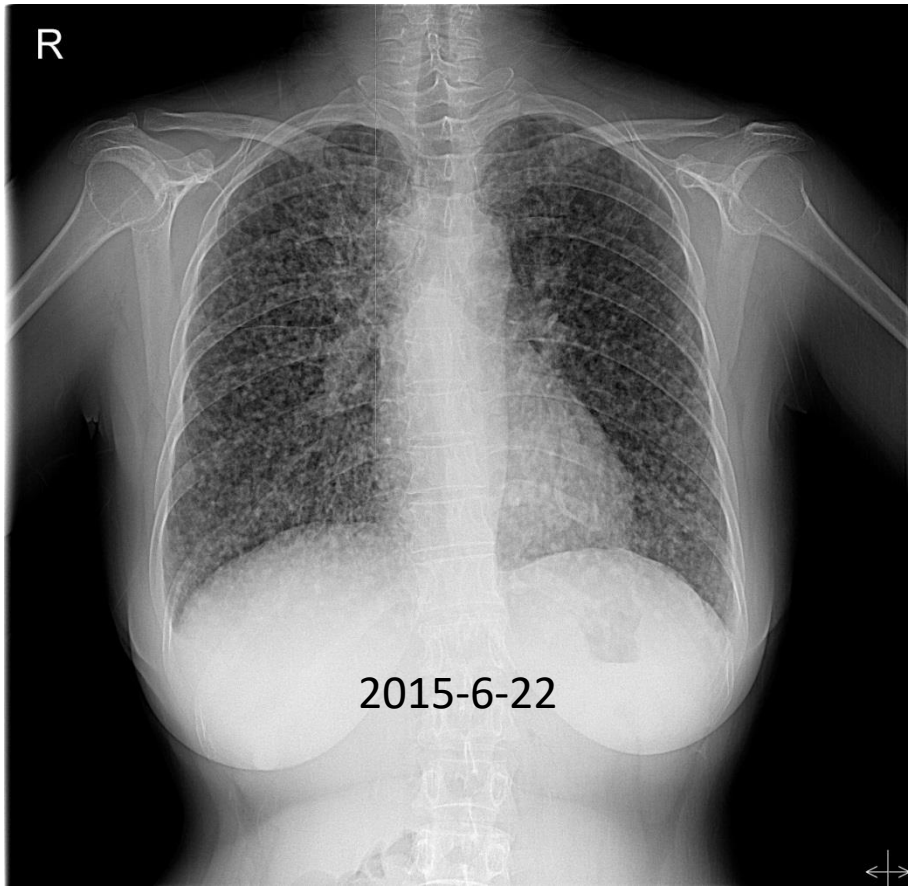


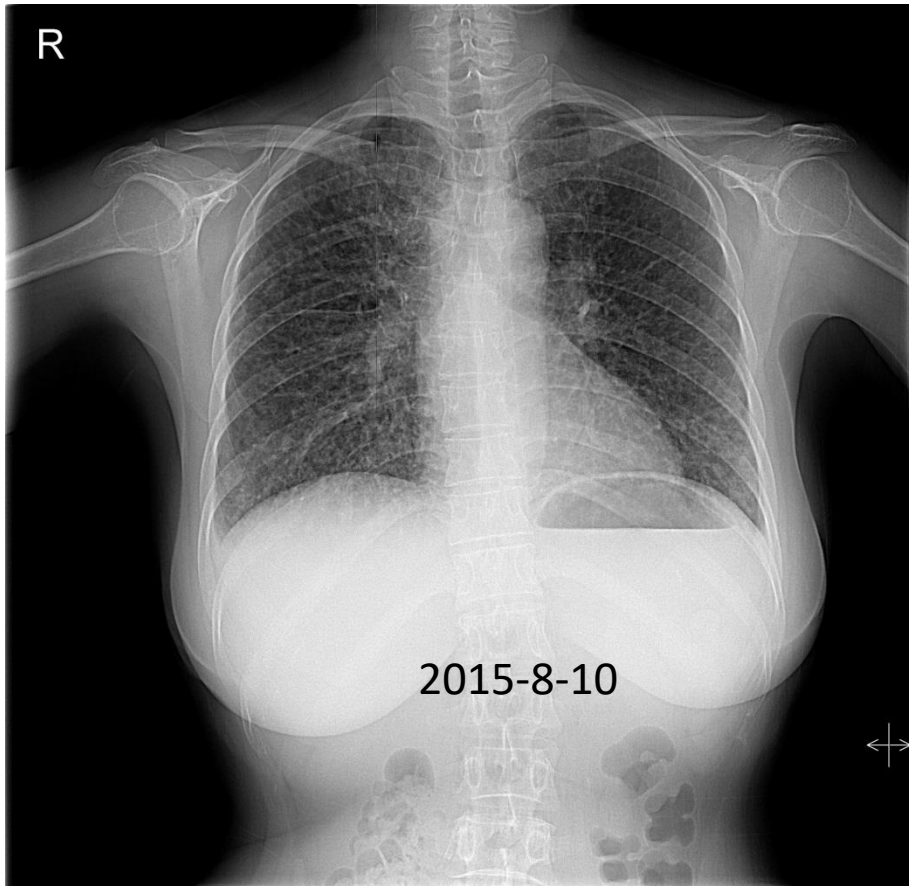
ADC,RUL(2015.2.26) IV(T4N3M1b) - lung to lung, T12, Lt femur, Rt frontal mets
EGFR PNA: wild , ALK IHC(1+)
- 1AP4 : 2015.3.6 ~ 5.7





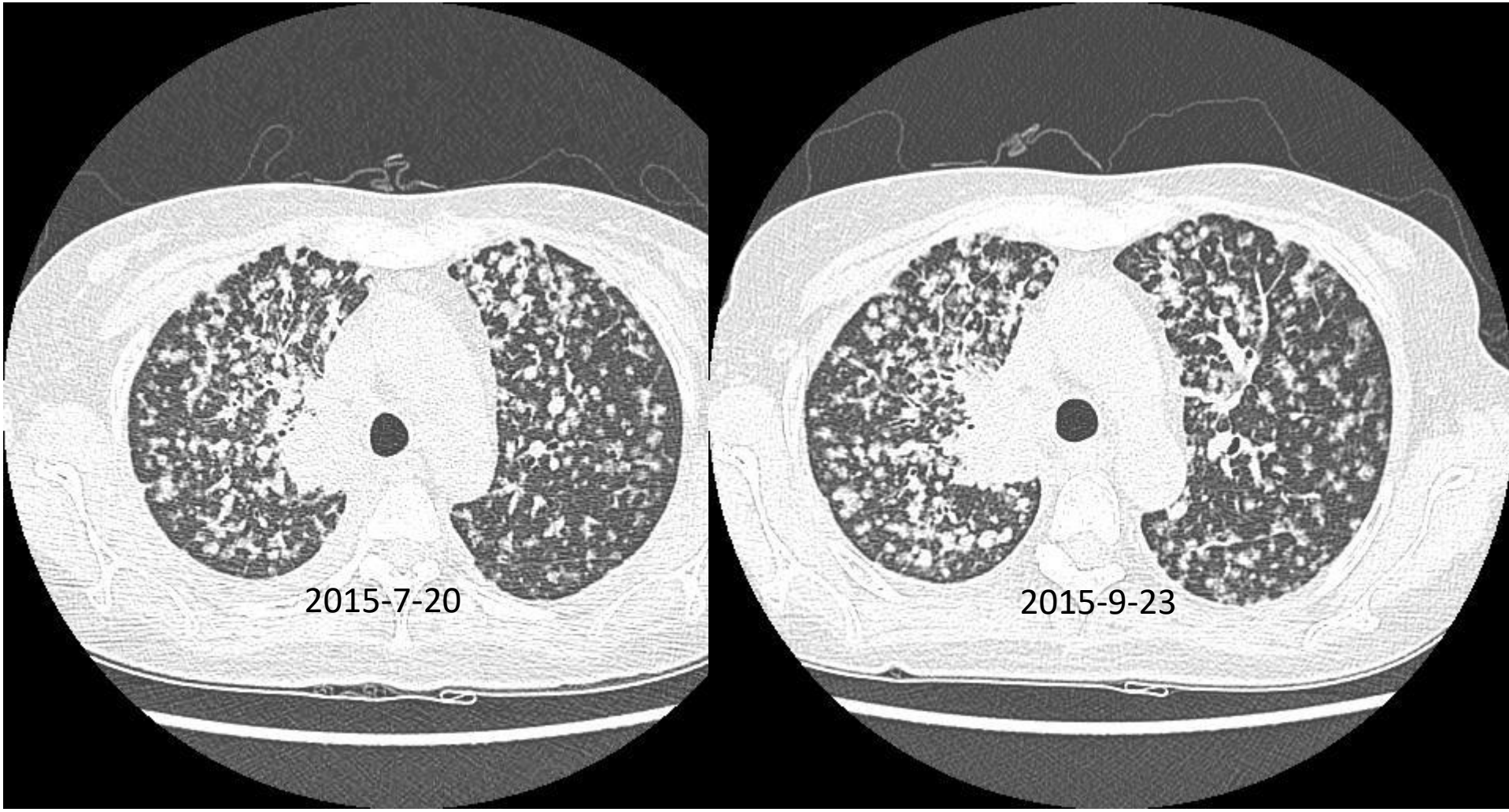
ADC,RUL(2015.2.26) IV(T4N3M1b) - lung to lung, T12, Lt femur, Rt frontal mets
EGFR PNA: wild , ALK IHC(1+)
- 1AP4 : 2015.3.6 ~ 5.7
- 2Iressa: 2015.7.27 ~ 9.23





ADC,RUL(2015.2.26) IV(T4N3M1b) - lung to lung, T12, Lt femur, Rt frontal mets
EGFR PNA: wild , ALK IHC(1+), ALK FISH(-)

- 1AP4 : 2015.3.6 ~ 5.7
- 2Iressa: 2015.7.27 ~ 9.23



전남대 3269-15 NGS 결과, N813D (c.2437 A>G)

HER2 exon20

```
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 770   E   A   Y   V   M   A   G   V   G   S   P   Y   V   S   R   L   L   G   I   C   L   T   S   T   V   Q   L
2389 GTG ACA CAG CTT ATG CCC TAT GGC TGC CTC TTA GAC CAT GTC CGG GAA GAC CGC GGA CGC CTG GGC TCC CAG GAC CTG CTG
 797   V   T   Q   L   M   P   Y   G   C   L   L   D   H   V   R   E   D   R   G   R   L   G   S   Q   D   L   L
2470 AAC TGG TGT ATG CAG ATT GCC AAG G
 824   N   W   C   M   Q   I   A   K
```
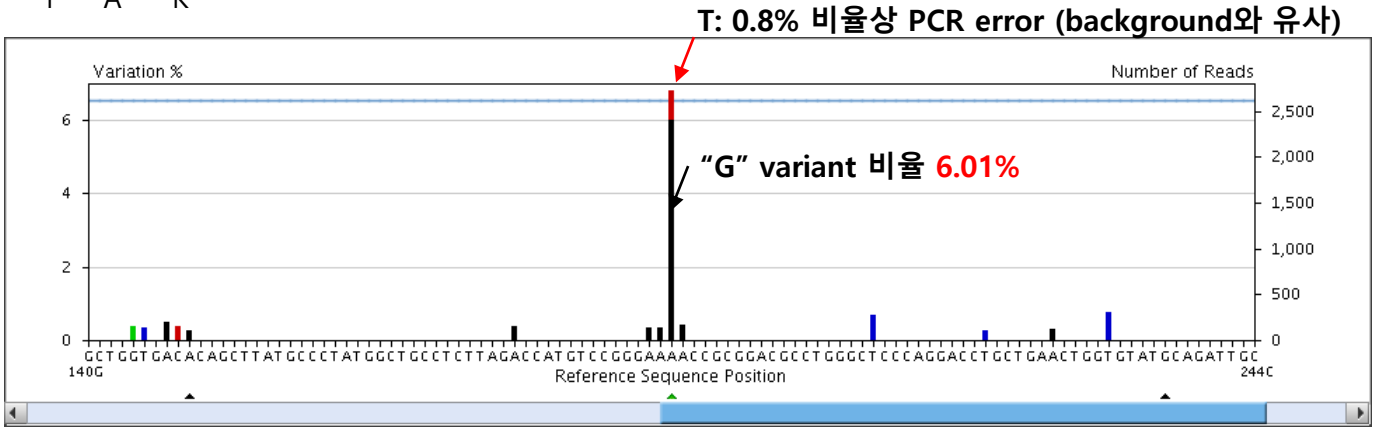
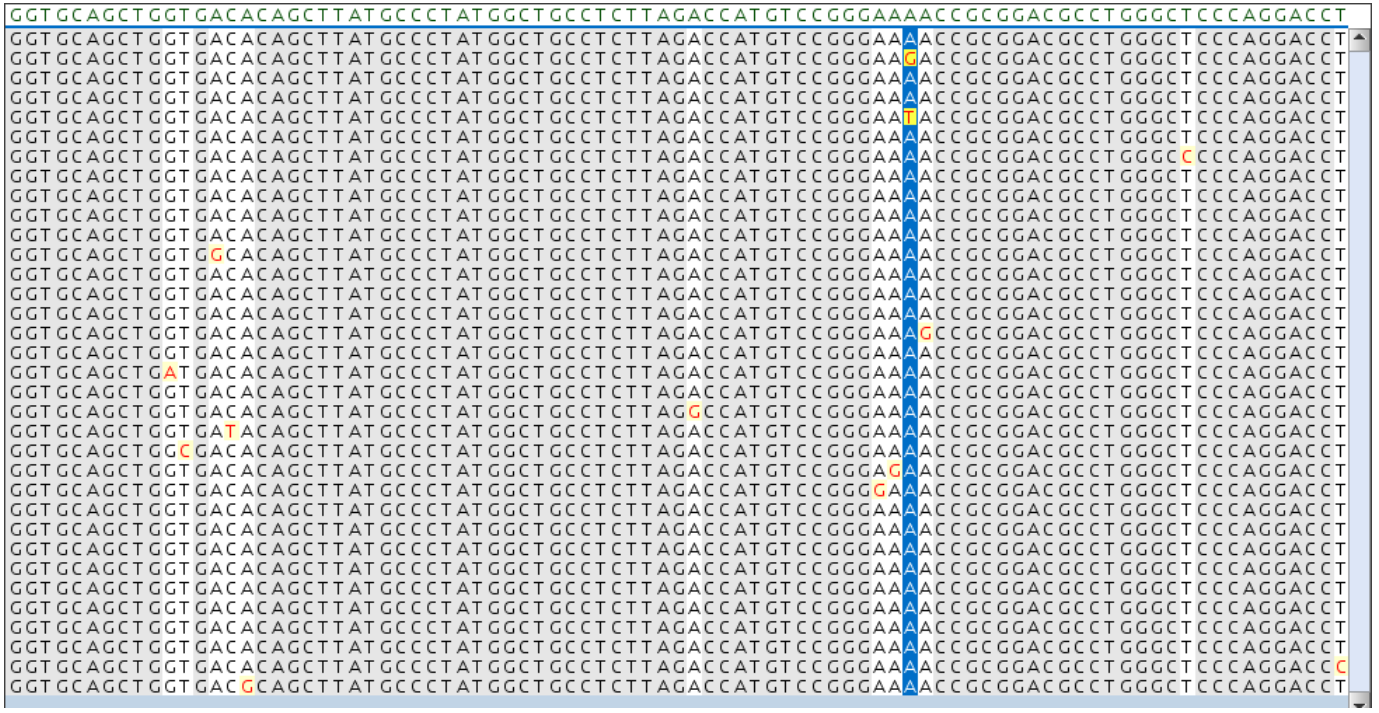

Plot Snapshot to Image



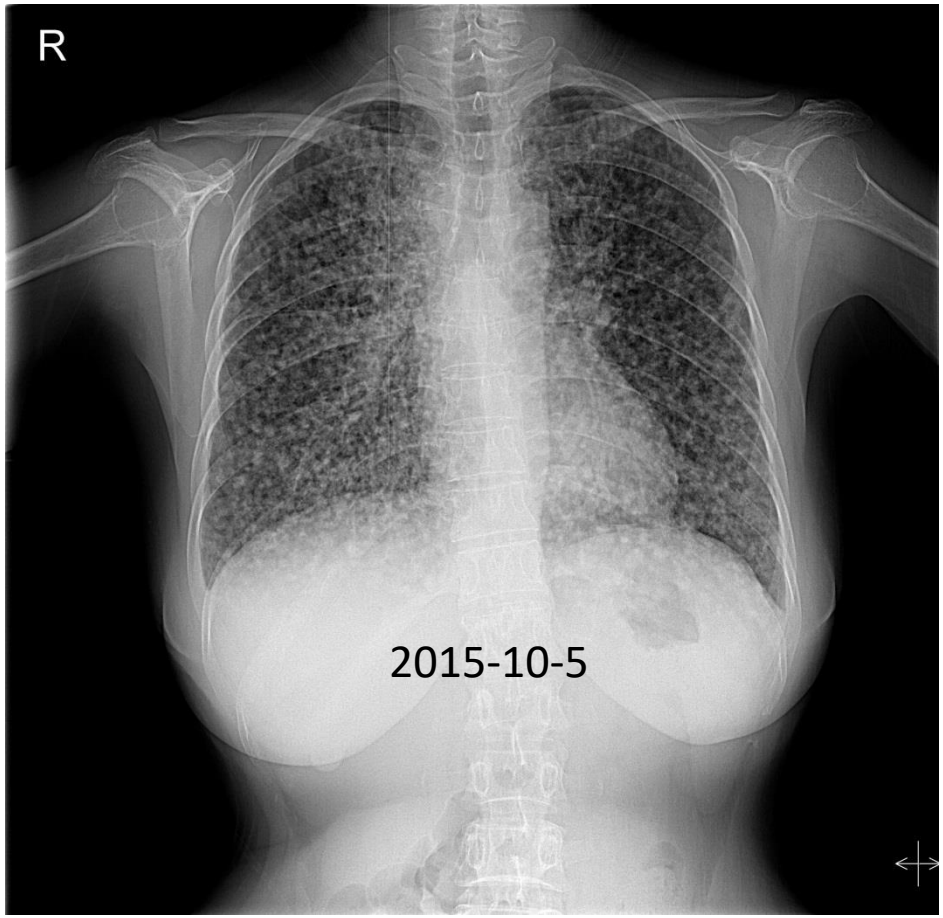
Reference

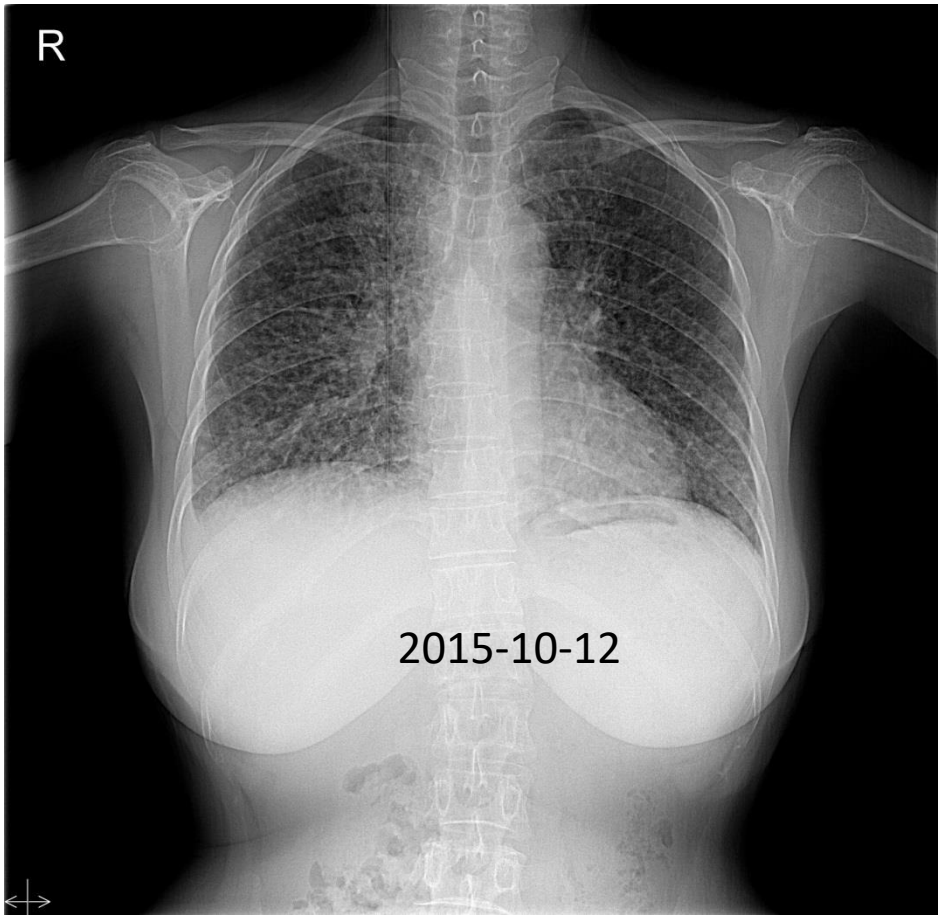
NGS sequence



ADC,RUL(2015.2.26) IV(T4N3M1b) - lung to lung, T12, Lt femur, Rt frontal mets
EGFR PNA: wild , ALK IHC(1+), ALK FISH(-), HER2 N813D (c.2437 A>G)

- 1AP4 : 2015.3.6 ~ 5.7
- 2Iressa: 2015.7.27 ~ 9.23
- 3Giotrif: 2015.10.6 ~

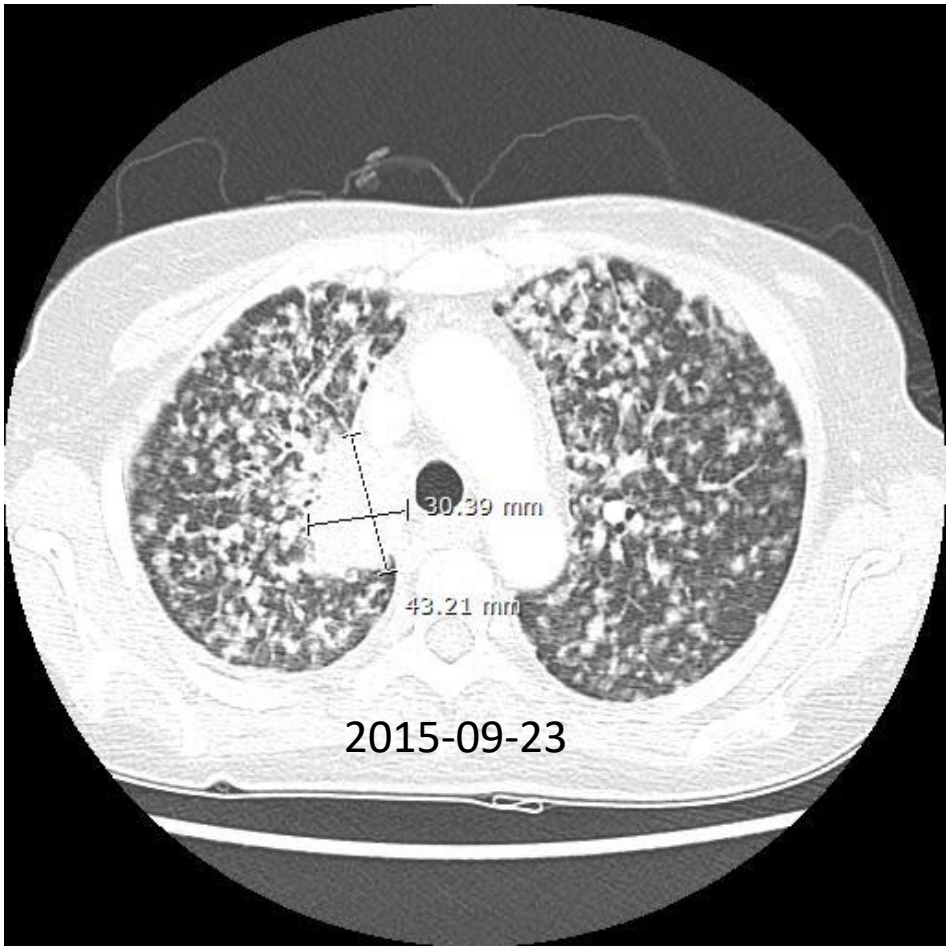


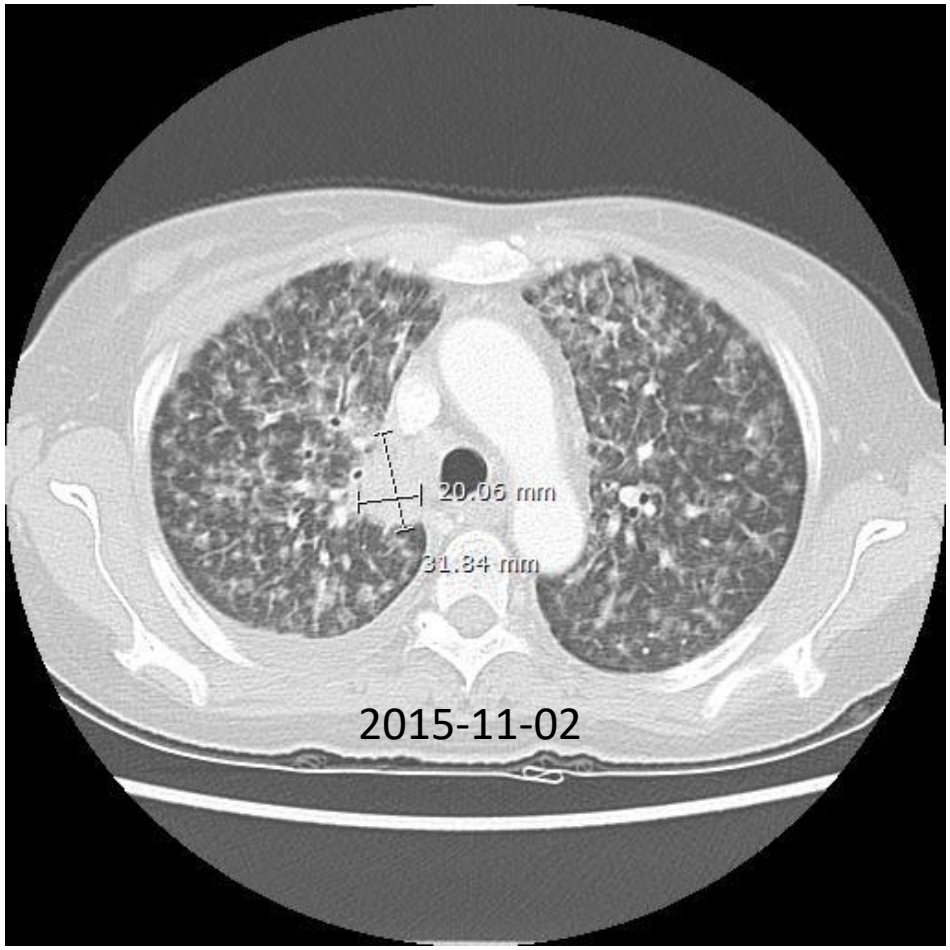


J Korean Med Sci (in press)

ADC,RUL(2015.2.26) IV(T4N3M1b) - lung to lung, T12, Lt femur, Rt frontal mets
EGFR PNA: wild , ALK IHC(1+), ALK FISH(-), HER2 N813D (c.2437 A>G)

- 1AP4 : 2015.3.6 ~ 5.7
- 2Iressa: 2015.7.27 ~ 9.23
- 3Giotrif: 2015.10.6 ~ 2016.2.





J Korean Med Sci (in press)