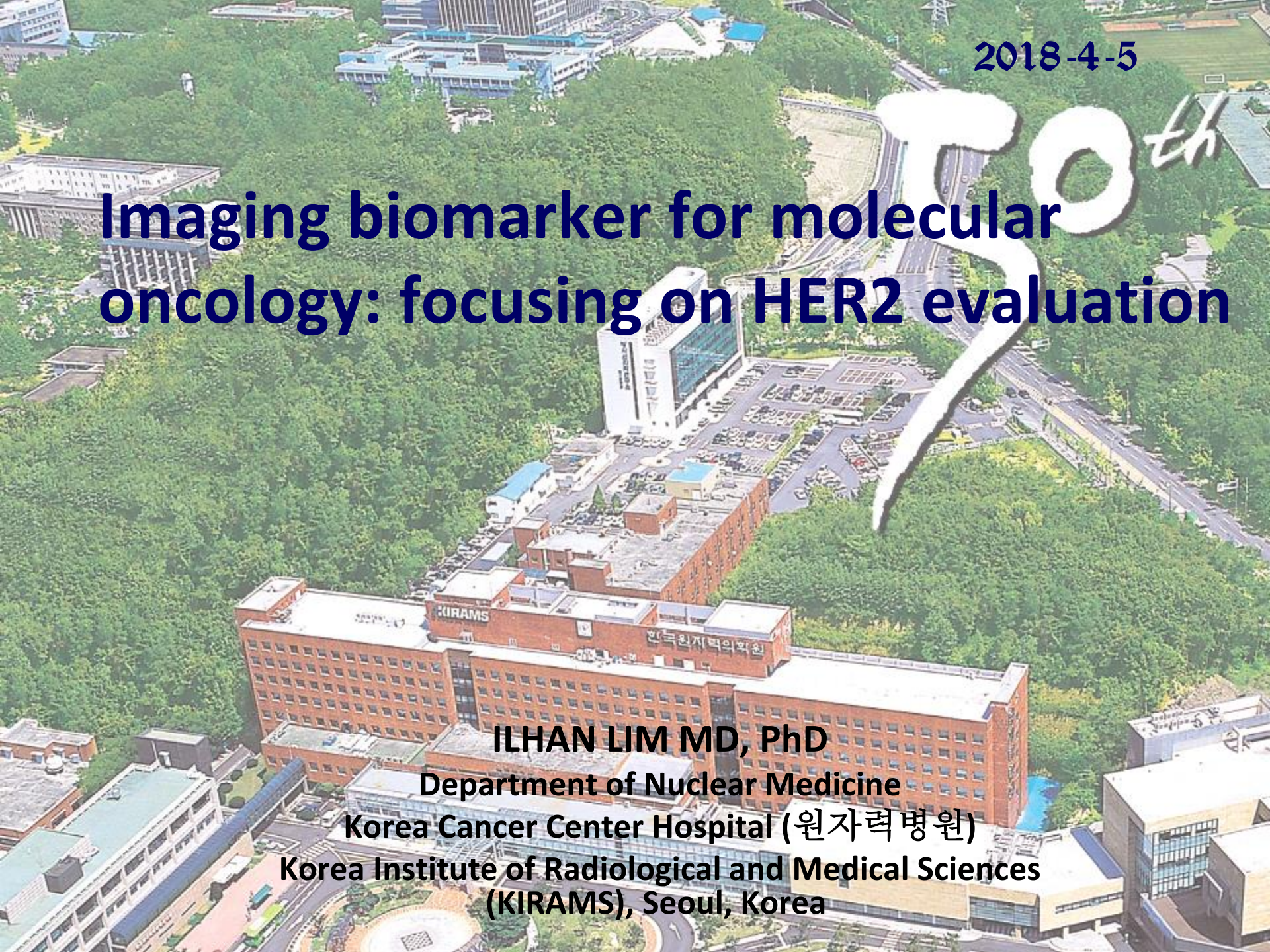
2018-4-5

Imaging biomarker for molecular oncology: focusing on HER2 evaluation



ILHAN LIM MD, PhD

Department of Nuclear Medicine

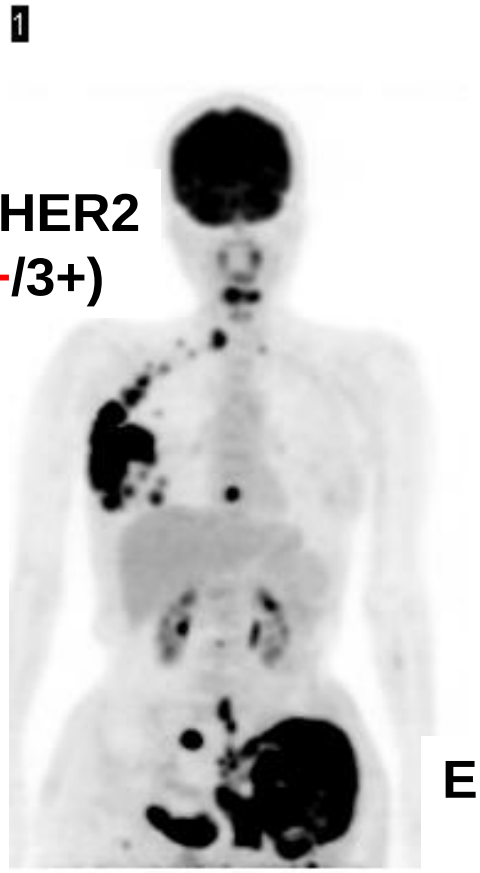
Korea Cancer Center Hospital (원자력병원)

Korea Institute of Radiological and Medical Sciences (KIRAMS), Seoul, Korea

Contents

- New paradigm of Precision medicine
- Advantage of Imaging biomarker
- Imaging biomarker in Breast cancer
  - Evaluation of HER2 expression

Pt with Lt hip joint pain



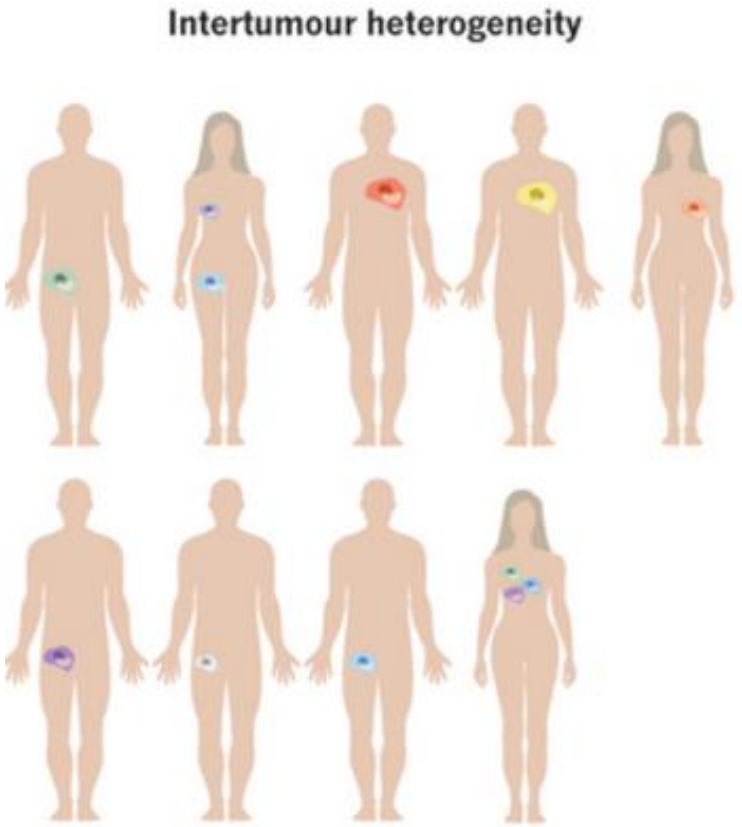
ER/PR/HER2
(3+/3+/3+)

ER/PR/HER2
(-/-/3+)

- F/52
- CC; Lt. hip joint pain (onset; 10 MA)
- Sx started after slipping down at mountain
- Tx at Oriental medicine clinic for 7 M
- Imp) malignant bone tumor in Lt. pelvis
- Bone Bx
  - Metastatic cancer

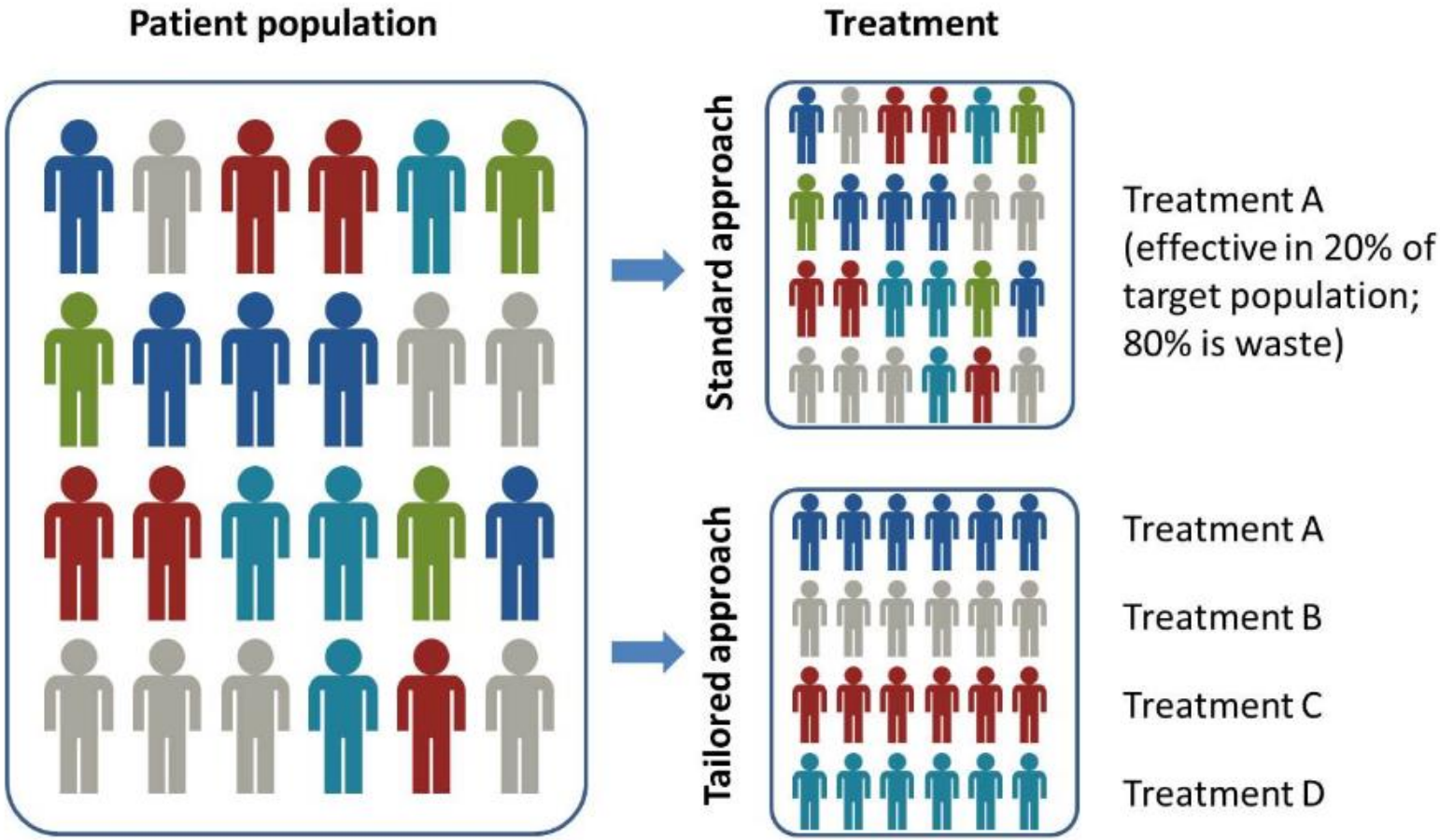
Courtesy of Dr. KimHA

Tumor heterogeneity



Burrell et al, Nature, 2013

Precision medicine



Iressa story

폐암환자, 장관집 시위…'이레사' 급여확대?

[2004년 02월 19일 11시 19분]

말기폐암에 걸린 한 환자가 김화중 보건복지부장관 집을 찾아 이레사 보험범위를 확대해 줄 것을 호소했고, 김 장관도 급여범위를 재검토하겠다고 약속했던 것으로 뒤늦게 알려졌다.

말기폐암환자 K씨는 암환자살리기운동본부에 가입한 회원으로 말기폐암치료제 '이레사'에 대한 요구가 수용되지 않자 최근 답답한 마음을 억누르지 못하고 혼자 직접 김화중 장관의 자택을 항의 방문했던 것으로 전해졌다.

그는 당초 복지부 보험급여과에 이레사의 보험확대를 요구했지만 별다른 소득을 얻지 못하자 김 장관에게 환자들의 고충을 직접 전할 목적으로 김 장관 집 앞에서 무작정 기다린 것으로 알려졌다.

김화중 장관의 귀가가 늦어지면서 아쉽게도 면담을 하지 못하자 K씨는 이미 준비해 간 서류를 집사에게 전달하고 발길을 돌렸다.

Lung ca Pt visited the Minister of Health to ask the reimbursement of Iressa.

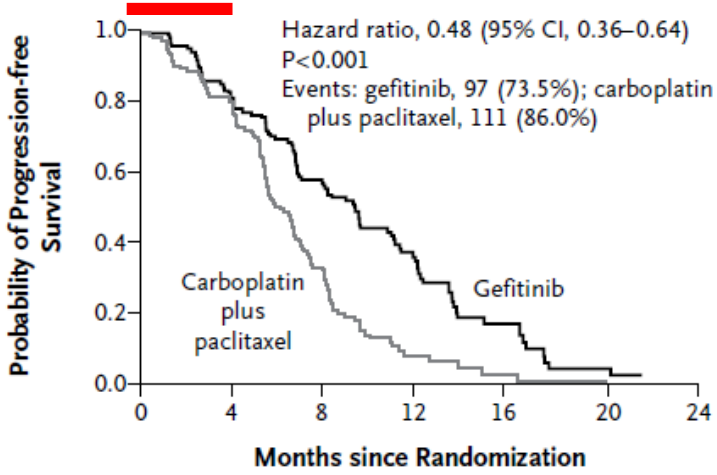
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2009 VOL. 361 NO. 10

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

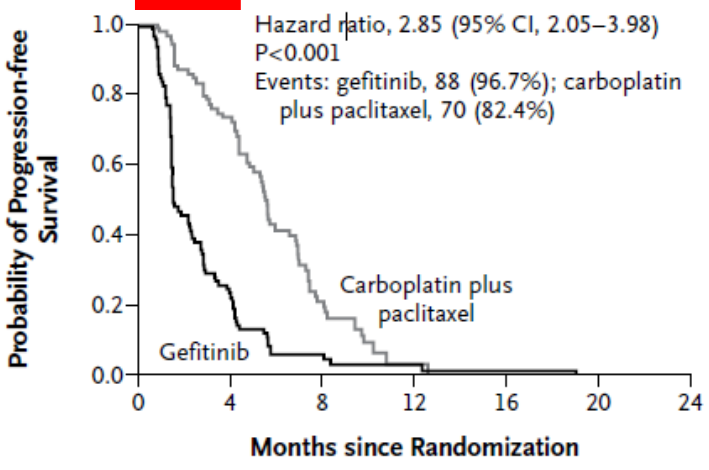
Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D.,

B ***EGFR*-Mutation–Positive**



No. at Risk							
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

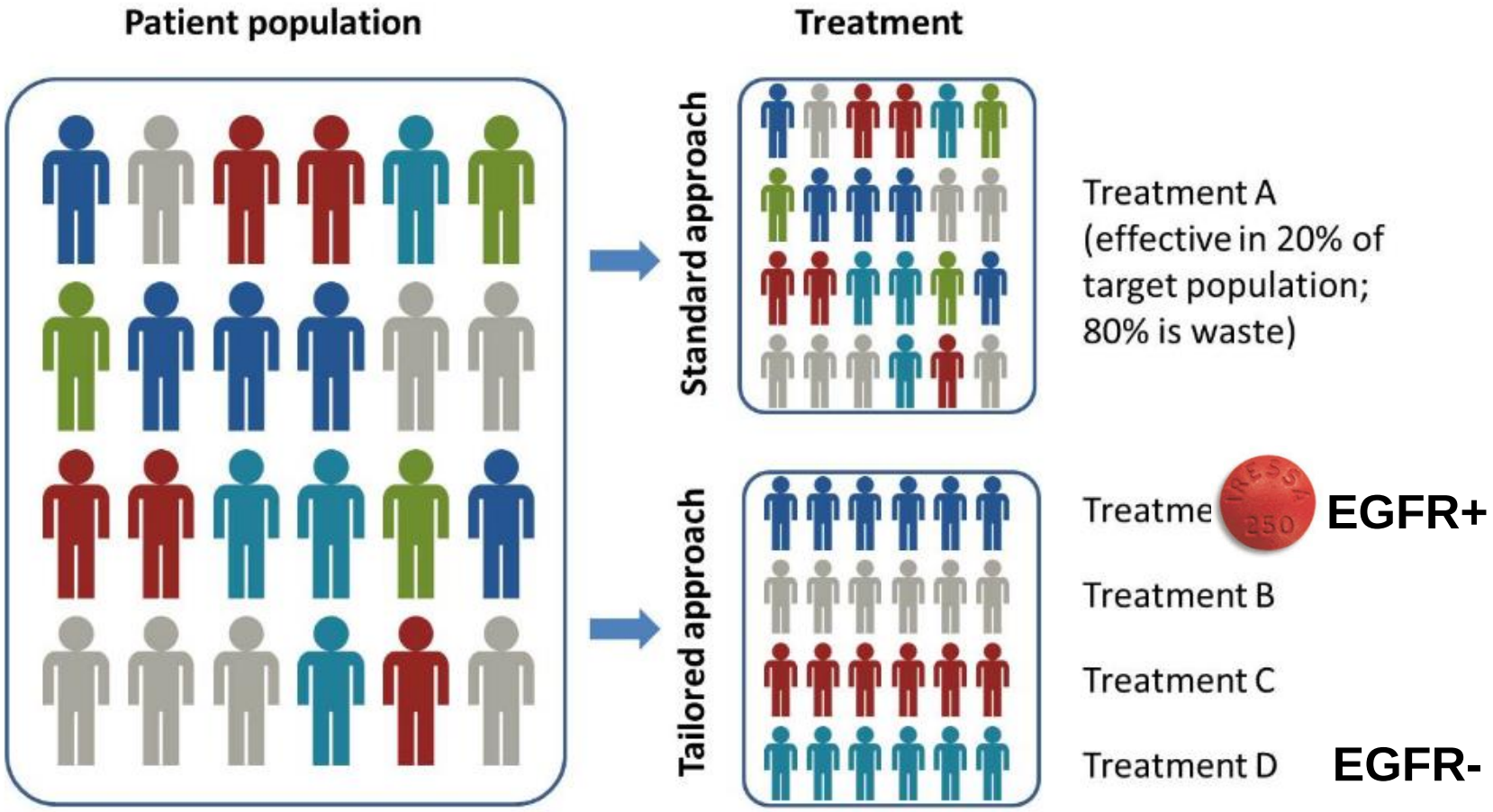
C ***EGFR*-Mutation–Negative**



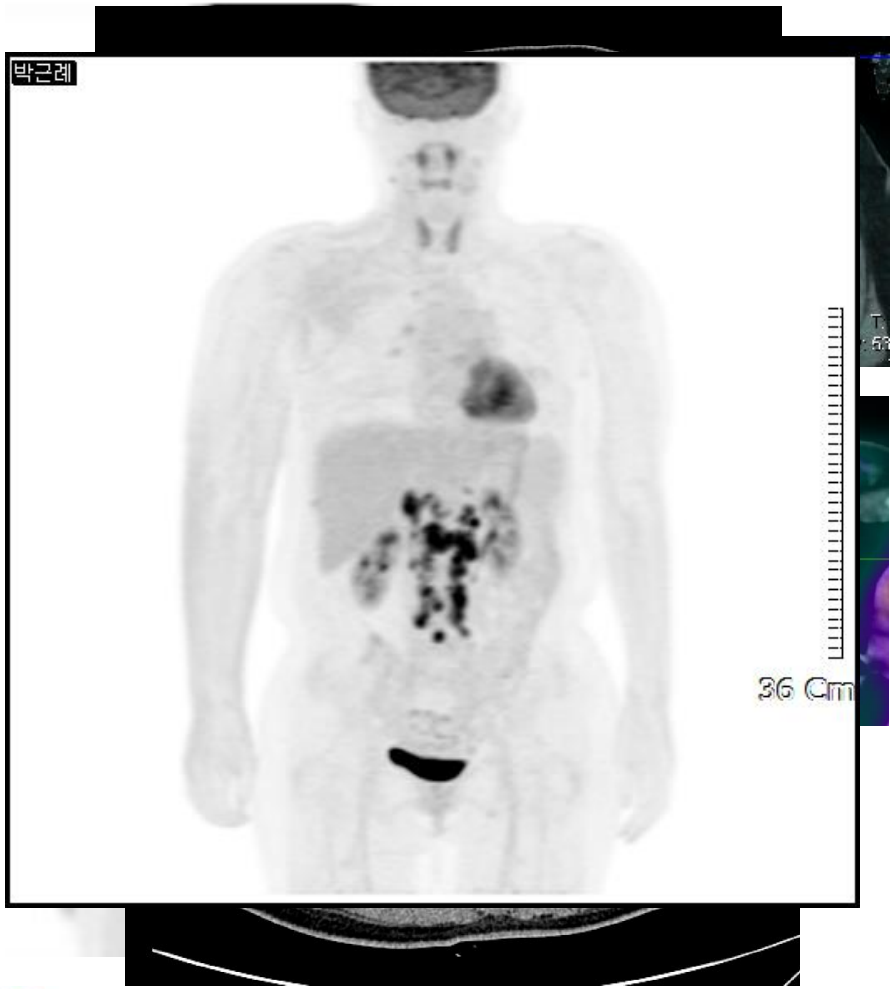
No. at Risk							
Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

Mok et al, NEJM, 2009

Precision medicine



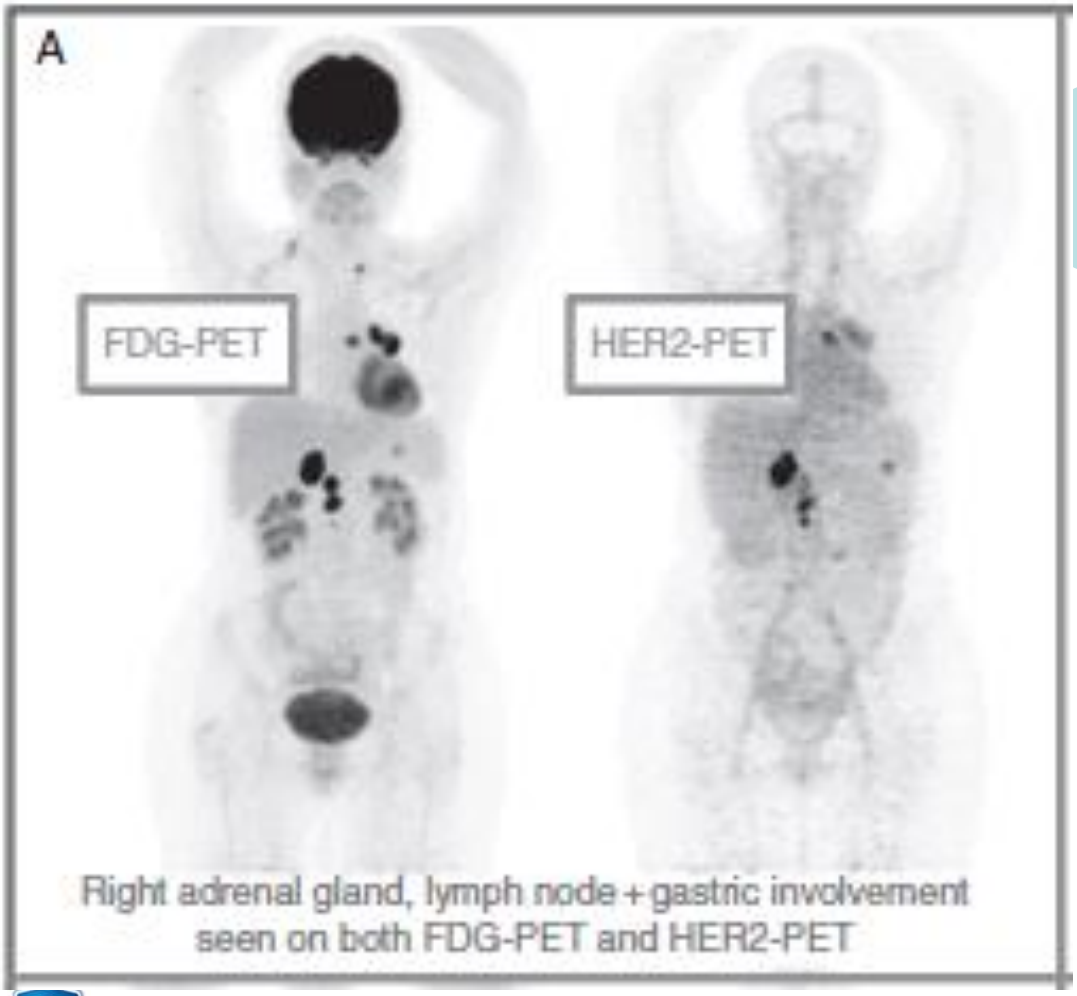
Breast cancer Pt with Abd LN during F/U



- F/48
- CC; Rt. Breast thickness (onset; 1 MA)
- 2014-7 Rt. NASSM+SLNB
  - T2N1M0
  - ER(-)/PR(-)/HER2(3+)/Ki-67(60%)
- 2014-8 ~ 2015-11 AC-TH, herceptin 1yr
- 2017-1 Rt. Axillary LN mass
- 2017-2 RTx: Rt. axilla + CTx
- 2017-6 Nipple areolar wide excision
  - ER(-)/PR(-)/HER2(3+)/Ki-67(10%)
- 2018-1 Rt. Pleural effusion, Abd LN
  - Pleural effusion – malignant cell (-)
- Hx of NTM
- Metastases vs. NTM infection
- Laparoscopic Bx?

Courtesy of Dr. KimHA

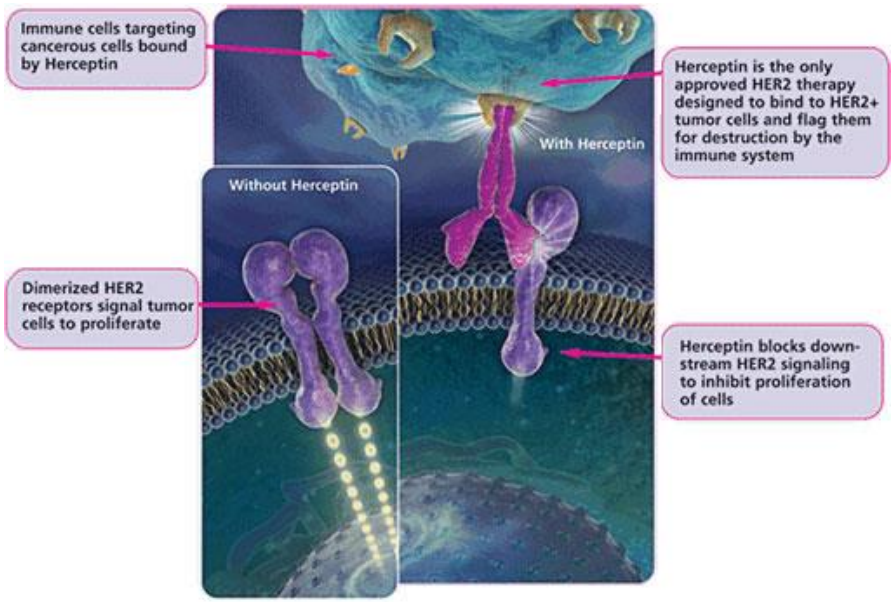
Advantage of Imaging biomarker



Non-invasiveness

Gebhart et al, Ann Oncol, 2016

Human Epidermal growth factor Receptor 2 (HER2)



- Epidermal growth factor receptor family
- Cell membrane surface-bound receptor tyrosine kinase
- 15-20 percent of breast cancers - *her2/neu* overexpression
  - Increased disease recurrence and worse prognosis
- Incorrect result from IHC and FISH – 20%
- In vivo evaluation of HER2 expression
  - Metastasis, Hard to Bx
  - Change after Tx

Olayiove et al, Breast cancer research,2001

Trastuzumab reimbursement in Korea

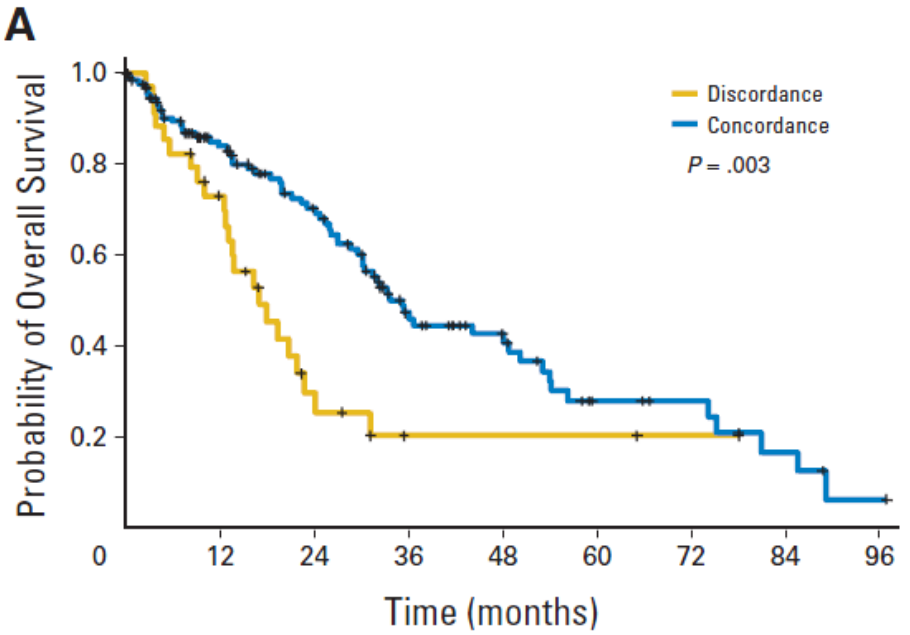
- HER2 test mandatory before Tx
- Metastatic breast cancer
  - Single Tx to previous chemotherapy Pt
  - Paclitaxel or Docetaxel combined therapy without previous chemotherapy
  - Aromatase inhibitor combined therapy to HR+ post menopausal Pt without trastuzumab Hx
- Early breast cancer
  - After chemotherapy (or RT)
  - Paclitaxel or Docetaxel combined therapy after adjuvant chemotherapy
- Metastatic stomach cancer

Discordance of primary and metastatic tumor

Table 3. Concordance Rates by Clinical Factors (all patients)

Subgroup	HER2 Status: Concordant (n = 139) No.	%	Discordant (n = 43) No.	%	P
Trastuzumab					
None	78	74	28	26	.296
Before biopsy	61	80	15	20	
Timing of metastasis diagnosis					
At presentation	30	88	4	12	.077
At recurrence	109	74	39	26	
Metastatic location					
Local	53	72	21	28	.212
Distant	86	80	22	20	
Hormone receptor status					
Positive	79	77	23	23	.865
Negative	58	74	20	26	
Unknown	2				
Chemotherapy with or without trastuzumab					
None	36	90	4	10	.022
Before biopsy	103	73	39	27	
Time from diagnosis of breast cancer to biopsy, years					
≤ 5	95	78	27	22	.498
> 5	44	73	16	27	
Years of breast cancer diagnosis					
1997-2004	102	76	32	24	.893
2005-2008	37	77	11	23	
	(n = 78)		(n = 28)		
Chemotherapy without trastuzumab*					
None	36	90	4	10	
Before biopsy	42	64	24	36	

Abbreviation: HER2, human epidermal growth factor receptor 2.
*Among 106 patients who had chemotherapy without trastuzumab, the total number of patients with HER2 status concordance was 78; total with discordance, 28.



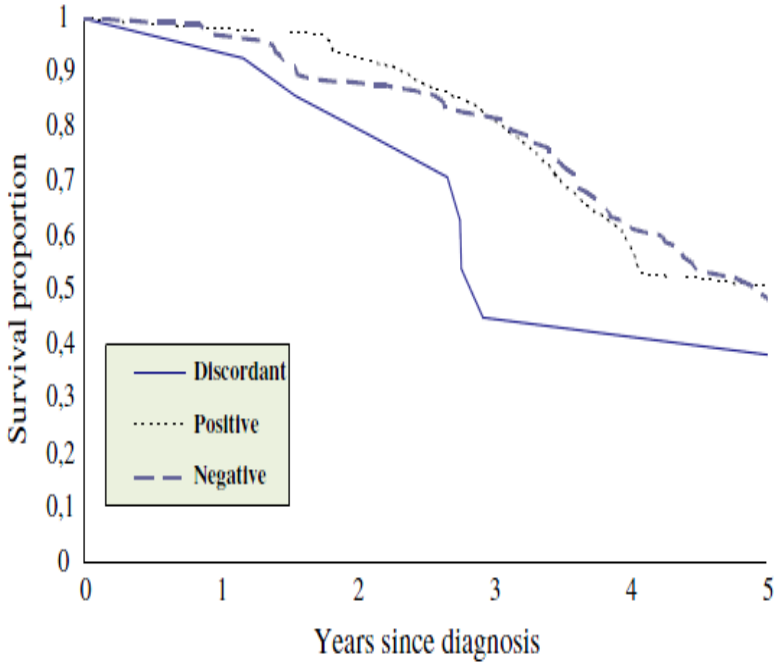
- N=182, HER2+ primary tumor
- 43 Pt (24%) HER2 – metastatic tumor
- Need for Bx of metastasis
  - Px
  - Targeted therapy

Niikura et al, JCO, 2012

HER2 status in a population-derived breast cancer cohort: discordances during tumor progression

Ulla Wilking · Eva Karlsson · Lambert Skoog · Thomas Hatschek · Elisabet Lidbrink · Goran Elmberger · Hemming Johansson · Linda Lindström · Jonas Bergh

- N=151
- 15 Pt (10%) HER2 change
  - 7/108 HER2- to HER2+
  - 8/43 HER2+ to HER2-
- HER2 stable
  - 101 HER2-
  - 35 HER2+



Negative = Patients with stable HER2 negative primary tumor and recurrence

Positive = Patients with stable HER2 positive primary tumor and recurrence

Discordant = Patients with a change in HER2 status between primary tumor and recurrence

Niikura et al, JCO, 2012

諸行無常 Everything is changing

사랑은 움직이는 거야
Love is moving

^{64}Cu-DOTA-Trastuzumab PET Imaging in Patients with HER2-Positive Breast Cancer

Kenji Tamura[1], Hiroaki Kurihara[2], Kan Yonemori[1], Hitoshi Tsuda[3], Junko Suzuki[4], Yuzuru Kono[2], Natsuki Honda[2], Makoto Kodaira[1], Harukaze Yamamoto[1], Mayu Yunokawa[1], Chikako Shimizu[1], Koki Hasegawa[5], Yousuke Kanayama[5], Satoshi Nozaki[5], Takayuki Kinoshita[4], Yasuhiro Wada[5], Shusaku Tazawa[5], Kazuhiro Takahashi[5], Yasuyoshi Watanabe[5], and Yasuhiro Fujiwara[1]

[1]Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [2]Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan; [3]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan; [4]Department of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan; and [5]RIKEN Center for Molecular Imaging Science, Hyogo, Japan

Patient no.	Age (y)	Histology	Stage	HER2 expression (FISH score)	Interval from CNB to ^{64}Cu (mo)	Primary or metastatic size (cm) or location	No. of lesions visualized by MR imaging/CT/^{64}Cu	History of trastuzumab treatment	Days from trastuzumab treatment to imaging
1	73	IDC-st	IV	3+	20	M, brain	6/4/4	Weekly	1 d
2	42	IDC-SC	IIB	3+	11	P, 2.3 × 2.1	NA/1/1	Triweekly	20 d
3	49	Lobular	IIA	2+ (3.9)	3	P, 2.0 × 2.0	NA/1/1	—	—
4	75	IDC-SC	IV	3+	10	M, brain	1/0/1	Weekly	1 d
5	55	IDC-st	IIA	3+	22	P, 3.5 × 3.5	NA/1/1	Triweekly	8 d
6	45	IDC-SC	IV	3+	1	M, hilar node	NA/1/1	—	—

CNB = core-needle biopsy; ^{64}Cu = ^{64}Cu-DOTA-trastuzumab PET; IDC-st = invasive ductal carcinoma–solid tubular; IDC-SC= invasive ductal carcinoma–scirrhous; M = metastatic breast cancer; P = primary breast cancer; NA = not applied within 1 mo before or after ^{64}Cu-DOTA-trastuzumab PET imaging; weekly = 2 mg/kg/wk; triweekly = 8 mg/kg/3 wk.

Tamura et al, JNM,2013

PET imaging and analysis

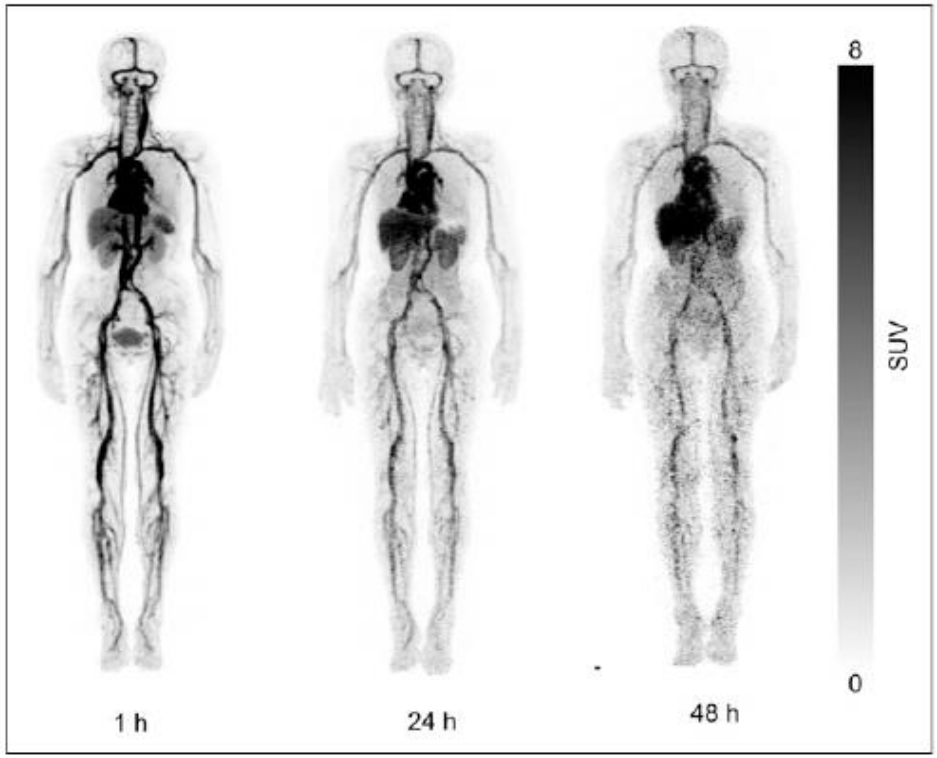


FIGURE 1. Whole-body ^{64}Cu-DOTA-trastuzumab PET images at 1, 24, and 48 h after injection (patient 4).

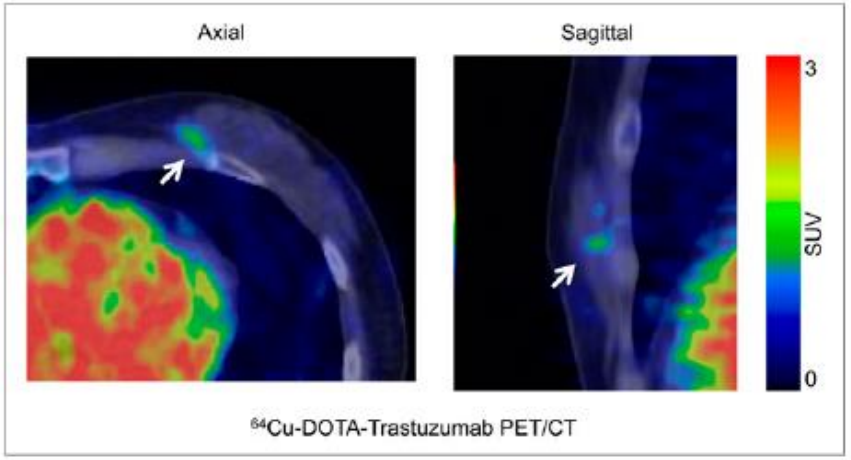
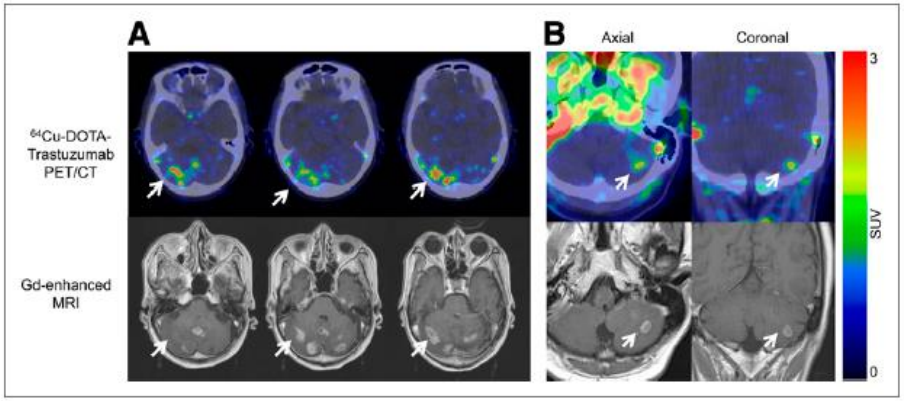


FIGURE 3. ^{64}Cu-DOTA-trastuzumab PET images of HER2-positive primary breast tumor. Arrows show primary breast tumor in patient 3. Red regions indicate high uptake ^{64}Cu-DOTA-trastuzumab in heart and blood vessels.



Functional Imaging of Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Using ^{64}Cu-DOTA-Trastuzumab PET

Joanne E. Mortimer[1], James R. Bading[2], David M. Colcher[2], Peter S. Conti[3], Paul H. Frankel[4], Mary I. Carroll[1], Shan Tong[2], Erasmus Poku[2], Joshua K. Miles[2], John E. Shively[5], and Andrew A. Raubitschek[2]

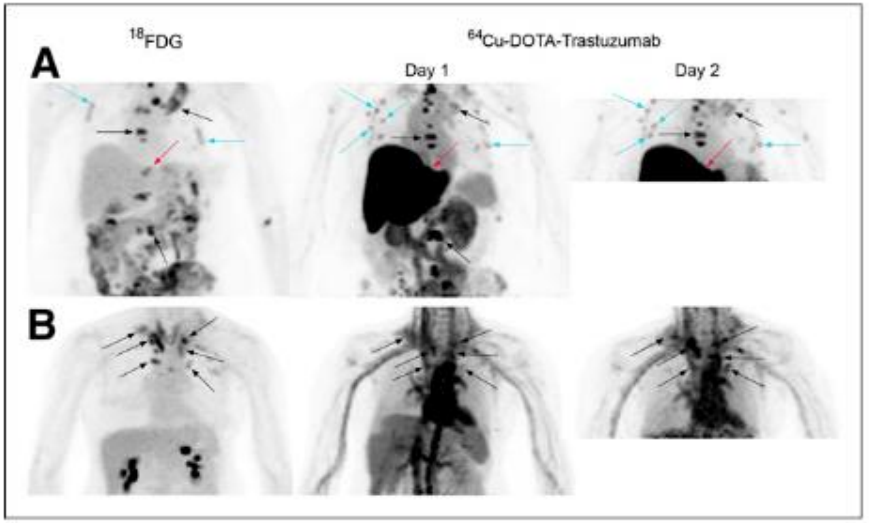
[1]Department of Medical Oncology and Experimental Therapeutics, City of Hope, Duarte, California; [2]Department of Cancer Immunotherapeutics and Tumor Immunology, Beckman Research Institute of the City of Hope, Duarte, California; [3]Molecular Imaging Center, Department of Radiology, University of Southern California, Los Angeles, California; [4]Department of Information Sciences, City of Hope, Duarte, California; and [5]Department of Immunology, Beckman Research Institute of the City of Hope, Duarte, California

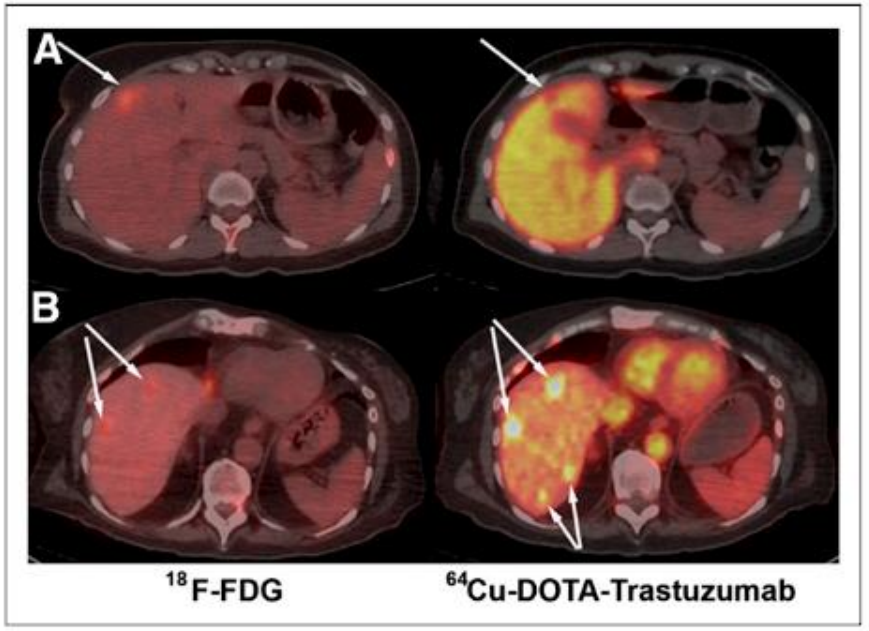
Mortimer et al, JNM,2014

PET imaging

Characteristic	Trastuzumab protein dose (mg) 5	50	All patients
No. of patients	2	6	8
Age (y)			
Median	60	54	56
Range	44–75	39–69	39–75
Prior anti-HER2 therapy			
None		1	1
Adjuvant trastuzumab	1	2	3 (14, 18, 18)†
Trastuzumab for metastasis	1	3	4 (4, 6, 14, 18)†
Hormone receptor and HER2 status of recurrent disease			
ER or PR positive	1	3	4
ER and PR negative	1	3	4
HER2			
IHC3+	2	5	7
IHC2+/FISH positive		1	1
Sites of metastatic disease			
Bone	2	4	6
Lymph nodes	2	5	7
Liver	2	2	4
Lung	1	1	2
Pleural effusion		1	1
Breast		2	2

*Entries are numbers of patients unless otherwise indicated.
†Months since last anti-HER2 therapy administration.
ER = estrogen receptor; PR = progesterone receptor; IHC = immunohistochemistry; FISH = fluorescence in situ hybridization.



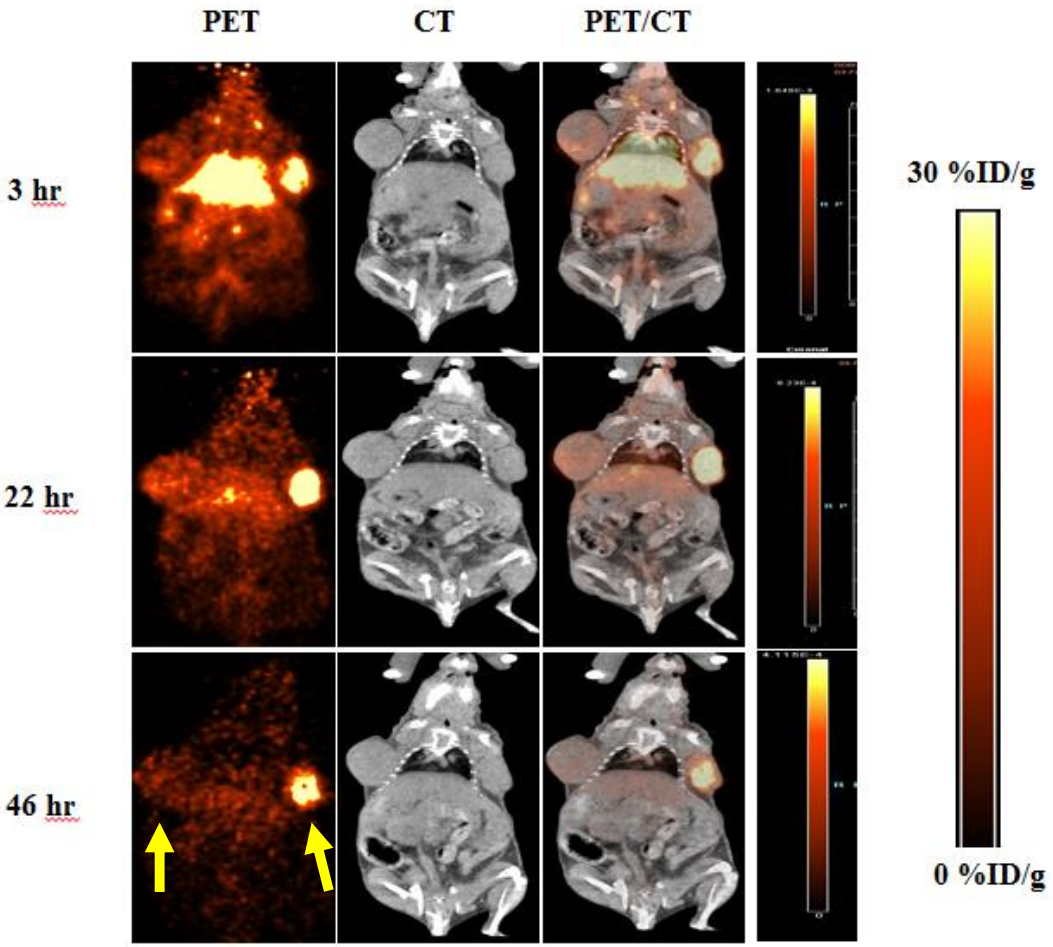


PET imaging of breast cancer using a ^{64}Cu-DOTA-Trastuzumab for pharmacokinetics study: Microdose PET clinical trial

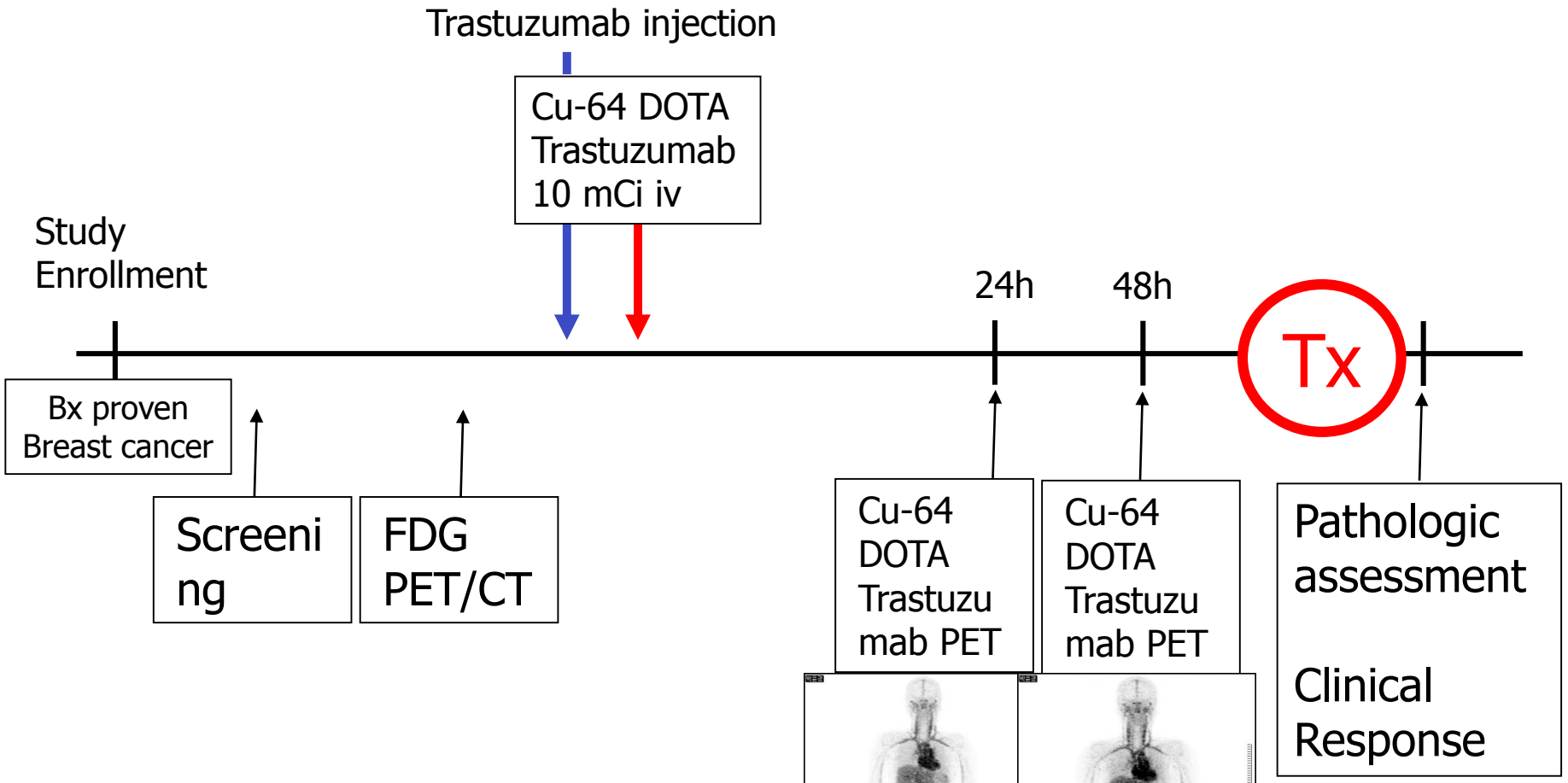
Korea Cancer Center Hospital

Korea Institute of Radiological and Medical Sciences (KIRAMS), Seoul, Korea

Cu-64 DOTA Trastuzumab



Study protocol



2016-6-30 KFDA submission
2017-7-6 KFDA approval

KFDA approval

제 31371 호

임상시험계획 승인서

의뢰자	성명	한국원자력의학원			
	명칭	노우철			
	소재지				
시험약 정보	제품명 (또는 코드명)	별첨	주성분명 (또는 코드명)	별첨	
	제형	용액 주사			
	단위 함량	별첨			
	사용(유효)기간	3년			

계획서 정보	계획서 승인번호	제목	임상단계	계획서 식별번호
	제 31371 호	유방암에서 HER2 발현 평가를 위한 64Cu-DOTA-Trastuzumab PET 연구자 임상시험 (KCCHNM201606 Ver 1.0_20170515(동의서 Version 1.0_20160615))	연구자 임상 시험	KCCHNM201606 Ver 1.0_20170515(동의서 Version 1.0_20160615)

승인 조건 : 없음

「약사법」 제34조제1항 및 「의약품 등의 안전에 관한 규칙」 제24조제7항에 따라 위와 같이 승인합니다.

2017.7.6

식품의약품안전처장

제 31369 호

임상시험계획 승인서

의뢰자	성명	한국원자력의학원			
	명칭	노우철			
	소재지				
시험약 정보	제품명 (또는 코드명)	별첨	주성분명 (또는 코드명)	별첨	
	제형	용액 주사			
	단위 함량	별첨			
	사용(유효)기간	3년			

계획서 정보	계획서 승인번호	제목	임상단계	계획서 식별번호
	제 31369 호	유방암에서 64Cu-NOTA-trastuzumab의 약물동태학적 특성 평가 마이크로도즈 PET 임상시험 (KCCHNM201606 Ver 1.0_20170515(동의서 Version 1.0_20160615))	연구자 임상 시험	KCCHNM201606 Ver 1.0_20170515(동의서 Version 1.0_20160615)

승인 조건 : 없음

「약사법」 제34조제1항 및 「의약품 등의 안전에 관한 규칙」 제24조제7항에 따라 위와 같이 승인합니다.

2017.7.6

식품의약품안전처장

Case1

F/45

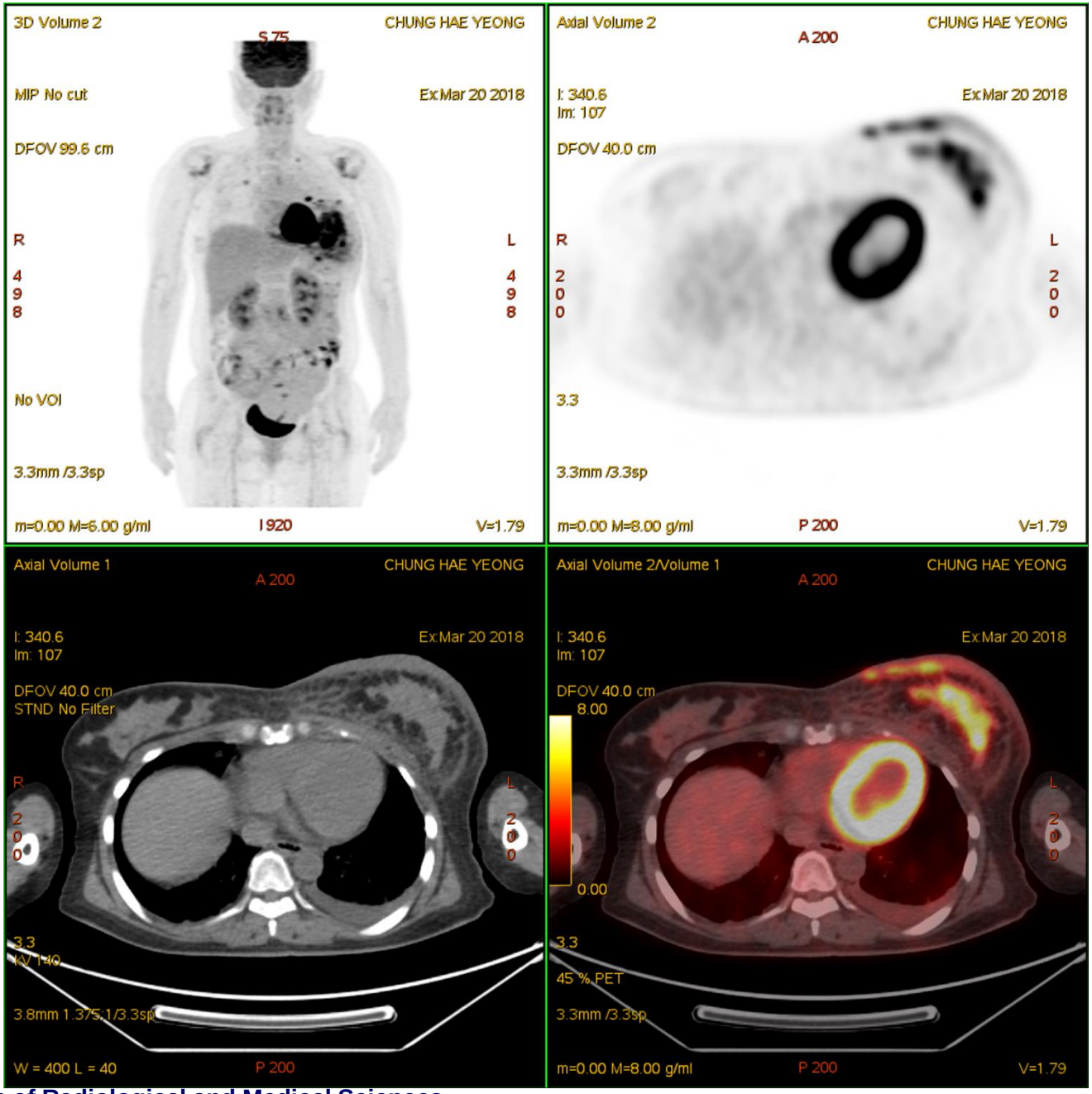
r/o bilateral breast cancer, c lung mets, cT4N2M1

- ER(+)/PR(+)/HER2(3+)/Ki-67(70%) (2017.04.24)
- s/p #8 herceptin, #5 perzeta ~2017.10

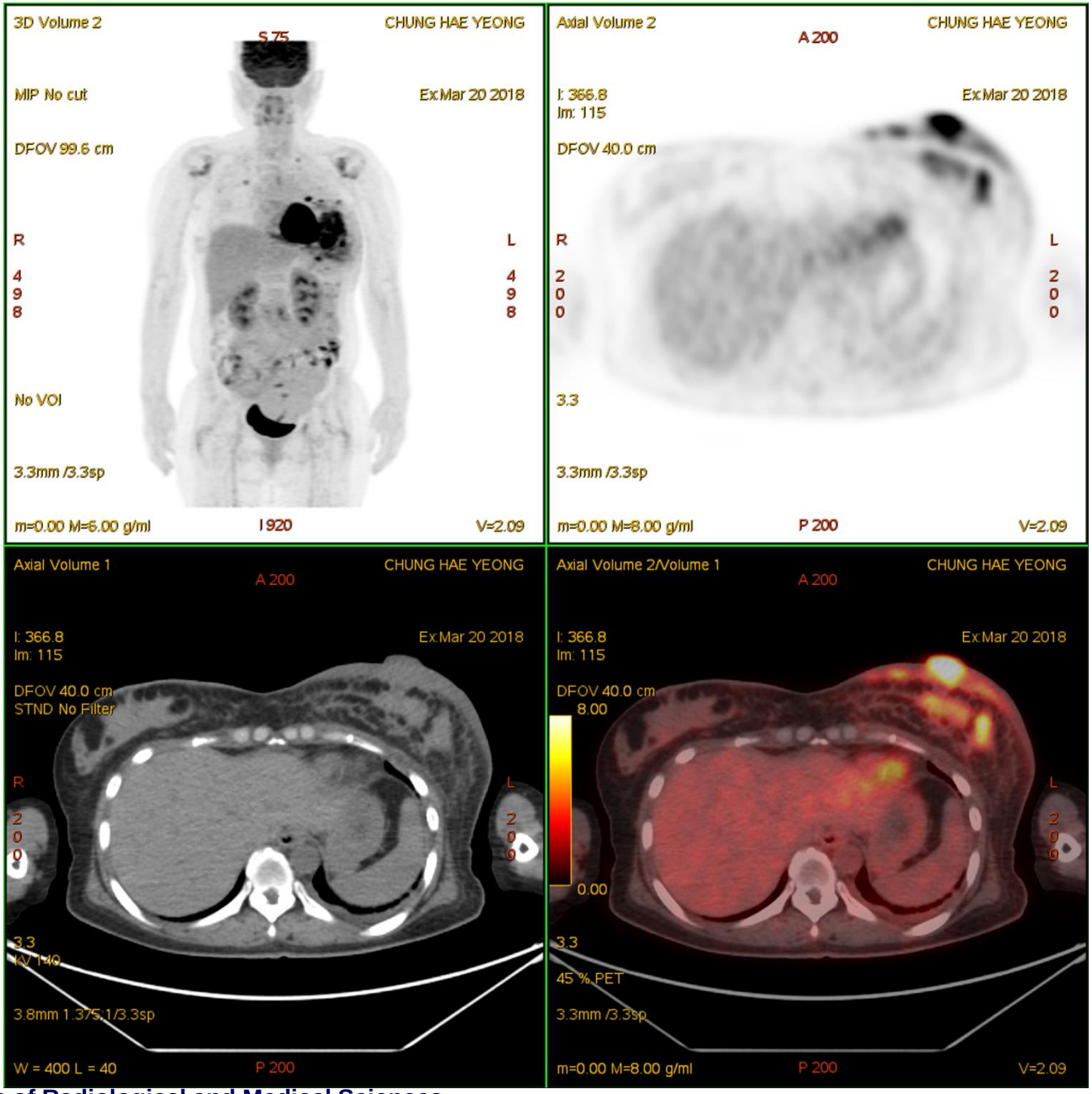
[PD] Lt. breast on P/E

- s/p #6 FEC ~2018.02
- serum HER2 52.1 (2018.03.07)

FDG PET/CT 2018.03.20



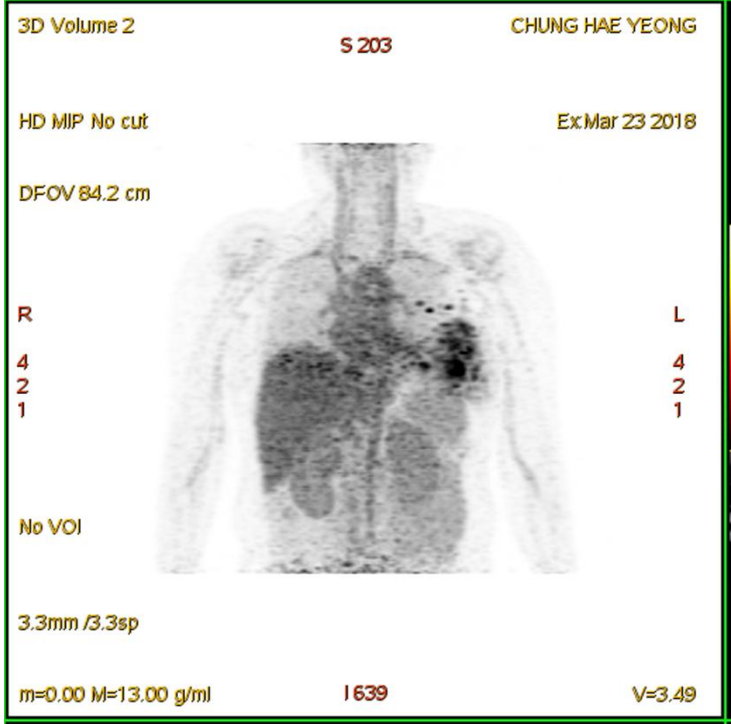
FDG PET/CT 2018.03.20

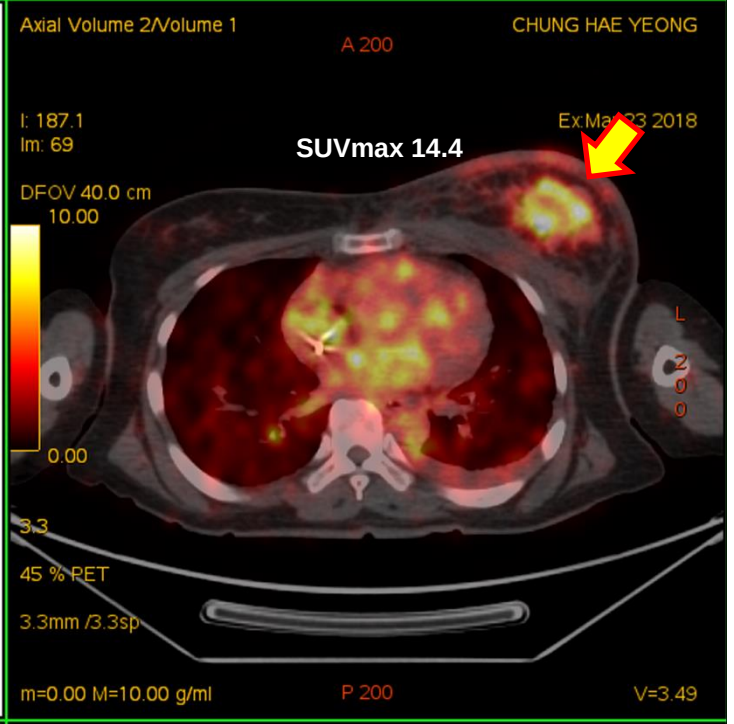


^{64}Cu-DOTA-Trastuzumab PET/CT

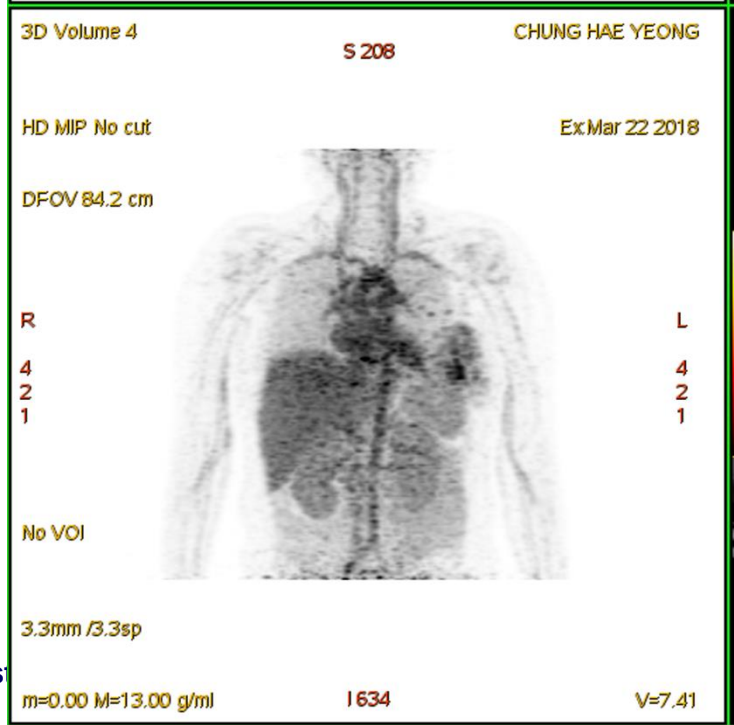
^{64}Cu-DOTA

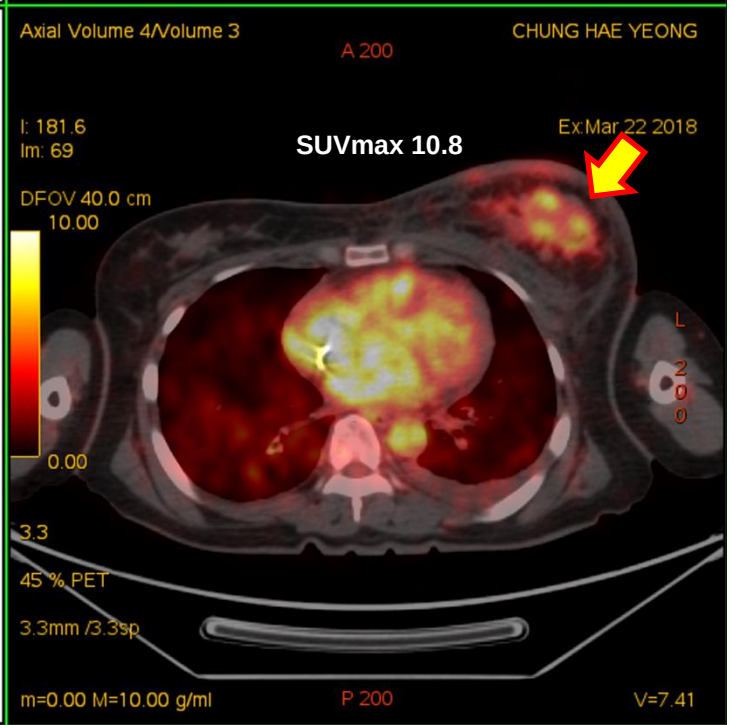
48hour





24hour

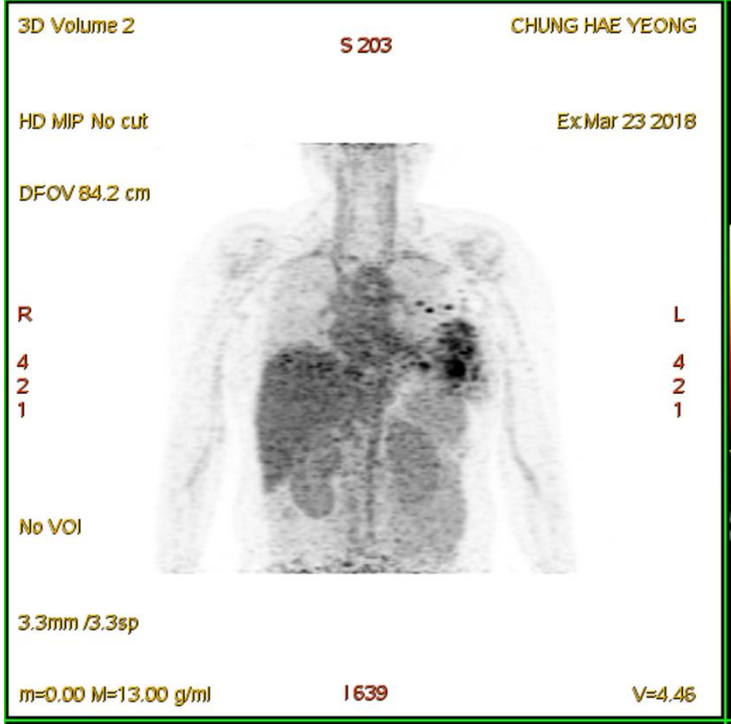


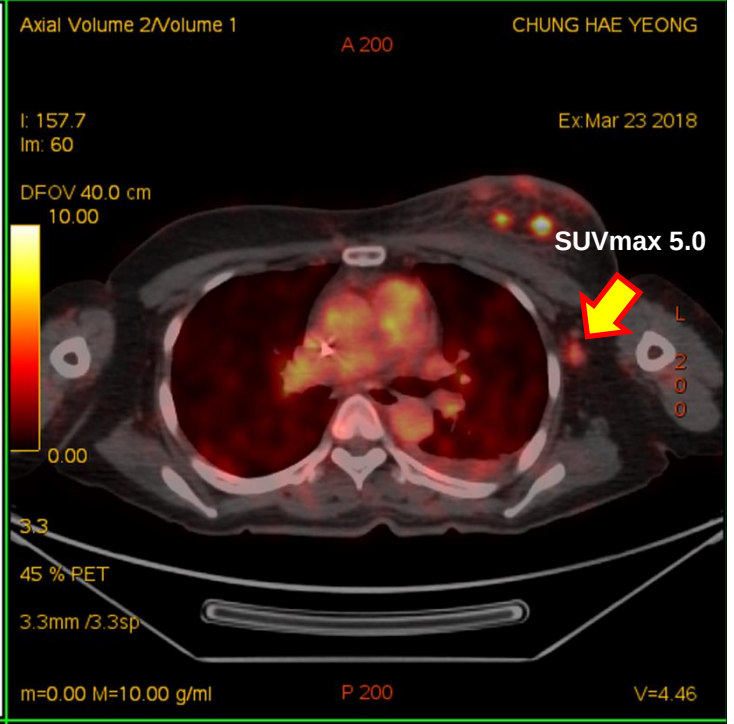


KIRAMS
Korea Inst

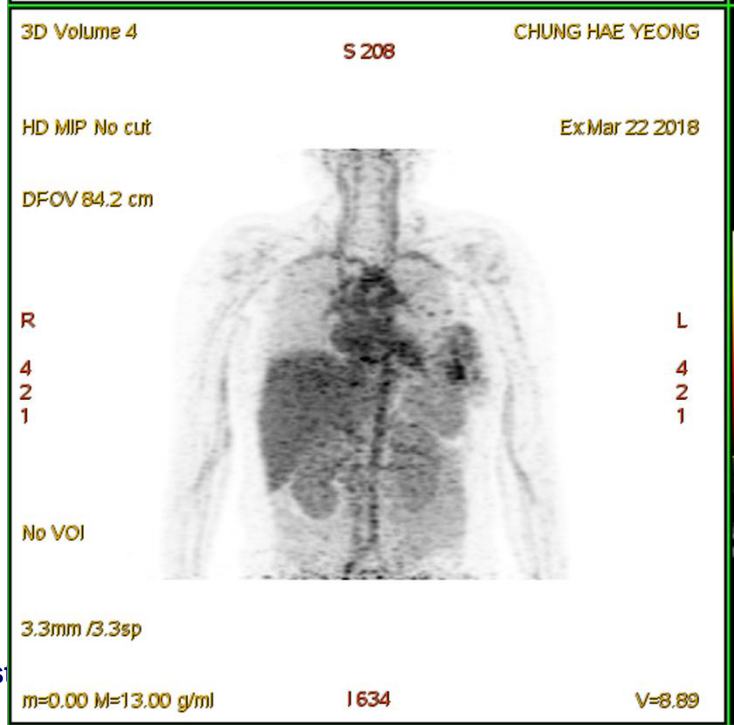
^{64}Cu-DOTA

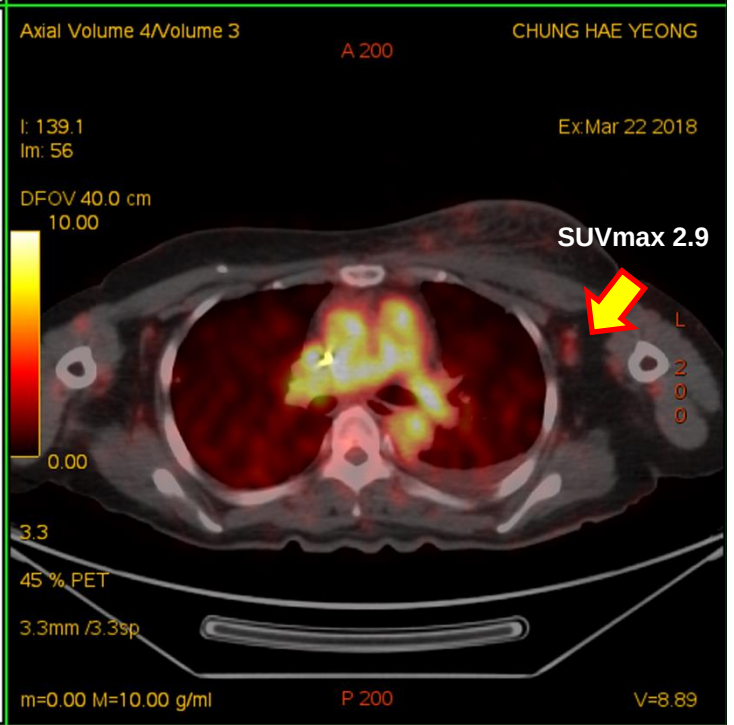
48hour





24hour





KIRAMS
Korea Inst

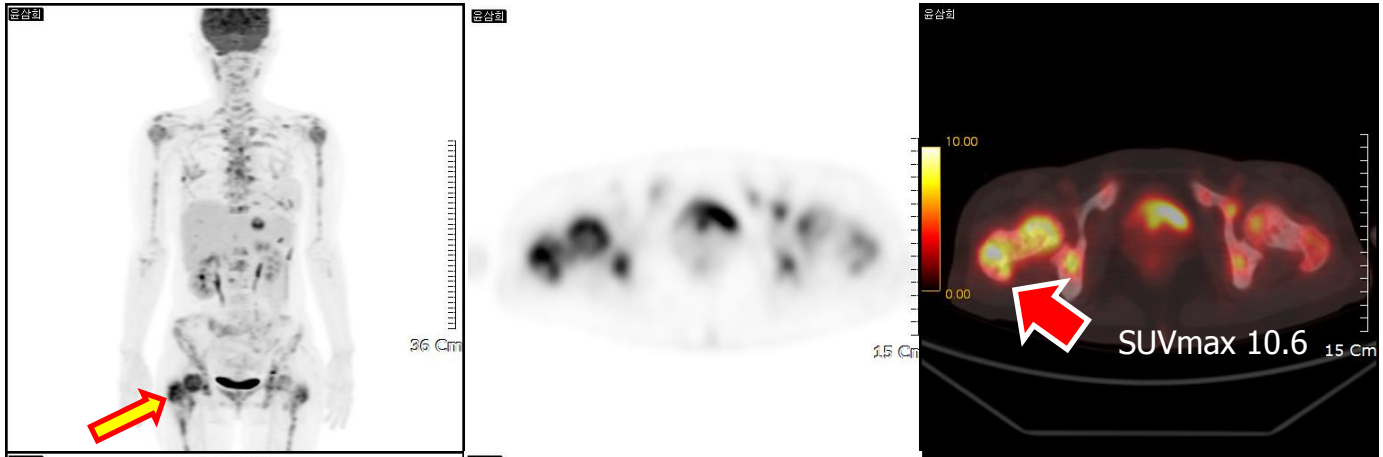
Case2

F/48

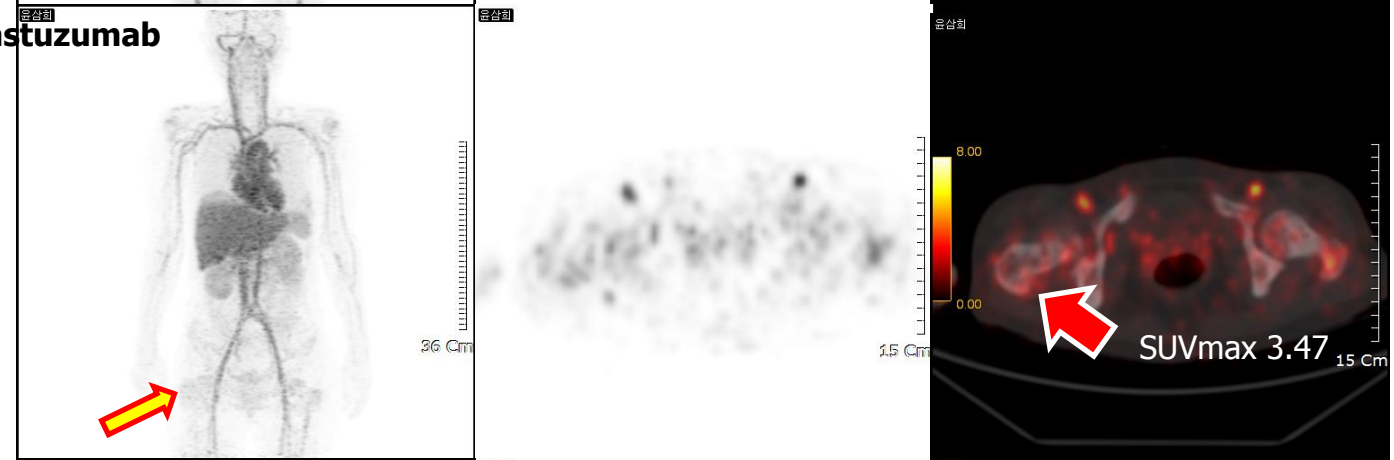
Metastatic breast cancer: bone&liver

ER+/PR+/HER2 1+ Ki67 3%

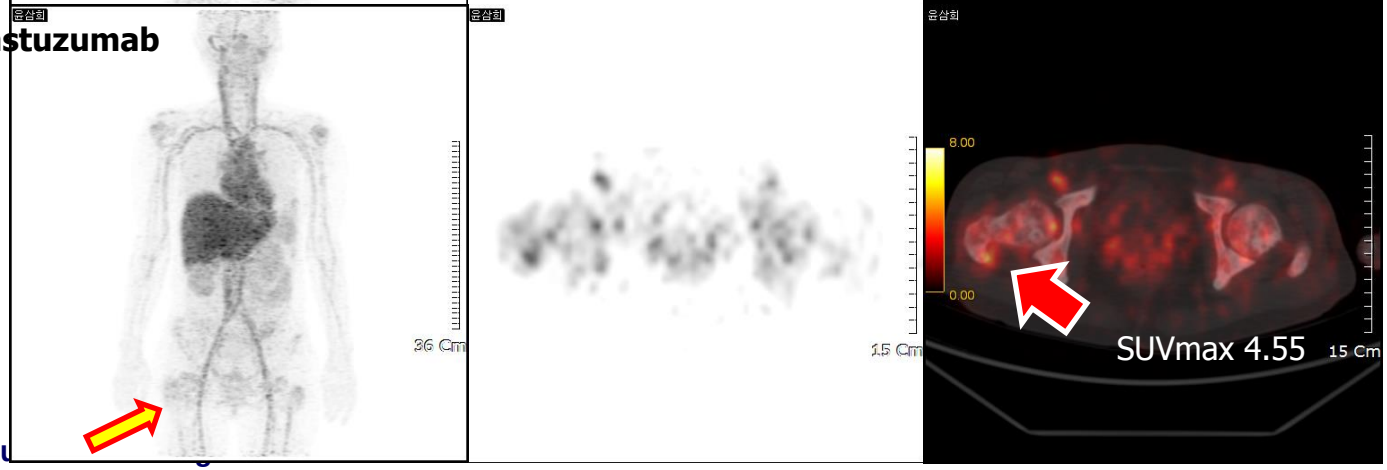
^{18}FDG PET/CT



^{64}Cu-DOTA-Trastuzumab 24hour



^{64}Cu-DOTA-Trastuzumab 48hour



Case 3

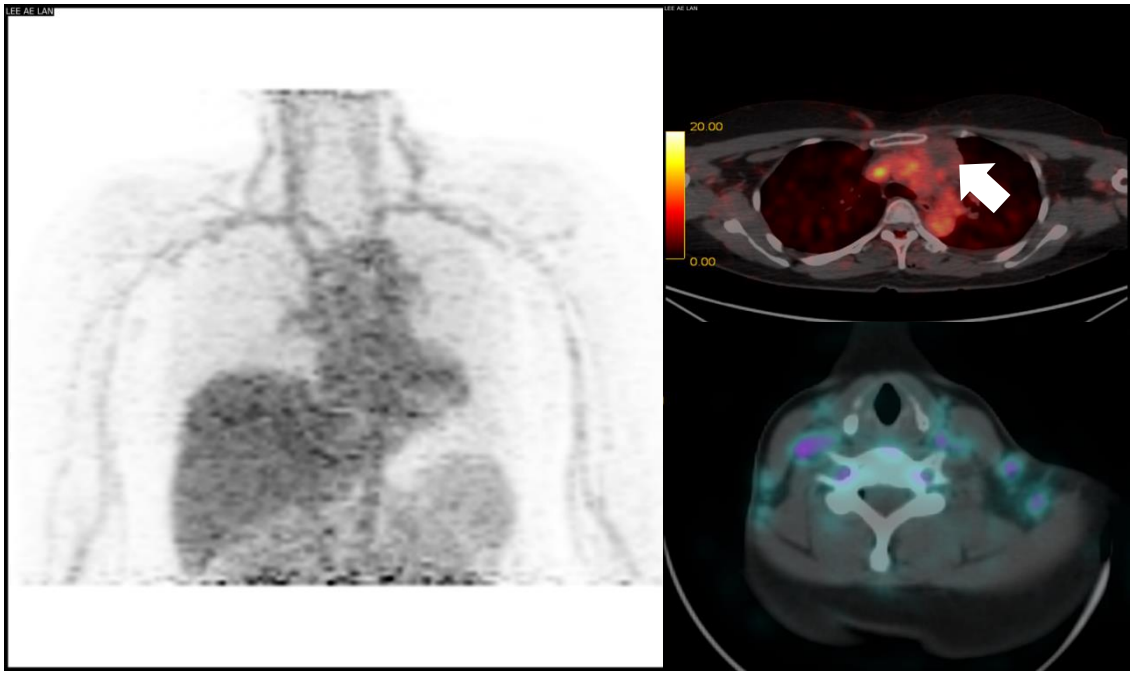
F/44, Left breast cancer
s/p BCS 2015.11
s/p Herceptin ~2017.05
ER(-)/PR(-)/HER2(3+)/Ki-67(60%)

New mediastinal LN

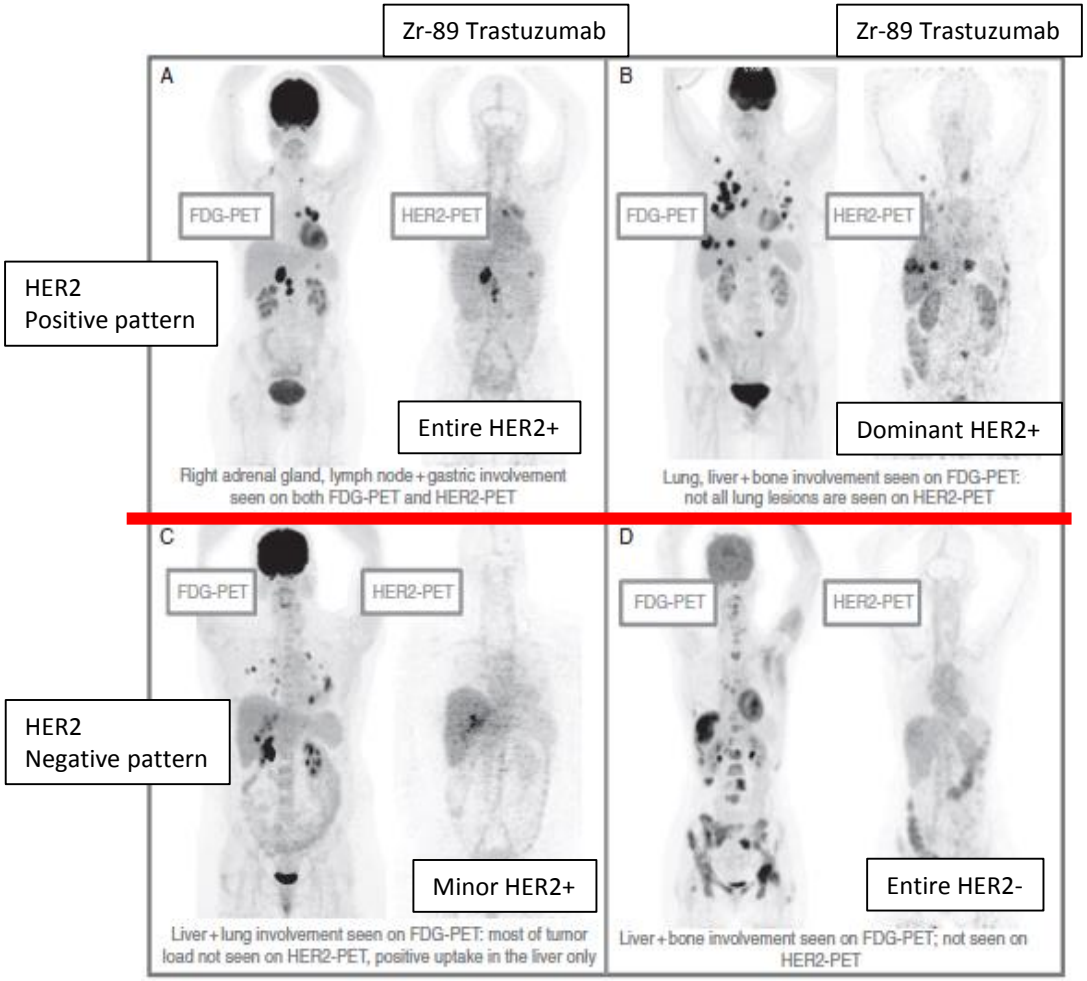
Lt. supraclavicular LN - Bx: Mets HER2+++

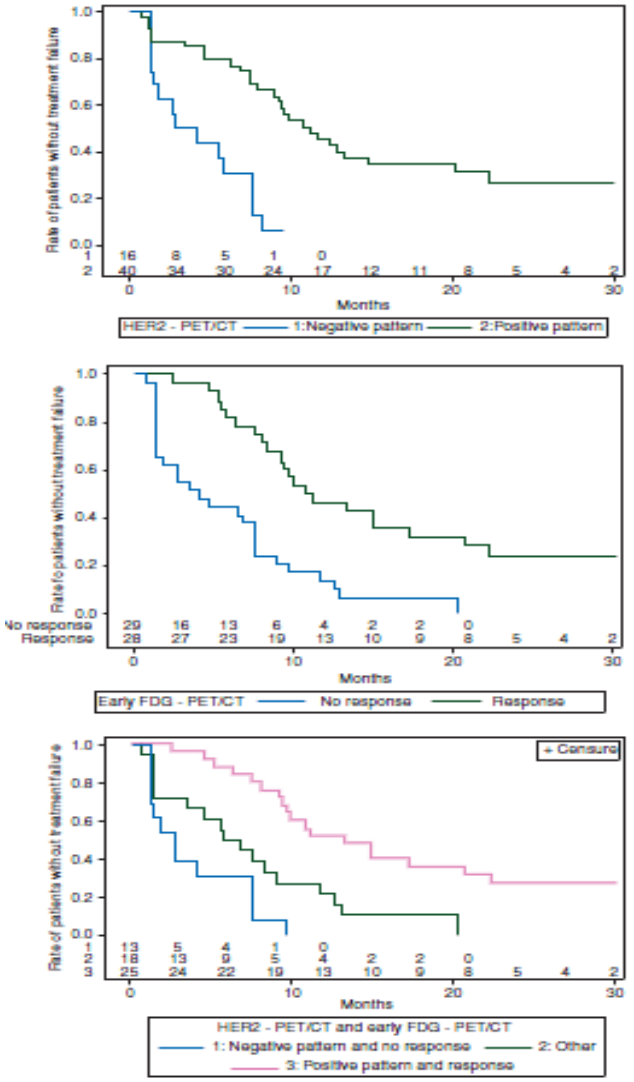
FDG PET/CT

Cu-64 DOTA-trastuzumab



Molecular imaging as a tool to investigate heterogeneity of advanced HER2-positive breast cancer and to predict patient outcome under trastuzumab emtansine (T-DM1): the ZEPHIR trial





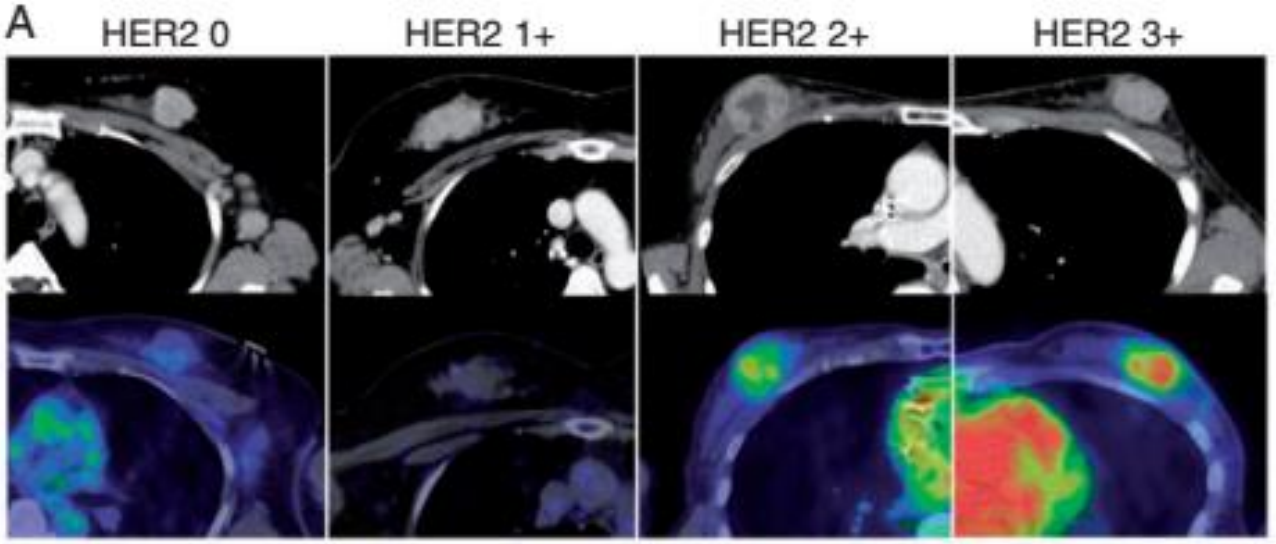
KIRAMS
Korea Institute of Radiological and Medical Sciences

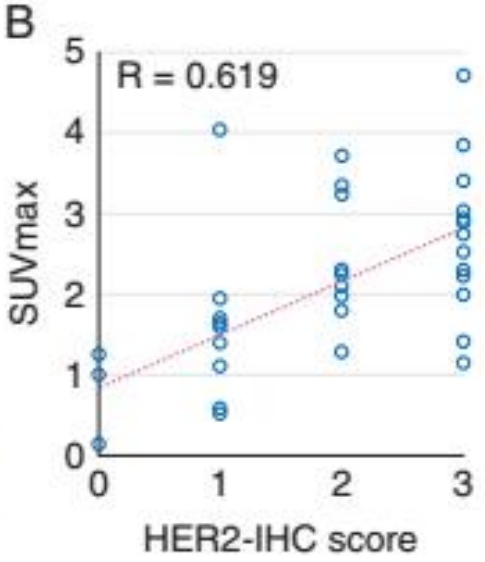
Gebhart et al, Ann Oncol, 2016

^{64}Cu-DOTA-trastuzumab PET imaging for HER2-specific primary lesions of breast cancer

S. Sasada[1], H. Kurihara[2], T. Kinoshita[3], M. Yoshida[4], N. Honda[2], T. Shimoi[1], A. Shimomura[1], M. Yunokawa[1], K. Yonemori[1], C. Shimizu[1], A. Hamada[5], Y. Kanayama[6], Y. Watanabe[6], Y. Fujiwara[1] & K. Tamura[1*]

Departments of [1]Breast and Medical Oncology; [2]Diagnostic Radiology; [3]Breast Surgery; [4]Pathology and Clinical Laboratories, National Cancer Center Hospital; [5]Division of Molecular Pharmacology and Pharmacokinetics, National Cancer Center Research Institute, Tokyo; [6]RIKEN Center for Life Science Technologies, Hyogo, Japan
(*E-mail: ketamura@ncc.go.jp)



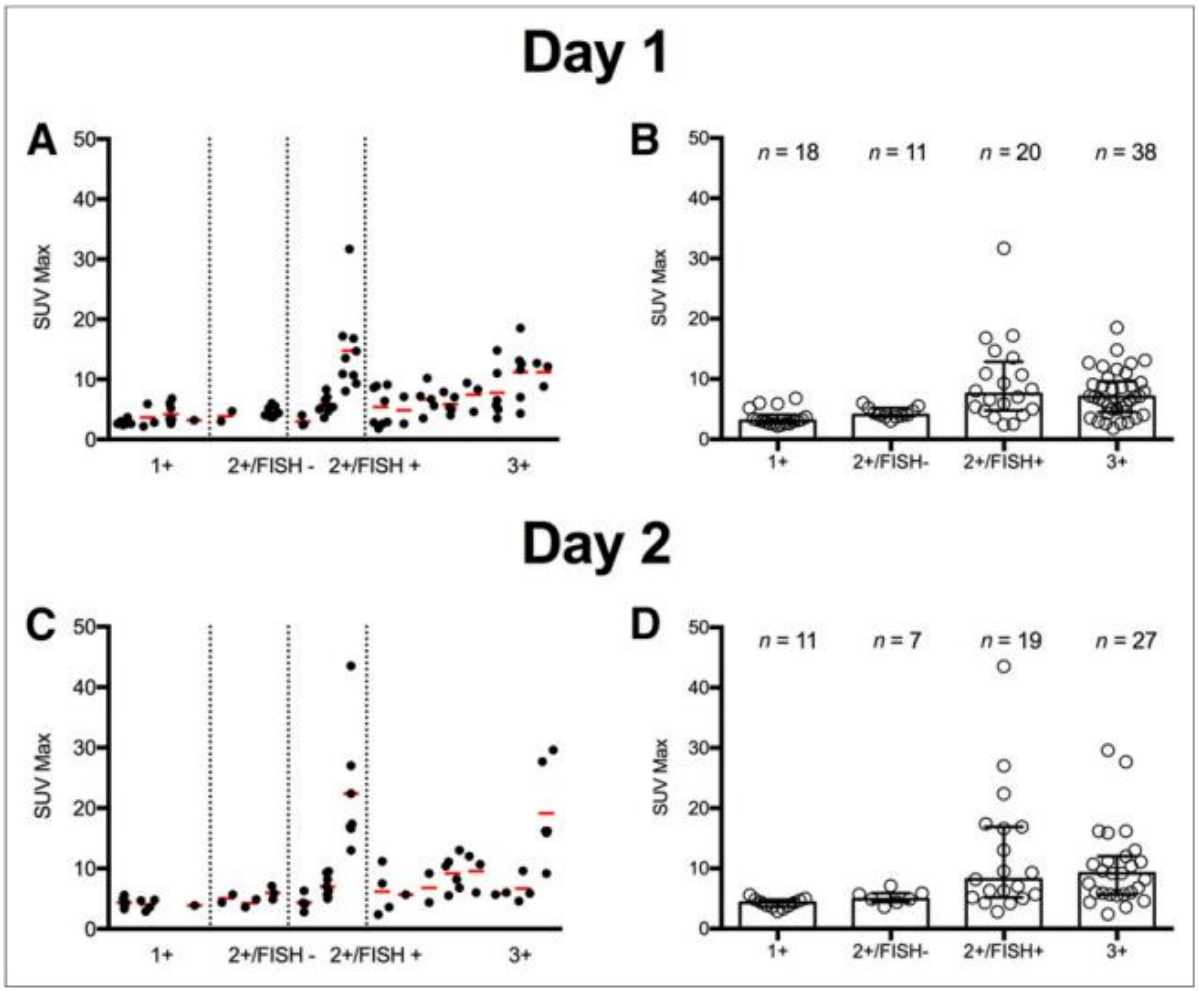


Sasada et al, Annal Oncol, 2017

Tumor Uptake of ^{64}Cu-DOTA-Trastuzumab in Patients with Metastatic Breast Cancer

Joanne E. Mortimer[1], James R. Bading[1], Jinha M. Park[2], Paul H. Frankel[3], Mary I. Carroll[1], Tri T. Tran[2], Erasmus K. Poku[4], Russell C. Rockne[3], Andrew A. Raubitschek[4], John E. Shively[5], and David M. Colcher[4]

[1]Department of Medical Oncology and Experimental Therapeutics, City of Hope, Duarte, California; [2]Department of Radiology, City of Hope, Duarte, California; [3]Department of Information Sciences, City of Hope, Duarte, California; [4]Department of Cancer Immunotherapy and Tumor Immunology, Beckman Research Institute of the City of Hope, Duarte, California; and [5]Department of



Mortimer et al, JNM, 2018

Evaluation of HER2 expression using imaging biomarker

- Need to assess HER2 expression non-invasively
- HER2 expression heterogeneity
  - Metastatic lesion
  - Temporal
- Cu-64 DOTA Trastuzumab
  - Uptake at HER2 positive metastatic breast ca
  - Imaging timing; 1 D, 2D after injection
  - Trastuzumab predosing favorable
  - Well correlated with IHC
- Zr-89 DOTA Trastuzumab
  - Proper half life for Ab (3.3 d)
  - Response of TDM-1

Breast cancer Pt with Abd LN during F/U

F/48, Right breast cancer
ER(-)/PR(-)/HER2(3+)/Ki-67(60%)
s/p Right NACSSM+SLNB 2014.07
s/p AC-TH -> Herceptin

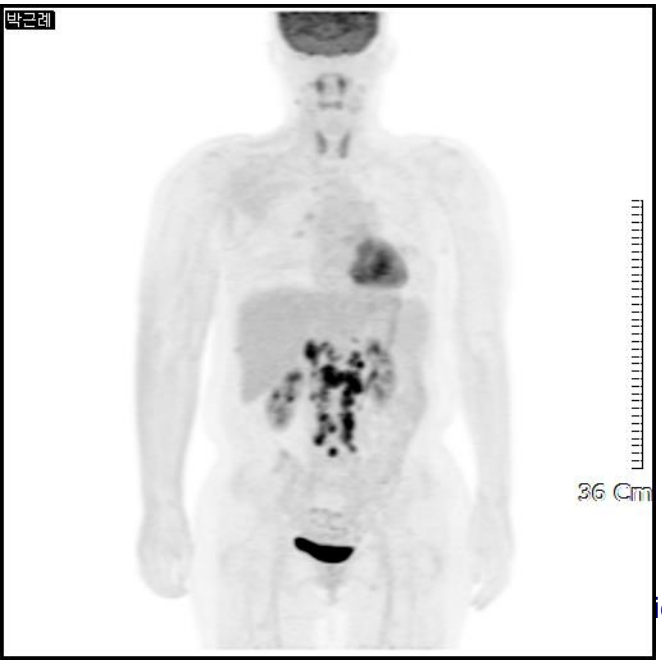
Regional recurrence, right axillary LNs on 2017.01.16
s/p RTx: right axilla
s/p CTx, palliative wide excision of NAC
ER(-)/PR(-)/HER2(3+)/Ki-67(10%)

Serum HER2 32.1 on 2018.1
Hx of NTM

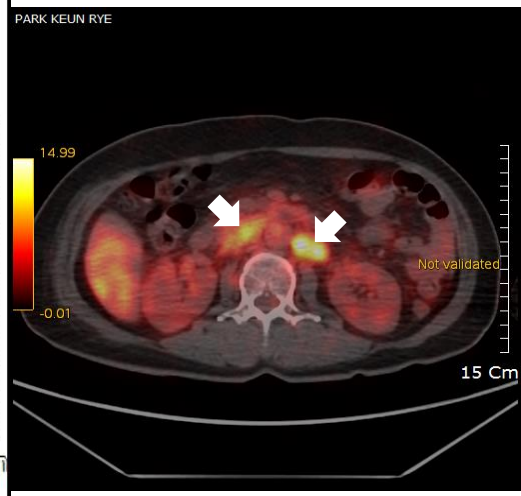
HER2 Positive tumor

CTx Responder

FDG PET/CT



Cu-64 DOTA-trastuzumab



Acknowledgment

Korea Institute of Radiological and Medical Sciences (KIRAMS)

Korea Cancer Center Hospital

Breast cancer center

Woo Chul Noh

Hyun-Ah Kim

Min Ki Sung

Seung Sook Lee

Hye Sil Sul

Jae Kyung Myung

Ko Woon Park

Sun Ah Chang

Molecular Imaging Research Center

Joo Hyun Kang

Kwang Il Kim

Chang Kyun Ahn

Seung Bum Choi

Jae Hyung Kim

Korea Cancer Center Hospital

Department of Nuclear Medicine

Inki Lee

Byung Hyun Byun

Byung Il Kim

Chang Woon Choi

Sang Moo Lim

Thank you for
your attention