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U3-1402 Workshop
Hosted by UBS Securities

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Agenda

1. Background
2. Pre-clinical data
3. Clinical data
4. Vision

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Background

Pipeline of ADC Franchise

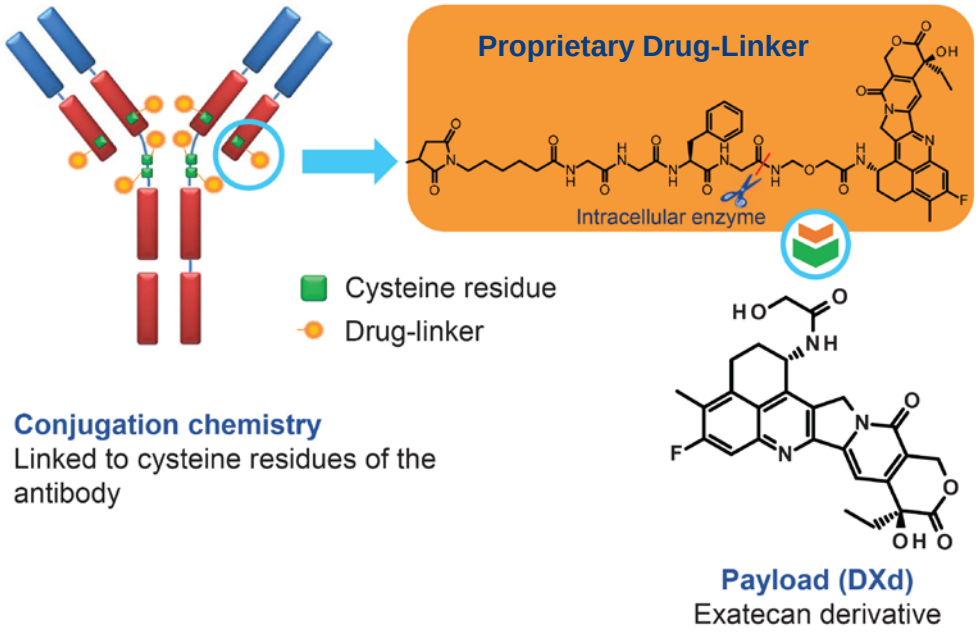
ADC Franchise

Clinical stage

	Project (Target)	Potential Indication	Discovery	Pre-Clinical	Phase 1	Pivotal
1	DS-8201 (HER2)	Breast, Gastric, CRC, NSCLC				
2	U3-1402 (HER3)	Breast, NSCLC				
3	DS-1062 (TROP2)	NSCLC				
4	DS-7300 (B7-H3)	Solid tumor				
5	DS-6157 (undisclosed)	GIST				
6	DS-6000 (undisclosed)	Renal, Ovarian				
7	TA-MUC1	Solid tumor				

CRC: colorectal cancer, GIST: gastrointestinal stromal tumor, NSCLC: non-small cell lung cancer

Features of Daiichi Sankyo ADC



Critical DXd-ADC design features

- High drug-to-antibody ratio (DAR)
- Highly stable linker
- Tumor-selective linker cleavable
- Unique and high potency payload
- Bystander effect
- Payload with short systemic half-life

Features of ADCs

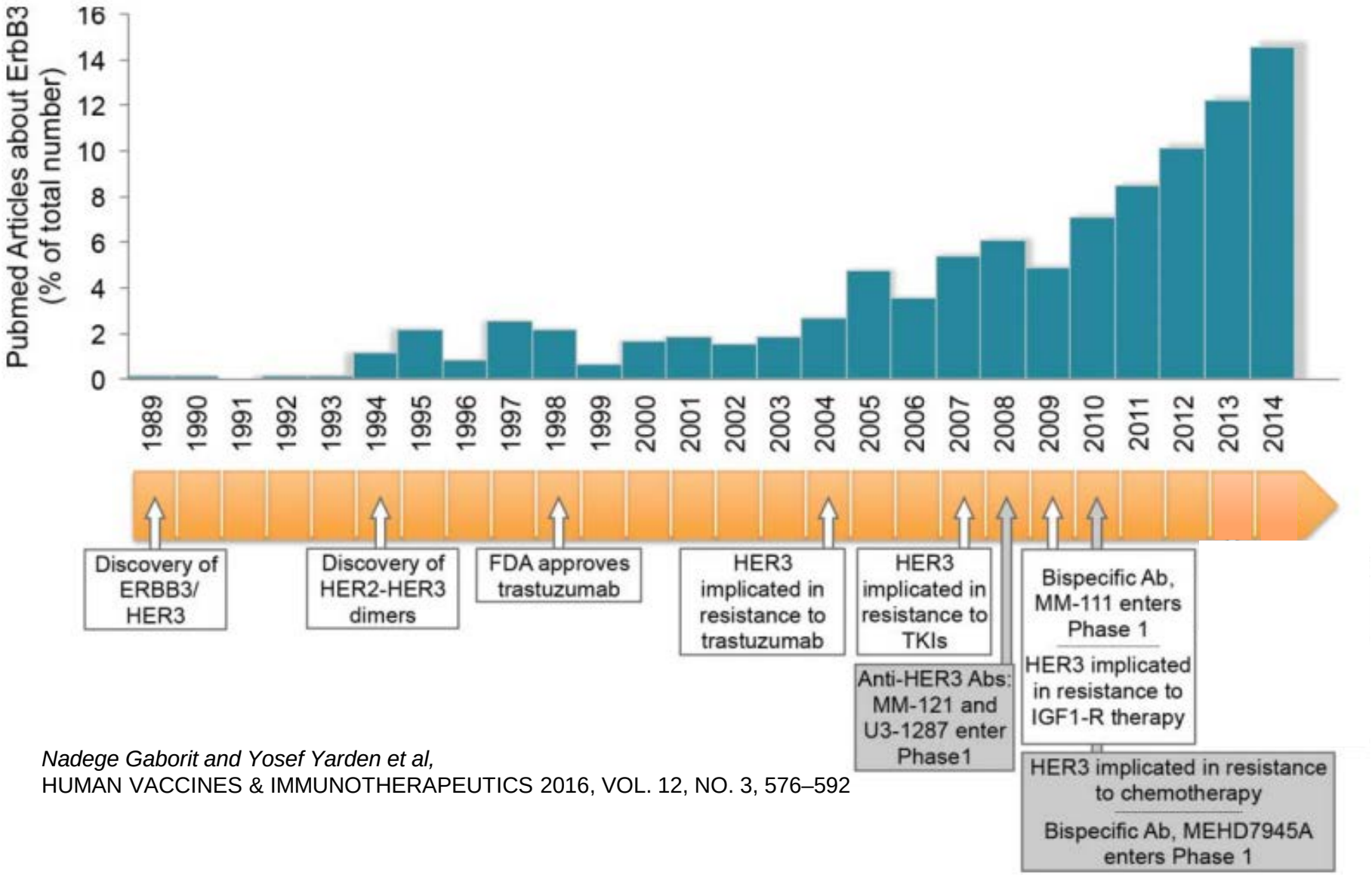
	T-DM1	DS-8201	U3-1402
Antibody	Trastuzumab	Trastuzumab	Patritumab
Payload	Tubulin inhibitor (DM1)	Topoisomerase I inhibitor (DXd)	Topoisomerase I inhibitor (DXd)
DAR	3.5	7-8	7-8
Origin	Genentech/ Roche	Daiichi Sankyo (DS)	Former U3 Pharma / DS

Comparison of U3-1402 to DS-8201

Similarity	Difference
◆ Same linker and payload ◆ Both HER3 and HER2 express in similar cancer types (e.g. breast and lung cancer) ◆ Early efficacy profile, e.g. ORR, is similar	◆ Different target / antibody ◆ Dynamic expression from drug resistance and high internalization ability ◆ HER3 expresses on non-HER2 expressing cancer ◆ Early safety profile indicates different character ◆ No approved drug (potential first-in-class) ➢ Needs to find appropriate indication(s) from scratch since there are no approved drugs nor competitors ➢ Need to determine biomarker and validate CDx ➢ Need to assess safety profile in detail ◆ Potential for broad combination strategy because of scientific rationale based on HER3 characteristics

History of HER3

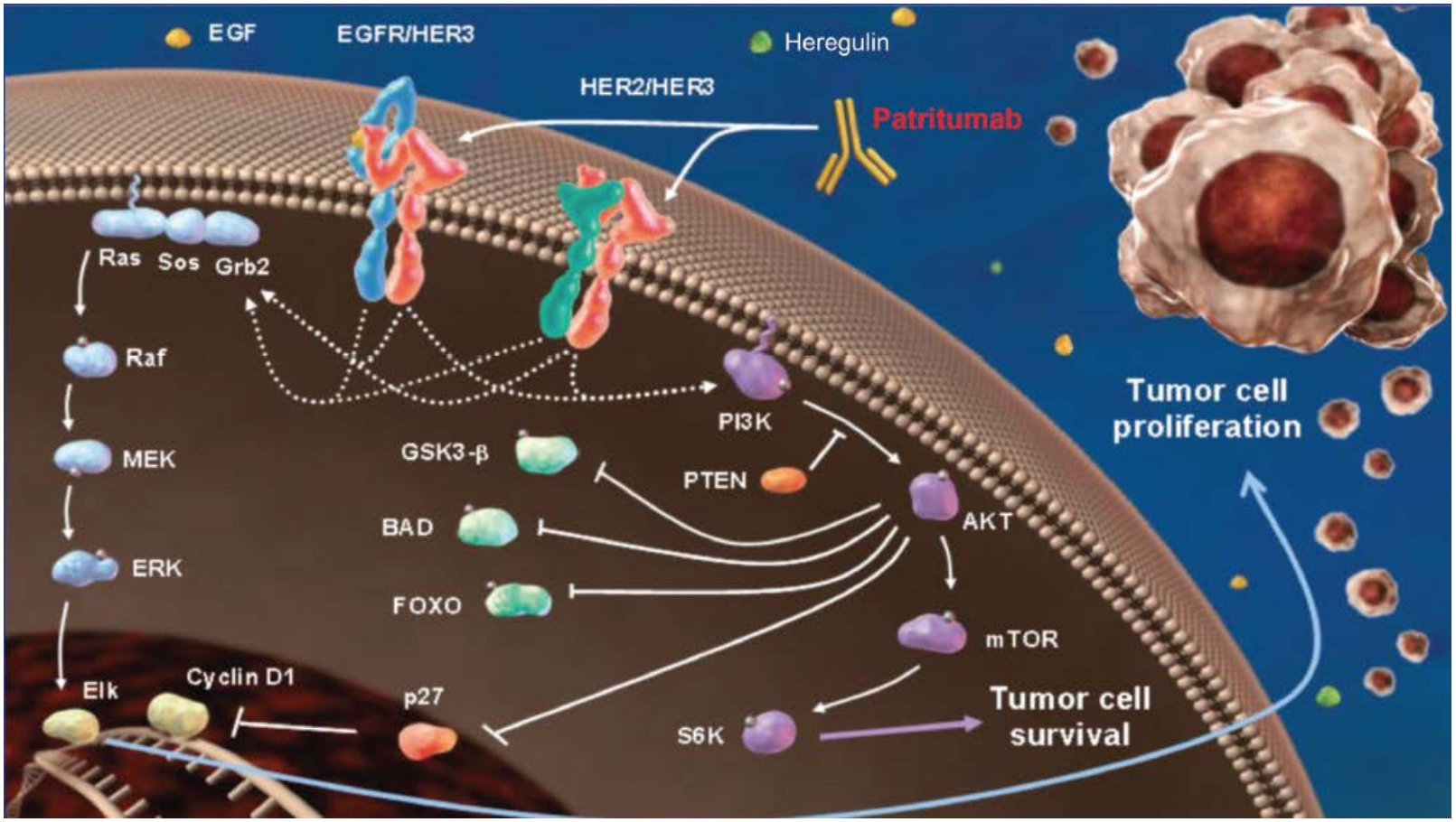
HER3 is known for 30 years, started clinical trial from 2008



Nadege Gaborit and Yosef Yarden et al,
HUMAN VACCINES & IMMUNOTHERAPEUTICS 2016, VOL. 12, NO. 3, 576–592

Role of HER3: Complement Signaling

- HER3 dimerizes with EGFR, HER2 & HER4 those belong to same HER family, and involved in tumor cell survival and proliferation through signaling cascade
  (Pertuzumab is designed to block HER2-HER3 dimerization)



Background of Patritumab (Anti-HER3 Ab) Development

- Patritumab is anti-HER3 antibody, researched by collaboration of former U3 Pharma and former Abgenix (current Amgen) in Germany, which binds to the extracellular domain of HER3[1-3]

- Non-clinical data suggested when combined with EGFR inhibitor, patritumab enhances antitumor activity and prevents HER3 activation following initial anti-EGFR treatment[1,3,4]

- Although, clinical trial was started from 2008, clinically meaningful efficacy were not observed in NSCLC, breast cancer and H&N cancer.

1. Freeman D, et al. *AACR Meeting Abstracts*. 2008;2008:LB-21-;
2. Treder M, et al. *AACR Meeting Abstracts*. 2008;2008:LB-20-;
3. Treder M, et al. *EJC Supplements.* 2008;6:99;
4. Wenzl C, et al. Presented at ESMO 2014. Abstract 7188.

Current Development Status of Anti-HER3 Antibody

Compounds	Company	Status	Target indication
MM-121	Merrimack	Phase2	NSCLC, Breast
CDX/KTN3379	Celldex	Phase2	H&N
MCLA-128 (HER2/3)	Mersena	Phase2	Breast
GSK-2849330	GSK	Phase1	Solid tumor
AV203	AVEO	Pre-clinical	Esophageal
U3-1287 (patritumab)	**Daiichi Sankyo**	**Not enough efficacy (NSCLC/ BC/ H&N)**	
MM-111 (HER2/3)	Merrimack	Terminated	
LJM716	Novartis	Terminated	
MEHD7945 (EGFR/HER3)	Roche	Terminated	
RG-7116	Roche	Terminated	
REGN1400	Regeneron	Terminated	

Source: Adis R&D Insight

- **Most anti-HER3 antibodies target signal inhibition and majority were terminated due to lack of enough efficacy by signal inhibition**
- **Most of monotherapy could not show partial response even in biomarker-selected population**
  （*Cancer Treat Rev.* 2018 Jul;68:111-123.）

Lessons and Learned from HER3 Development

Efficacy

- Most of anti-HER3 antibody could not show tumor regression in pre-clinical xenograft model
  => Lack of efficacy
- Competitor used heregulin (ligand of HER3) as biomarker but did not lead to enough efficacy
  => Lack of stratification biomarker

Safety

- HER3 signaling may be engaged in normal cell function
  => Not appropriate for its signal blocking
- Could have predicted combination toxicity in pre-clinical studies
  => Not enough evaluation of safety

- **Efficacy evaluation based on novel biomarker**
- **Pre-evaluation of efficacy and safety balance**

Summary - 1

- Most of competitive anti-HER3 antibody developments were terminated due to lack of efficacy or toxicity, thus there are no approved anti-HER3 antibody at this point

- No HER3-ADC competitor before U3-1402

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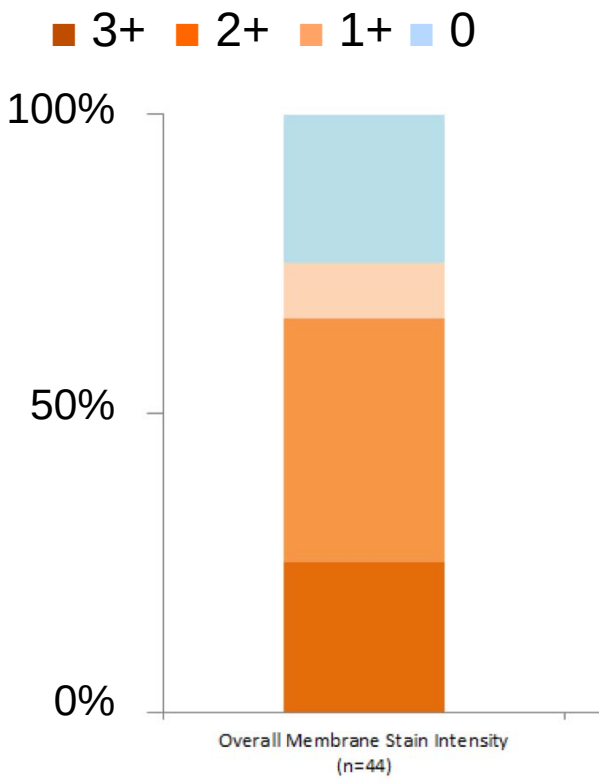
Pre-clinical Data

Feature 1 of HER3: Express in Multiple Tumor Types

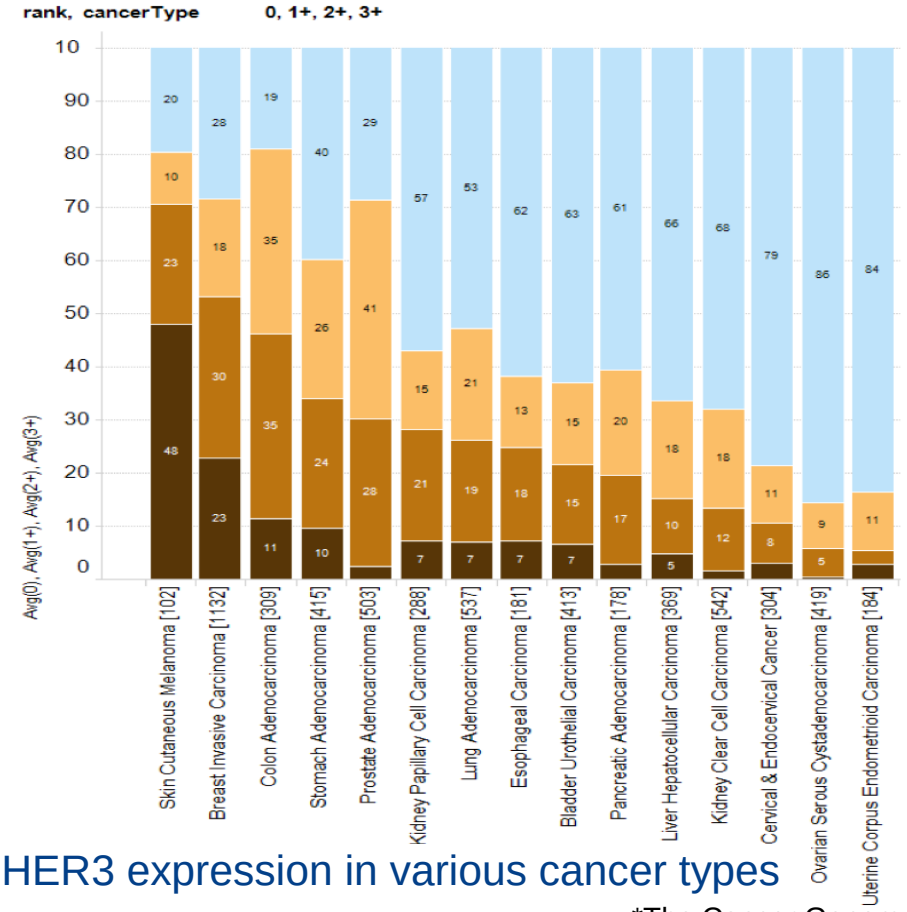
HER3 expression IHC | mRNA

NSCLC EGFRmt

Ventana formulation lock assay
N=44 clinical samples (data on file)



TCGA* mRNA HER3

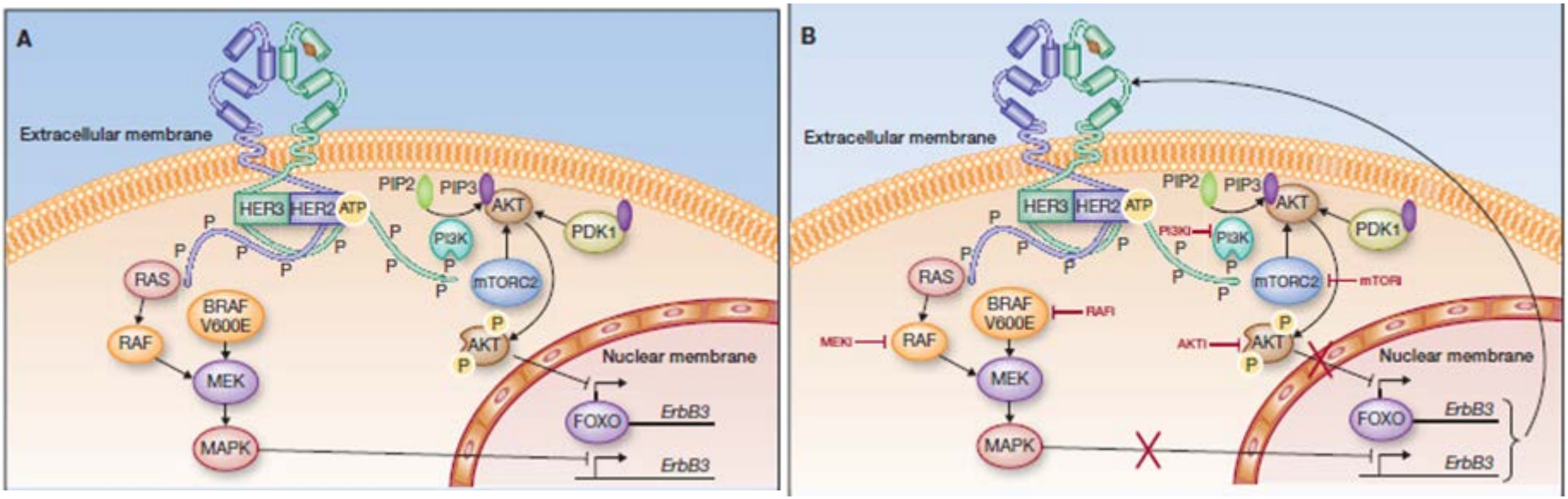


HER3 expression in various cancer types

*The Cancer Genome Atlas

High HER3 expression was observed in Melanoma, Breast, Colorectal, Lung cancer etc

Feature 2 of HER3: Up-regulation by Pre-Treatment
MAPK / PI3K Inhibitors



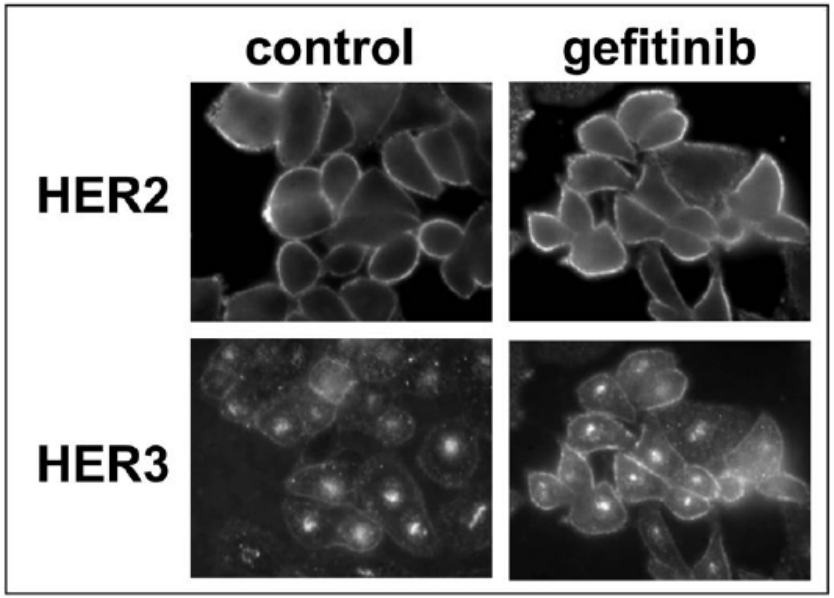
Clin Cancer Res. 2014 Feb.

- In general, HER3 expression is negatively regulated by MAPK or PI3K signaling
- When those signaling are switched off by inhibitors like MEKi, RAFi, PI3Ki, mTOR and AKTi, HER3 will be up-regulated

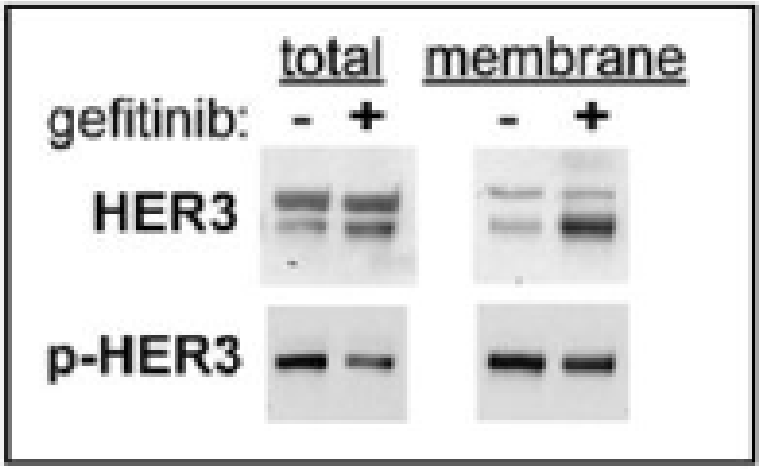
MAPK/ PI3K inhibitors up-regulate HER3 expression

Feature 2 of HER3: Up-regulation by Pre-Treatment

HER3 Up-regulation by Gefitinib



Nature. 2007 January 25; 445(7126): 437–441.

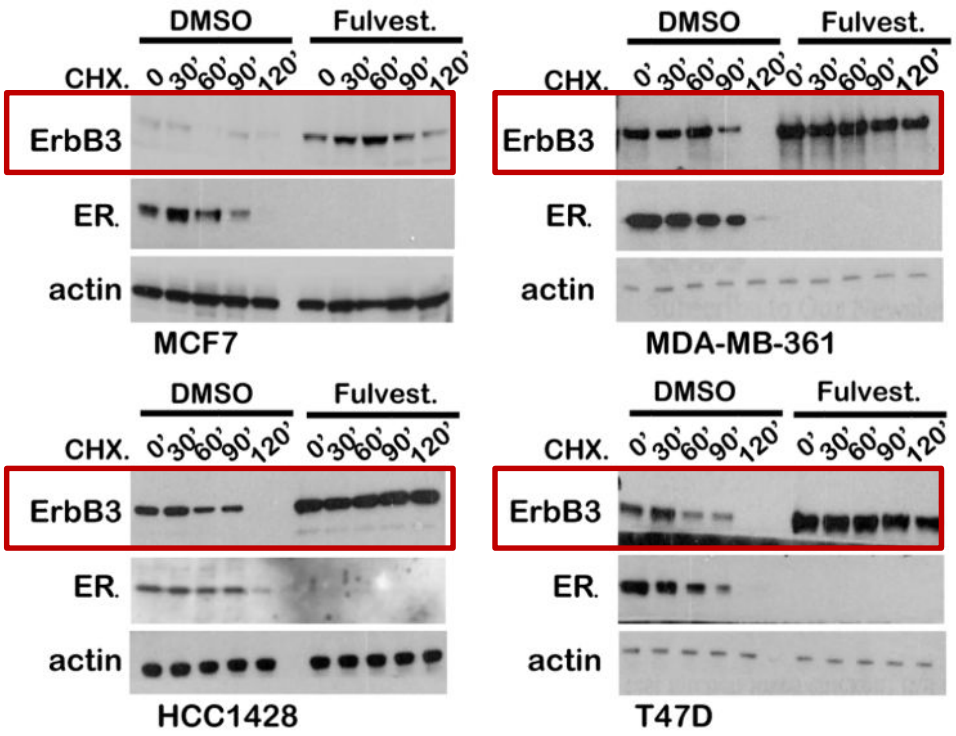


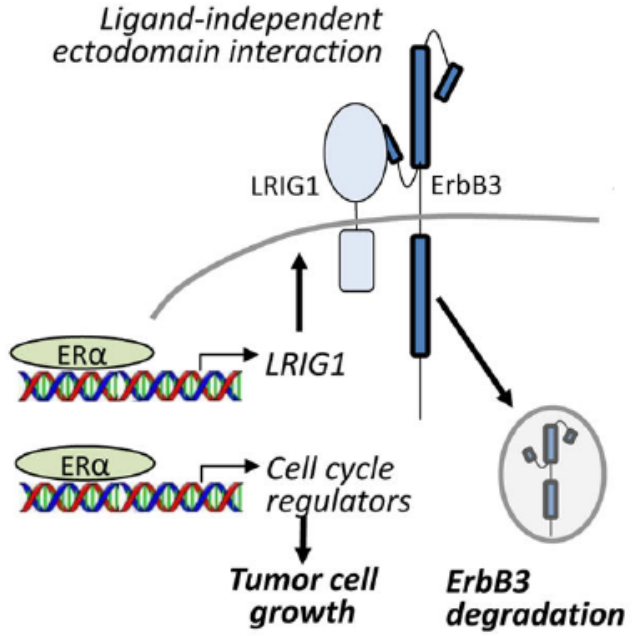
- Gefitinib upregulates the total HER3 expression
- HER3 localization at membrane occurs after gefitinib treatment

EGFR TKi promotes HER3 up-regulation

Feature 2 of HER3: Up-regulation by Pre-Treatment

HER3 Upregulation by Fulvestrant



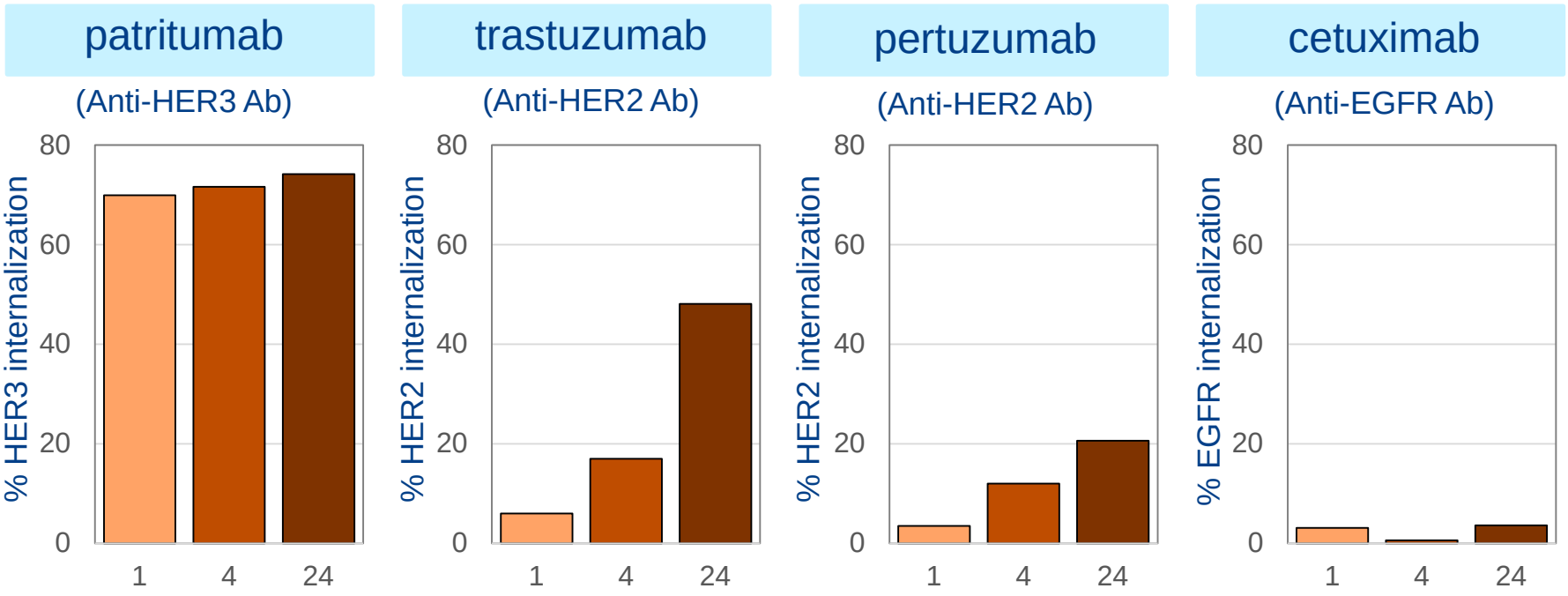


Oncogene; 2016 Mar 3;35(9):1143-52

- LRIG1 maintains HER3 (ErbB3) at low levels in luminal breast cancer cells
- Endocrine inhibitors, such as fulvestrant, tamoxifen, or aromatase inhibitors cause reduced LRIG1 expression levels, allowing HER3 accumulation at the cell surface

Hormone therapy upregulates HER3 expression by inhibiting its degradation

Feature 3 of HER3: Internalization
Rapid / high Internalization by Antibody



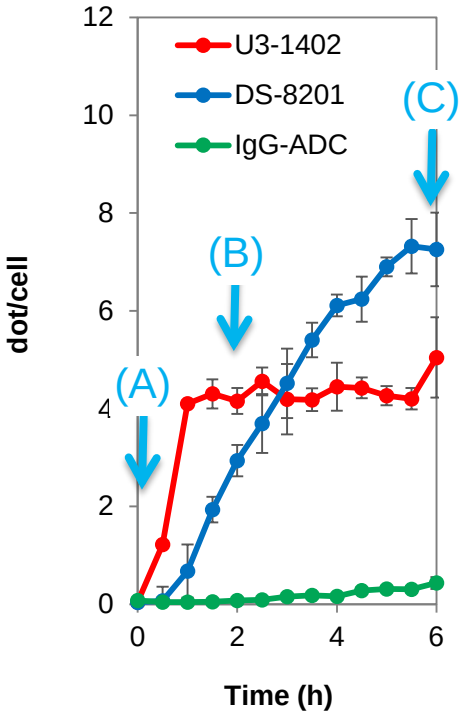
Hettmann T et al, AACR2010

HER3 is rapidly/ highly internalized into cells comparing to other targets

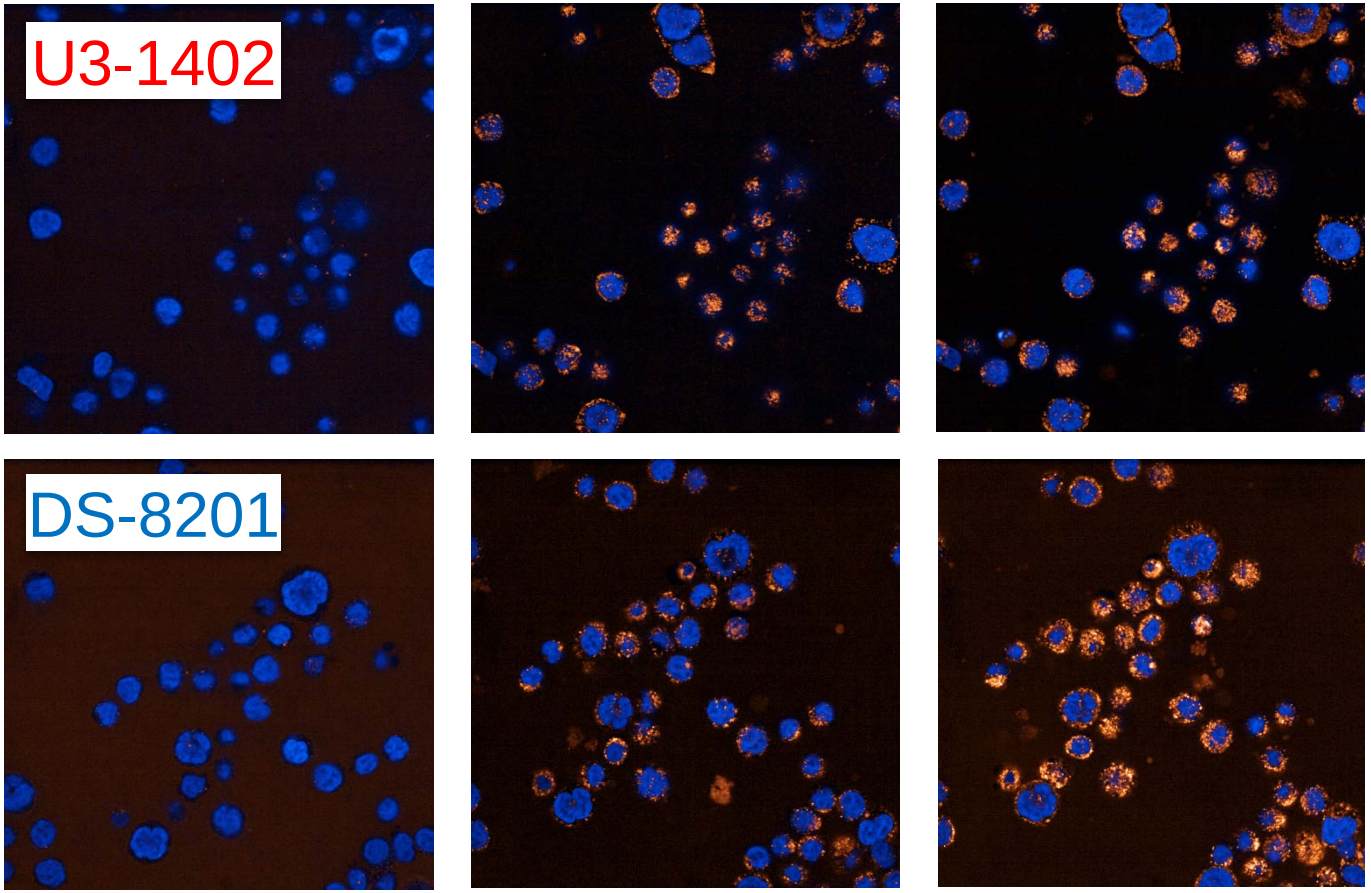
U3-1402 & DS-8201: ADC-trafficking to Lysosome

HER2 positive breast cancer cell line

Trafficking



(A) 0 h (B) 2 h (C) 6 h



U3-1402 showed a faster time-lapse imaging trafficking to lysosomes than DS-8201, reaching a steady state at around 1 hour

ADC to lysosome
Nucleus

Renovates HER3 as Cancer Target

Feature 1: Dynamic expression on various cancer types

- HER3 expression is observed in several cancer tissues like breast cancer, NSCLC, colorectal cancer, ovarian cancer and melanoma

Feature 2: Up-regulation of HER3 by pre-treatment

- HER3 upregulation related to resistance from anti-hormone, MAPKi, PI3K/AKTi therapeutic agents are observed in nonclinical / clinical studies
  - *J Steroid Biochem Mol Biol*. 2005 Feb;93(2-5):249-56.
  - *Int J Oncol.* 2007 Feb;30(2):509-20.
  - *Sci Signal*. 2014 Mar 25;7(318):ra29.

Feature 3: Rapid and high internalization

- HER3 is well internalized into cancer cells (50-80%) comparing to EGFR or HER2

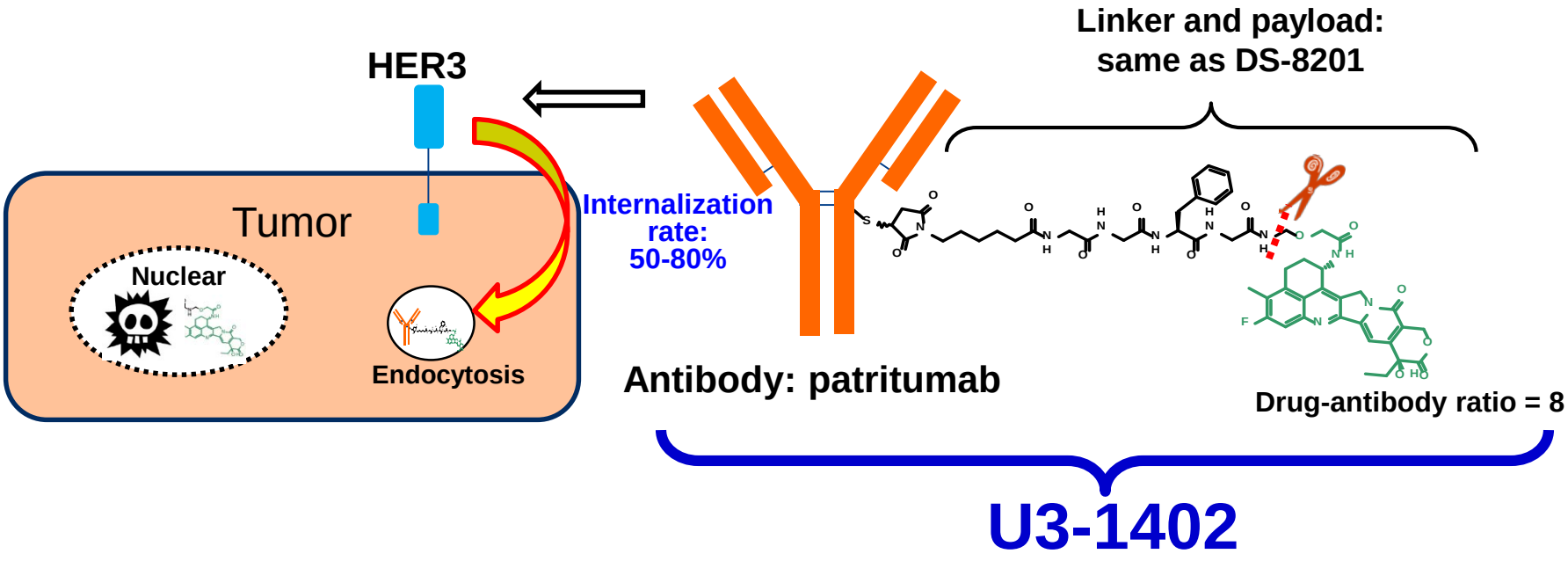
Daiichi Sankyo renovated HER3 character as ADC target

U3-1402: HER3 Targeted ADC

Product concept

Highly-internalized ADC:

Patritumab (anti-HER3 mAb) armed with topoisomerase I inhibitor, to target HER3 expressing tumors



Potential first-in-class drug

Summary - 2

- Daiichi Sankyo renovated HER3 character as ADC target
  - Feature 1: Dynamic expression on various cancer types
  - Feature 2: Up-regulation by pre-treatment
  - Feature 3: Rapid and high internalization
- U3-1402 indicated anti-tumor efficacy in HER2-positive and triple negative breast cancer models
- Pre-clinical studies supported to select patients by IHC with HER3 expression level (IHC 3+, 2+)
  - Result applied to clinical trial with CDx development

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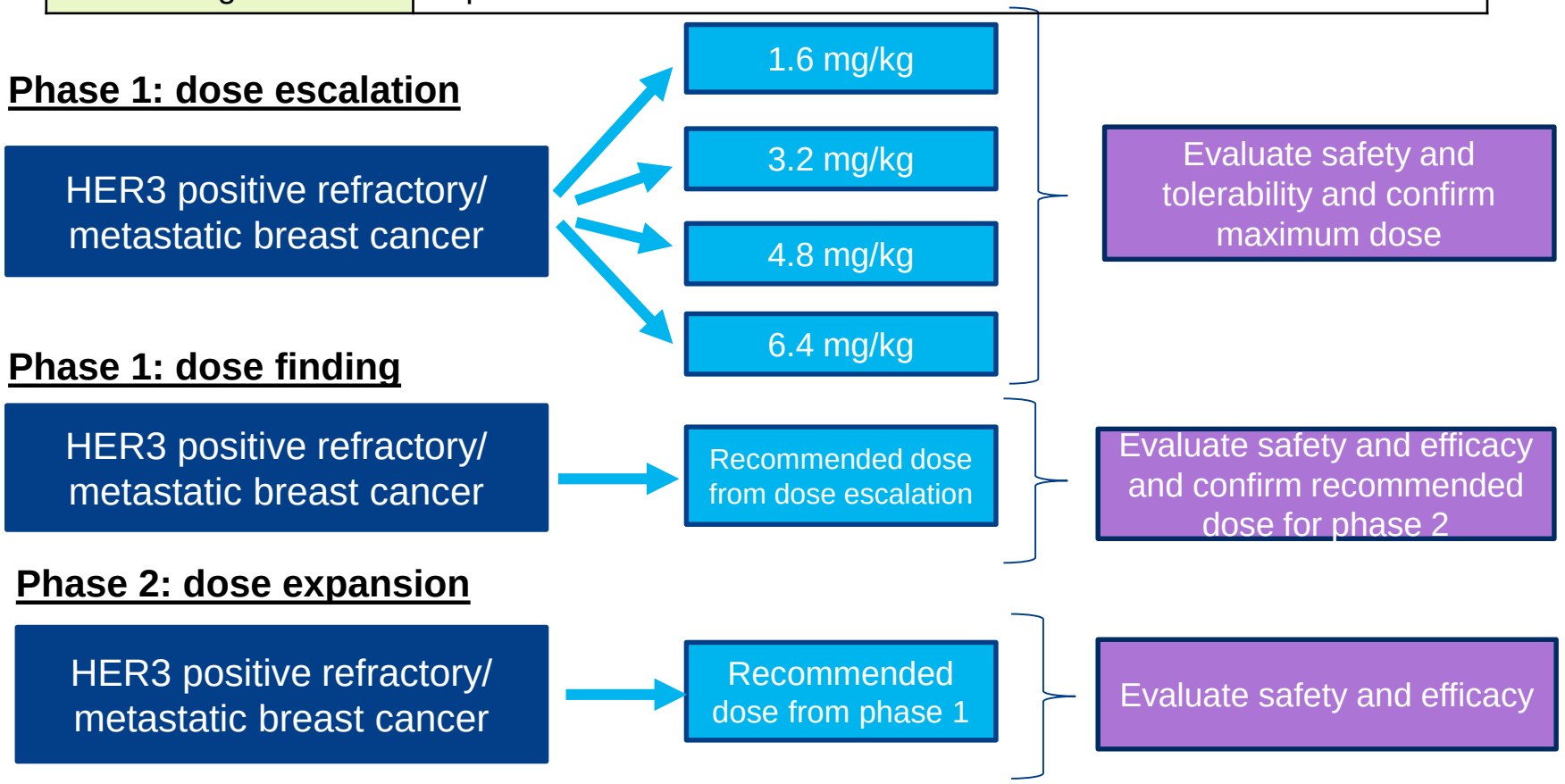
Clinical data

HER3 Positive Breast Cancer P1/2 study (JP/US)

Study patients	HER3-positive refractory/ metastatic breast cancer
Estimated enrollment	80 patients
Primary endpoint	Safety, tolerability and efficacy
Secondary endpoint	PK, anti-ADC antibody etc.
JAPIC/CT.gov	JapicCTI-163401 / NCT02980341



U3-1402: BC P1/2 Study Overview

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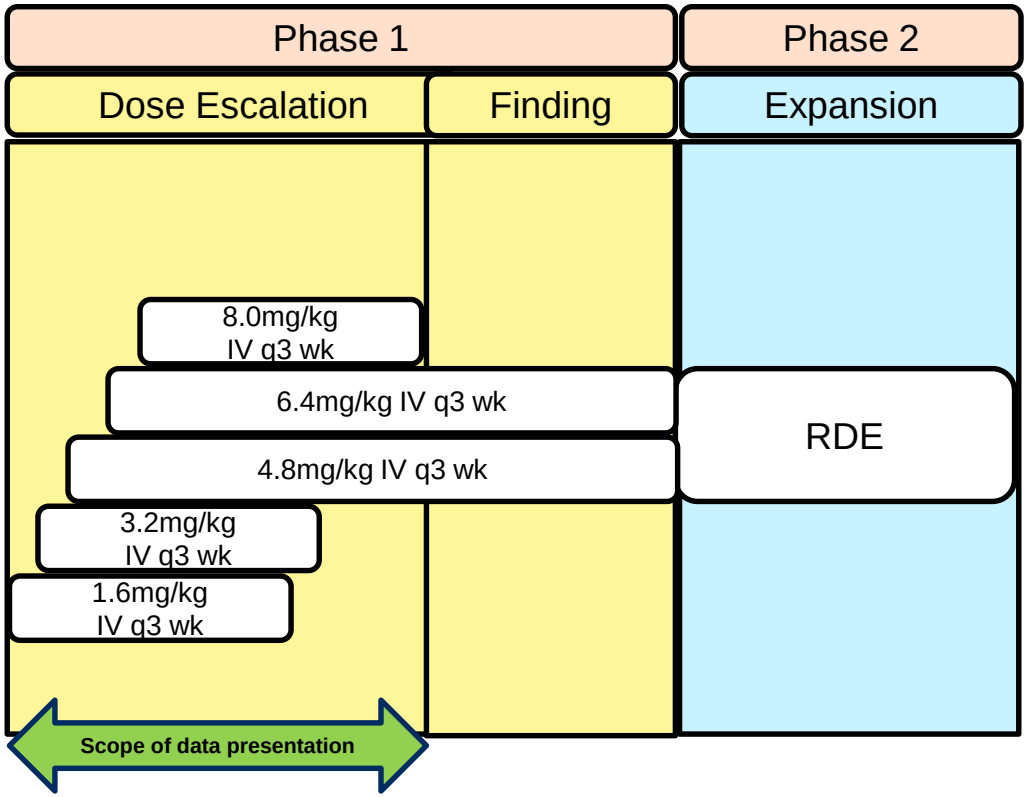
Study Design



Based on April 27, 2018 data cutoff.
RDE: recommended dose(s) for expansion

Demographics

	BC (N=34)
Age, median (range), y	55 (37-81)
ECOG PS, N(%)	
0	25 (74)
1	9 (26)
No. of Prior Treatment Regimens, N(%)	
0-2	2 (6)
≧3	32 (94)
Tumor Molecular Profiles, N(%)	
HER2 BC	3 (9)
Luminal BC	23 (68)
TNBC	7 (21)
Unknown	1 (3)
No. of Patients Receiving ≥ 1 Prior Cancer Regimen, N(%)	
HER2 therapy	7 (21)
HR therapy	23 (68)

- Target of this study is HER3-positive (IHC3+/2+) advanced/ unresectable or metastatic breast cancer

U3-1402: BC P1/2 Study Safety

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Treatment-Emergent Blood and Liver related AE in ≥ 15% Patients, Dose Escalation Phase (Total N = 34)*

Preferred Term	All Grades (%)	Grade ≥ 3 (%)
Platelet count decreased/Thrombocytopenia	23 (68)	10 (29)
Neutrophil count decreased/Neutropenia	20 (59)	9 (27)
White blood cell count decreased	18 (53)	6 (18)
Anemia	13 (38)	4 (12)

Preferred Term	All Grades (%)	Grade ≥ 3 (%)
ALT increased	13 (38)	3 (9)
AST increased	13 (38)	3 (9)
Blood alkaline phosphatase increased	6 (18)	0

*Analysis set: Patients who received at least one dose of U3-1402. Percentage is calculated using the number of patients in the column heading as the denominator.
TEAE = treatment-emergent adverse event.
Based on April 27, 2018 data cutoff.

DLTs consisted of the followings:

- 4.8 mg/kg: one case of Gr.4 platelet count decreased
- 6.4 mg/kg: one case of Gr.4 platelet count decreased
- 8.0 mg/kg: one case of Gr.4 platelet count decreased, Gr.3 AST increased, Gr.3 ALT increased
  one case of Gr.3 ALT increased

MTD has not been reached

Serious AE's noted in 11 (32%) of treated patients

Majority of TEAEs were Grades 1 and 2 and toxicities have so far been manageable

U3-1402: BC P1/2 Study Efficacy

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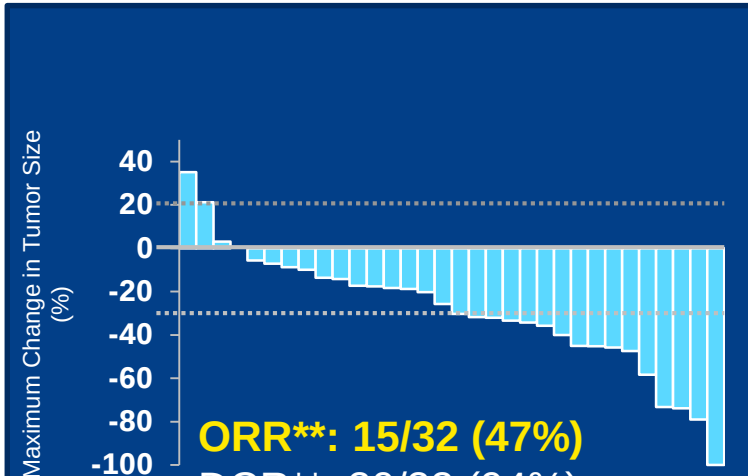
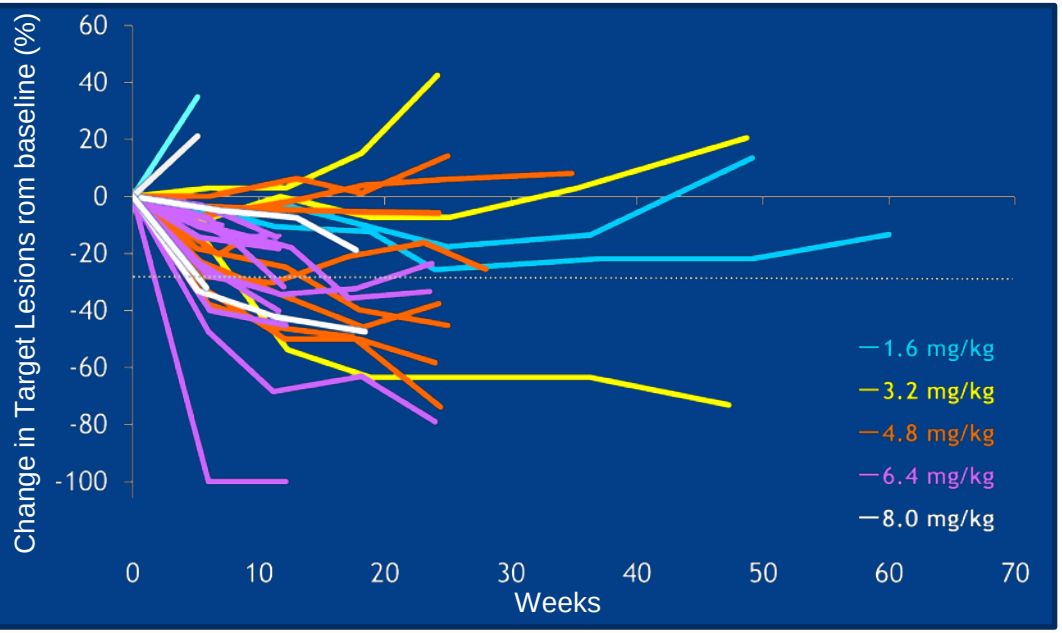
Best Percentage Change in Sum of Diameters From Baseline in Target Lesions*



Percentage Change in Sum of Longest Diameters



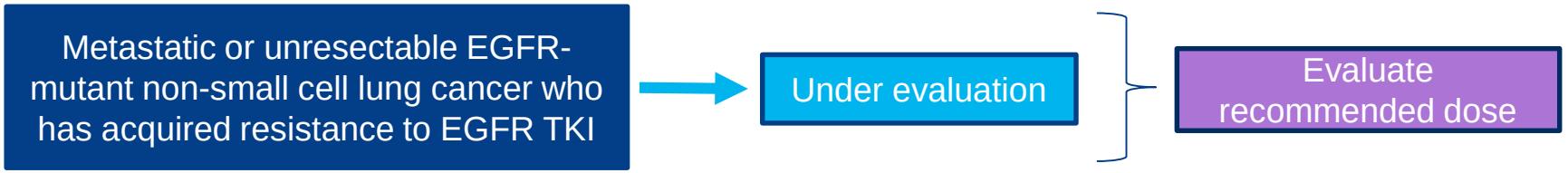
*Analysis set: Efficacy evaluable patients with at least one scan. Baseline is defined as the last measurement taken before the first dose of study drug.
**Investigators assessment. For each patient, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.
DCR = disease control rate; ORR = objective response rate.
Based on April 27, 2018 data cutoff.

- U3-1402 data resembles that of early DS-8201 data
  - U3-1402 ASCO 2018 ORR：15/32（47%）
  - DS-8201 ESMO 2016 ORR：7/20（35%）
- Validates portability of ADC technology

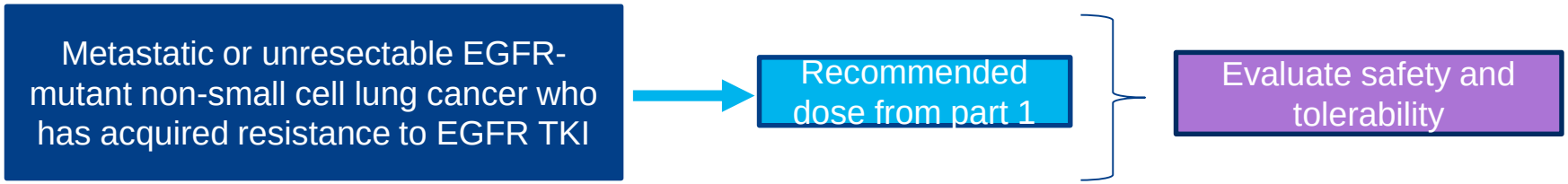
EGFRmt NSCLC P1 Study (US)

Study patients	Metastatic or unresectable EGFR-mutant non-small cell lung cancer with acquired resistance to EGFR TKI
Estimated enrollment	63 patients
Primary endpoint	Safety, tolerability
Secondary endpoint	ORR, DCR, PFS, OS etc.
JAPIC/CT.gov	TBD / NCT03260491

Part 1: dose escalation



Part 2: dose expansion



Summary - 3

- U3-1402 proceeds two phase 1 trials in breast and lung cancer

- In BC phase 1 study, dose escalation data was prevailed in ASCO2018, with promising clinical efficacy (ORR : 47% in 32pts) and manageable safety profile in HER3-selected 34 patients
  - This showed the portability of DS ADC technology to other target other than HER2
  - This achieves first partial response as anti-HER3 drug

- Lung cancer study is ongoing for its phase 1 dose escalation phase

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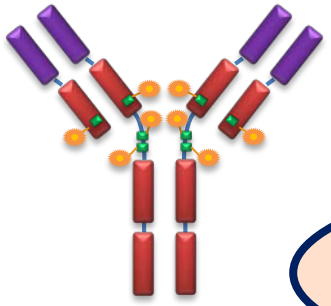
Vision

Necessity of U3-1402 Translational Research

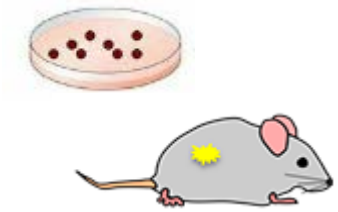


U3-1402

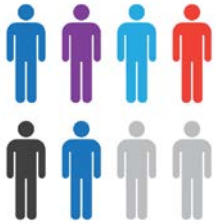
Challenges as first-in-class drug

- Characteristic of HER3 receptor Ex: Expression / Dynamics
- Mechanism of action
- Drug linker chemistry
- Effect of HER3 on normal cells
- Safety mechanism
- Efficacy in combination therapy
- Mechanism of resistance
- Drug-drug interaction

Pre-clinical samples



Clinical samples



Science-driven Translational Research activities are necessary

Summary: Take home message

- **U3-1402 is Daiichi Sankyo's original compound**
  - Highly internalized patritumab (antibody) is conjugated to same linker and payload as DS-8201
- **Indicated portability of DS's ADC technology**
  - U3-1402's clinical anti-tumor efficacy with manageable safety in addition to DS-8201 demonstrated portability of ADC technology
- **Potential first-in-class drug**
  - Tolerability was observed in phase 1 study
  - There are no approved drug for HER3 and big potential for HER3 market
  - It can expand to TNBC, lung cancer and colorectal cancer etc.
  - Potential for broad combination strategy because of HER3 characteristics