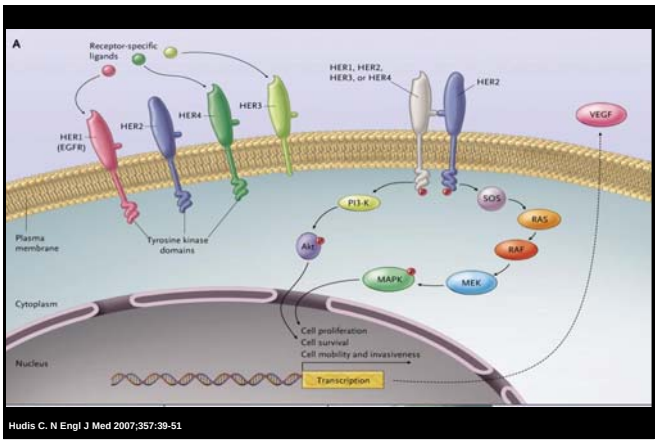
2014年4月12日（土）
第2回 浜松オンコロジーフォーラム
アクトシティ浜松 コングレスセンター 5階

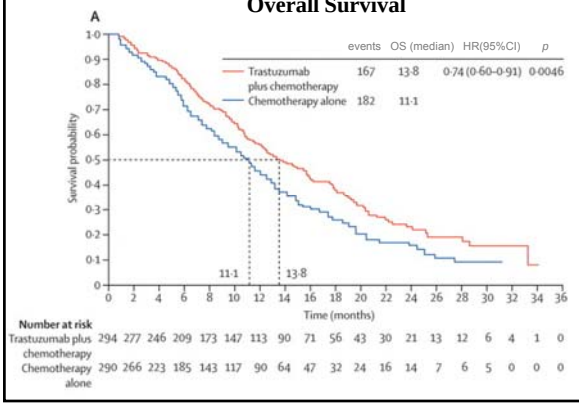
「抗HER2療法の正しい使い方」

圭友会　浜松オンコロジーセンター
腫瘍内科　渡辺　亨
twatanab@oncoloplan.com

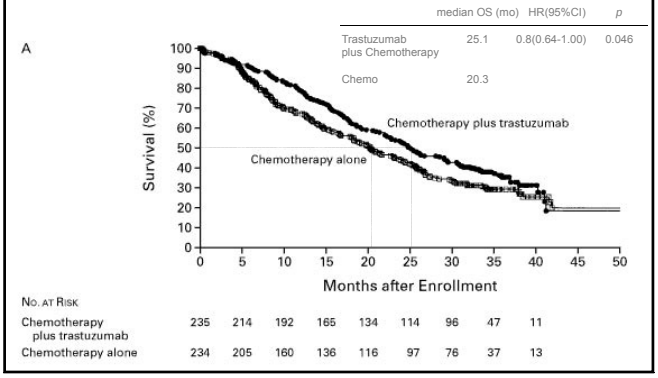


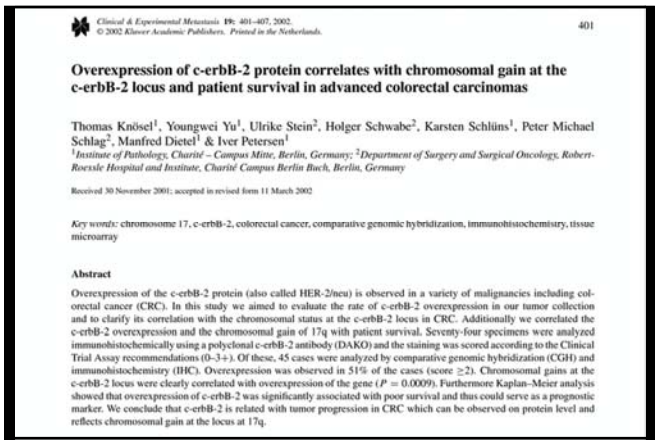
Hudis C. N Engl J Med 2007;357:39-51

Overall Survival



Overall Survival





Clinical & Experimental Metastasis **19:** 401–407, 2002.
© 2002 *Kluwer Academic Publishers. Printed in the Netherlands.*

401

Overexpression of c-erbB-2 protein correlates with chromosomal gain at the c-erbB-2 locus and patient survival in advanced colorectal carcinomas

Thomas Knösel[1], Youngwei Yu[1], Ulrike Stein[2], Holger Schwabe[2], Karsten Schlüns[1], Peter Michael Schlag[2], Manfred Dietel[1] & Iver Petersen[1]
[1]*Institute of Pathology, Charité – Campus Mitte, Berlin, Germany;* [2]*Department of Surgery and Surgical Oncology, Robert-Roessle Hospital and Institute, Charité Campus Berlin Buch, Berlin, Germany*

Received 30 November 2001; accepted in revised form 11 March 2002

Key words: chromosome 17, c-erbB-2, colorectal cancer, comparative genomic hybridization, immunohistochemistry, tissue microarray

Abstract

Overexpression of the c-erbB-2 protein (also called HER-2/neu) is observed in a variety of malignancies including colorectal cancer (CRC). In this study we aimed to evaluate the rate of c-erbB-2 overexpression in our tumor collection and to clarify its correlation with the chromosomal status at the c-erbB-2 locus in CRC. Additionally we correlated the c-erbB-2 overexpression and the chromosomal gain of 17q with patient survival. Seventy-four specimens were analyzed immunohistochemically using a polyclonal c-erbB-2 antibody (DAKO) and the staining was scored according to the Clinical Trial Assay recommendations (0–3+). Of these, 45 cases were analyzed by comparative genomic hybridization (CGH) and immunohistochemistry (IHC). Overexpression was observed in 51% of the cases (score ≥2). Chromosomal gains at the c-erbB-2 locus were clearly correlated with overexpression of the gene ($P = 0.0009$). Furthermore Kaplan–Meier analysis showed that overexpression of c-erbB-2 was significantly associated with poor survival and thus could serve as a prognostic marker. We conclude that c-erbB-2 is related with tumor progression in CRC which can be observed on protein level and reflects chromosomal gain at the locus at 17q.

Lung (2006) 184:267–272
DOI 10.1007/s00408-005-2591-y

LUNG CANCER

The Role of c-erbB-2 Expression on the Survival of Patients with Small-Cell Lung Cancer

Ozlem Cansu · Metin Ozkan · Vedat Arsav · Ozlem Er · H. Senol Coskun · Serdar Soyuer · Mustafa Altinbas

Received: 1 March 2006

Abstract The aim of this study was to determine the incidence and role of c-erbB-2 overexpression as a predictive/prognostic marker in small-cell lung carcinoma (SCLC). We performed a retrospective study on subjects with a biopsy-proven diagnosis of SCLC. A chart review for demographic and clinical data was performed on patients with SCLC diagnosed between 1998 and 2004. c-erbB-2 overexpression was evaluated using immunohistochemistry performed on archival paraffin-embedded specimens. Sixty-seven patients with SCLC were identified (6 females, 61 males; median age- 56.5 yr., range-34-75) all of whom had adequate tissue specimens available for c-erbB-2 testing. Of the 67 specimens, 12 (17.9%) showed c-erbB-2 overexpression. Seventy-five of the cases were positive for c-erbB-2, had extensive disease. The median overall survival of patients with SCLC whose tumors were positive and negative for c-erbB-2 were 8 ± 0.9 months (95%CI 6.3–9.7) and 11 ± 1.5 months (95%CI 8.0–14.0), respectively. c-erbB-2 overexpression detected using immunohistochemistry is observed in 17.9% of patients with SCLC and has statistically significant prognostic value. Our findings suggest that c-erbB-2 may be a potential target for site-specific immunotherapy in SCLC. Considering one technique examined, further molecular investigation is needed to confirm these preliminary findings.

Keywords Small-cell lung carcinoma · c-erbB-2 · Prognosis

Introduction

Annals of Oncology

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Oxford Journals › Medicine › Annals of Oncology › Volume 4, Issue 9 › Pp. 775-779.

Overexpression of p185 is not related to erbB2 amplification in ovarian cancer

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This Article

Ann Oncol (1993) 4 (9): 775-779.

» Abstract *Free*
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F. Morali[1], M. Cattabeni[1], E. Tagliabue[2], M. Campiglio[2], S. Menard[2], M. Marzola[1,3], V. Lucchini[3], N. Colombo[3], C. Mangioni[3], L. Redaelli[4] and M. D'Incalci[1]

+ Author Affiliations

Correspondence to: Maurizio D'Incalci, M.D., Istituto Mario Negri, Via Eritrea 62, 20157 Milano, Italy

Received May 18, 1993.
Accepted June 22, 1993.

Abstract

Background: While in breast cancer the amplification and overexpression of the erbB2 gene has been reported in numerous

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British Journal of Cancer (1999) 81(8), 1419–1425
© 1999 Cancer Research Campaign
Article no. bjoc.1999.0861

Dose escalation and pharmacokinetic study of a humanized anti-HER2 monoclonal antibody in patients with HER2/*neu*-overexpressing metastatic breast cancer

Y Tokuda[1], T Watanabe[2], Y Omuro[3], M Ando[3], N Katsumata[2], A Okumura[1], M Ohta[1], H Fujii[3], Y Sasaki[3], T Niwa[4] and T Tajima[1]

[1]Department of Surgery, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-1193, Japan; [2]National Cancer Center Hospital, Tokyo 104-0045, Japan; [3]National Cancer Center Hospital East, Kashiwa, Chiba 277-0882, Japan; [4]Mitsubishi Chemical Corporation, Yokohama Research Center, Kanagawa 227-8502, Japan

Summary We conducted a phase I pharmacokinetic dose escalation study of a recombinant humanized anti-p185^{HER2} monoclonal antibody (MKC-454) in 18 patients with metastatic breast cancer refractory to chemotherapy. Three or six patients at each dose level received 1, 2, 4 and 8 mg kg^{-1} of MKC-454 as 90-min intravenous infusions. The first dose was followed in 3 weeks by nine weekly doses. Target trough serum concentration has been set at 10 μg ml^{-1} based on in vitro observations. The mean value of minimum trough serum concentrations at each dose level were 3.58 ± 0.63, 6.53 ± 5.26, 40.2 ± 7.12 and 87.9 ± 23.5 μg ml^{-1} respectively. At 2 mg kg^{-1}, although minimum trough serum concentrations were lower than the target trough concentration with a wide range of variation, trough concentrations increased and exceeded the target concentration, as administrations were repeated weekly. Finally 2 mg kg^{-1} was considered to be sufficient to achieve the target trough concentration by the weekly dosing regimen. One patient receiving 1 mg kg^{-1} had grade 3 fever, one at the 1 mg kg^{-1} level had severe fatigue defined as grade 3, and one at 8 mg kg^{-1} had severe bone pain of grade 3. No antibodies against MKC-454 were detected in any patients. Objective tumour responses were observed in two patients; one receiving 4 mg kg^{-1} had a partial response in lung metastases and the other receiving 8 mg kg^{-1} had a complete response in soft tissue metastases. These results indicate that MKC-454 is well tolerated and effective in patients with refractory metastatic breast cancers overexpressing the HER2 proto-oncogene. Further evaluation of this agent with 2–4 mg kg^{-1} weekly intravenous infusion is warranted. © 1999 Cancer Research Campaign

Keywords: HER2/neu; humanized monoclonal antibody; pharmacokinetics; phase I study

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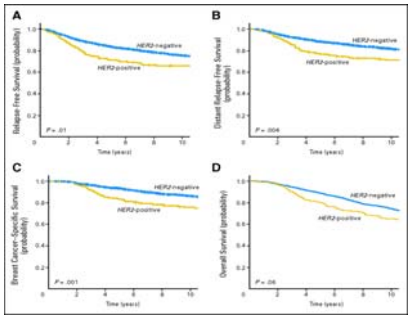
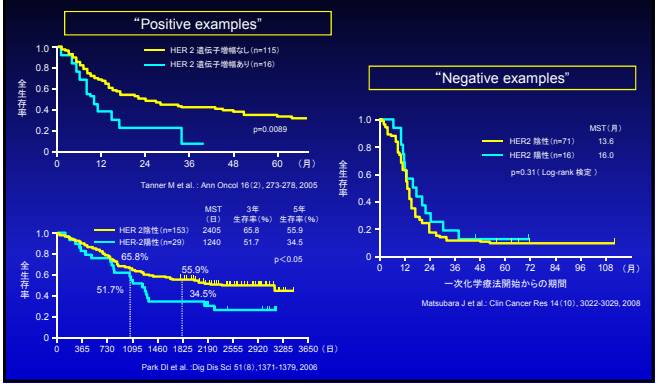
Kaplan-Meier curves for 10-year outcomes based on HER2 status for the entire node-negative cohort (N = 2,026).



Chia S et al. JCO 2008;26:5697-5704

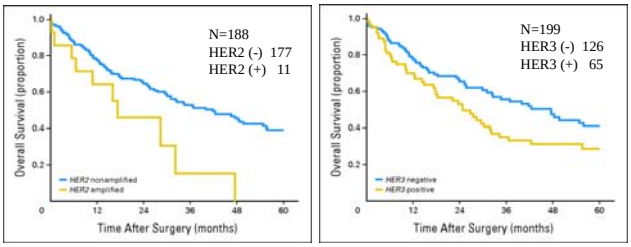
胃癌におけるHER2発現と予後との関連



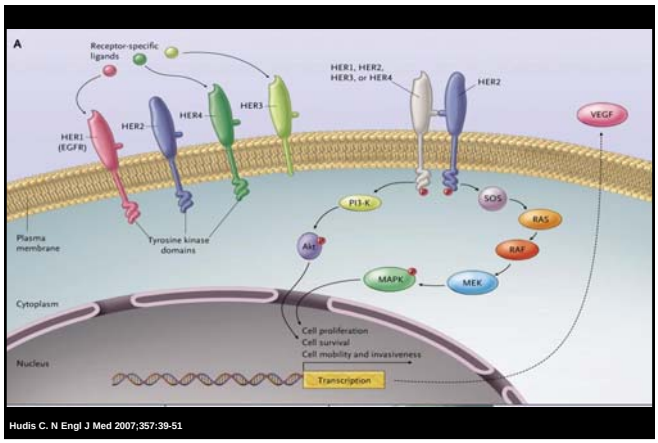
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

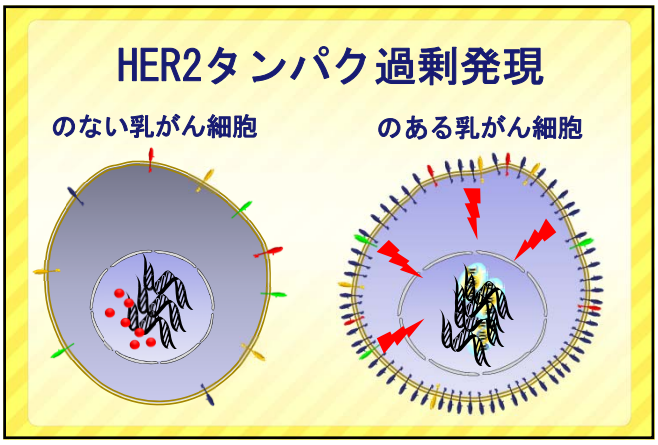
Prognostic Implications of Altered Human Epidermal Growth Factor Receptors (HERs) in Gastric Carcinomas: HER2 and HER3 Are Predictors of Poor Outcome

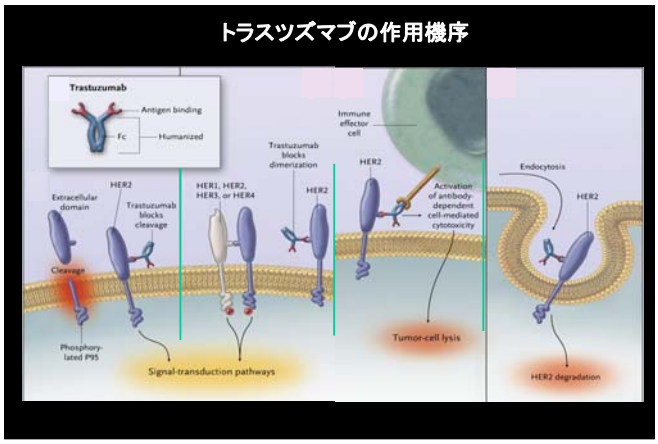
Maria D. Begnami, Emy Fukuda, José H.T.G. Fregnani, Suely Nonogaki, André L. Montagnini, Wilson L. da Costa Jr, and Fernando A. Soares

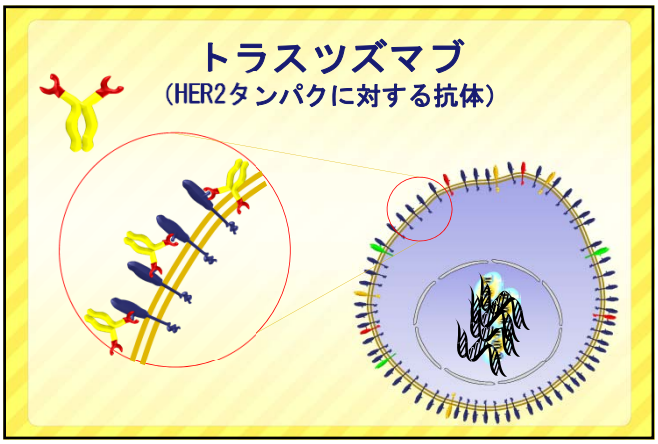


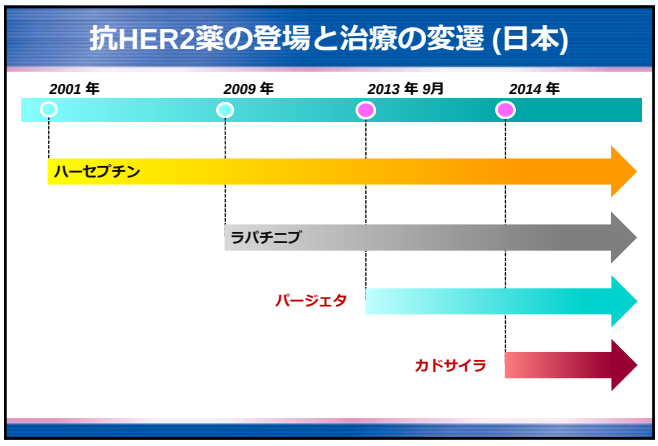
HER2タンパクと抗HER2薬







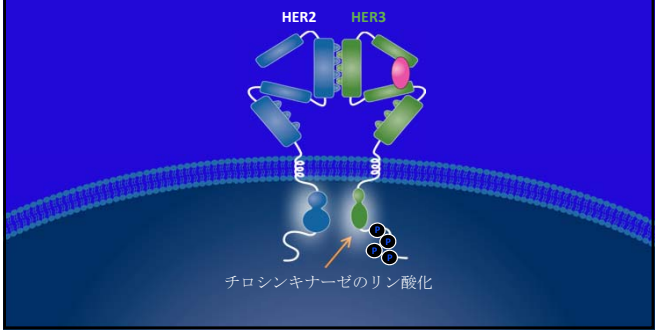




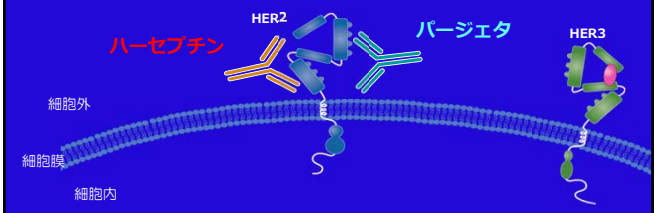
パージェタ®　ペルツズマブ

HER2-を含むダイマー(二量体)は強力な細胞増殖シグナルを発生し細胞分裂･増殖を刺激する

HER2 二量体形成とシグナル伝達



ハーセプチンとパージェタは HER2タンパクの異なる部位に結合する



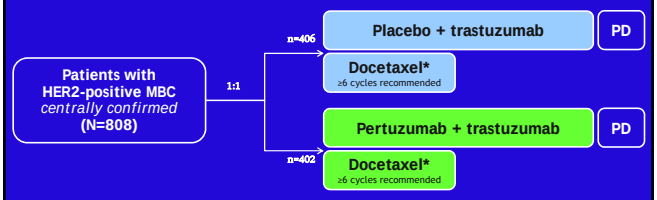
パージェタは HER2と他のHERタンパクとの二量体形成を阻する

CLEOPATRA study

New England Journal of Medicine 366:109-119, 2012

Lancet Oncol 14:461-71, 2013

試験デザイン

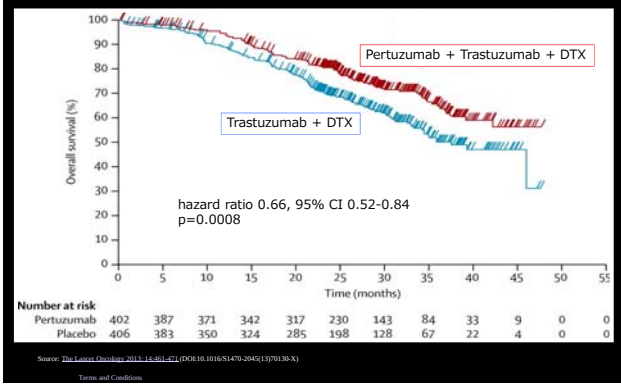


- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated

*<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

MBC, metastatic breast cancer; PD, progressive disease

Overall Survival



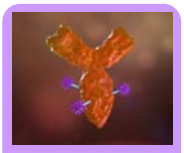
Source: The Lancet Oncology 2013; 14:461-471 (DOI:10.1016/S1470-2045(13)70130-X)

Terms and Conditions

カドサイラ®
トラスツズマブ-エムタンシン

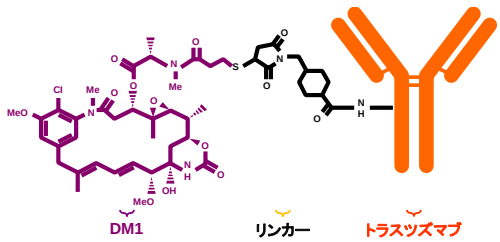
カドサイラの概要

- 抗HER2抗体チューブリン重合阻害剤複合体
  - ✓ 一般名：トラスツズマブ エムタンシン（遺伝子組換え）（Trastuzumab Emtansine ）（JAN）
  - ✓ 構造式：アミノ酸214個の軽鎖2分子とアミノ酸450個の重鎖2分子からなる糖タンパク質であるトラスツズマブ（遺伝子組換え）の、平均3.5個の主にリシン残基のε アミノ基に、エムタンシンが結合した抗体薬物複合体
  - ✓ 分子量：エムタンシン：958.53
  - ✓ トラスツズマブ（遺伝子組換え）：約148,000
  - ✓ トラスツズマブ エムタンシン（遺伝子組換え）：約151,000



トラスツズマブ1分子に対して平均約3.5分子のDM1が結合

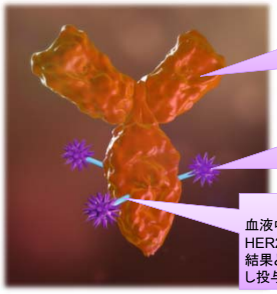
分子構造



	DM1	リンカー	トラスツズマブ
分子量:	738	238	~150,000
比:	3.5	3.5	1

作用機序

抗体薬物複合体（Antibody drug conjugate：ADC）



【トラスツズマブ】
HER2に特異的に結合し、“HER2シグナルの遮断“、“ADCC活性“、“HER2の細胞外ドメインの切断を防ぐ“ 等の作用を有する

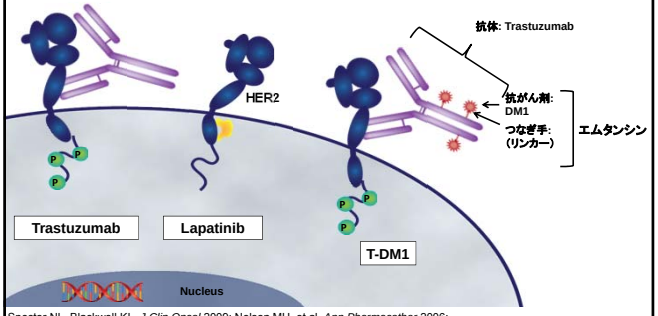
【DM1】
チューブリン重合阻害剤であるメイタンシノイド系薬剤の誘導体のひとつ
ビンカアルカロイド、タキサンよりも100倍強い細胞毒性を有する

【チオエーテルリンカー】
血液中でDM1の遊離を最小限に抑えることで、HER2細胞への曝露量を保つ
結果として、DM1による全身毒性は少なく、繰り返し投与による蓄積性も無い

チューブリン重合阻害剤DM1とトラスツズマブは安定なリンカーにより結合

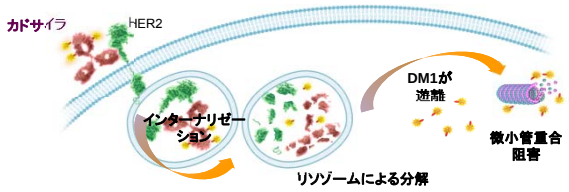
乳がんのHER2を標的とした治療

Trastuzumab　Lapatinib　T-DM1



Spector NL, Blackwell KL. *J Clin Oncol* 2009; Nelson MH, et al. *Ann Pharmacother* 2006; Lewis Phillips GD, et al. *Cancer Res* 2008.

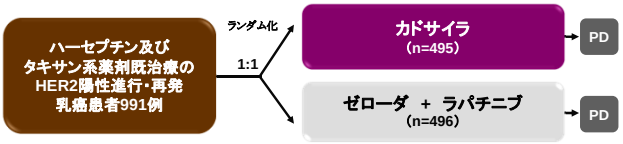
カドサイラの作用機序



カドサイラはハーセプチンに加えてDM1による作用機序を有する
カドサイラがHER2と結合することで・・・

- ✓ レセプターを介したインターナリゼーションが起きる
- ✓ リソゾームによる分解がおきる
- ✓ 細胞内にDM1の代謝産物が放出される
- ✓ DM1がチューブリンに結合することで微小管重合を阻害し、細胞周期の停止およびアポトーシスを引き起こす

海外第Ⅲ相臨床試験: TDM4370g（EMILIA試験）試験デザイン



層別因子： 地域(米国、西欧州、その他)、進行再発乳癌への治療歴数(0/1、2以上)、内臓転移の有無(あり、なし)

カドサイラ 3.6mg/kgを3週間間隔で点滴静注
セローダ 1,000mg/m²を1日2回2週間投与、1週間休薬
ラパチニブ 1,250mgを1日1回経口投与

- **主要評価項目：** 独立判定委員会による無増悪生存期間(PFS)、全生存期間(OS)、安全性
- **副次的評価項目：** 奏効率、奏効期間、臨床的有用率、症状悪化までの期間 など

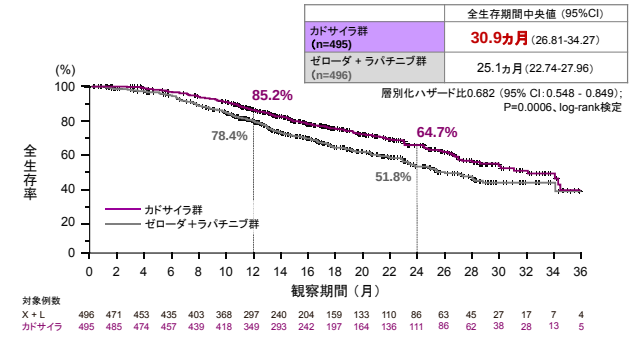
Verma S, et al. N Engl J Med 2012; 367:1783–1791.

海外第Ⅲ相臨床試験: TDM4370g（EMILIA試験）
患者背景 ①

	カドサイラ (n=495)	ゼローダ+ラパチニブ (n=496)
年齢中央値、歳（範囲）	53 (25 - 84)	53 (24 - 83)
人種、例数 (%)		
白人	358 (72)	374 (75)
アジア人	94 (19)	86 (17)
黒人	29 (6)	21 (4)
その他	7 (1)	10 (2)
データなし	7 (1)	5 (1)
地域、例数(%)		
米国	134 (27)	136 (27)
西欧州	157 (32)	160 (32)
アジア	82 (17)	76 (15)
その他	122 (25)	124 (25)
ECOG PS, 例数 (%)		
0	299 (60)	312 (63)
1	194 (39)	176 (35)

Verma S, et al. N Engl J Med 2012; 367:1783–1791.

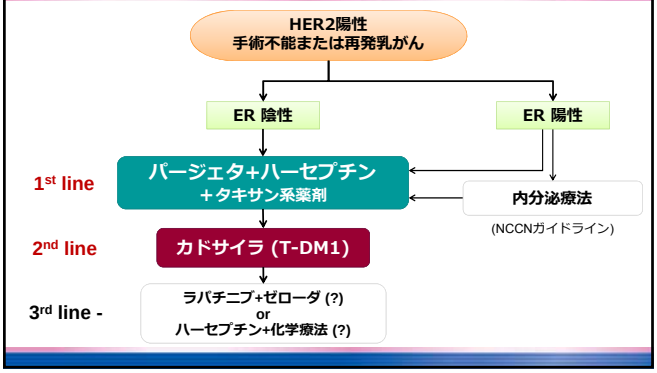
海外第Ⅲ相臨床試験: TDM4370g（EMILIA試験）
全生存期間

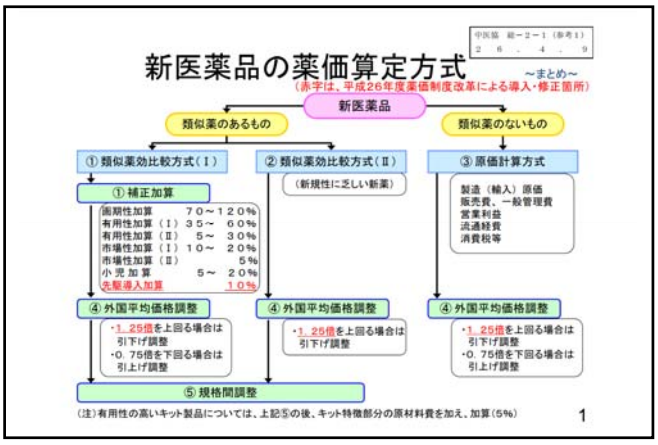


X：ゼローダ、L：ラパチニブ

Verma S, et al. N Engl J Med 2012; 367:1783–1791.

HER2陽性 手術不能・再発乳がん
2014年以降の 治療指針





平均的日本人女性（50-54才）

身長157.26 cm 体重53.16 kg 体表面積 1.52 m^2

薬剤名		単位あたり投与量	実投与量 (mg)	バイアル				薬価
				規格	単価	使用数	価格	
ハーセプチン（中外）		6mg/kg	319	60mg	24,567	3	73,701	131,216
				150mg	57,515	1	57,515	
パージェタ（中外）		420 mg/body	420	420mg	238,491	1	238,491	238,491
カドサイラ（中外）		3.6mg/kg	191	100mg	235,108	2	470,216	470,216
				160mg	373,945	0	0	
AC	ドキソルビシン（日本化薬）	60 mg/m^2	91.2	10 mg	1,293	0	0	11,344
				50 mg	5,672	2	11,344	
	エンドキサン（塩野義）	600 mg/m^2	912	100mg	320	0	0	2,508
				500mg	1,254	2	2,508	
ドセタキセル（サノフィ）		75 mg/m^2	114	20 mg	17,322	2	34,644	93,800
				80 mg	59,156	1	59,156