Discrepancies Between Ideals and Reality in Management of Breast Cancer in Korea

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Contents

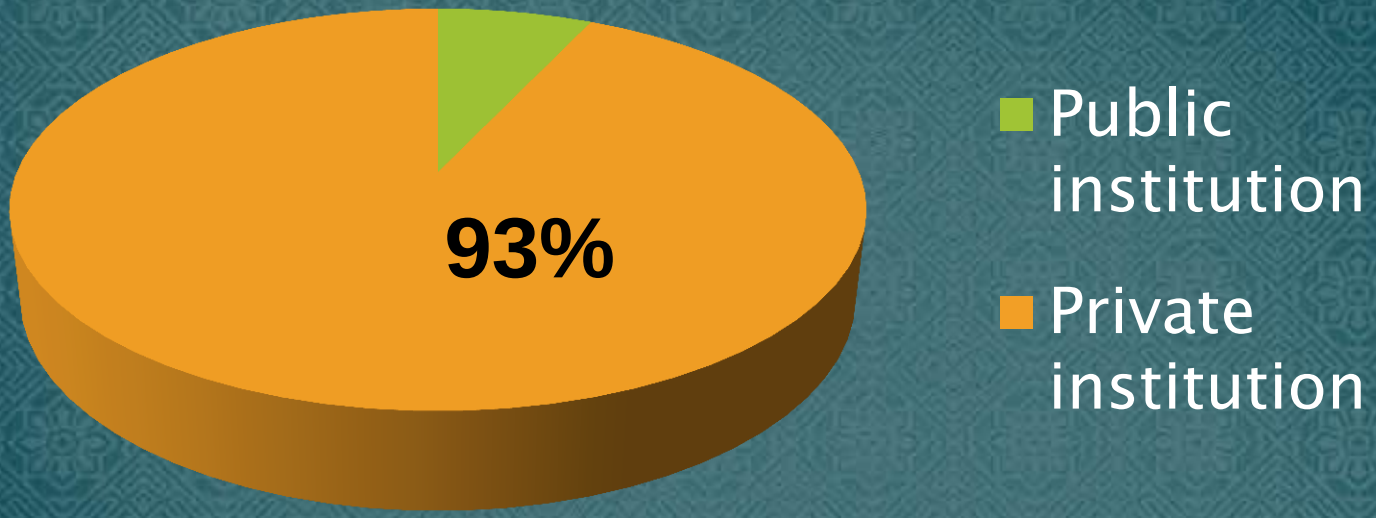
- Medical insurance system in Korea
- Current evidence and real management for breast cancer patients in Korea

National medical insurance system in Korea

- Only one provider, Government (National Health Insurance Corporation)

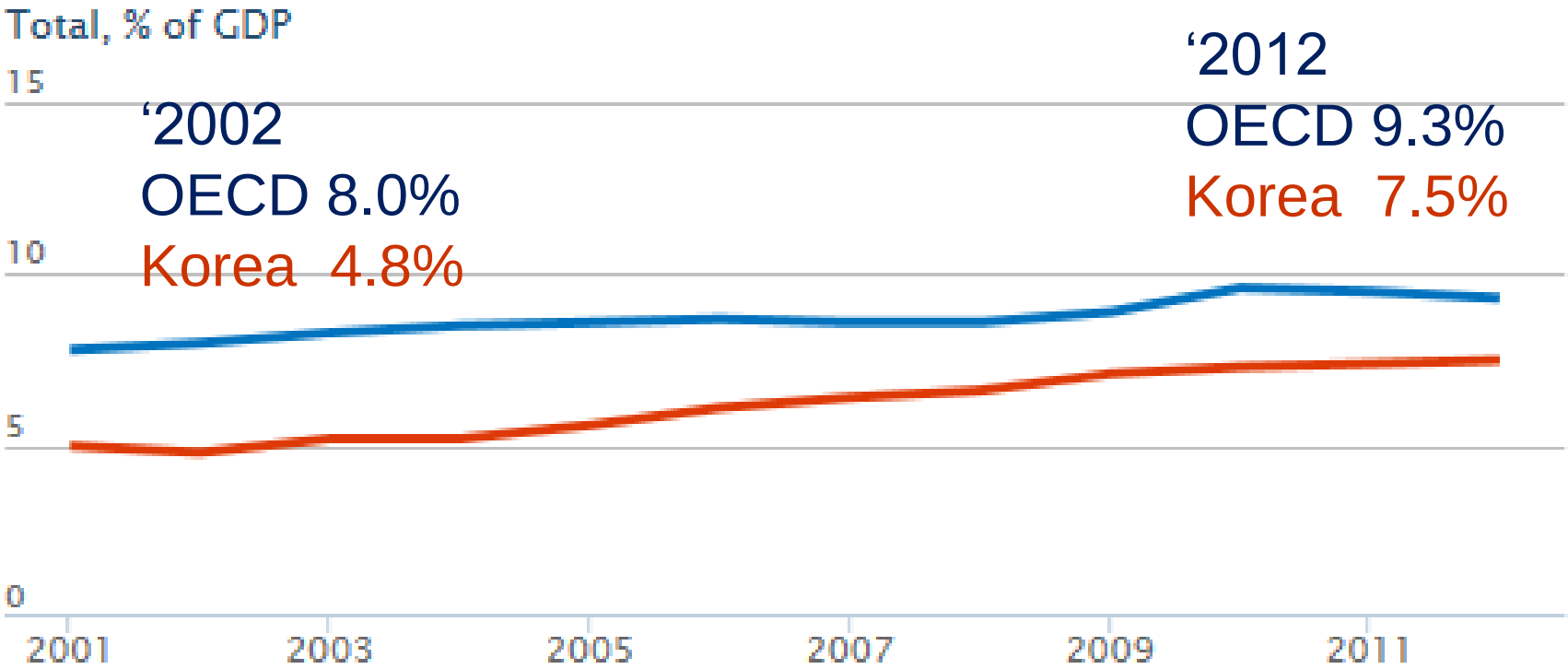
- All people have mandatorily joined the medical insurance policy since 1989

The Medical Insurance Natural Nomination System



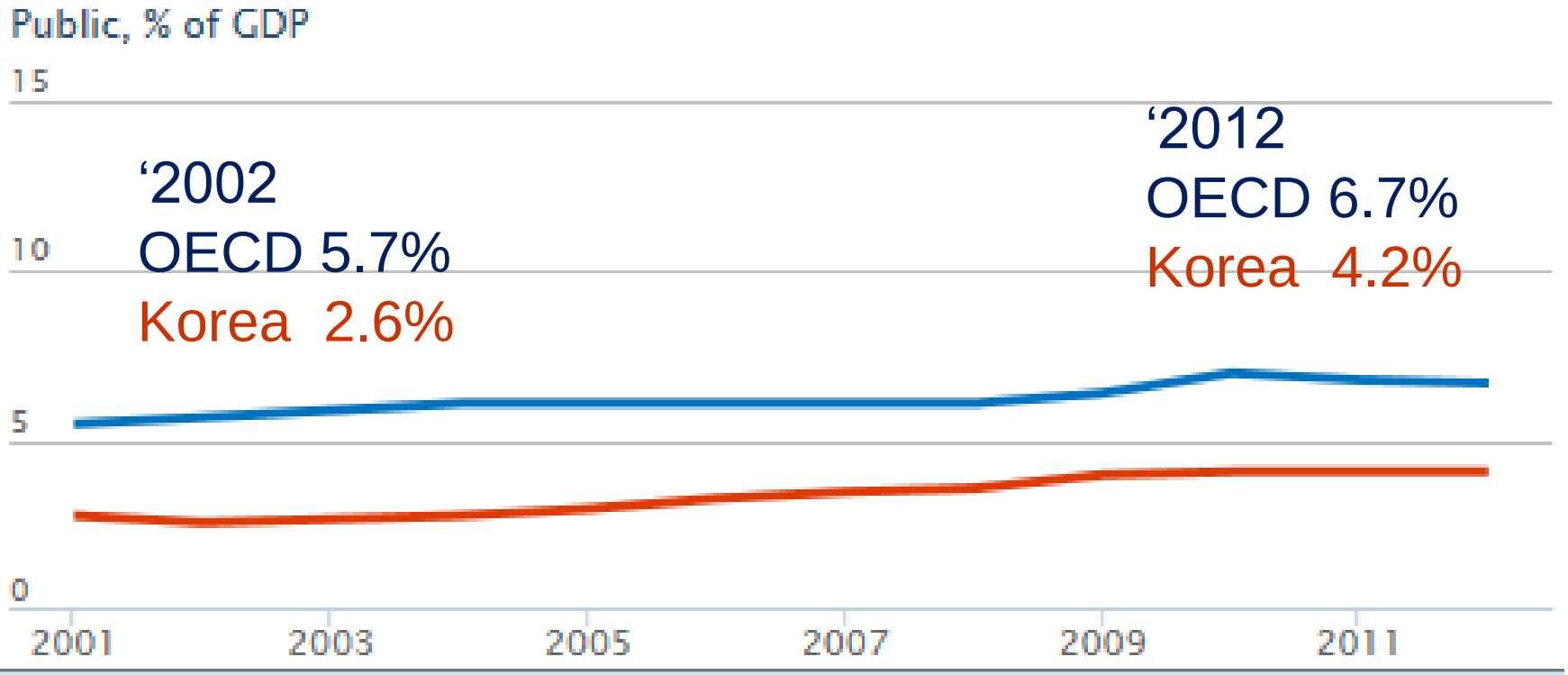
Is meant for all the hospital or organization for medical treatment not to reject application of medical insurance but to offer an appropriate medical care to the patients.

Health expenditure: Total



OECD Health Data 2012

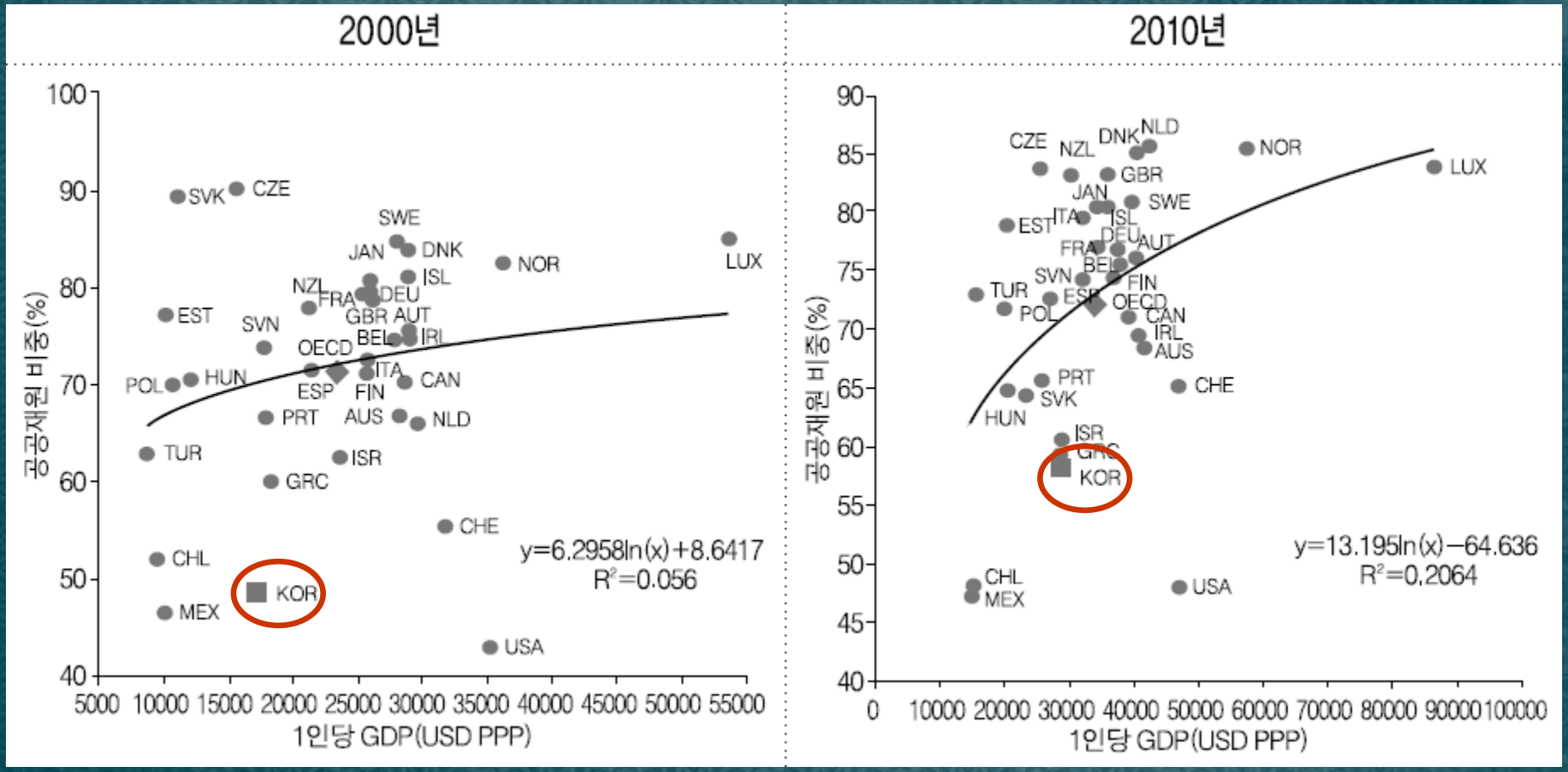
Health expenditure: Public



	2002	2003	2004	2005	2006	2007	2008	2009	2010
Korea	53.7	52.4	52.6	52.9	55.3	55.8	55.9	58.2	58.2
OECD av.	71.9	71.4	71.0	71.0	71.3	71.3	72.0	72.4	72.2

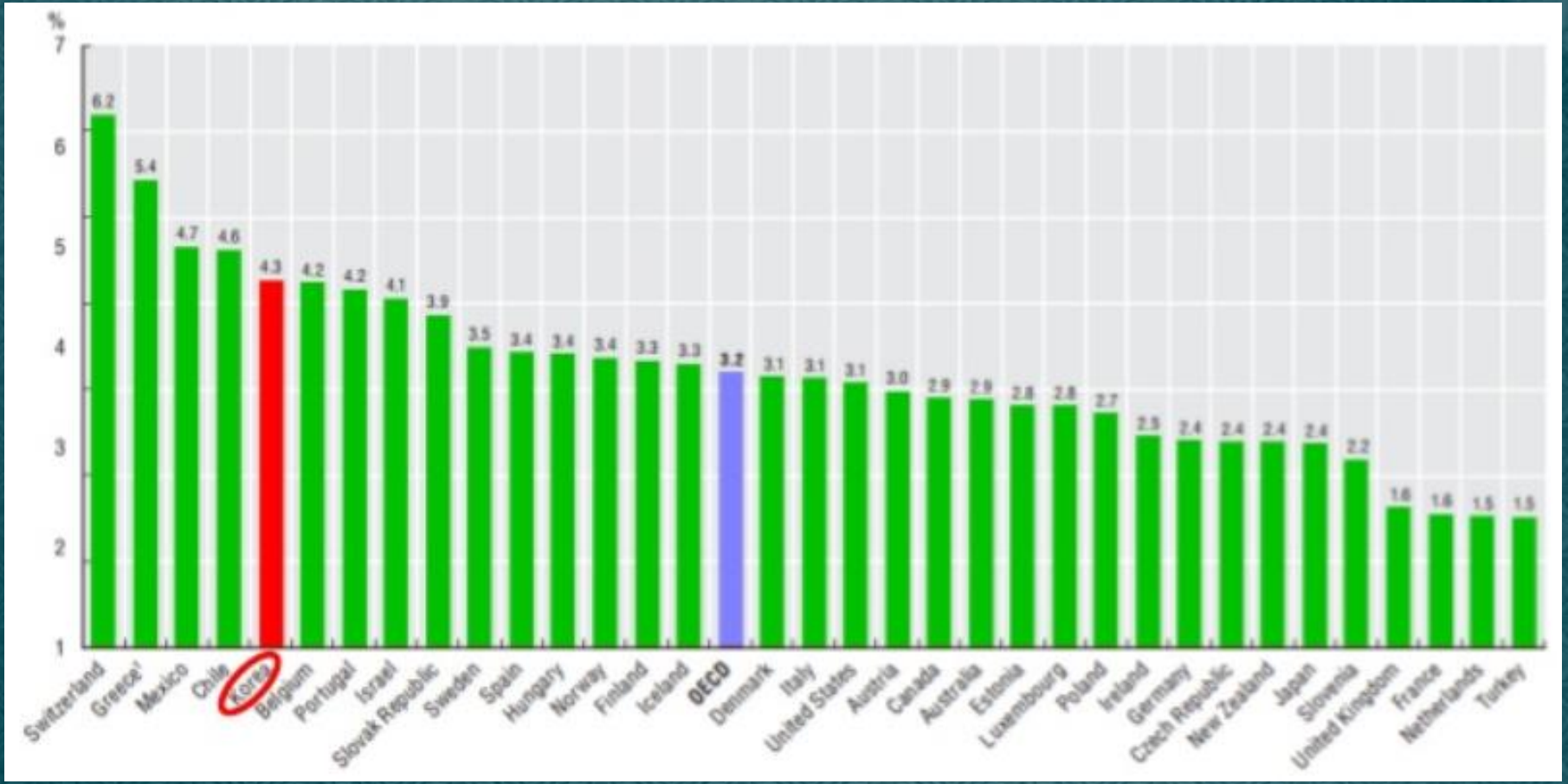
OECD Health Data 2012

Public Health expenditure (% of GDP)



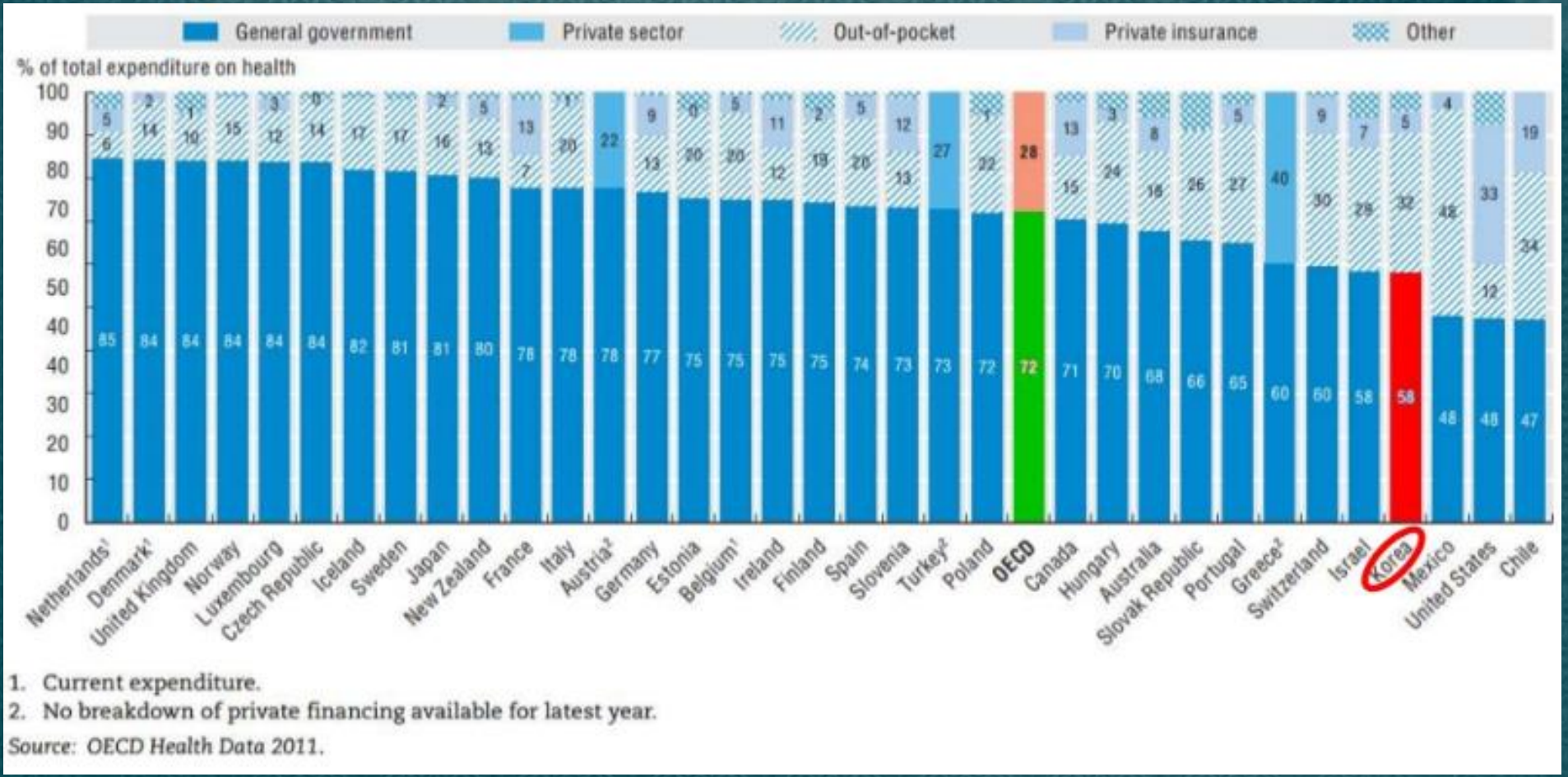
Health & Welfare Policy Forum 2013;196:89-102

Out-of-pocket expenditure on health as a percentage of total expenditure on health



OECD Health Data 2011

Expenditure on health by type of financing, 2009



1. Current expenditure.
2. No breakdown of private financing available for latest year.

Source: OECD Health Data 2011.

Requirements for reimbursement

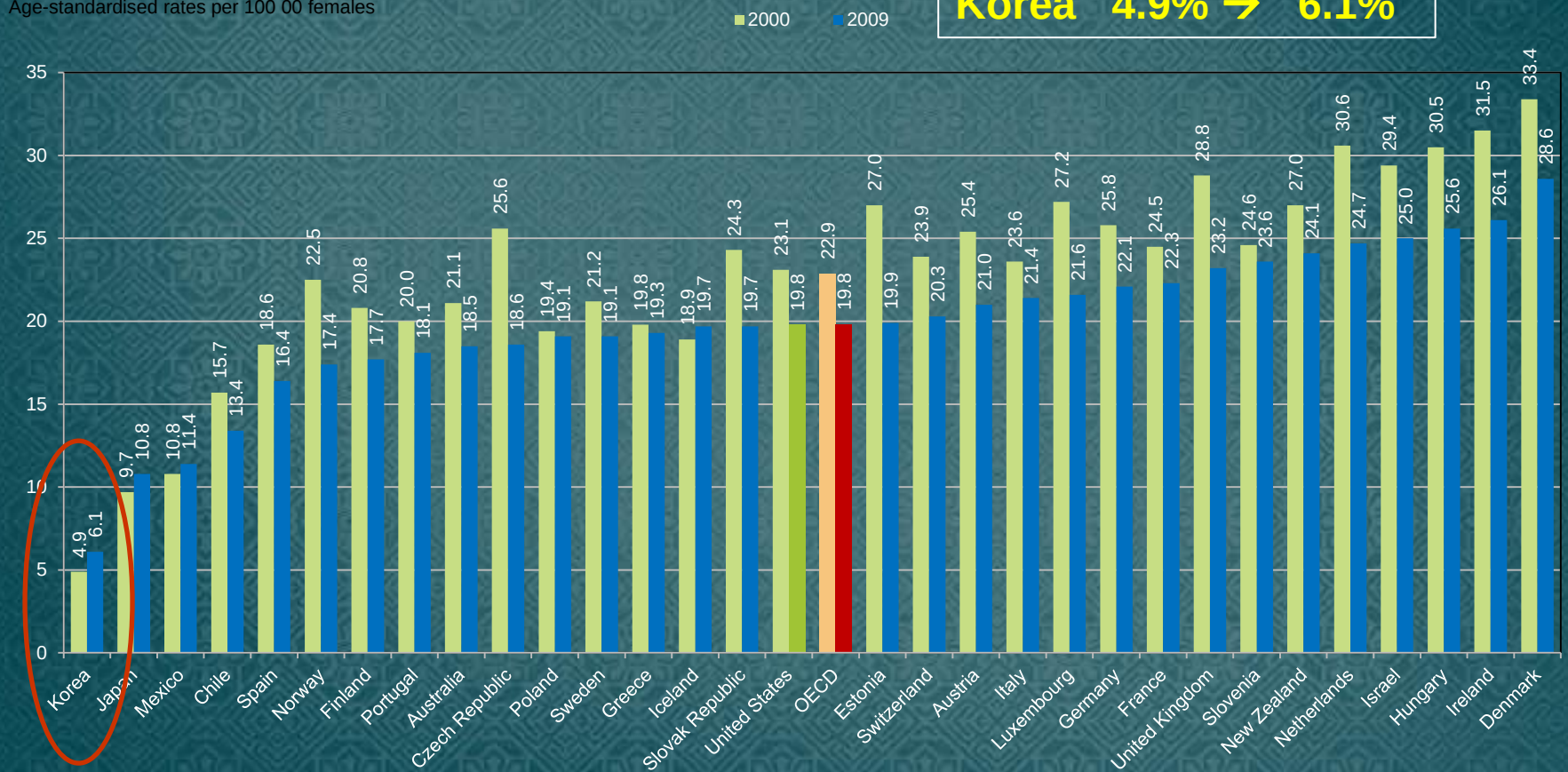
- Level of evidence : Category 1
- No drug for replacement or substitution
- No increase in financial burden for provider

- But, cancer patients pay only 5% of all medical cost if covered by insurance

- Usually they are provided with good quality cancer care with low economic burden.

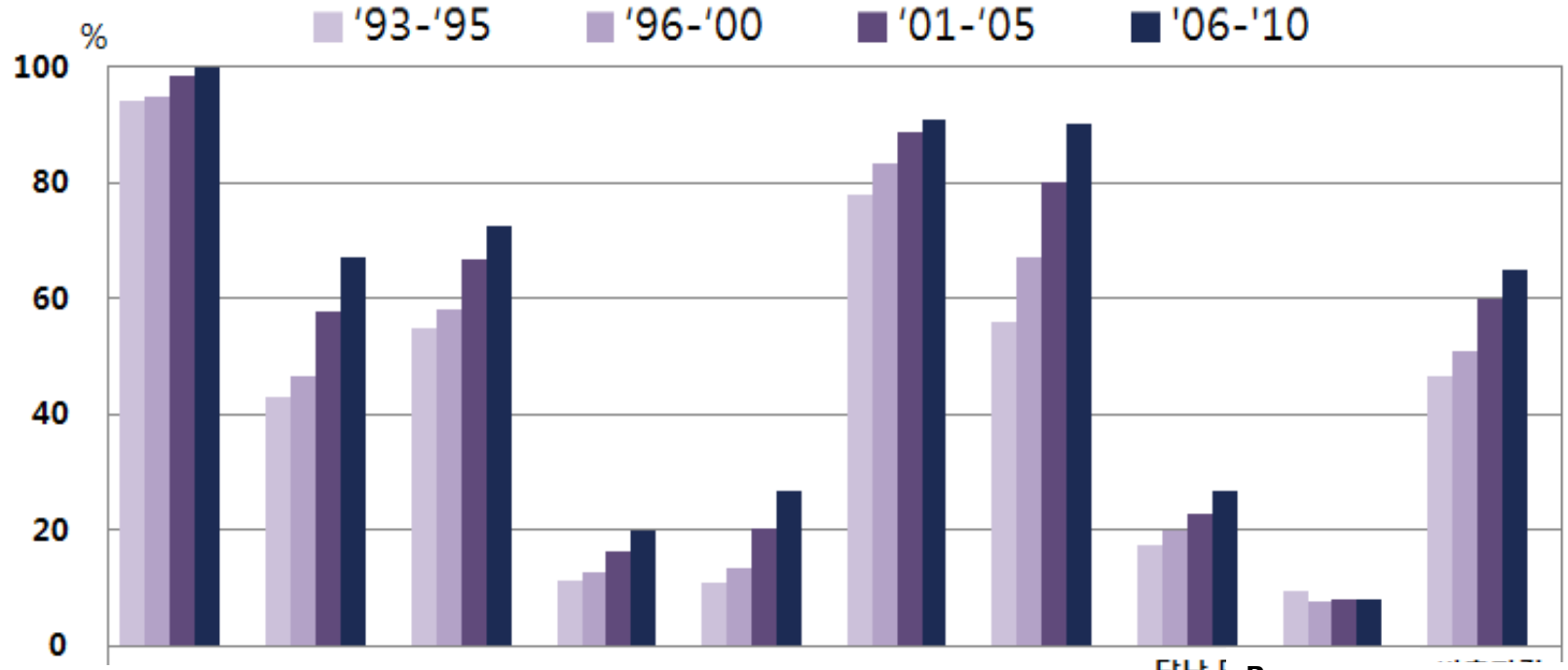
Breast cancer mortality, female, 2000 to 2009, age-adjusted

OECD 22.9% → 19.8%
Korea 4.9% → 6.1%



OECD Health Care Quality Indicators

5 year survival rate of major cancer



	Thyroid	Stomach	Colon	Lung	Liver	Breast	Prostate	담낭 및 Biliary	Pancreas	NHL
'93-'95	94.2	42.8	54.8	11.3	10.7	77.9	55.9	17.3	9.4	46.6
'96-'00	94.9	46.6	58.0	12.7	13.2	83.2	67.2	19.7	7.6	50.8
'01-'05	98.3	57.7	66.6	16.2	20.1	88.5	80.1	22.8	8.0	59.9
'06-'10	99.8	67.0	72.6	19.7	26.7	91.0	90.2	26.7	8.0	64.9
증감*	5.6	24.2	17.8	8.4	16.0	13.1	34.3	9.4	-1.4	18.3

* 증감: '93~'95년 대비 '06~'10년 암발생자의 생존율 차이

Korea Central Cancer Registry, 2010

Randomized phase III trials beyond progression during trastuzumab

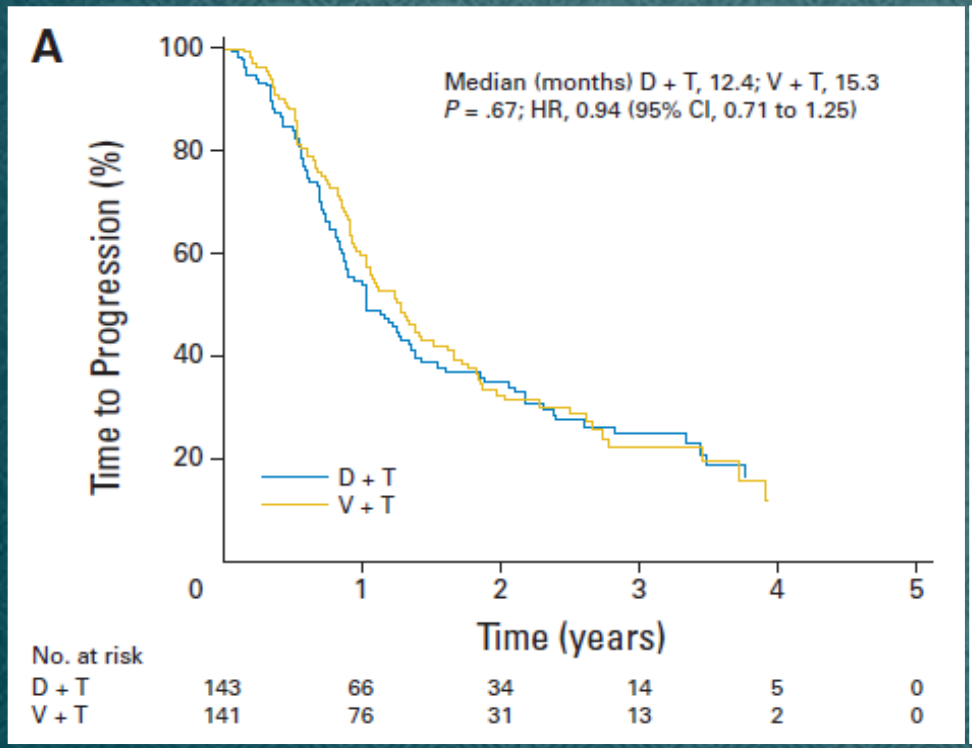
Trial	N	ORR	TTP/PFS (months)	OS (months)
von Minckwitz et al. (2009)	156		TTP	
Capecitabine		27%	5.6	20.4
Capecitabine+Trastuzumab		48.1%	8.2	25.5
			P=0.03	P=0.26
Geyer et al. (2006)	324		TTP	
Capecitabine		14%	4.4	
Capecitabine+Lapatinib		22%	8.4	
		P=0.009	P<0.001	
Blackwell et al (2010)	296			
Lapatinib		6.9	8.4 wks	39 wks
Lapatinib+Trastuzumab		10.3	12 wks	51.6 wks
		P=0.46	P=0.008	P=0.016

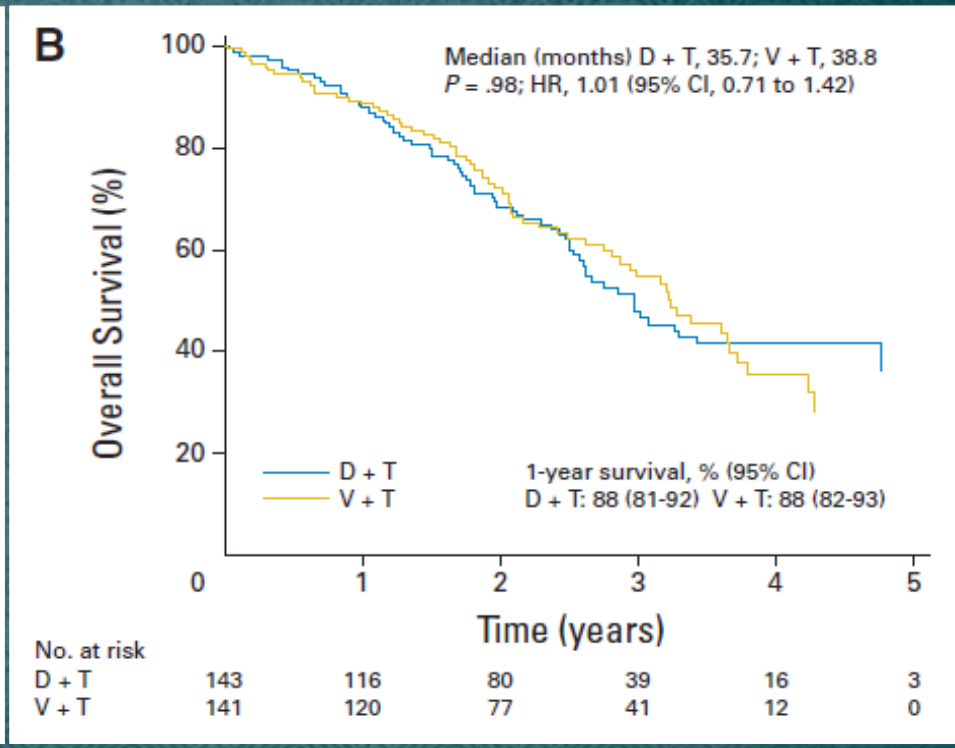
In Korea…

- Beyond progression during or within 1 year of adjuvant trastuzumab, physicians have to change to lapatinib/capecitabine in HER2-positive metastatic breast cancer.

- And then, no anti-HER2 targeted agents are allowed anymore.

HERNATA study:1st line Trastuzumab/Docetaxel vs. Trastuzumab/Vinorelbine





Anderson M et al. JCO 2011;29:264-271

HERNATA study:1st line Trastuzumab/Docetaxel vs. Trastuzumab/Vinorelbine

Table 3. Incidence of Drug-Related Toxicities Grade 2 to 4 Observed With Grade 3 to 4 in More Than 3% of Patients in Any Treatment Arm

Toxicity	% of Patients						*P* (grade 3 + 4, docetaxel *v* vinorelbine)
	Gr						
Hematologic							
Leucopenia							< .001
Neutropenia							.81
Febrile neutropenia							< .001
Nonhematologic							
Nausea							.72
Infection							.006
Pain							.55
Fatigue							.30
Diarrhea							.11
Neuropathy, motor							.75
Neuropathy, sensory							< .001
Edema							.003
Dyspnea							.54
Fever							.03
Nail changes	29.5	7.9	0	1.4	0.7	0	.005

More Gr ¾ toxicities in Docetaxel arm :

- Febrile neutropenia (36.0% vs 10.1%)
- Leucopenia (40.3% vs 21.0%)
- Infecttion (25.1% vs 13.0%)
- Fever (4.3% vs 0%)
- Neruopathy (7.9% vs 0.7%)
- Edema (6.5% vs 0%)

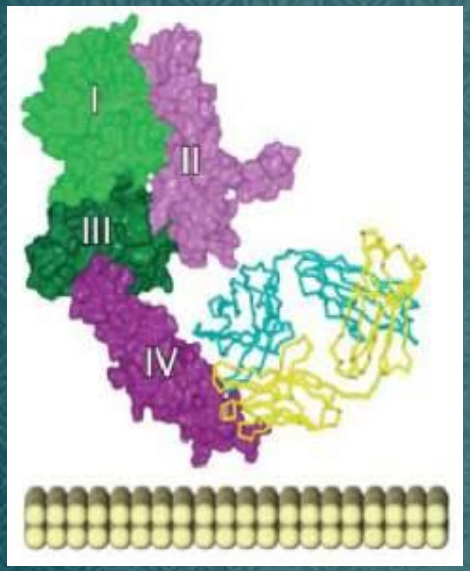
Anderson M et al. JCO 2011;29:264-271

In Korea…

- Trastuzumab combined with taxane is the only one regimen allowed to use and reimburssed.

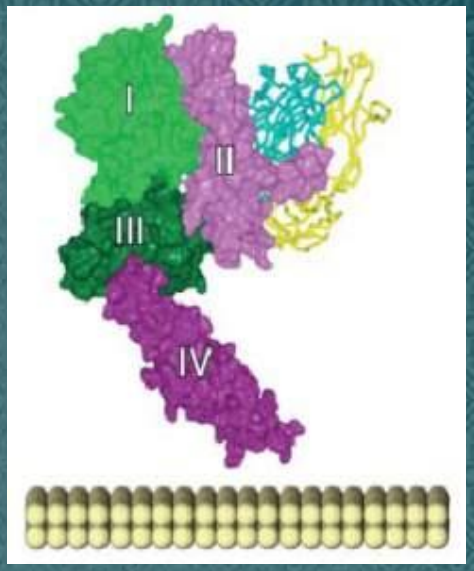
- Other combinations in current NCCN guideline, such as trastuzumab with vinorelbine, capecitabine, or lapatinib should not be used.

Trastuzumab and Pertuzumab (Perjeta)



Trastuzumab

- Activates antibody-dependent cellular cytotoxicity
- Inhibits HER2-mediated signalling
- Inhibits shedding and, thus, formation of new p95
- Inhibits HER2-related angiogenesis

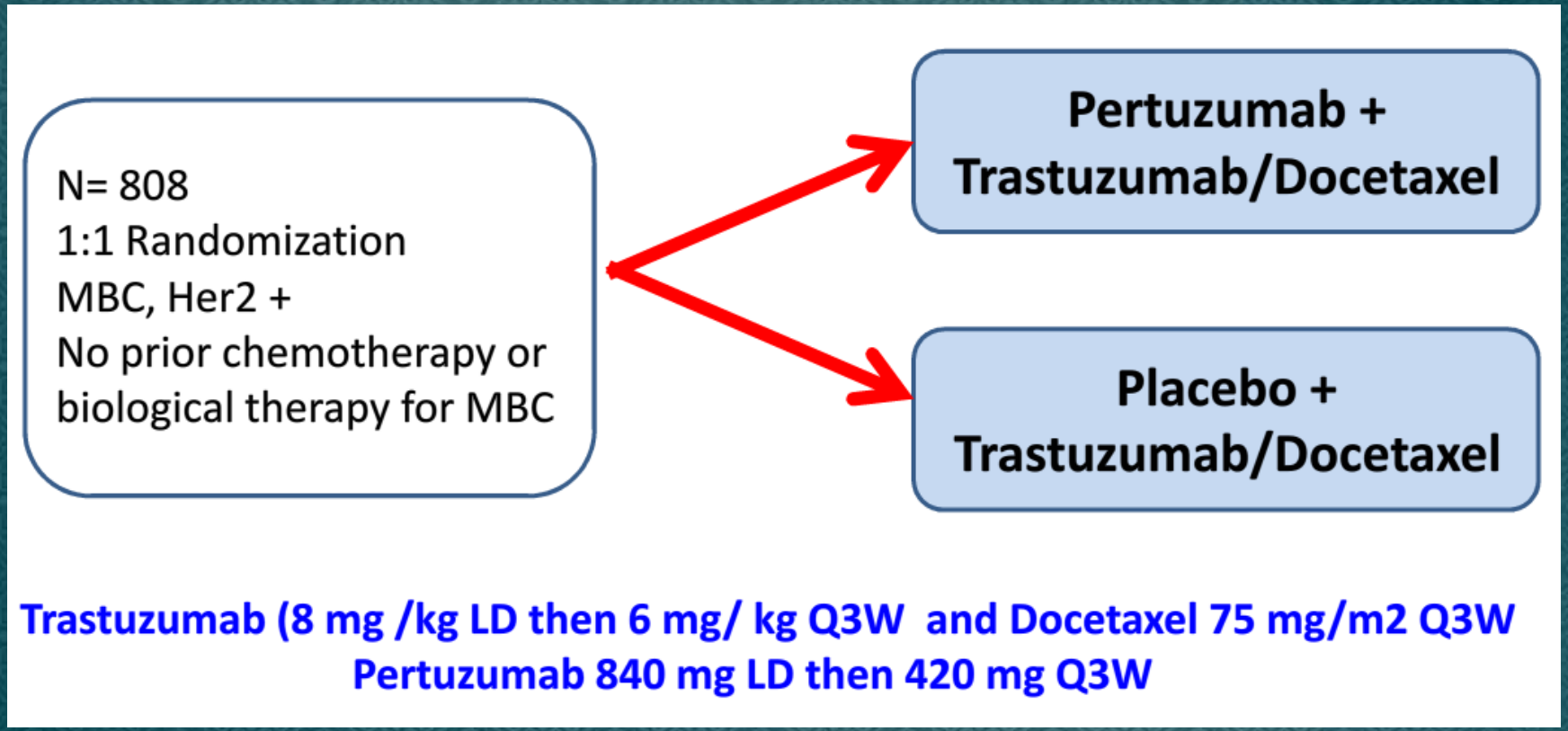


Pertuzumab

- Activates antibody-dependent cellular cytotoxicity
- Prevents receptor dimerization
- Potent inhibitor of HER2/HER2- and HER2/HER3-mediated signalling pathways

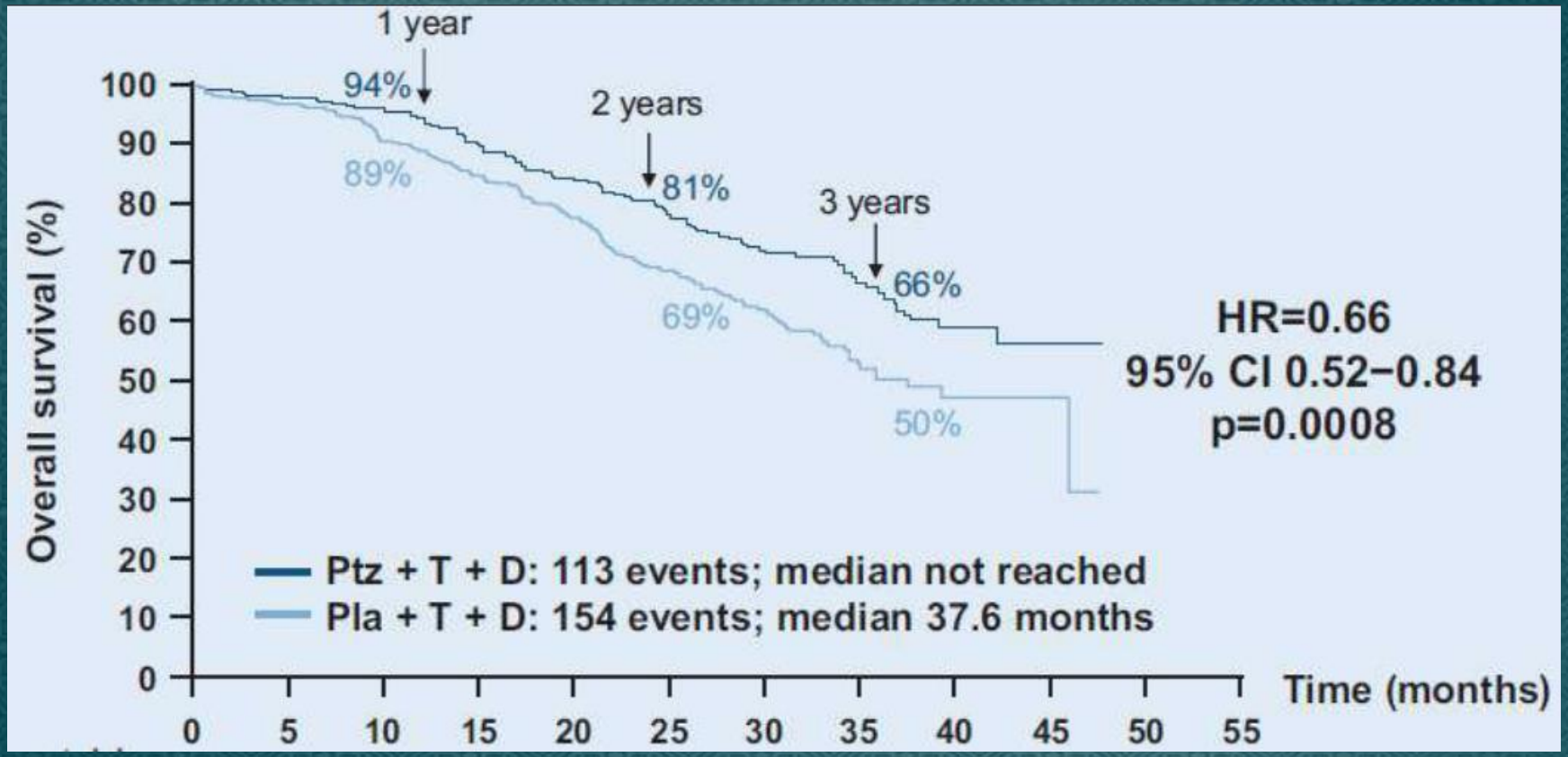
Hubbard 2005

Phase III trial of Pertuzumab in combination of Trastuzumab/Docetaxel (Cleopatra)



Baselga et al. N Engl J Med 2012;366:109-19.

Cleopatra : OS



At 30 months median follow up

Baselga et al. N Engl J Med 2012;366:109-19.

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CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:

Trastuzumab with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

T-DM1 (Ado trastuzumab emtansine)

Target expression: HER2

Monoclonal antibody: trastuzumab

Cytotoxic agent: DM1

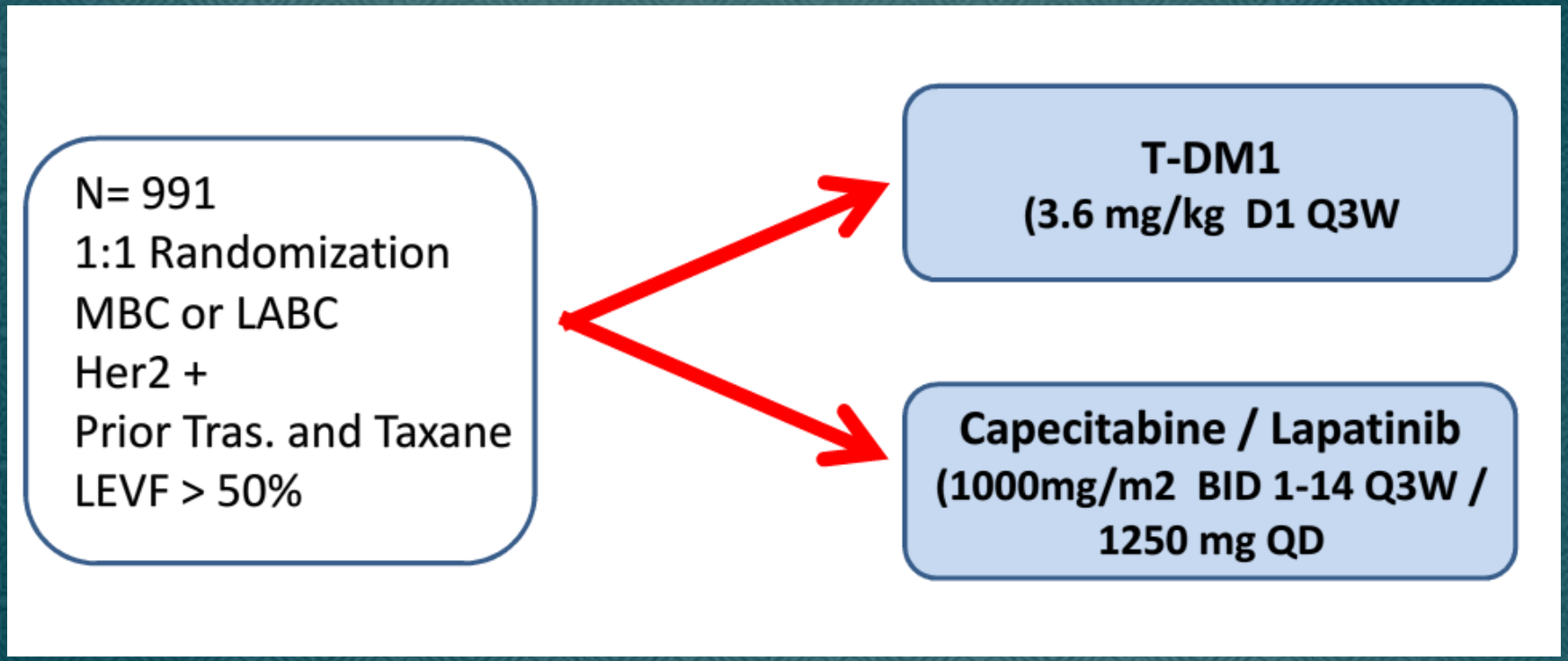
Highly potent chemotherapy
(maytansine derivative)

Linker

Systemically stable
Breaks down in target cancer cell

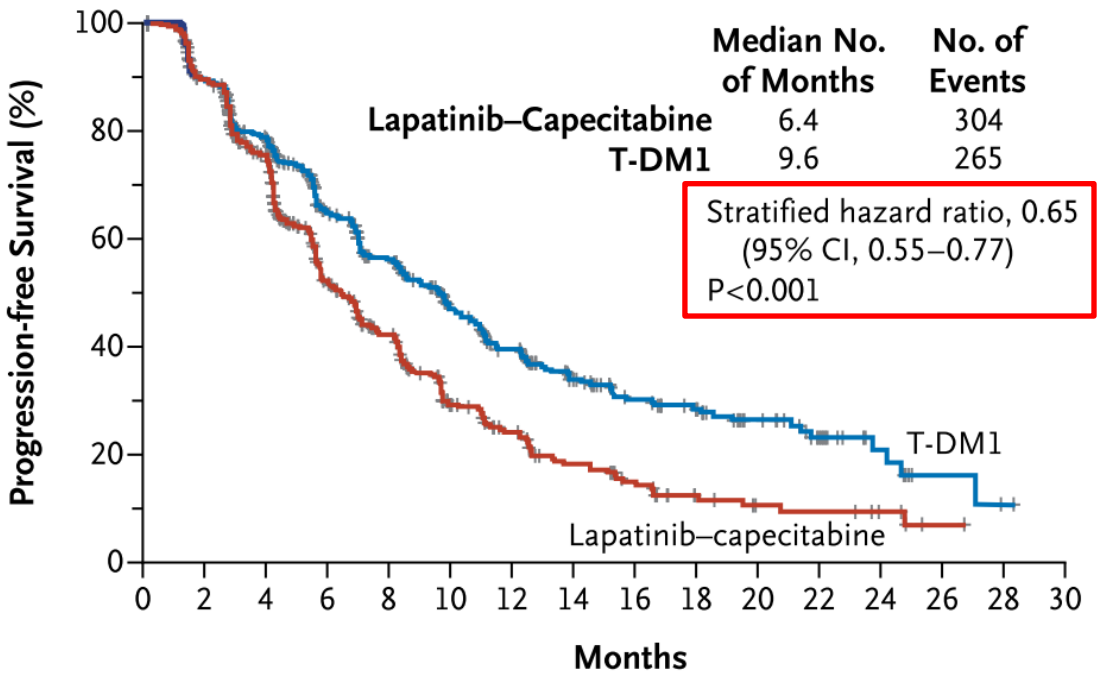
T-DM1
(Kadcyla®)

EMILIA : phase III 2nd line in MBC



Verma et al, N Engl J Med 2012;367:1783-91

EMILIA : PFS



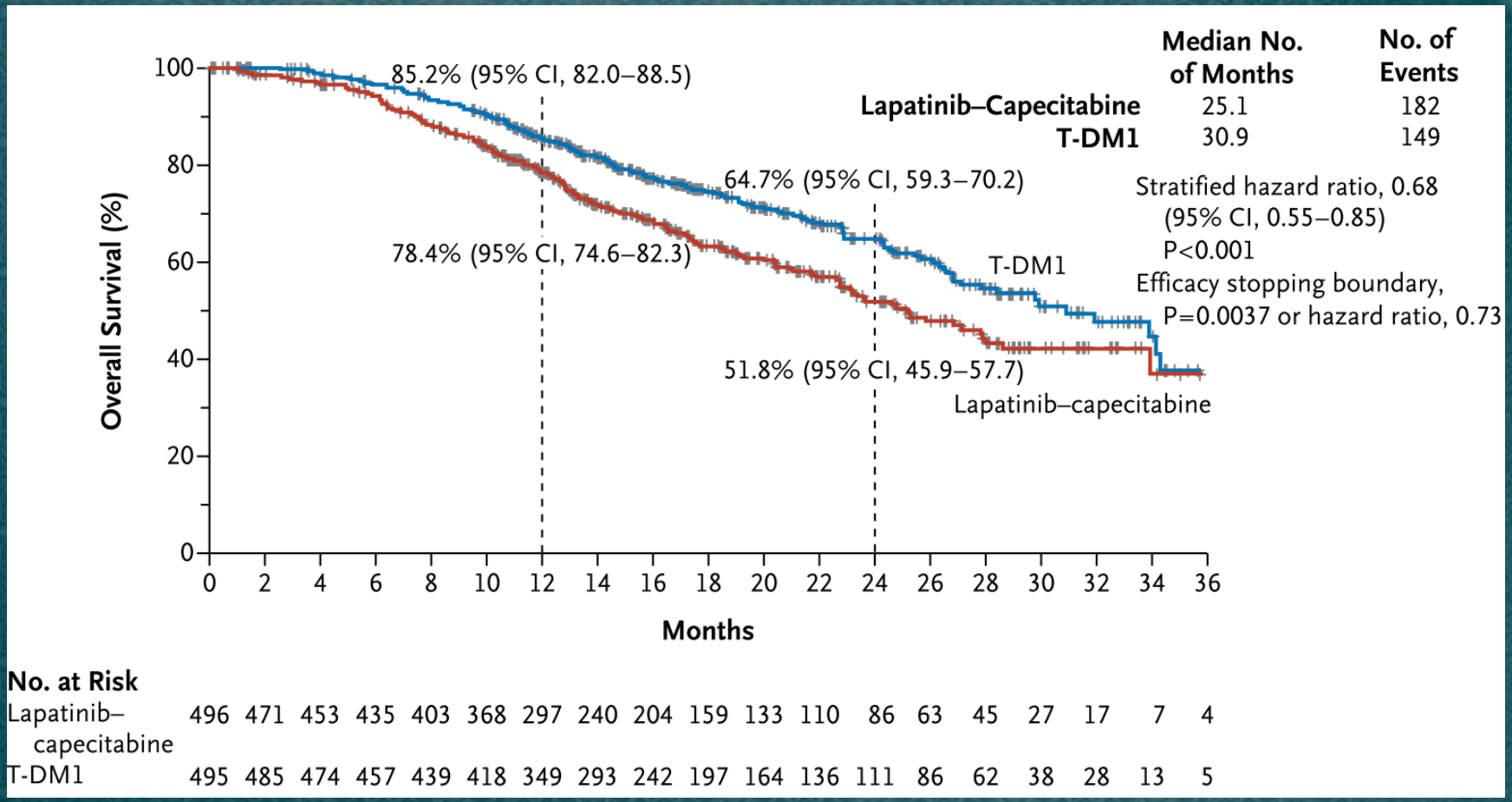
No. at Risk

Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

ORR : Cape/Lap : 31%, T-DM1 : 44%, p<0.002

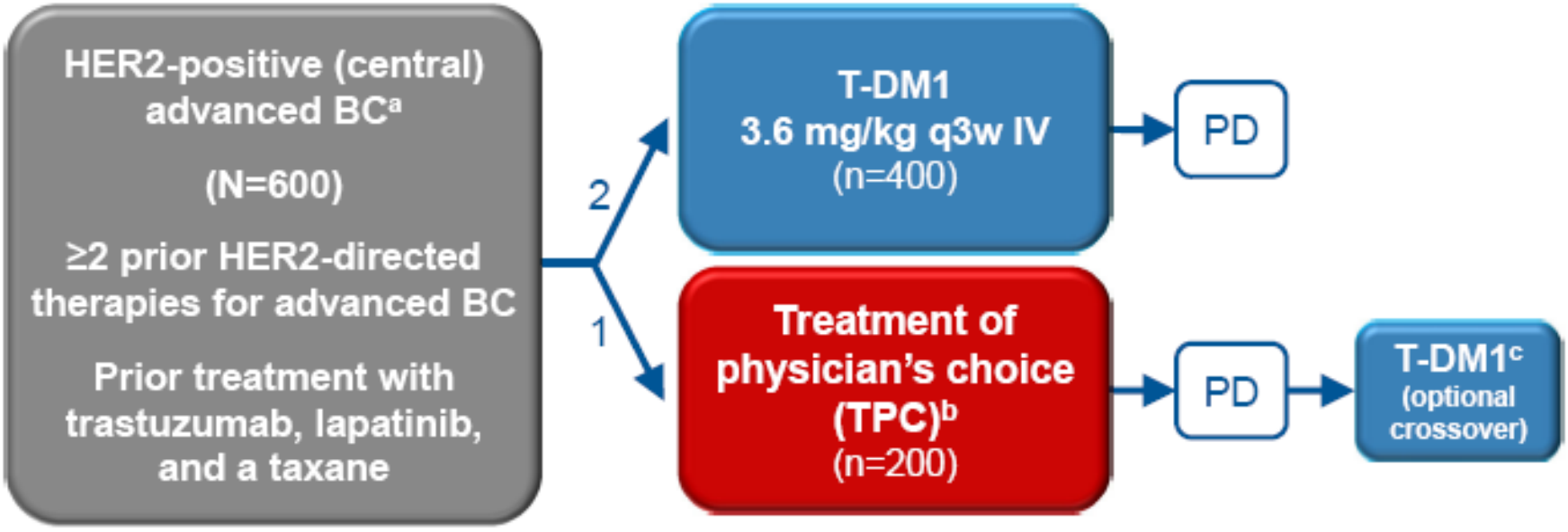
Verma et al, N Engl J Med 2012;367:1783-91

EMILIA : OS



Verma et al, N Engl J Med 2012;367:1783-91

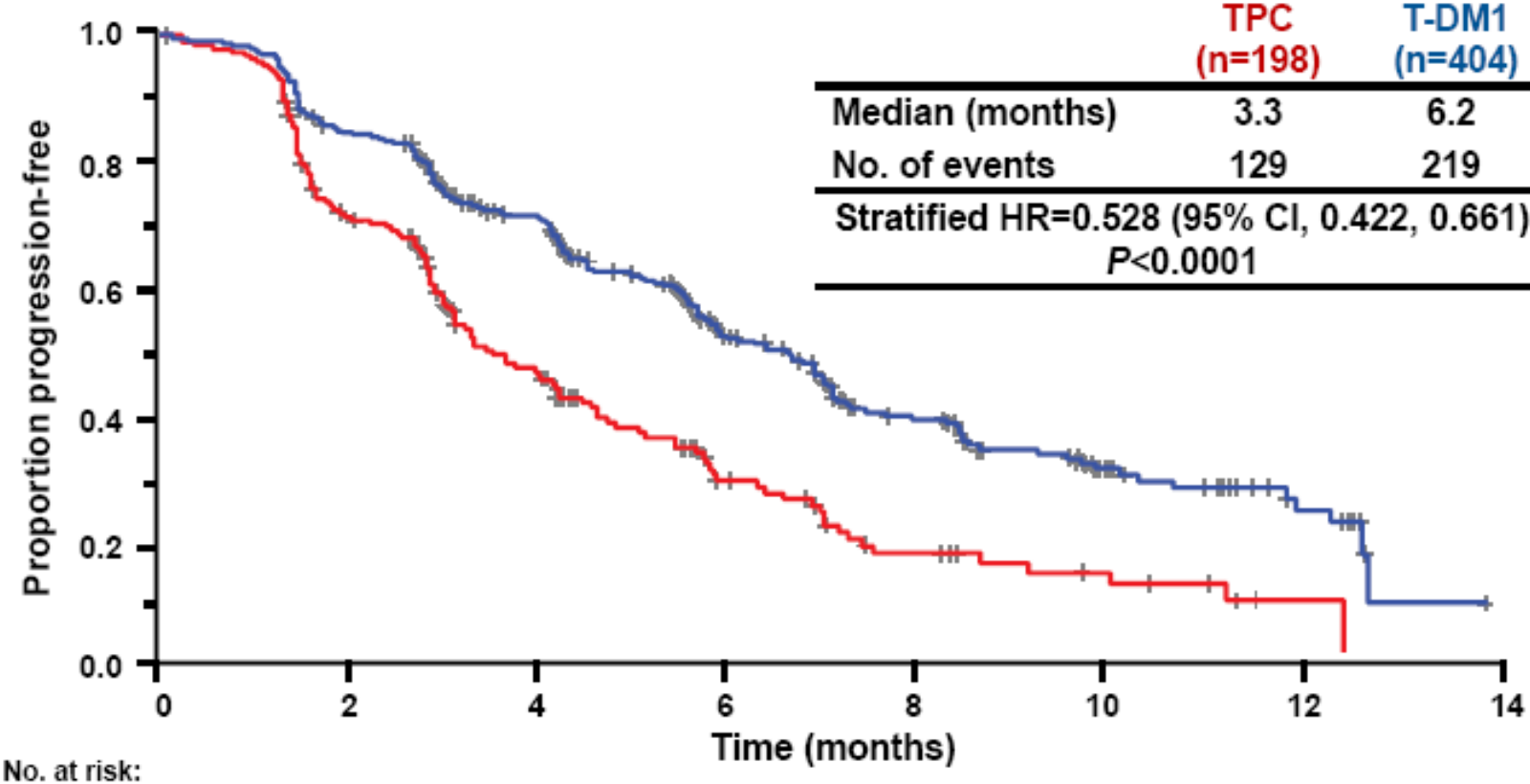
TH3RESA : phase III 3rd line in MBC



- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

Wildiers H, SB Kim et al, ECCO 2013

PFS by investigator assessment



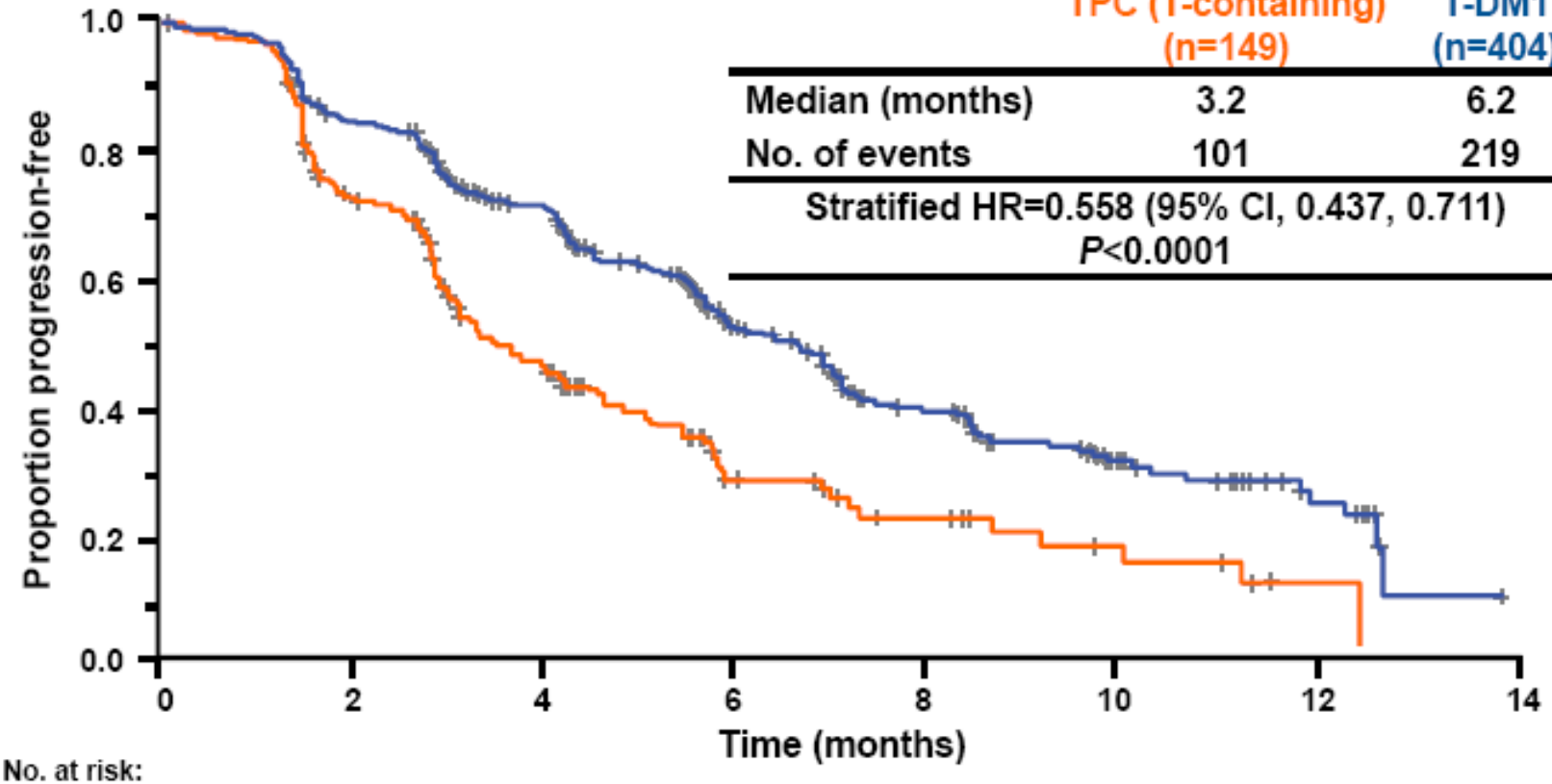
	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219
Stratified HR=0.528 (95% CI, 0.422, 0.661) *P*<0.0001		

No. at risk:

TPC	198	120	62	28	13	6	1	0
T-DM1	404	334	241	114	66	27	12	0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

PSF for pts treated with trastuzumab-containing regimens



	TPC (T-containing) (n=149)	T-DM1 (n=404)
Median (months)	3.2	6.2
No. of events	101	219

Stratified HR=0.558 (95% CI, 0.437, 0.711)
P<0.0001

No. at risk:								
TPC	149	99	50	20	12	5	1	0
T-DM1	404	334	241	114	66	27	12	0

Unstratified HR=0.54 (*P*<0.0001).

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- Trastuzumab + capecitabine
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- Trastuzumab + other agents

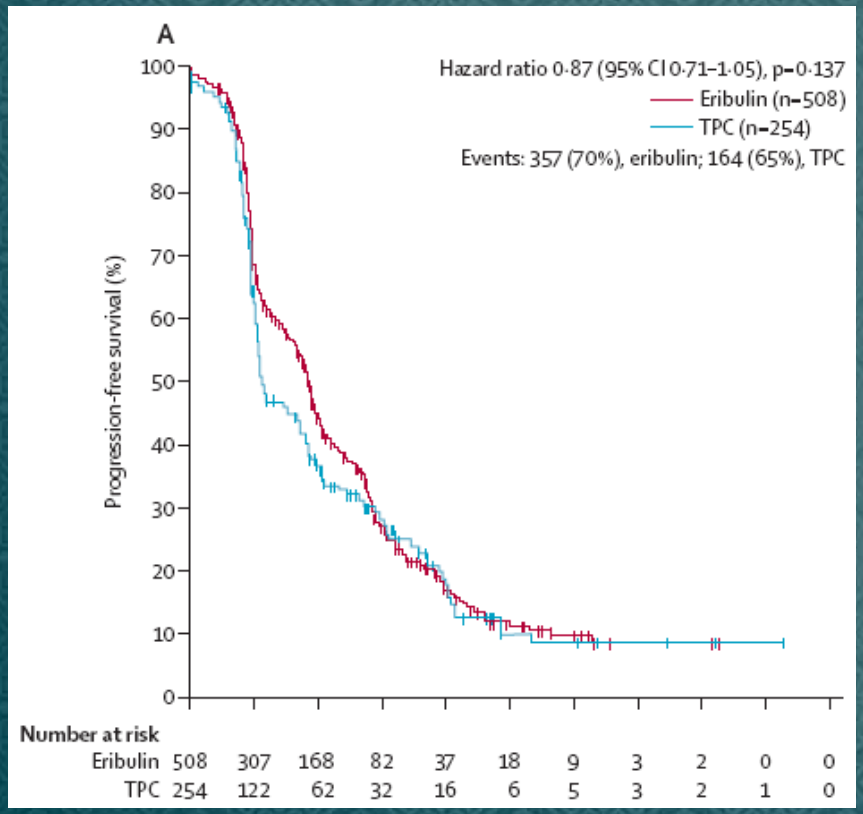
In Korea…

- New anti-HER2 targeted agents, pertuzumab and T-DM1, are not available now.

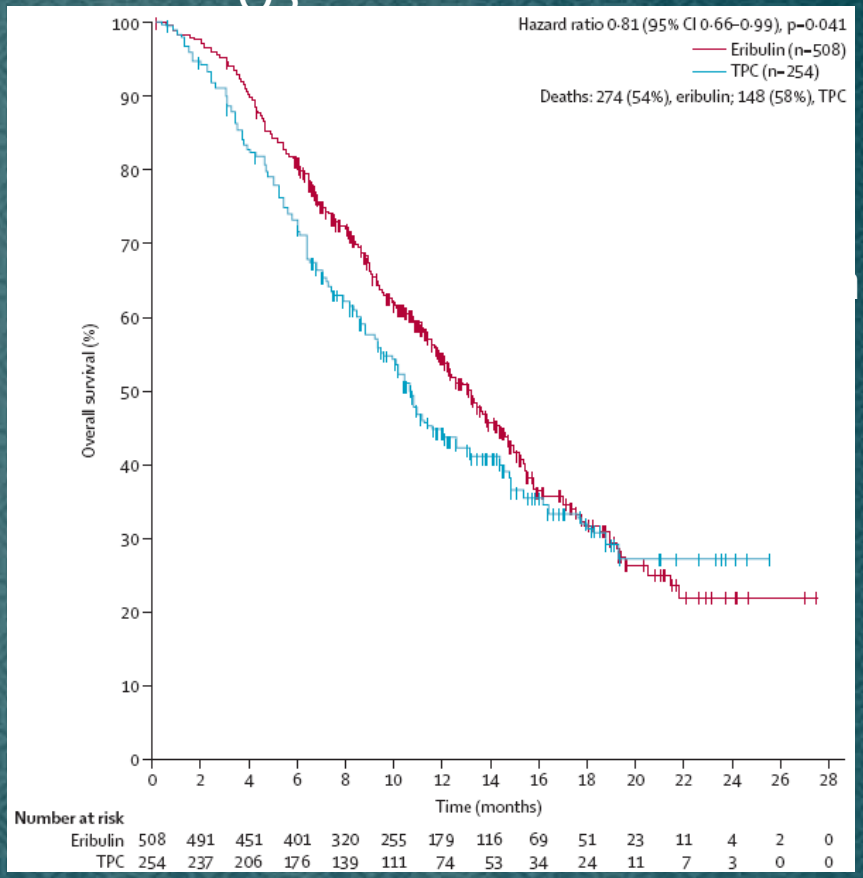
- Outlook of their reimbursement in the near future is very dim.

Eribulin
EMBRACE trial: PFS & OS

PFS

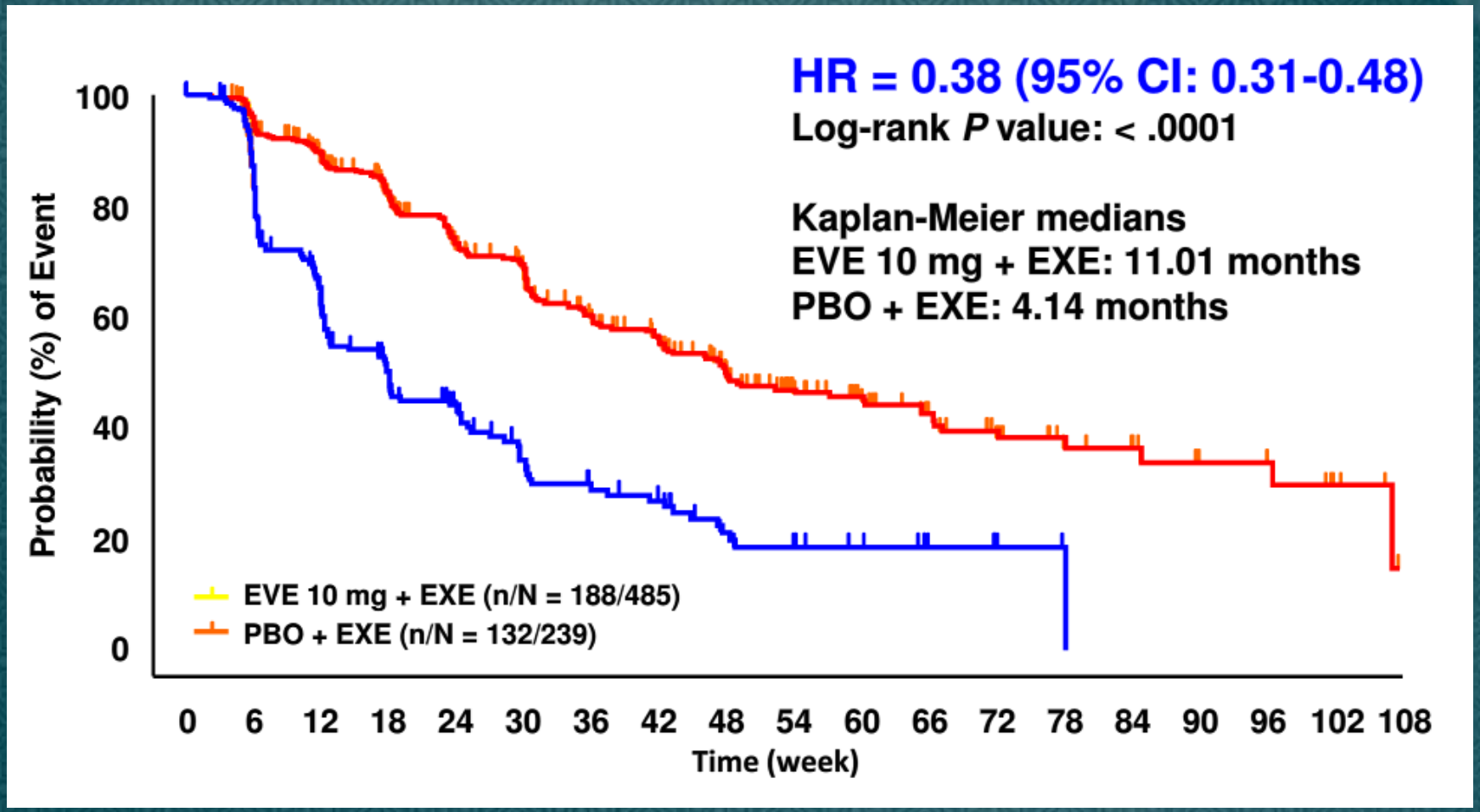


OS



Lancet 2011; 377: 914–2

Everolimus + exemestane BOLERO-2 trial: PFS

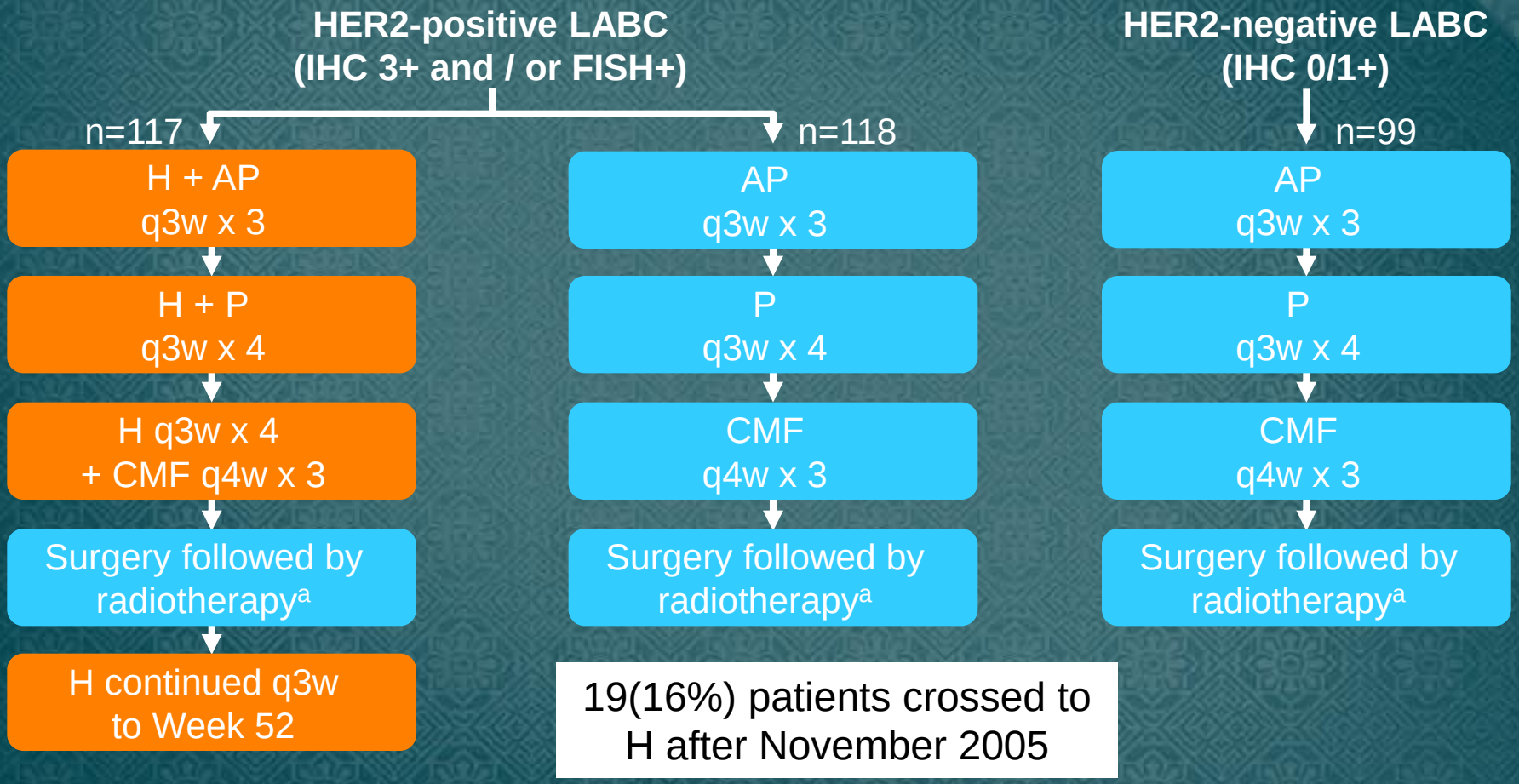


2012 SABCS

In Korea…

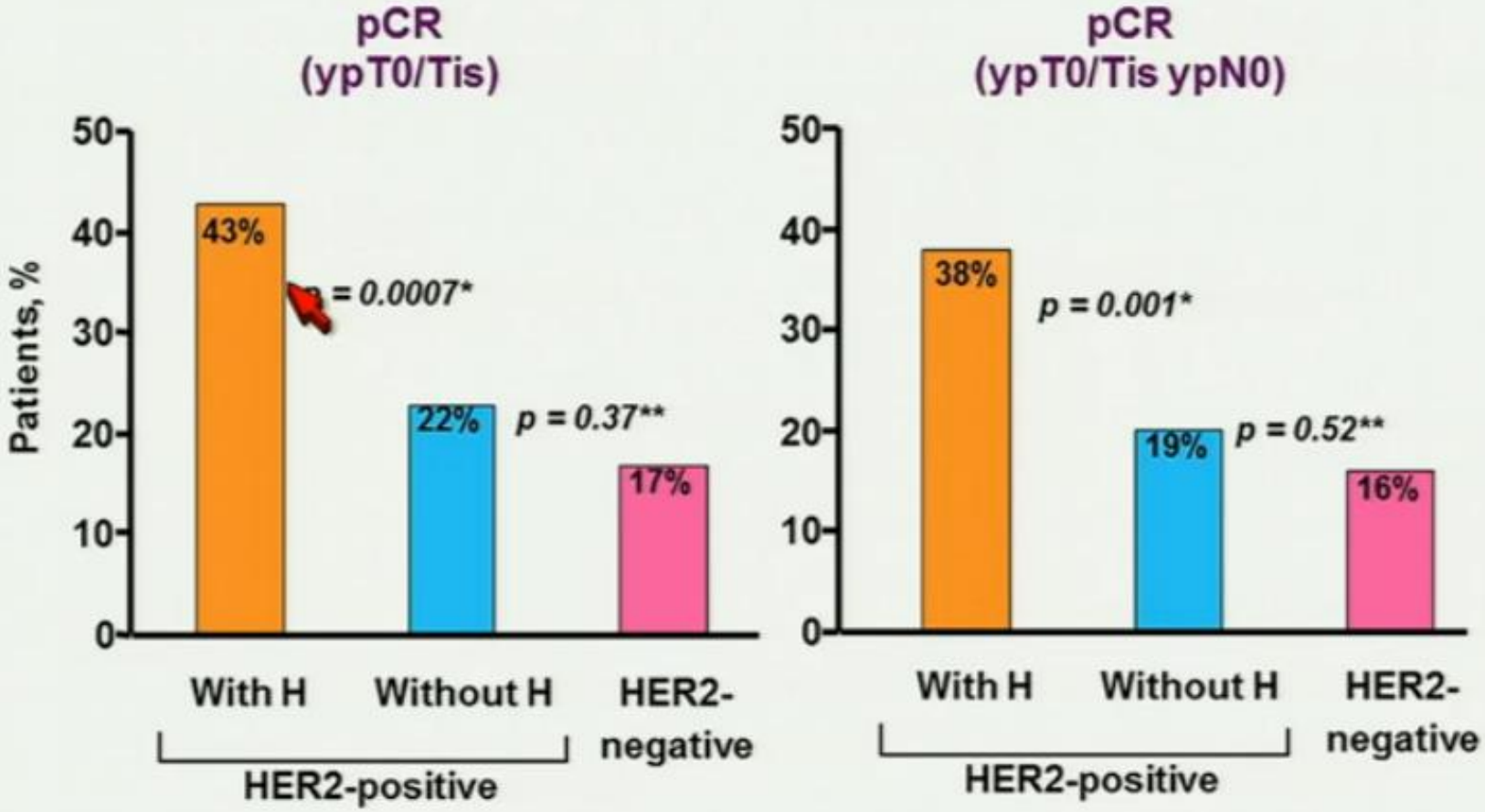
- New drugs for patients with HER2-negative cancer are very expensive and not reimbursed, yet.
  - Eribulin ca 4,000 USD/cycle
  - Everolimus/Exemestane ca 2,700 USD/month
- Less than 5% of patients indicated are treated with these drugs.

NOAH trial



[a]Hormone receptor-positive patients receive adjuvant tamoxifen;
AP, doxorubicin 60 mg/m^2, paclitaxel 150 mg/m^2; H, Herceptin® 8 mg/kg loading then 6 mg/kg;
LABC, locally advanced breast cancer; P, paclitaxel 175 mg/m^2; q3w, every 3 weeks; q4w, every 4 weeks

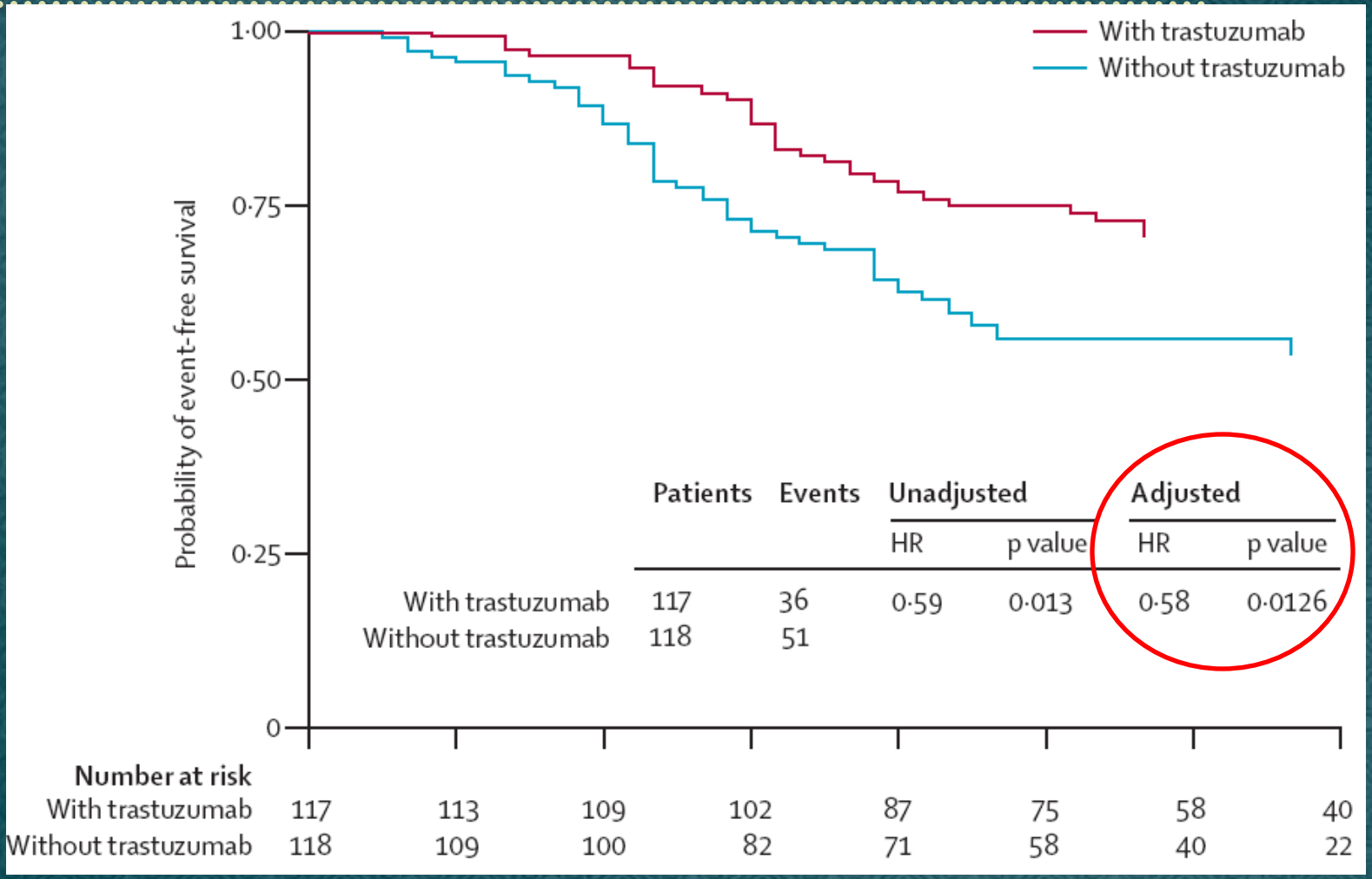
pCR in intent-to-treat population



*p-value for HER2-pos with H vs w/o H; **p-value for HER2-pos vs HER2-neg

L. Gianni et al, Lancet 2010

EFS in HER2+ ITT population



	Patients	Events	Unadjusted		Adjusted	
			HR	p value	HR	p value
With trastuzumab	117	36	0·59	0·013	0·58	0·0126
Without trastuzumab	118	51				

Number at risk								
With trastuzumab	117	113	109	102	87	75	58	40
Without trastuzumab	118	109	100	82	71	58	40	22

Gianni, et al. Lancet 2010;375:377

Summary

- Reveals a significant interaction (p=0.037) of treatment and pCR
  - EFS benefit from trastuzumab is significantly linked to pCR, and almost restricted to pCR
  - pCR with trastuzumab is linked to significant EFS benefit, while association of pCR and EFS is smaller and non significant without trastuzumab

Same chemotherapeutic regimens in neoadjuvant and adjuvant setting

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Breast Cancer Table of Contents
Discussion

NEOADJUVANT/ADJUVANT CHEMOTHERAPY [1,2,3,4,5]

Non-trastuzumab-containing regimens (all category 1)

Preferred regimens:
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:
- AC (doxorubicin/cyclophosphamide)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Trastuzumab-containing regimens (all category 1)

Preferred regimens:
- AC followed by T + concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab)

Other regimens:
- Docetaxel + trastuzumab followed by FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC followed by docetaxel + trastuzumab

Neoadjuvant only:
- T + trastuzumab followed by FEC + trastuzumab (paclitaxel plus trastuzumab followed by cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

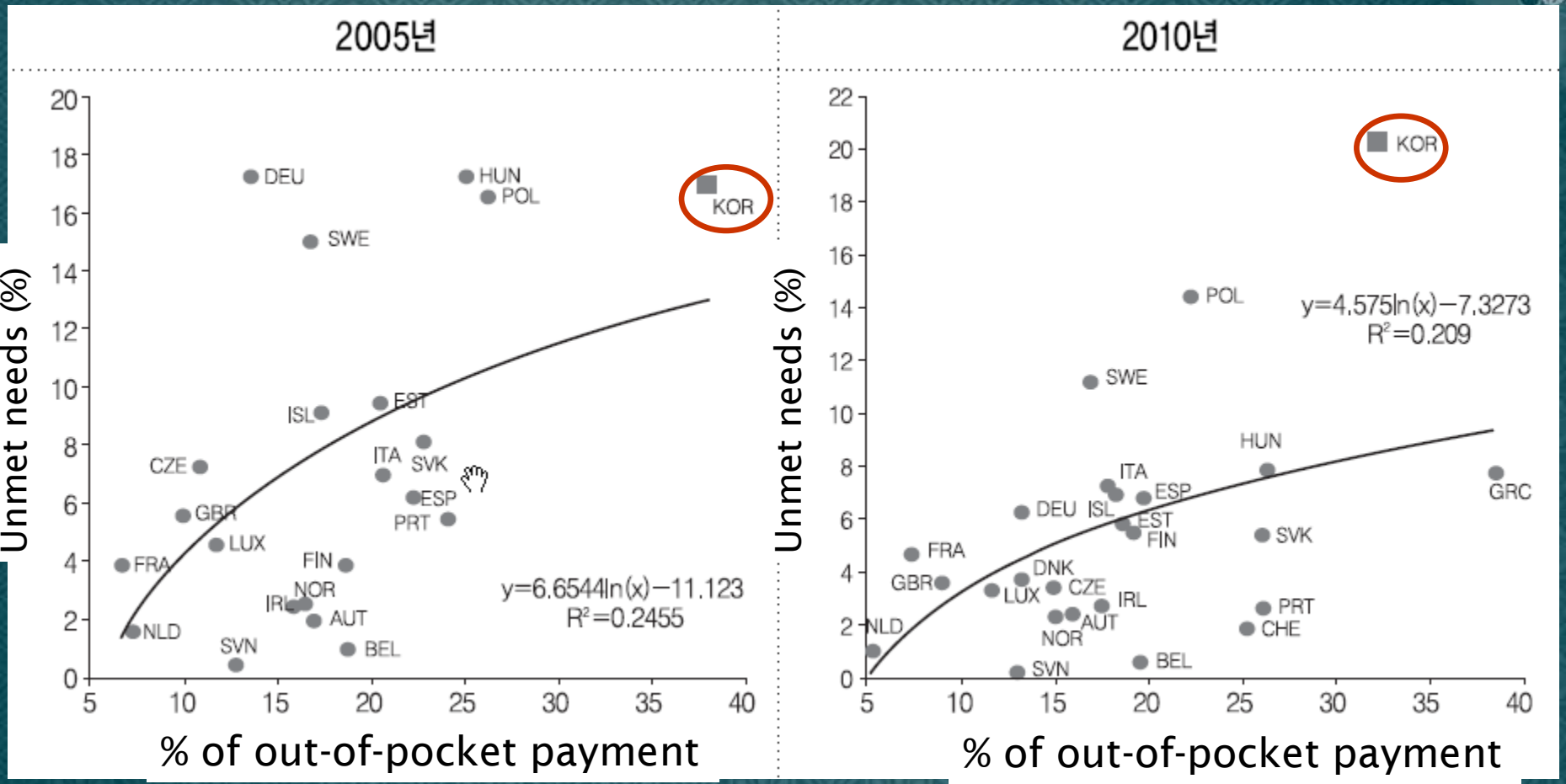
In Korea…

- The regimen used in NOAH trial is the only one approved as neoadjuvant treatment in HER2-positive breast cancer.

- But it's not reimbursed now.

How do patients feel in current medical environment in Korea?

Unmet needs and out-of-pocket payment



Health & Welfare Policy Forum 2013;196:89-102

Conclusions

- Patients and doctors in Korea have many obstacles to access to modern &/or expensive drugs proven to increase clinical outcome and feel uncomfortable.
- We need more information on predicting benefits and toxicities of treatment in individual patient.
- Consensus and wisdom are eagerly needed for fair distribution of limited medical resources.

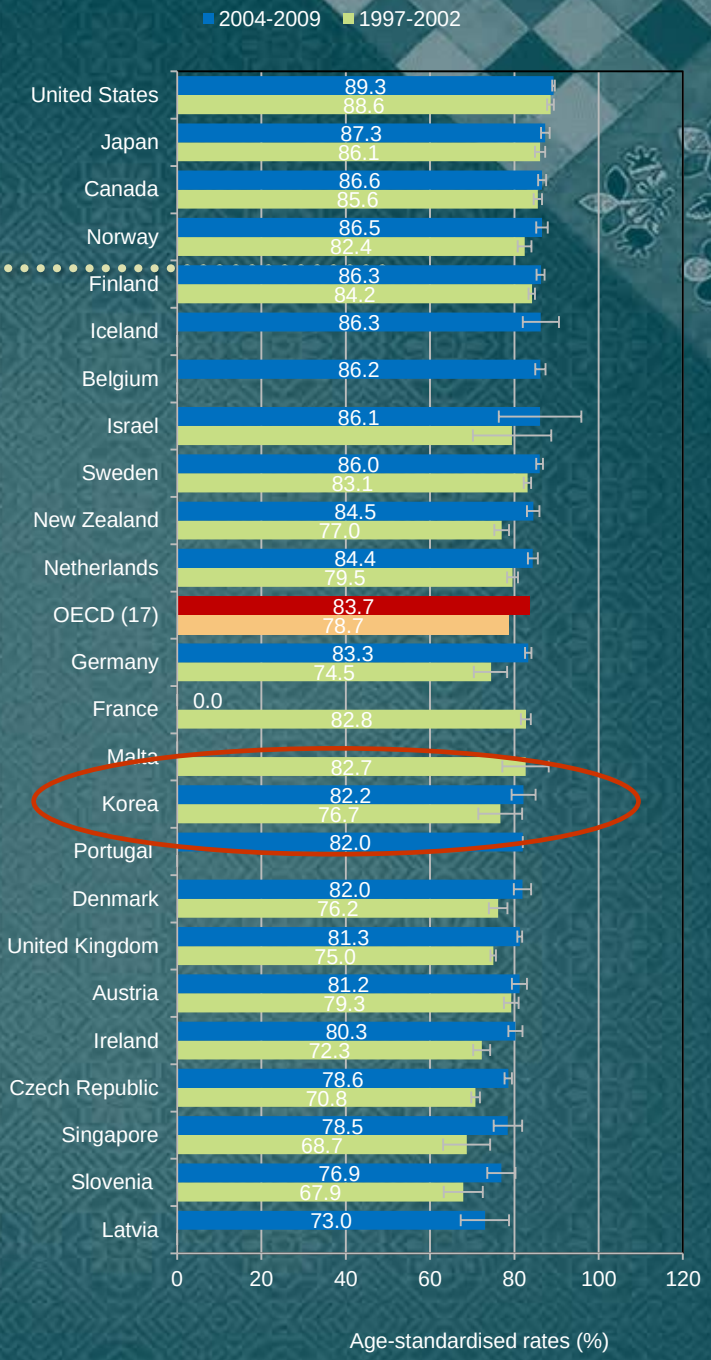
Thank you for your attention !

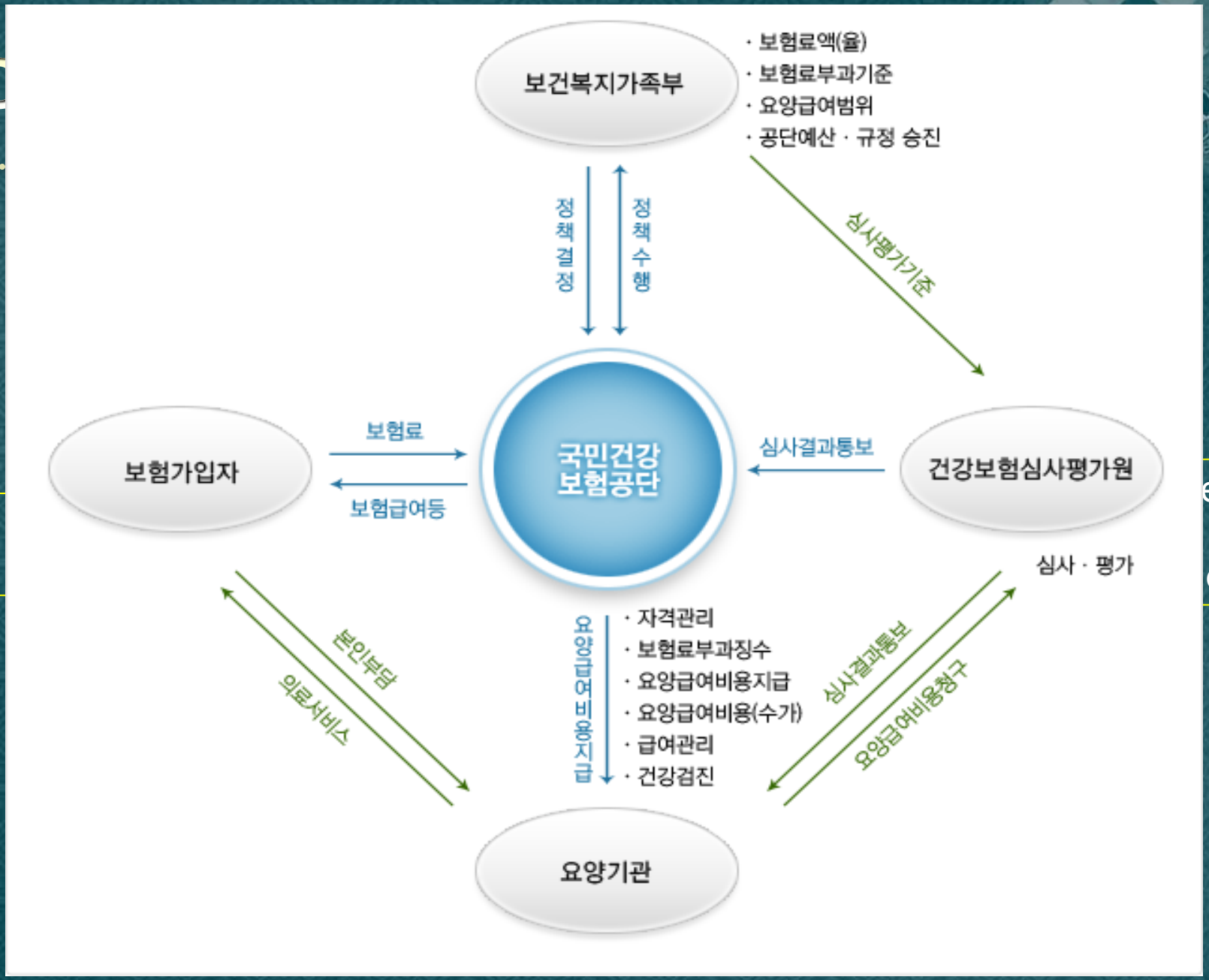
....???


터키 713
멕시코 716
칠레 1,202
에스토니아 1,274
폴란드 1,387
헝가리 1,601
체코 1,884
한국 2,035
슬로바키아 2,095
이스라엘 2,165
슬로베니아 2,428
포르투갈 2,728
그리스 2,914
이탈리아 2,964
뉴질랜드 3,022
일본 3,035
스페인 3,056
핀란드 3,251
OECD 3,268
아이슬란드 3,307
영국 3,433
호주 3,670
아일랜드 3,718
스웨덴 3,758
벨기에 3,767
프랑스 3,774
독일 4,338
오스트리아 4,375
캐나다 4,445
덴마크 4,464
룩셈부르크 4,786
네덜란드 5,056
스위스 5,270
노르웨이 5,388
미국 8,233
0
2000
4000
6000
8000

Breast cancer 5-year relative survival rate: (1997-2002 and 2004-2009 or nearest period)

	1997-2002	2004-2009
OECD (17)	78.7	83.7
Korea	76.7	82.2
Japan	86.1	87.3
Singapore	68.7	78.5




보건복지가족부
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· 요양급여범위
· 공단예산 · 규정 승진
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정책수행
심사평가기준
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심사결과통보
요양급여비용청구
요양기관