Behandeling op maat

Mammacarcinoom en targeted therapy

4e mammacongres Harderwijk

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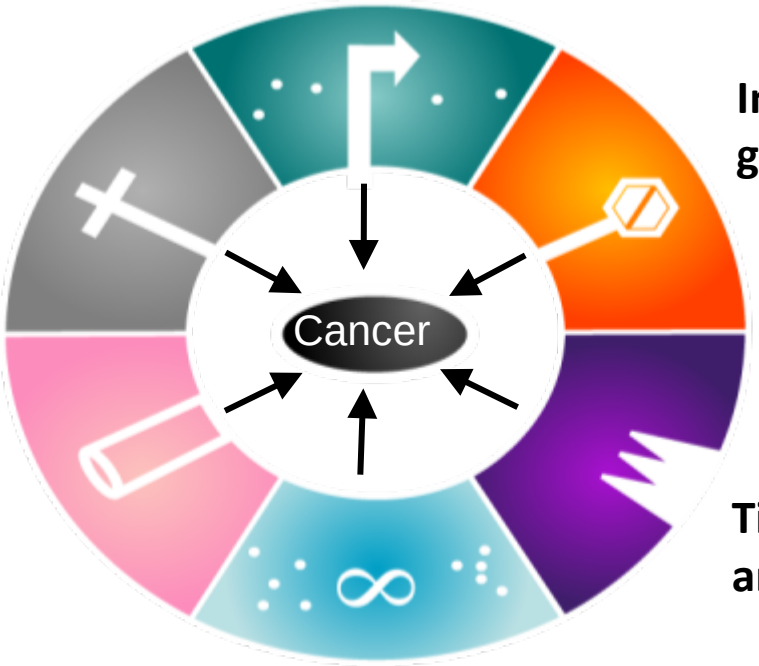
Mammacarcinoom en targeted therapy

schier toveren…
maar hoe beperken we de schade?

- **inleiding**
- **nieuwe targeted agents (doelgerichte middelen)**
- **oude targeted agents, nieuwe toepassingen**
- **toxiciteit, kosten**
- **selectie patiënten**
- **conclusie**

Inleiding: werking targeted agents

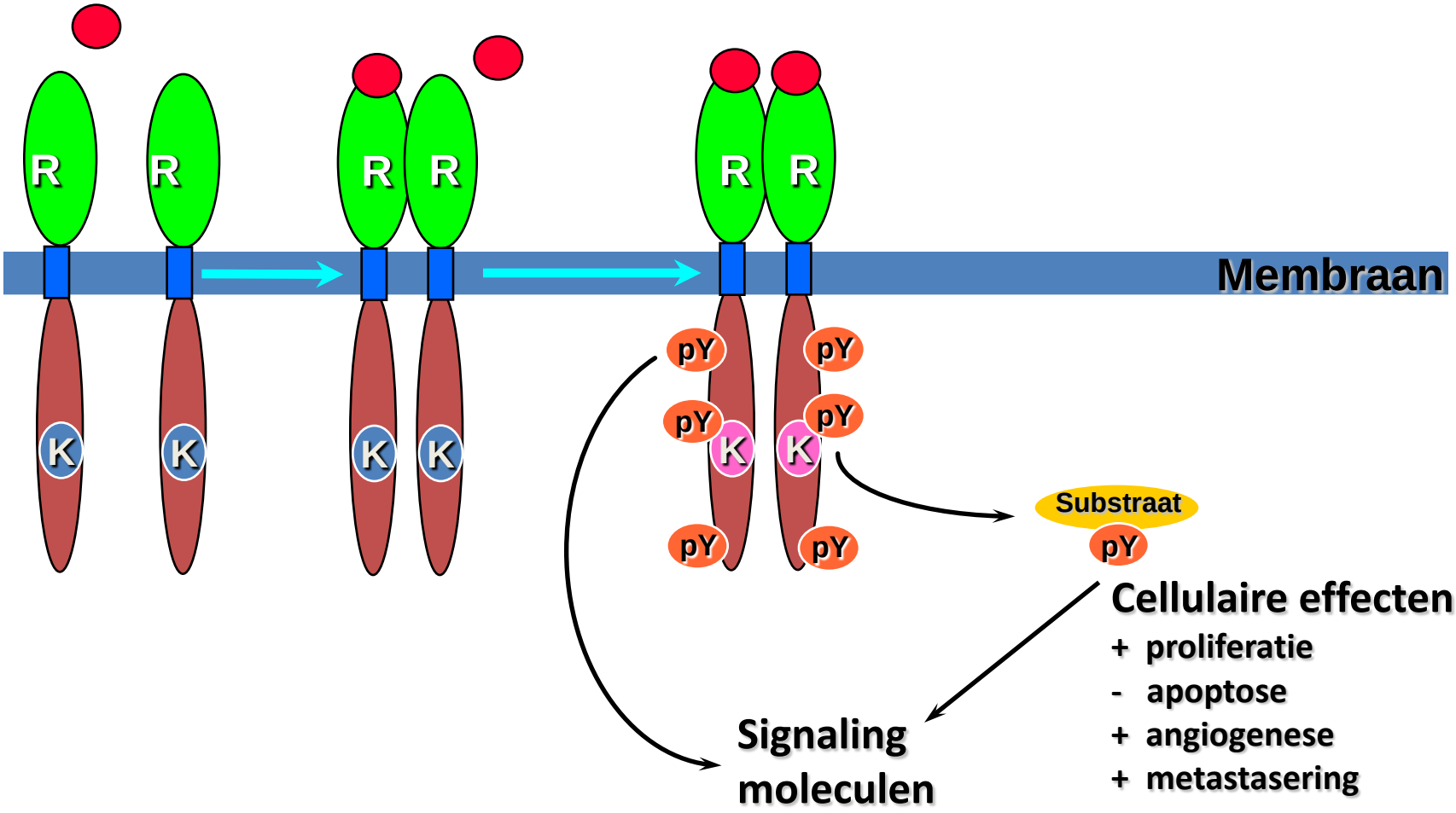
gericht op signaleringsroutes van “hallmarks of cancer”



Hanahan, Weinberg, Cell 2011

Targeted agents: werking

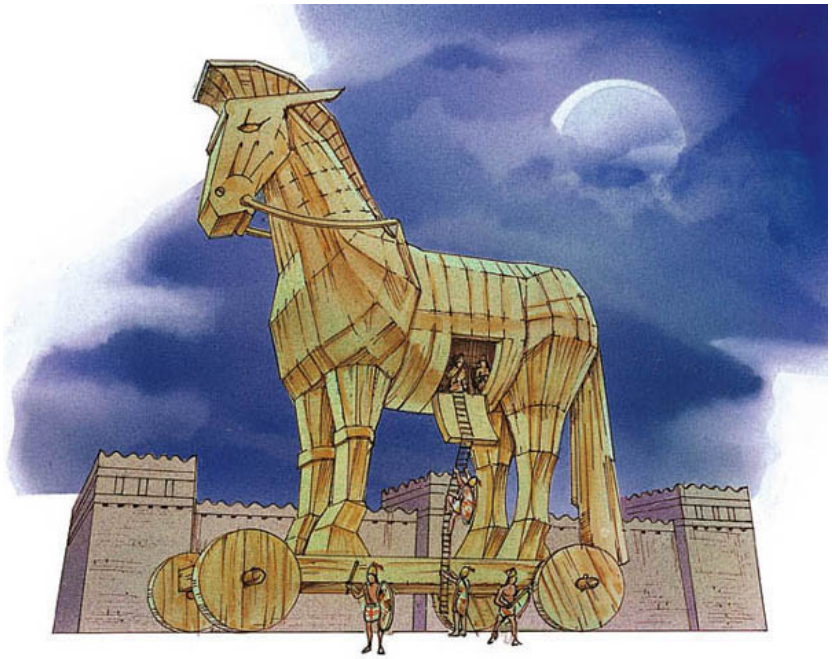
signaleringsroute: via transmembraan signaaltransductie

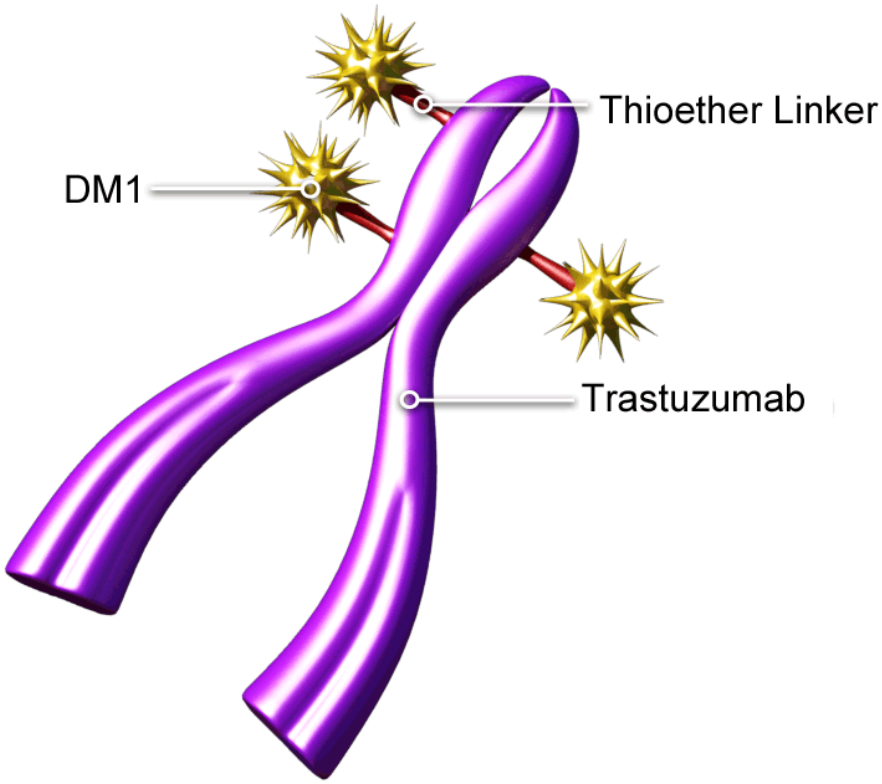


Nieuwe targeted agents

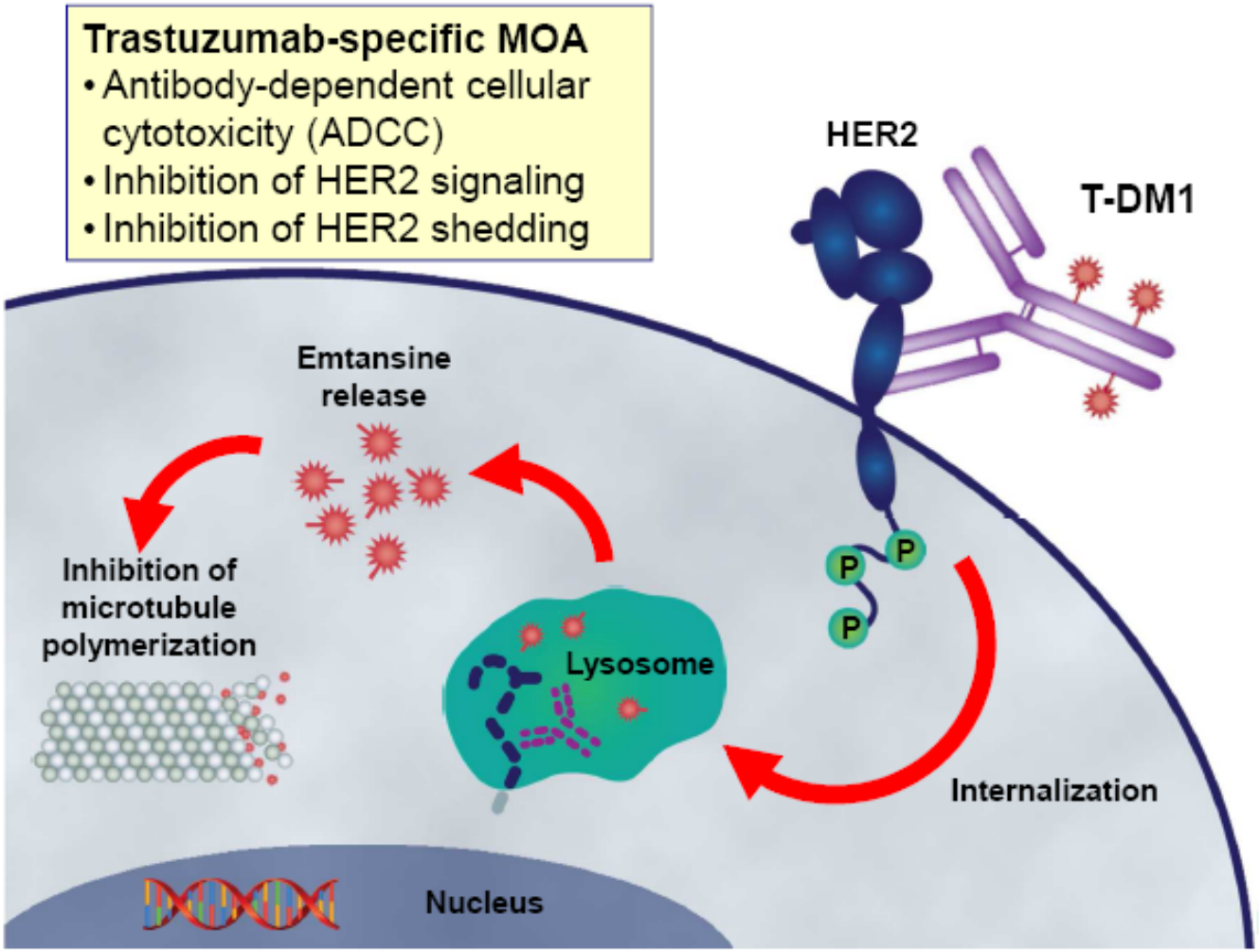
Nieuwe targeted agents

trastuzumab emtansine (T-DM1)





Nieuwe targeted agents:
T-DM1

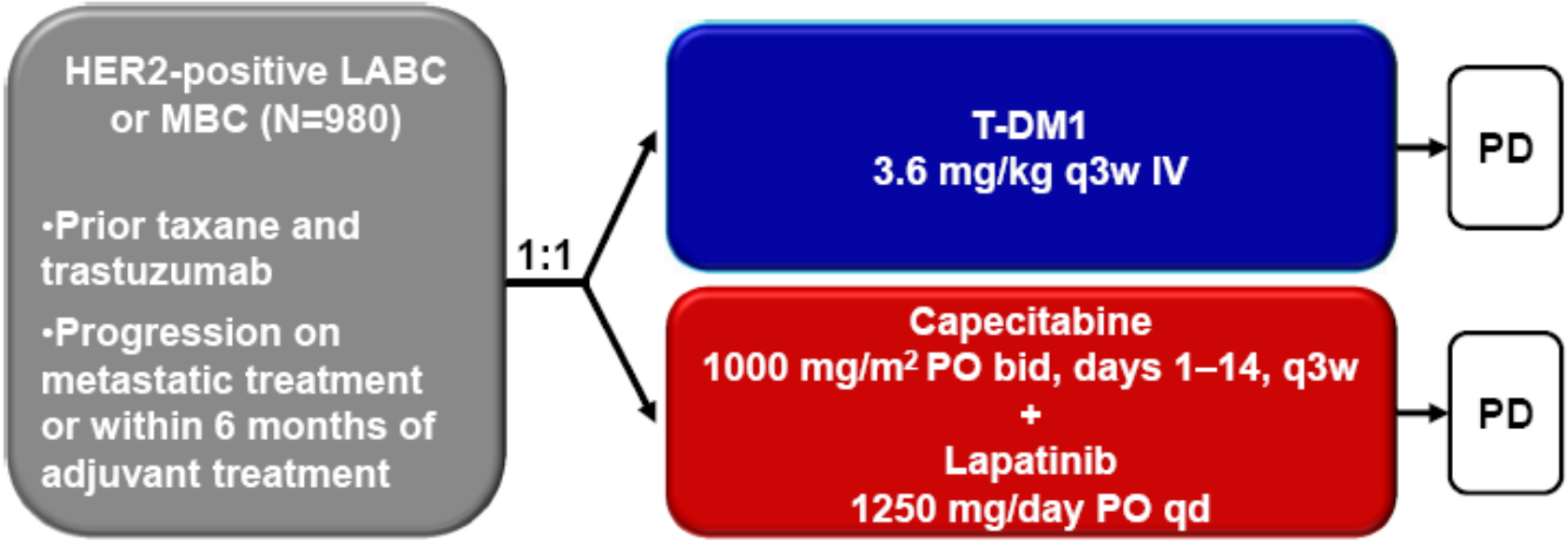


Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

Nieuwe targeted agents

T-DM1 vs lapatinib + capecitabine (EMILIA)

- fase 3, na eerder taxaan + trastuzumab voor HER2+ MBC (n=991)
- primair eindpunt: PFS
- interim OS data

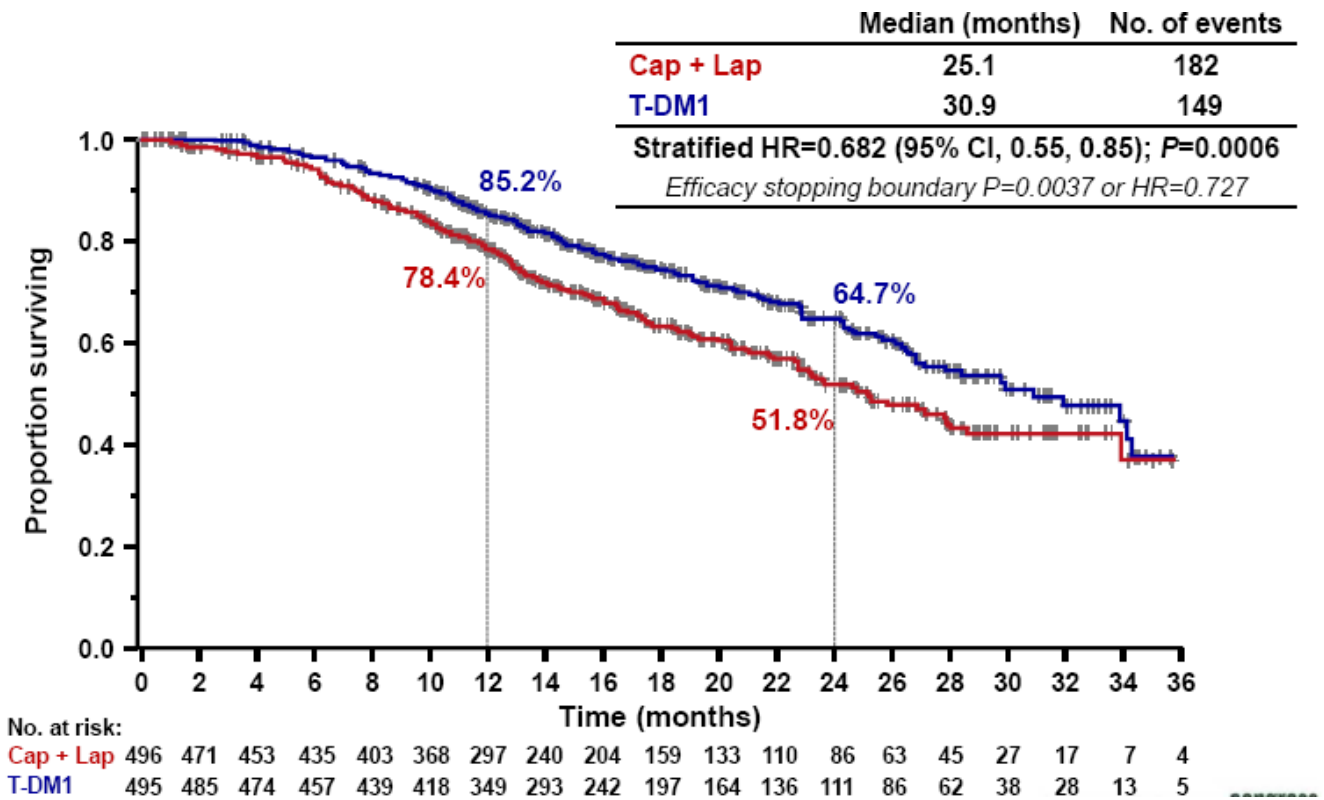


Verma et al, ESMO 2012

Nieuwe targeted agents

EMILIA

- OS: 30,9 vs 25,1 mnd (HR 0.68; p<0.001)
- Response rate 43,6 vs 30,8% (p=0,0002)



Verma et al, ESMO 2012

Nieuwe targeted agents

EMILIA

- **gunstig bijwerkingen profiel T-DM1**

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Lapatinib plus Capecitabine (N=488)		T-DM1 (N=490)	
	Events of Any Grade	Grade 3 or 4 Events	Events of Any Grade	Grade 3 or 4 Events
	number of patients (percent)			
Any event	477 (97.7)	278 (57.0)	470 (95.9)	200 (40.8)
Specific events†				
Diarrhea	389 (79.7)	101 (20.7)	114 (23.3)	8 (1.6)
Palmar–plantar erythrodysesthesia	283 (58.0)	80 (16.4)	6 (1.2)	0
Vomiting	143 (29.3)	22 (4.5)	93 (19.0)	4 (0.8)
Neutropenia	42 (8.6)	21 (4.3)	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	20 (4.1)	42 (8.6)	11 (2.2)
Fatigue	136 (27.9)	17 (3.5)	172 (35.1)	12 (2.4)
Nausea	218 (44.7)	12 (2.5)	192 (39.2)	4 (0.8)
Mucosal inflammation	93 (19.1)	11 (2.3)	33 (6.7)	1 (0.2)
Anemia	39 (8.0)	8 (1.6)	51 (10.4)	13 (2.7)
Elevated ALT	43 (8.8)	7 (1.4)	83 (16.9)	14 (2.9)
Elevated AST	46 (9.4)	4 (0.8)	110 (22.4)	21 (4.3)
Thrombocytopenia	12 (2.5)	1 (0.2)	137 (28.0)	63 (12.9)

Verma et al, NEJM 2012

Nieuwe targeted agents

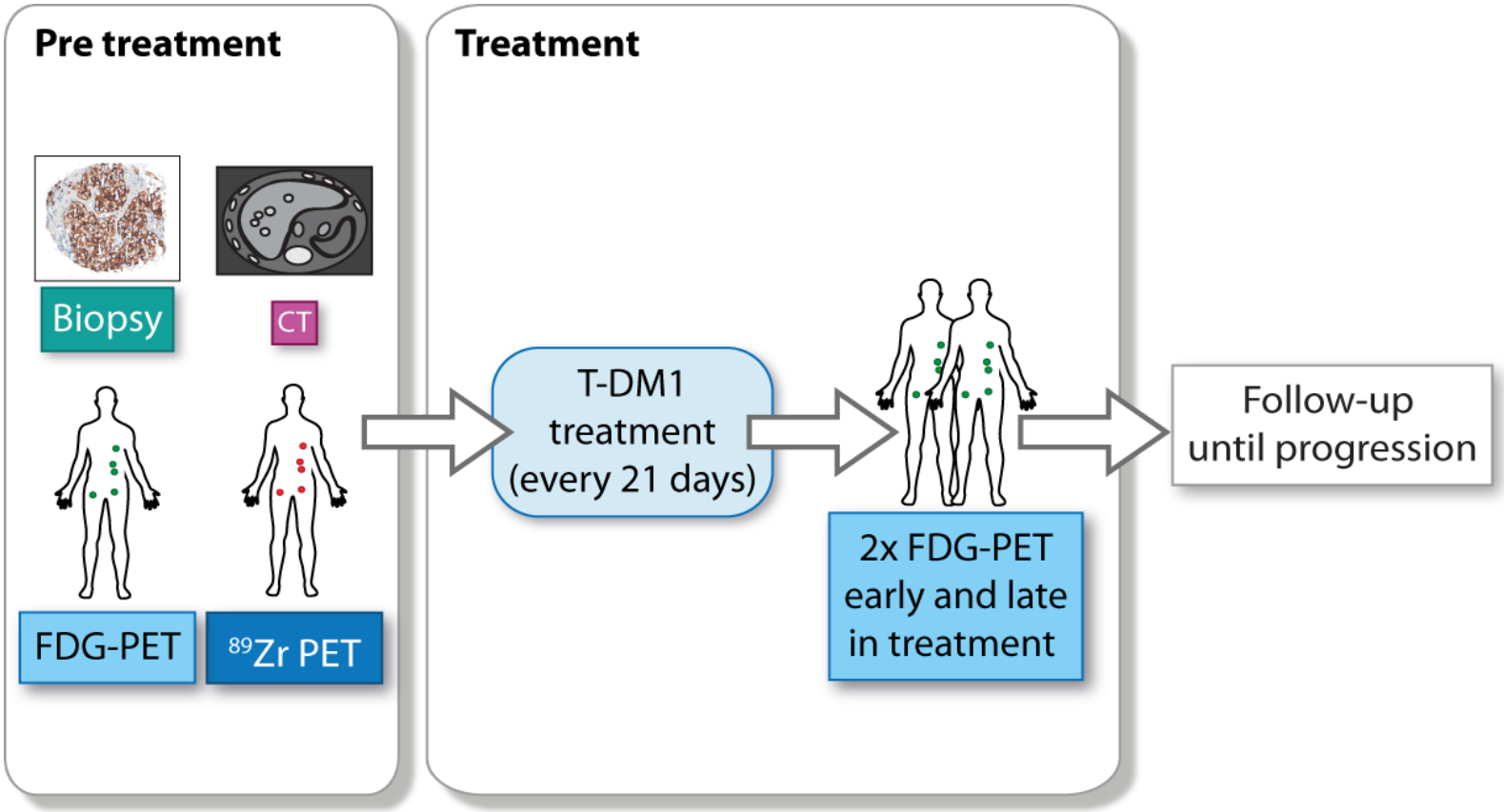
T-DM1 voor HER2 positief mammacarcinoom

- verwachting: standaard 2e lijn MBC
  (na 1e lijn trastuzumab, pertuzumab en taxaan)

- studies 1e lijn MBC (MARIANNE trial), adjuvant
- in NL: studie UMCG met Bordet

Zephir T-DM1 study

T-DM1 response prediction with HER2-PET



NCT01565200

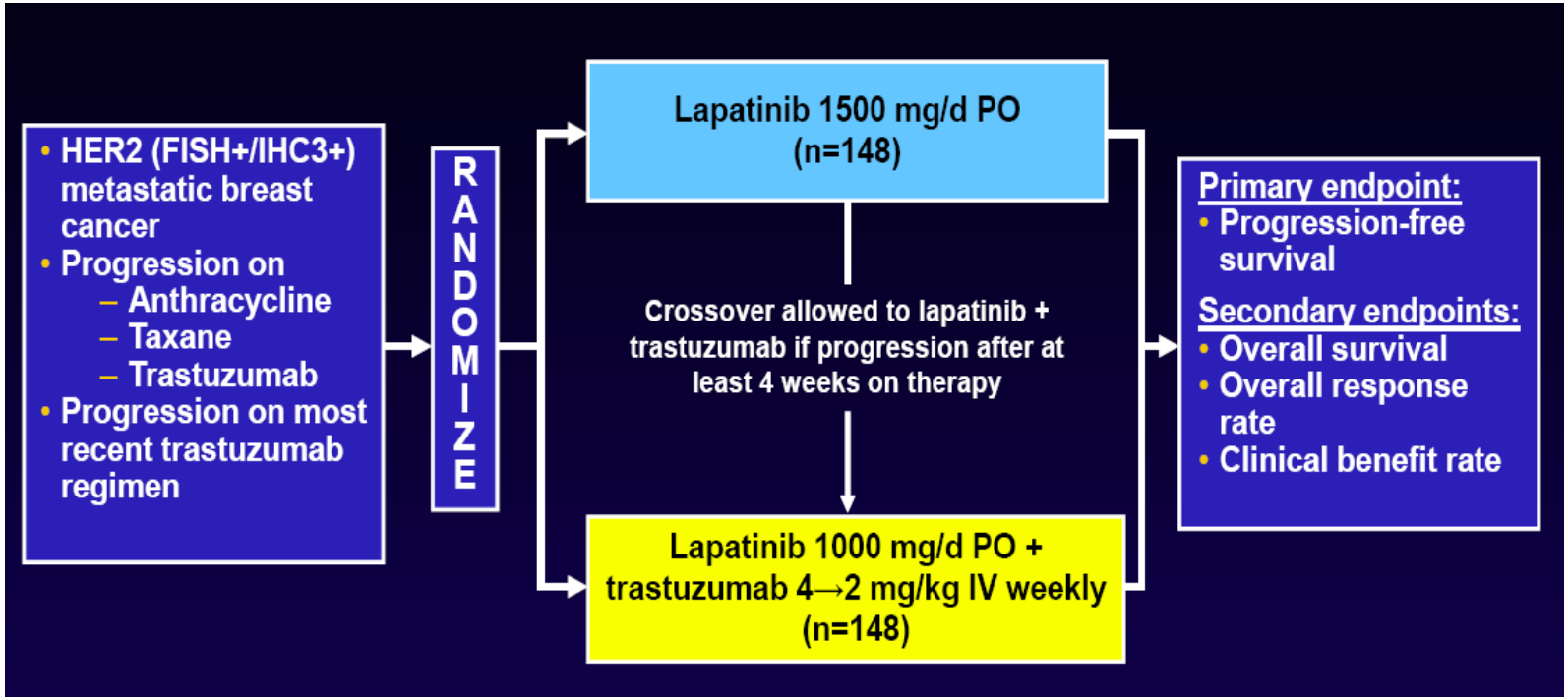
Oude agents, nieuwe toepassingen

Combinaties van agents bij resistentie

combinaties targeted agents: verworven trastuzumab resistentie

Lapatinib +/- trastuzumab (EGF104900)

- fase 3, na 3 eerdere lijnen met trastuzumab voor HER2+ MBC
- primair eindpunt: PFS
- secundair eindpunt: OS

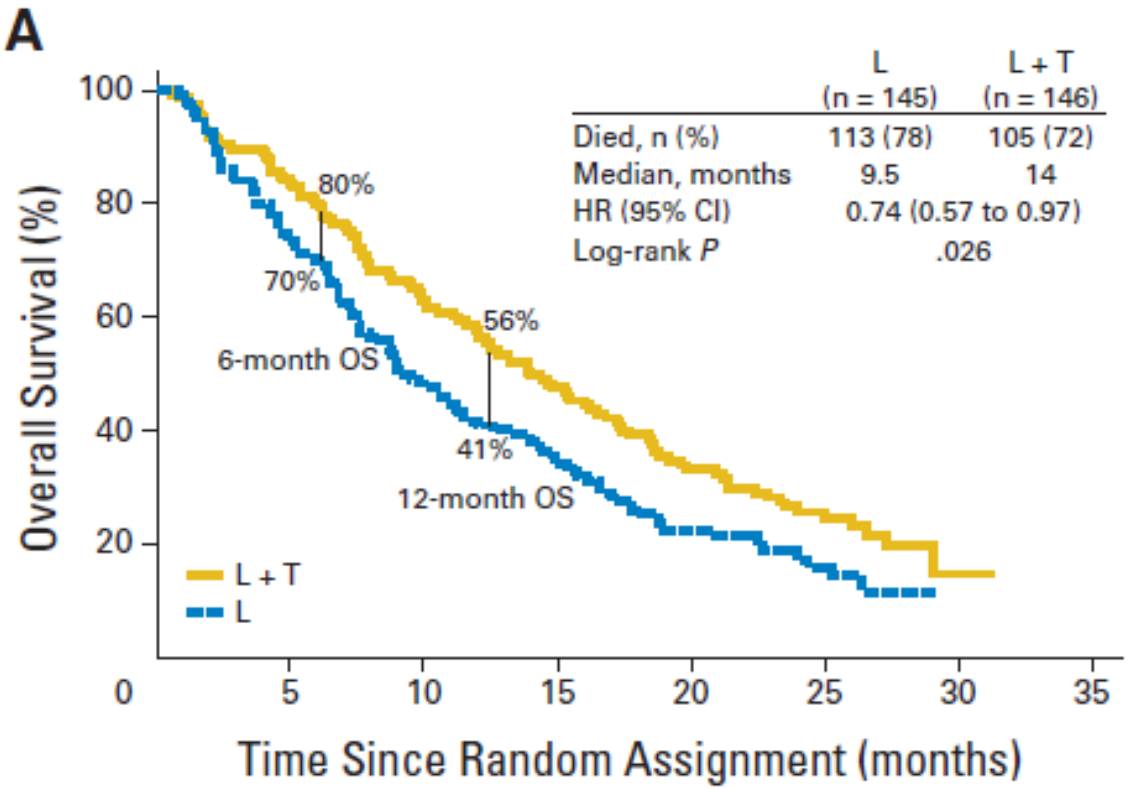


Blackwell et al, JCO 2010

combinaties targeted agents: verworven trastuzumab resistentie

EGF104900

- mediane OS 14 mnd vs 9,5 mnd (lapatinib +/- trastuzumab)
- NB: cross over, voorbehandeling, geen chemotherapie!
- acceptabel bijwerkingen profiel

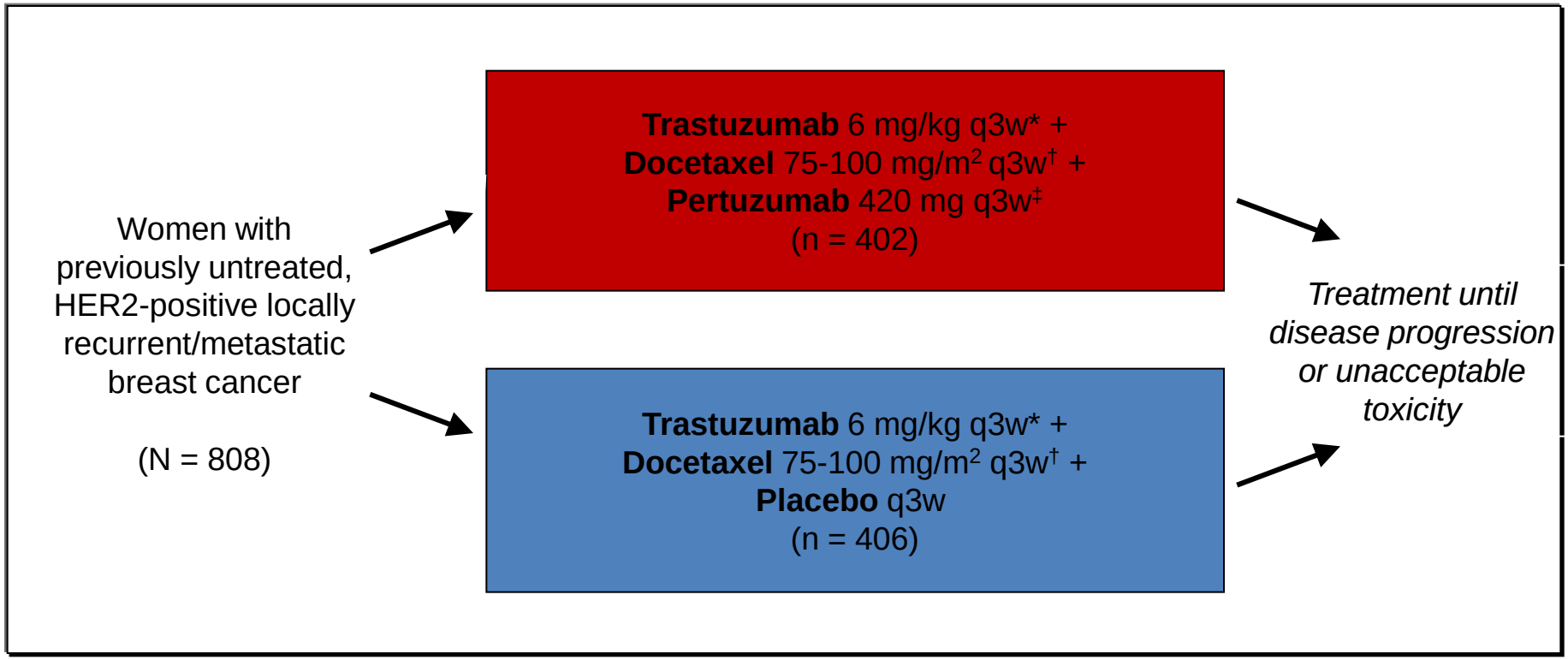


Blackwell et al, JCO 2012

combinaties targeted agents: primaire trastuzumab resistentie

Docetaxel, trastuzumab +/- pertuzumab (CLEOPATRA)

- **fase 3, *1e lijn* HER2+ MBC**
- **eindpunt PFS (interim analyse)**

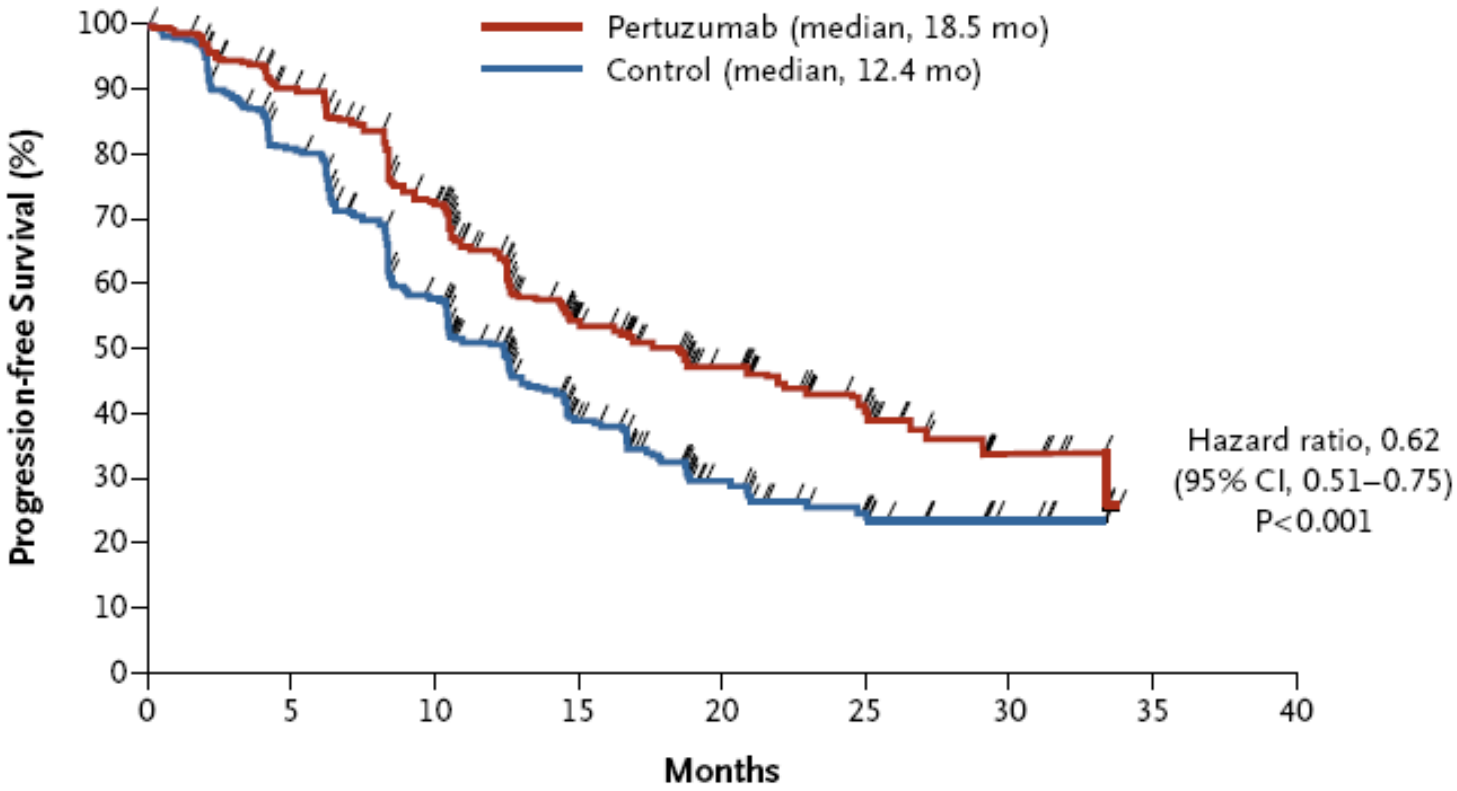


Baselga et al, NEJM 2012

combinaties targeted agents: primaire trastuzumab resistentie

CLEOPATRA

- **mediane PFS 18,5 vs 12,4 mnd (+/- pertuzumab)**
- **geen toename cardiale toxiciteit**

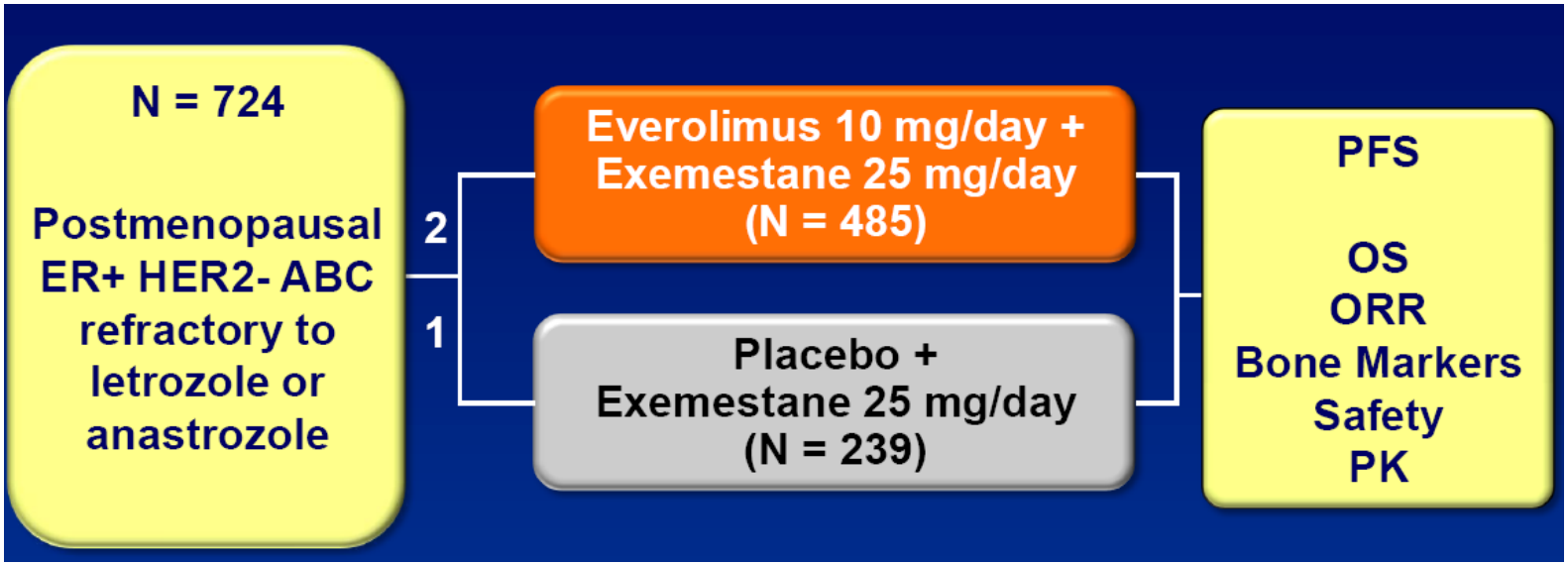


Baselga et al, NEJM 2012

combinaties targeted agents: verworven hormoon resistentie

BOLERO-2 trial

- exemestaan +/- everolimus (fase 3) HER2 negatief MBC
- na progressie op eerdere aromatase remmer (n=724)
- primair eindpunt PFS. Interim analyse (12 month FU).

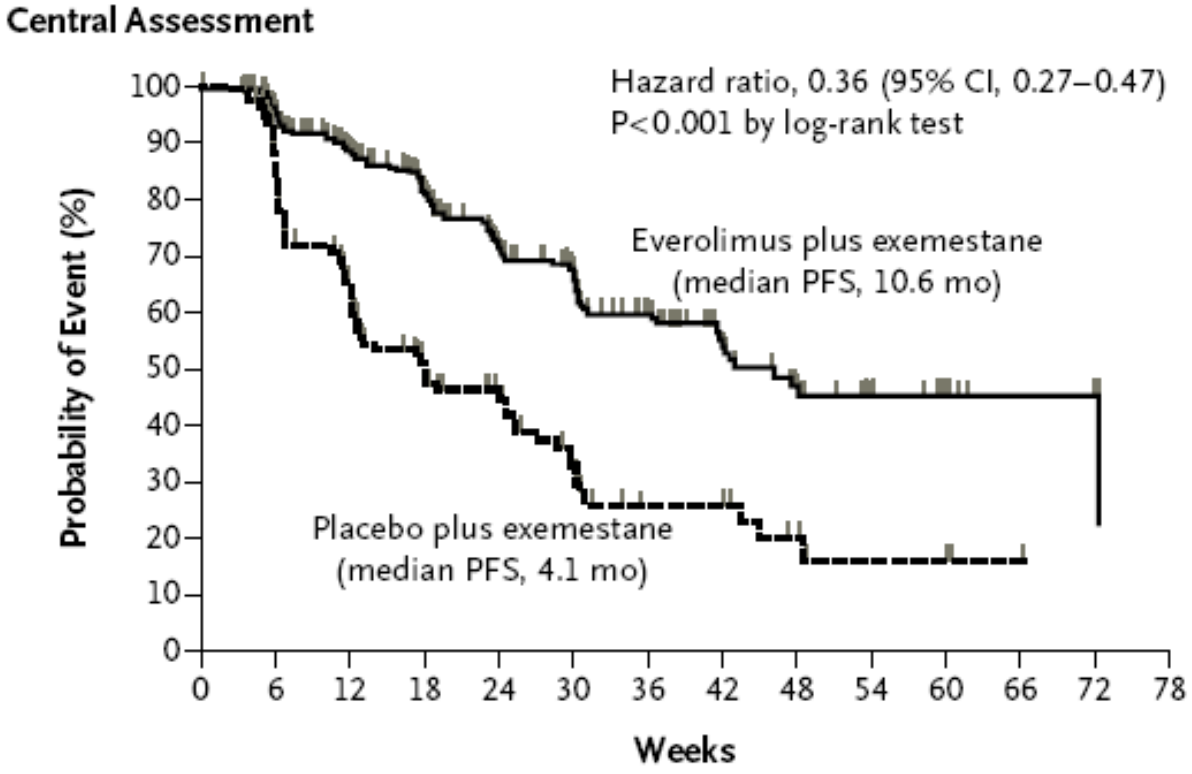


Baselga, NEJM 2012

combinaties targeted agents: verworven hormoon resistentie

BOLERO-2 trial

- **PFS: 10,6 vs 4,1 mnd (+/- everolimus)**
- **clinical benefit 33,4% vs 18% (p<0,001)**

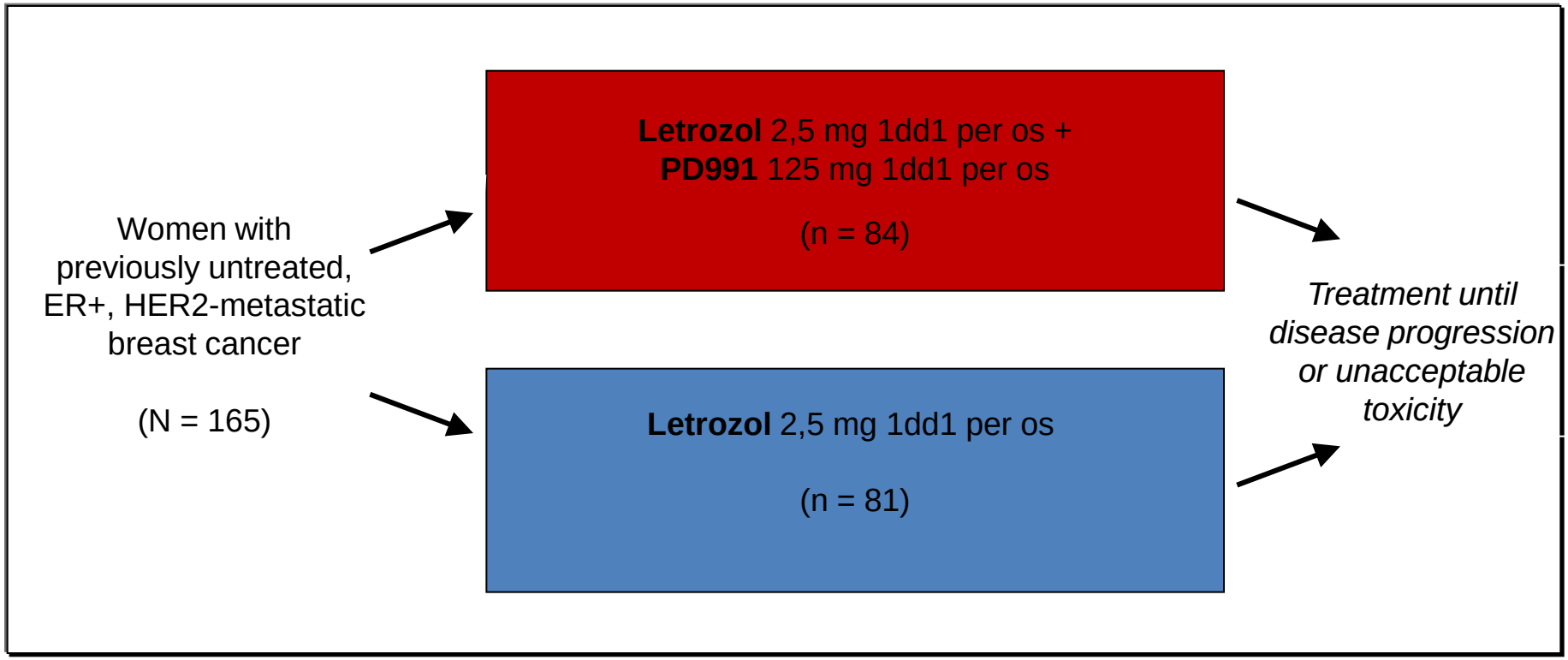


Baselga, NEJM 2012

combinaties targeted agents: primaire hormoon resistentie

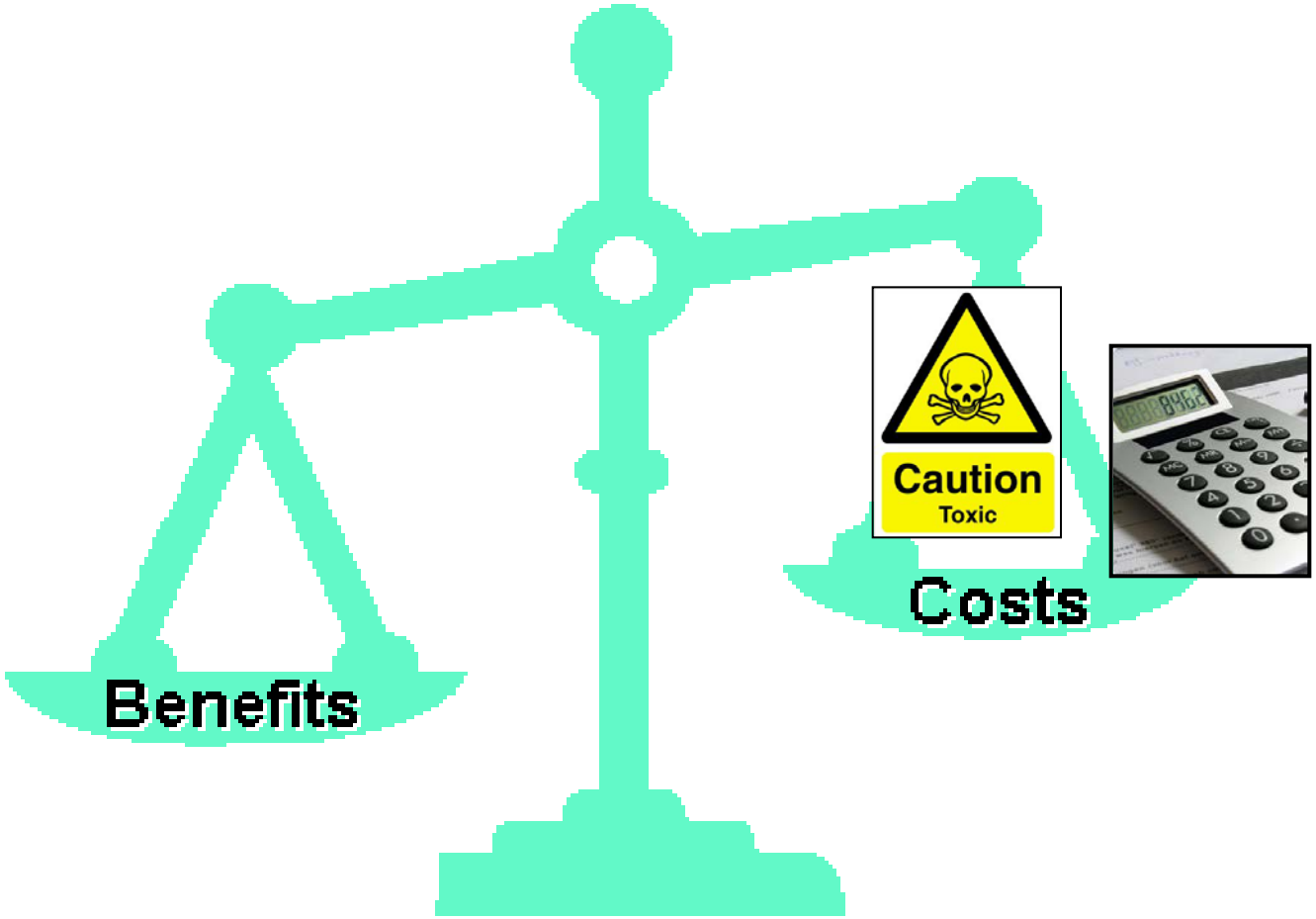
Letrozol +/- CDK remmer PD991(TRIO-18 trial)

- **fase 2, *1e lijn E*R+, HER2- MBC (CDK remming: DNA synthese remming)**
- **eindpunt PFS: 28,1 vs 7,5 mnd (+/- PD991) (HR 0,37; p<0,001)**
- **wel >50% graad 3 of 4 neutropenie en 35% ptn: dosis reductie**



Finn et al, SABCS 2012

Targeted agents
de balans



Toxiciteit

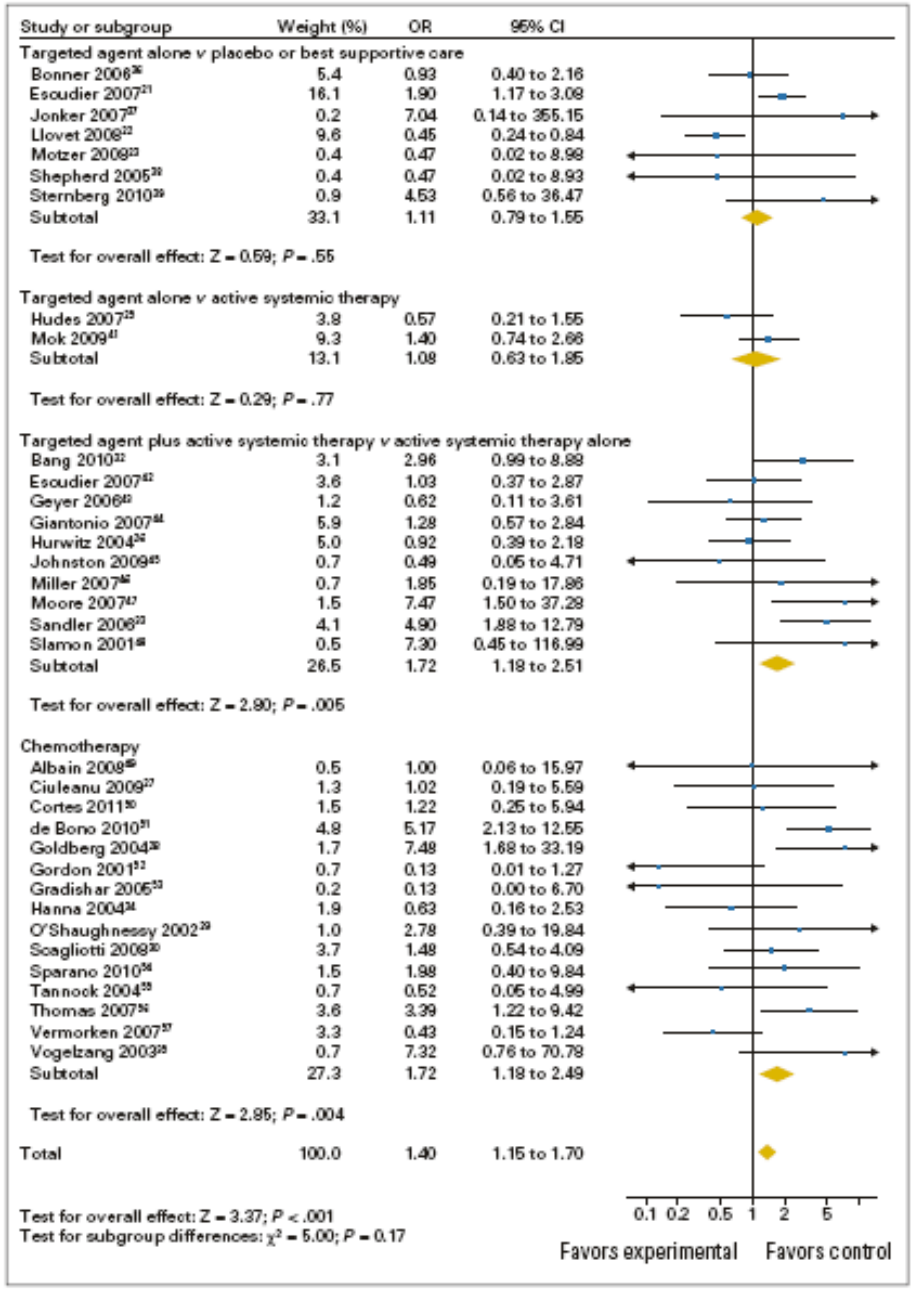
Table 2. Adverse Events, with a Special Focus on Cardiotoxicity, among Patients Included in the Safety Analysis.*

Adverse Event	1 Yr of Trastuzumab (N=1677)	Observation (N=1710)	P Value
	no. (%)		
Patients with at least one grade 3 or 4 event†	132 (7.9)	75 (4.4)	<0.001
Patients with at least one serious adverse event‡	117 (7.0)	81 (4.7)	0.007
Fatal adverse events	6 (0.4)§	3 (0.2)¶	0.34
Treatment withdrawals‖	143 (8.5)	—	
Cardiac events			
Death from cardiac causes**	0	1 (0.06)	1.00
Severe CHF††	9 (0.54)	0	0.002
Symptomatic CHF, including severe CHF‡‡	29 (1.73)	1 (0.06)	<0.001
Decrease in LVEF§§	113 (7.08)	34 (2.21)	<0.001

Piccart, NEJM 2005

- doelgericht is betrekkelijk!

Toxiciteit



Meta analyse RCTs:

Risico toxic death bij nieuwe agents groter dan in controle groep (OR 1.4, P<0,001)

Niraula, JCO 2012

Targeted agents kosten

HER2+ MBC

- **1e lijn: taxaan met trastuzumab en pertuzumab**
- **2e lijn T-DM1**

Combinatie van trastuzumab en pertuzumab (kosten in V.S.)

- **18 maanden gemiddeld tot progressie: $187,000,-**

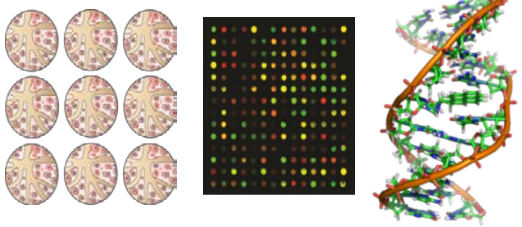
Discussie binnen beroepsgroep van belang

Dure oncologische zorg

Medische Oncologie nummer 4 ▪ september 2012

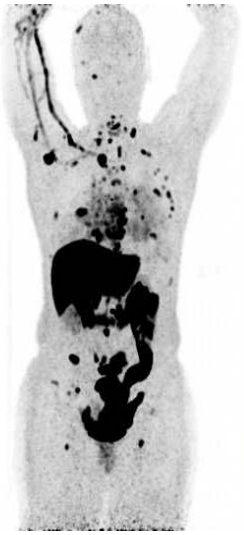
Selectie van de juiste therapie voor de juiste patiënt

‘Omics’



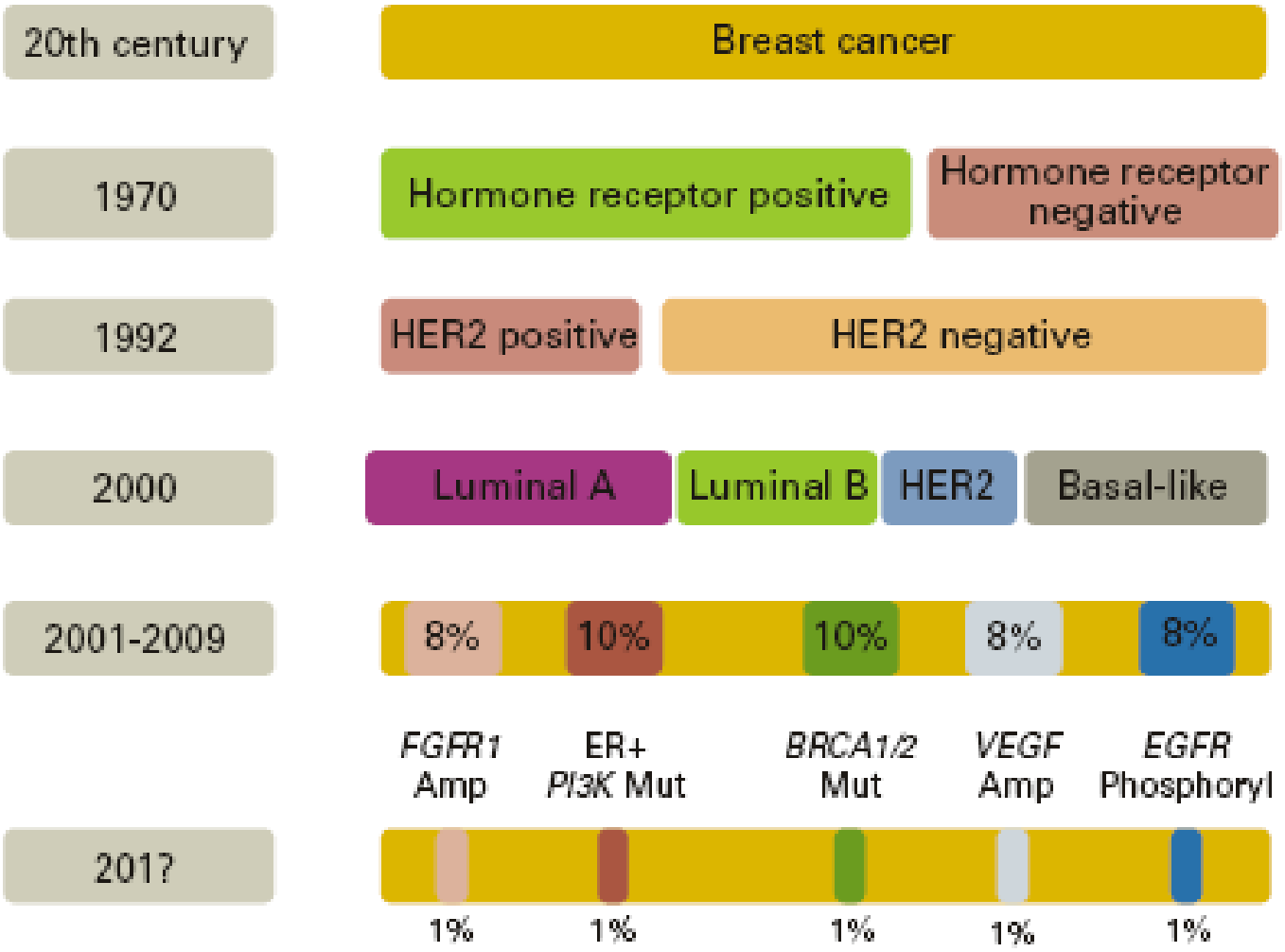
TMA RNA DNA

Molecular imaging



optimale kosten-baten balans

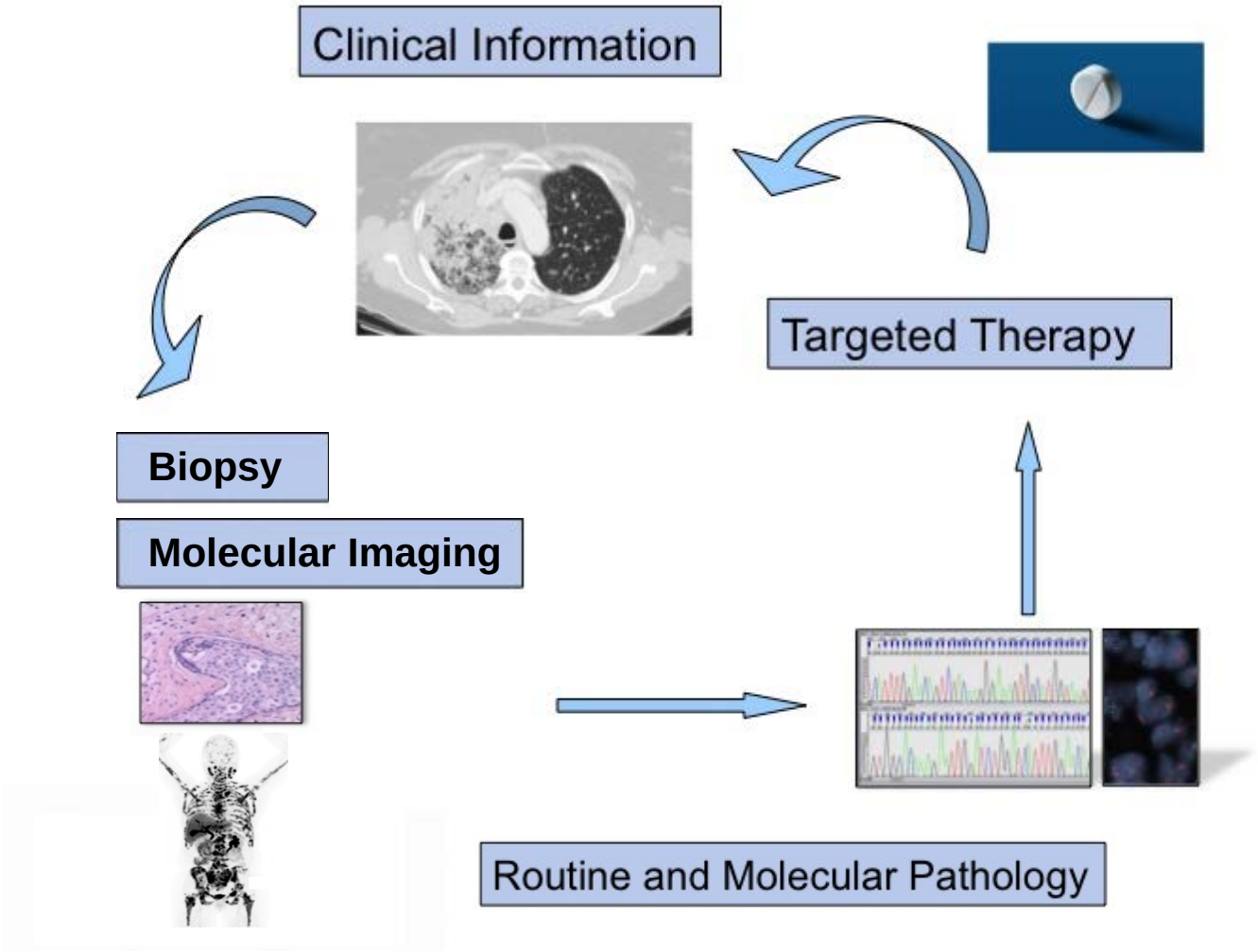
Selectie patiënt: toenemend complex



Harbeck, JCO 2012

Optimaliseren patiëntenselectie

achterhalen welke targets de tumor heeft: steeds meer werk



Conclusie: mammacarcinoom en targeted therapy

Schier toveren…
met nieuwe middelen
en nieuwe toepassingen

Maar: niet alles voor iedereen!

Selectie cruciaal
Zo beperken we de schade