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## State of the Art

# BREAST CANCER

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## Disclosures

- honoraria: Amgen, AstraZeneca, Cancérodigest, Clinigen, Curio Science, Egis, Eli Lilly, Genomic Health, Gilead, high5md, Novartis, Oncompass Medicine, Pfizer, Pierre Fabre, Roche, Sandoz, TLC Biopharmaceuticals
- travel support: Amgen, AstraZeneca, Egis, Gilead, Novartis, Pfizer, Roche
- clinical research: Amgen, AstraZeneca, Eli Lilly, Novartis, Pfizer, Roche, Samsung
- stock: AstraZeneca, Eli Lilly, Pfizer

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# BREAST CANCER - epidemiology

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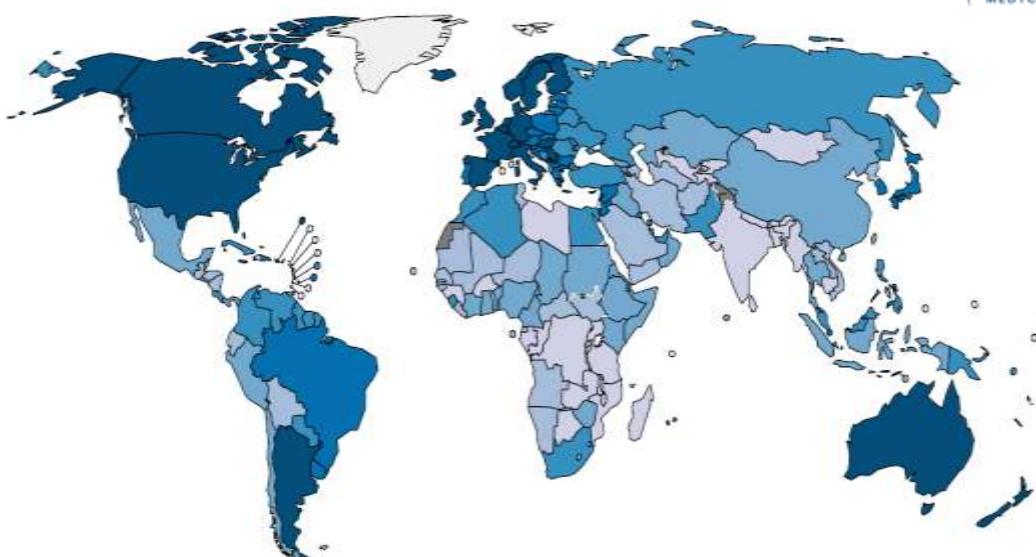
## WORLD 2020

- 2,26 million new cases
  - most frequent female malignancy
- 685.000 deaths
  - one of the most frequent causes of cancer death in females
- >7,5 million of prevalent cases
  - most frequent cause of female cancer prevalence
- 1% of breast cancer - men

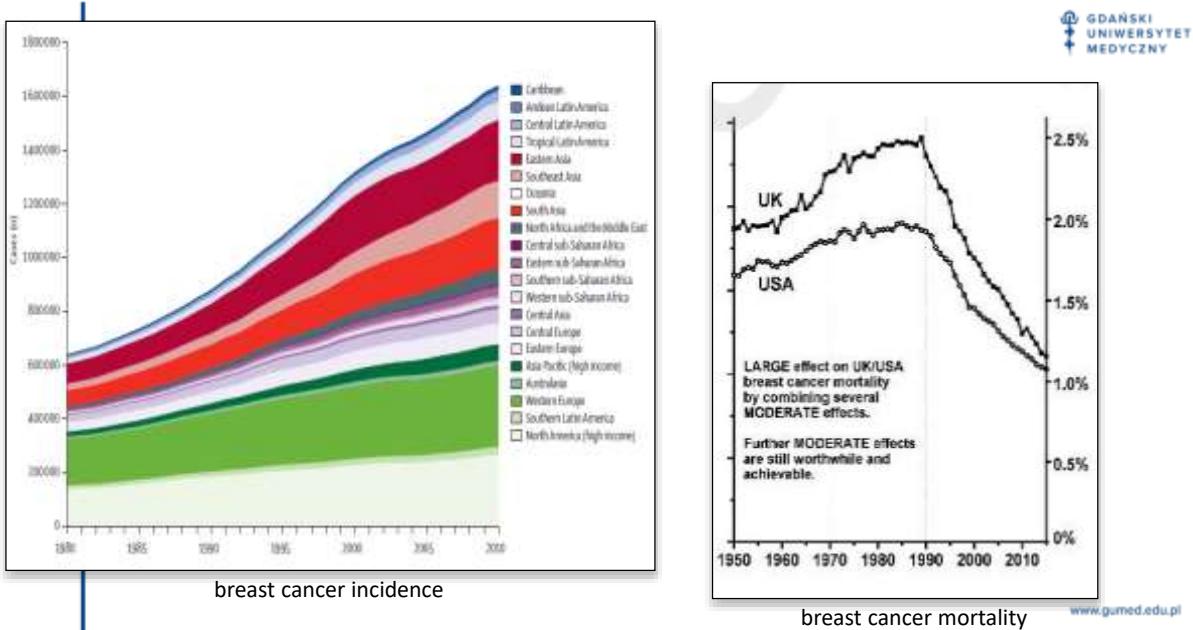
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GLOBOCAN 2020

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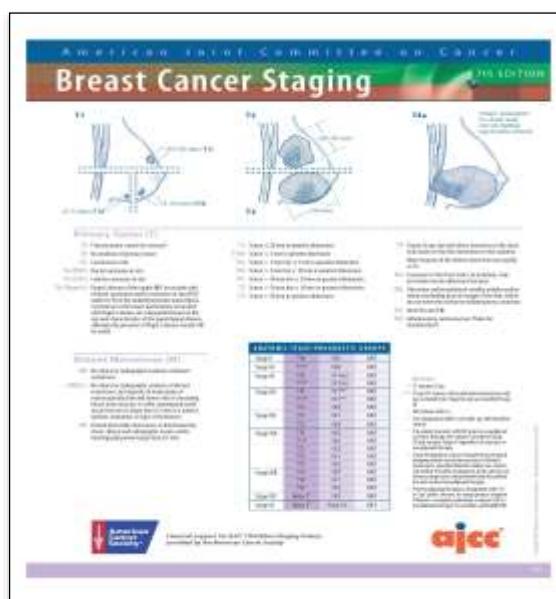


GLOBOCAN 2020



Peto, SABCS 2017

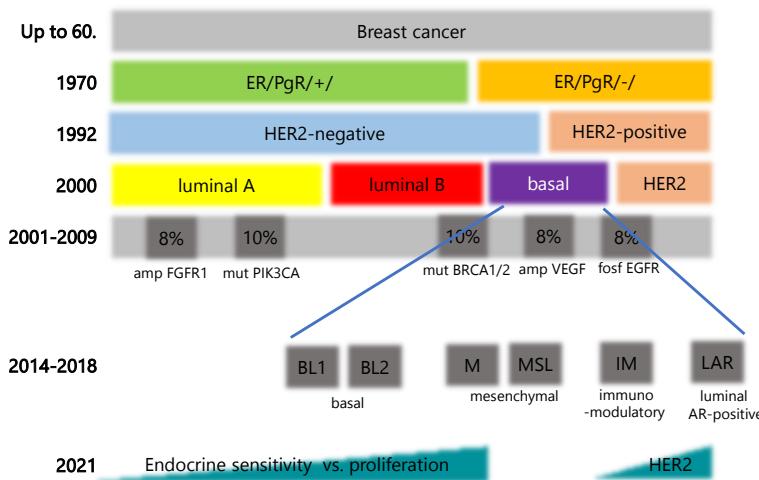
## Breast cancer staging



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# Heterogeneity of Breast Cancer

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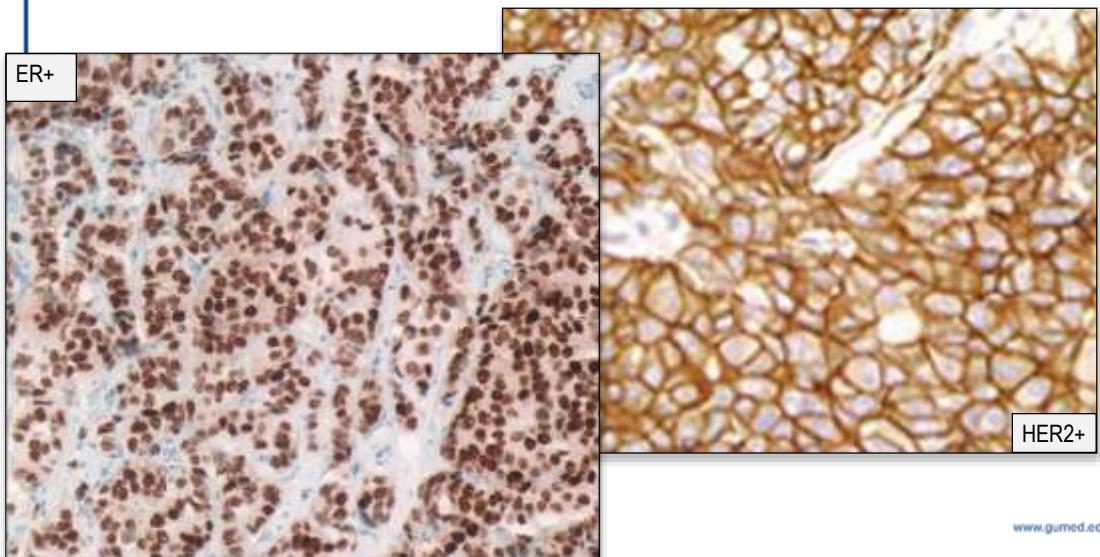


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adapted from Harbeck et al. and Jarzab

## How to define a phenotype in practice?

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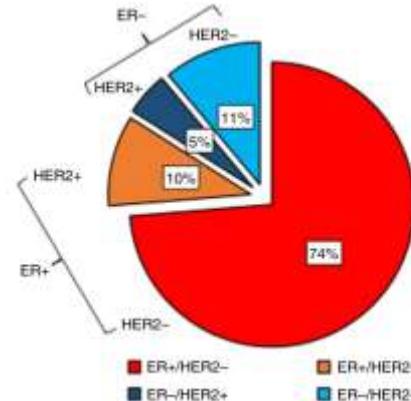
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## Breast cancer phenotypes

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	ER+	ER-
HER2-	luminal HER2-	triple negative
HER2+	HER2+	

„new” biomarkers:  
 - *BRCA* mutation  
 - *PIK3CA* mutation  
 - PD-L1 expression  
 - genomic grade/proliferation



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Mesa-Eguíagaray, Br J Cancer. 2020

## Systemic treatment of breast cancer

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- chemotherapy
- endocrine-based therapy
- targeted anti-HER2 therapy



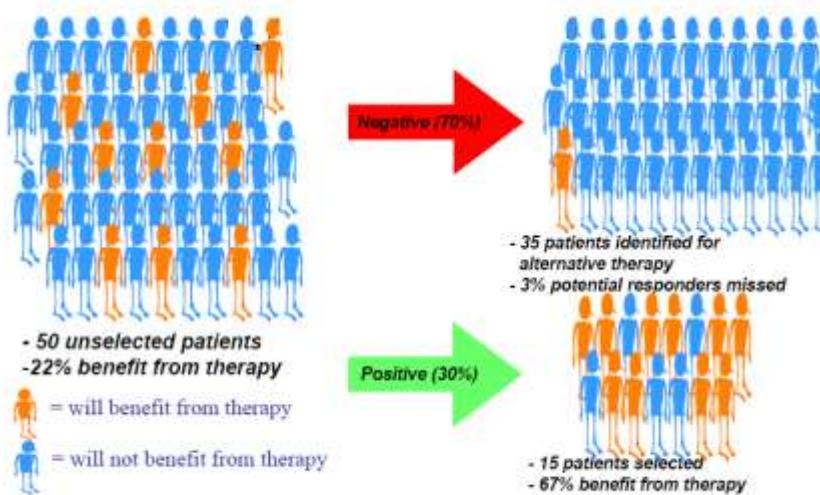
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## Chemotherapy

- narrow therapeutic window
- drug development by screening molecules,  
rarely „designed”
- no predictive factors (active in all phenotypes)

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## Targeted therapy – patient selection



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# Endocrine therapy of breast cancer = estrogen depletion

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- estrogen depletion
  - estrogen source ablation
    - castration (surgery or RT)
  - inhibition of gonadotropin action
    - LHRH agonists
  - inhibition of peripheral estrogen synthesis
    - aromatase inhibitors
- estrogen receptor blocking
  - tamoxifen and other SERMs
  - fulvestrant and other SERDs

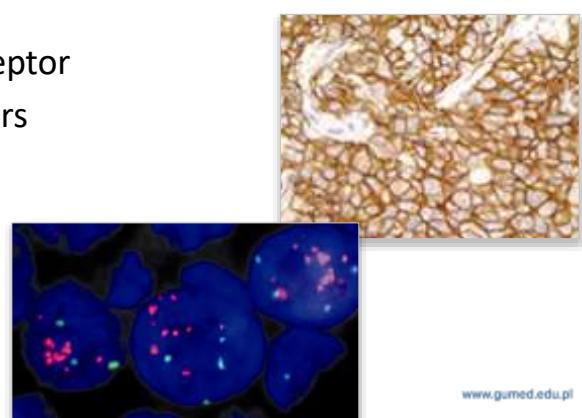
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## Anti-HER2 therapy

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HER-2 (Human Epidermal growth factor Receptor-2)

- gene amplification and/or receptor overexpression – 15-20% tumors
- Her-2 (+) – worse prognosis,  
↓ DFS and OS

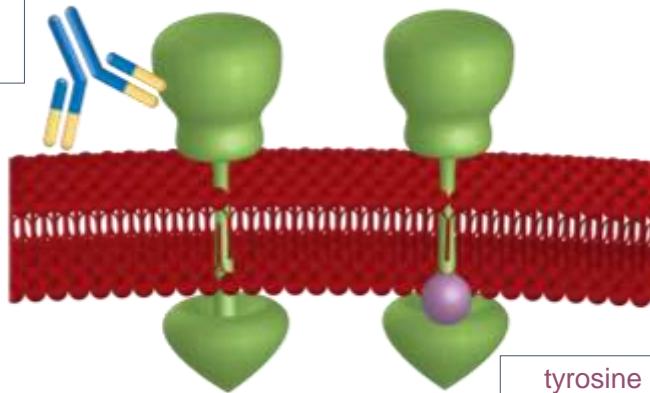


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## Anti-HER2 drugs

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monoclonal  
antibody-  
based

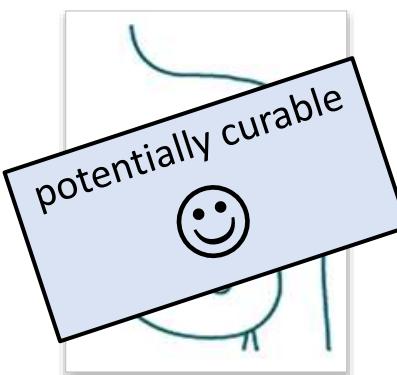


tyrosine  
kinase  
inhibitors

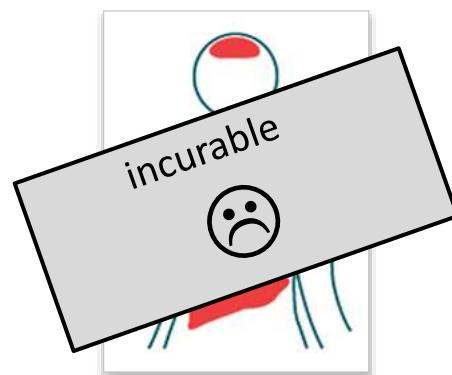
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## Treatment strategy

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locoregional disease



distant disease

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## Early breast cancer

### Treatment tailoring

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- tumor biology
  - Phenotype/genetic
  - BRCA WT/mut ?
  - Other mutations ?
  - PDL-1 ?
- risk of recurrence
  - High risk- intensification
  - Low risk- deescalation
- patients' characteristic
  - dd CT: premenopausal pts; HR/-/
- tumor response
  - objective response (clinical/MR/MMG)
  - metabolic response (PET)
  - pathologic response/proliferation dynamic

- Concomitant diseases;
- Age (biologic) – risk of side effects which may impact ADL etc.
- Patients preferences.
- Other (social, financial etc), e.g. frequency of visits
- .....

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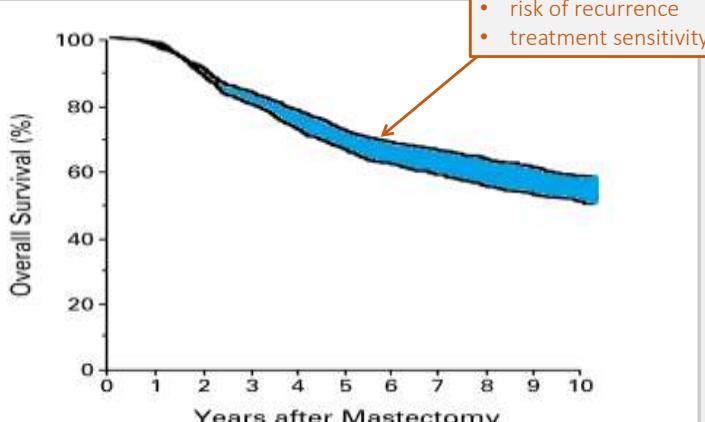
courtesy of Aleksandra Łacko

## Who benefits (neo)adjuvant treatment?



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## Who benefits (neo)adjuvant treatment?



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risk of recurrence



prognostic factors

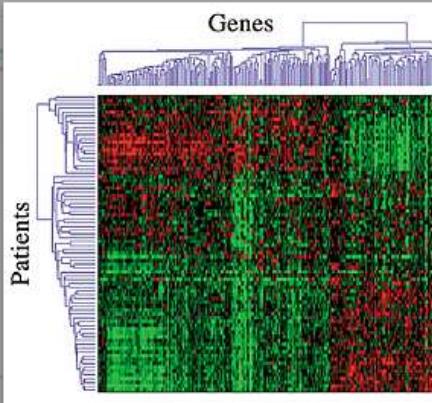
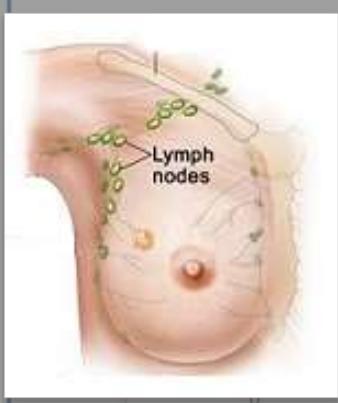
treatment sensitivity



predictive factors

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## What defines the risk of recurrence??



## Perioperative treatment strategy

preoperative/neoadjuvant/induction ChT



postoperative/adjuvant ChT



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## Why preop systemic therapy???



PRIMARY SYSTEMIC THERAPY  
= treatment of choice

LOCALLY ADVANCED  
OR INFLAMMATORY BC

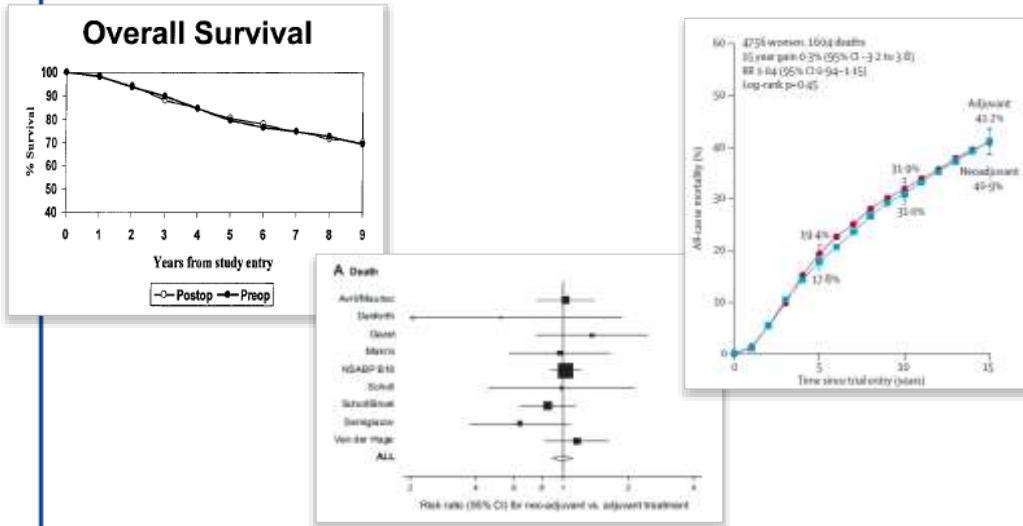


PRIMARY SYSTEMIC THERAPY  
= option

OPERABLE BC

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# Efficacy = adjuvant ChT



Wolmark, JNCI Monogr 2001, Mauri, JNCI 2005, EBCTCG, Lancet Oncol 2018

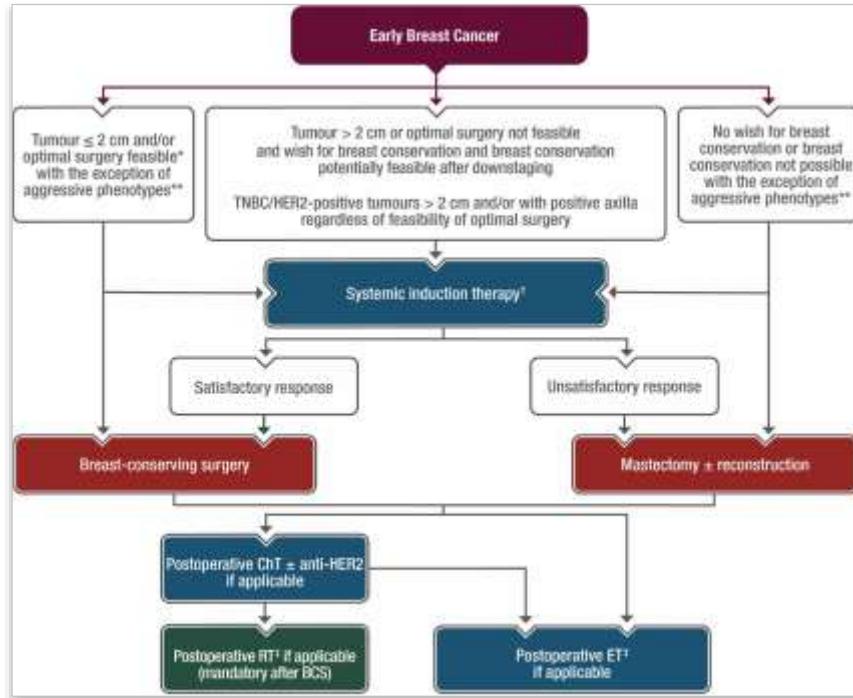
## PROS

- earlier treatment of micrometastatic disease
- in vivo* treatment sensitivity assessment/prognostic information
- translational studies

- increased operability of inoperable tumors
- decreased extent

selection for post-neoadjuvant therapies

- delay in local treatment (risk of tumor progression)
- loss of prognostic information from full pathological assessment of untreated tumor  
→ risk of under/overtreatment



## St Gallen 2009 guidelines

Endocrine therapy	Any ER staining (>1%)
Anti-HER2 therapy	HER2+ (+/++)
Chemotherapy	<ul style="list-style-type: none"> <li>In HER2+ disease (with anti-HER2)</li> <li>In triple-negative disease (with chemotherapy)</li> <li>In ER+, HER2+ disease (with chemotherapy)</li> </ul>

**each treatment decided separately**

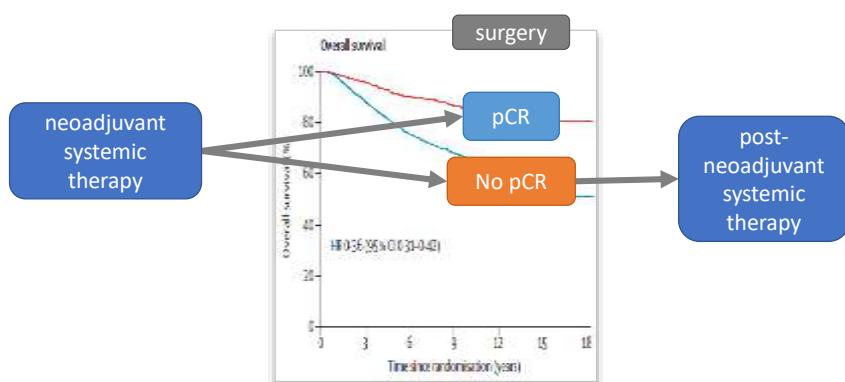
# ChT-ET in ER+HER2- disease

Clinopathologic features	Relative indications for chemoendocrine therapy	Factors not useful for decision	Relative indications for endocrine therapy alone
ER and PgR	Lower ER and PgR		Higher ER and PgR
Histological grade	Grade 3	Grade 2	Grade 1
Proliferation	High	Intermediate	Low
Nodes	Node positive ≥4	Node positive 1-3	Negative nodes
PVI	Presence of extensive PVI		Absence of extensive PVI
pT size	>5 cm	2.1 – 5 cm	≤2 cm
Patient's preference	Use all available treatments		Avoid chemotherapy related side-effects
Multigene assays gene signature	High score	Intermediate score	Low score

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Goldhirsch, Ann Oncol 2009

## Concept of post-neoadjuvant therapy



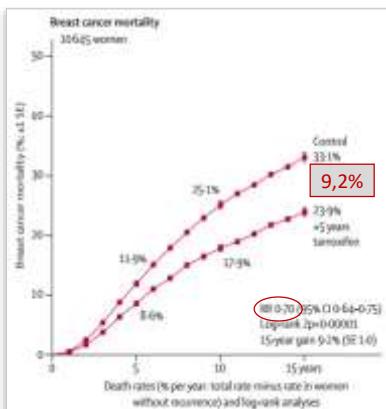
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# Luminal BC

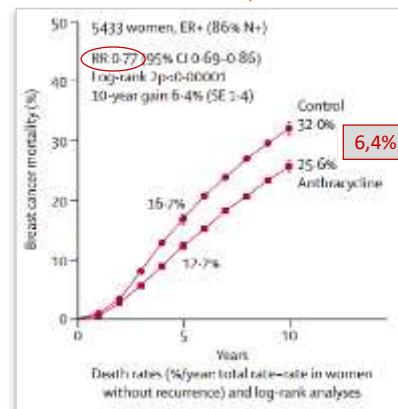
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## Why endocrine therapy???

TAM 5 lat



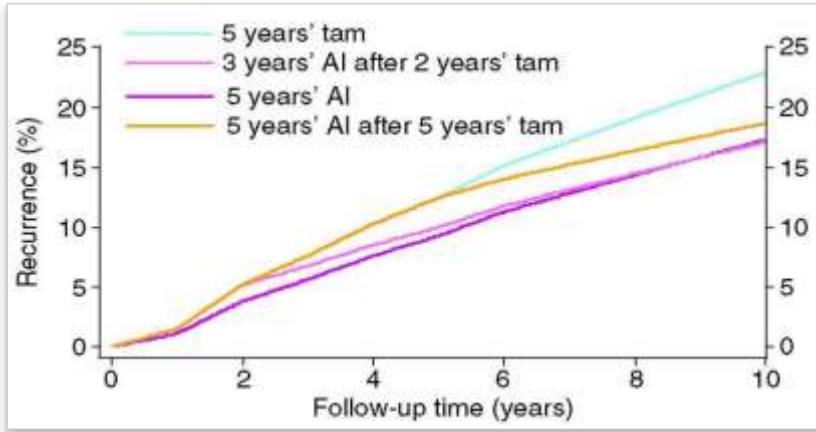
ChT - anthracyclines


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EBCTCG, Lancet 2011, EBCTCG, Lancet 2012

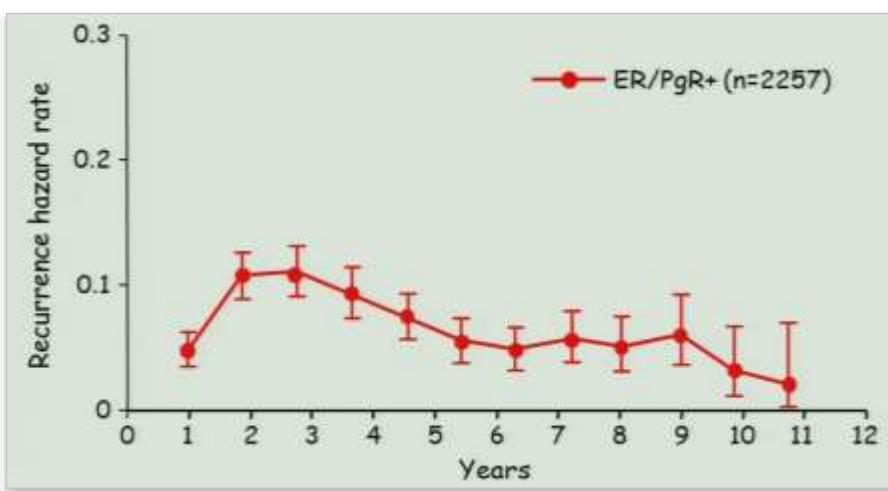
## Endocrine therapy - postmenopausal

- AI vs TAM



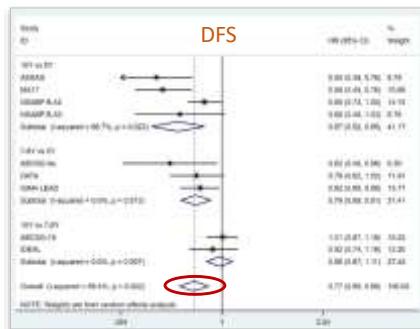
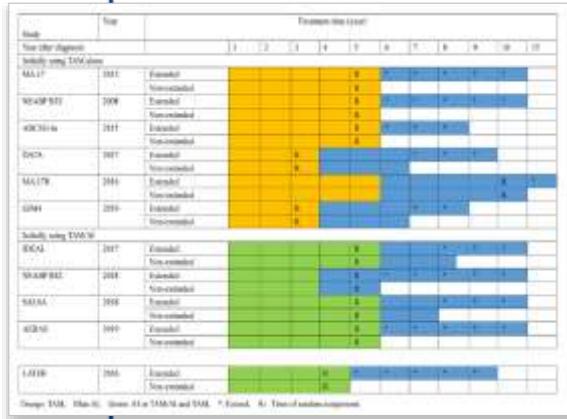
Cuzick, BJC 2006

## Endocrine therapy – how long?

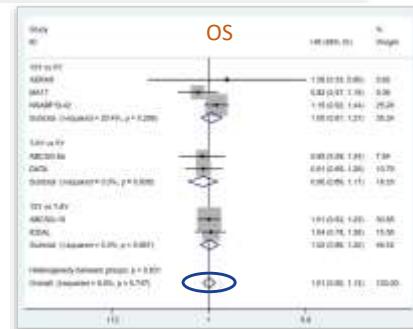


Saphner, JCO 1996

## Endocrine therapy – how long?



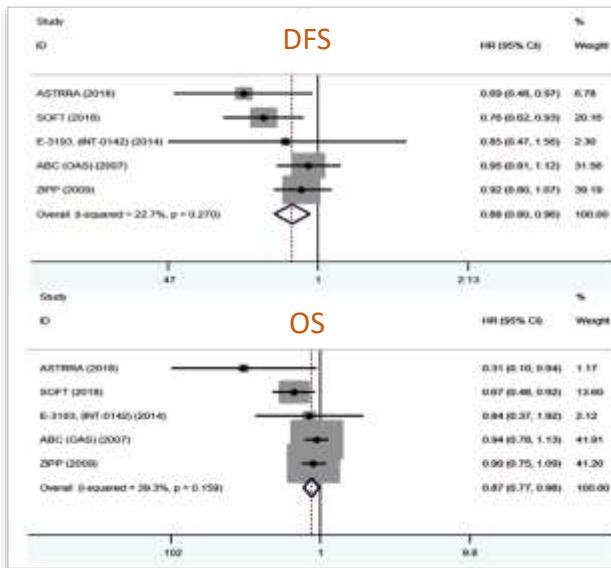
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Zhao, Crit Rev Oncol Hematol 2020; Chen, Breast Cancer 2021

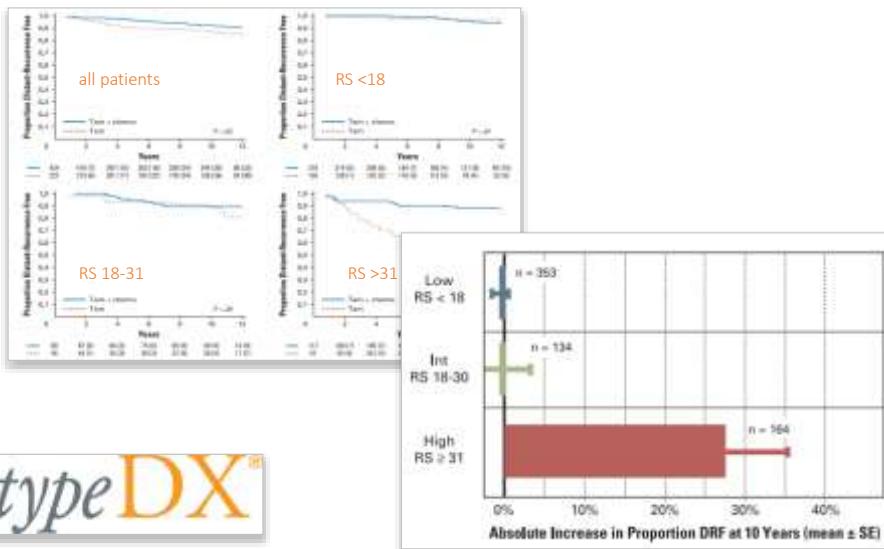
## OFS in premenopausal women



www.gumed.edu.pl

Azim, Curr Probl Cancer 2020

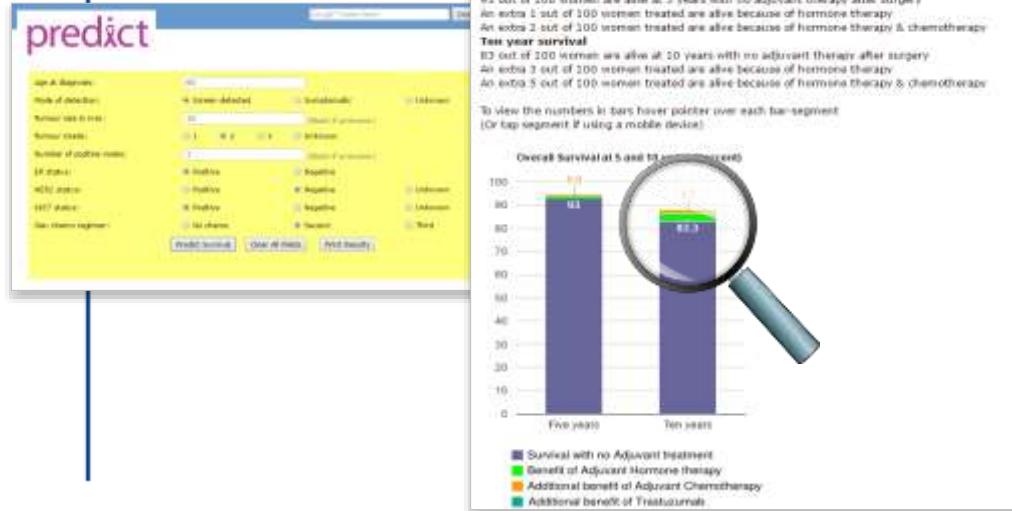
## Who benefits from ChT?



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Paik, JCO 2006

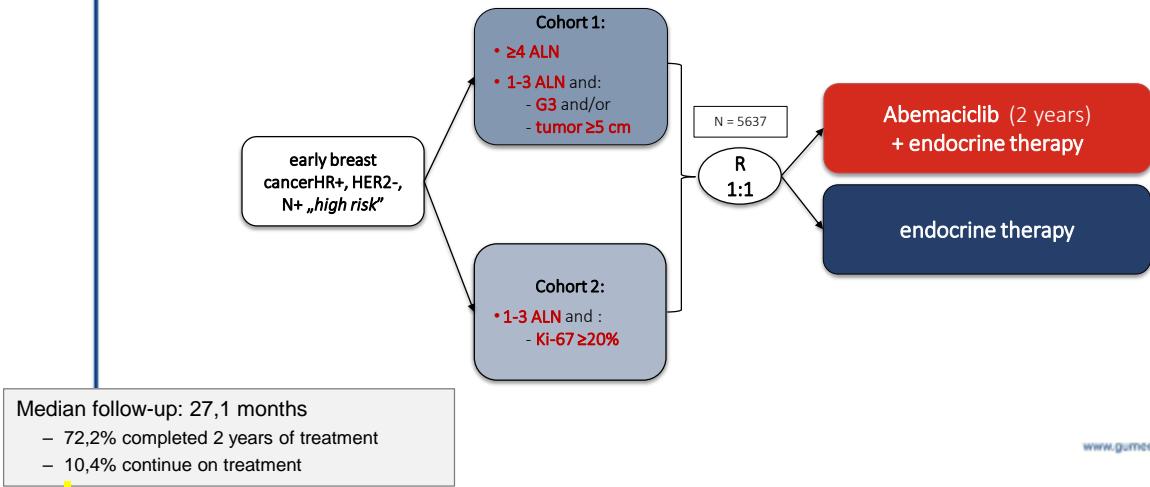
## How much can be gained?



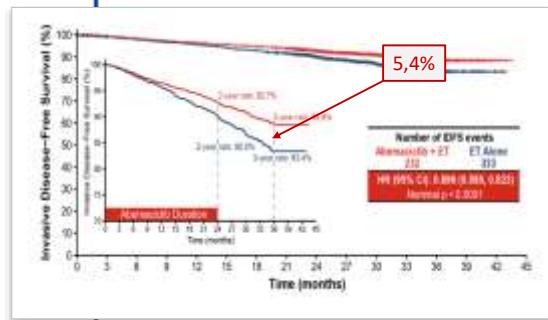
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## What if the risk is still high?

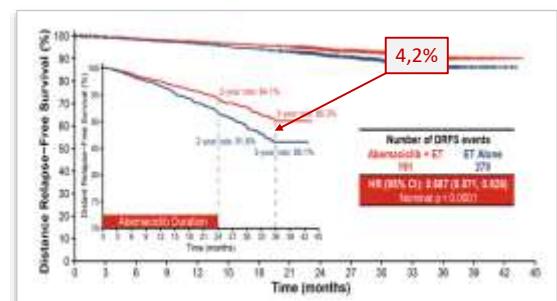
### monarchE



### monarchE



iDFS



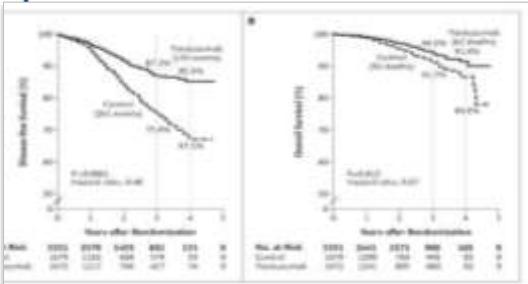
dRFS

# HER2+ BC

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## Trastuzumab in EBC

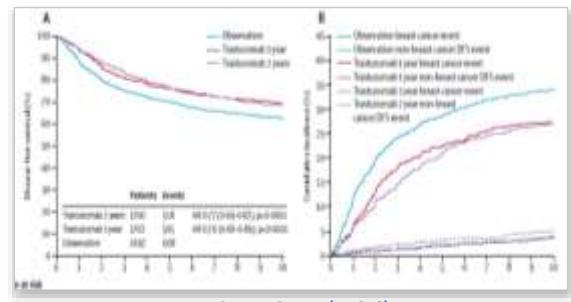
### NCCT 9831/NSABP- B31



DFS HR=0,60 (Δ11%)

OS HR=0.63 (Δ9%)

### HERA



DFS HR=0, 75 (Δ 6%)

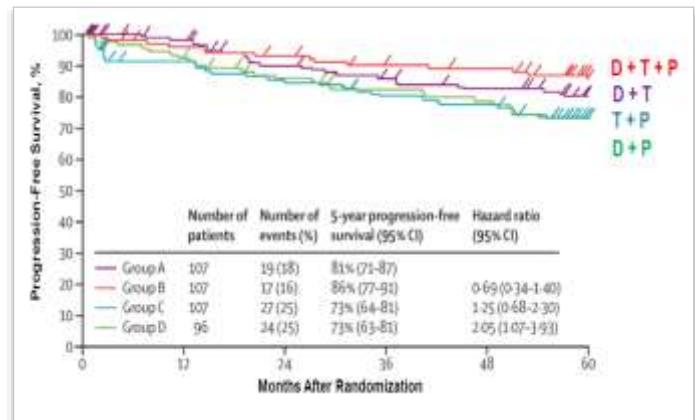
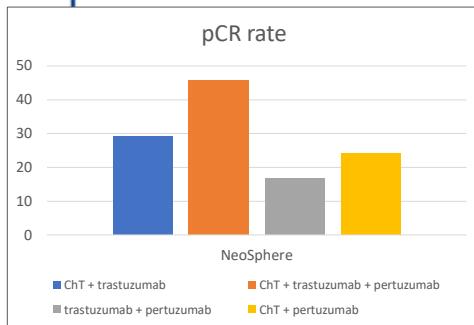
OS HR=0,74 (Δ 6 %)

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Romond, NEJM 2005 Perez, JCO 2014; Cameron, Lancet 2017

# HER2+ escalation

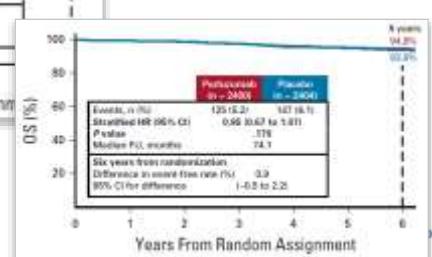
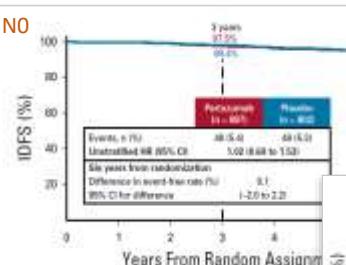
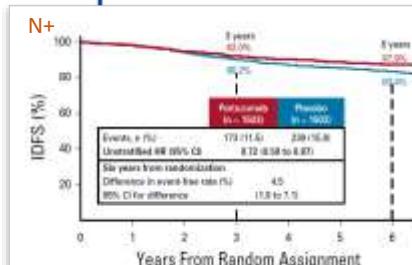
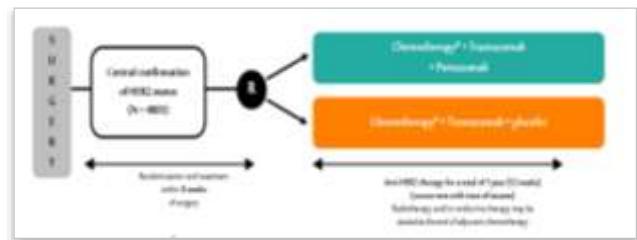
## NeoSphere



Gianni, Lancet Oncol 2012

# HER2+ escalation

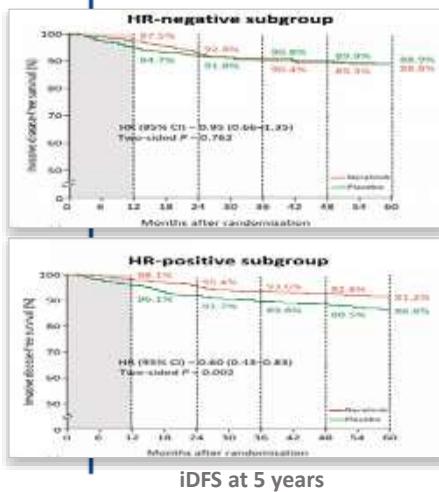
## Aphinity



Piccart, JCO 2021

## HER2+ escalation

ExteNET



N %	Neratinib (n=14080)		Placebo (n=1408)	
	All grades	G3-4	All grades	G3-4
Diarrhea	1343 (95.4)	<b>562 (39,9)</b>	499 (35,4)	23 (1,6)
Dose reduction:	26%			
Tx termination:	17%			

What does G 3 diarrhea mean ?

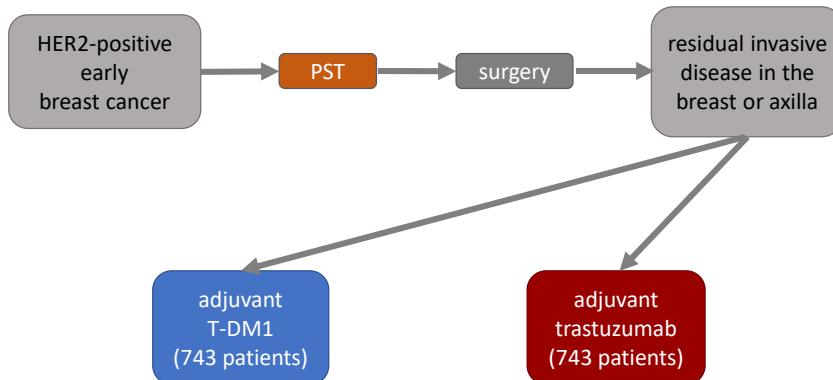
- ≥ 7 stools daily
- incontinence;
- hospitalization indicated
- limiting self care ADL



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Martin, Lancet Oncol 2017

## KATHERINE

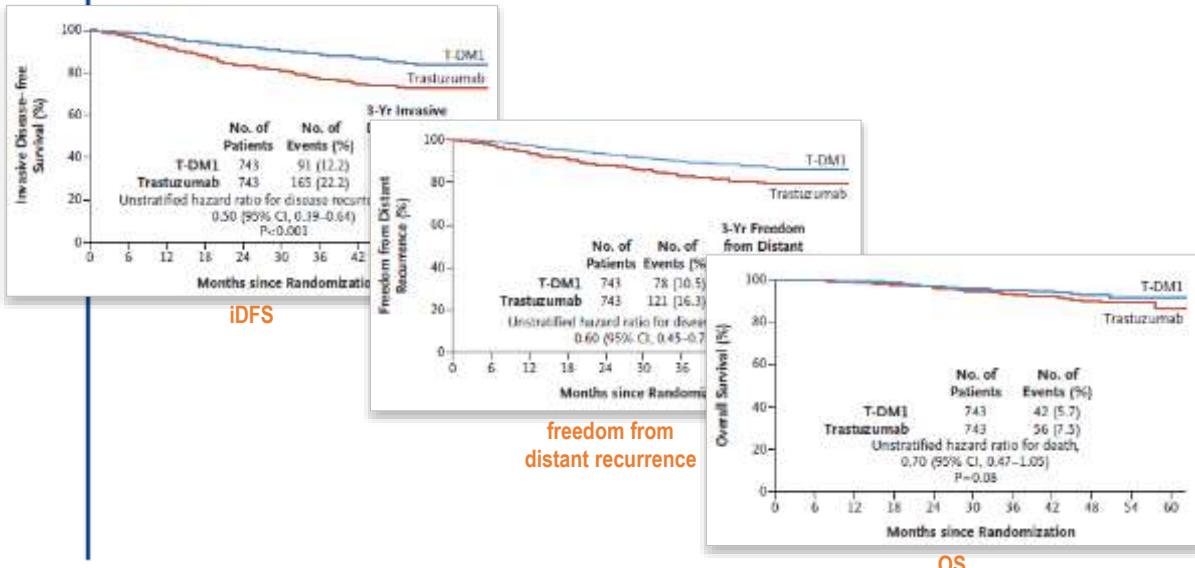


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von Minckwitz, NEJM 2018

# KATHERINE

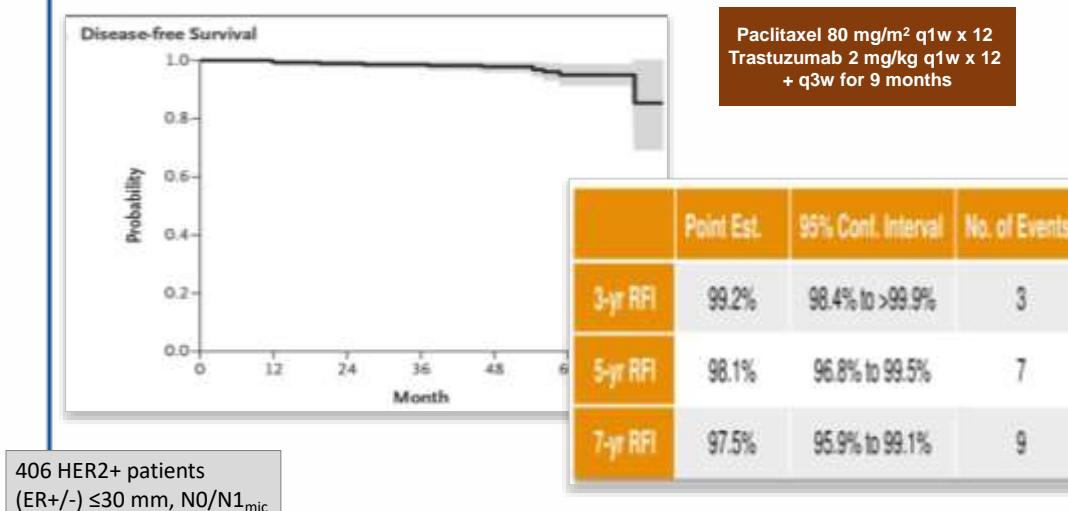
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von Minckwitz, NEJM 2018

## HER2+ deescalation

MEDICAL  
UNIVERSITY  
OF GDANSK



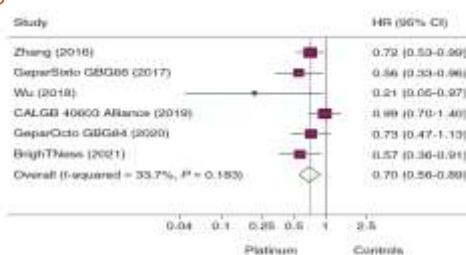
Tolaney, NEJM 2015, Tolaney, ASCO 2017

# TNBC

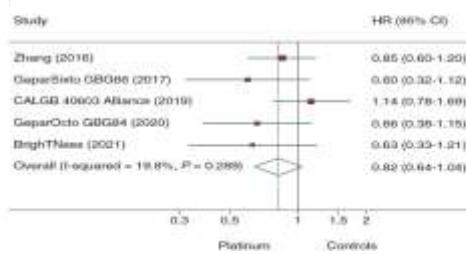
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## Role of platinum?

EFS



OS

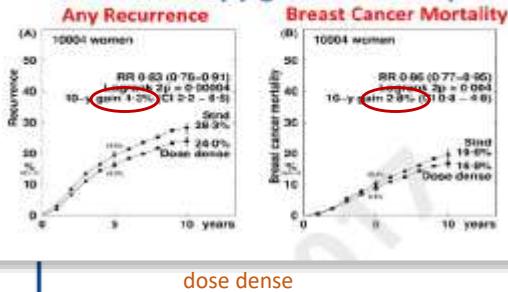

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Poggio, Ann Oncol 2022

# Alternative scheduling???

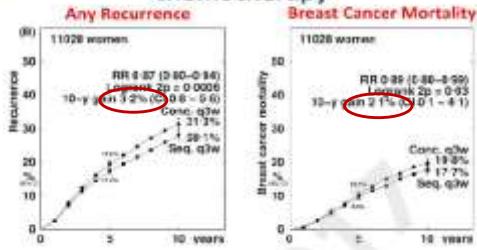
## EBCTCG metaanalysis

### 2-weekly (dose dense) vs the same chemotherapy given 3-weekly



dose dense

### Sequential (3-weekly) vs Concurrent (3-weekly) chemotherapy

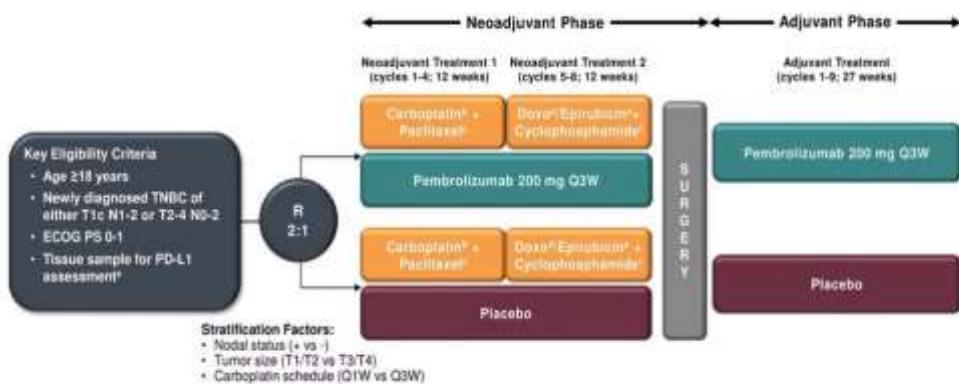


sequential vs concurrent

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Gray, SABCS 2017

# KEYNOTE-522

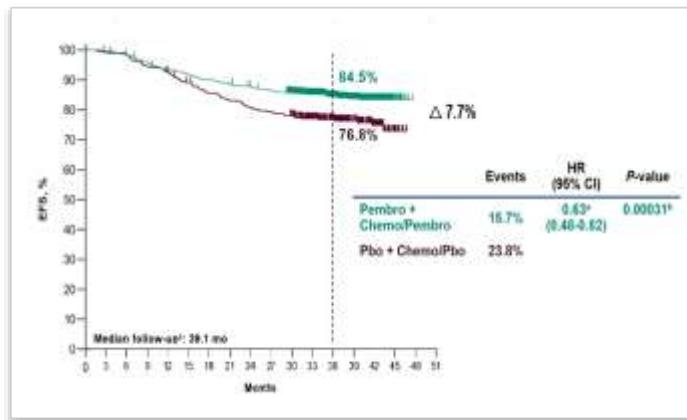
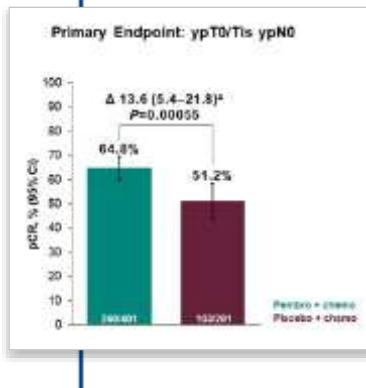


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Schmid, NEJM 2022

## KEYNOTE-522

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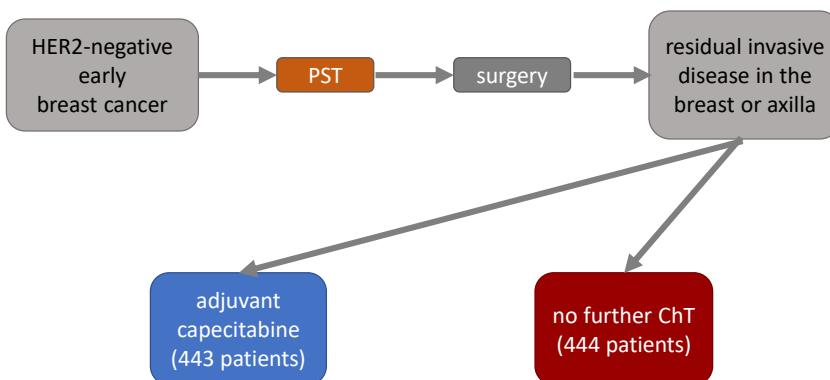


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Schmid, NEJM 2022

## CREATE-X

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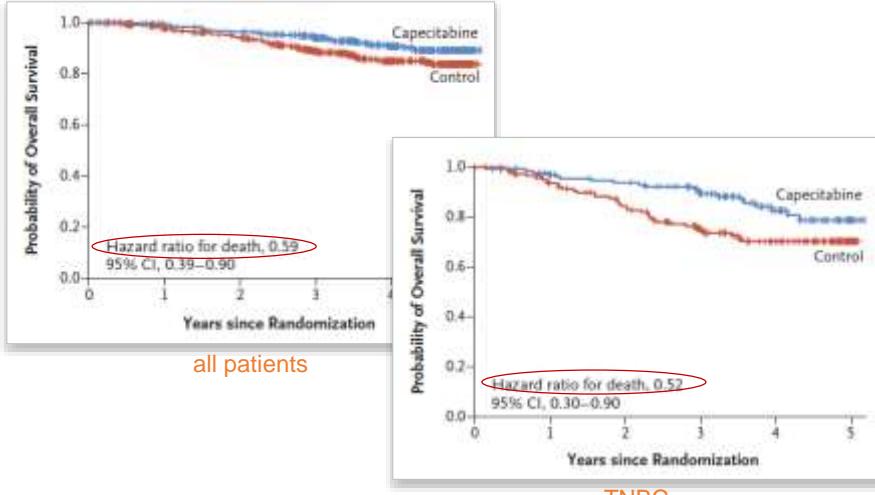


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Masuda, NEJM 2017

## CREATE-X

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Masuda, NEJM 2017

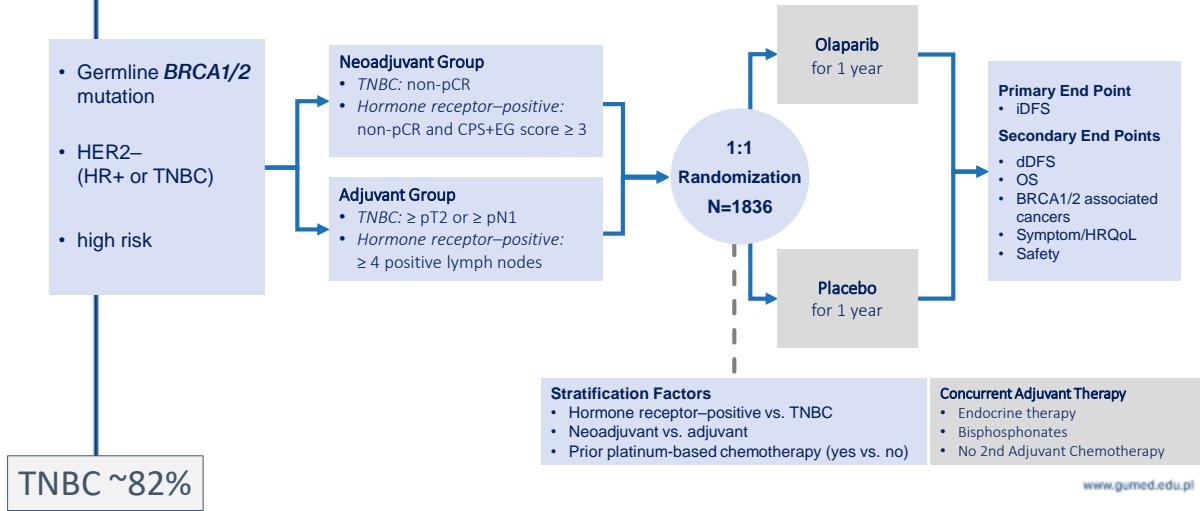
## BRCA mutation carriers

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# OlympiA

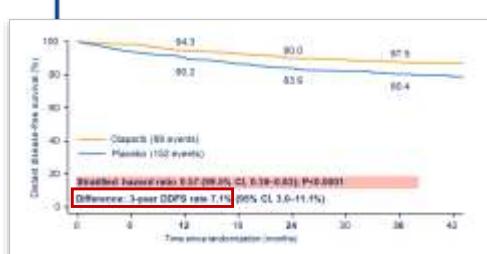
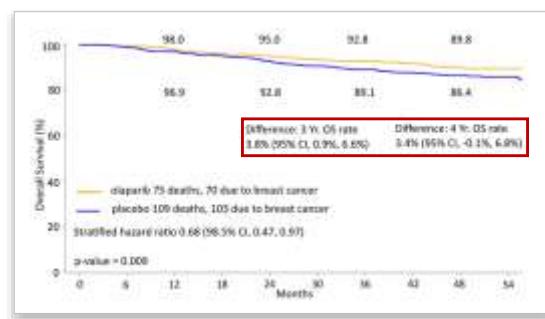
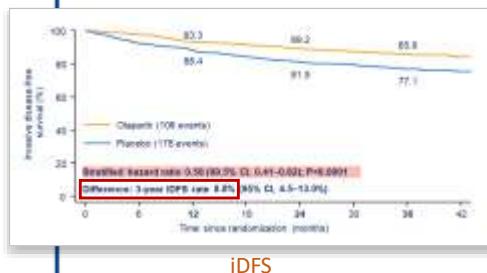
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Tutt, NEJM 2021

# OlympiA

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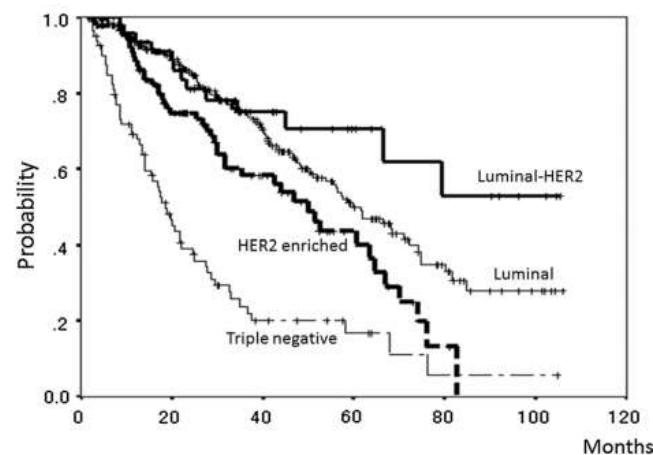
Tutt, NEJM 2021, Tutt, ESMO Virtual Plenary 2022



## Advanced breast cancer

[www.gumed.edu.pl](http://www.gumed.edu.pl)

### Intrinsic phenotype

[www.gumed.edu.pl](http://www.gumed.edu.pl)

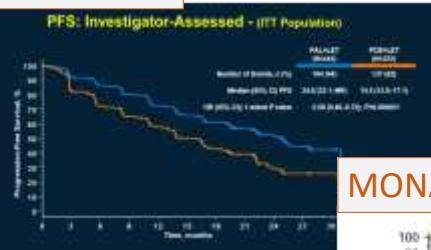
Kobayashi, Surg Today 2015

# Luminal BC

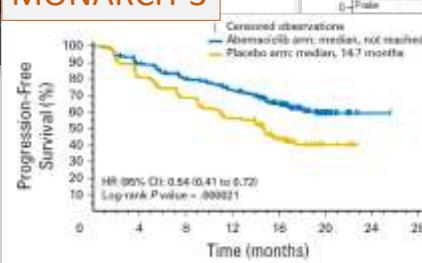
[www.gumed.edu.pl](http://www.gumed.edu.pl)

## Success of CDK4/6 inhibitors in MBC – 1<sup>st</sup> line

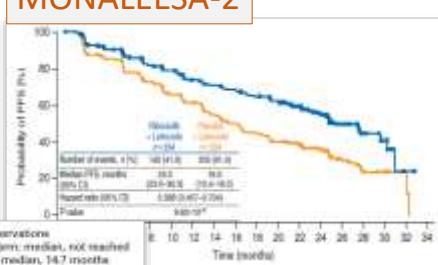
### PALOMA-2



### MONARCH-3



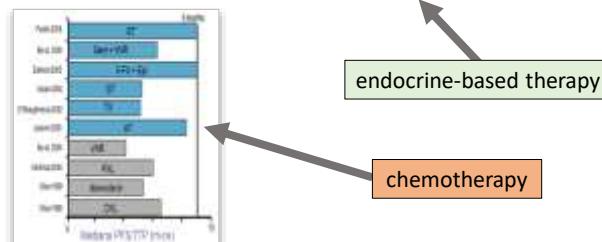
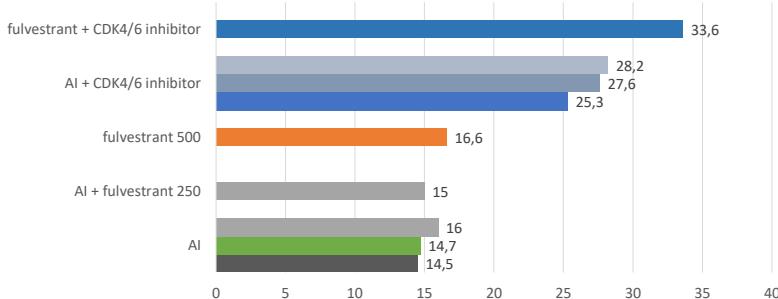
### MONALEESA-2


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Finn, N Engl J Med. 2016; Hortobagyi, Ann Oncol 2018; Goetz, JCO 2017

## Efficacy of endocrine therapy – 1<sup>st</sup> line (PFS)

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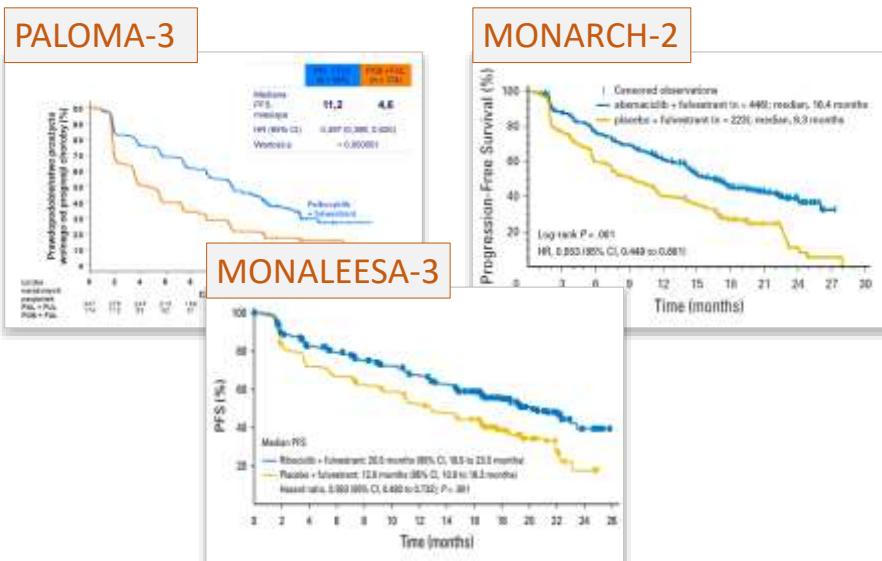
[www.gumed.edu.pl](http://www.gumed.edu.pl)

endocrine-based therapy

chemotherapy

## Success of CDK4/6 inhibitors in MBC – 2<sup>nd</sup> line

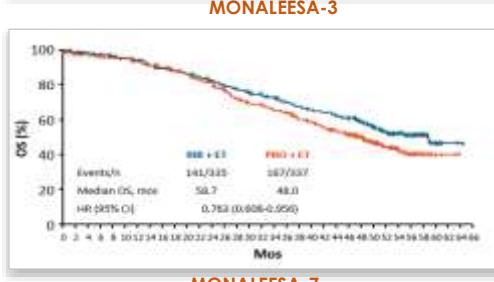
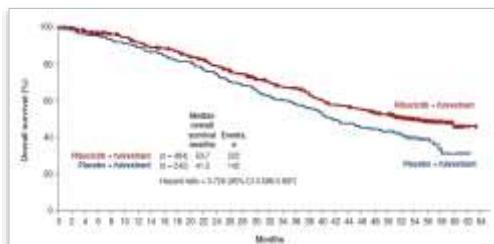
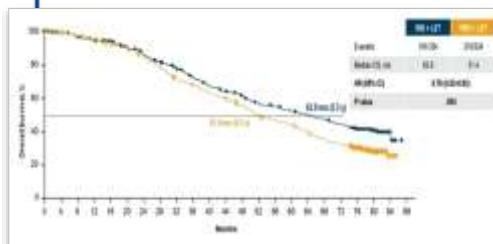
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Cristofanilli, Lancet Oncol. 2016; Sledge, JCO 2017, Slamon, JCO 2018

## Success of CDK4/6 inhibitors in MBC – overall survival benefit

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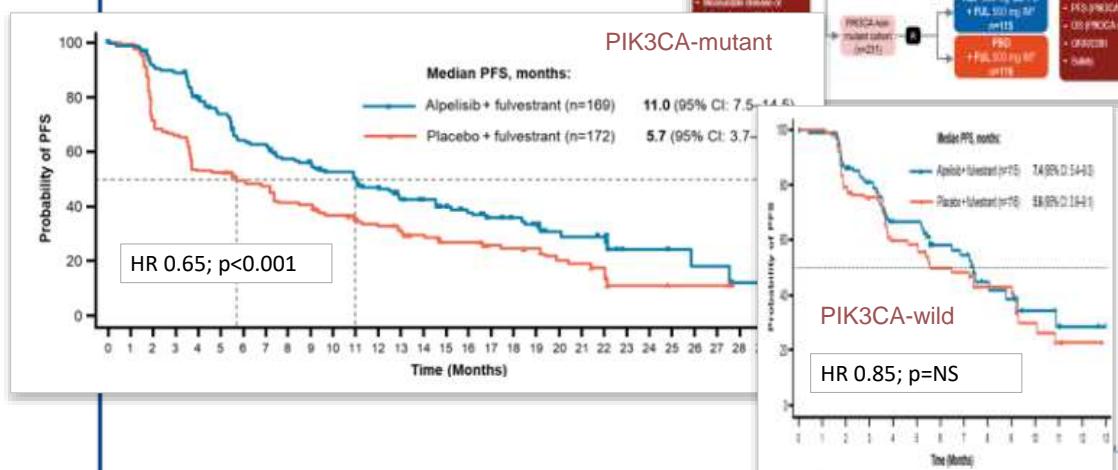


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Hortobagyi, ESMO 2021; Slamon, Ann Oncol 2021; Sledge, ESMO 2019; Tripathy, SABCS 2020

## PI3K-α inhibitors

SOLAR-1

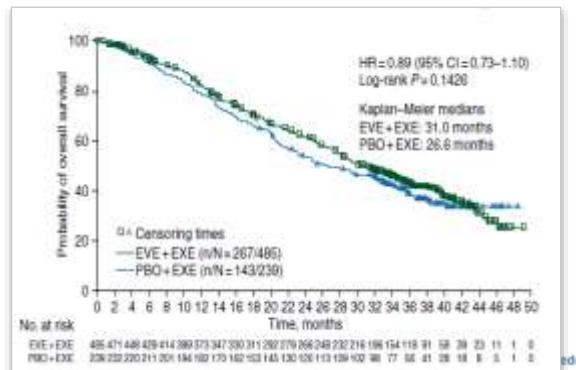
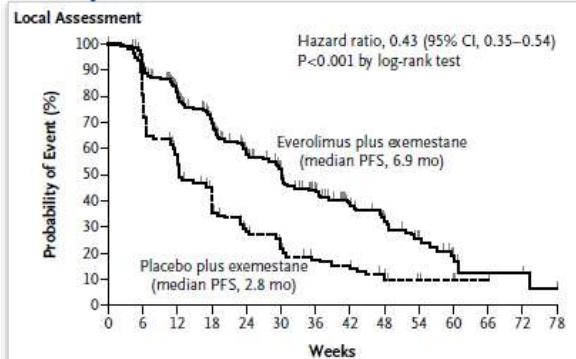


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Andre, NEJM 2019

## BOLERO-2

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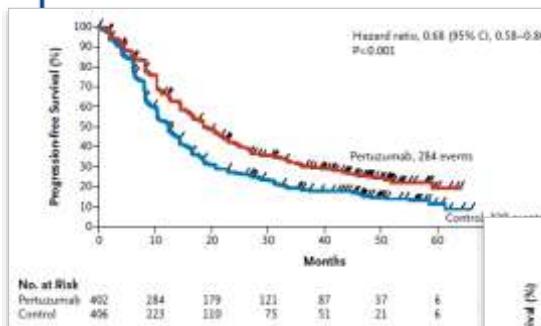
Baselga, NEJM 2011; Piccart, Ann Oncol 2014

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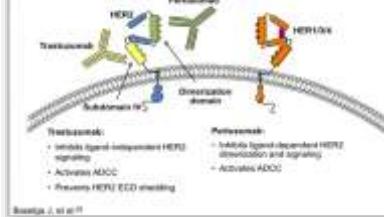
## HER2+ BC

[www.gumed.edu.pl](http://www.gumed.edu.pl)

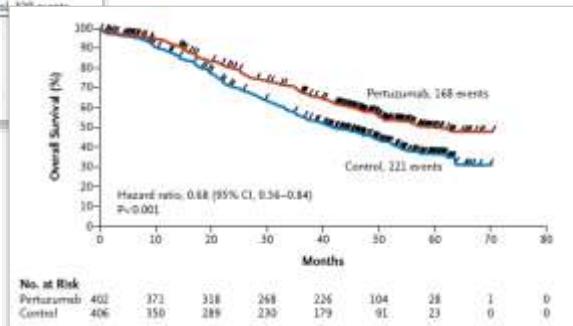
## 1<sup>st</sup> line therapy



### Pertuzumab and Trastuzumab Complementary Mechanisms of Action

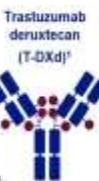


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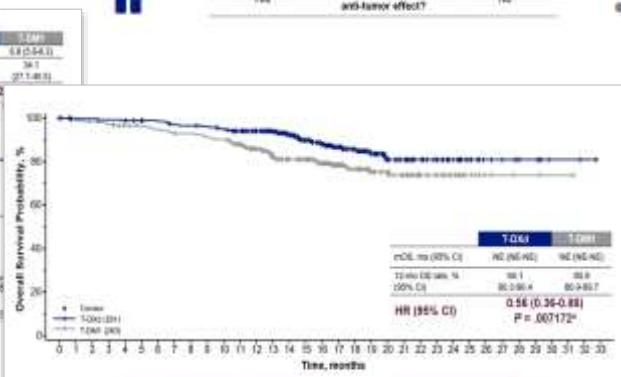
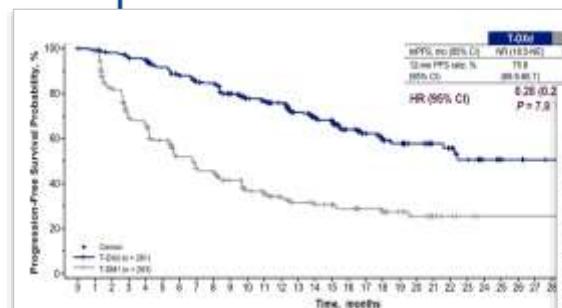
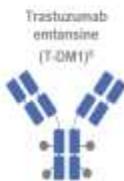


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Swain, NEJM 2015

## 2<sup>nd</sup> line therapy



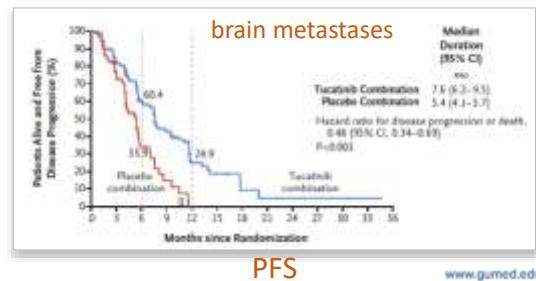
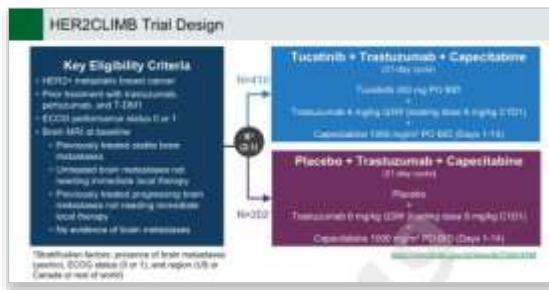
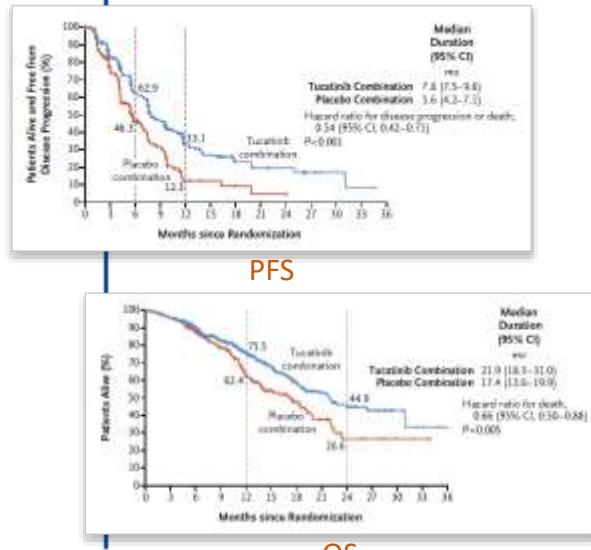
T-DXd <sup>®</sup>	ADC Attributes	T-DM1 <sup>®</sup>
Topoisomerase I inhibitor	Payload MoA	Anti-microtubule
>E1	Drug-to-antibody ratio	>3.1
Yes	Tumor-selective cleavable linker?	No
Yes	Evidence of bystander anti-tumor effect?	No



xgumed.edu.pl

Cortes, ESMO 2021

## Beyond 2<sup>nd</sup> line



[www.gumed.edu.pl](http://www.gumed.edu.pl)

Murthy, NEJM 2020

# TNBC

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# Immunotherapy

## IMpassion130

Advanced TNBC  
(N = 902)

Atezolizumab  
+ nab-Paclitaxel (n = 451)  
  
Placebo  
+ nab-Paclitaxel (n = 451)

## IMpassion131

Advanced TNBC  
(N = 902)

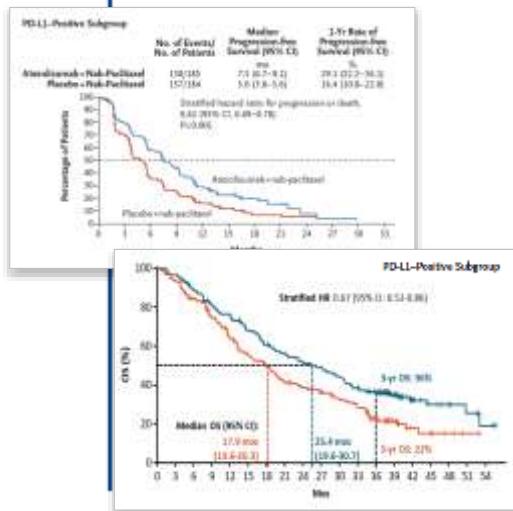
Atezolizumab  
+ Paclitaxel (n = 451)  
  
Placebo  
+ Paclitaxel (n = 451)

[www.gumed.edu.pl](http://www.gumed.edu.pl)

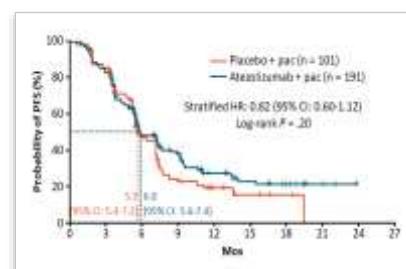
Schmid, NEJM 2018, Miles, ESMO 2020

# Immunotherapy

## IMpassion130



## IMpassion131



[www.gumed.edu.pl](http://www.gumed.edu.pl)

Schmid, NEJM 2018, Miles, ESMO 2020

# Immunotherapy

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## IMpassion130

Advanced TNBC  
(N = 902)

Atezolizumab  
+ nab-Paclitaxel (n = 451)  
Placebo  
+ nab-Paclitaxel (n = 451)

## IMpassion131

Advanced TNBC  
(N = 902)

Atezolizumab  
+ Paclitaxel (n = 451)  
Placebo  
+ Paclitaxel (n = 451)

## KEYNOTE-355

Advanced TNBC  
(N = 847)

Pembrolizumab + ChT\*  
(n = 566)  
Placebo + ChT\*  
(n = 281)

- Nab-paclitaxel
- Paclitaxel
- Gem + carbo

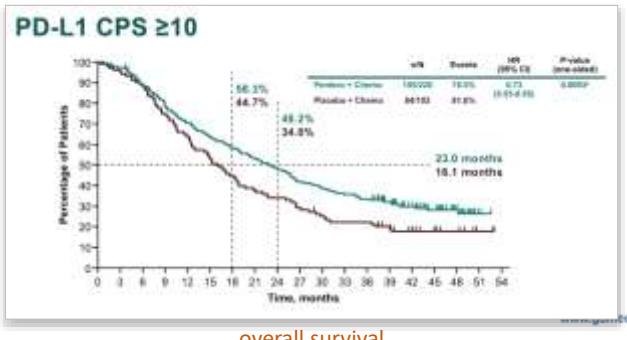
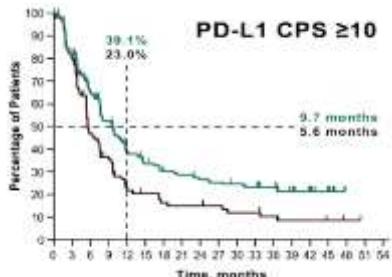
[www.gumed.edu.pl](http://www.gumed.edu.pl)

Schmid, NEJM 2018, Miles, ESMO 2020, Cortes, Lancet 2020

# Immunotherapy

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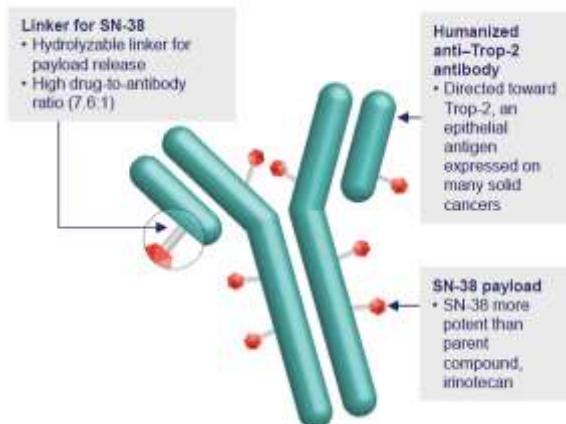
## KEYNOTE-355



Cortes, Lancet 2020

# Sacituzumab Govitecan

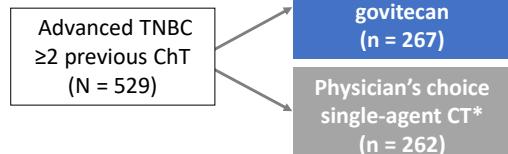
GDANSKI  
UNIWERSYTET  
MEDYCZNY



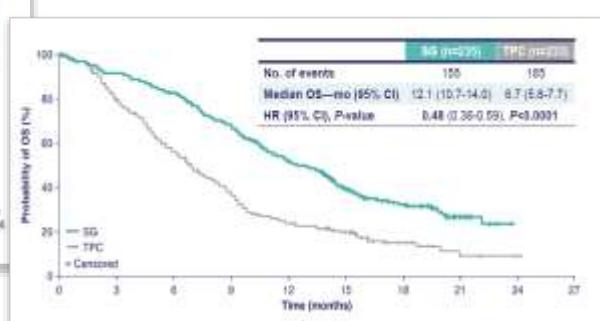
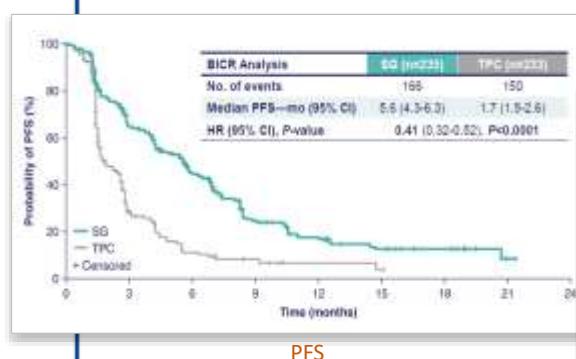
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## ASCENT

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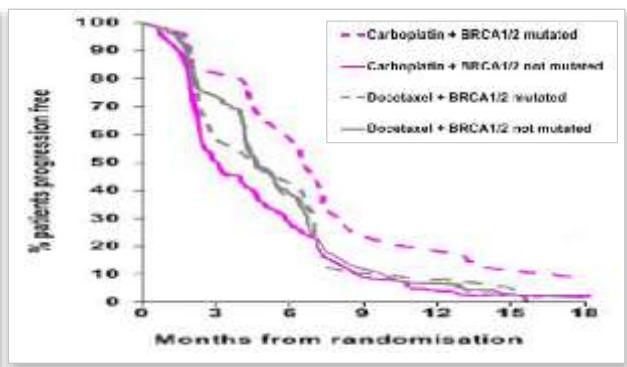
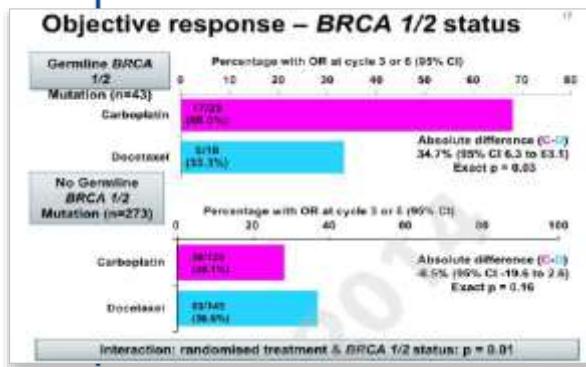
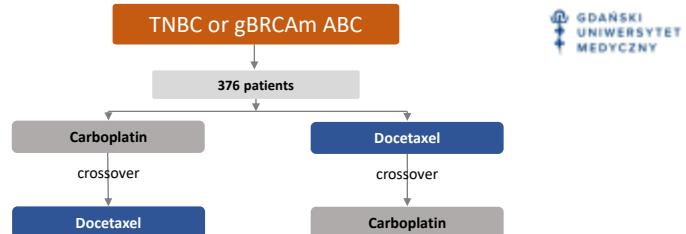
- eribulin
- vinorelbine
- gemcitabine
- capecitabine



# BRCA mutation carriers

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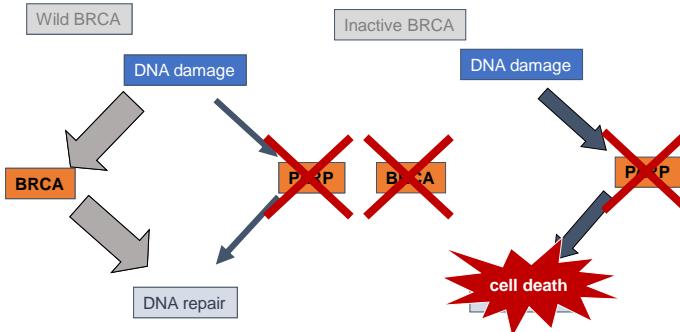
## Role of platinum

**TNT**


Tutt, Nat Med. 2018

# PARP inhibitors

## Synthetic lethality



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## OlympiAD

- gBRCAm mBC
- TNBC or HER2-negative, ER/PR positive
- ≤2 prior chemotherapy lines for mBC

### Stratification by:

- Prior chemotherapy regimens for metastatic breast cancer
- Hormonal receptor (HR) status
- Prior platinum therapy

Randomise 2:1  
N=302

Olaparib  
300mg po bid

Treatment of  
Physician's Choice

Primary endpoint  
• PFS (RECIST 1.1, Independent Review)

### Secondary endpoints

- OS
- PFS2
- ORR
- PFS, PFS2 and OS based on Myriad gBRCAm status
- HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

## EMBRACA

- Locally advanced breast cancer and / or metastatic disease appropriate for systemic single cytotoxic chemotherapy
- gBRCAm
- ≤3 prior lines of chemotherapy for locally advanced/metastatic disease
- HER2-negative

### Patients stratified by:

- Number of prior chemotherapy regimens (0 vs 1,2,3)
- Triple negative status (HR+ vs TNBC)
- History of CNS metastasis (y/n)

Randomise  
2:1

talazoparib  
(N=287)  
1 mg/day 21 day cycles  
PO

Therapy of physician's choice (TPC)  
(N=144)  
(capecitabine, eribulin,  
gemcitabine or  
vinorelbine)

Primary endpoint:  
• PFS (BICR)

### Secondary endpoints include:

- ORR
- OS
- Safety and tolerability
- PK

### Exploratory endpoint:

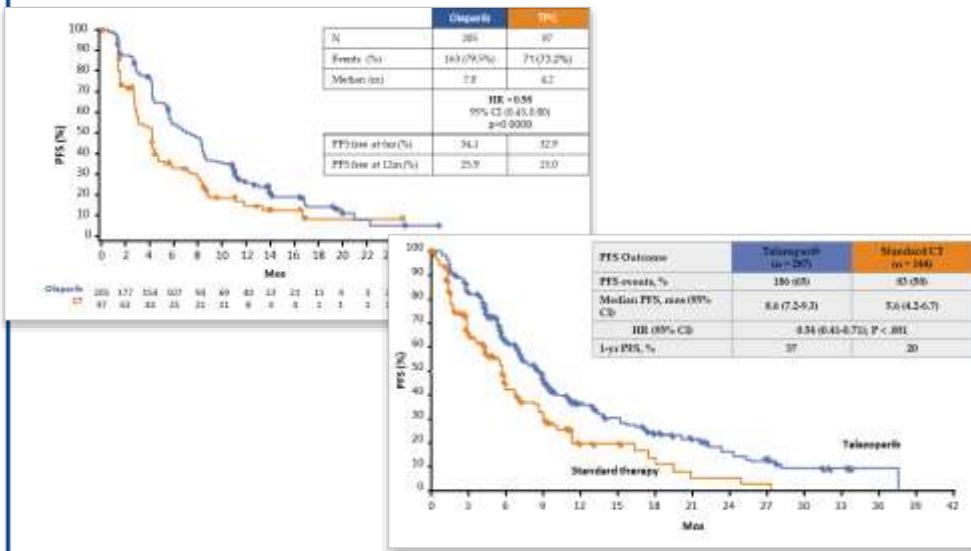
- HRQoL

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Robson, NEJM 2017; Litton, NEJM 2018

# OlympiAD, EMBRACA - PFS

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Robson, NEJM 2017; Litton, NEJM 2018

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Thank you  
for your attention😊

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