Optimization of adjuvant therapy-hormone receptor negative (N0-N1) breast cancer

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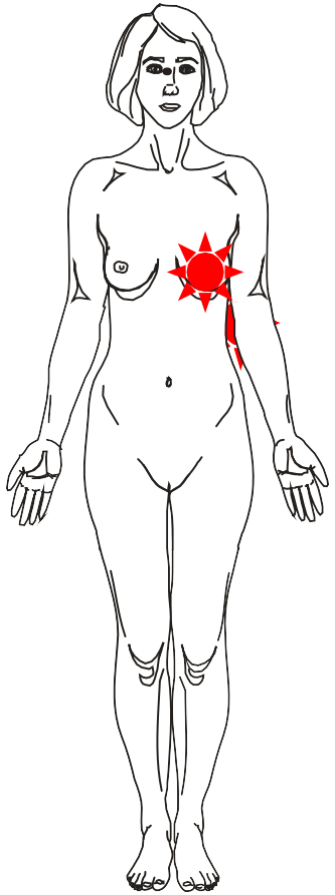
Breast cancer—How can we make a difference?

- Identifying who may be at higher **risk** for developing breast cancer
  - Genetic testing: Who needs it, and what to test for?

- Increasing the chance of cure for **early stage breast cancer**
  - Adjuvant chemotherapy: Who needs it? and who doesn't?
  - Adjuvant endocrine therapy: How long is long enough?

BREAST CANCER

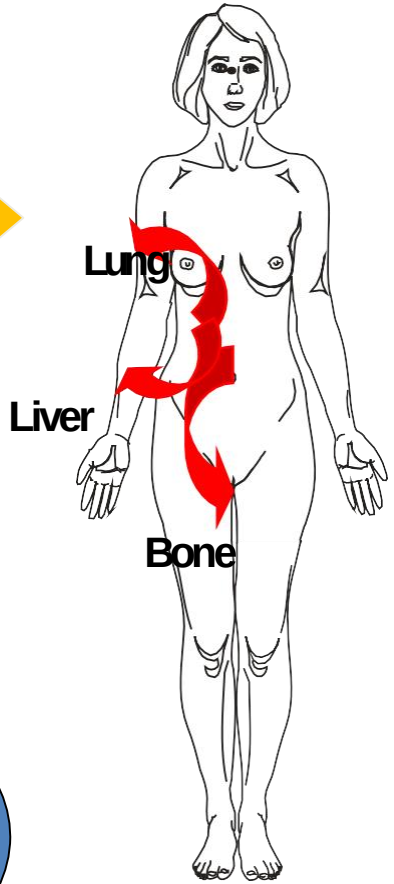


Localized disease

Curable

« Adjuvant » medical therapies

But risk of :
- overtreatment
- undertreatment
- wrong treatment
- suboptimal treatment



Generalized disease

Very difficult to cure

Adjuvant chemotherapy in early breast cancer
Benefit / Risk Balance

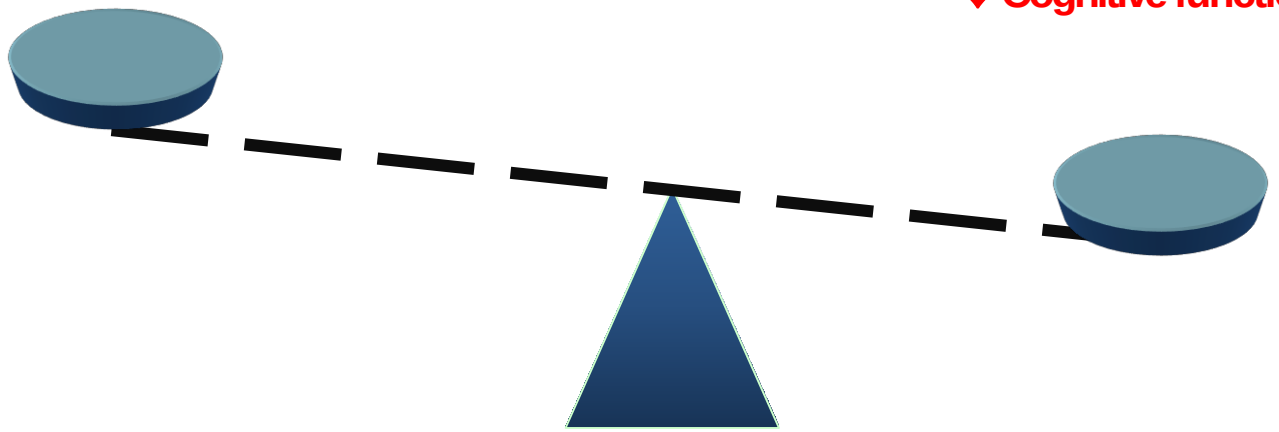
Lessons learned from 3 decades of clinical trials

BENEFIT

↑ Survival
(2 to 12%)

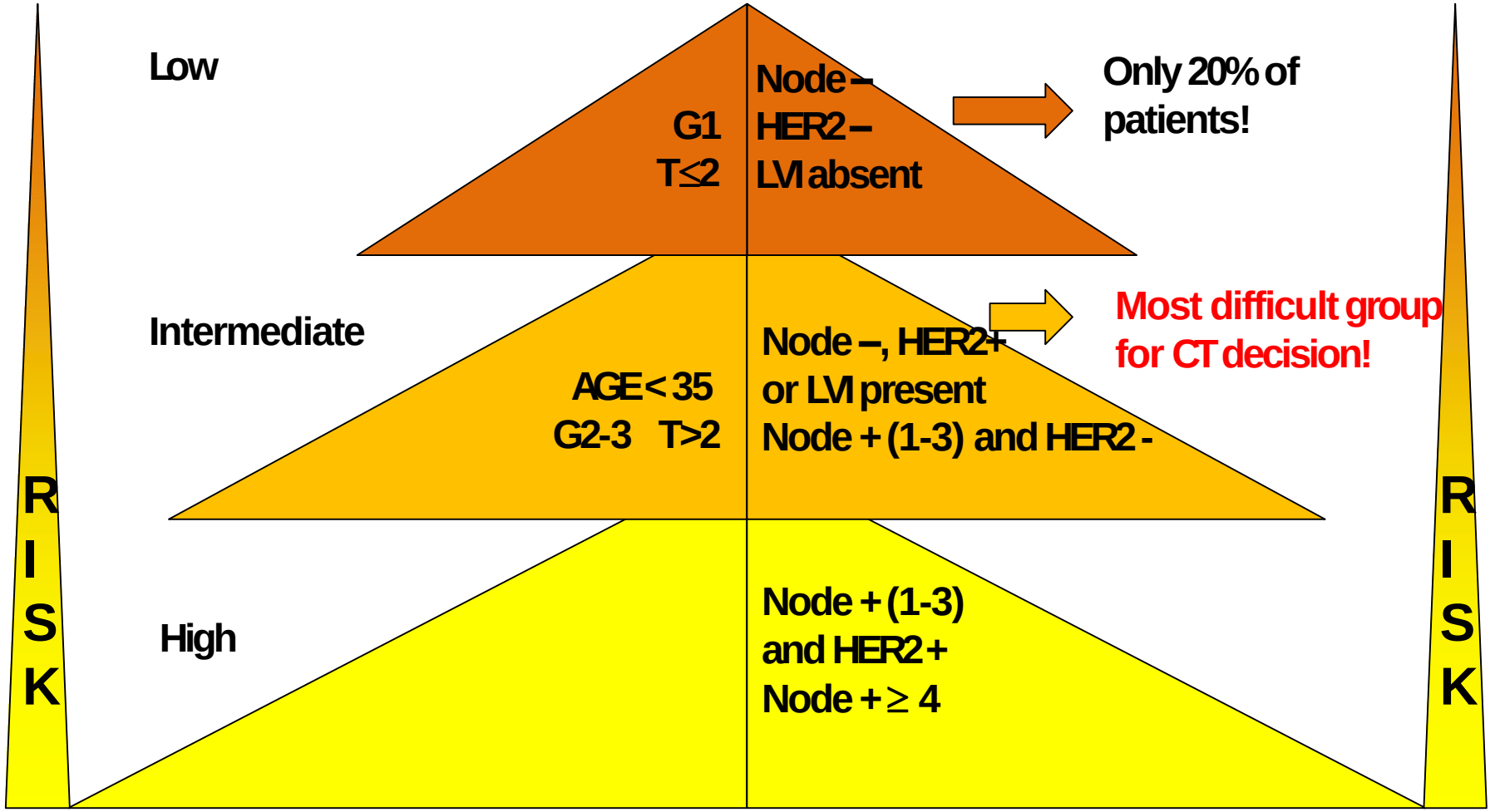
LONG-TERM RISKS

- Secondary cancers
- Cardiac toxicity
- Early menopause
- ↓ Cognitive function



…AND SOCIO-ECONOMIC BURDEN

ST. GALLEN DEFINITIONS OF RISK

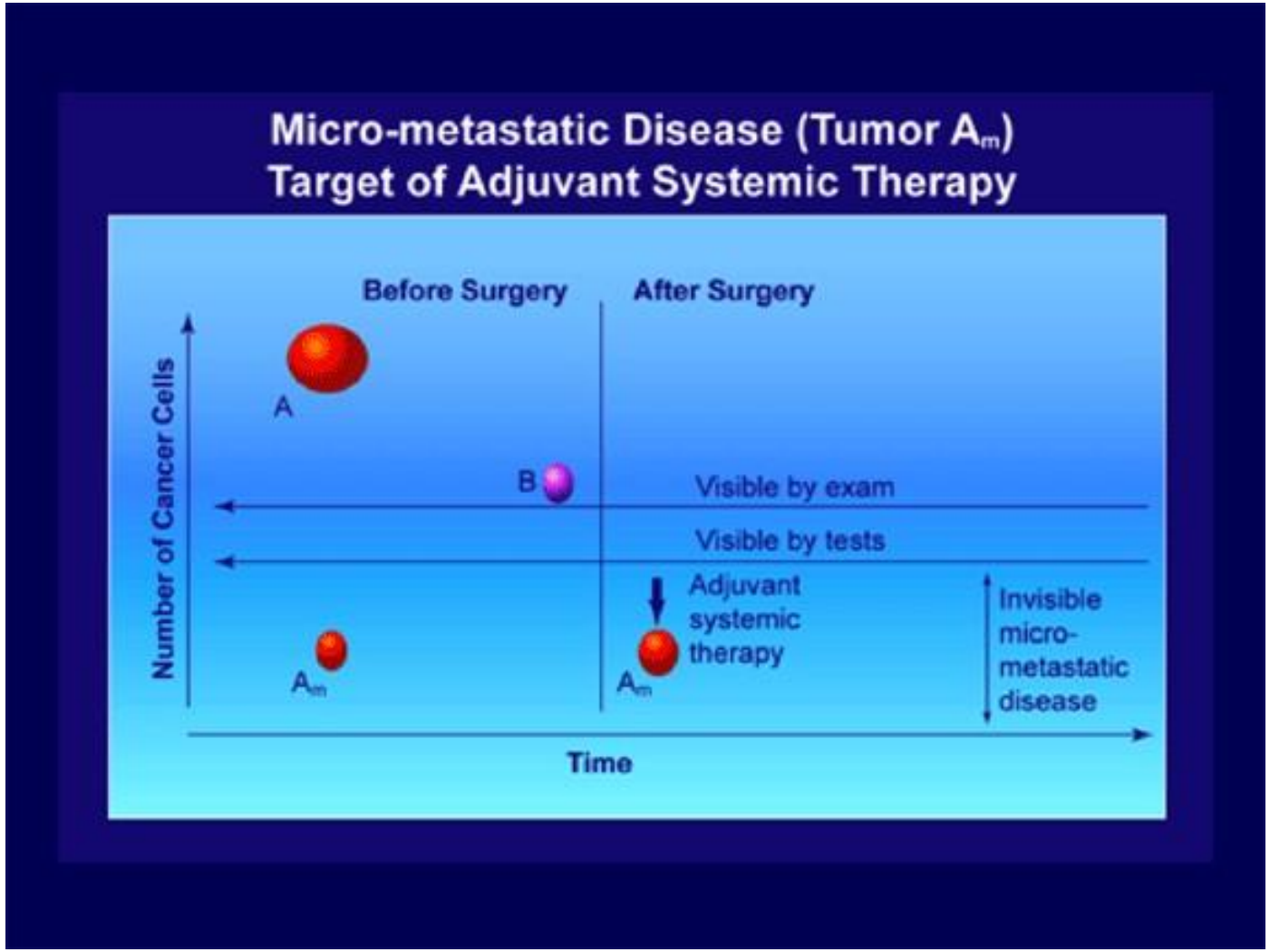


Other similar guidelines exist : NCCN, ESMO,…

Systemic therapy (drugs) early stage disease-rationale

Early stage disease (stage I, II, III)

- Given after (or before) surgery for finite duration
- Kill micro-metastatic disease
- Primary goal is to reduce chances of future breast cancer relapse and reduce chances of eventual death from breast cancer

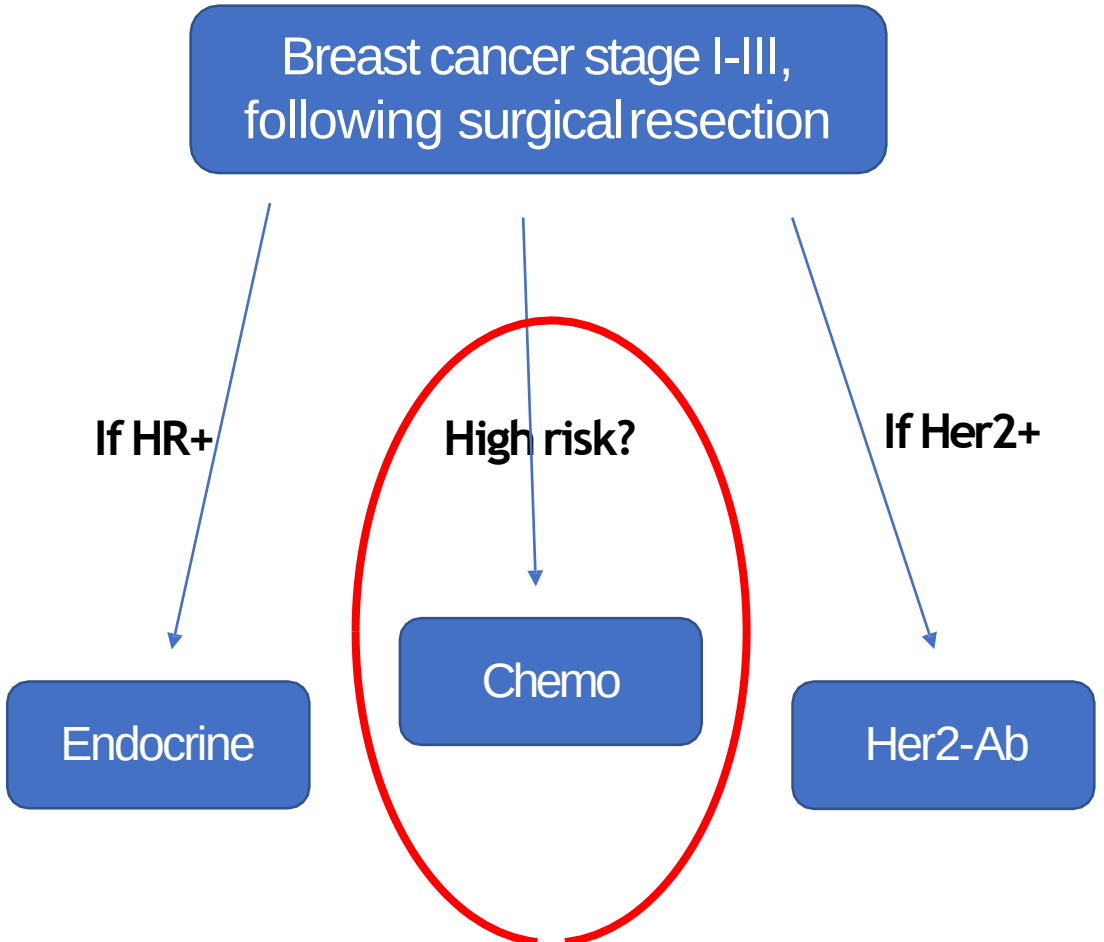


Adjuvant systemic therapy

Types

- Endocrine therapy
  - Tamoxifen
  - Aromatase inhibitors
  - Ovarian suppression
- Chemotherapy
  - Adriamycin, Cyclophosphamide, Paclitaxel, Docetaxel, 5-FU
- Her2 monoclonal antibodies (Ab)
  - Trastuzumab
  - Pertuzumab

Who gets what? Andwhen?



Adjuvant chemotherapy: How do we decide who is ‘high risk’?

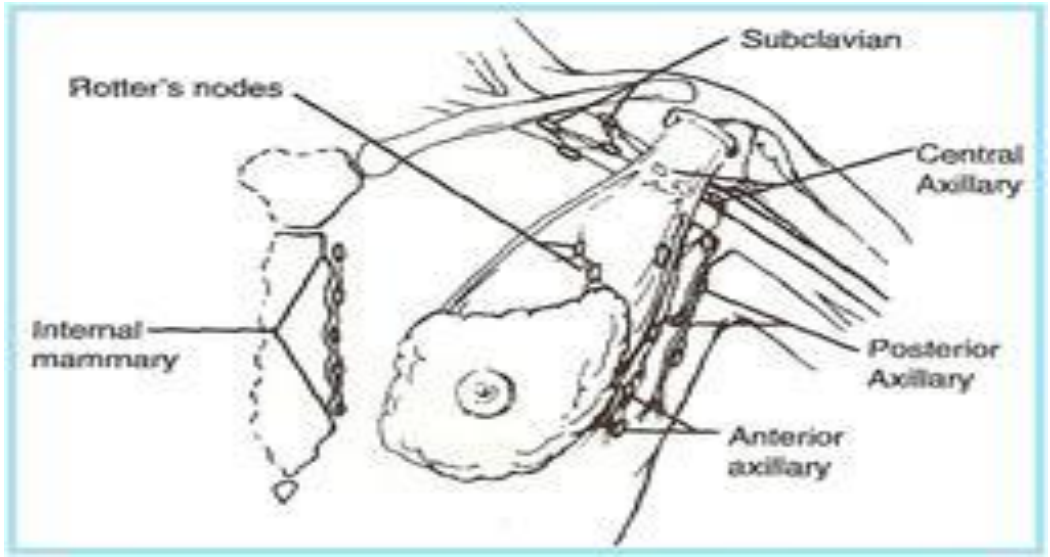
- **CLINICAL/PATHOLOGICAL/GENOMIC FACTORS ARE BEST USED IN COMBINATION.**
- **Responsiveness is a continuum.**
- **PATIENT PREFERENCE!**

In favor of adjuvant chemotherapy

- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1
- Basal and *HER2* positive
- High MammaPrint® or Oncotype DX® or GGI

Against adjuvant chemotherapy

- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A
- Low MammaPrint® or Oncotype DX® or GGI



Without Systemic Treatment

1-3 LN: 25-35% recurrence rate

4-9 LN: 25-55% recurrence rate

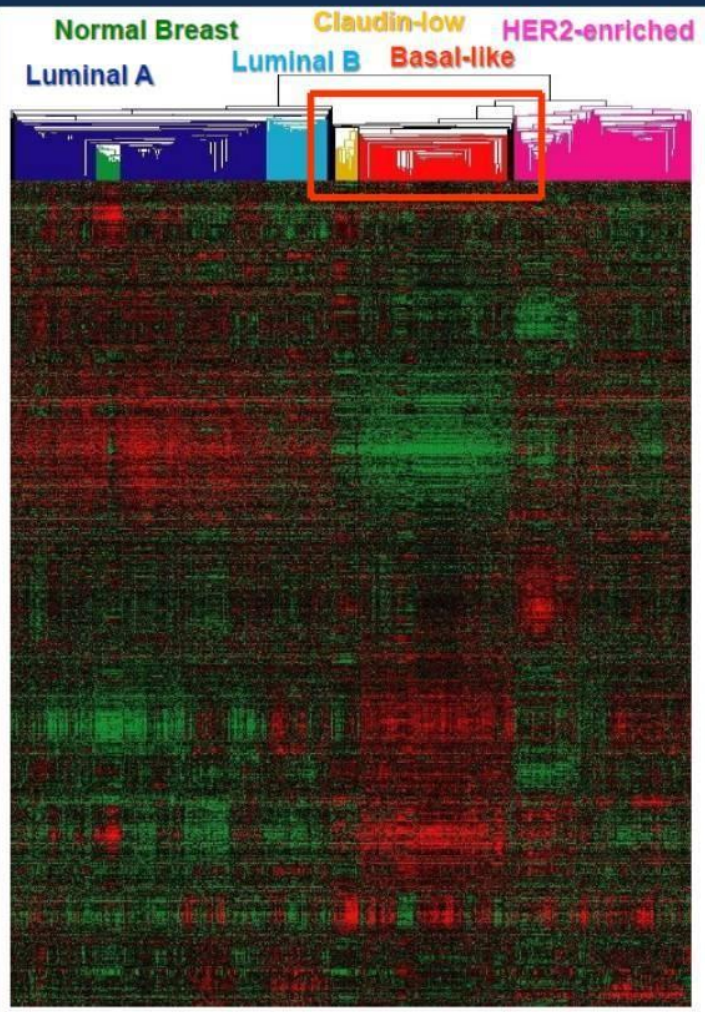
>10 LN: >70% recurrence rate

Quiet et al. Natural History of node positive breast cancer: the curability of small cancers with a limited number of positive nodes. *J Clin Oncol.* 1996; 14:3105-3111

Triple Negative (TNBC): The Basics…

- Defined as negative for ER/PR and Her2/neu
- 20% of breast cancers worldwide
  - 200,000 cases per year
- Higher incidence in age <40, and AA race
- Up to 20% harbor BRCA mutation
- Higher grade, present aggressively with rapid growth
- Worse prognosis compared to other breast cancers

Incidence of TNBC



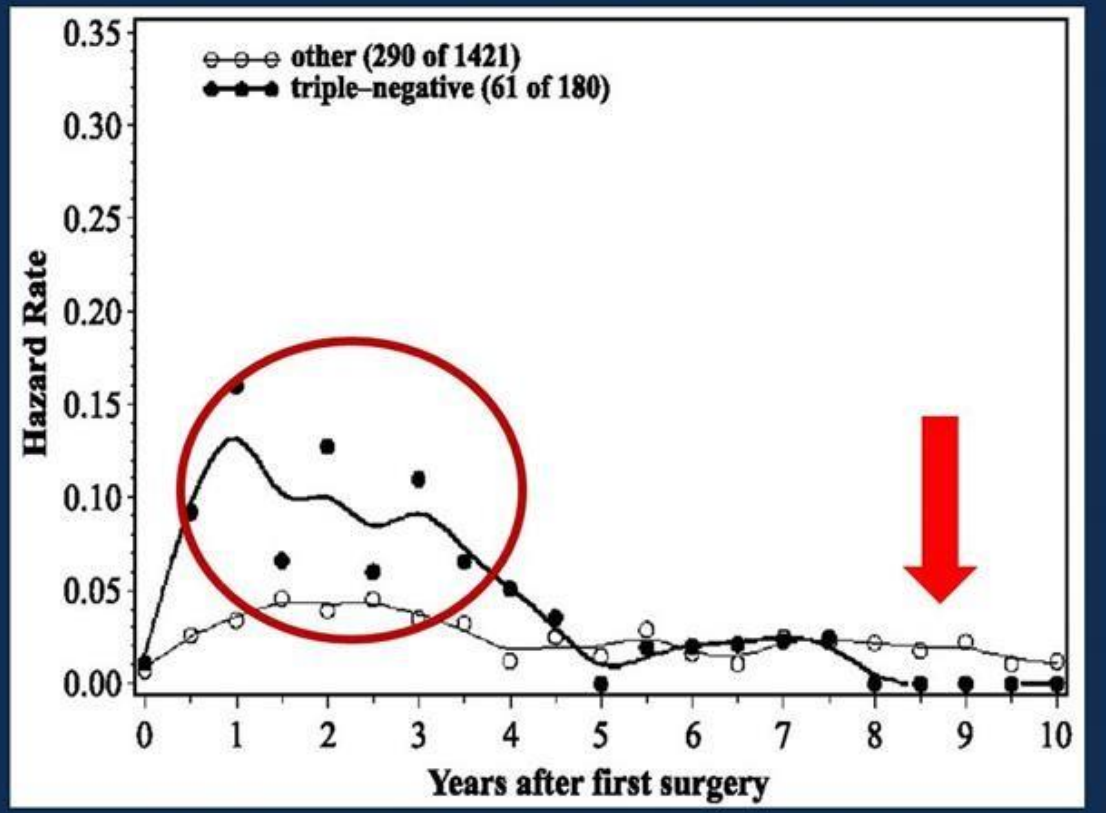
Estimated Cancer Deaths per year in the USA

Women
270,290

26%	Lung & bronchus
10%	Breast Luminal
9%	Colon & rectum
7%	Pancreas
5%	Ovary
5%	Triple-Negative BC (ER-, PR-, HER2-)
4%	Non-Hodgkin lymphoma
3%	Leukemia
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/Other nervous system
24%	All other sites

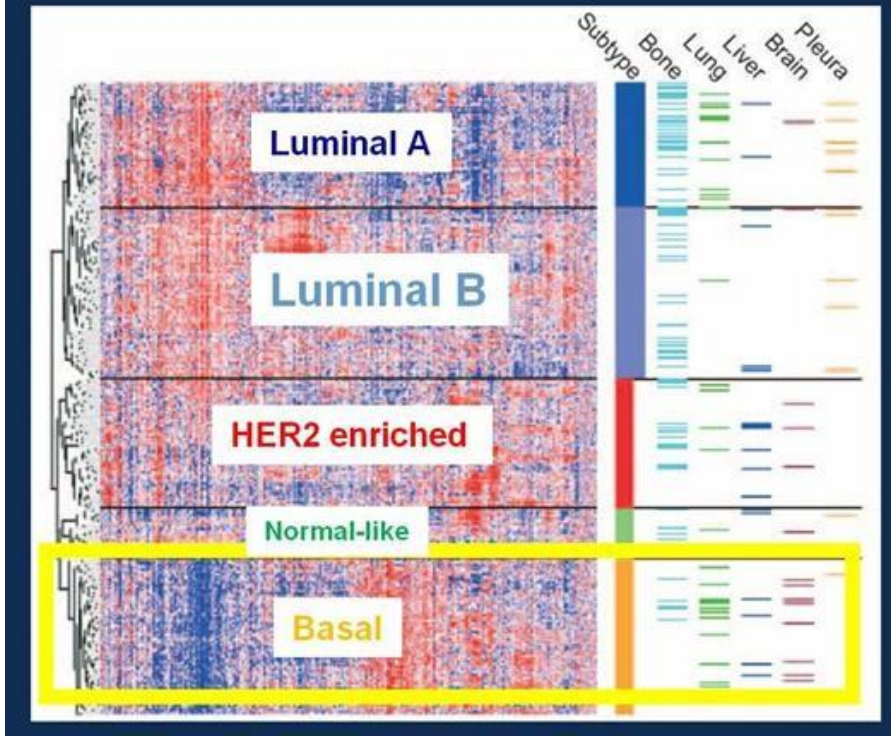
Triple negative: Natural history

Natural History of TNBC



TNBC recurrences peak at 1 – 3 years;
Sharp decline thereafter….

Recurrence Patterns of TNBC



TNBC recurrences more likely to be Visceral – involving Lung and brain; less likely Bone only recurrences

No target to chase? Rely on chemotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Invasive Breast Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1,2]

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[3]

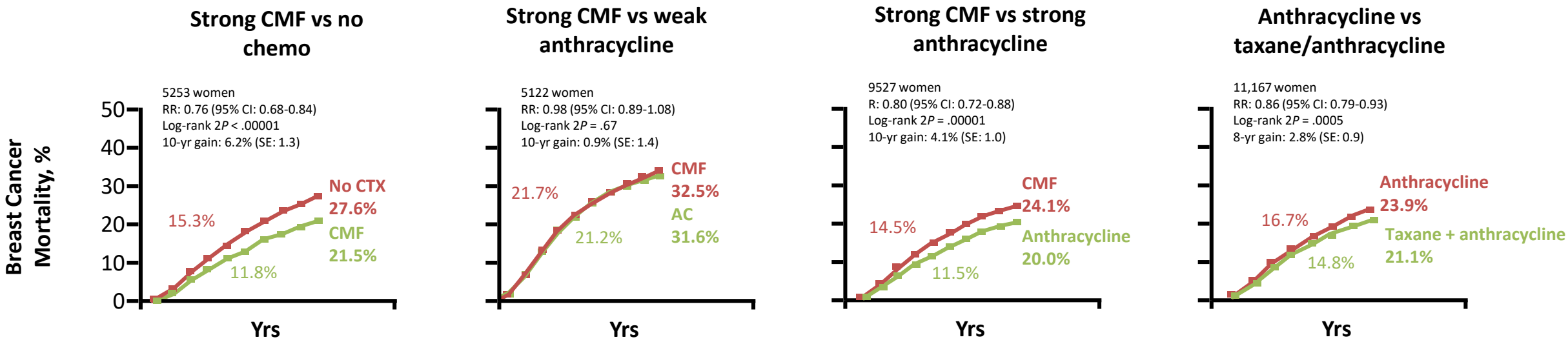
Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)[4]
- Pertuzumab + trastuzumab + paclitaxel[4]

Other agents for HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[4,5,6]

[1]There is no compelling evidence that combination regimens are

Meta-analysis: Long-term Outcomes With Polychemotherapy Regimens for EBC



24% PRR in BCM

2% PRR in BCM

20% PRR in BCM

14% PRR in BCM

Rough estimate: ~ 35% PRR in BC mortality for anthracycline/taxane regimen

"Little affected by age, nodal status, tumor diameter or differentiation (moderate or poor; few were well differentiated), estrogen receptor status, or tamoxifen use"

EBCTCG, et al. Lancet. 2012;379:432-444.

NSABP B-36: AC vs FEC-100 in Node-Negative Breast Cancer

Stratified by ER/PgR status and type of surgery

Pts with node-negative breast cancer (N = 2722)

Doxorubicin 60 mg/m^2 + Cyclophosphamide 600 mg/m^2 q3w x 4 (n = 1361)

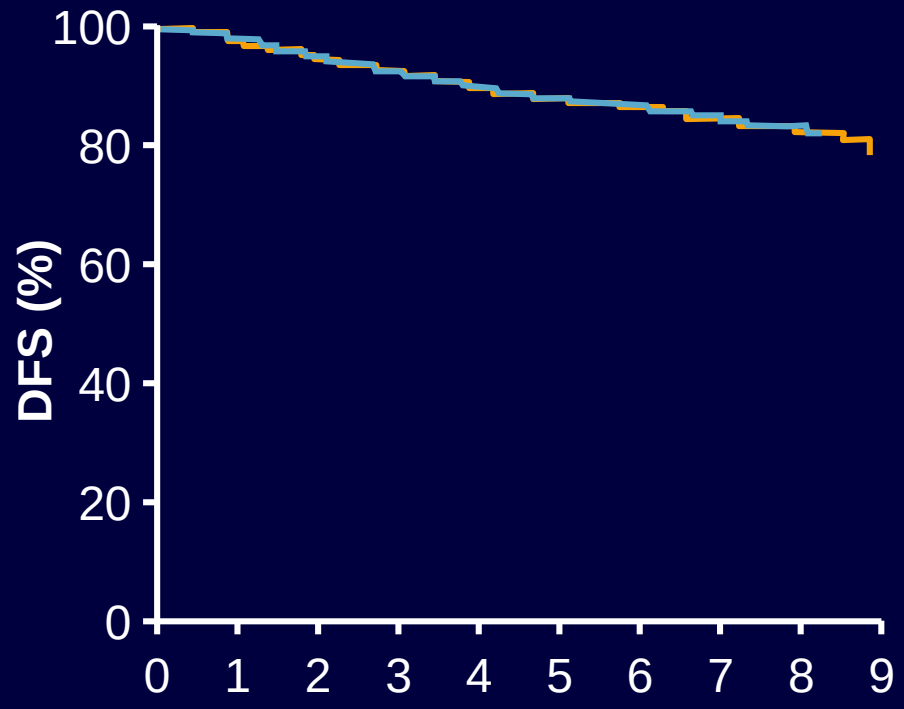
5-FU 500 mg/m^2 + Epirubicin 100 mg/m^2 + Cyclophosphamide 500 mg/m^2 q3w x 6 (n = 1361)

- Treatment after chemotherapy
  - ER/PgR+: endocrine
  - HER2+: trastuzumab

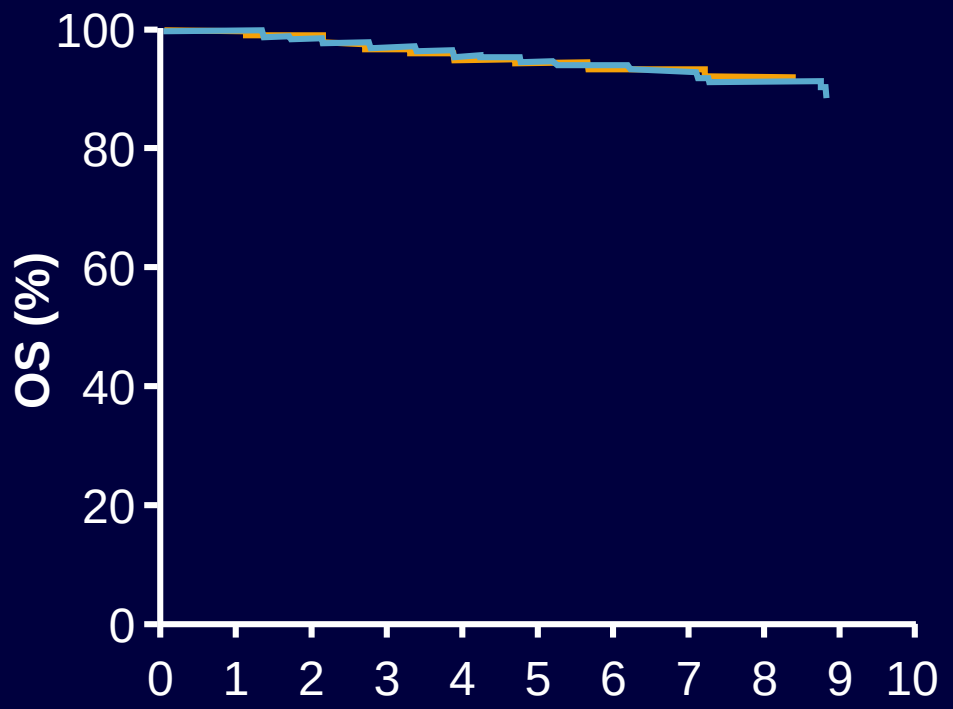
- Primary endpoint: DFS
- Secondary endpoints: OS, AEs, symptoms, QoL

Jacobs SA, et al. SABCS 2014. Abstract S3-02.

AC vs FEC-100 in Node-Negative Breast Cancer (NSABP B-36): DFS and OS



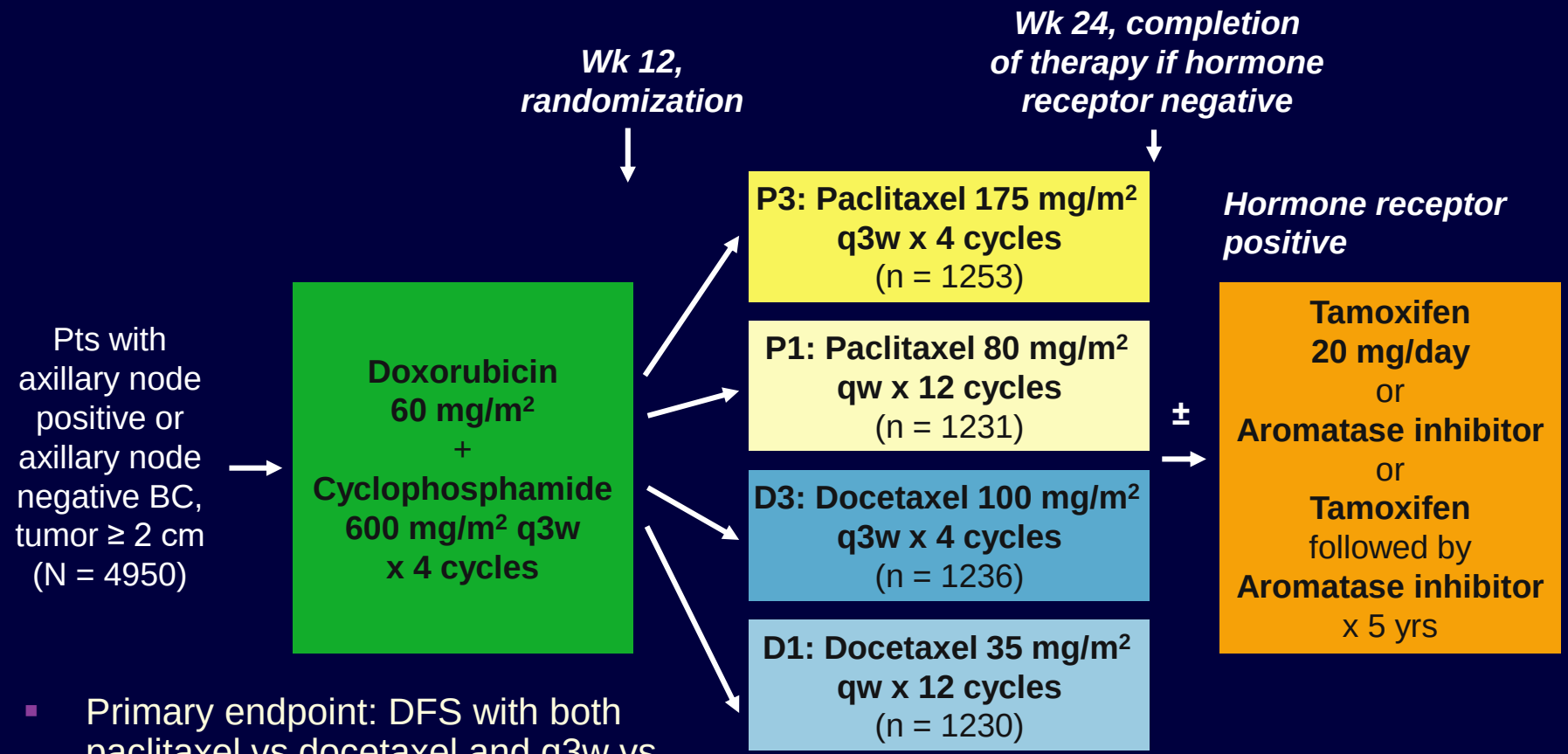
	N	Events, n	HR	*P* Value	8-Yr DFS, %
AC	1361	198			82.3
FEC	1361	202	1.03	.74	82.1



	N	Deaths, n	HR	*P* Value	8-Yr DFS, %
AC	1361	100			91.2
FEC	1361	92	0.94	.65	92.0

Jacobs SA, et al. SABCS 2014. Abstract S3-02.

Phase III ECOG 1199: Adjuvant Paclitaxel vs Docetaxel, both q3w and qw, in EBC

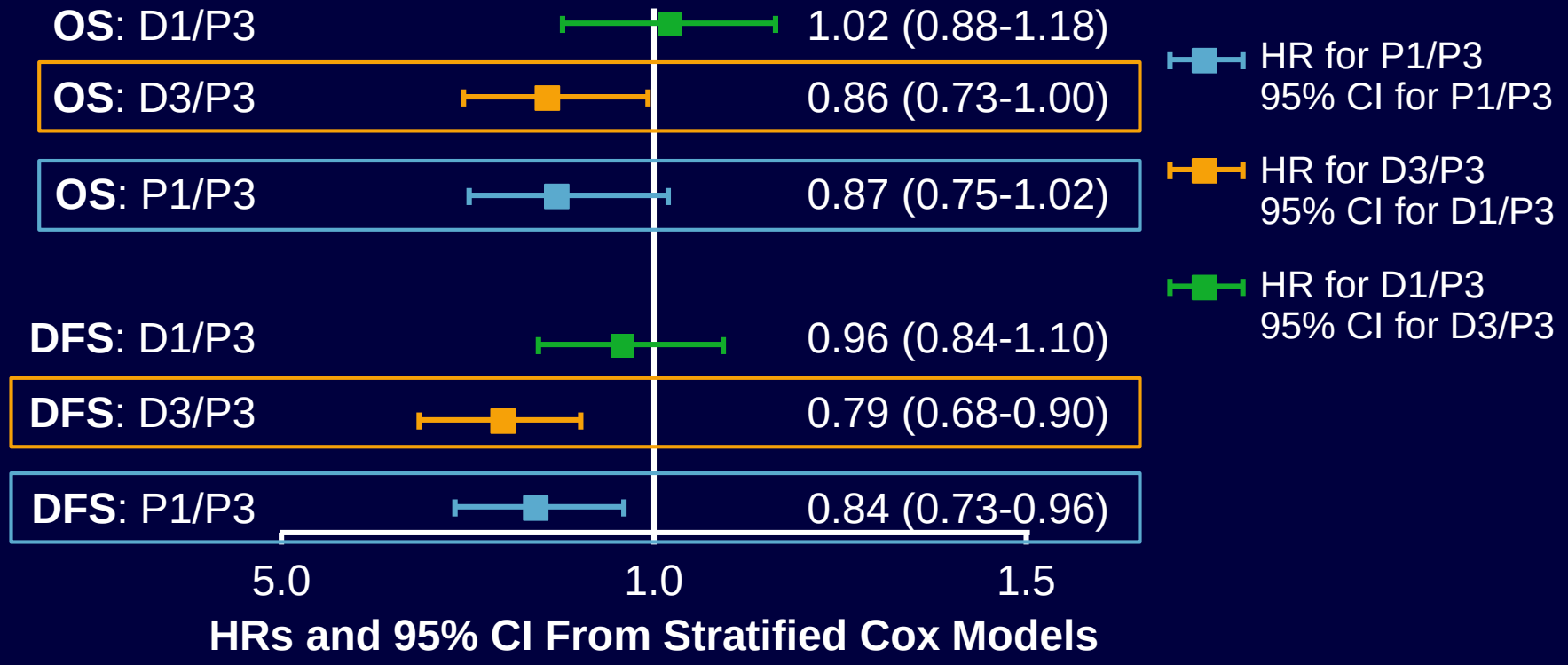


- Primary endpoint: DFS with both paclitaxel vs docetaxel and q3w vs weekly schedule

Sparano J, et al. N Engl J Med. 2008;358:1663-1671.

Adjuvant Paclitaxel vs Docetaxel (E1199): Secondary Comparison of DFS and OS

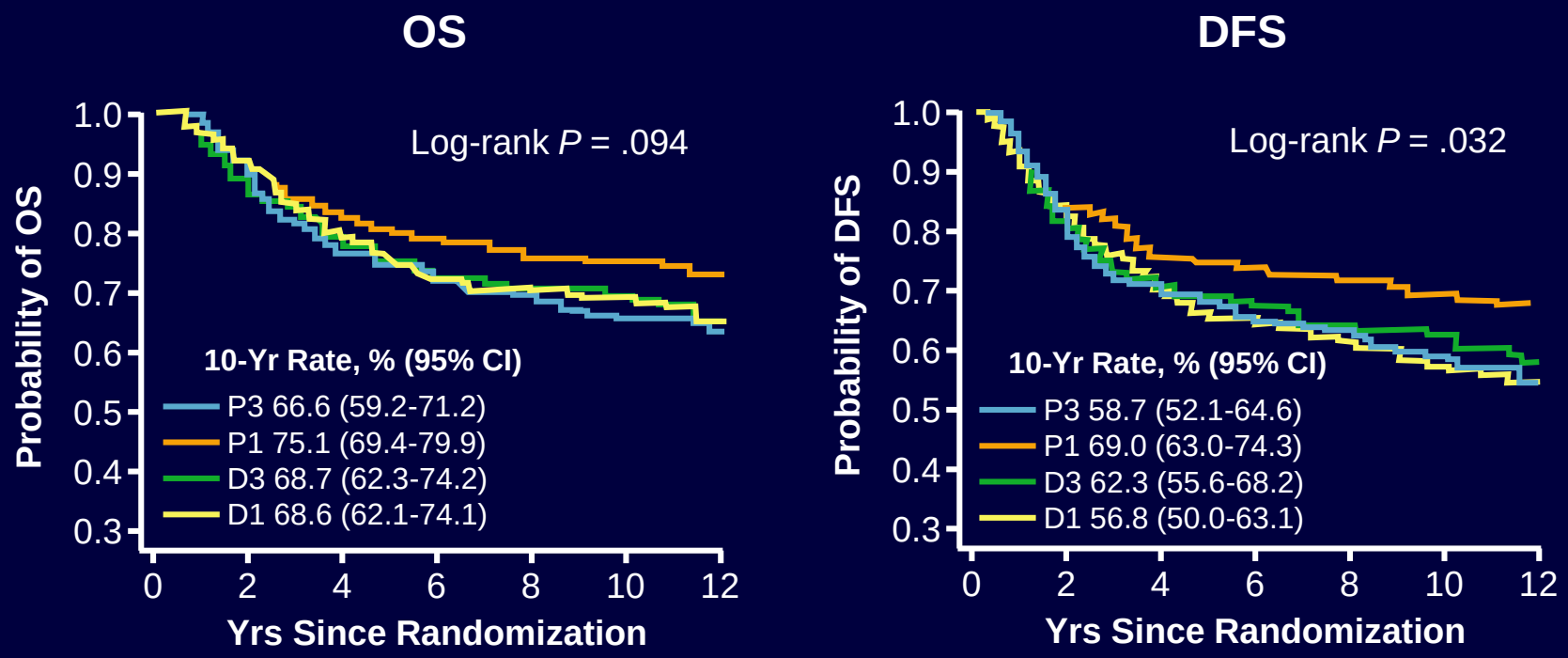
Both paclitaxel qw and docetaxel q3w were superior to paclitaxel q3w



Sparano J, et al. SABCS 2014. Abstract S3-03.

Adjuvant Paclitaxel vs Docetaxel (E1199): Results in Triple-Negative Pts

- Exploratory analysis: paclitaxel qw superior to q3w in triple-negative breast cancer



Sparano J, et al. SABCS 2014. Abstract S3-03.

Adjuvant TC vs EC→T in High-Risk HER2-Negative Early Breast Cancer: Background

- Role of anthracycline-containing regimens for pts with early BC still debated
  - EBCTCG meta-analysis: reduced BC mortality with anthracycline + taxane regimens, increased cardiac mortality with anthracyclines[1]
  - USOR 9735: superior DFS and OS with TC x 4 vs AC x 4[2]
  - ABC joint analysis: improved iDFS with taxane + AC regimens vs TC x 6[3]
- PlanB: prospective, randomized, open-label phase III trial of TC vs EC→T in HER2-negative pts with early BC
  - Current analysis reports final 5-yr results[4]

References in slidenotes.

PlanB: Study Design

Pts ≤ 75 yrs of age
with pN+ or high-risk* pN0
HER2-negative EBC
(N = 2449)†

6 x Docetaxel 75 mg/m² **+ Cyclophosphamide** 600 mg/m²
(n = 1222)

4 x Epirubicin 90 mg/m² **+ Cyclophosphamide** 600 mg/m² →
4 x Docetaxel 100 mg/m²
(n = 1227)

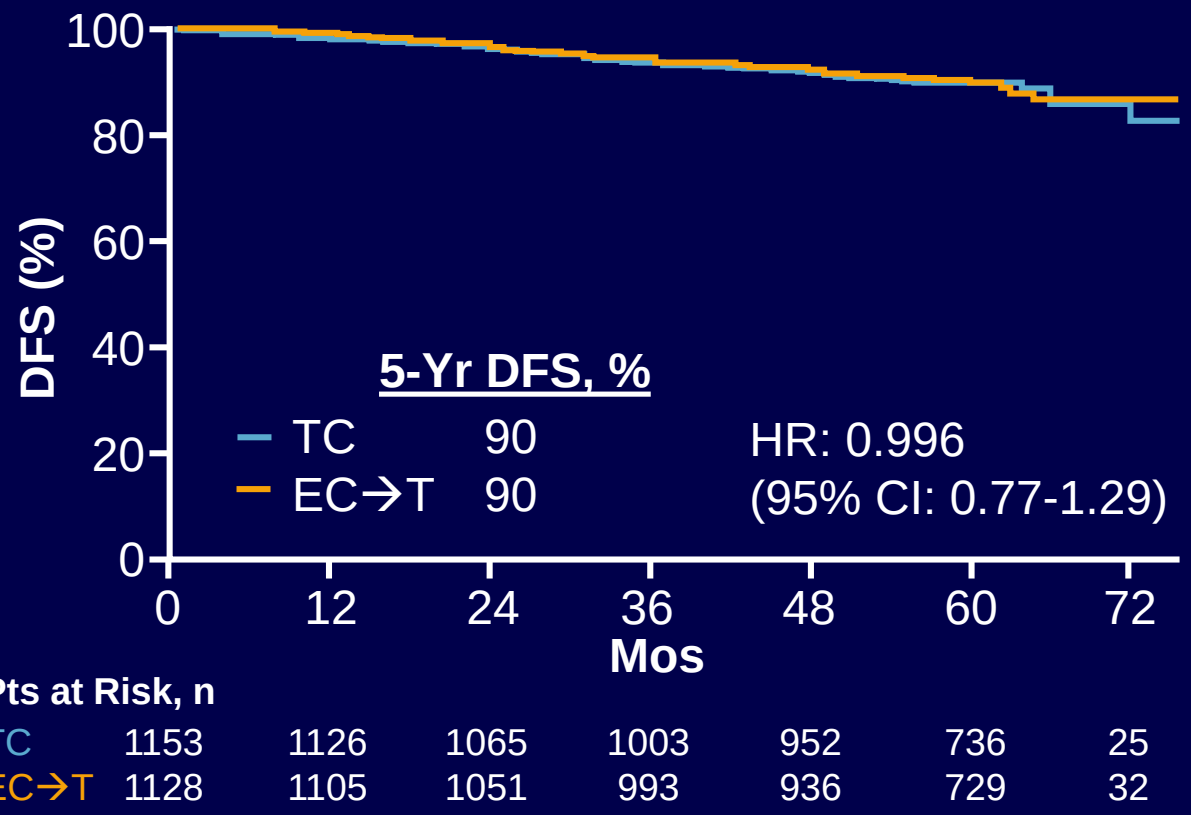
All agents given IV Day 1 Q3W. RT per national guidelines.

*High-risk disease included those with pT ≥ 2, grade 2-3, uPA/PAI-1 high, HR-, or young age (≤ 35 yrs of age).
†In protocol amendment after 263 pts enrolled, HR+ pts with 0-3 LN and RS ≤ 11 excluded from randomization, given endocrine therapy per national guidelines. HR+ pts with 0-3 LN and RS > 11 or ≥ 4 LN randomized per original trial design.

- Primary endpoint: DFS, noninferiority margin: 4.4%
- Secondary endpoints: safety, OS
- Translational subprotocol: prognostic impact of RS vs clinicopathology, outcome in pts with RS ≤ 11 treated with endocrine therapy

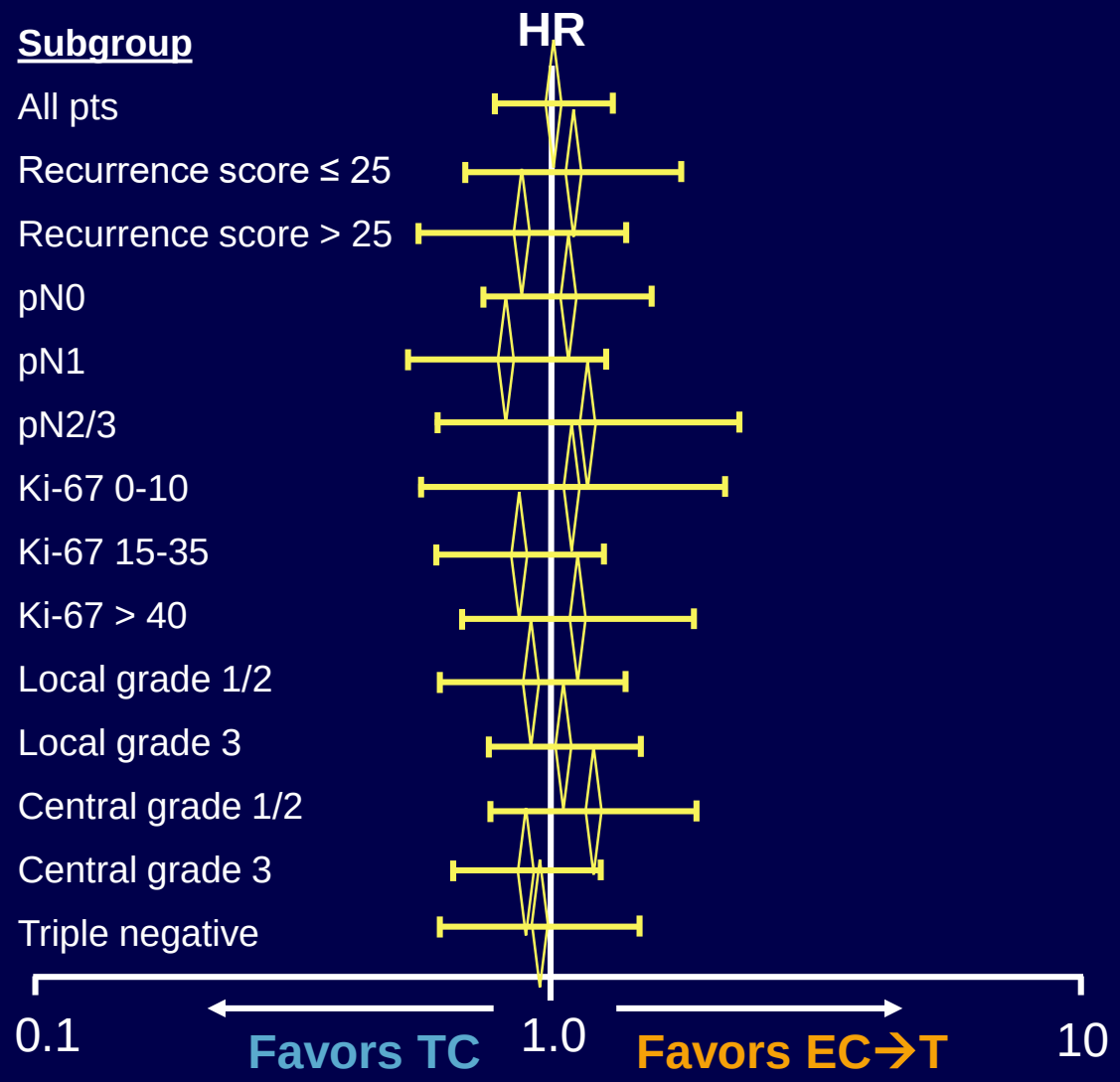
Harbeck N, et al. ASCO 2017. Abstract 504.

PlanB: DFS



Pts at Risk, n

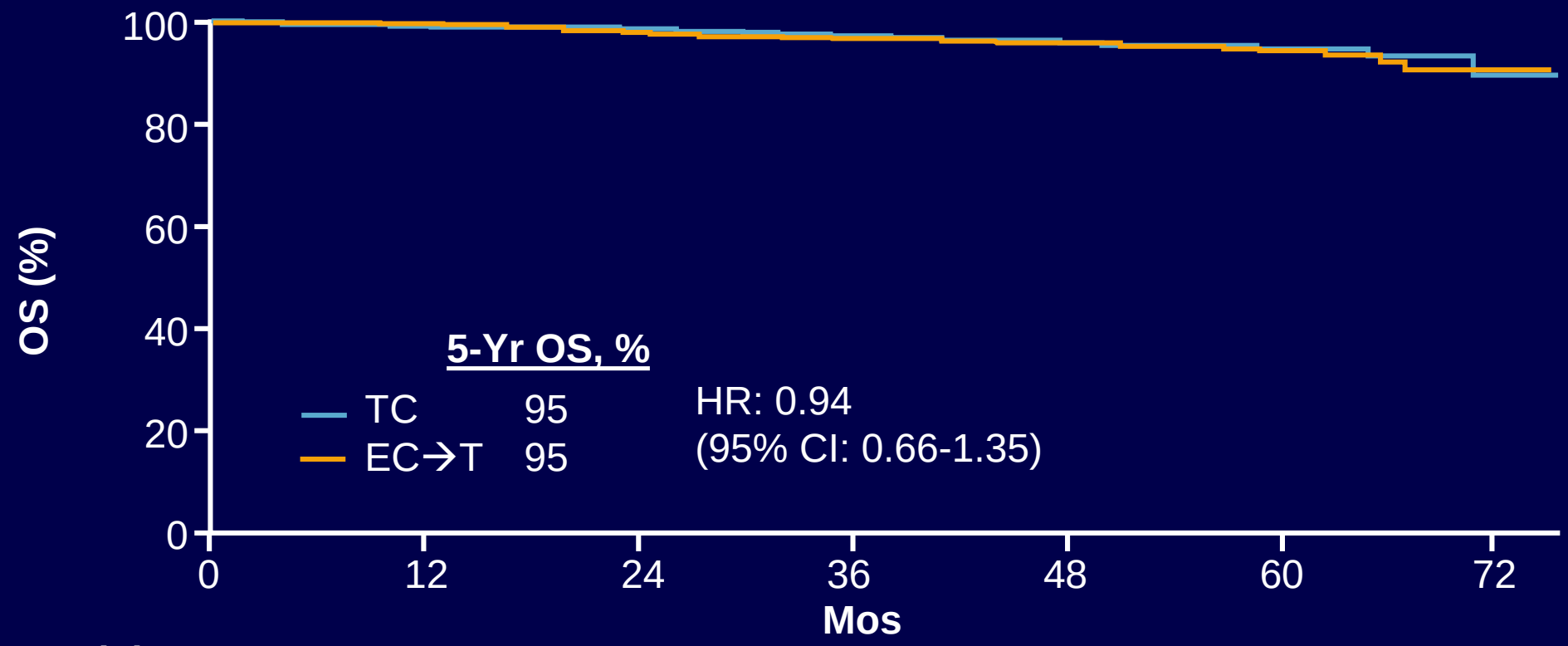
TC	1153	1126	1065	1003	952	736	25
EC→T	1128	1105	1051	993	936	729	32



- Difference in DFS within margin of noninferiority from original trial design

Harbeck N, et al. ASCO 2017. Abstract 504. Reproduced with permission.

PlanB: OS



Pts at Risk, n

TC	1153	1137	1087	1032	979	751	16
EC→T	1128	1112	1063	1016	963	751	25

Harbeck N, et al. ASCO 2017. Abstract 504. Reproduced with permission.

PlanB: Conclusions

- In pts with clinically high-risk or genomically intermediate-/high-risk HER2-negative early BC, TC noninferior to EC→T for DFS
  - Similar 5-yr DFS and OS for TC vs EC→T
  - No subgroup-specific benefit with anthracycline-containing EC→T
- Fewer grade 3/4 AEs, dose reductions/cycle delays with TC vs EC→T
- Study investigators conclude 6 x TC represents effective CT option for HER2-negative early BC, evaluation of novel therapeutics needed in subgroup of pts with high-RS tumors
  - Potential overtreatment with CT suggested by prolonged 5-yr DFS in intermediate-RS tumors to be addressed in WSG-ADAPT trial

Harbeck N, et al. ASCO 2017. Abstract 504.

Maintain full dose density
Women > 70 need more individualized decisions
There is no added benefit to dose escalation in adjuvant treatment
Poly-chemotherapy is preferred

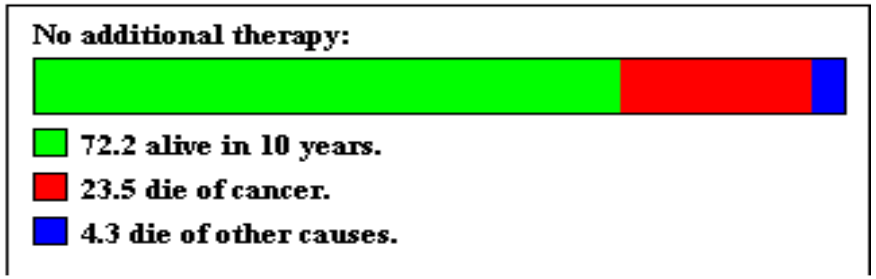
Adjuvant! Online for breast cancer (Updated version) used for a standardized approach to "Clinical Risk"

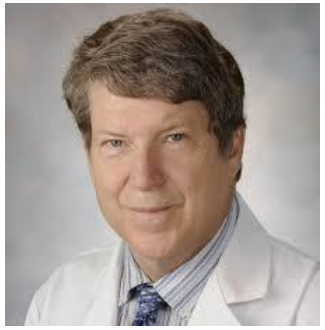
Patient Information

Age:	50
Comorbidity:	Average for Age
ER Status:	Positive
Tumor Grade:	Grade 3
Tumor Size:	2.1 - 3.0 cm
Positive Nodes:	0
Calculate For:	Mortality
10 Year Risk:	24 Prognostic

Adjuvant Therapy Effectiveness

Horm:	Overview 98 (Tamoxifen)
Chemo:	Overview 98 (CMF-Like)
Hormonal Therapy:	28
Chemotherapy:	11
Combined Therapy:	36





P. Ravdin

L. van 't Veer

IMPROVED RISK ASSESSMENT OF EARLY BREAST CANCER THROUGH GENE EXPRESSION PROFILING

R. Bernards

78 untreated N⁻ primary tumors

295 partially treated N⁻ / N⁺ tumors

44 w/o relapse at 8 y follow-up

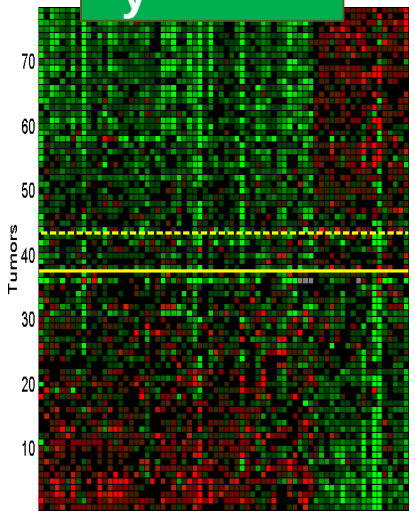
34 with a relapse within 5 y

5000 genes

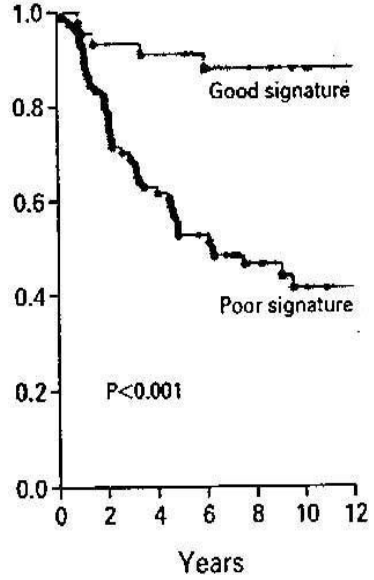
231 genes

70 genes
Poor prognosis signature

microarray



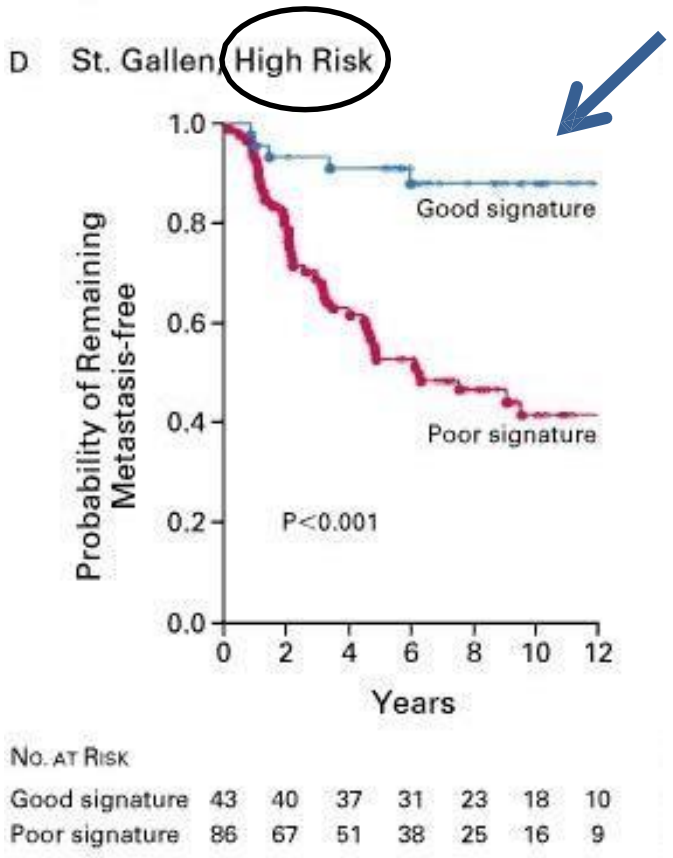
Gene-expression profile

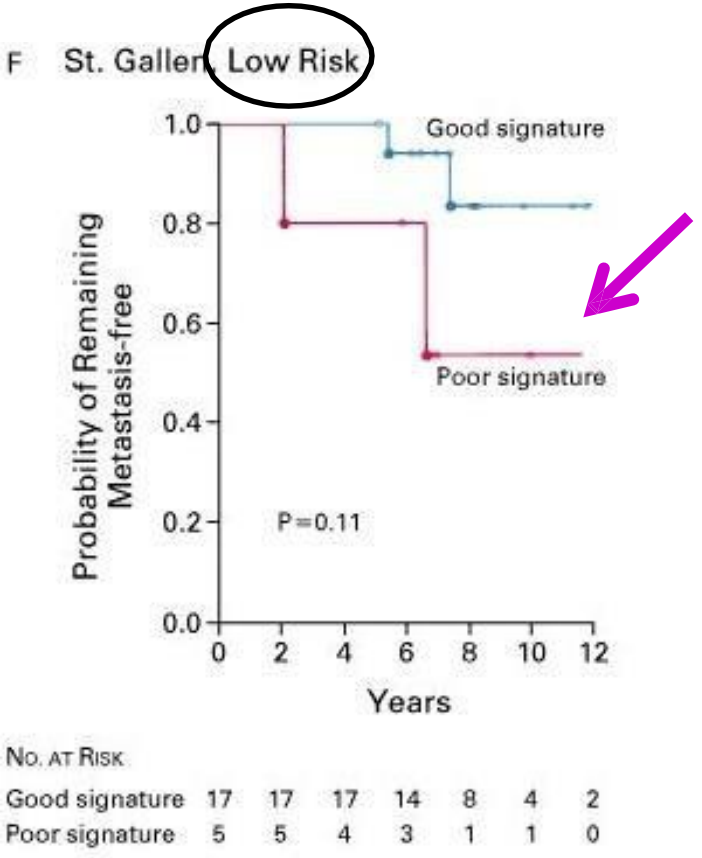


van 't Veer L., Nature 2002; 415(31): 530-536

Van de Vijver MJ, N Engl J Med 2002; 347 (24):

B.C. CLINICAL OUTCOME PREDICTION
70-gene profiler outperforms St Gallen criteria





Van de Vijver MJ, N Engl J Med 2002; 347 (24): 1999-2009

Amsterdam gene-expression prognostic signature N=78 / 151

Independent validation study on archive material

- Other populations
- Internal + external quality assurance

High powered clinical trial specifically addressing the gene signature's utility: MINDACT

Level 5 and 4

Level 3

Level 1

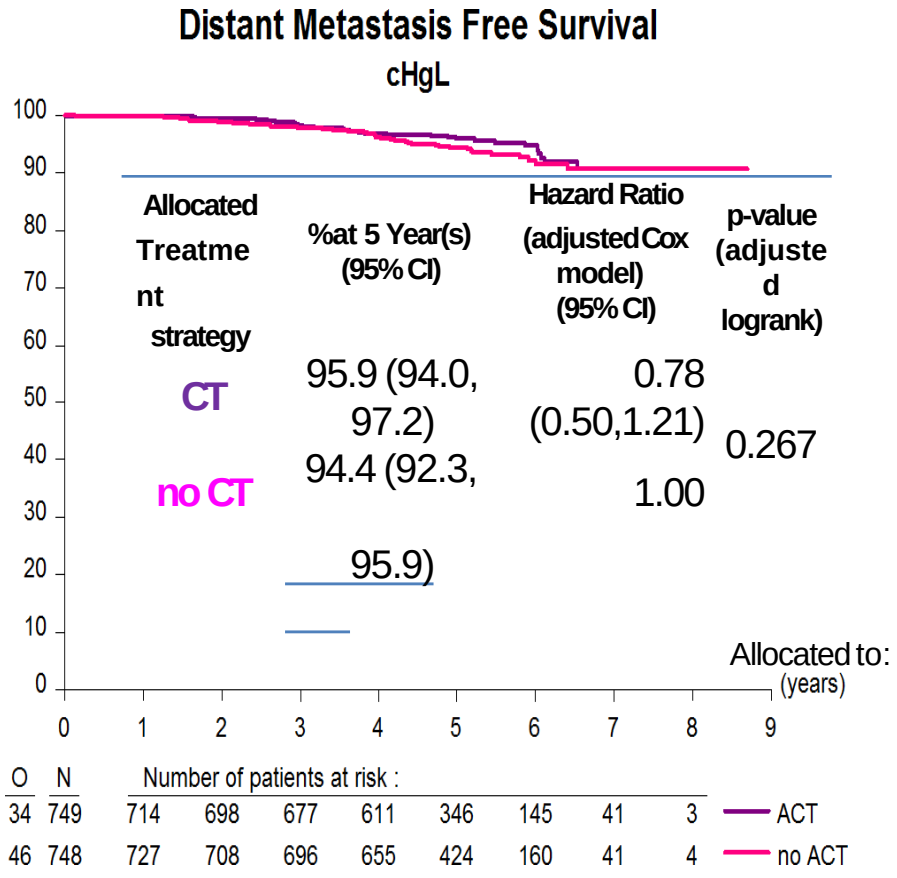
Levels of evidence for biomarker studies

E.U. GRANT, 6th Framework Programme
Coordination: F. Cardoso, M.

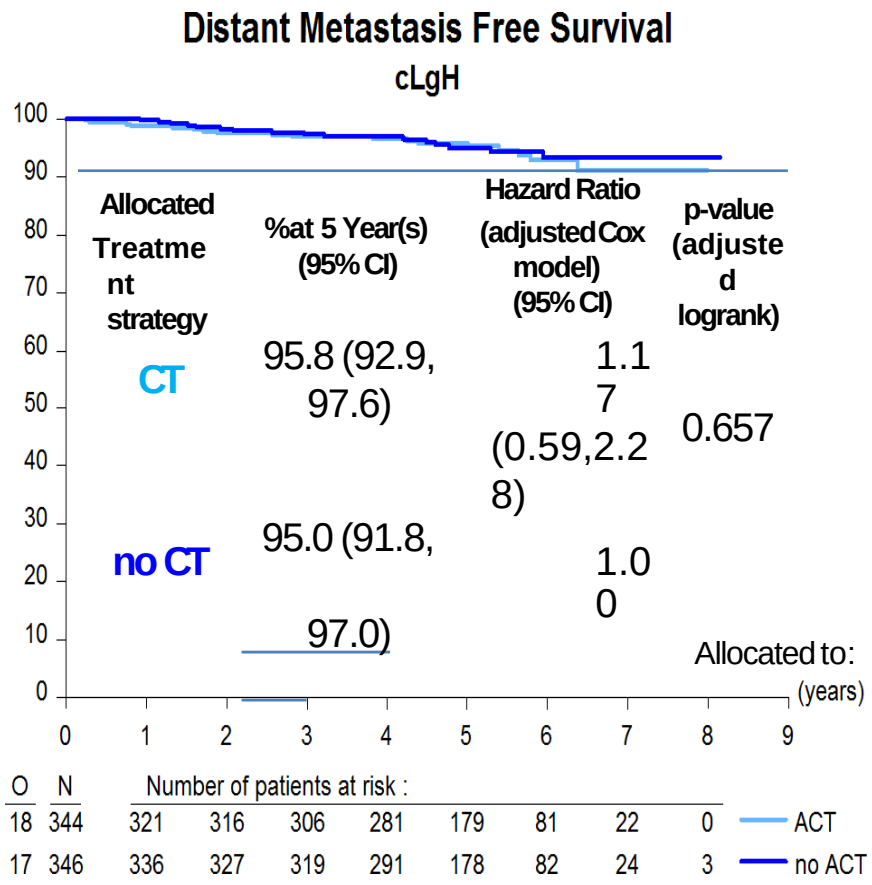
Efficacy: CT vs no CT in discordant risk groups

Intent-to-treat analysis

Distant Metastasis Free Survival
c-High/g-Low



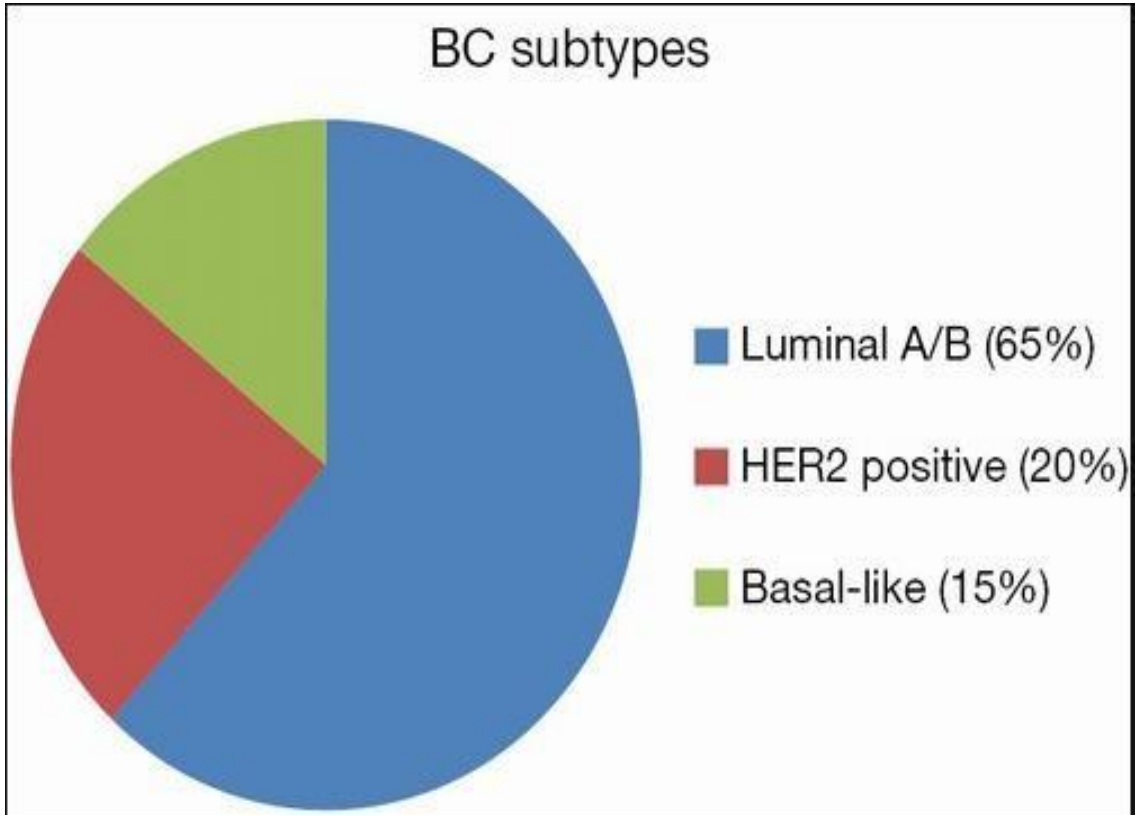
Distant Metastasis Free Survival
c-Low/g-High



Breast cancer is many diseases!

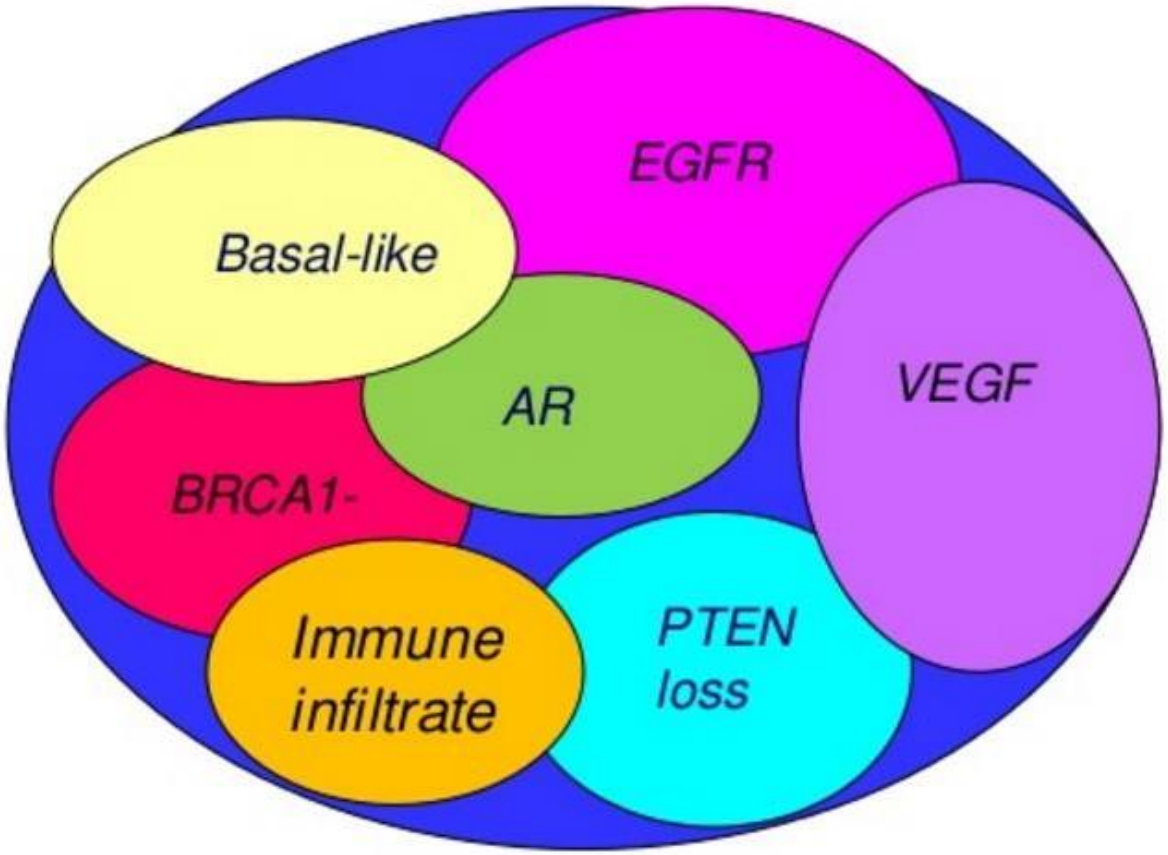
MOLECULAR CLASSIFICATION OF BREAST CANCER

Subtype	Molecular characteristics	Histological characteristics SURROGATES	Biology/treatment
Luminal A	• luminal CK expression • resembles normal epithelium cells	• ER+ • low grade	• indolent behaviour • sensitive to hormonal therapy
Luminal B	•*similar than luminal A*	• ER+ (lower expression than in luminal A) • high grade	• more aggressive behaviour than luminal A •less sensitive to hormonal therapy than luminal A
Basal-like	• without expression of ER, PR and HER-2 genes •basal CK expression (CK5) • expression of growth factors (EGFR, c-kit, HGF, IGF) • BRCA disfunction • genetic instability	•" Triple negative" (ER-, PR -, HER 2-) • high grade	• aggressive behaviour • sensitive to chemotherapy
Her-2 enriched	• amplification of HER-2 gene and overexpression of HER-2 receptor	• HER 2+ • high grade	• aggressive • sensitive to anti-HER-2 therapy • sensitive to chemotherapy



Heterogeneity of TNBC: It is not one disease

Different subtypes may have different 'Achilles heels'



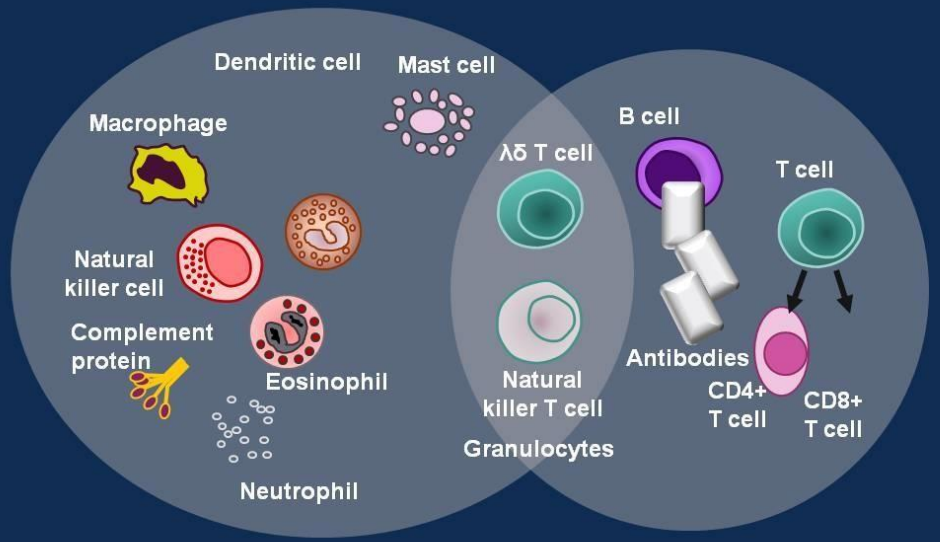
Many Approaches Under Evaluation for TNBC in Clinical Trials

Pathway/Drug type	Drugs in development
DNA repair	PARP inhibitors (olaparib, rucaparib, veliparib), platinum agents (cisplatin, carboplatin)
PI3K/Akt/mTOR	PI3K inhibitors (buparlisib, taselisib, GDC0941, AZD8186, many others); Akt inhibitors (GDC0068, others), mTOR inhibitors (everolimus, others)
Androgen (testosterone) signaling	Anti-androgens (bicalutamide, enzalutamide)
Immune	CTLA4 blockade (ipilumumab), PD1/PD-L1 blockade (nivolumab, pembrolizumab, atezolizumab),
Antibody-drug conjugates	IMMU-132, SGN-LIV1A, PF06647263, CDX-011
Cell cycle	Dinaciclib, seleciclib
Chk1	GDC0575
Bromodomain	TEN-101, GSK525762
Heat shock (stress)	Ganetespib, others
Angiogenesis	Ramucirumab, cedirinib

Background: The Immune System

Innate Immunity

- Nonspecific, activated quickly in response to a pathogen
- Activates the adaptive response



Adaptive Immunity

- Specific, activated in response to recognition of a specific pathogen
- Includes T-cell stimulation, B-cell antibody production
- Has a memory component

What should happen: tumor-associated antigens recognized by the immune system and destroyed by both innate and adaptive immune mechanisms (including activation of T cells)

What often happens: Tumors evade detection and destruction by the immune system through immune tolerance and acquiring resistance to killing by activated immune cells.

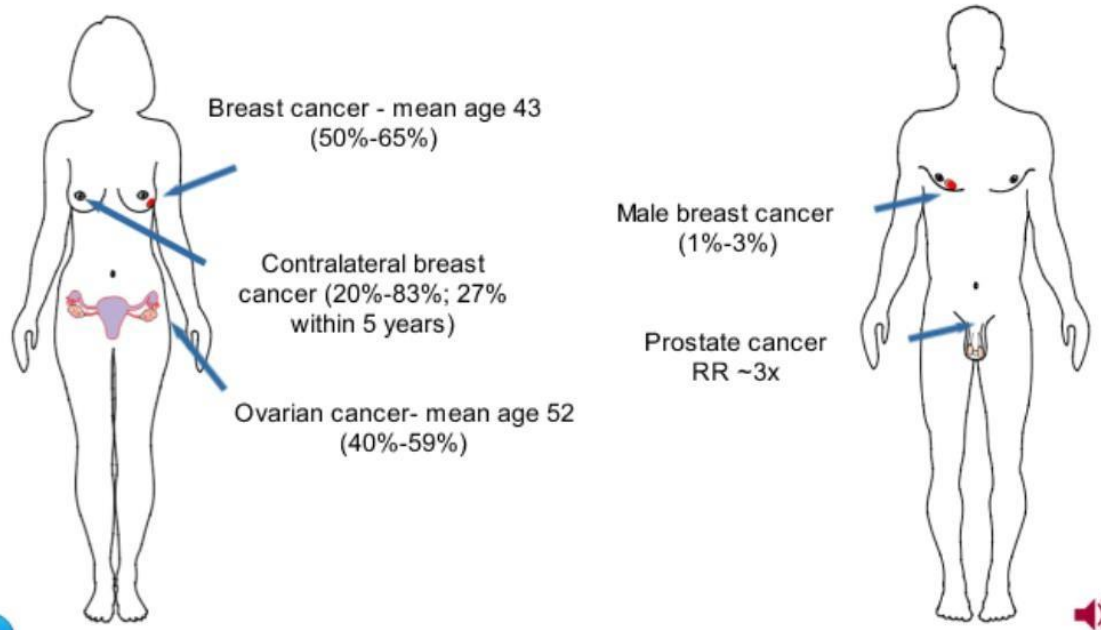
Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

Why is TNBC a good target for immunotherapy?

- High mutation rate, which can produce neoantigens that induce an immune response
- Increased number of tumor-infiltrating lymphocytes, which can facilitate an immune response
- Higher PD-L1 expression levels, which can inhibit T-cell antitumor responses, as compared with other breast cancer subtypes

BRCA mutation- Cancer risks

BRCA1-Associated Breast and Ovarian Cancers: Risk to Patients Age 70 Years



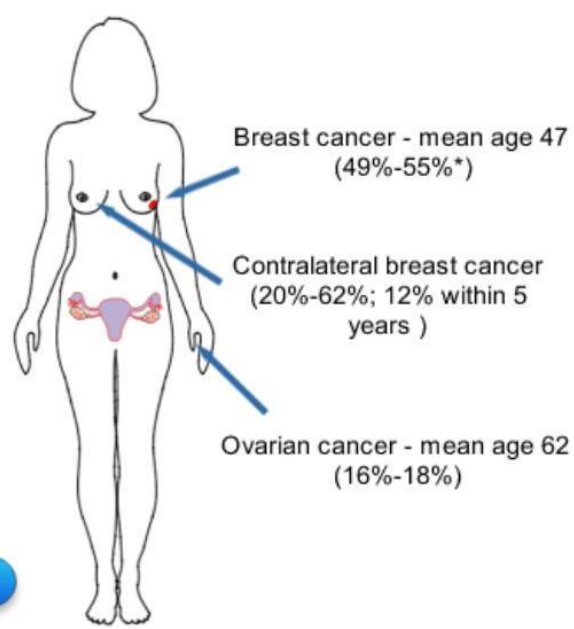
Audio

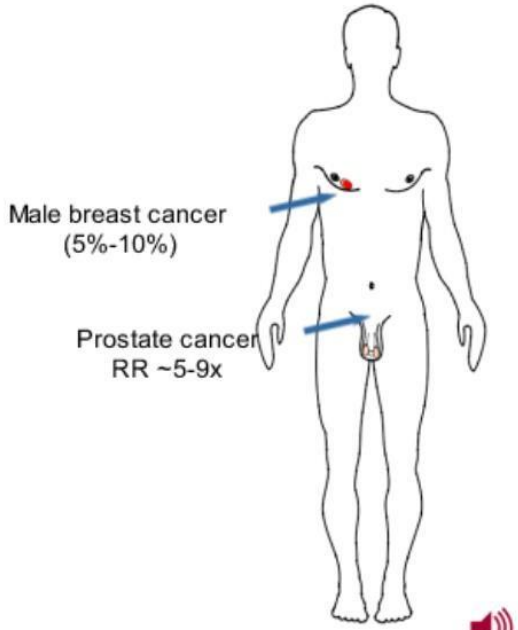
Dr. Lindor

ASCO University

Cancer Genetics Program

BRCA2-Associated Breast and Ovarian Cancers: Risk to Patients Age 70 Years





*28% in Jewish populations with *BRCA2* 6174delT

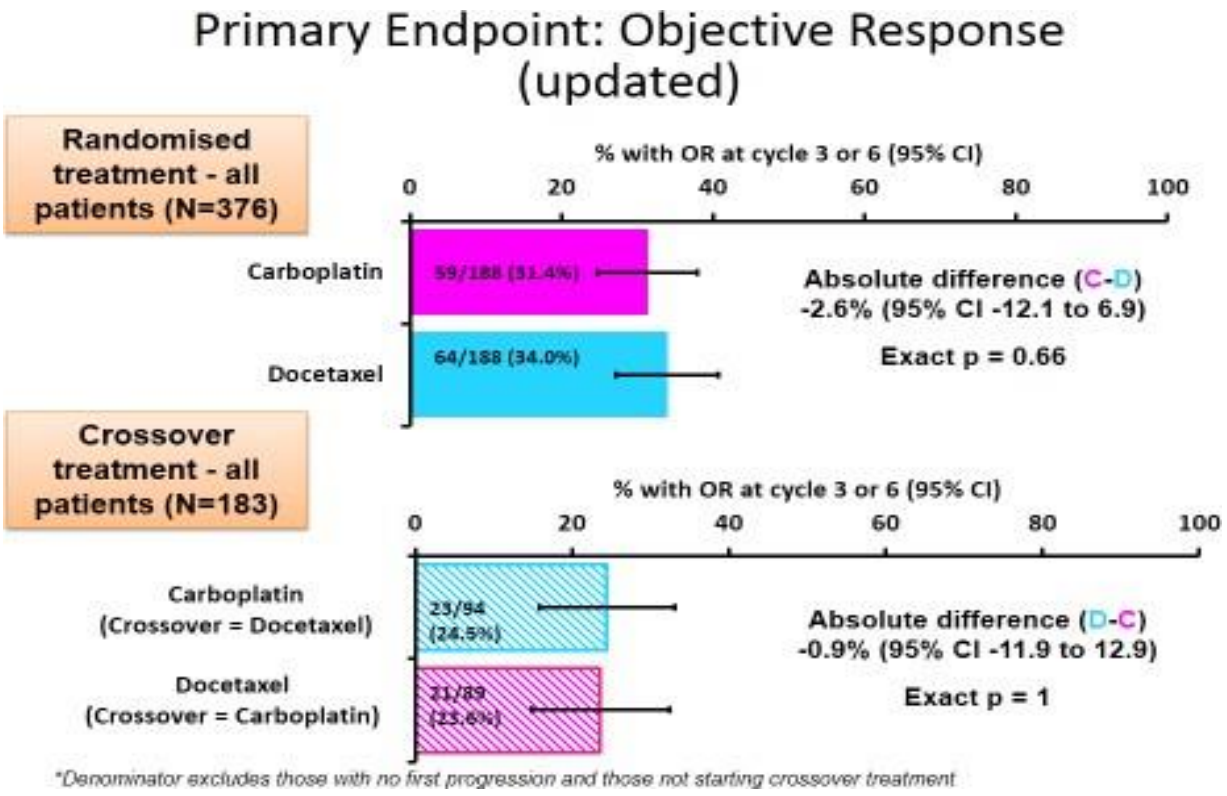
Audio

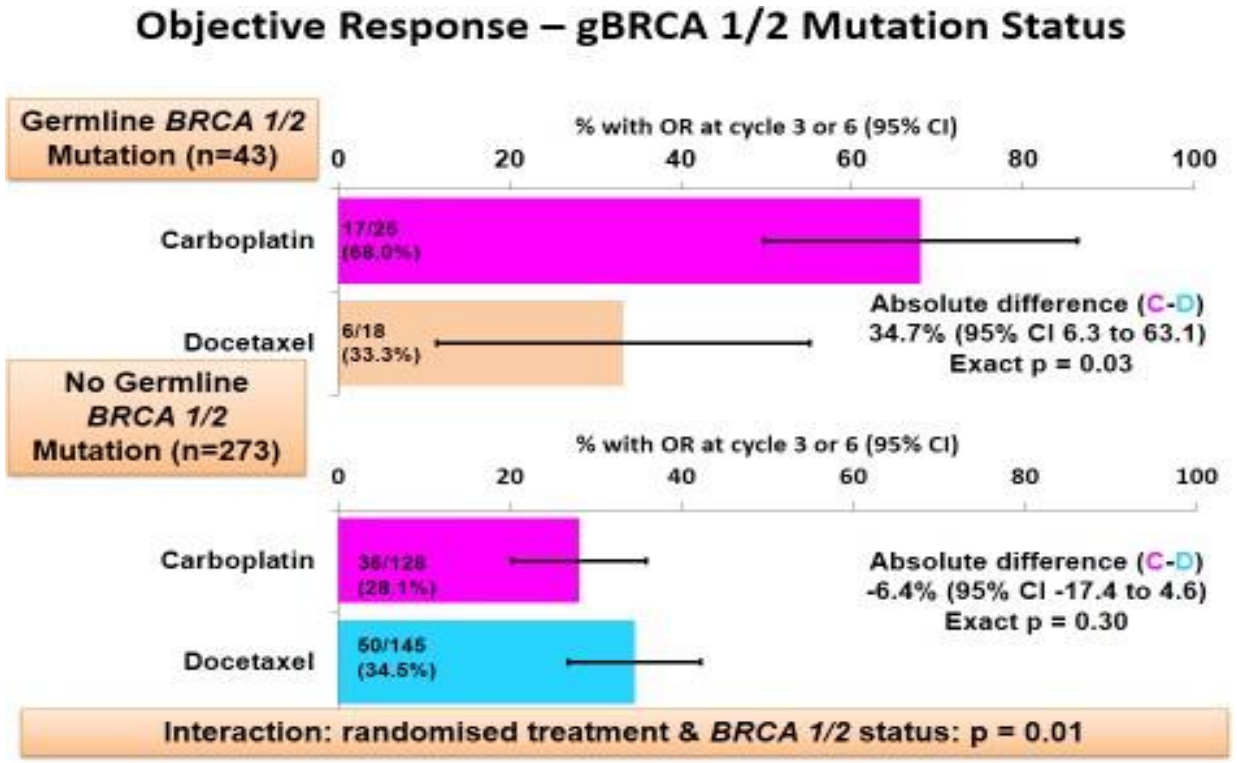
Dr. Lindor

ASCO University

Cancer Genetics Program

TNT Trial: First-Line Chemotherapy for TNBC





HRD did not predict benefit from carboplatin

In *BRCA* wildtype with *BRCA* gene silencing or low expression, no additional impact of carboplatin

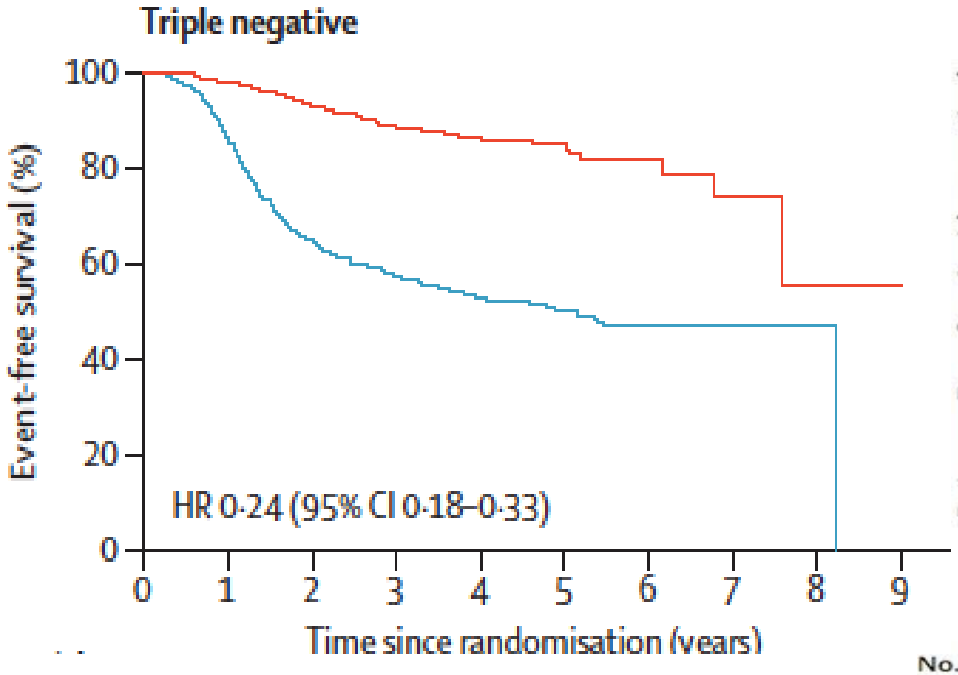
PFS by *BRCA* mutation status

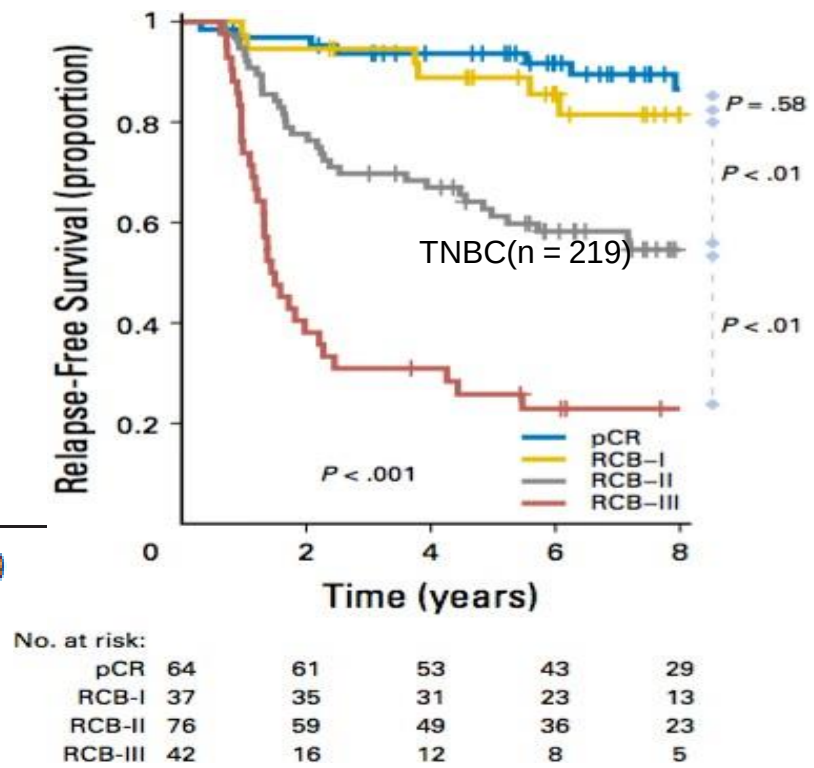
	BRCA 1/2 mutated	*BRCA* 1/2 not mutated
D	4.4 mo (1.9-7.0)	4.6 mo (4.2-5.5)
C	6.8 mo (4.6-8.5)	2.9 mo (2.3-4.2)

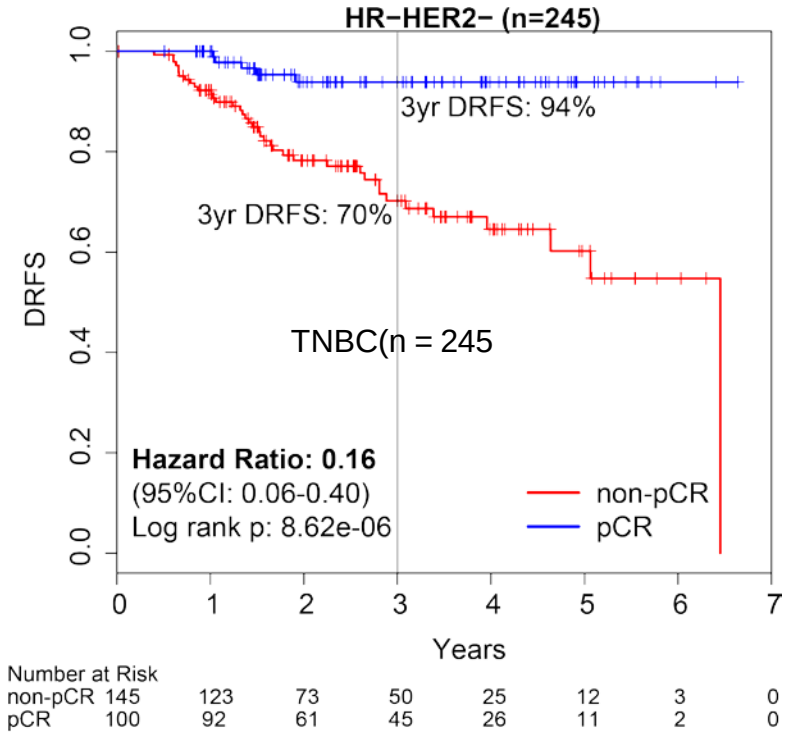
Tutt A, et al. *Nat Med.* 2018;24(5):628-637.

Prognostic Implications: Neoadjuvant Therapy for TNBC

- **Among the highest pCR rates are seen in TNBC**
- **pCR associated with excellent outcomes**





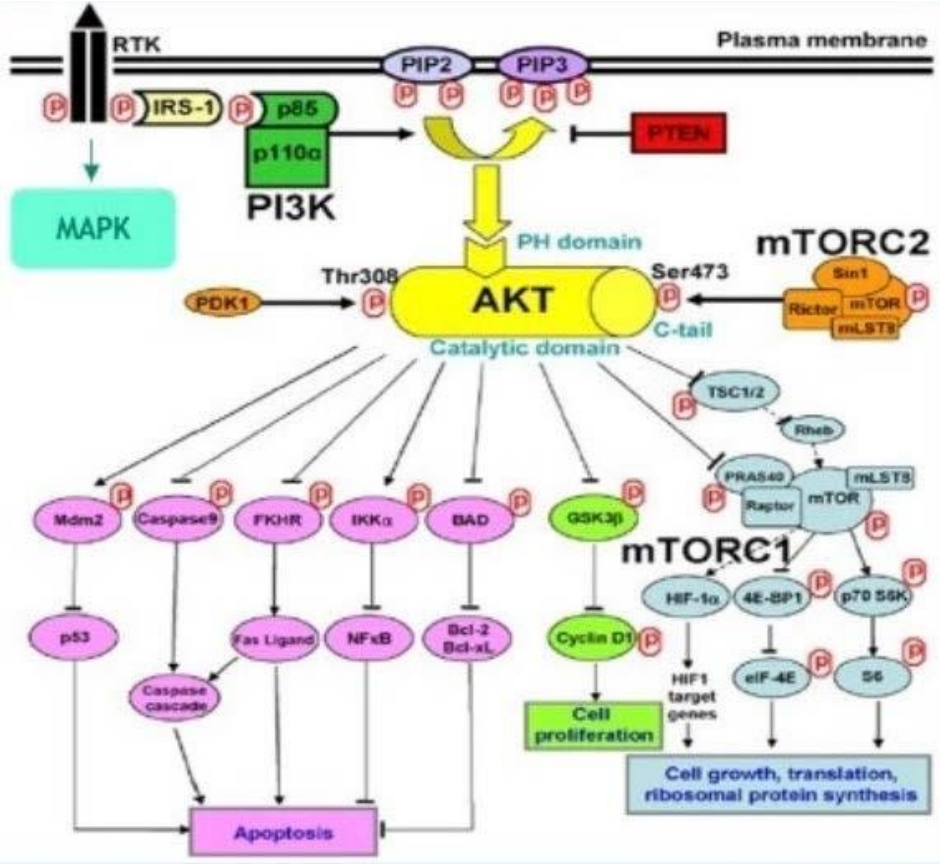


Cortazar P, et al. *Lancet.* 2014;384(9938):164-172. Symmans WF, et al. *J Clin Oncol.* 2017;35(10):1049-1060. Yee D, et al. *Cancer Res.* 2018;78(4 Suppl): Abstract GS3-08.

- **The bottom line:**
  - **Carboplatin improves pCR in sporadic TNBC**
  - **Less benefit in patients with g*BRCA* mutations when added to standard chemotherapy**
  - **Survival benefit remains uncertain**
  - **May be a replacement for anthracyclines in patients with an excellent response**
- **No evidence that any known marker identifies a group that will benefit other than *BRCA* germline mutations**
  - **HRD has not yet defined a group of patients who benefit more from DNA-damaging agents**
  - **Higher response in *BRCA* mutation carriers in MBC (TNT) is not powered to correlate with survival**

Breast Cancer and PI3K/AKT Pathway

The PI3K/AKT pathway is one o the most frequently altered pathways in breast cancer and is key for survival and growth of tumors

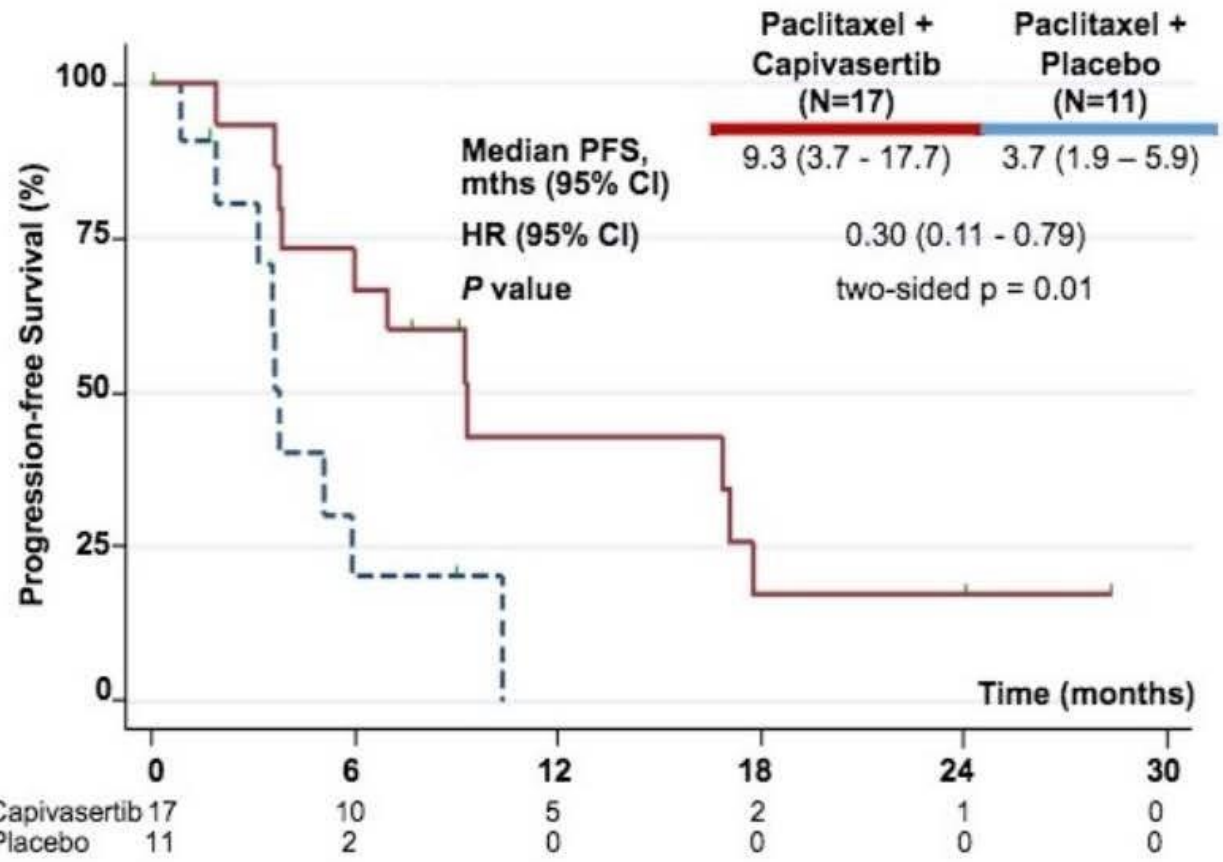


AKT can be activated by:

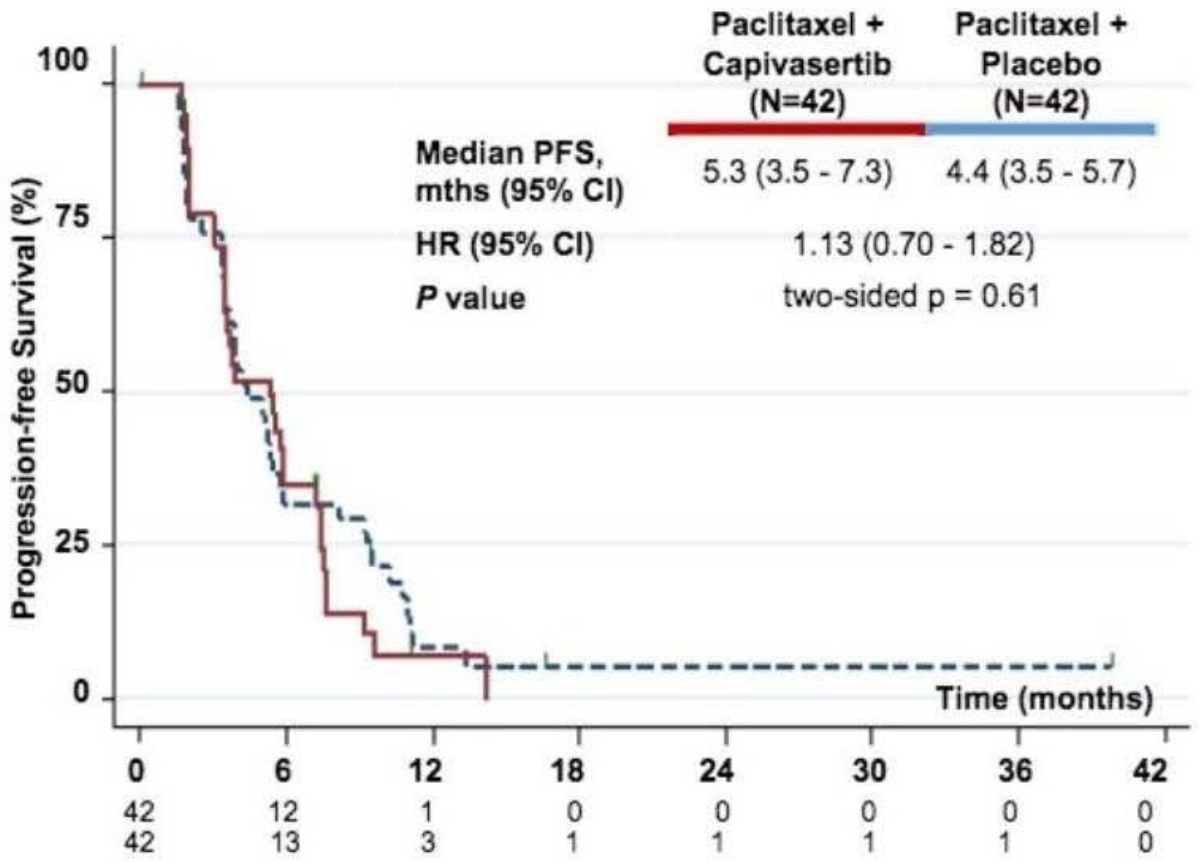
- **Loss of function of negative regulators:**
  - **PTEN**
  - **INPP48**
  - **PHLPP**
  - **PP2A**
- **Gain of function of positive regulators:**
  - **PI3K**
  - **AKT**
  - **Receptor tyrosine kinases (HER2)**
- **Therapy-induced survival response**
  - **Chemotherapy**
  - **Hormone therapy**

Yap TA, et al. *Curr Opin Pharmacol.* 2008;8(4):393-412. Manning BD, et al. *Cell.* 2017;169(3):381-405.
Dent R, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 1008.

PI3KCA/AKT1/PTEN Altered



PI3KCA/AKT1/PTEN Not Altered

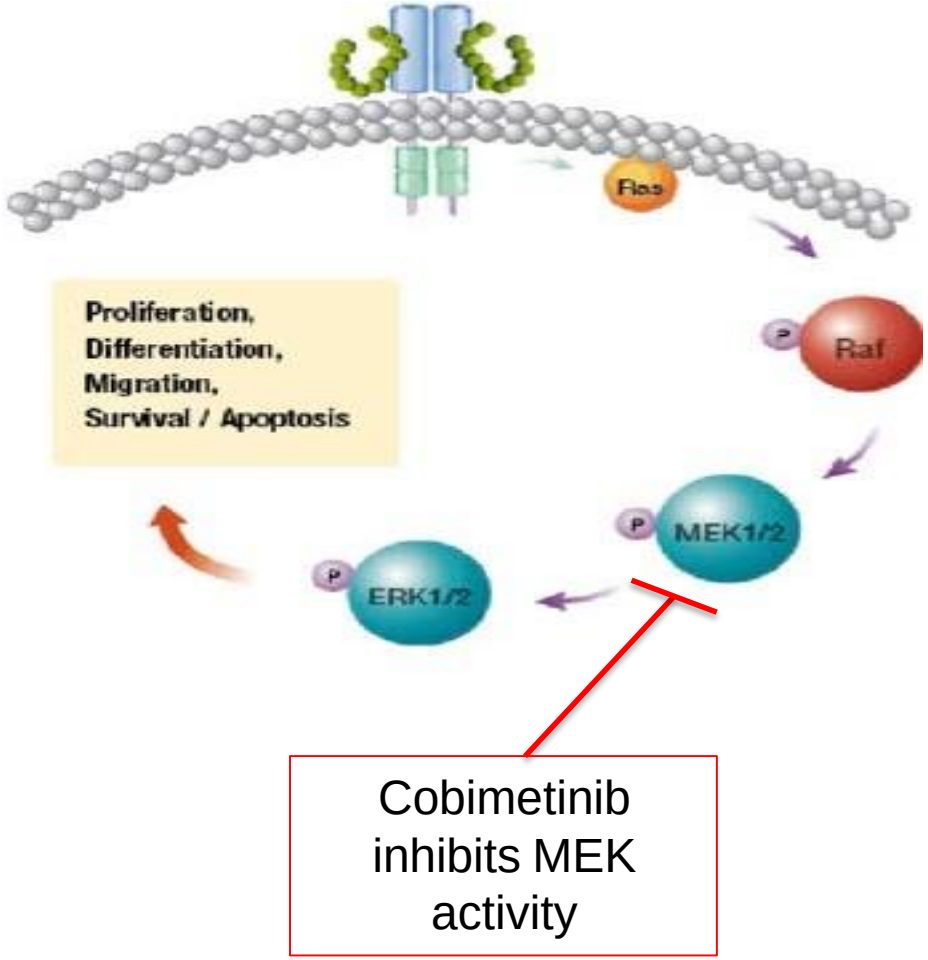


CI = confidence interval; HR = hazard ratio; mths = months; PFS = progression-free survival

Schmid P, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 1007.

Targeting MEK

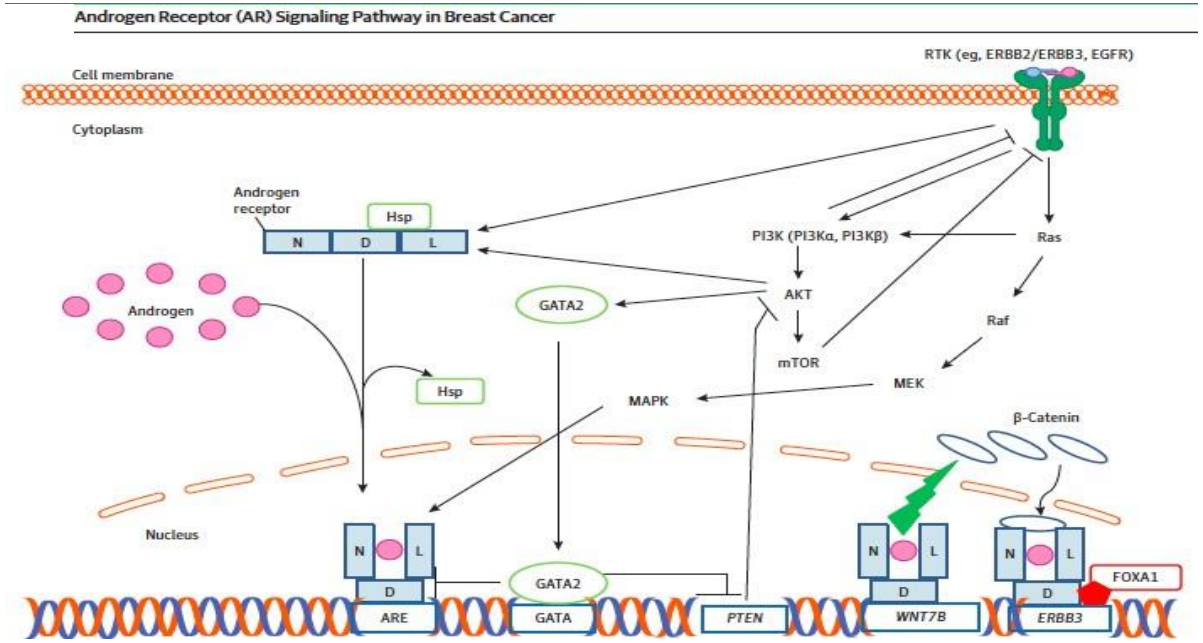
- **Increased activation of the MAPK pathway is associated with:**
  - **Reduced TILS, poorer tumor-specific immune response**
  - **Upregulation of MAPK confers resistance to taxanes**
- **This pathway is altered in many TNBC**
  - **Adding MEK inhibitor to taxane increased the sensitivity of breast cancer cells to taxanes**
- **Cobimetinib**
  - **Potent highly selective MEK inhibitor**
  - **COLET (NCY02322814), n = 90 in randomized phase II multicohort trial**
    - **Cobimetinib plus paclitaxel as first-line therapy for mTNBC**
    - **PFS 3.8 mo vs 5.5 mo (HR 0.73; 0.43-1.24, *P* = .2); ORR 21% vs 38%**
    - **Next stage in combination with immunotherapy ongoing**
    - **Toxicity is GI and hematologic**



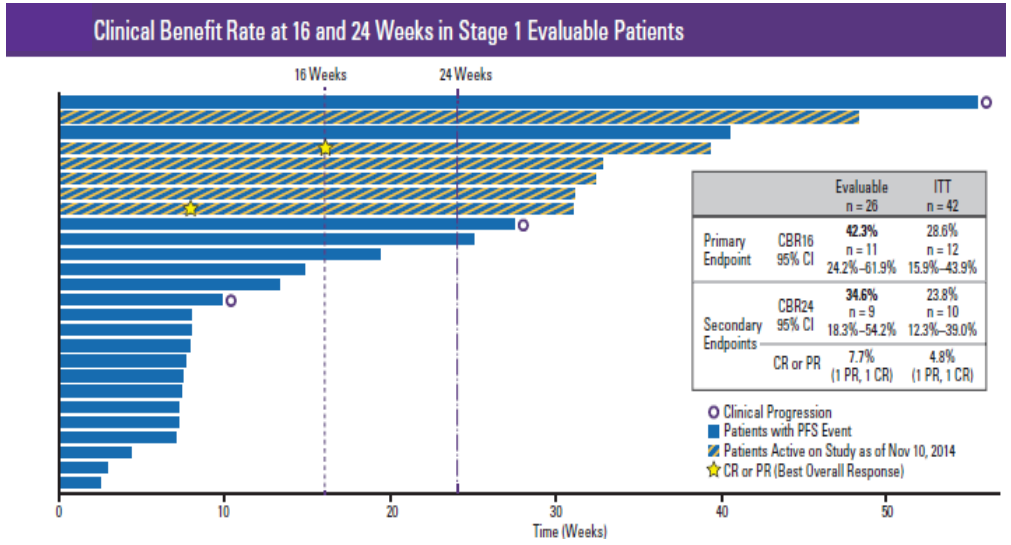
Brufsky A, et al. *Cancer Res.* 2018;78(4 Suppl): Abstract P5-21-01.

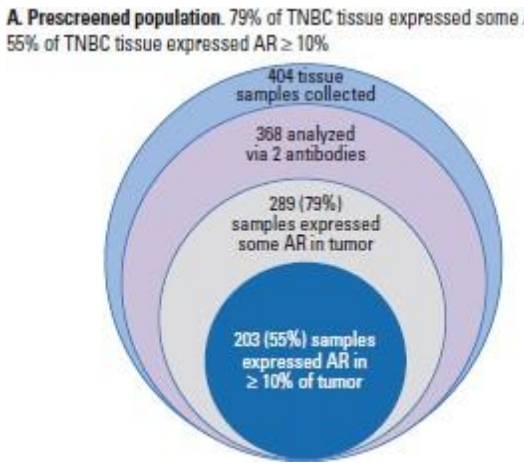
Targeting the Androgen Receptor

- **Bicalutamide in AR+ TNBC**
  - **452 screened, 12% AR+**
  - **28 on study, CBR 21%**
- **Enzalutamide in AR+ TNBC**
- **118 enrolled, 78 evaluable**
  - **CBR 16 weeks: 25% in ITT, 33% in the evaluable pts**



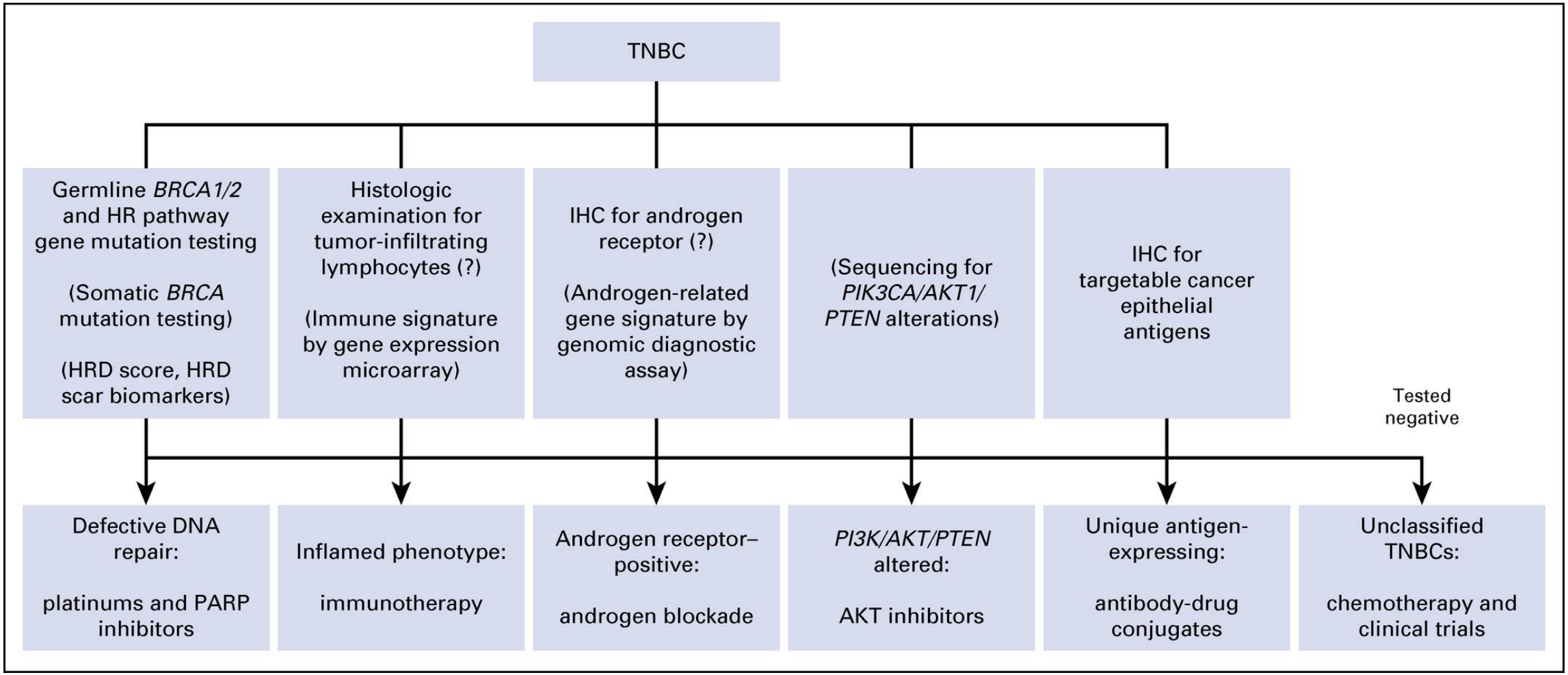
Kono M, et al. *JAMA Oncol.* 2017;3(9):1266-1273.





Gucalp A, et al. *Clin Cancer Res.* 2013;19(19):5505-5512.
Traina TA, et al. *J Clin Oncol.* 2018;36(9):884-890.

Overview of TNBC



HR, homologous recombination; HRD, homologous recombination deficiency; IHC, immunohistochemistry

Chan JJ, et al. *J Oncol Pract.* 2018;14(5):281-289.

Conclusions: 'Take home' points

- Identifying 'at risk' populations for breast cancer has become increasingly complex...more genes=more questions. Knowledge/research must catch up to technology!
- Increasing use molecular testing-- prognostic and predictive tools, to customize adjuvant therapies to each individual. No two cancers are the same!
- Molecular characterization of metastatic breast cancer has allowed us to identify, and better target, various subtypes of breast cancer. Promising drugs have been approved--with many others on the horizon!