New Approaches in Breast Cancer Treatment

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Disclosures

Advisory board/honorarium (commercial):

- Genomic Health
- NanoString

Clinical trial participation (commercial):

- Roche
- Novartis
- Pfizer
- AstraZeneca
- Amgen

Mitigation of CoI

- Generic drug names only
- Balanced pros and cons
- Evidence based

Objectives

By the end of this session, participants will be able to:

1. Understand the context for introducing new drug treatments
2. Identify and justify the selection of novel approaches and therapies available for management of breast cancer
3. Supervise the management of side-effects of these therapies

Context and Background

- Drug development and reimbursement
- Endpoints and Goals of Therapy
- Biomarkers

Newer treatments

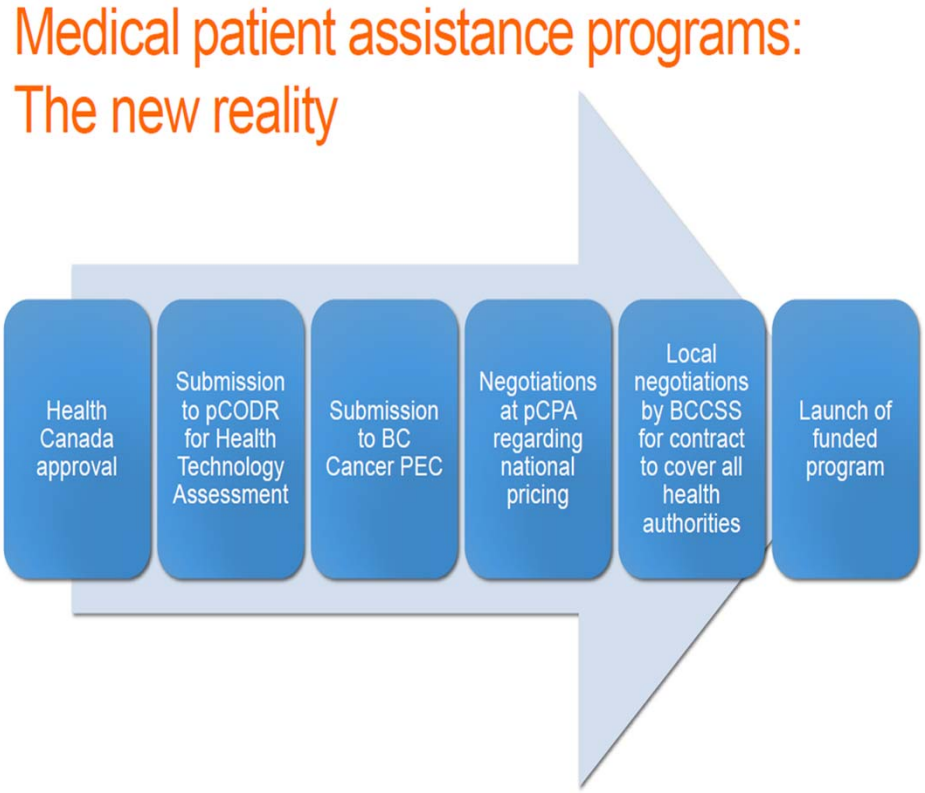
Drug Development

- Preclinical
- Clinical Trials:
  - Phase One: Investigational New Drug
  - Phase Two: Efficacy
  - Phase Three: Compare to standard of care
- New Drug Application
- HPFB of Health Canada issues Notice of Compliance (NOC)

- Special Access Program
  - allows physicians to gain access to drugs not available in Canada

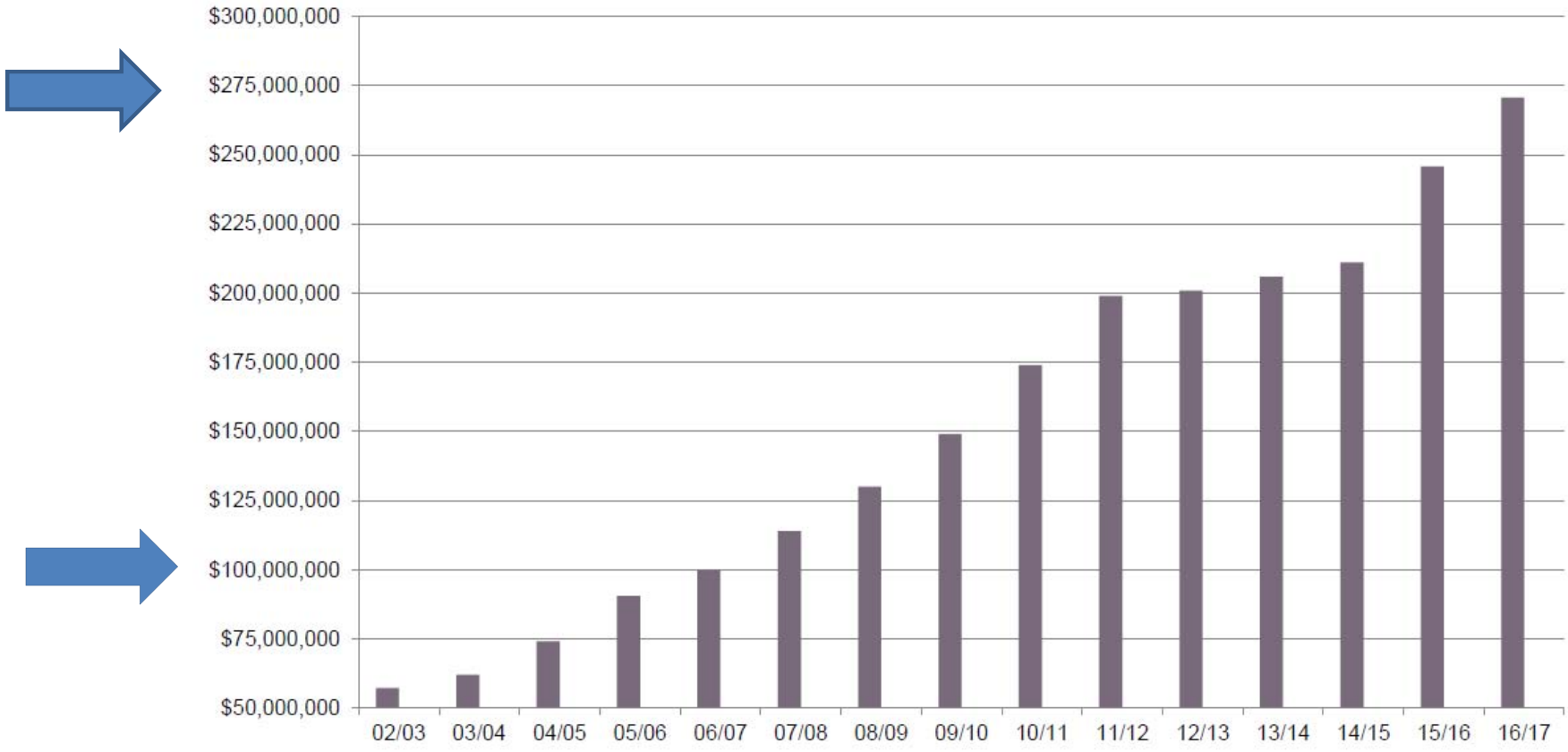
Newer treatments: Reimbursement

- National
  - Pan Canadian Oncology Drug Review (pCODR); value
- Provincial
  - Final reimbursement decisions: cancer agencies/drug plans
    - pCODR recommendations
    - other factors
      - program mandates, jurisdictional priorities, budget impact
- British Columbia
  - BC Cancer Priorities Evaluation Committee (PEC)
    - cost benefit ratio: palliative and curative
    - total life support drug budget
  - Compassionate Access Program (CAP)



Courtesy Dr Cheryl Ho

Growth in BC Cancer Drug budget



Newer treatments by biomarker subtype and stage

	ER positive	HER2 positive	Triple Negative	Other
Adjuvant **Neoadjuvant**	**TAILORx** **OFS+TAM** **OFS+EXE** **Endocrine beyond 5 years** (Palbociclib)	(Pertuzumab) Pertuzumab	Platinum agents	**Postmenopausal: bisphosphonate** denosumab (BRCA1/2 mutated: PARPi eg olaparib)
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Adjuvant and Metastatic: Endpoints and Goals

Adjuvant (early, curable)

Clinical Endpoints

- Disease free survival
- Distant DFS
- Overall survival
- Return to pre cancer baseline

Goals

- Delay relapse and improve DFS
- Cure a larger proportion
- Benefit must be > risk/toxicity

Metastatic (advanced, treatable)

Clinical Endpoints

- CR+ PR (ORR) + stable disease = clinical benefit rate
- Progression Free Survival
- Overall Survival

Goals

- Prolong PFS
- Prolong OS
- Maintain/improve quality of life
  - Manage toxicities

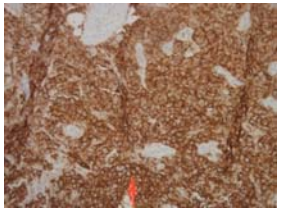
Neoadjuvant Therapy (NAT)

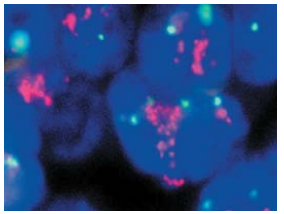
a.k.a. Primary Systemic

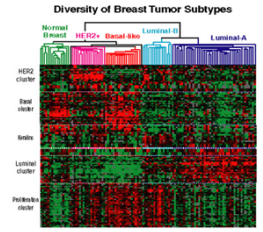
- Clinical Endpoints:
  - pathologic complete remission (pCR)
  - DFS or PFS
- Benefits
  - pCR is a reliable prognostic marker
  - Time to prepare for type of surgery
  - Genetic testing
  - Clinical trials: e.g. upfront www.ispytrials.org and post NAT
- Increasing use when chemotherapy is certain regardless of surgical staging
  - Stage II and III
  - Triple Negative (TNBC) and HER2 positive
  - Young patients

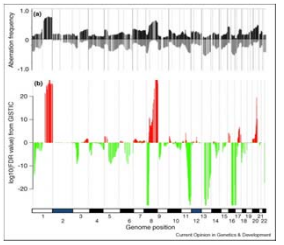
Biomarker History in Breast Cancer

- 1st generation: protein expression ~ 1970
  - ER/PR IHC
- 2nd generation: gene amplification ~ 1990
  - HER2/neu FISH
- 3rd generation: gene expression ~ 2005
  - Oncotype DX, Mammaprint, BCI, PAM50
- 4th generation: mutational profiling ~ 2010
  - Academic (*ESR1m, PIK3CA-mutant)*
  - Commercial (FoundationOne CDx)







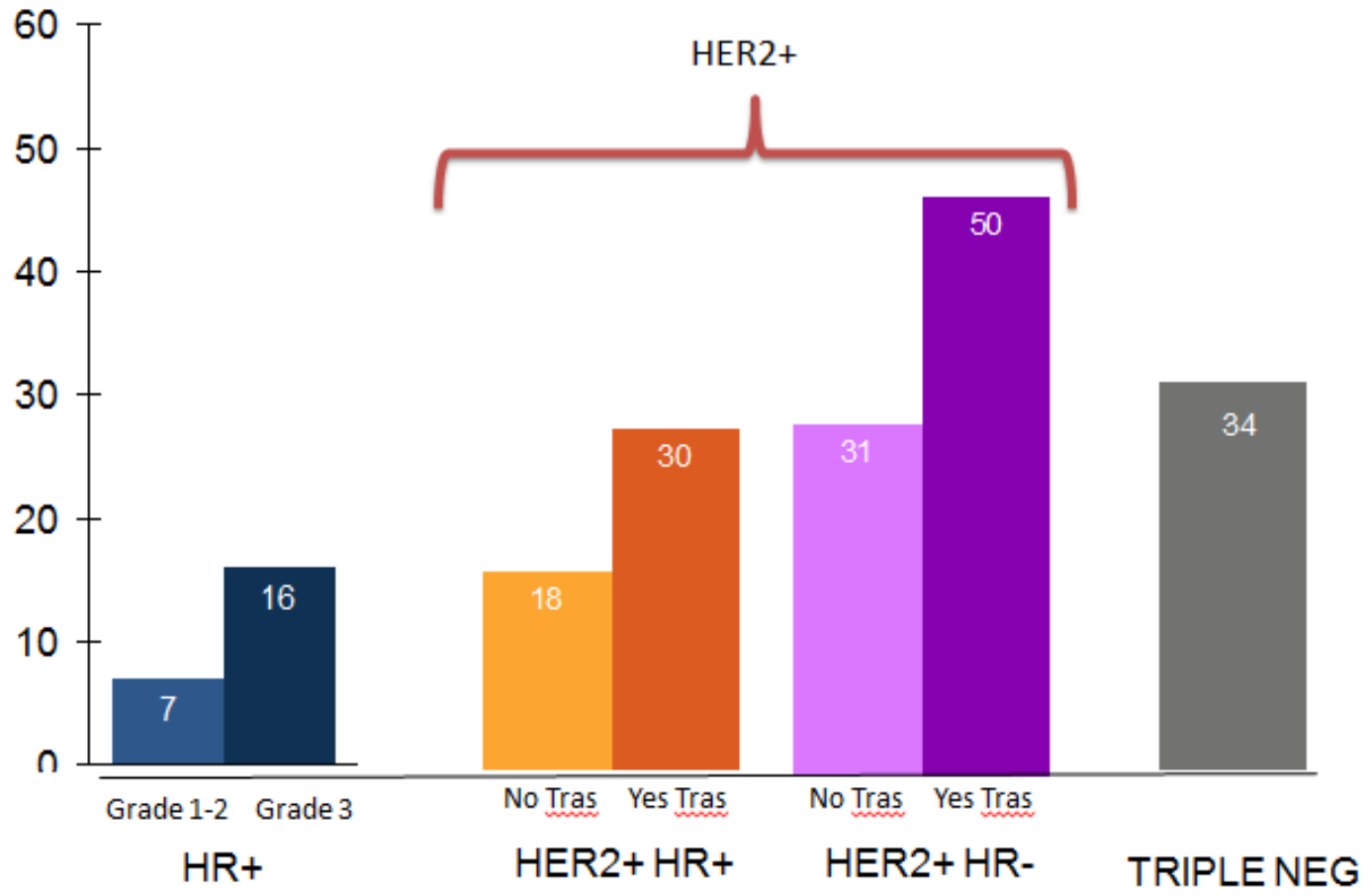


Adapted from Ian S. Hagemann, Molecular Testing in Breast Cancer: A Guide to Current Practices. Archives of Pathology & Laboratory Medicine: August 2016, Vol. 140

Standard Biomarkers in Clinical Use

- Mandatory:
  - Estrogen receptor (ER)
  - Progesterone receptor (PR)
  - Human epidermal growth factor receptor 2 (HER2)
- Recommended:
  - Oncotype Dx Recurrence Score (or Prosigna)
  - pT1b-3 pN0 and ER+ HER2-
    - in BC, depends on age and grade, includes N1mic in one node
- Other:
  - Ki67 proliferation index
  - *BRCA* mutation status

Pathologic CR Rates By Tumor Subtype



Individuals with pCR have better prognosis

Cortazar et al, AACR 2013, Lancet 2014

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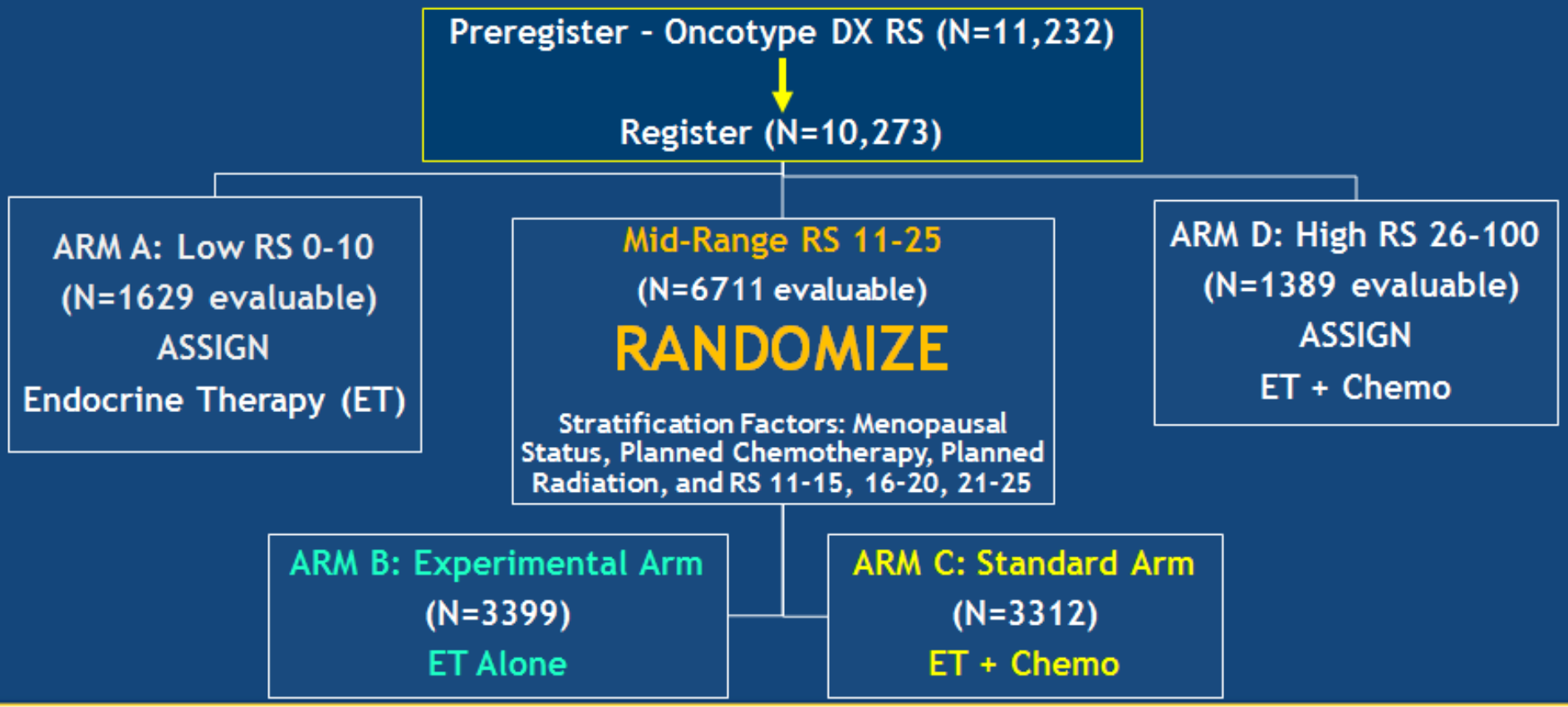
TAILORx Treatment Assignment & Randomization 04/2006 - 10/2010



TAILORx Results - RS 11-25 (Arms B & C)

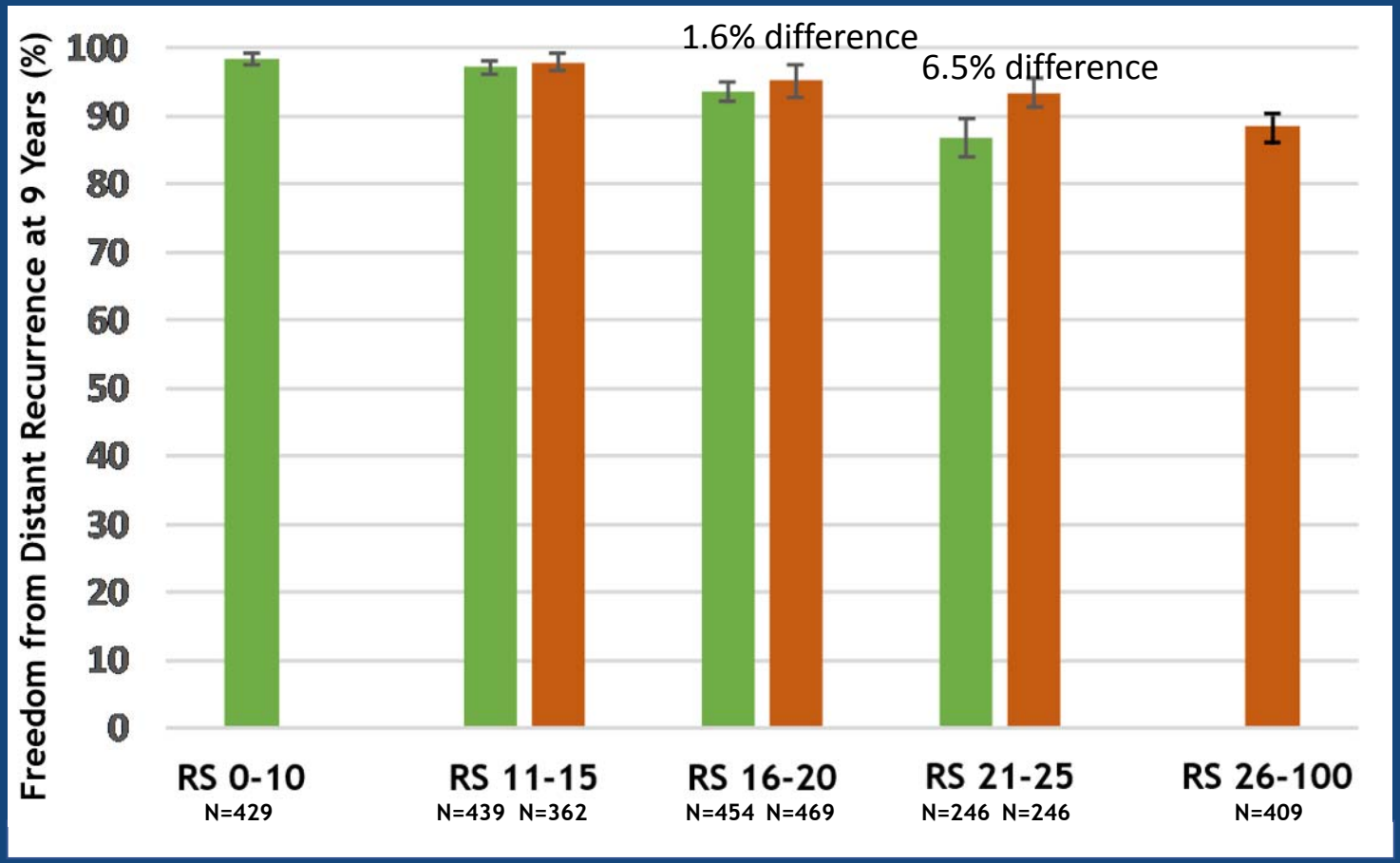
9-Year Freedom from Event Rate

RS 11-25	Arm B ET Alone	Arm C ET+Chemo
IDFS	83.3%	84.3%
DRFI	94.5%	95.0%
RFI	92.2%	92.9%
OS	93.9%	93.8%

≤ 1% difference for all endpoints

Used with permission from Dr. J Sparano and ASCO.

TAILORx Results - Freedom From Distant Recurrence at 9 Years According to Assigned Treatment in Women ≤50 Years (N=3,054)



*Number of patients per arm displayed under bar chart segments

Sparano et al. *N Engl J Med* 2018

How do I a manage patients with ER/PR positive breast cancer in the current era?

- 60 y healthy
- T2 (2.5 cm) N0, ER 7/8, PR 6/8, HER2 -, grade III
- Local therapy complete

Oncotype Dx Recurrence Score **22**

Adjuvant endocrine therapy YES

Adjuvant chemotherapy NO

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ORIGINAL ARTICLE

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

NEJM June 4 2018

Prudence A. Francis, M.D., Olivia Pagani, M.D., Gini F. Fleming, M.D., Barbara A. Walley, M.D., Marco Colleoni, M.D., István Láng, M.D., Ph.D., Henry L. Gómez, M.D., Ph.D., Carlo Tondini, M.D., Eva Ciruelos, M.D., Harold J. Burstein, M.D., Ph.D., Hervé R. Bonnefoi, M.D., Meritxell Bellet, M.D., et al., for the SOFT and TEXT Investigators and the International Breast Cancer Study Group*

	TAMOXIFEN	OFS + TAMOXIFEN	OFS + EXEMESTANE	HR	95% CI	
N = 3047 **SOFT**						
DFS (%) at 8 y	78.9	83.2	85.9	0.76 0.65	0.62-0.93 0.53-0.81	518 events 279 distant
Chemo = Y	71.4	76.7	80.4	0.76 0.68	0.60-0.97 0.53-0.88	
OS (%) at 8 y	91.5	93.3	92.1	0.67 0.85	0.48-0.92 0.62-1.15	225 deaths
Chemo = Y	85.1	89.4	87.2	0.59 0.79	0.42-0.84 0.57-1.09	
N = 4690 **SOFT/TEXT**	N/A					
DFS (%) at 9 y		82.8	86.8	0.77	0.67-0.90	720 events
DDFS(%) at 9 y		89.7	91.8	0.80	0.66-0.96	433 distant
OS (%) at 9 y		93.3	93.4	0.98		320 deaths

Disease free but not free of “dis-ease”
OFS at what cost ?

Francis et al,
NEJM, 2018
Table 2

Newer treatments by biomarker subtype and stage

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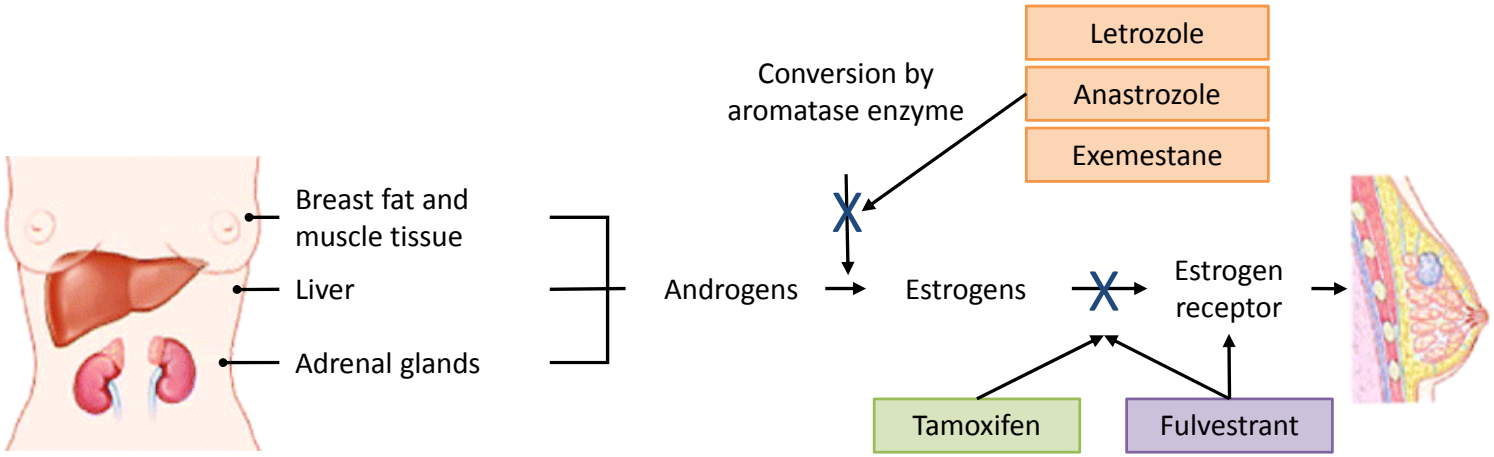
Manipulating the hormonal milieu in the postmenopausal woman

- Treatments for postmenopausal women with ER+ breast cancer target estrogen or the estrogen receptor directly



- Letrozole is a commonly used aromatase inhibitor
- PFS for first line AI in advanced disease about 12 months

Author: Erling Donnelly
Source:
[1]Mouridsen H, et al. J Clin Oncol, 2003.
Figure adapted from Encyclopedia of Cancer, 2011, Fulvestrant section, figure 3

Recommendations for Hormone Receptor Positive Advanced Breast Cancer

- Offer endocrine therapy as initial Rx for all patients except
  - with imminent life-threatening disease
  - with rapid visceral recurrence during adjuvant endocrine Rx
- To choose the type of endocrine therapy consider
  - Type of adjuvant Rx
  - Disease free interval
  - Extent of disease at time of recurrence
  - Patient preference
- Treat until unequivocal progression

Rugo, HS et al, J Clin Oncol 2016; 34: 3069-3103

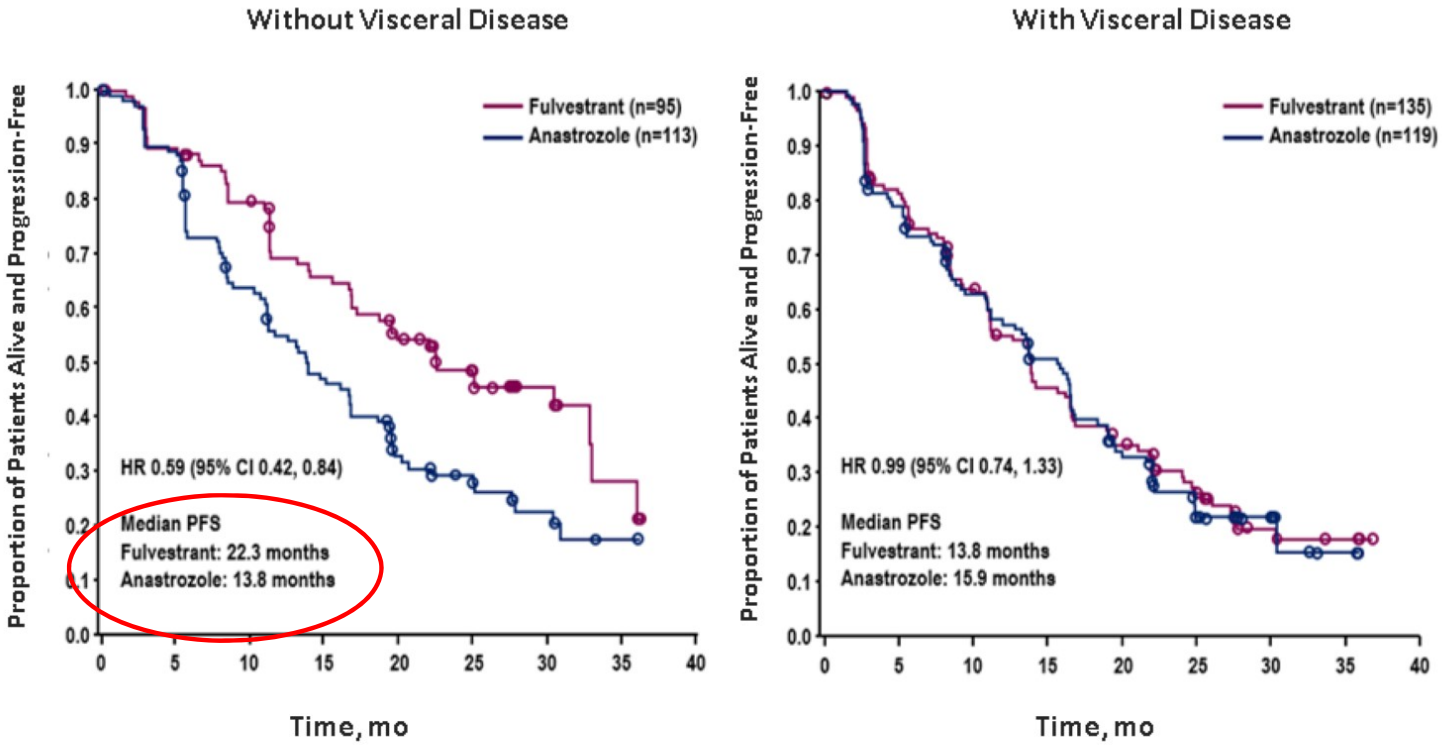
Fulvestrant 500 mg vs anastrozole 1 mg (FALCON): double blind, RCT

- First line advanced ER positive, endocrine Rx naive
- N = 462 patients
- Median progression-free survival
  - Fulvestrant 16.6 mo
  - Anastrozole 13.8 mo
  - HR 0.8 p = 0.0486
- Most common adverse events: arthralgias, hot flushes

Robertson J et al Lancet 2016 Vol 388

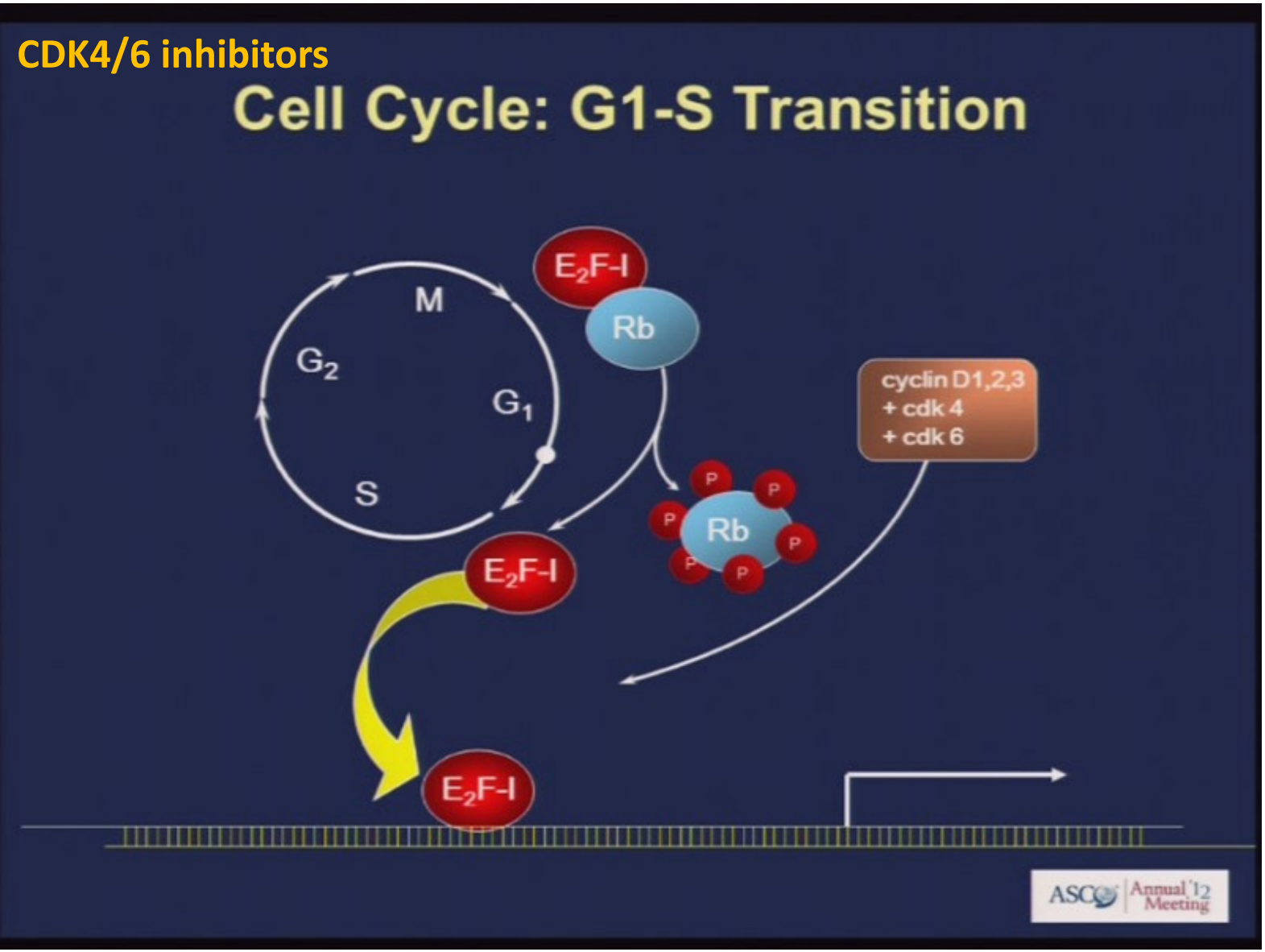
FALCON Study

PFS in Patients With or Without Visceral Disease



Robertson J, et al. Lancet. 2016.

CDK4/6 inhibitors



Rb phosphorylation by CDK 4/6 promotes G1-to-S phase transition

Pathway may be upregulated in endocrine-resistant cells

CDK 4/6 inhibition may lead to control over the cell cycle

Cancer cells could remain sensitive to endocrine therapy

CDK4/6 inhibitors Phase III Advanced Breast Cancer

Study Name	Design	Setting	Intervention	HR and Median PFS
PALOMA 2	Randomized Phase III	Advanced **first** line; ER+ HER2-	Letrozole +/- Palbociclib	HR: 0.58 **24.8 vs 14.5 mo** Finn, NEJM 2016
MONALEESA 2	Randomized Phase III	Advanced **first** line; ER+ HER2-	Letrozole +/- Ribociclib	HR: 0.57 **25.3 vs 16 mo** Hortobagyi, NEJM, 2017 Ann Oncol, 2018
PALOMA 3 **MONALEESA 3**	Randomized Phase III	Advanced **second** line; pre & postmen; ER+ HER2- Advanced **first and second** line	Fulvestrant (goserelin) +/- Palbociclib Fulvestrant +/- Ribociclib	HR: 0.42 **9.2 vs 3.8 mo** Turner , NEJM 2015 HR: 0.57 **20.5 vs 12.8 mo** Slamon, JCO, 2018

At What Cost?
Common Terminology Criteria for Adverse Events (CTCAE)

CTCAE Term (Grade)	1	2	3	4	5
Adverse event	mild	moderate	severe	life-threatening	fatal
diarrhea	Increase < 4 /d over baseline	Increase 4-6/d over baseline	>= 7 stool/d hospitalisation	urgent intervention	Death
Neutrophils (x 10 9/L)	< LLN to 1.5	1.0 to < 1.5	0.5 to < 1.0	< 0.5	
Platelets (x 10 9/L)	< LLN to 75	50 to < 75	25 to < 50	< 25	

LLN = lower limit of normal

PALOMA 2 Hematologic Treatment-Emergent Adverse Events Occurring in ≥10% of Patients

	Palbociclib + Letrozole (n=444)			Placebo + Letrozole (n=222)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE, n (%)	439 (99)	276 (62)	60 (14)	212 (95)	49 (22)	5 (2)
Neutropenia[a]	353 (80)	249 (56)	46 (10)	14 (6)	2 (1)	1 (<1)
Leukopenia[a]	173 (39)	107 (24)	3 (1)	5 (2)	0	0
Anemia[a]	107 (24)	23 (5)	1 (<1)	20 (9)	4 (2)	0
Thrombocytopenia[a]	69 (16)	6 (1)	1 (<1)	3 (1)	0	0

Adapted from Finn et al, NEJM 2016

PALOMA 2 Nonhematologic Treatment-Emergent AEs Occurring in ≥10% of Patients

	Palbociclib + Letrozole (n=444)			Placebo + Letrozole (n=222)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any adverse event, n (%)	439 (99)	276 (62)	60 (14)	212 (95)	49 (22)	5 (2)
Fatigue	166 (37)	8 (2)	0	61 (28)	1 (<1)	0
Nausea	156 (35)	1 (<1)	0	58 (26)	4 (2)	0
Arthralgia	148 (33)	3 (1)	0	75 (34)	0	0
Alopecia	146 (33)	0	0	35 (16)	0	0
Diarrhea	116 (26)	6 (1)	0	43 (19)	3 (1)	0
Cough	111 (25)	0	0	42 (19)	0	0
Back pain	96 (22)	6 (1)	0	48 (22)	0	0
Headache	95 (21)	1 (<1)	0	58 (26)	4 (2)	0
Hot flush	93 (21)	0	0	68 (31)	0	0
Constipation	86 (19)	2 (<1)	0	34 (15)	1 (<1)	0
Rash	79 (18)	4 (1)	0	26 (12)	1 (<1)	0
Asthenia	75 (17)	10 (2)	0	26 (12)	0	0
Vomiting	69 (16)	2 (<1)	0	37 (17)	3 (1)	0
Pain in extremity	68 (15)	1 (<1)	0	39 (18)	3 (1)	0
Stomatitis	68 (15)	1 (<1)	0	13 (6)	0	0
Decreased appetite	66 (15)	3 (1)	0	20 (9)	0	0
Dyspnea	66 (15)	5 (1)	0	30 (14)	3 (1)	0
Insomnia	66 (15)	0	0	26 (12)	0	0

Adapted from Finn et al, NEJM 2016

Management of adverse events associated with combination therapy

Palbociclib, ribociclib

- Blood work : baseline, q2w x 2 cycles, then q4w
- grade 3/4 **neutropenia** (not cumulative)
- very low incidence FN
- monitor and dose reduce for grade 4 or persistent grade 3 neutropenia
- no role for cytokine support

Ribociclib

monitor **LFT**s over first 6 months

monitor QTc three times in first month of therapy

avoid methadone, IV ondansetron, drugs that prolong the QTc interval

All 3 CDK4/6 inhibitors

- avoid grapefruit juice and other strong CYP3A4 inhibitors

Practical Considerations

- More toxicity than hormones alone (but minimal)
- Take time to assess response
- Overall survival data pending

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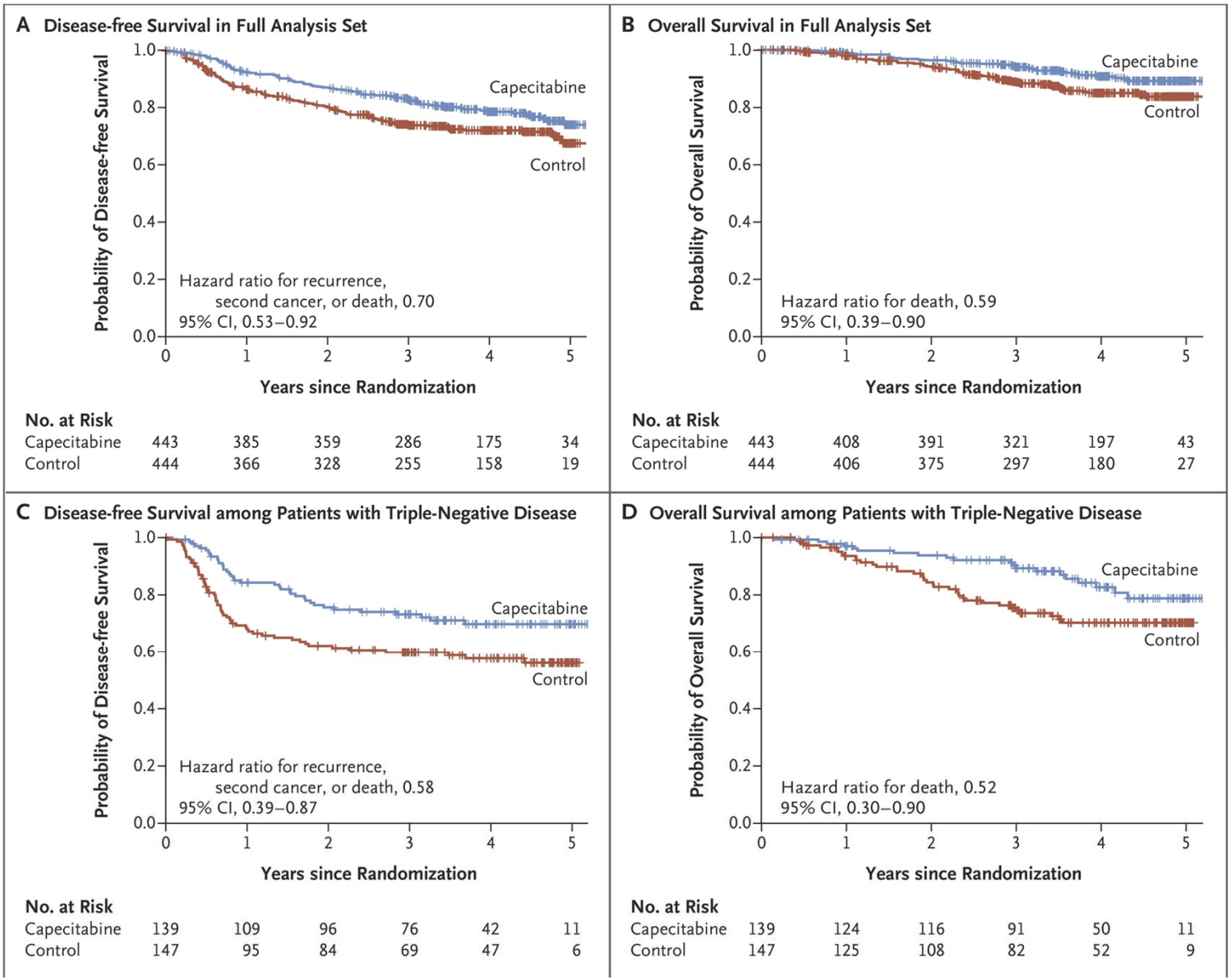

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy
Masuda et al
NEJM 2017

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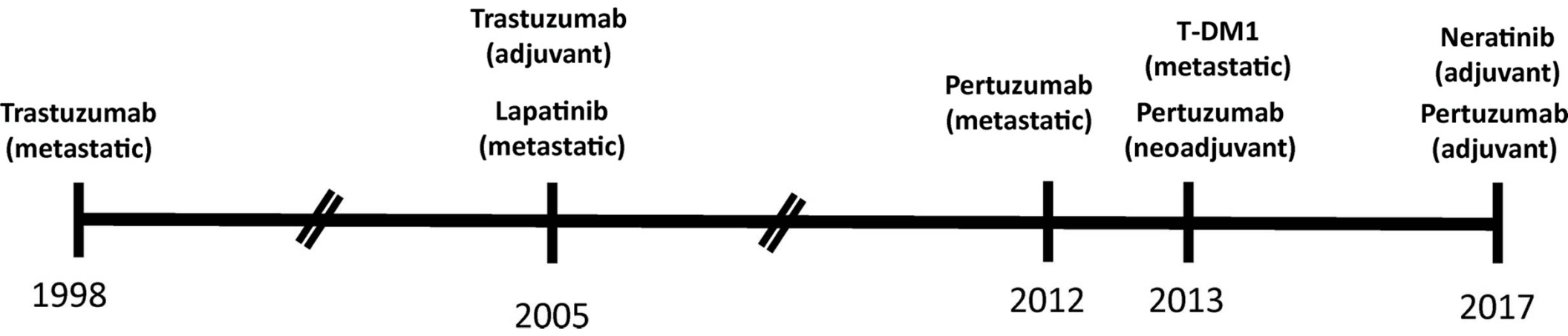
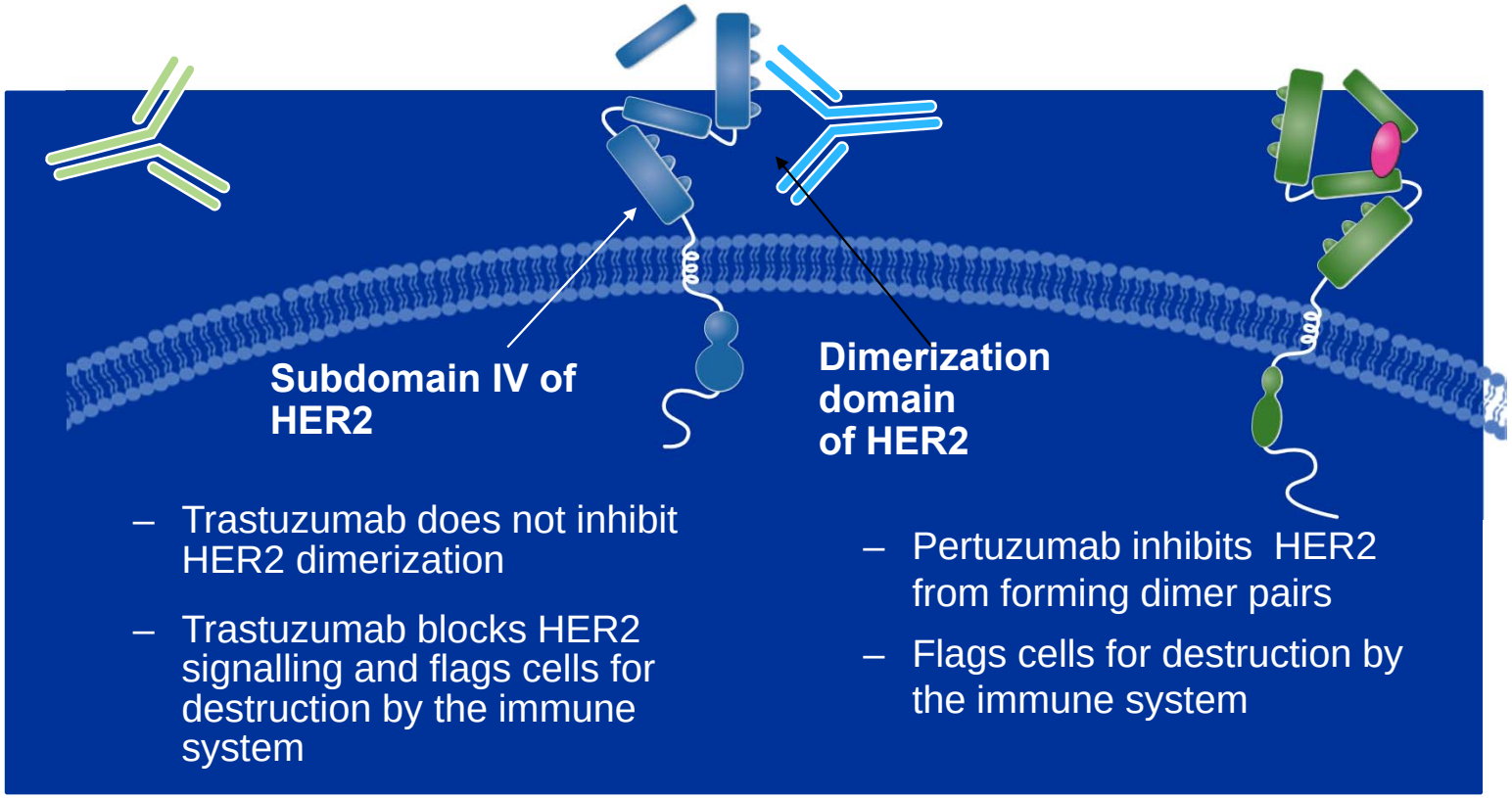
Timeline for FDA Approval of anti-HER2 Therapies



Published in: Jane Lowe Meisel; Vyshak Alva Venur; Michael Gnant; Lisa Carey; *American Society of Clinical Oncology Educational Book* 38, 78-86.

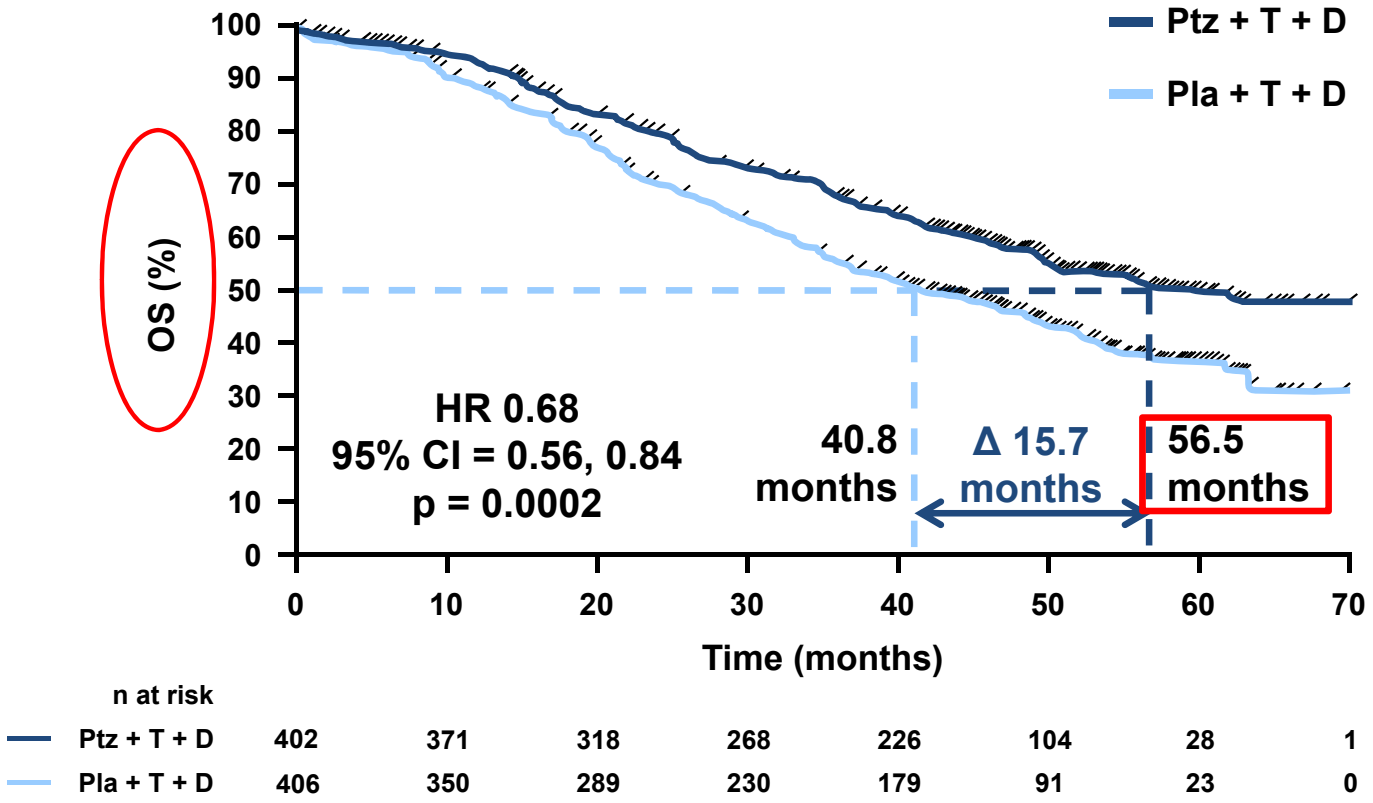
Pertuzumab and trastuzumab bind to different sites of HER2: together provide more comprehensive blockade of HER2



Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA)

Swain et al NEJM 2015

Median follow-up 50 months (range 0–70 months)



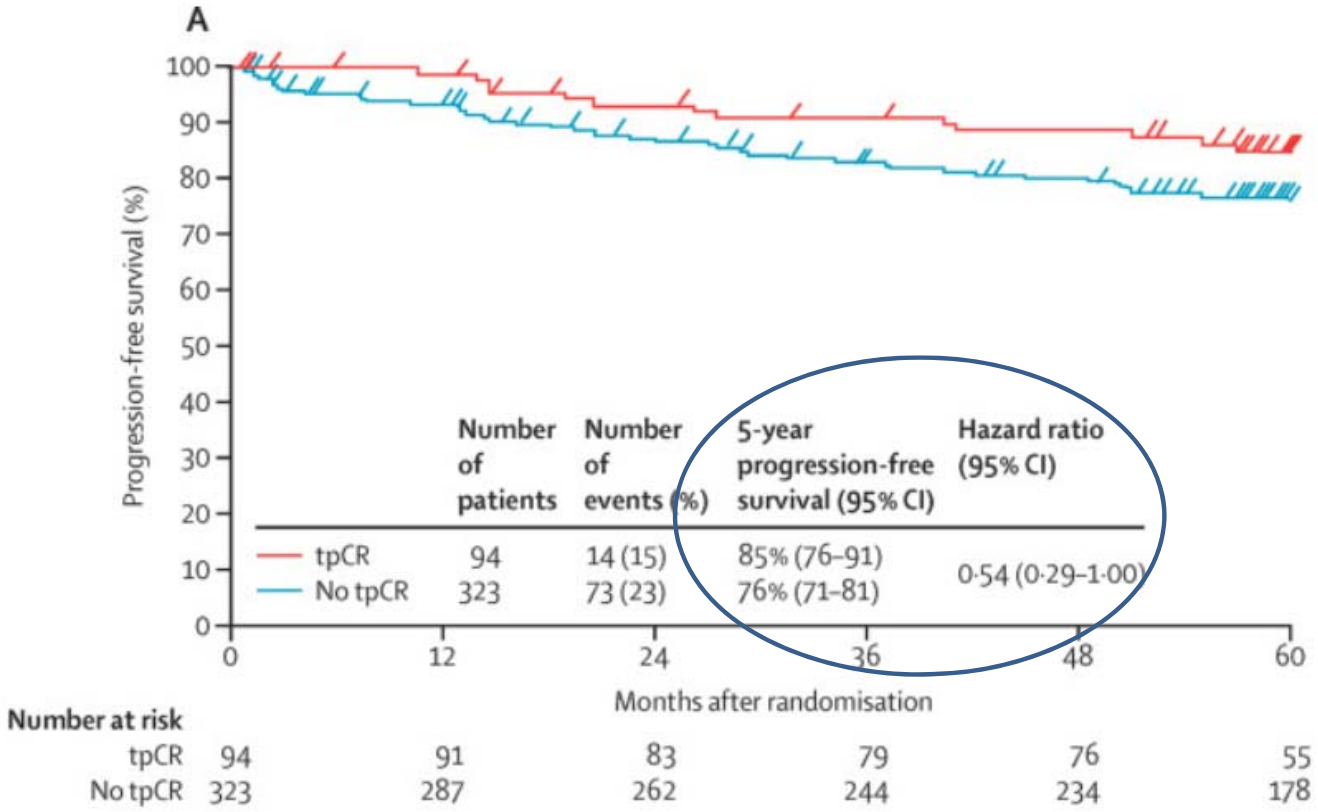
n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

PFS
18.7 mo
vs
12.4 mo

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

40

5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial (n = 417)

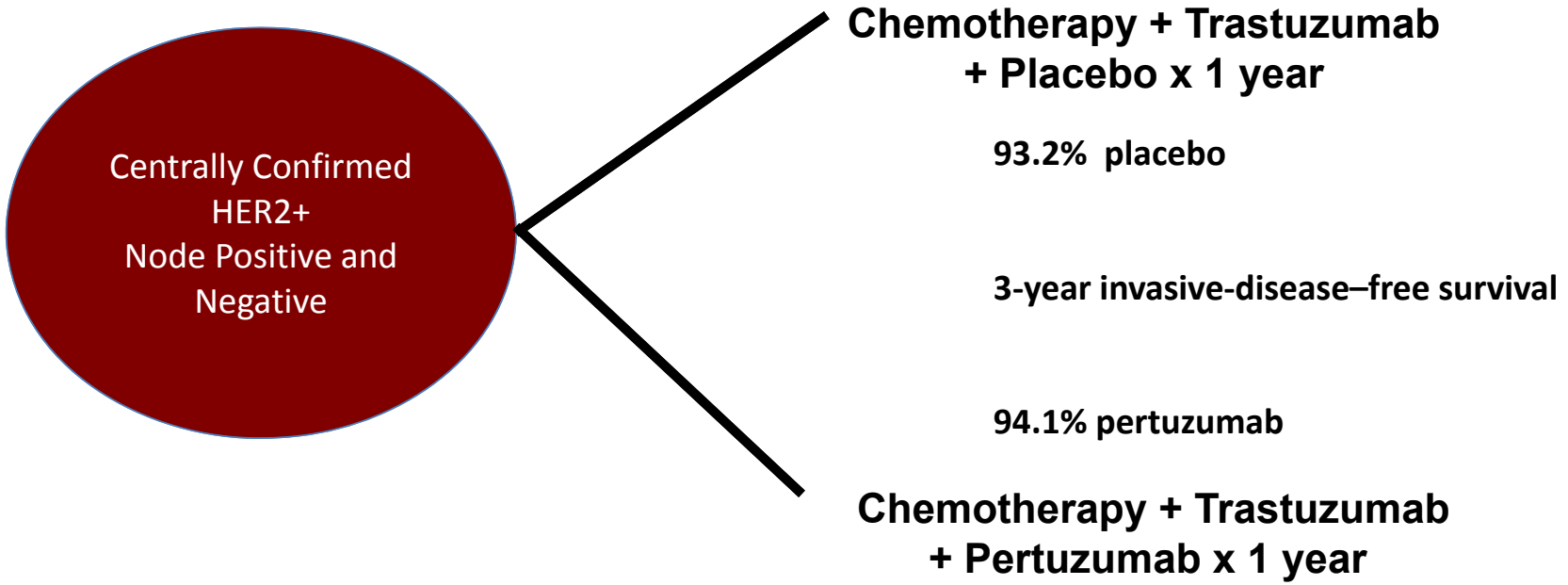


tpCR
Pertuzumab, Trastuzumab, Docetaxel arm

49 of 107 [46%]

Gianni, Lancet Oncology, June 2016

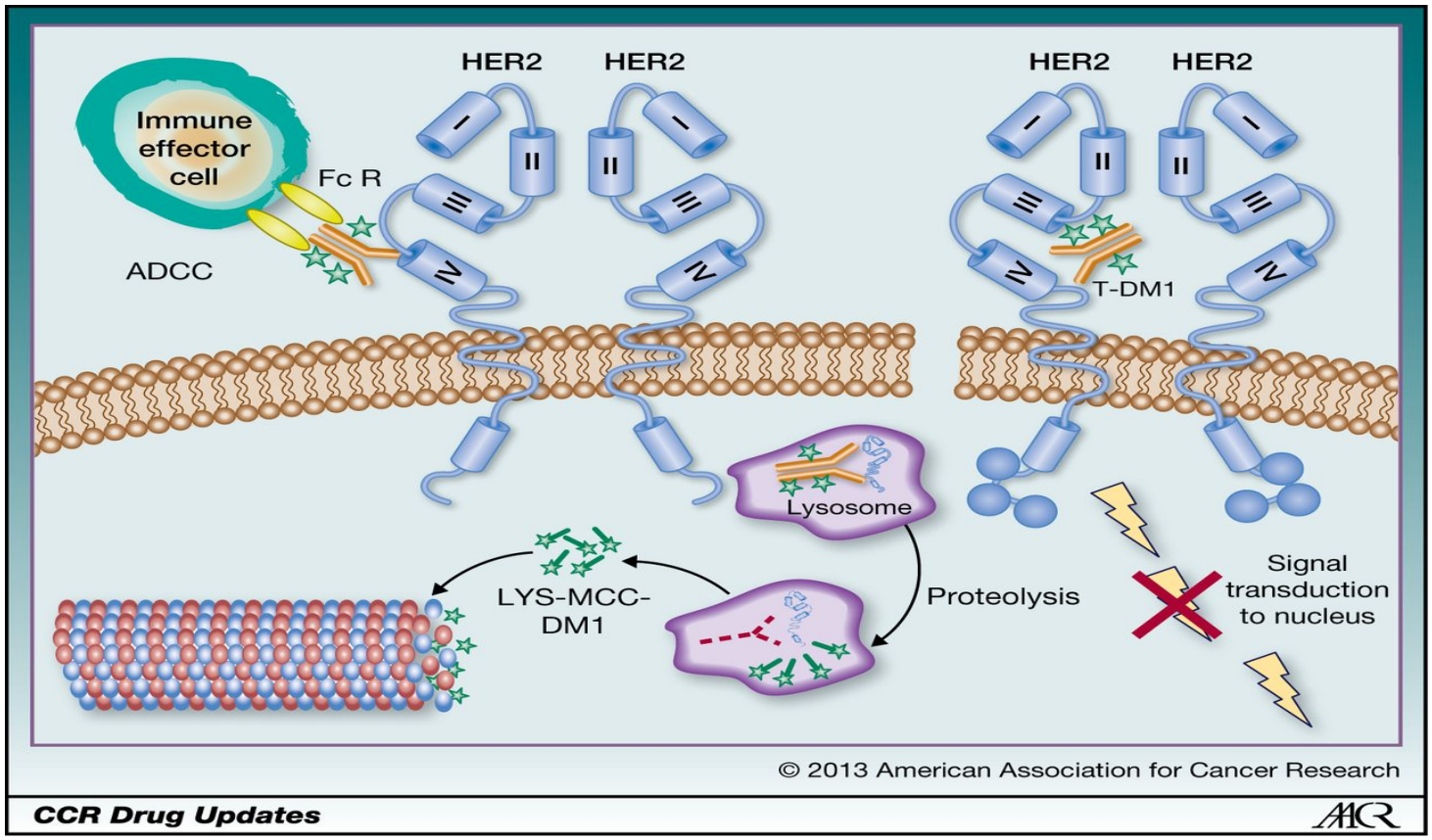
APHINITY
Adjuvant Pertuzumab Trial



92% vs 90.2% in the Node Positive subgroup

Von Minckwitz et al NEJM 2017

Mechanism of action of Trastuzumab Emtansine (T-DM1)



Ian Krop, and Eric P. Winer Clin Cancer Res 2014;20:15-20

Clinical Cancer Research
AACR American Association for Cancer Research

Side effects

Pertuzumab

- Manage milder diarrhea with loperamide
- Grade 3 or > diarrhea seen mostly with chemotherapy
- Febrile neutropenia seen mostly with chemotherapy
- Skin and nail infections

- Monitor for cardiac symptoms

TDM-1

- Thrombocytopenia, epistaxis : monitor and dose adjust
- Transaminitis
- Headache, pyrexia, and chills
- Peripheral neuropathy
- Rarely: pneumonitis

- Monitor for cardiac symptoms

Newer treatments by biomarker subtype and stage

	ER positive	HER2 positive	Triple Negative	Other
Adjuvant **Neoadjuvant**	**TAILORx** **OFS+TAM** **OFS+EXE** **Beyond 5 years** (Palbociclib)	(Pertuzumab) Pertuzumab	Platinum agents	**Postmenopausal: bisphosphonate** denosumab (BRCA1/2 mutated: PARPi eg olaparib)
Post NAT: **Residual disease** **Post Adjuvant**	**Capecitabine** (Palbociclib)	(Neratinib) (Trastuzumab emtansine)	**Capecitabine**	(BRCA1/2 mutated: PARPi eg olaparib)
Metastatic	**First line CDK4/6i** **Palbociclib** (Ribociclib) (Abemiciclib) (Fulvestrant)	**Pertuzumab** **Trastuzumab emtansine**	**Platinum agents** (Checkpoint inhibitors/IO)	(BRCA1/2 mutated: PARPi eg olaparib)

Triple Negative Breast Cancer

- Heterogeneous group of cancers

  Basal-like subtype most common

- BRCA germline mutations

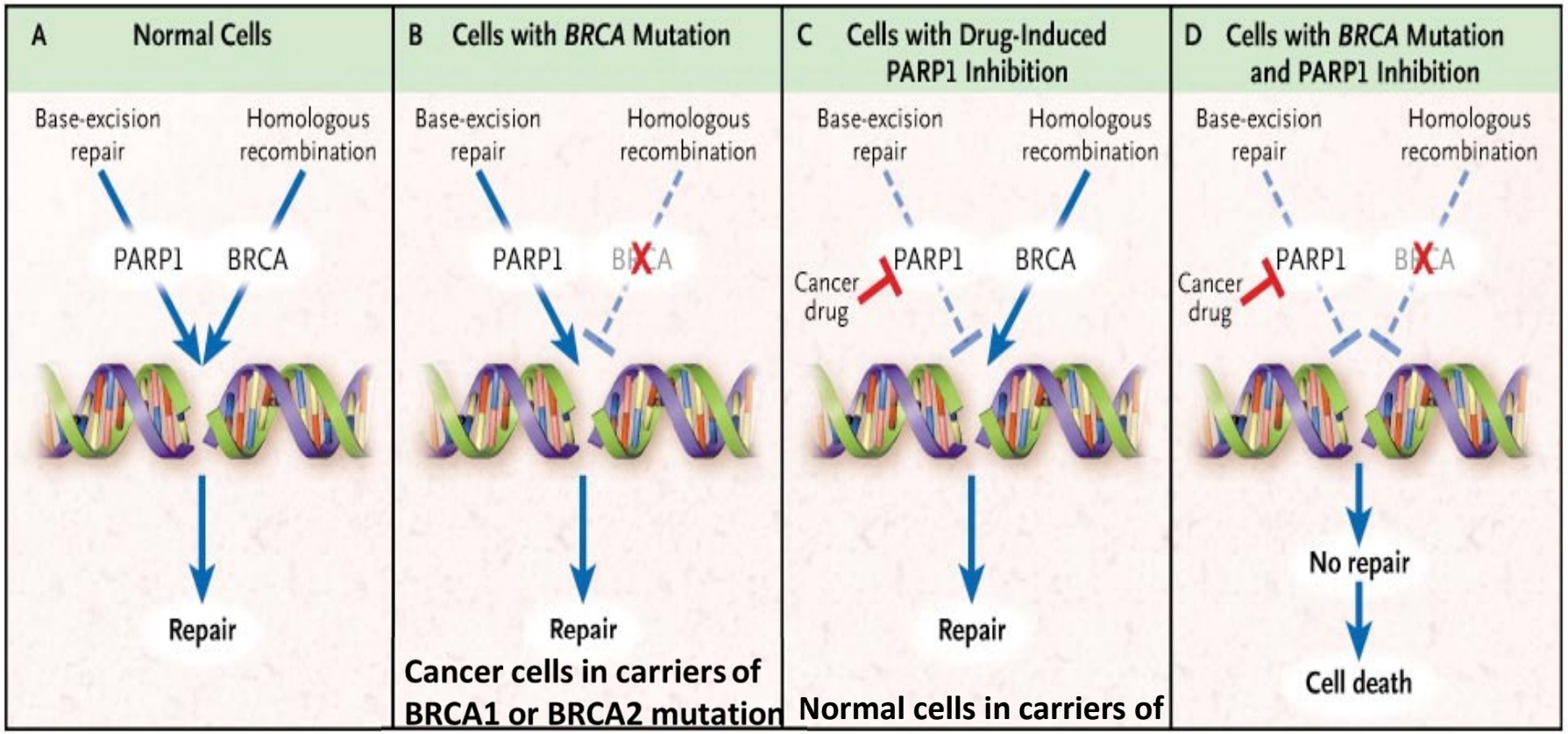
  More common than in other subtypes

- BRCA associated defective DNA repair

  Leads to sensitivity to platinum and PARP inhibition

Foulkes et al, NEJM, Nov 2010
Denkert et al, The Lancet June 2017
Greenup et al, Ann Surg Oncol 2013
Iglehart JD, Silver DP. N Engl J Med 2009;361:189-191

Mechanism of Cell Death from Synthetic Lethality
Induced by Inhibition of Poly ADP–Ribose Polymerase 1 (PARP1)



Iglehart JD, Silver DP. N Engl J Med 2009;361:189-191

Phase III trials of PARPi in *BRCAm* advanced breast cancer

OlympiAD Robson et al NEJM 2017

- Olaparib 300 mg tabs BID vs capecitabine, eribulin, vinorelbine q21d
- Median PFS 7.0 vs 4.2 mo HR 0.58 (95% CI 0.43 to 0.80)
- No difference in median OS (19 mo)

EMBRACA Litton et al SABCS Dec 2017

- Talazoparib 1 mg tab daily vs chemotherapy choice
- Median PFS 8.6 vs 5.6 mo HR = 0.54 (P < .0001)
- Time to clinical deterioration 24.3 months vs 6.3 months

SIDE EFFECTS

  - anemia, neutropenia, nausea, fatigue (Table 2, NEJM)

Newer treatments by biomarker subtype and stage

	ER positive	HER2 positive	Triple Negative	Other
Adjuvant **Neoadjuvant**	**TAILORx** **OFS+TAM** **OFS+EXE** **Endocrine beyond 5 years** (Palbociclib)	(Pertuzumab) Pertuzumab	Platinum agents	**Postmenopausal: bisphosphonate** denosumab (BRCA1/2 mutated: PARPi eg olaparib)
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Bone modifying agents: understand context
Bisphosphonates or RANKL inhibitor

Depending on context dose, drug, schedule differs

Treat a problem

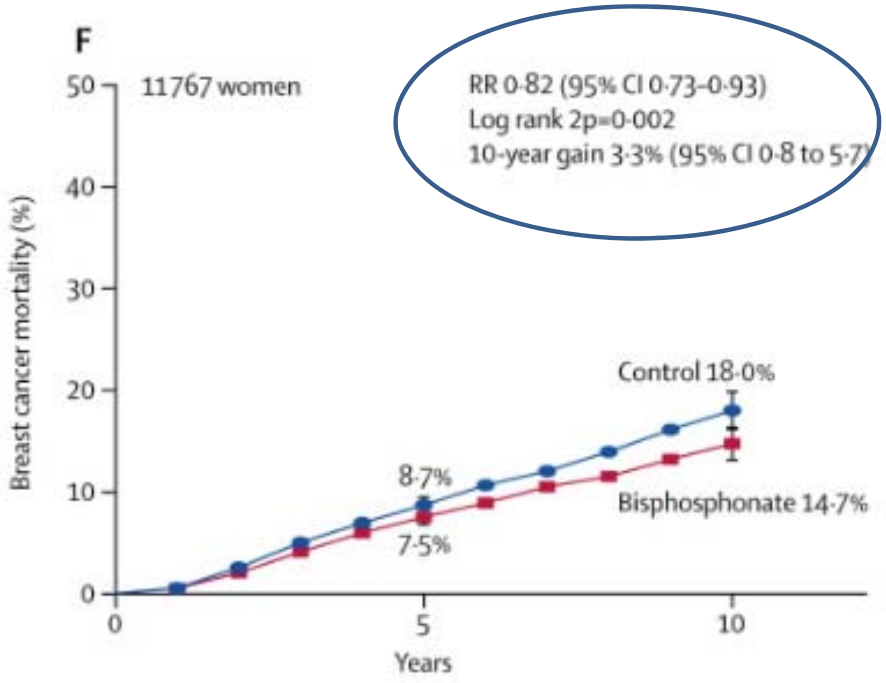
- Osteoporosis (usual definition)
- Established bone metastases in stage IV cancer to prevent SRE

Prevent a problem

- Osteoporosis
- Relapse of breast cancer (to bone)

SRE = skeletal related event:
pain crisis, hypercalcemia, pathologic fracture, epidural cord compression

Adjuvant Bisphosphonates



Coleman RE, Gnant, M,Paterson A, et al; EBCTCG Bisphosphonate Working Group. Adjuvant bisphosphonate treatment in early breast cancer: meta-analysis of individual patient data from randomized trials. Lancet. 2015;386:1353-1361

- Postmenopausal women
- (y)pT2 or larger or pN1 of higher
- CrCl ≥ 30 mL/min
- within 1 year of diagnosis
- Complete necessary dental work prior
- Cr: baseline and prior to each treatment
- corrected calcium if indicated

Osteoclast inhibition in postmenopausal breast cancer: Is the evidence too strong to ignore?
AT Stopeck - Cancer. 2017 Jul 1;123(13):2392-2394

Conclusions

1. Methodical process for introducing new drug treatments
   - regulatory approval ≠ value or reimbursement
2. New approaches and treatments for management of breast cancer
   - improve outcomes with manageable toxicities
3. Unmet needs persist in specific cancer subtypes and for treatment following several lines of therapy
4. Molecular based approaches and clinical trials are ongoing to address these needs

Immune Oncology (IO) Agents

Activity in TNBC with Studies Ongoing