PRECISION IN BREAST CANCER & CARING FOR THE SURVIVOR

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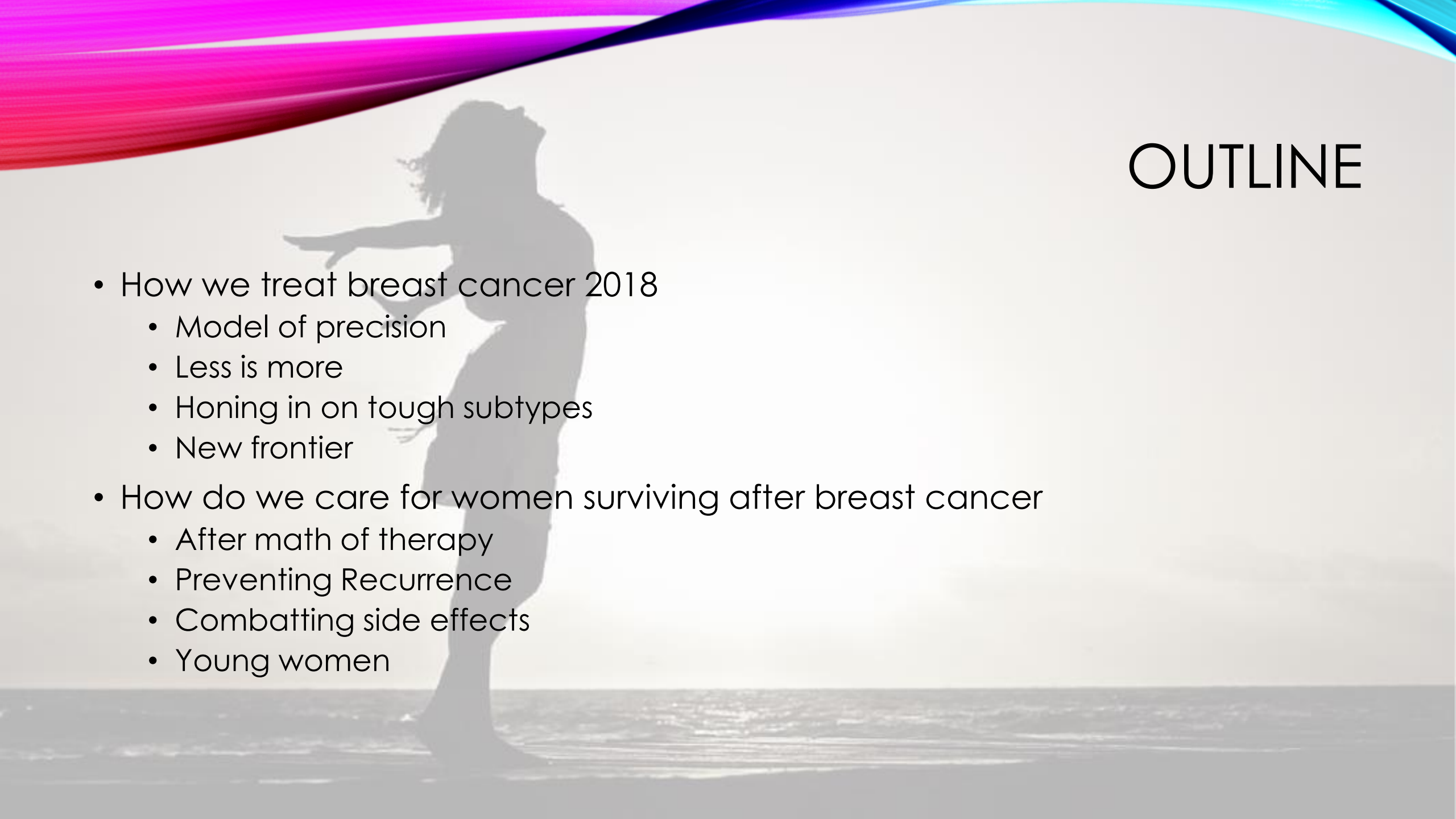


OUTLINE

- How we treat breast cancer 2018
  - Model of precision
  - Less is more
  - Honing in on tough subtypes
  - New frontier
- How do we care for women surviving after breast cancer
  - After math of therapy
  - Preventing Recurrence
  - Combatting side effects
  - Young women

FACTS

- 1 in 8 women BCA
- Incidence increases with age
- Greater prevalence in whites, blacks higher mortality
- Young women <40 make up 7% of BCA
- Men make up 1% of BCA
- 70% of BCA ER+
- Most women will go on to survive their cancer

MULTIDISCIPLINARY APPROACH

Comprised of radiologists, pathologists, radiation oncologists, medical oncologists, breast surgeons, genetic counselors, psychologists, & nurse navigators

- **Multidisciplinary clinic**
  - Clinical evaluation
- **Tumor board review**
  - Films
  - Pathology
  - Surgical approach
  - Chemotherapy/hormones
  - Radiation therapy

AGE OF PRECISION

LOOKING BACK

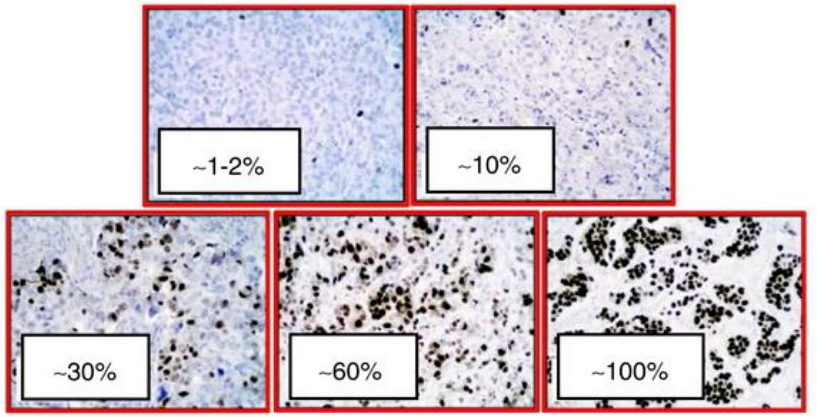
ER+ Disease

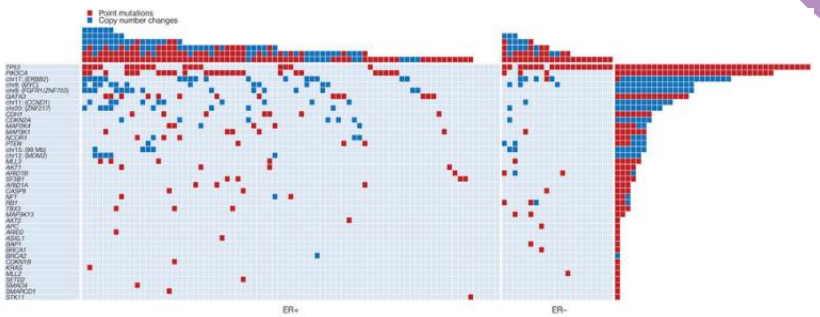
Her2 Neu

Grade, proliferation % ER positivity

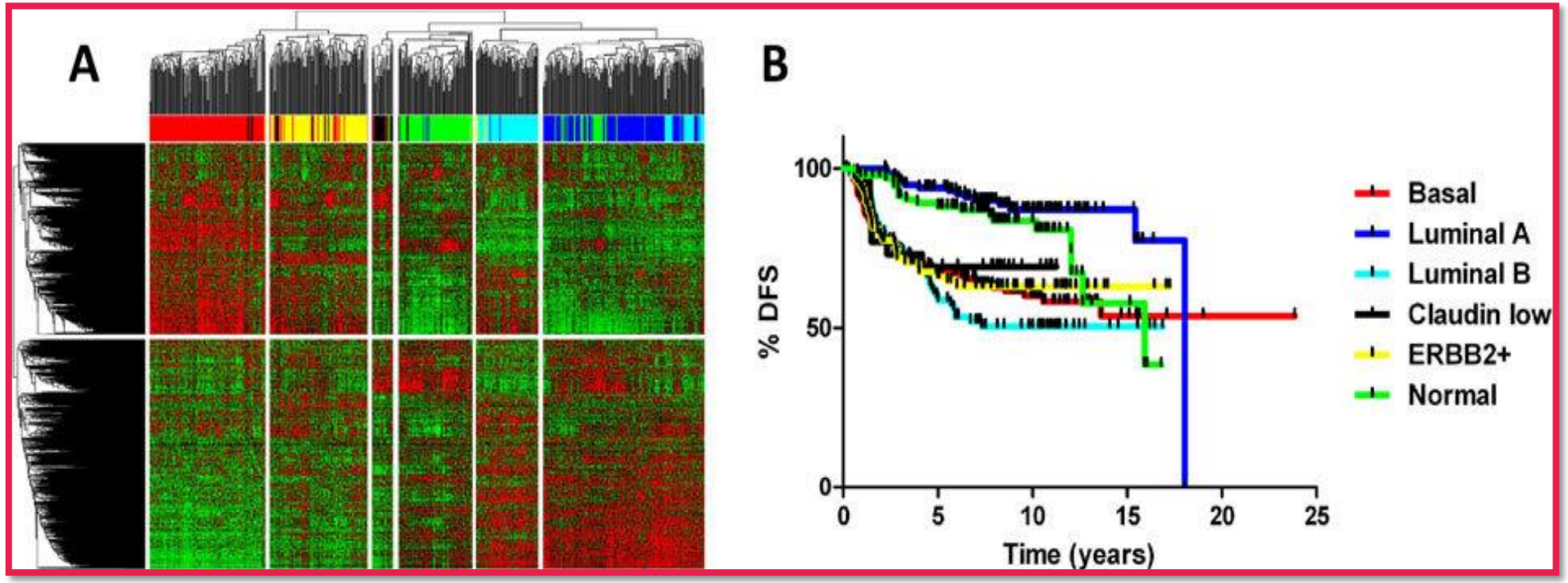
Multigene Molecular Subtyping

Next Generation Sequencing

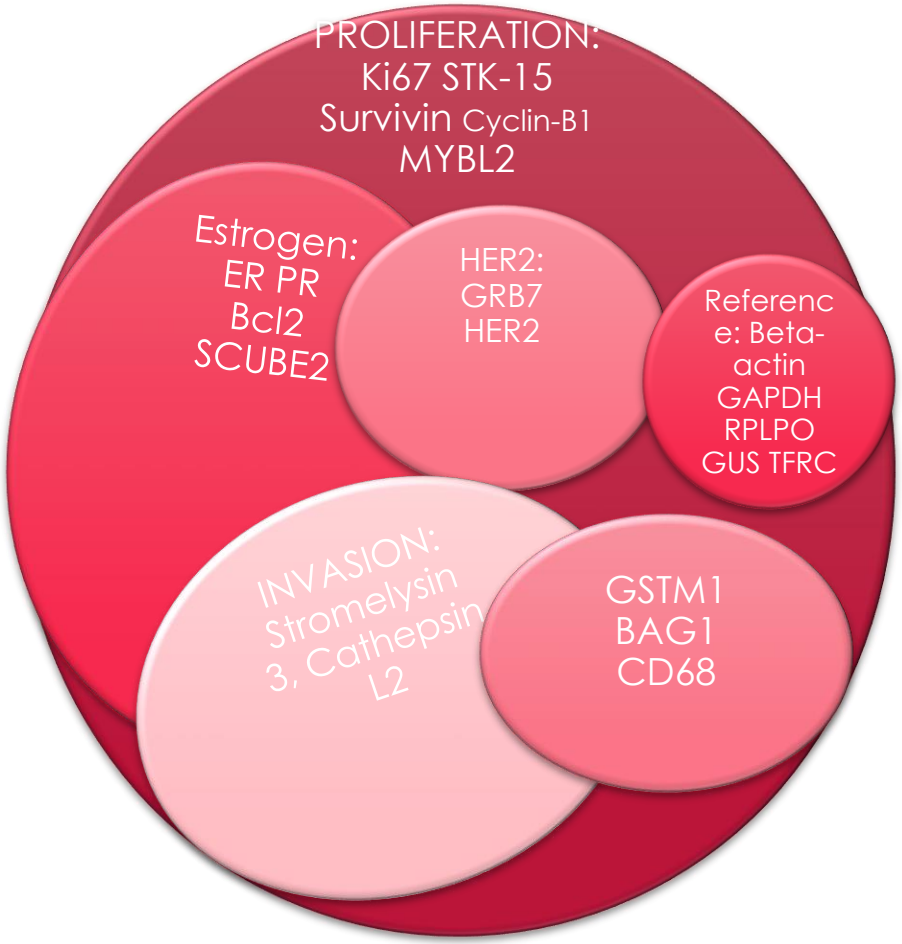




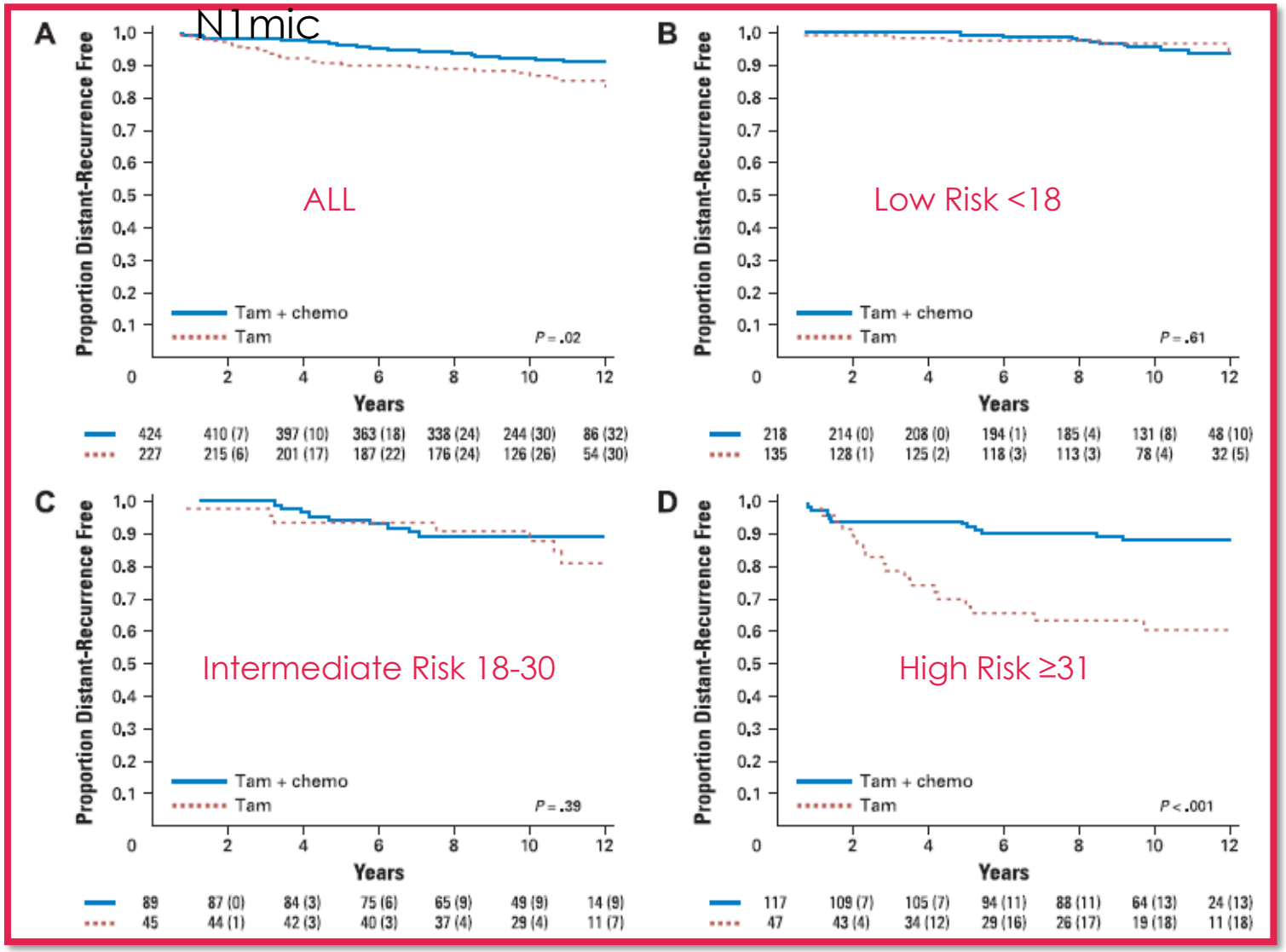
MOLECULAR FINGERPRINT



Nature Scientific Reports 2012



NSABP-B20: T1-T3, Node Negative, N1mic



J Clin Oncol 2006. 24: 3726-3724.

SHIFT IN TREATMENT PARADIGM

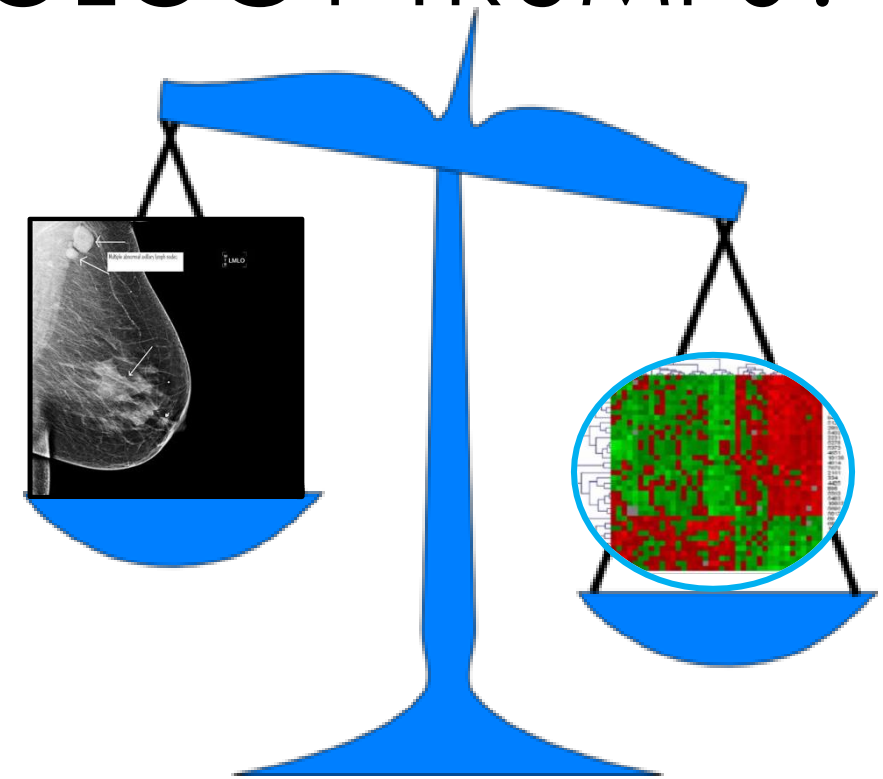
- 37 % change adjuvant treatment recommendations
- Observed shift: chemo & endocrine→ endocrine alone
- 20-84% reduction in chemo use after RS from prior recommendation based on clinicopathologic tumor characteristics
- Spared long-lasting chemo effects
- Decreased financial burden

"We've found a mass. The good news is we have weapons of mass destruction."

Curr Oncol Rep 2014: 16-30

BIOLOGY TRUMPS?

- ER+ Tumors: Magnitude of chemo benefit?
- SWOG-8814: Post Menopausal Node (+)1-3
  - RS low=NO benefit vs. RS high recurrence/death at 5yr
- NCCN: "consider" oncotype 1-3+ LN
- USA survey: > half of US physicians changed reccs after RS, reflecting a reduction in tx intensity



Lancet Oncol 2010; 11: 55-65
Curr Oncol Rep 2014: 16-30

8TH EDITION: INCLUDES BIOLOGY!

- Two staging systems: TNM & Prognostic staging
- Prognostic staging includes ER, PR, Her2, grade & multigene panel analysis

TABLE 8. Examples of Revisions to Breast Cancer Staging Using Biomarkers and Oncotype DX

T	N	M	G	HER2	ER	PR	SEVENTH EDITION ANATOMIC STAGE/ PROGNOSTIC GROUP	EIGHTH EDITION PROGNOSTIC STAGE GROUP
Biomarkers								
1	0	0	1	−	−	−	IA	IIA
1	0	0	3	−	+	−	IA	IIA
3	1-2	0	1	+	+	+	IIIA	IB
Oncotype DX recurrence score- < 11 for ER-positive tumors								
2	0	0	Any	−	+	Any	IIA	IB
1-2	1	0	Any	−	+	Any	IIA/IIB	IB
0-2	2	0	1-2	+	+	+	IIIA	IB

Abbreviations: −, negative; O+, positive; ER, estrogen receptor; G, grade; HER2, human epidermal growth factor receptor 2; M, metastasis classification; N, lymph node classification; PR, progesterone receptor; T, tumor classification.

Cancer J Clin 2017;67:29 0–303. 2017

SMALL DO WELL

Table 3. Survival Outcomes of Patients With T1a,bN0 Breast Cancer, NCCN 2000-2009

Outcome	Patients With T1aN0 Breast Cancer						Patients With T1bN0 Breast Cancer					
	No Chemotherapy or Trastuzumab			Chemotherapy With or Without Trastuzumab			No Chemotherapy or Trastuzumab			Chemotherapy With or Without Trastuzumab		
	5-Year Estimate (%)	95% CI	Total No. of Events	5-Year Estimate (%)	95% CI	Total No. of Events	5-Year Estimate (%)	95% CI	Total No. of Events	5-Year Estimate (%)	95% CI	Total No. of Events
HR-positive/HER2-negative		(n = 972)			(n = 12)			(n = 2,005)			(n = 241)	
OS	98	97 to 99	38	100		1	97	96 to 97	111	98	94 to 99	6
BCSS	100	99 to 100	3	100		0	99	99 to 100	16	99	95 to 100	4
IDFS	93	90 to 94	96	100		1	91	90 to 93	211	95	91 to 97	14
DRFS	98	96 to 99	41	100		1	96	95 to 97	124	96	92 to 98	9
HR-positive/HER2-positive		(n = 102)			(n = 33)			(n = 89)			(n = 110)	
OS	95	88 to 98	5	100		0	95	88 to 98	8	99	90 to 100	3
BCSS	99	90 to 100	1	100		0	98	91 to 99	3	100		1
IDFS	86	76 to 92	13	100		0	86	76 to 92	17	90	81 to 95	8
DRFS	96	89 to 98	5	100		0	94	86 to 98	10	96	88 to 99	5
HR-negative/HER2-positive		(n = 49)			(n = 32)			(n = 17)			(n = 88)	
OS	93	79 to 98	3	100		0	100		2	95	86 to 98	6
BCSS	95	81 to 99	2	100		0	100		1	96	89 to 99	3
IDFS	84	69 to 92	7	89	70 to 96	4	68	40 to 86	6	94	86 to 97	9
DRFS	93	80 to 98	4	100		0	94	63 to 99	3	94	85 to 97	7
HR-negative/HER2-negative		(n = 74)			(n = 25)			(n = 94)			(n = 170)	
OS	94	85 to 98	9	100		0	91	82 to 95	14	96	91 to 98	7
BCSS	95	86 to 99	5	100		0	95	88 to 98	5	98	94 to 99	4
IDFS	86	75 to 92	13	91	68 to 98	3	81	71 to 88	25	88	81 to 92	20
DRFS	93	84 to 97	10	100		0	90	81 to 95	15	96	90 to 98	8

Abbreviations: BCSS, breast cancer–specific survival; DRFS, distant relapse-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; NCCN, National Comprehensive Cancer Network; OS, overall survival.

Vaz-Luis et al. J Clin Oncol 32 2142-2150

APT Trial: ≤3cm tumors node (-) Her2neu (+)

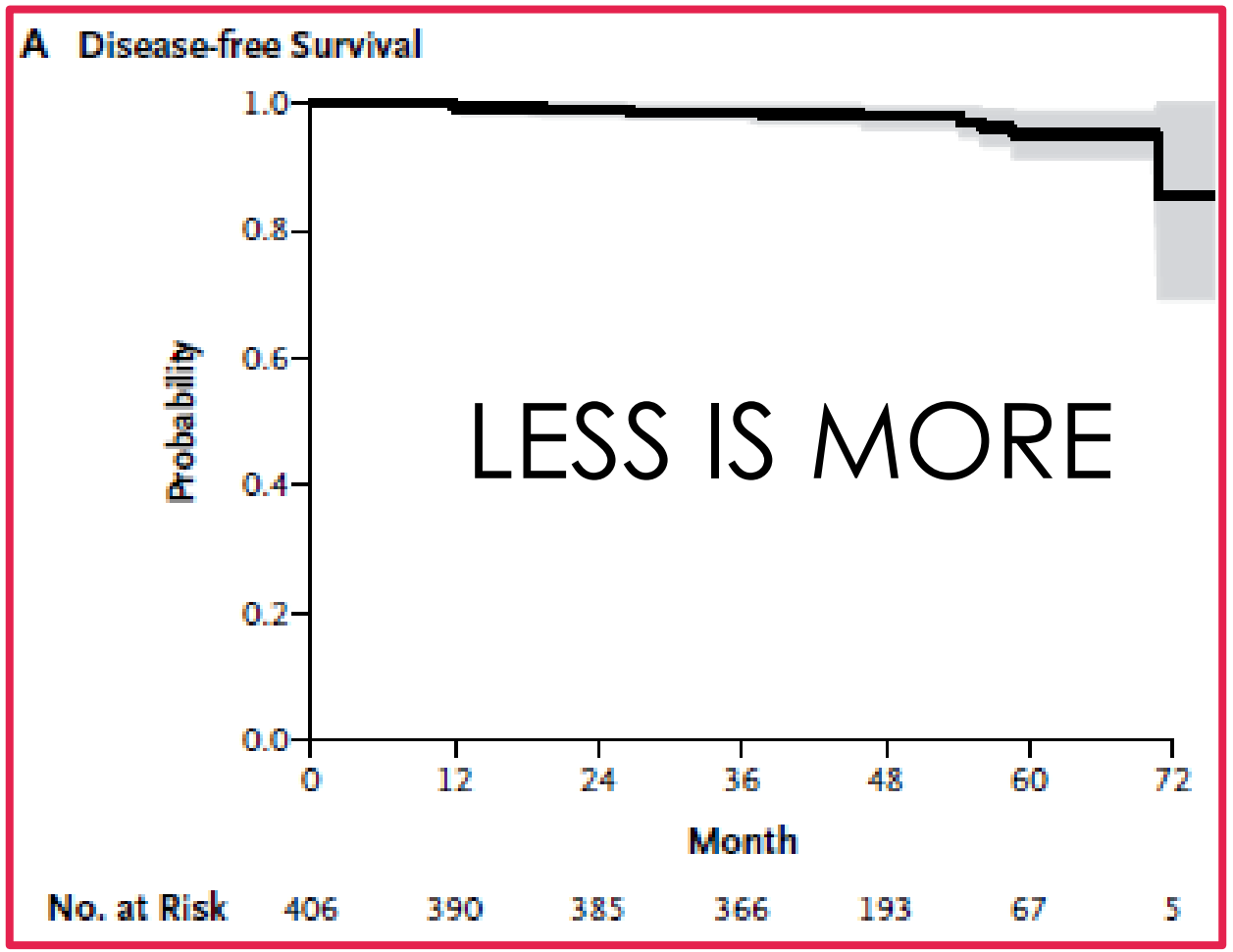
1 chemo drug
Paclitaxel

+ Trastuzumab

Vs.

Combination chemo drugs + Trastuzumab

(ACTH or TCH)



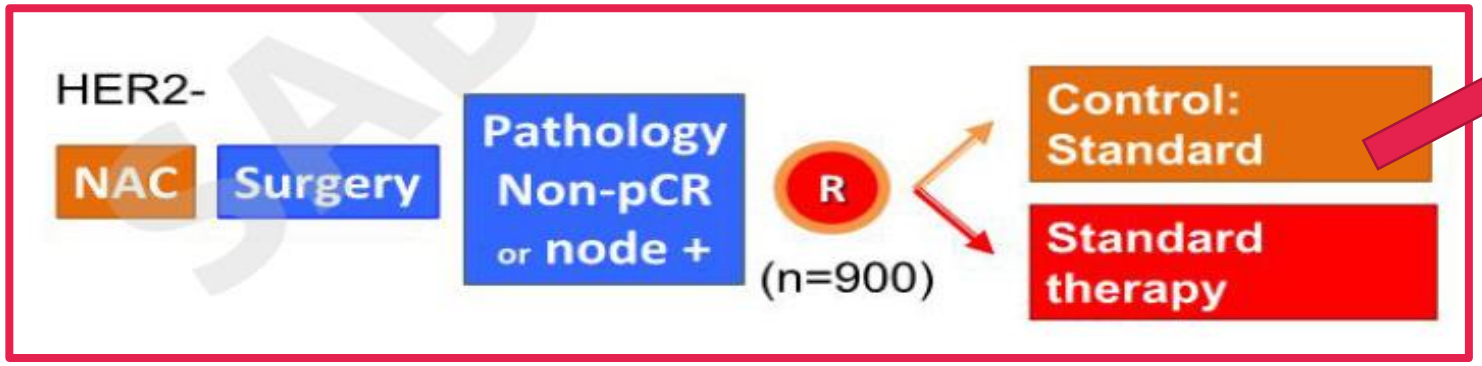
1º Outcome: Survival free from invasive disease at 3yrs

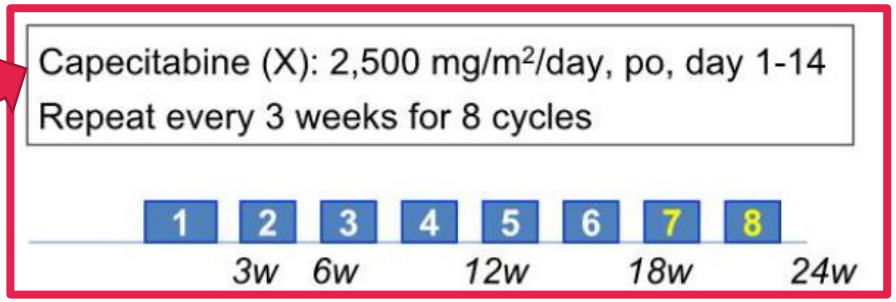
Tolaney et al. N Engl J Med 2015; 372: 134-41.

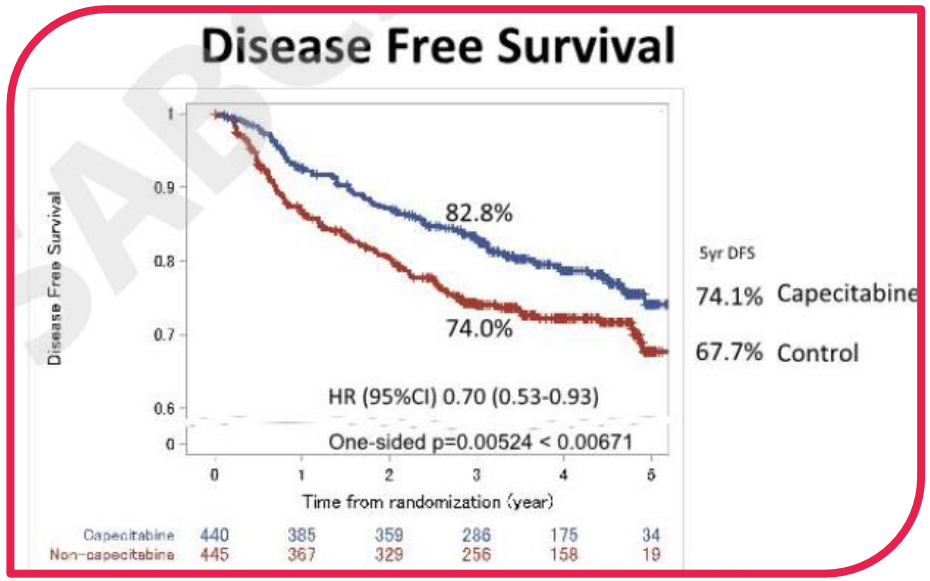
WHO ARE WE NOT DOWN-SIZING?

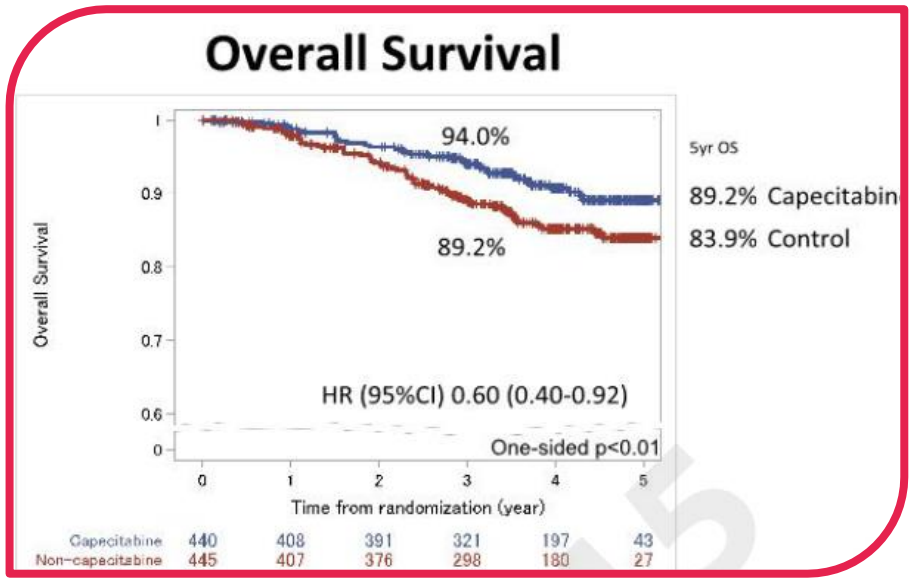
- TNBC- worst prognosis, high propensity for metastasis, least understood
- De-escalation for stage I may be reasonable however stage II & III not ready yet
- WHO NEEDS MORE?
- Response to Neoadjuvant Chemo: prognostic information!
- Absent PCR 10-20% risk of recurrent disease
- Interest in **escalating** therapy to improve outcome

CREATE-X TRIAL



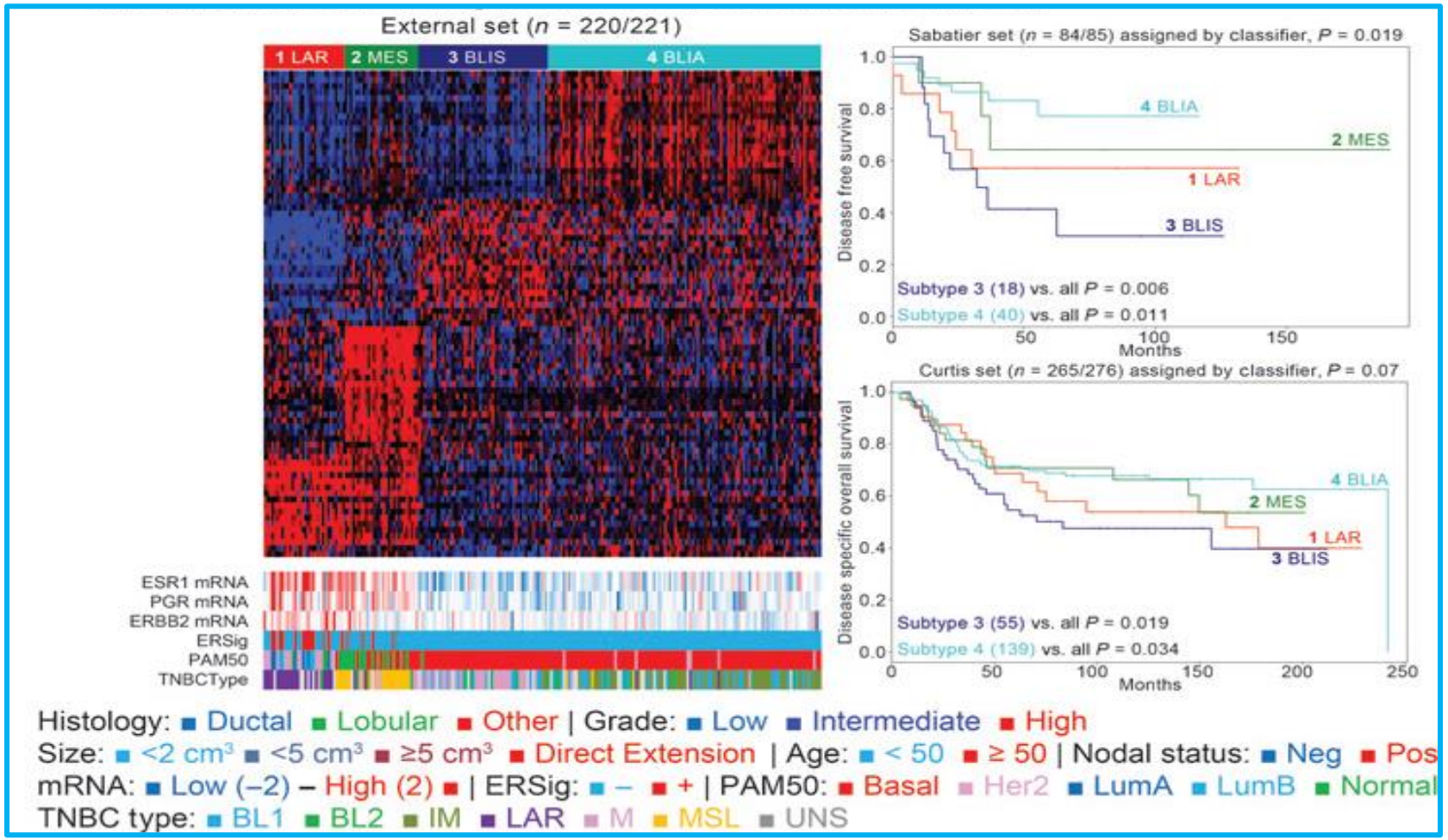






Adapted from Soo Jung Lee's slides @SABCS 2015
Masuda et al. NEJM 2017

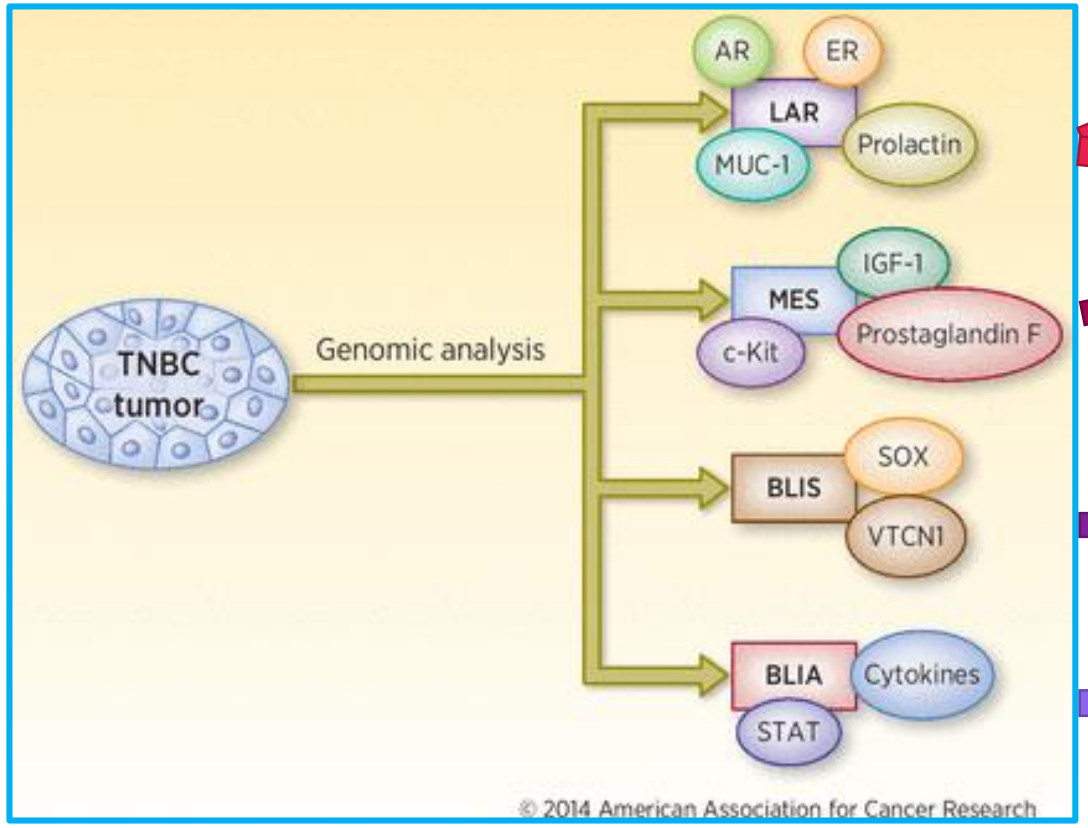
DEMYSTIFYING TRIPLE NEG CA



- **LAR:** Androgen receptor, Cell Surface Mucin (MUC1)
- **MES:** Growth Factor Receptor A (PDGF), C-KIT
- **BLIS:** Immunosuppressing molecule aka (VTGN1)
- **BLIA:** Stat signal transduction molecule & cytokines

Clin Cancer Res; 21(7) April 1, 2015

FUTURE PATHWAYS



- Biclutimide (AR Antagonist) resulted in 19% 6mo clinical benefit rate
- Enzalutimide in bone-only MBCA showed clinical activity. Future combo w/ Taxol

CK 4/6 Inhibition (Palbociclib): Those RB+ have 10-15% response

- IGF1, Prostaglandin Inhibitors exist

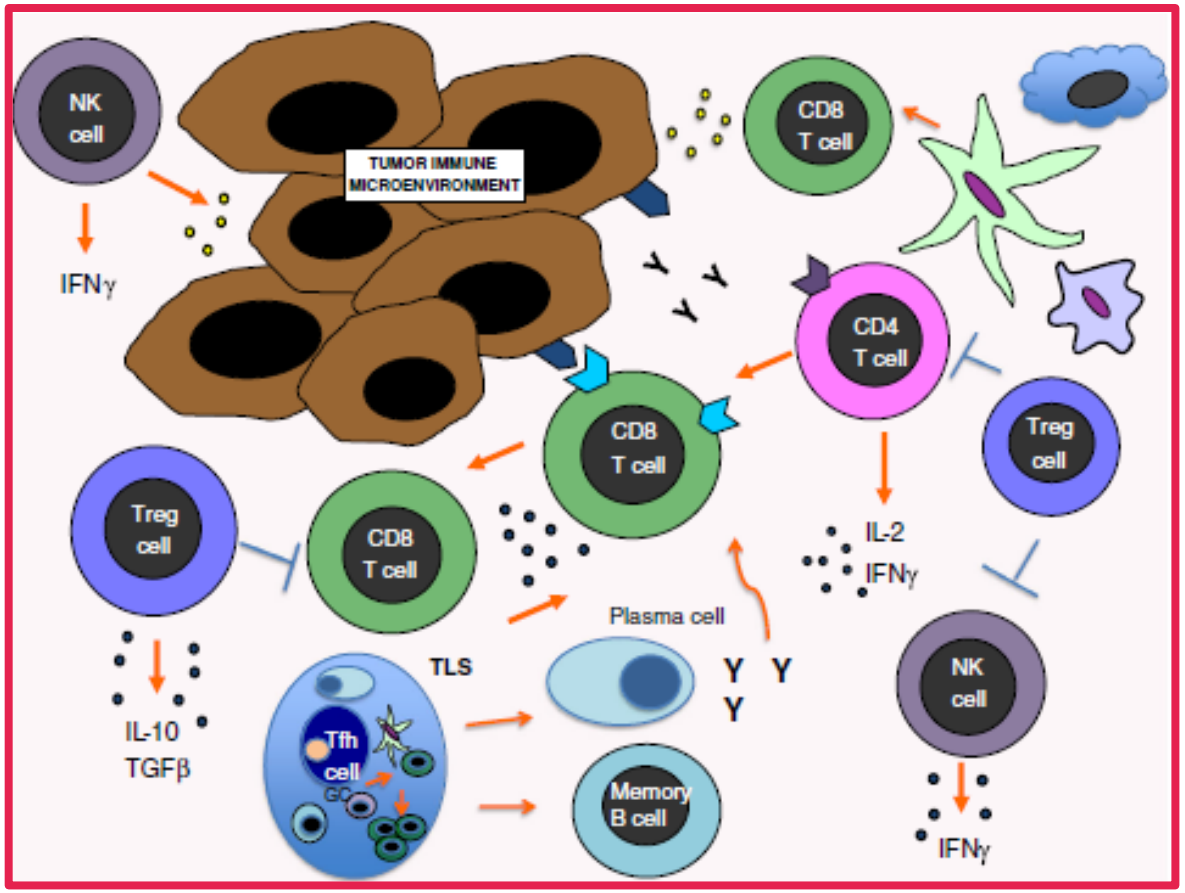
- Pembrolizumab (anti programmed cell death ab) and VTCN1 antibody

- STAT inhibitors & anti CTLA-4 like Ipilimimbab

Vidula & Rugo *Clin Cancer Res; 21(7); 1511–3*
Asghar ASCO 2015

HARNESSING IMMUNE SYSTEM

- Immune cells in microenvironment~ good prognostic indicator!
- Triple Neg & Her-2 neu enriched TILS
- Prognostic~ survival even in those not receiving chemotherapy (+/-) trastuz
- Predictive more robust response in those receiving chemotherapy



Pustzai et al. Clin Cancer Res; 22(9); 2105–10. 2016

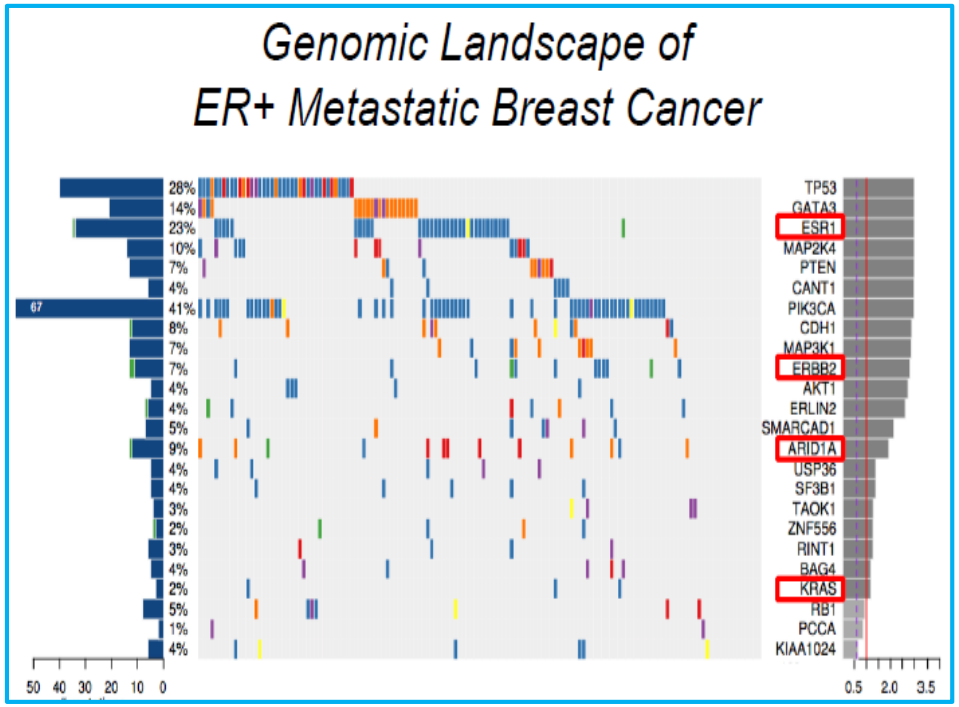
ON THE HORIZON-IMMUNE THERAPY

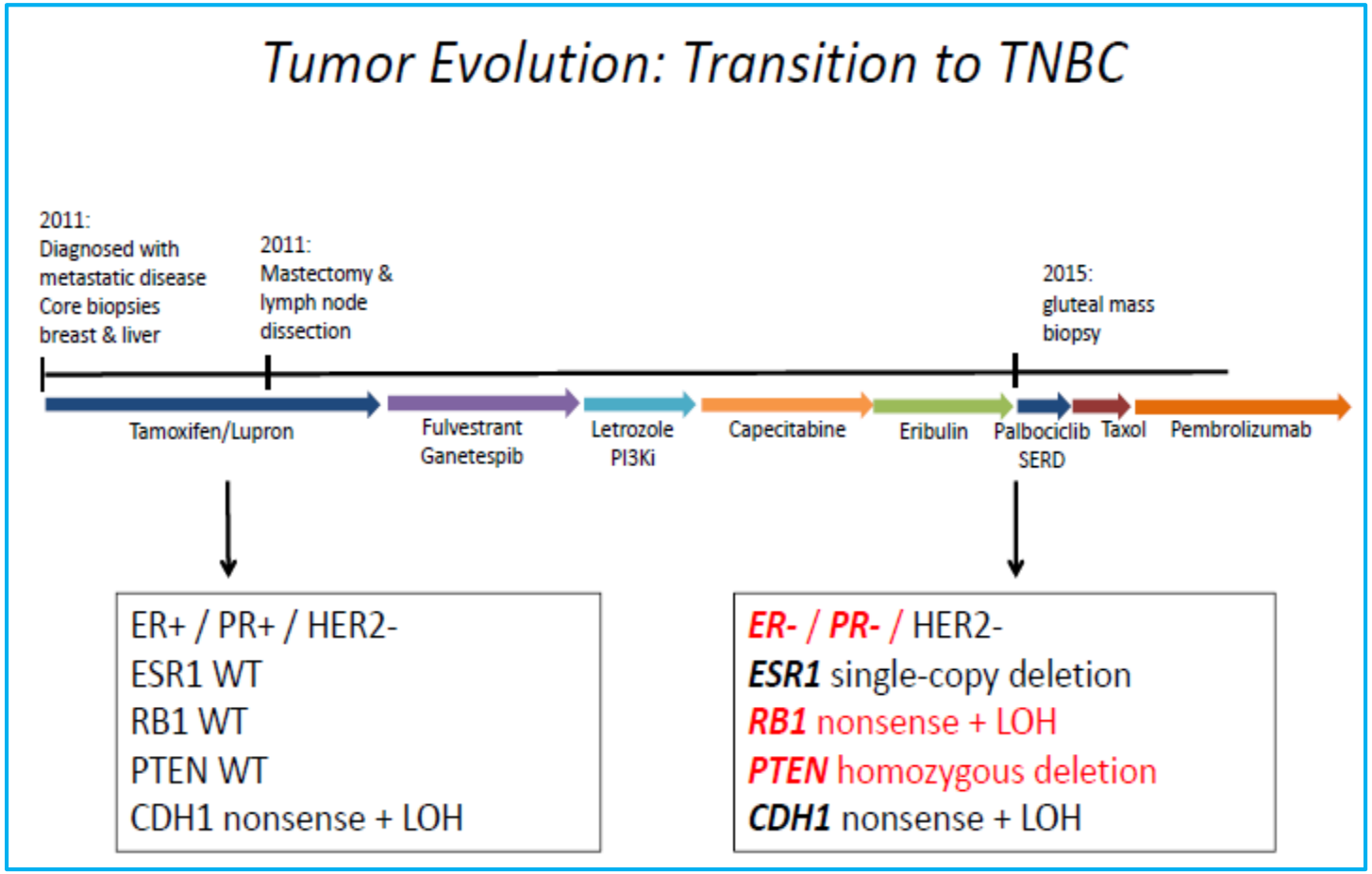
- Incorporation into prognostic models
- TIL count/gene signatures predictors for response to immunotherapy
- Met setting:
  - CTLA-4ab +AI= stable ds
  - Pembrolizumab/Avelumab/Atezolizumab: 19% rr in those with PDL-1 expression
  - Atezolizumab+abraxane 42% RR in triple neg

Phase	Clinicaltrials.gov ID	Disease setting	Type of disease	Breast cancer subtype	Immunotherapies	Combined treatments
I	NCT02303366	Metastatic	Only BC	All	Pembrolizumab	Stereotactic ablative radiosurgery
I	NCT02605915	Metastatic and neoadjuvant	Only BC	HER2$^+$	Atezolizumab	Trastuzumab/pertuzumab or T-DM1 or trastuzumab/pertuzumab/carboplatin/docetaxel
I	NCT02649686	Metastatic	Only BC	HER2$^+$	Durvalumab	Trastuzumab
I/II	NCT02129556	Metastatic	Only BC	HER2$^+$	Pembrolizumab	Trastuzumab
I/II	NCT02513472	Metastatic	Only BC	TNBC	Pembrolizumab	Eribulin mesylate
I/II	NCT02628132	Metastatic	Only BC	TNBC	Durvalumab	Paclitaxel
II	NCT02411656	Metastatic[a]	Only BC	TNBC or ER$^+$/HER2$^-$	Pembrolizumab	
II	NCT02447003	Metastatic	Only BC	TNBC	Pembrolizumab	
II	NCT02499367	Metastatic	Only BC	TNBC	Nivolumab	Doxorubicin (low dose), cyclophosphamide metronomic, radiotherapy, or cisplatin
II	NCT02411656	Metastatic	Only BC	HER2$^-$	Pembrolizumab	
II	NCT02447003	Metastatic	Only BC	TNBC	Pembrolizumab	
II	NCT02395627	Metastatic	Only BC	HR$^+$ (endocrine-resistant BC)	Pembrolizumab	Vorinostat and tamoxifen
II	NCT02536794	Metastatic	Only BC	TNBC ER$^+$/HER2$^-$	Durvalumab and tremelimumab	
II	NCT02563925	Metastatic (brain)	Only BC	All	Tremelimumab	Brain radiotherapy or stereotactic
II	NCT00083278	Metastatic	Only BC	All	Ipilimumab	
II	NCT02648477	Metastatic	Only BC	TNBC and ER$^+$/HER2$^-$	Pembrolizumab	Doxorubicin or letrozole or anastrozole or exemestane
III	NCT02555657	Metastatic	Only BC	TNBC	Pembrolizumab[b]	
III	NCT02425891	Metastatic	Only BC	TNBC	Atezolizumab[c]	Nab-paclitaxel
I	NCT02620774	Neoadjuvant	Only BC	TNBC (LABC)	Pembrolizumab	Nab-paclitaxel → AC or nab-paclitaxel/carboplatin → AC
I/II	NCT02489448	Neoadjuvant	Only BC	TNBC	Durvalumab	Nab-paclitaxel → ddAC
II	NCT01042379	Neoadjuvant	Only BC	All	Pembrolizumab	Paclitaxel
II	NCT02530489	Neoadjuvant	Only BC	TNBC	Atezolizumab	Nab-paclitaxel
III	NCT02620280	Neoadjuvant	Only BC	TNBC	Atezolizumab[c]	Nab-paclitaxel/carboplatin
II	NCT01502592	Presurgical	Only BC	All	Ipilimumab	Cryoablation
I	NCT02453620	Metastatic or LABC	Multiple	TNBC ER$^+$/HER2$^-$	Nivolumab ± ipilimumab	Entinostat
I	NCT01375842	Metastatic	Multiple	TNBC	Atezolizumab	
I	NCT02309177	Metastatic	Multiple	TNBC ER$^+$/HER2$^-$	Nivolumab	Nab-paclitaxel
I	NCT00836888	Metastatic	Multiple	All	Nivolumab	
I	NCT02655822	Metastatic	Multiple	TNBC	CPI-444 ± atezolizumab	
I	NCT01848834	Metastatic	Multiple	TNBC	Pembrolizumab	
I	NCT02554806	Metastatic	Multiple	All	Pembrolizumab	
I	NCT01772004	Metastatic	Multiple	All	Avelumab	
I	NCT01975831	Metastatic	Multiple	ER$^+$/HER2$^-$ and HER2$^+$	Durvalumab and tremelimumab	
I	NCT02658214	Metastatic	Multiple	TNBC	Durvalumab and tremelimumab	Gemcitabine/carboplatin or nab-paclitaxel/carboplatin
I/II	NCT02318901	Metastatic	Multiple	HER2$^+$	Pembrolizumab	Trastuzumab or TDM1
I/II	NCT02543645	Metastatic	Multiple	TNBC	Atezolizumab and varlilumab	
I/II	NCT02657889	Metastatic	Multiple	TNBC	Pembrolizumab	Niriparib
I/II	NCT02178722	Metastatic	Multiple	TNBC	Pembrolizumab and INCB024360 (IDO inhibitor)	
I/II	NCT02331251	Metastatic	Multiple	TNBC and ER$^+$/HER2$^-$	Pembrolizumab	Vinorelbine (ER$^+$/HER2$^-$) and gemcitabine (TNBC)
I/II	NCT01928394	Metastatic	Multiple	TNBC	Nivolumab ± ipilimumab	
I/II	NCT02452424	Metastatic	Multiple	TNBC	Pembrolizumab and PLX3397 (anti-CSFIR)	
I/II	NCT02331251	Metastatic	Multiple	All	Pembrolizumab	Various CT
I/II	NCT02318901	Metastatic	Multiple	HER2$^+$	Pembrolizumab	Trastuzumab or TDM1
I/II	NCT02543645	Metastatic	Multiple	TNBC	Atezolizumab and varlilumab (CD27 agonist)	
I/II	NCT02403271	Metastatic	Multiple	TNBC and HER2$^+$	Durvalumab	Ibrutinib
I/II	NCT02404441	Metastatic	Multiple	TNBC	PDR001	
I/II	NCT02643303	Metastatic	Multiple	All	Durvalumab and Poly-ICLC ± tremelimumab	
II	NCT02661100	Metastatic	Multiple	TNBC	CDX-1401 + Poly-ICLC and pembrolizumab	
II	NCT02644369	Metastatic	Multiple	TNBC	Pembrolizumab	
II	NCT02527434	Metastatic	Multiple	TNBC	Tremelimumab	
II	NCT02478099	Metastatic	Multiple	TNBC	Atezolizumab	

Pustzai et al. Clin Cancer Res; 22(9); 2105–10. 2016

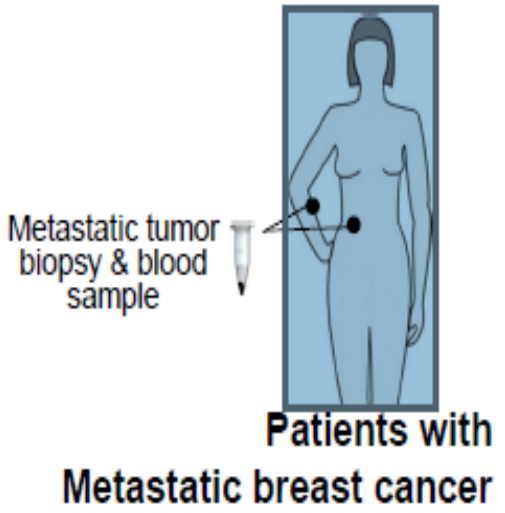
MOLECULAR EVOLUTION





Adapted from Dr. Nikhil Wagle's slides DFCI symposium

FOUNDATION TESTING & MATCH TRIAL



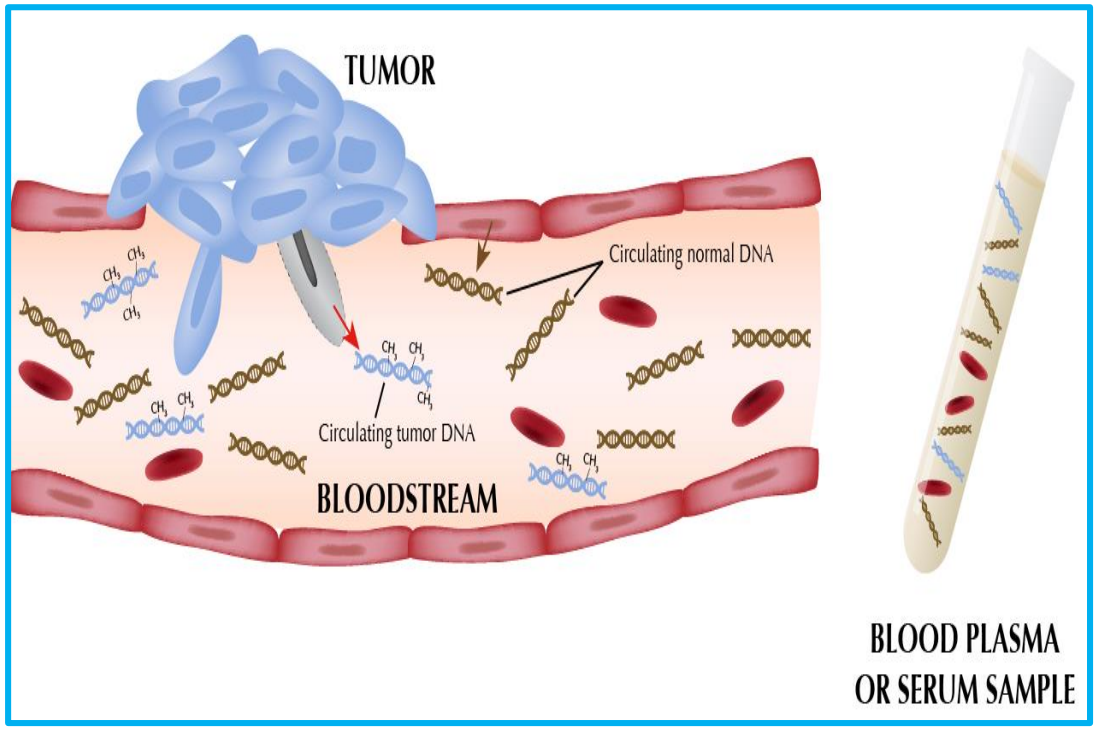
Evaluate for mutations

TRIAL MATCH

- Trial #1
- Trial #2
- Trial #3

CELL-FREE DNA

- NEJM 2013: **CFDNA** vs. CTC vs. CA15-3
  - Detected at a greater frequency
  - Greater correlation to tumor burden
  - Earliest measurement of treatment response
- Future:
  - Monitor cancer burden & response to Tx
  - Non-invasive way to identify genomic alterations
- Shown beneficial in identifying ESR-1 mutations



Clin Cancer Res; 22(5); 1130–7 2015.
N Engl J Med. 2013 Mar 28;368(13):1199-209.

SURVIVING BREAST CANCER

HOT BUTTON TOPICS

AFTER THE STORM

- Peripheral edema
- Alopecia
- Hyperpigmentation
- Nail changes
- Fatigue
- Neuropathy
- Periods

RECURRENCE

Follow clinically & breast imaging, healthy living

- No tumor markers, scans, labs

- **Her2 neu/Triple Neg ds**
  - 2-5 year window
- **Hormone positive disease**
  - Analogous ~chronic ds
  - Late relapse 20 yrs out
  - Endocrine back bone

Table 1: Risk of Distant Recurrence 10 to 20 Years After Diagnosis and Discontinuation of Endocrine Therapy at 5 Years

Tumor Subgroup	10 Years	15 Years	20 Years
T1N0	4%	9%	14%
T1N1 (1–3 nodes)	8%	15%	23%
T1N2 (4–9 nodes)	16%	30%	41%
T2N0	8%	14%	21%
T2N1 (1–3 nodes)	12%	20%	29%
T2N2 (4–9 nodes)	20%	35%	47%

Pan H, et al: 2016 ASCO Annual Meeting. Abstract 505. Presented June 6, 2016.

HORMONAL THERAPY

BENEFITS

- **Decrease risk of recurrence & improve survival in Invasive cancer**
- Prevent contralateral cancer 50%
- Tam promotes bone health
- AI no endo CA or VTE risk

RISKS

Aromatase Inhibitors: Anastrazole

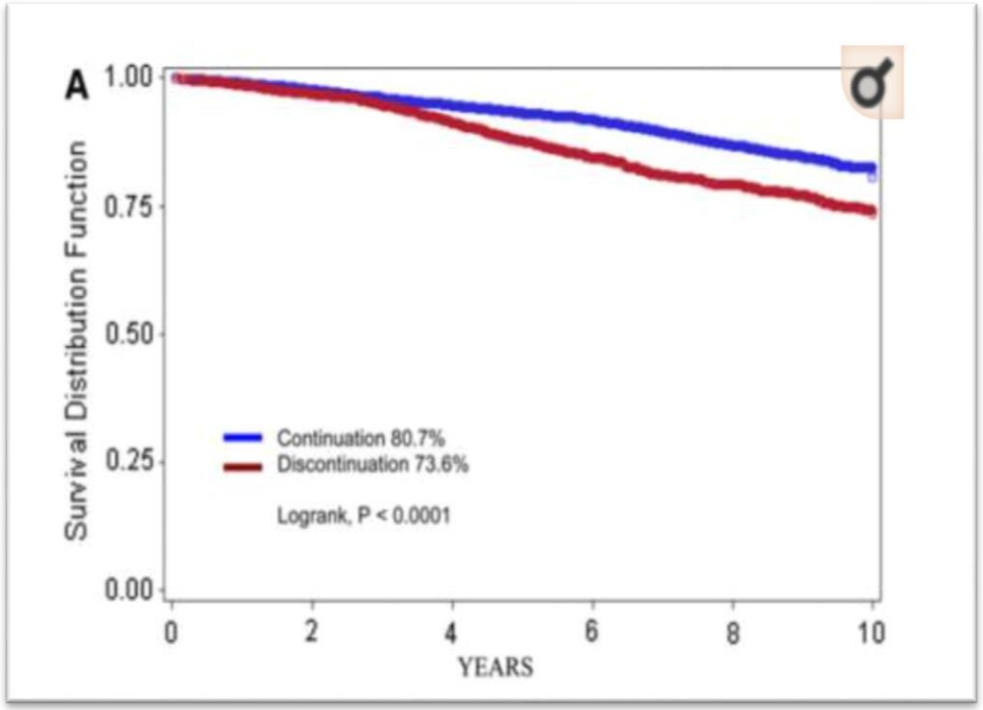
- Joint aches & stiffness (35%)
- Vaginal dryness
- Bone density loss (6-7%)
- Fracture risk (2.93% yearly, 11%)
- Mild hair thinning

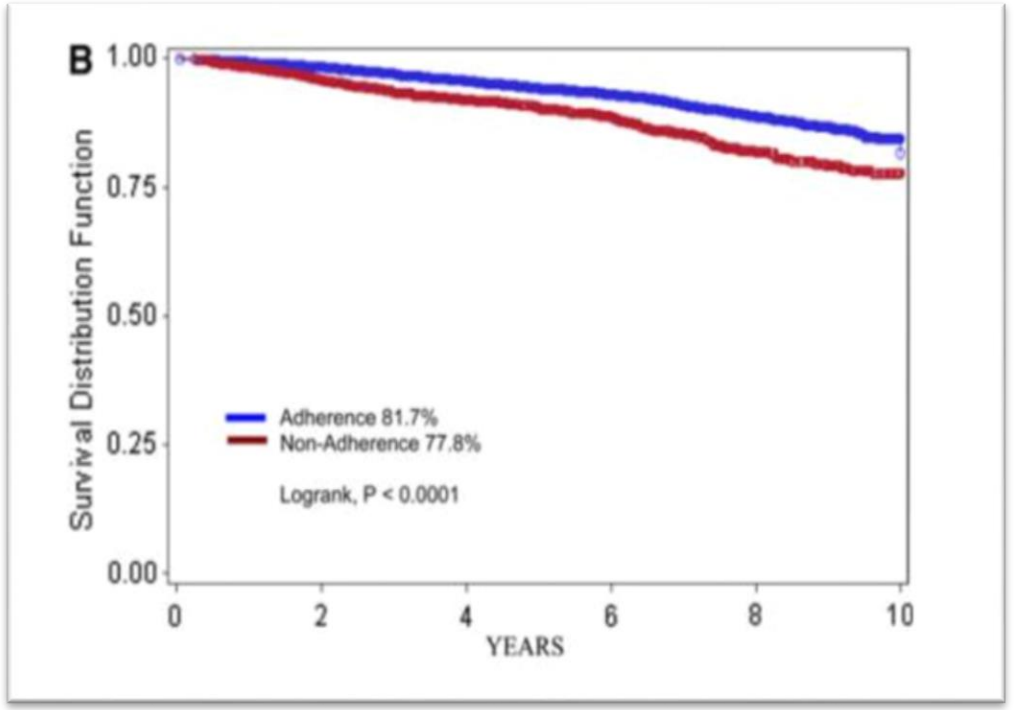
SERM: Tamoxifen

- Hot flashes (35%)
- Vaginal discharge (13%)
- Endometrial Ca (0.8%)
- VTE (2-5%)

ATAC trial Lancet 2005; 365: 60-62.

INCREASED MORTALITY WITH EARLY DISCONTINUATION/NON-ADHERENCE





Breast Cancer Res Treat. 2011 Apr; 126(2): 529–537.

TACKLING JOINT ACHES

- Most common reason for aromatase inhibitor discontinuation

Recommendations:

- **EXERCISE!!**
  - Reduction of arthralgia by 30% with exercise combination of strength training and aerobic at least 150 mins per week
- **Acupuncture**
  - 2x/wk for 6 wks, then 1x/wk for 12 improvement in msk symptoms compared to sham
- Vitamin D thus far no large benefit
- Glucosamine Chondroitin (tx vs. unblinided-?mod improvement in n=53)
- AI rotation

Irwin, M etal. J Clin Oncol; 2014
Hershman SABCS 2018-SWOG

VAGINAL DRYNESS

- Fissures, dyspareunia, UTIs
- Moisturizers, lubricants **First-line**
  - Liqui beads
  - Over-the-counter agents
  - Coconut, Avocado, olive oil
  - **Replens** weekly with taper
  - Vitamin E
- **Estrogen preparations**

Table 1. Low-Dose Vaginal Estrogen Preparations and Suggested Regimens

Formulation	Composition	FDA-Approved Dosages*
Vaginal cream	17β-estradiol	The usual dosage range is 2–4 g (marked on the applicator) daily for 1 week or 2 weeks, then gradually reduced to one half of the initial dosage for a similar period. A maintenance dosage of 1 g one to three times a week may be used after restoration of the vaginal mucosa has been achieved.†
Vaginal cream	Conjugated equine estrogen	Cyclic administration of 0.5 g intravaginally (daily for 21 days then off for 7 days) for treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Twice weekly administration of 0.5 g intravaginally (for example, Monday and Thursday) for treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.‡
Vaginal ring	17β-estradiol	2-mg ring releasing 7.5 micrograms/d for 90 days
Vaginal tablet	Estradiol hemihydrate	10 micrograms/d for 2 weeks and then 10 micrograms/d two times a week

Abbreviation: FDA, U.S. Food and Drug Administration.

*FDA-approved dosages of conjugated estrogen and estradiol creams are greater than those currently used in clinical practice that are proven to be effective.

†In clinical practice, these protocols also are used: 1 g every night for 2 weeks, then two times per week or 0.5 g twice weekly.

‡In clinical practice, this protocol also is used: 0.5 g twice weekly.

ACOG committee opinion 2018

ESTROGEN PREPARATIONS

- **Mayo clinic systematic review:** increased systemic estrogen levels with estrogen preparations
- **Am Coll of Obgyn Consensus 2018:** Not felt to increase risk of breast cancer recurrence
- Patient should be counseled on absorption & current consensus
- **AVOID** oral estrogen

Table 1. Estradiol Preparations and Maximum Annual Delivered Dose

Product name	Route/Type of administration	Typical regimen	Nominal daily delivery rate or administered lowest approved dose (mg/day)	Typical serum level (pg/mL)	Maximum annual delivered dose (mg)[1]
Vaginal estradiol					
Vagifem	Vaginal tablet	1 Tablet daily × 14 then 2 × weekly	10 μg	4.6	1.14
Estring	Vaginal ring	1 Ring vaginally q 3 months	7.5 μg	8.0	2.74
Estrace	Vaginal cream	1 g cream vaginally q week[2]	variable[2]	NA	7.1
FemRing	Vaginal ring	1 Ring vaginally q 3 months	0.05 mg	40.6	18.25
Oral estradiol					
Estrace tablets and generics	Oral tablet	1 Tablet p.o. qd	0.5 mg	55.4	182.5
Transdermal estradiol					
Divigel[3]	Gel	0.25 mg packet qd	0.003	9.8	1.09
Estrogel	Gel	0.75 mg/pump qd	0.035	28.3	12.78
Evamist[3]	Spray	1.53 mg spray qd	0.021	19.6	7.67
Climara[4]	Patch	1 Patch weekly	0.025	22	9.13
Menostar	Patch	1 Patch weekly	0.014	13.7	5.11
Vivelle-Dot[5]	Patch	1 Patch twice weekly	0.0375	34	12.78

Pruthi et al. Breast J 2011; 17: 403-408
Krychman et al. J Sex Med 2012; 9:5-13
ACOG committee opinion 2018

SEXUAL HEALTH

- 64% of BCA survivors report reduced sexual desire & >50% long-term dysfunction
- Chemotherapy: greater sexual dysfunction lasting up to 5 years
  - Vaginal sequelae, lubrication, sexual pain, arousal, orgasm
  - Increased severity in younger women
- Vaginal atrophy therapy: lubricants, oils, replens
- Viscous Lidocaine to vulvar vestibule
- Vaginal Dilators
- Maintenance of sexual activity
- Pelvic physical therapy & prescribed devices
- Sexual health clinic

Krychman et al. J Sex Med 2012; 9:5-13
Carter et al. J Sex Med 2011; 8; 549-559
Burwell et al. J Clin Oncol 24:2815-2821

BONE LOSS

HUGE IMPACT ON QOL IN SUVIVORS!

Estrogen inhibits rank-ligand (promotor of osteoclastic activity)

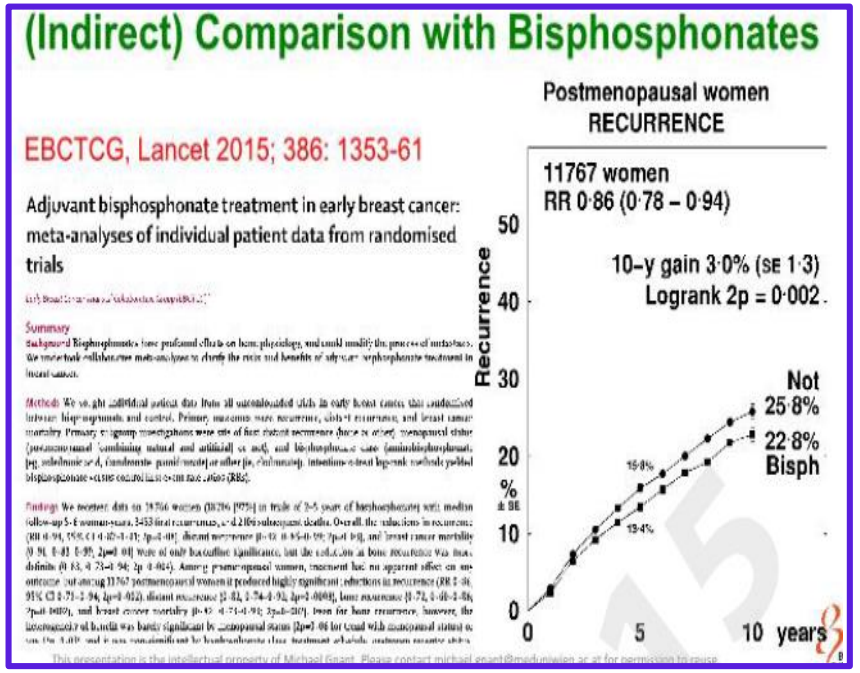
- Premenopausal s/p chemo 3-8% BMD loss L-spine
  - Aromatase Inhibition & ovarian suppression in premenopausal=bone loss
- Post menopausal 1-10% loss of BMD s/p 1yr of chemo (limited data)
  - AI: Decrease BMD, increase fractures
  - Tamoxifen promotes stabilization in BMD

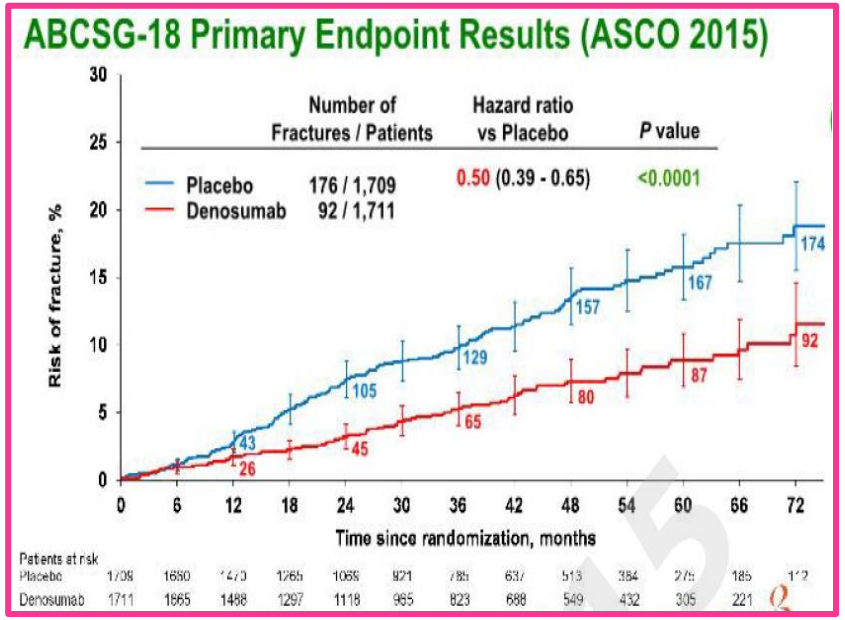
  ***ADJUVANT THERAPY TO TREAT BONE LOSS MOST STUDIED IN THIS POPULATION!**

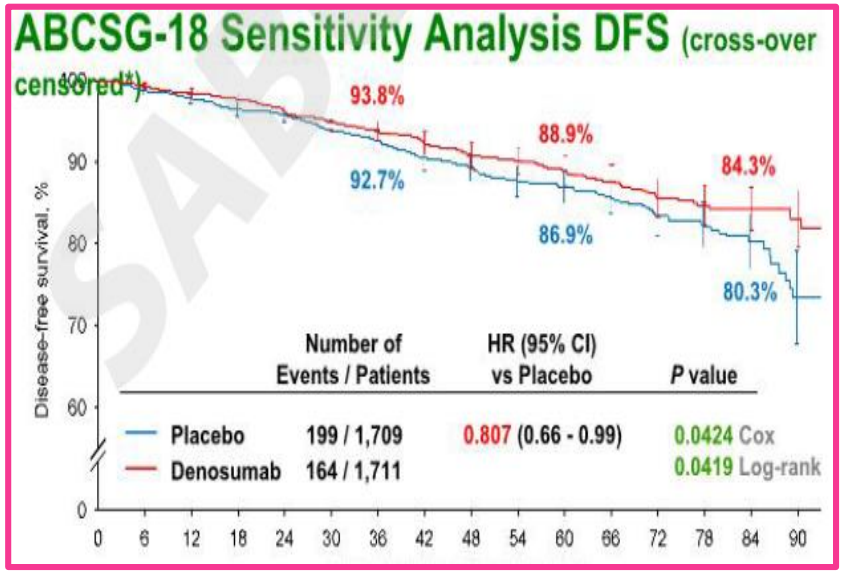
Shapiro CL JClinOncol 2001; 19(4): 3306.
ChenZ etal. Arch Intern Med. 2005; 165 (5): 552.

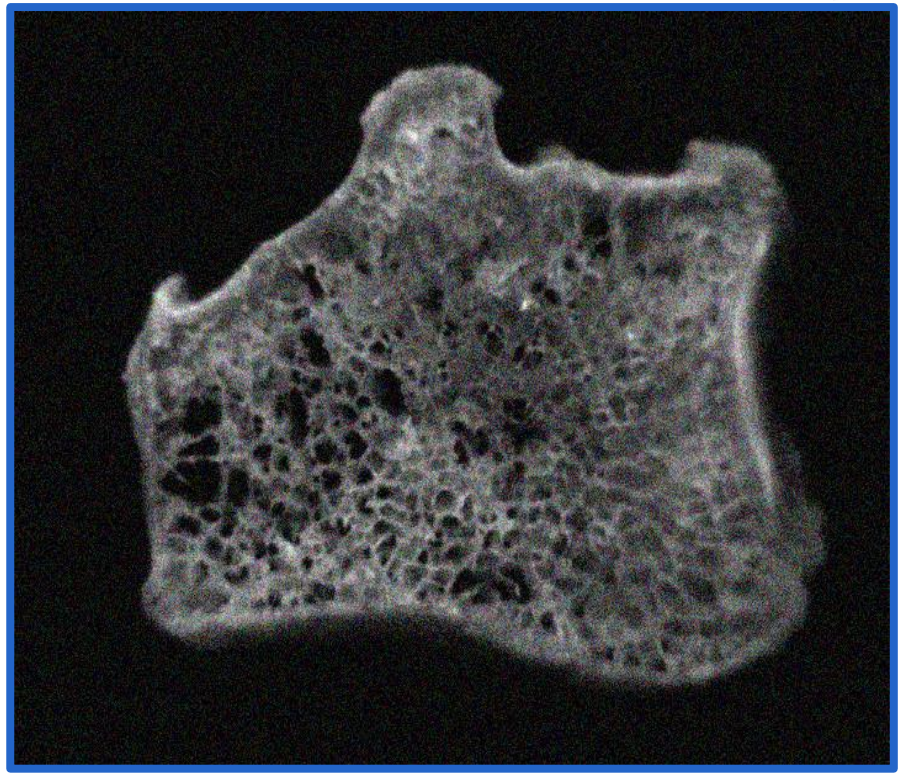
BONE MODIFICATION

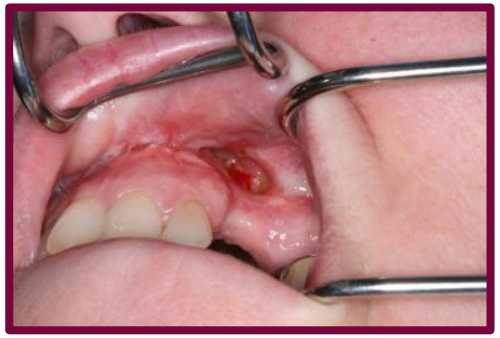
- 2017 Meta-analysis: SOC Bisphosphonate
- Zometa 4mg IV q6 mo
- **Post-menopausal** women improve survival & reduce recurrence in bone
- ABCSG-18: Denosumbab 60mg 2x/yr premenopausal BCA
  - Decreased risk of fracture (p=0.0001), improves bone health, no added toxicity
  - Improved DFS











BONE MODIFICATION

- **Benefits:** 50% decr frx denosumab, DFS 2% at 5yrs, 3% 7-10yr, mortality 2-3% benefit
- **Risks:** MC joint, muscle aches, F/N (flu-like)
  - less common hypocalcemia (dose-adjusted), renal toxicity, **1%** risk osteonecrosis of jaw
- ~2 years of therapy
- Monitoring: DEXA q 2 years on therapy
- Recommend: Vitamin D, Calcium in Diet, Weight bearing exercise, reduction of tobacco
- Improvement seen in BMD after therapy w/ similar rates of fractures to controls

HOT FLASHES

Improve w/ Time!

- Avoid Triggers: alcohol, caffeine, spicy food!
- Fan at bedside, decrease ambient temp
- Slow breathing
- Down pillow, moisture-wicking pajamas, sheets
- Dress in layers
- Exercise/stretching
- **NO** convincing evidence for: acupuncture, yoga, Chinese herbs, dong quai, evening primrose oil, ginseng, kava, soy or red clover extract
- **NOT** recommend phytoestrogens, black cohosh, or oral estrogen
- Meds: Venlafaxine, SSRIs, Gabapentin

www.cooljams.com www.wickedsheets.com

Grady D. N Engl J Med 2006; 355:2338-2347

TAMOXIFEN & CYP2D6 INHIBITORS

Table 3. Major Drug Classes Divided by Known CYP2D6 Inhibitory Activity

Class	Moderate to Potent Inhibitors With Clearly Demonstrated or Expected In Vivo Inhibition†	Weak-to-Moderate Inhibitors That Have Demonstrated or Could Potentially Have Some In Vivo Effect‡	Alternative Drugs Expected to Have Little In Vivo Inhibition§
SSRI/SNRIs	Paroxetine* Fluoxetine* Bupropion Duloxetine	Sertraline* Citalopram* Fluvoxamine	Venlafaxine* Desvenlafaxine Reboxetine Escitalopram Mirtazapine
Tricyclic antidepressants		Clomipramine Doxepin Desipramine Imipramine Amitriptyline Nortriptyline	
Antipsychotics	Thioridazine Perphenazine Pimozide	Chlorpromazine Fluphenazine Haloperidol	Thiothixene Clozapine Risperidone Clozapine Olanzapine Ziprasidone Quetiapine
Cardiac medications	Quinidine Ticlopidine	Amiodarone Nicardipine Verapamil Amlodipine Felodipine Nifedipine	Diltiazem
Medications for infectious diseases	Terbinafine Quinidine‖	Ritonavir Halofantrine Chloroquine	Indinavir Saquinavir Nelfinavir Delavirdine Nevirapine Efavirenz
H2 blockers		Cimetidine	Ranitidine
H1 blockers¶		Clemastine Tripelennamine Promethazine Hydroxyzine Diphenylpyraline	Chlorpheniramine Cetirizine Loratadine
Miscellaneous medications	Cinacalcet	Celecoxib	Gabapentin

ASCO Clinical Practice Guidelines:

- Despite accumulating evidence of drug-drug interactions, the data remains LIMITED & INDIRECT linking the interactions
- Those with clear benefit from CYP2D6 drugs may want to avoid Tam bc of potential pharm interactions & vice versa.

J Clin Oncol 2010. 28: 2768-27776
Burstein HJ et al. J Clin Oncol 2010.

GYNECOLOGIC HEALTH ON TAMOXIFEN

- Agonist at endometrium=proliferation, hyperplasia, polyp formation, invasive carcinoma, sarcoma
- Risk in postmenopausal ONLY
- Consensus statement: Does **NOT** recommend a screening endo u/s unless high risk (ie. hx of polyps, fam hx)
  - Gynecologic yearly monitoring for hyperplasia, uterine bleeding
  - GYN f/u if vaginal bleeding
  - Reconsider Tamoxifen if atypical hyperplasia on drug
- Premenopausal patients:
  - Break-through bleeding
  - Recommend birth control (Ie. Condoms, copper IUD)

ACOG committee opinion 2017 revised

PREVENTION

- **Alcohol <3 drinks per week**
  - Lace trial: ≥6 grams of alcohol daily~ higher rates recurrence ([HR] **1.35,** 95% CI 1.0-1.83) & BCA death (HR **1.51**, 95% CI 1.0-2.29) vs. <0.5 grams daily. Overweight & postmenopausal women > harm of recurrence
- **Exercise**
  - Modest exercise tends to reduce the risk of breast cancer in post-menopausal women
  - BMI ≤24
  - Largely Mediterranean diet w/ olive oils, nuts supported

2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND POSTMENOPAUSAL BREAST CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Alcoholic drinks[1] Body fatness[2] Adult weight gain Adult attained height[3]
	Probable	Physical activity[4] Body fatness in young adulthood[5] Lactation[6]	
LIMITED EVIDENCE	Limited – suggestive	Non-starchy vegetables (ER– breast cancers only)[7] Foods containing carotenoids[8] Diets high in calcium	
	Limited – no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables (ER+ breast cancers); fruits; pulses (legumes); soya and soya products; red and processed meat; poultry; fish; eggs; dairy products; fats and oils; total fat; vegetable fat; fatty acid composition; saturated fatty acids; mono-unsaturated fatty acids; polyunsaturated fatty acids; trans-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; glycaemic load; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium supplements; iron; selenium; phytoestrogens; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; trans-nonachlor; polychlorinated biphenyls; acrylamide; dietary patterns; culturally defined diets; sedentary behaviour; energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		

WCRF Third Expert Report 2017

SURVEILLANCE

- Breast Cancer: (q6mos x 2years)
  - Yearly mammography (4% risk recurrence I/L, surveillance C/L)
  - MRI alt w/ mammography q6mos (BRCA, fam/hx)
  - B/l mastectomies & implants, autologous reconstruction: PE
  - Mammography in survivors (older women), reduction of death from BCA
- Metastatics
  - No mammograms….endocrine (+) probably?
  - No routine cancer screening…endocrine (+) probably?

Breast Cancer Res Treat. 2008;111(3):489. Epub 2007 Oct 24.

YOUNG WOMEN

- 6-7% of BCA is diagnosed in women ≤40 yo
- Growing population in US > women at risk!
- Leading cause of cancer related death
- Survival **inferior in young** women compared to older women
- More aggressive subtypes w/ unfavorable features
- Present more advanced ds

DIFFERING NEEDS

- Body Image
- Psychosocial Distress, Depression
- Fertility
- Sexuality/menopausal sxs
- Genetic implications
- Child care, education

+

YOUNGER WOMEN: REPRODUCTIVE & LATE HEALTH EFFECTS

- High level of physical functioning in younger women
- However social & emotional functioning, and vitality **lowest** amongst youngest women
- More depressive symptoms and more **negative** affect in youngest women
- Experience of menopausal transition w/ treatment was associated with **lower** mental health in youngest women

Ganz et al JCO 2003

PREGNANCY AFTER BREAST CANCER

- **Data:**
- Retrospective study, multi-centered, cohort study
- 333 pregnant pt ER(+) to 874 non-preg controls (686 ER +)
- No difference in ER (+) DFS (p=0.55)
- **Pregnancy is NOT detrimental or protective, but SAFE.**

- **Recommendations:**
  - Wait 2-3 yrs to get through early risk period, optimal endo therapy

- **POSITIVE TRIAL:** prospective trial ph II evaluate safety & pregnancy outcomes in interrupting ET in those who desire pregnancy


VOLUME 31 · NUMBER 1 · JANUARY 1 2013
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

Hatem A. Azim Jr, Niels Kroman, Marianne Paesmans, Shari Gelber, Nicole Rotmensz, Lieveke Ameye, Leticia De Mattos-Arruda, Barbara Pistilli, Alvaro Pinto, Maj-Britt Jensen, Octavi Cordoba, Evandro de Azambuja, Aron Goldhirsch, Martine J. Piccart, and Fedro A. Peccatori

BABIES AFTER CANCER

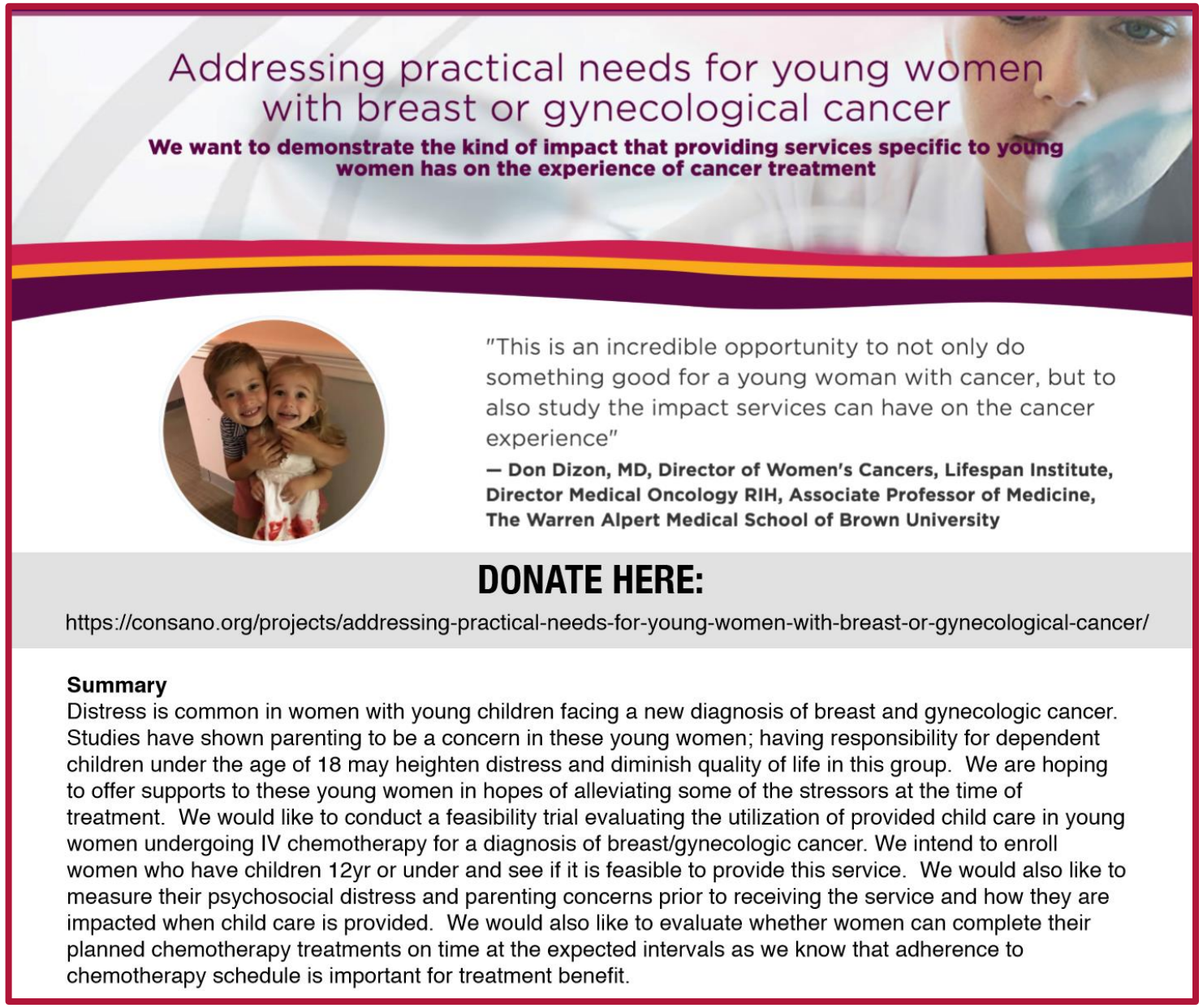
- Most retrospective studies do **NOT** report preterm birth, low birth weight, congenital abnormalities or neonatal death
- **No** negative impact of breast feeding on survivors.

Christinat A et al. maturitas 73 (2012)191-196
Azim H et al. J Clin Oncol (2013) 31: 71-79.

YOUNG FIGHT STRONG PROGRAM

For women 45 years old and younger with breast or gynecological cancer

CONSANO.ORG


Addressing practical needs for young women with breast or gynecological cancer
We want to demonstrate the kind of impact that providing services specific to young women has on the experience of cancer treatment
"This is an incredible opportunity to not only do something good for a young woman with cancer, but to also study the impact services can have on the cancer experience"
— Don Dizon, MD, Director of Women's Cancers, Lifespan Institute, Director Medical Oncology RIH, Associate Professor of Medicine, The Warren Alpert Medical School of Brown University
DONATE HERE:
https://consano.org/projects/addressing-practical-needs-for-young-women-with-breast-or-gynecological-cancer/
Summary
Distress is common in women with young children facing a new diagnosis of breast and gynecologic cancer. Studies have shown parenting to be a concern in these young women; having responsibility for dependent children under the age of 18 may heighten distress and diminish quality of life in this group. We are hoping to offer supports to these young women in hopes of alleviating some of the stressors at the time of treatment. We would like to conduct a feasibility trial evaluating the utilization of provided child care in young women undergoing IV chemotherapy for a diagnosis of breast/gynecologic cancer. We intend to enroll women who have children 12yr or under and see if it is feasible to provide this service. We would also like to measure their psychosocial distress and parenting concerns prior to receiving the service and how they are impacted when child care is provided. We would also like to evaluate whether women can complete their planned chemotherapy treatments on time at the expected intervals as we know that adherence to chemotherapy schedule is important for treatment benefit.

THANK YOU!
UNECOM CLASS 2018