Dr Mark Tuthill

Consultant medical oncologist

Mark.tuthill@ouh.nhs.uk

08/10/2019

Specialist Areas

- Breast cancer
- Prostate cancer
- Bladder cancer
- Testicular cancer
- Kidney cancer

- Emergency treatment of cancer

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Oxford

The Churchill Hospital: OUHFT

The Nuffield Manor Oxford

Genesis Care: Oxford

TMLEP Improving Healthcare Standards

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Medical treatment of breast tumours

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Aims

- Cover the principles of current medical breast cancer treatment
- Types of breast tumour and their consequences of a delay in diagnosis
- Complication of medical treatments for breast cancer
- Other medical therapies and immunotherapy

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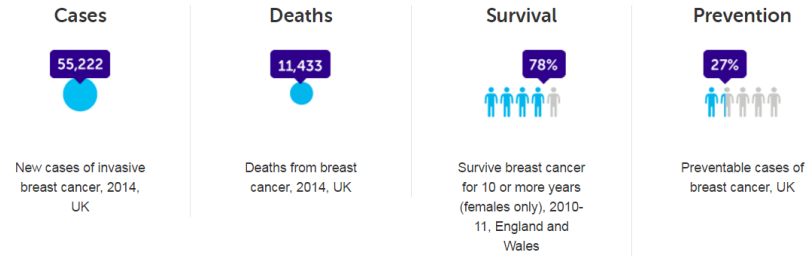
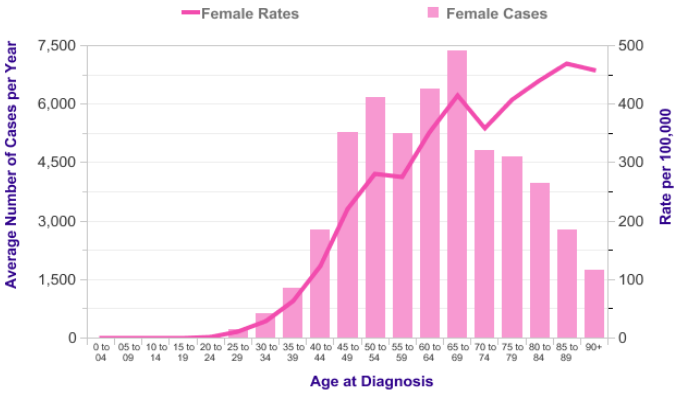
Breast Cancer Statistics



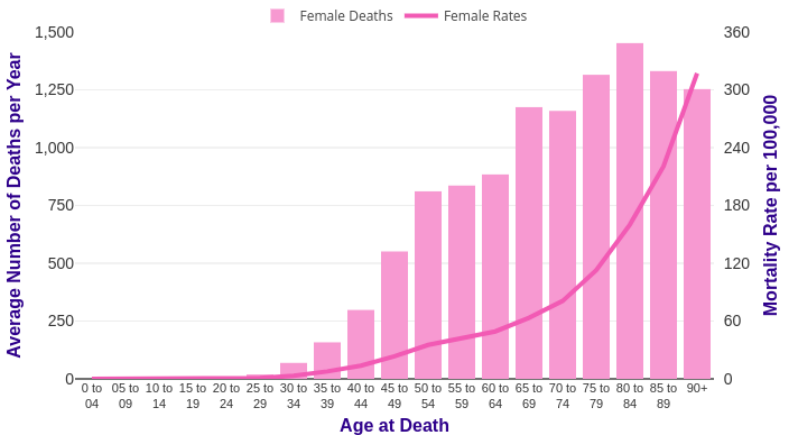
Breast Cancer (C50): 2012-2014
Average **Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, Females, UK**



CANCER RESEARCH UK

Breast Cancer (C50): 2014-2016

Average Number of Deaths Per Year and Age-Specific Mortality Rates per 100,000 Females, UK



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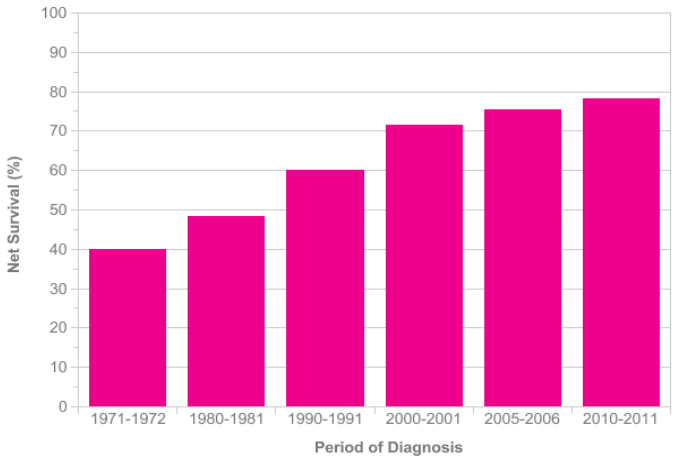
Breast Cancer (C50): 1971-2011

Age-Standardised Ten-Year Net Survival, England and Wales



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Breast cancer

Histology types

- IDC (70% to 80%)
- Lobular
- Pagets disease

Receptors and Targets

- ER (estrogen receptor)
- PR (Progesterone receptor)
- HER-2
- Triple negative breast cancer
- Androgen receptor
- BRCA1/2
- PDL1
- Many others in trial

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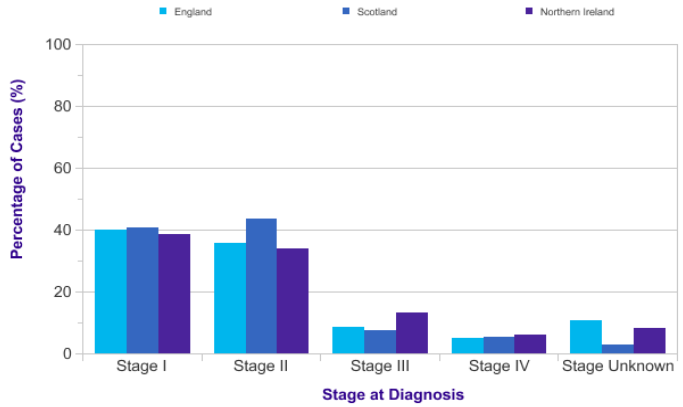
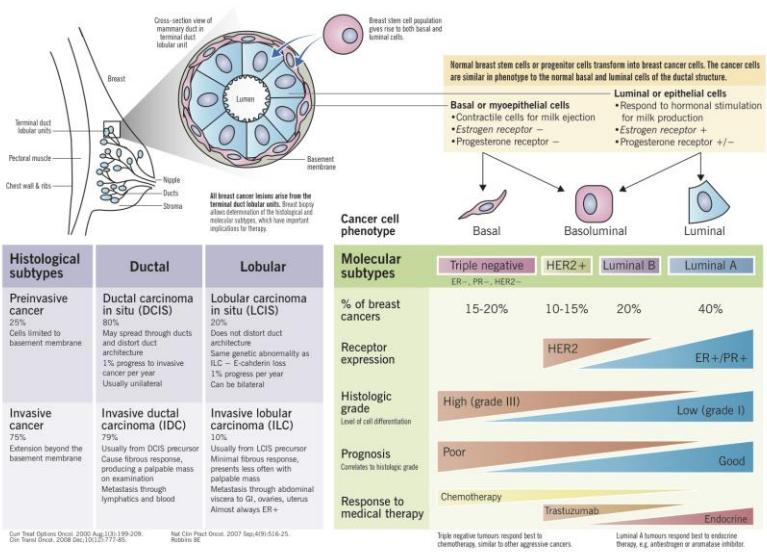
Breast Cancer (C50)
Proportion of Cases Diagnosed at Each Stage, All Ages



CANCER RESEARCH UK

Breast cancer pathogenesis and histologic vs. molecular subtypes



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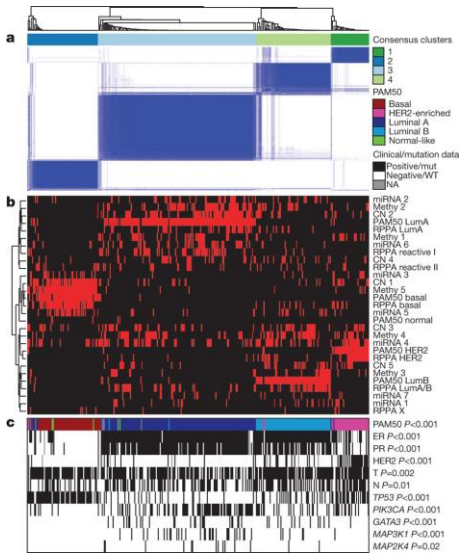
Coordinated analysis of breast cancer subtypes defined from five different genomic/proteomic platforms.



nature

DC Koboldt *et al. Nature* **000**, 1-10 (2012) doi:10.1038/nature11412

Common causation issues in breast cancer

- Delay in diagnosis – potentially leading to a worse breast cancer outcome
- Delay in treatment – failure to diagnose and treat cancer

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Consequences of delay in diagnosis in breast cancer

- Increase tumour burden – affecting prognosis
- Increased need for chemotherapy
- Missed opportunity for wide local excision – breast sparing
- Psychological distress
- Increased risk for litigation

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Tumour Doubling times in breast cancer by subtype ER+ versus TNBC

- Triple-negative tumors show greatest volume increases (40% vs. 20%, p = 0.001) and shorter DT (124 vs. 185 days, p = 0.027) than estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)– tumors.
- HER-2 similar high growth rates to TNBC.

Reference

Breast Cancer. 2019 Mar;26(2):206-214. Tadokoro Y, Hayashi T, Sugino T. breast cancer growth rate really depend on tumor subtype? Measurement of tumor doubling time using serial ultrasonography between diagnosis and surgery. Nakashima K, Uematsu T, Takahashi K, Nishimura S,

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Case 1

- 35 year old woman underwent a breast reduction
- DCIS was found in the breast reduction but not acted upon
- The claimant presented with metastatic HER-2 positive breast cancer 15 months later

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Case 2

- The claimant had a long standing history of breast cysts which caused pain
- Multiple attendances at the breast clinic over many years
- Presented in 2014 with breast pain and was reassured.
- Represented in 2015 and a repeat mammogram was undertaken, which was reported as abnormal
- A 51mm grade II ER+ breast cancer was diagnosed in 2015 in her left breast with two micro- metastasis in her lymph nodes

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Why and when do we use medical treatments for breast cancer?

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Reasons for medical breast cancer treatment

- Reduce the size of a cancer before curative surgery – neo-adjuvant treatment
- Reduce the risk of recurrence after surgery- adjuvant chemotherapy
- Treat metastatic cancers – palliative chemotherapy and other therapies

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Neoadjuvant chemotherapy

- Common in HER-2+ breast cancer with chemotherapy + Herceptin and Pertuzumab
- Triple negative breast cancer - chemotherapy
- Lack of disappearance of the cancer after neoadjuvant treatment is associated with a worse outcome.
- Can prevent the need for mastectomy

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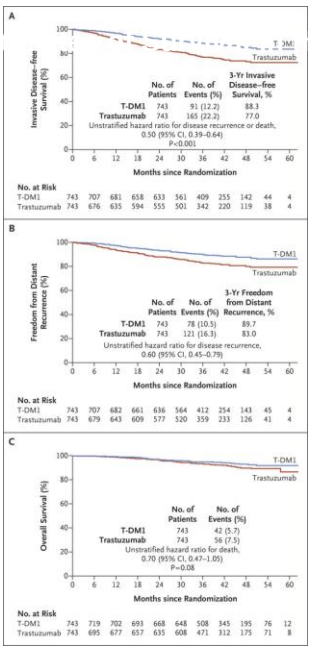

G von Minckwitz et al. N Engl J Med 2019;380:617-628.

Post Surgery treatment

- Adjuvant chemotherapy (can be before surgery)
- Adjuvant Radiotherapy
- Adjuvant Hormone based treatments
- Herceptin + pertuzumab
- bisphosphonates
- Follow up – mammograms or MRI if younger

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Chemotherapy in early breast cancer

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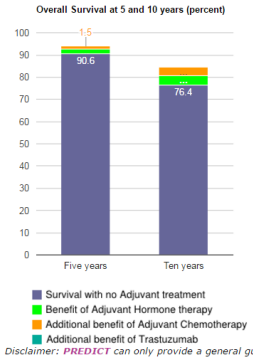
NHS predict

PREDICT Tool Version 2.0: Breast Cancer Survival; Results

Five year survival
91 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 2 out of 100 women treated are alive because of hormone therapy
An extra 3 out of 100 women treated are alive because of hormone therapy & chemotherapy
Ten year survival
76 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 4 out of 100 women treated are alive because of hormone therapy
An extra 8 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)



*Disclaimer: **PREDICT** can only provide a general guide to possible outcomes in any individual*

- 3.6% chance of benefit of chemotherapy
- Would you have chemo for this benefit?

Genomic scoring will become important over the next few years

- Oncotype dx
- Prosigna
- EndoPredict

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Recurrence Score® Result

16

Oncotype DX® Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score result is calculated from the gene expression results and ranges from 0-100.

The findings are applicable to women who have estrogen receptor positive (ER+) breast cancer with 1-3 positive nodes, and who will be treated with 5 years of tamoxifen (tam). It is unknown whether the findings apply to other patients outside these criteria.

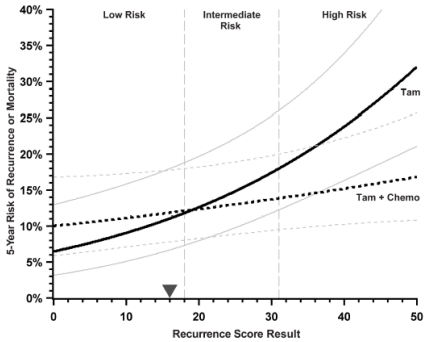
Clinical Experience: The following results are from a clinical validation study that included 367 patients from the SWOG 8814 study. The study included post-menopausal patients with N+, ER+ breast cancer who were randomized to either tam alone or CAF chemotherapy followed by tam (CAF-T). The endpoint for this study was disease-free survival (time to local or distant recurrence, new primary breast cancer, or death from any cause) and 5-year risks are presented.[1]

Prognosis and Chemotherapy Benefit: 5-Year Risk of Recurrence or Mortality after 5 Years of Tam, Based on the Recurrence Score Result

1-3 Positive Nodes
5-Year Risk of Recurrence or Mortality

Tam Alone
11% ——
(95% CI: 7%-18%)

Tam + Chemo
12% - - - - - - -
(95% CI: 8%-18%)



Common chemotherapy side effects

- Temporarily affect the number of healthy blood cells in the body
- Nausea and vomiting
- Diarrhoea or constipation
- Hair loss (alopecia)
- Fatigue (extreme tiredness)
- Numbness and tingling in hands and feet.
- Pain in the injection site
- Change in the colour of urine
- Heart failure
- Risk of death

- and many more …….

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Medico legal issues with chemotherapy

- Delay in diagnosis, leading to more intensive chemotherapy requirement
- Toxicity of agents – extravasation
- Acute and long term side effects

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Response to adverse events critical

- Extravasation – follow local guidelines and document following guidelines.
- Consent process – standard NHS forms now in use
- Clear local guidelines and national guidelines

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Breast Cancer radiotherapy

- 10-year risk of any (i.e., locoregional or distant) first recurrence from 35·0% to 19·3% (absolute reduction 15·7%, 95% CI 13·7–17·7, 2p<0·00001)
- 15-year risk of breast cancer death from 25·2% to 21·4% (absolute reduction 3·8%, 1·6–6·0, 2p=0·00005)
- Halves the rate at which the disease recurs
- Reduces breast cancer death rate by about a sixth

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Radiotherapy complications

- Common side effects during treatment may include:
- Mild to moderate fatigue
- Skin irritation — such as itchiness, redness, peeling or blistering — similar to what you might experience with a sunburn
- Breast swelling
- Changes in skin sensation
- Depending on which tissues are exposed, radiation therapy may cause or increase the risk of:
- Arm swelling (lymphedema) if the lymph nodes under the arm are treated
- Damage or complications leading to removal of an implant in women who have a mastectomy and undergo breast reconstruction with an implant
- Rib fracture or chest wall tenderness, rarely
- Inflamed lung tissue or heart damage, rarely
- Secondary cancers, such as bone or muscle cancers (sarcomas) or lung cancer, very rarely

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Hormone (endocrine treatment) for early and advanced breast cancer

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Tamoxifen

- Tamoxifen 20 once a day standard for pre-menopausal women
- Longer durations (10 versus 5 years) are better

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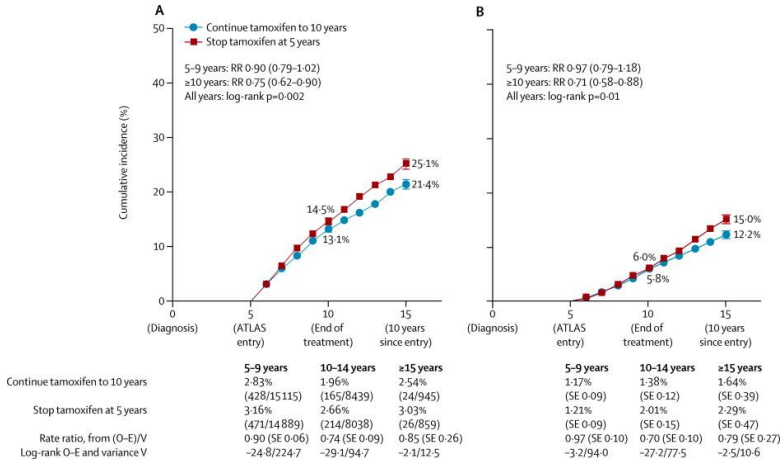


	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

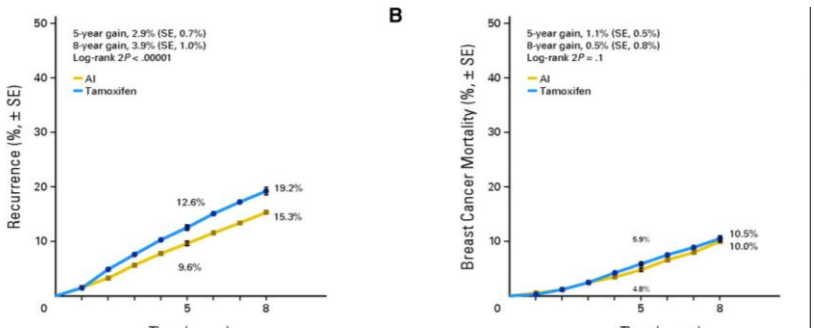
Lancet 2013

Case example

- 45 year old woman presents with early breast cancer
- Has a previous history of a blood clot in pregnancy.
- Undergoes chemotherapy and is started on hormonal therapy with tamoxifen
- Presents with a pulmonary embolism, likely precipitated by tamoxifen

Aromatase inhibitors

AI better than tamoxifen for post menopausal women



J Clin Oncol. 2010 Jan 20;28(3):509-18.

Induction of menopausal in pre- menopausal women with Zoladex

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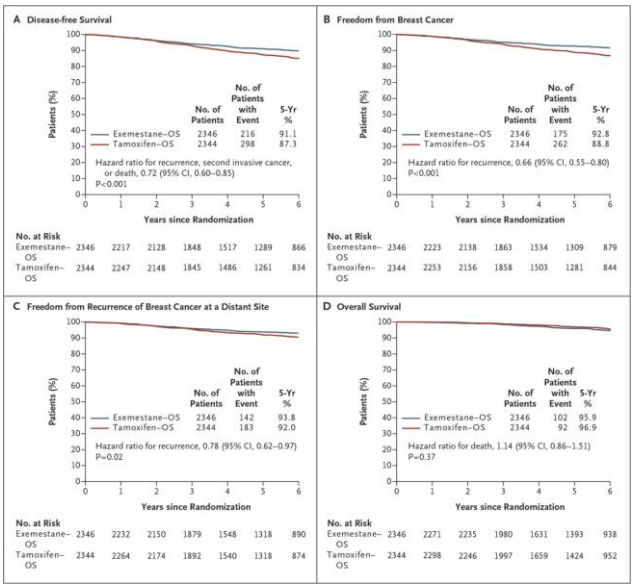


Pagani O et al. N Engl J Med 2014;371:107-118.

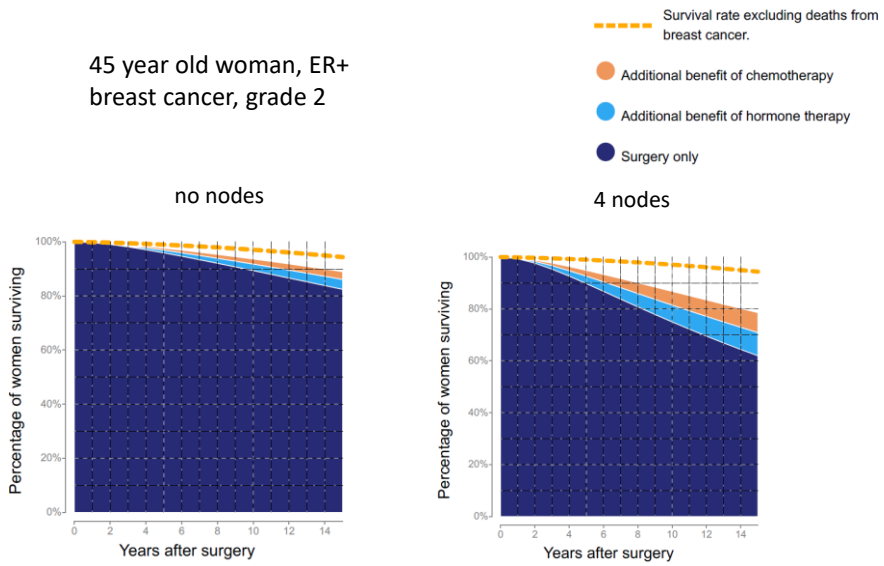
Prognosticating patients with breast cancer

Early breast cancer

- NHS predict 2.1 remains the most useful and well validated tool for UK women
- Age and grade and stage and receptor status matters to the prognosis in early and advanced breast cancer

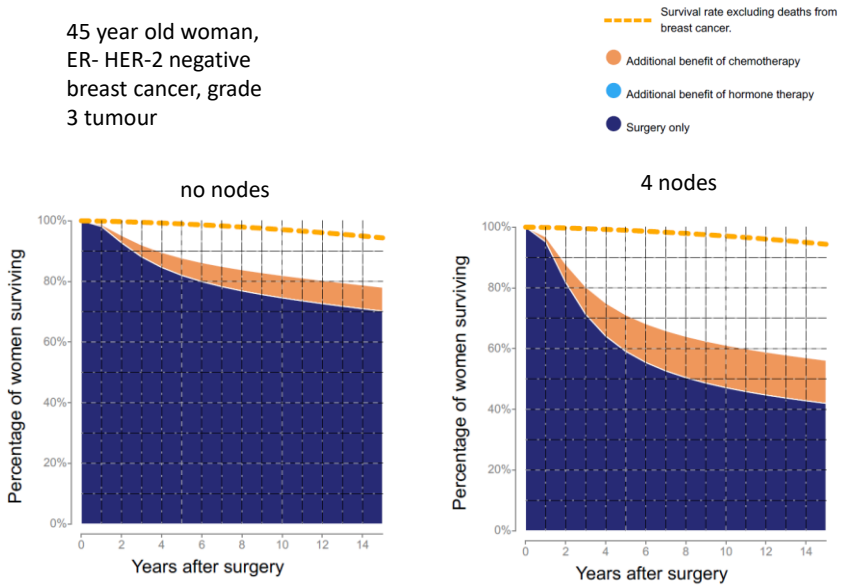
Example of the effect of nodes and receptors on prognosis

45 year old woman, ER+ breast cancer, grade 2



Example of the effect of nodes and receptors on prognosis

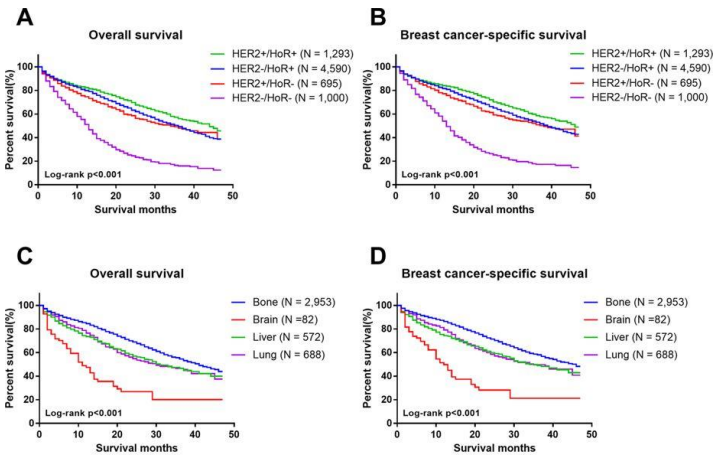
45 year old woman, ER- HER-2 negative breast cancer, grade 3 tumour



Treatment of metastatic breast cancer

- Complex – varies on receptor subtype.
- Treatment options constantly changing – experts needs to be up-to-date
- Ask your expert if they are actively practising in the area?
- Outcome highly variable between patients

Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study



Scientific Reports **volume7**, Article number: 45411 (2017)

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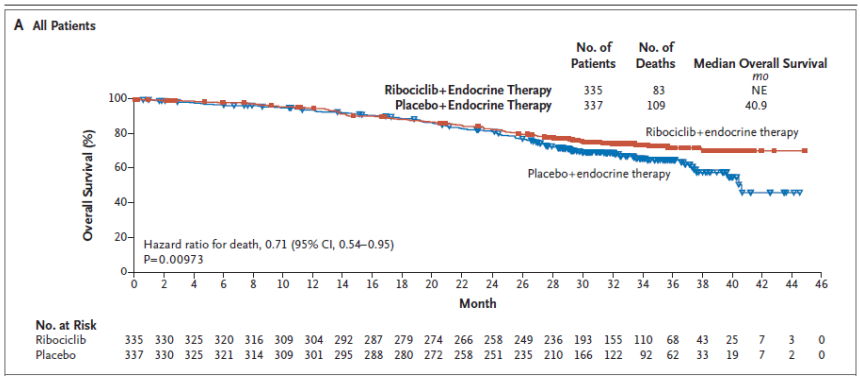
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

S.-A. Im, Y.-S. Lu, A. Bardia, N. Harbeck, M. Colleoni, F. Franke, L. Chow, J. Sohn, K.-S. Lee, S. Campos-Gomez, R. Villanueva-Vazquez, K.-H. Jung, A. Chakravartty, G. Hughes, I. Gounaris, K. Rodriguez-Lorenc, T. Taran, S. Hurvitz, and D. Tripathy

N Engl J Med 2019; 381:307-316



N Engl J Med 2019; 381:307-316

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Case 4

- 39 year old woman
- Diagnosed with small ER+ breast cancer 2013 2.5 MM grade II IDC
- Presented with a pathological fracture of her left hip and impending cord compression

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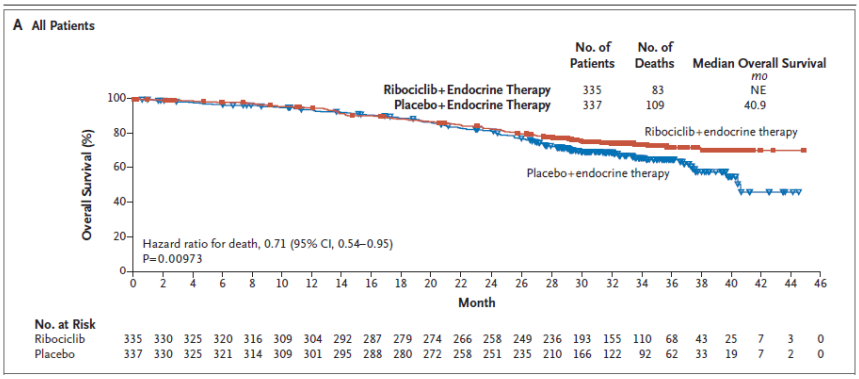

N Engl J Med 2019; 381:307-316

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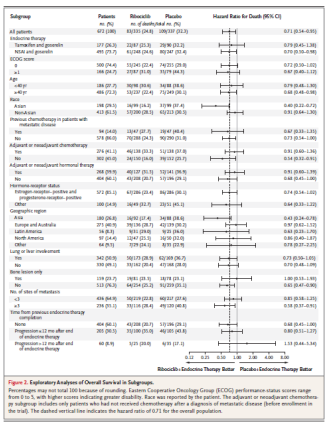

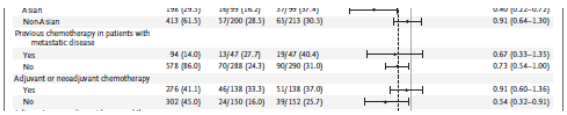

N Engl J Med 2019; 381:307-316

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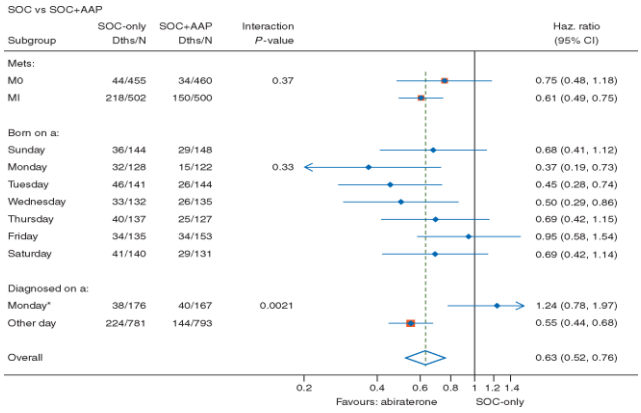
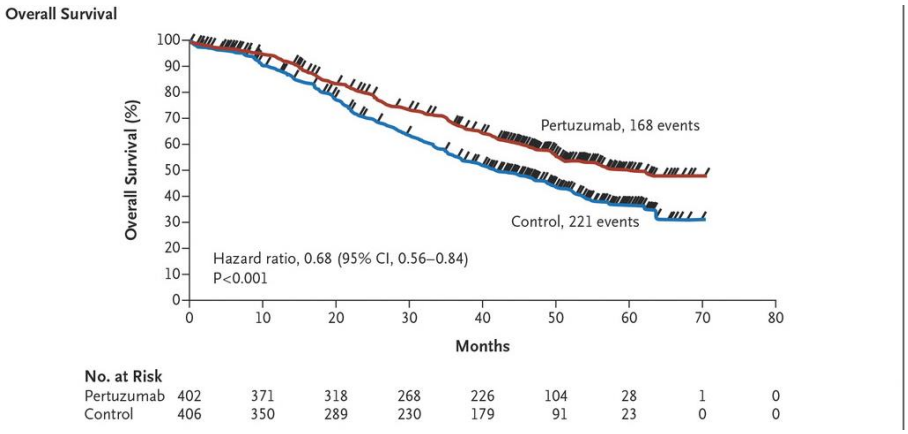
Figure 1. Forest plot from STAMPEDE data showing the effect on survival of adding abiraterone to SOC, within ...



Annals of Oncology, Volume 28, Issue 10, October 2017, Pages 2327–2330, https://doi.org/10.1093/annonc/mdx410

OXFORD UNIVERSITY PRESS

Pertuzumab improves overall l survival in advanced breast cancer > 1 year



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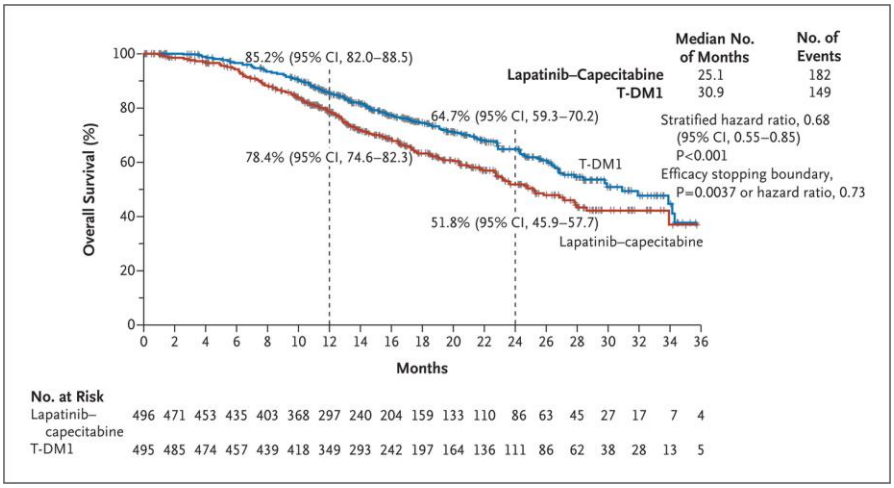
TDM1 improves survival in metastatic HER-2 + breast cancer



08/10/2019

Original Article

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

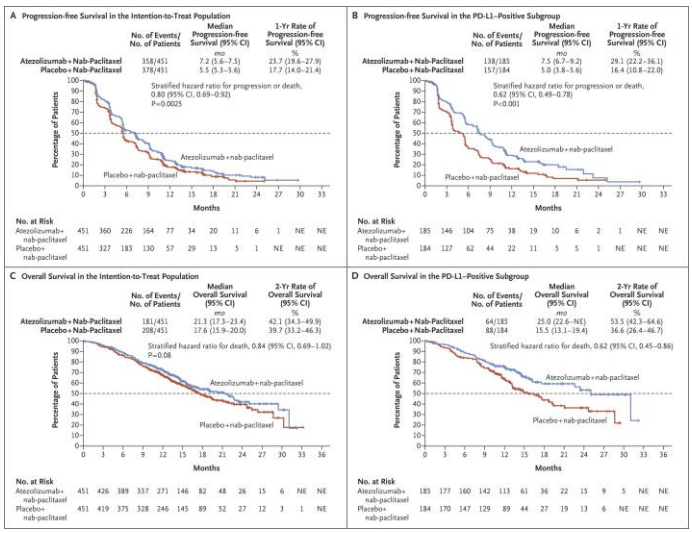
Peter Schmid, M.D., Ph.D., Sylvia Adams, M.D., Hope S. Rugo, M.D., Andreas Schneeweiss, M.D., Carlos H. Barrios, M.D., Hiroji Iwata, M.D., Ph.D., Véronique Diéras, M.D., Roberto Hegg, M.D., Seock-Ah Im, M.D., Ph.D., Gail Shaw Wright, M.D., Volkmar Henschel, Ph.D., Luciana Molinero, Ph.D., Stephen Y. Chui, M.D., Roel Funke, Ph.D., Amreen Husain, M.D., Eric P. Winer, M.D., Sherene Loi, M.D., Ph.D., Leisha A. Emens, M.D., Ph.D., for the IMpassion130 Trial Investigators

The NEW ENGLAND JOURNAL of MEDICINE

- Addition of the anti–PD-L1 antibody atezolizumab to nab-paclitaxel as first-line therapy for patients with advanced or metastatic triple-negative breast cancer significantly prolonged progression-free survival, particularly among those with PD-L1–positive tumors.

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Analysis of Progression-free Survival and Overall Survival.



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Characteristics of the Patients at Baseline.

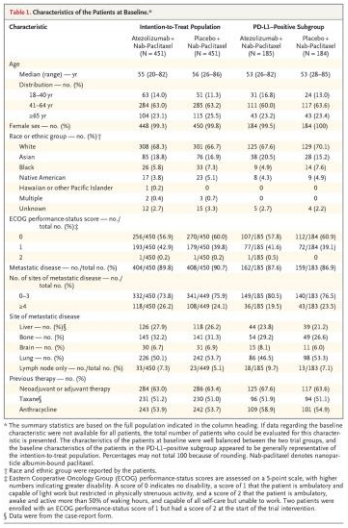

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intention-to-Treat Population		PD-L1–Positive Subgroup	
	Atezolizumab + Nab-Paclitaxel (N = 451)	Placebo + Nab-Paclitaxel (N = 451)	Atezolizumab + Nab-Paclitaxel (N = 185)	Placebo + Nab-Paclitaxel (N = 184)
Age				
Median (range) — yr	55 (20–82)	56 (26–86)	53 (26–82)	53 (28–85)
Distribution — no. (%)				
18–40 yr	63 (14.0)	51 (11.3)	31 (16.8)	24 (13.0)
41–64 yr	284 (63.0)	285 (63.2)	111 (60.0)	117 (63.6)
≥65 yr	104 (23.1)	115 (25.5)	43 (23.2)	43 (23.4)
Female sex — no. (%)	448 (99.3)	450 (99.8)	184 (99.5)	184 (100)
Race or ethnic group — no. (%)†				
White	308 (68.3)	301 (66.7)	125 (67.6)	129 (70.1)
Asian	85 (18.8)	76 (16.9)	38 (20.5)	28 (15.2)
Black	26 (5.8)	33 (7.3)	9 (4.9)	14 (7.6)
Native American	17 (3.8)	23 (5.1)	8 (4.3)	9 (4.9)
Hawaiian or other Pacific Islander	1 (0.2)	0	0	0
Multiple	2 (0.4)	3 (0.7)	0	0
Unknown	12 (2.7)	15 (3.3)	5 (2.7)	4 (2.2)
ECOG performance-status score — no./total no. (%)‡				
0	256/450 (56.9)	270/450 (60.0)	107/185 (57.8)	112/184 (60.9)
1	193/450 (42.9)	179/450 (39.8)	77/185 (41.6)	72/184 (39.1)
2	1/450 (0.2)	1/450 (0.2)	1/185 (0.5)	0
Metastatic disease — no./total no. (%)	404/450 (89.8)	408/450 (90.7)	162/185 (87.6)	159/183 (86.9)
No. of sites of metastatic disease — no./total no. (%)				
0–3	332/450 (73.8)	341/449 (75.9)	149/185 (80.5)	140/183 (76.5)
≥4	118/450 (26.2)	108/449 (24.1)	36/185 (19.5)	43/183 (23.5)
Site of metastatic disease				
Liver — no. (%)§	126 (27.9)	118 (26.2)	44 (23.8)	39 (21.2)
Bone — no. (%)	145 (32.2)	141 (31.3)	54 (29.2)	49 (26.6)
Brain — no. (%)	30 (6.7)	31 (6.9)	15 (8.1)	11 (6.0)
Lung — no. (%)	226 (50.1)	242 (53.7)	86 (46.5)	98 (53.3)
Lymph node only — no./total no. (%)	33/450 (7.3)	23/449 (5.1)	18/185 (9.7)	13/183 (7.1)
Previous therapy — no. (%)				
Neoadjuvant or adjuvant therapy	284 (63.0)	286 (63.4)	125 (67.6)	117 (63.6)
Taxane§	231 (51.2)	230 (51.0)	96 (51.9)	94 (51.1)
Anthracycline	243 (53.9)	242 (53.7)	109 (58.9)	101 (54.9)

* The summary statistics are based on the full population indicated in the column heading. If data regarding the baseline characteristic were not available for all patients, the total number of patients who could be evaluated for this characteristic is presented. The characteristics of the patients at baseline were well balanced between the two trial groups, and the baseline characteristics of the patients in the PD-L1–positive subgroup appeared to be generally representative of the intention-to-treat population. Percentages may not total 100 because of rounding. Nab-paclitaxel denotes nanoparticle albumin-bound paclitaxel.
† Race and ethnic group were reported by the patients.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability. A score of 0 indicates no disability, a score of 1 that the patient is ambulatory and capable of light work but restricted in physically strenuous activity, and a score of 2 that the patient is ambulatory, awake and active more than 50% of waking hours, and capable of all self-care but unable to work. Two patients were enrolled with an ECOG performance-status score of 1 but had a score of 2 at the start of the trial intervention.
§ Data were from the case-report form.

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Key Adverse Events.

Table 3. Key Adverse Events.*

Event	Atezolizumab + Nab-Paclitaxel (N=452)		Placebo + Nab-Paclitaxel (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Cough	112 (24.8)	0	83 (18.9)	0
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Hypothyroidism	62 (13.7)	0	15 (3.4)	0

* Shown are the single most frequent adverse event of any grade, adverse events of any grade for which the rates differed by at least 5 percentage points between groups, and adverse events of grade 3 or 4 for which the rates differed by at least 2 percentage points between groups.

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Breast cancer guidelines

Local guidelines

NICE guidelines

ESMO guidelines

ASCO guidelines

St Gallen

08/10/2019

Questions

08/10/2019