Non-hormonal therapies in advanced breast cancer: new and emerging approaches

Outline

- Review goals of treatment
- Demystify chemotherapy decision making
- Look at the evidence for improvements over time
- Discuss specific treatments (focusing on the last 5-10 years)
- Look to the horizon

Why,When,What,How

Why,When,What,How

- Experience varies widely in terms of survival time, extent and symptoms of disease
- Principles of treatment are the same
- Increase the duration of symptom-free survivorship and limit treatment related toxicity
  - Relief of symptoms
  - Maintenance of quality of life
  - Prolongation of survival
  - Development of treatment options
  - Balance of side effects and benefit is paramount

Why, **When**, What, How

- The decision to start chemotherapy is often complex and involves a careful assessment of:
  - The patient's history and what symptoms are occurring
  - Biological characteristics of the tumour such as subtype
  - How long since the primary breast cancer was treated
  - The site and extent of the relapse
  - How unwell/incapacitated the individual is in a global sense
- There isn't a fixed time to start and in most cases the likelihood of response is not related to the timing of chemotherapy.

Why,When,**What**,How

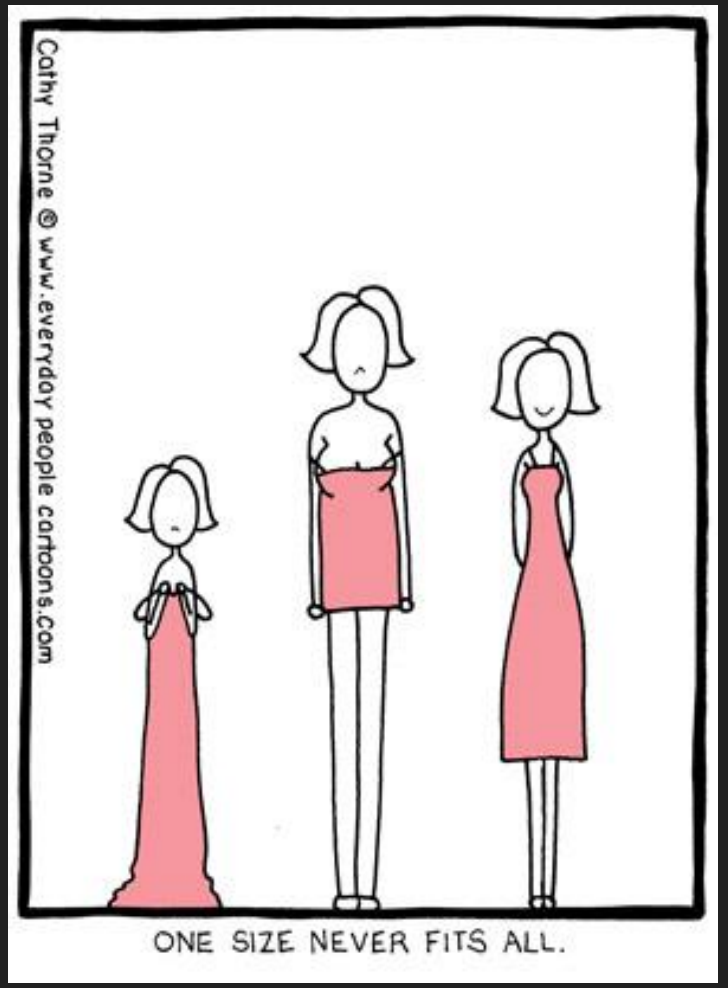
- What drug?
  - Activity level seen in clinical trials
  - Amount of active cancer/need for rapid response
  - Prior treatments
  - Route of administration (IV vs pills)
  - Side effect profile
  - Other health problems
- Anthracyclines (epirubicin or doxorubicin
- Taxanes (Docetaxel or Paclitaxel)
- Capecitabine
- Vinorelbine
- Gemcitabine

Why,When,**What**,How

- Is two better than one?
- The crux of the issue is toxicity
  - No benefit in overall survival using a combination chemo regimen
  - Combination therapy is associated with more frequent and severe side effects
  - Using single agents is preferred

Why,When,What,**How**

- Sequence
  - Order of chemotherapy doesn't appear to influence survival
- Duration / Is longer better?
  - 4-6 months is typical
  - Exceptions: capecitabine, Targeted therapy
  - Some suggestion that small improvements gained by longer duration , But,
  - Most of the benefit tends to be seen early
  - Cumulative treatment related toxicity may emerge later



Why,When,What,**How**

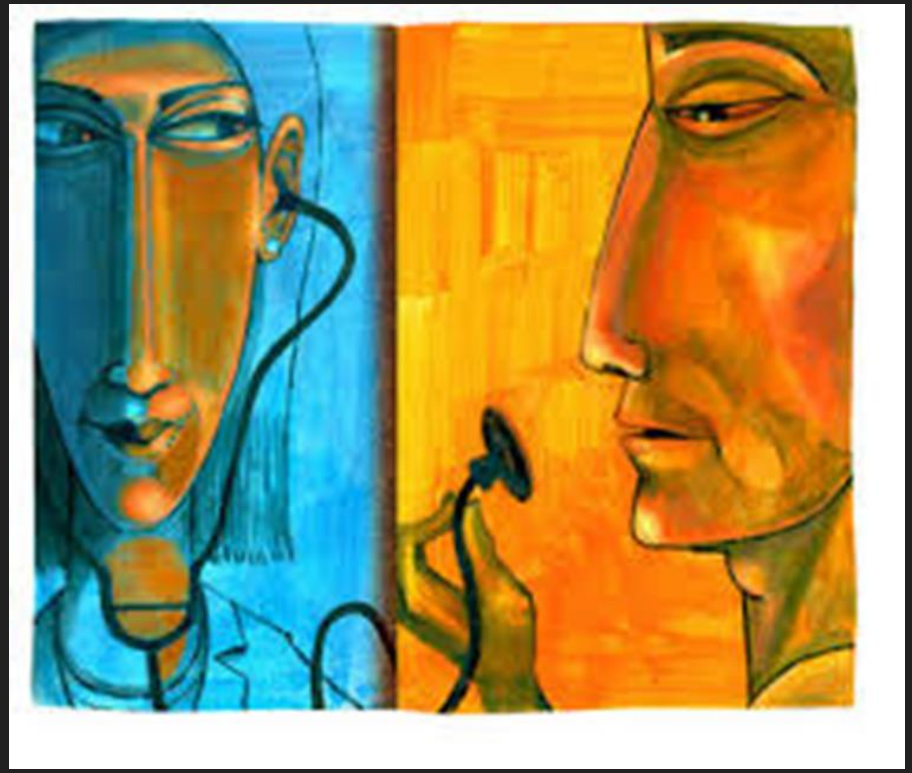
- Monitoring
  - Clinical assessment (history and examination)
  - Scans
  - Blood tests
- Definition of treatment failure
  - Increasing size or new metastases
  - Deterioration in symptoms
  - Worsening chemotherapy toxicity

Suggested intervals of follow-up for patients with metastatic diesase[1]

	Baseline Prior to New Therapy	Chemotherapy
Symptom assessment	Yes	Prior to each cycle
Physical examination	Yes	Prior to each cycle
Performance status	Yes	Prior to each cycle
Weight	Yes	Prior to each cycle
LFTs, CBC	Yes	Prior to each cycle
CT scan chest/abd/pelvis	Yes	Every 2-4 cycles

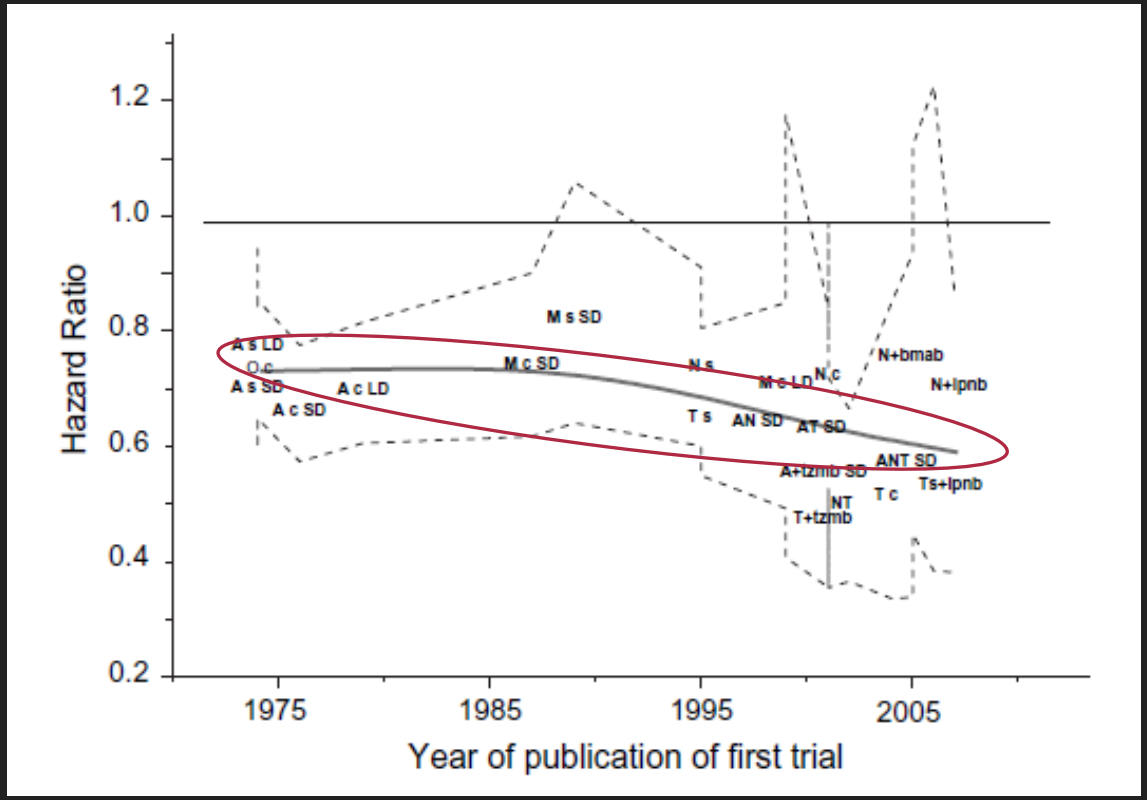
Why,When,What,**How**

- Why
- When
- What
- How
  - Sequence
  - Duration
  - Monitoring



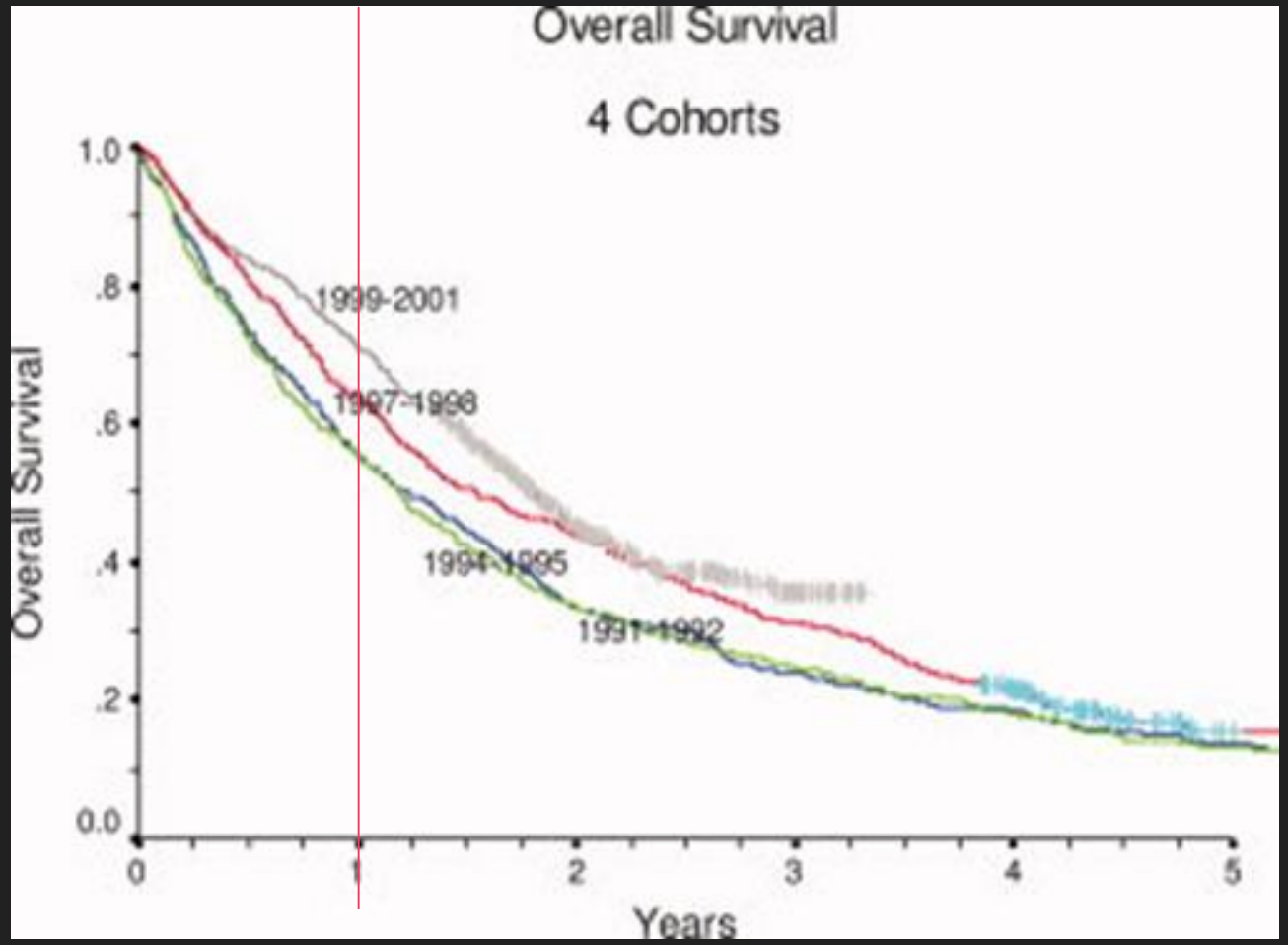
Have we made progress(what the trials say)

- **The trials tell us: YES!**
- Mammoth analysis of trials between 1973 – 2007
- Relative risk reduction improved from 25-30% to 30-50%
- Most regimens showed similar benefit when used as 1st or 2nd line of treatment

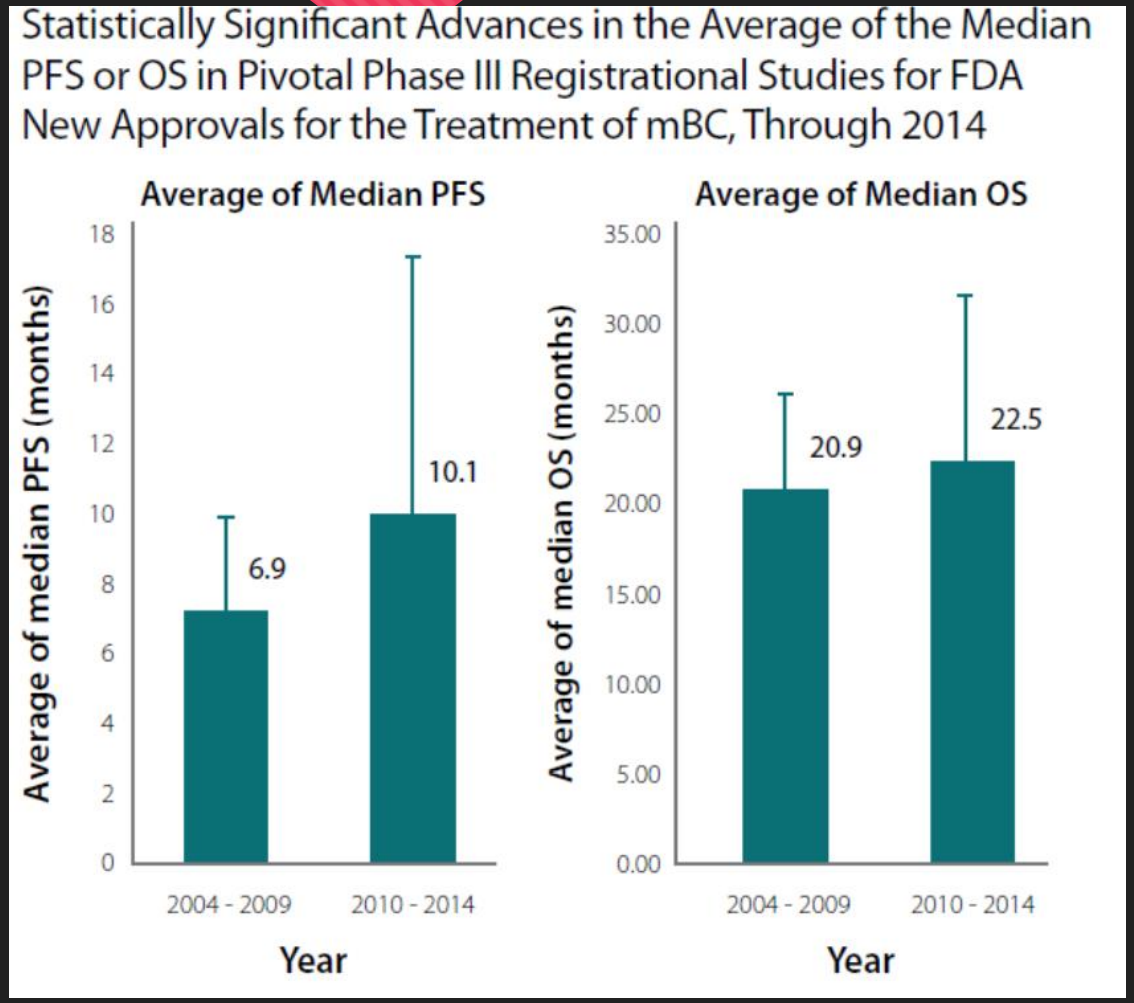


Have we made progress(in the real world)

- In the real world….
- Proportion of women alive at 1 year
  - 1991-1995 55%
  - 1997-1998 64%
  - 1999-2001 71%



Hey! That was a decade or more ago

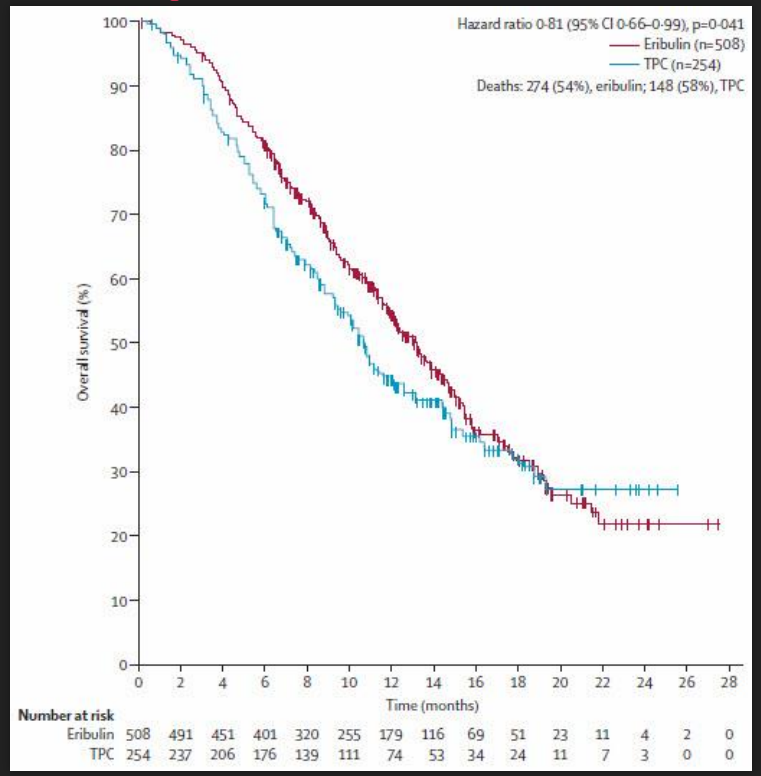


- Yes- progress continues but we still have a long way to go

Specific Agents

Chemotherapy

Erubulin



- When compared with other chemo as 3rd line of therapy
  - 10 weeks improvement in survival (10.6 months to 13.1 months)
  - Main side effect: neutropaenia

Targeted therapy

Cleopatra

Marianne (Marianne Faithful)

Elimia (Emilia Clark, Game of Thrones)

Th3esa (Theresa May)

Lapatinib

Lapatinib + capecitabine versus capecitabine

EGF100151[1,2]

Patients with ErbB2-positive locally advanced or metastatic breast cancer who progressed after prior anthracycline, taxane and trastuzumab
(N=399)

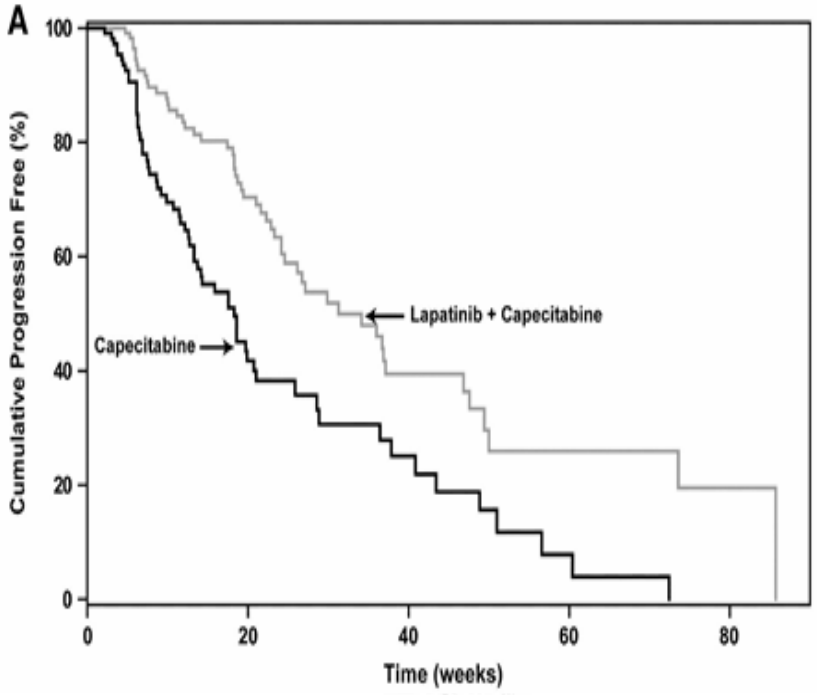
RANDOMIZATION

Lapatinib 1250 mg po qd continuously + capecitabine 2000 mg/m²/day po Days 1–14 q3wk	Capecitabine 2500 mg/m²/day po Days 1–14 q3wk

Trial stopped early due to achievement of primary endpoint (TTP) at planned interim analysis – analysed with 399 patients out of planned 528 patients

ESO Balkan Masterclass in Clinical Oncology
11.5.2011 - 15.5.2011
Dubrovnik, Croatia

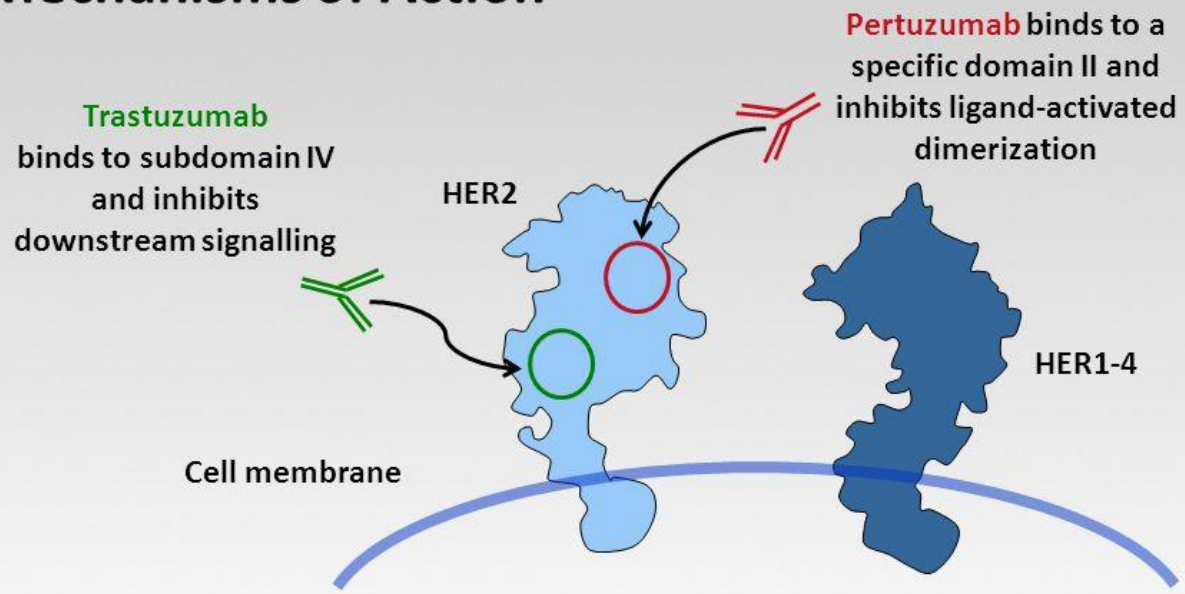
1. Cameron et al. Breast Cancer Res Treat 2008; **112**: 533–43; 2. Geyer et al. N Engl J Med 2006; **355**: 2733–43



David Cameron et al. The Oncologist 2010;15:924-934

Pertuzumab and Trastuzumab

Pertuzumab and Trastuzumab: Mechanisms of Action



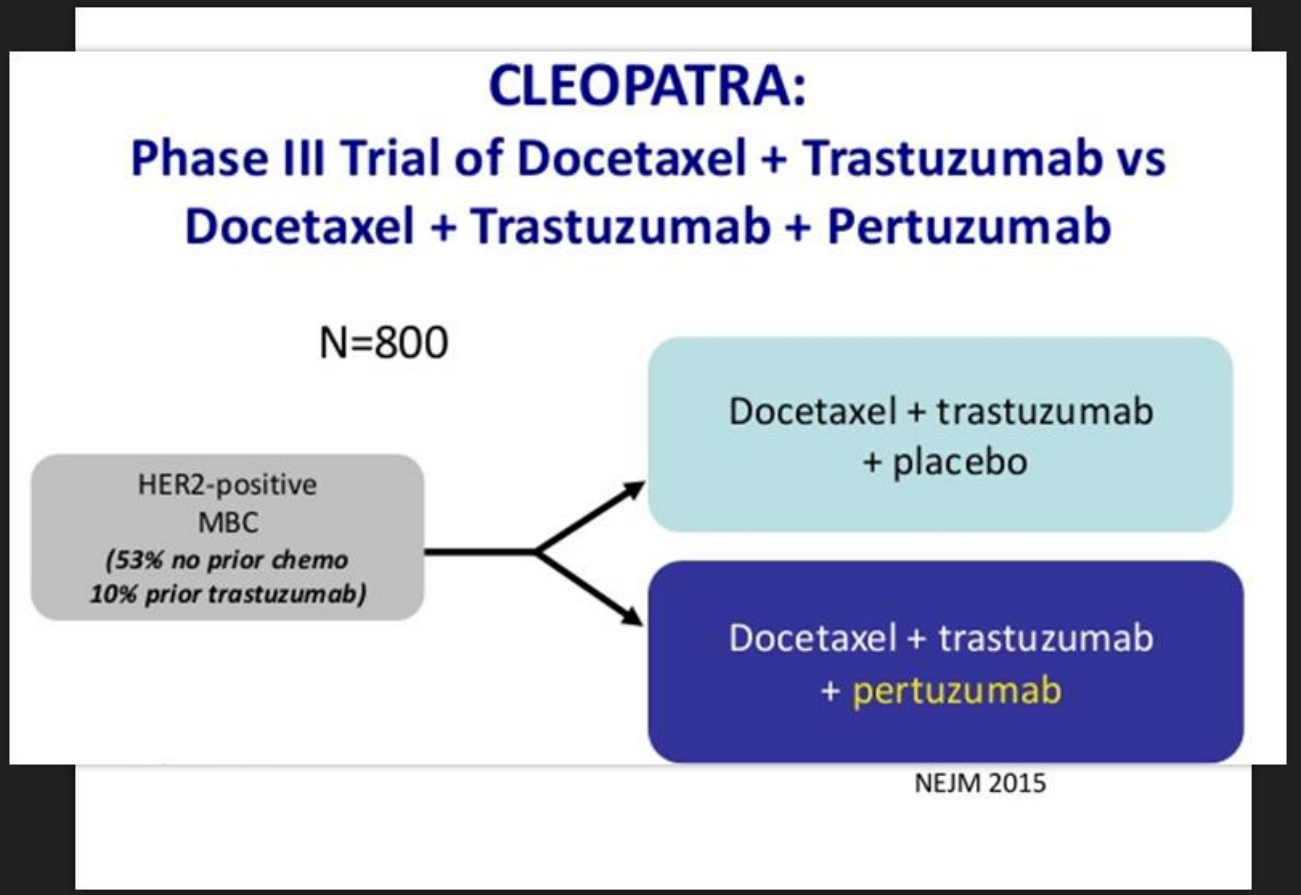
The combined regimen of pertuzumab and trastuzumab offers the potential for a more comprehensive HER blockade

Medscape EDUCATION

Franklin MC, et al. *Cancer Cell*. 2004;5(4):317-328.

Her-2 targeting agents

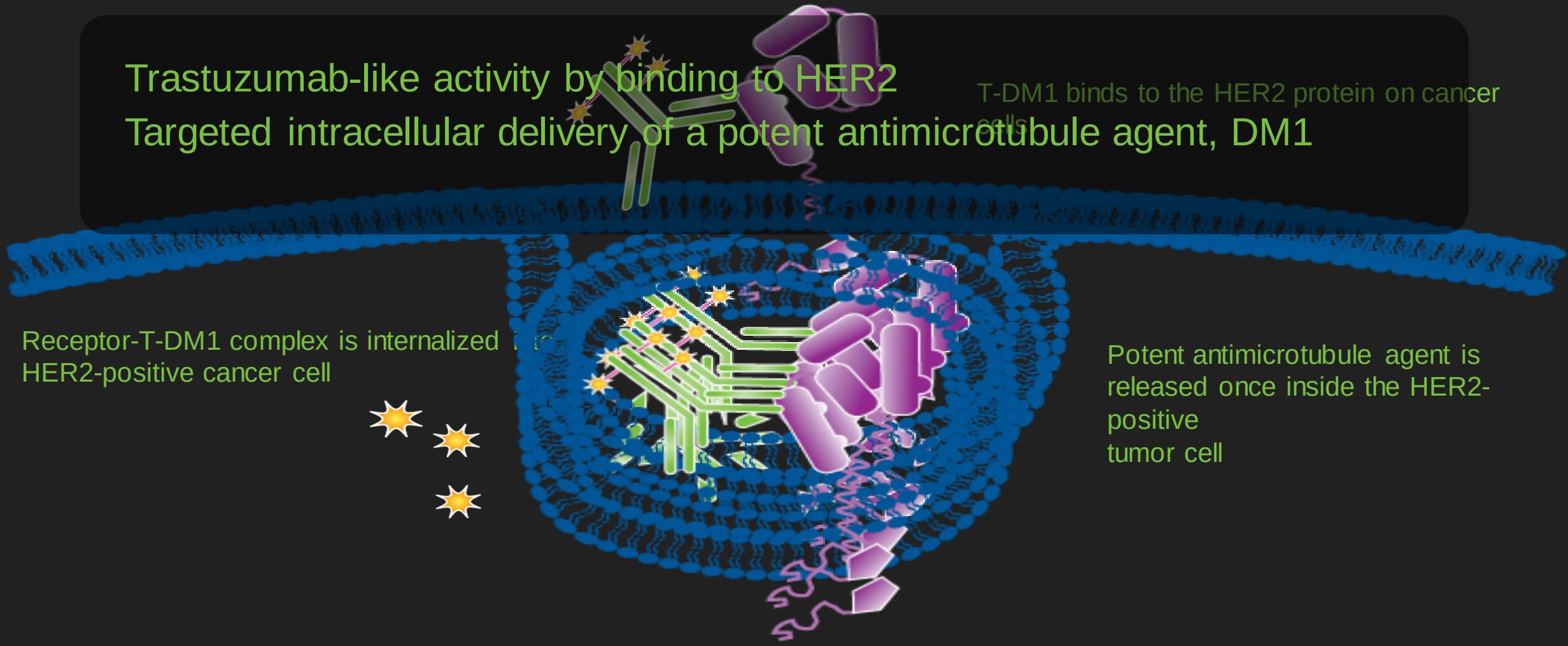
- CLEOPATRA
- Docetaxel + Herceptin + either Pertuzumab or Placebo
- As first line treatment for HER2 + ABC
- Initial report published in 2012
- Updated in 2015
- Funded in NZ 2017
- Median overall survival improved by just over 1 year (from around 3 ½ years to nearly 4 ¾ years)



T-DM1 selectively delivers a highly toxic payload to HER2+ tumor cells

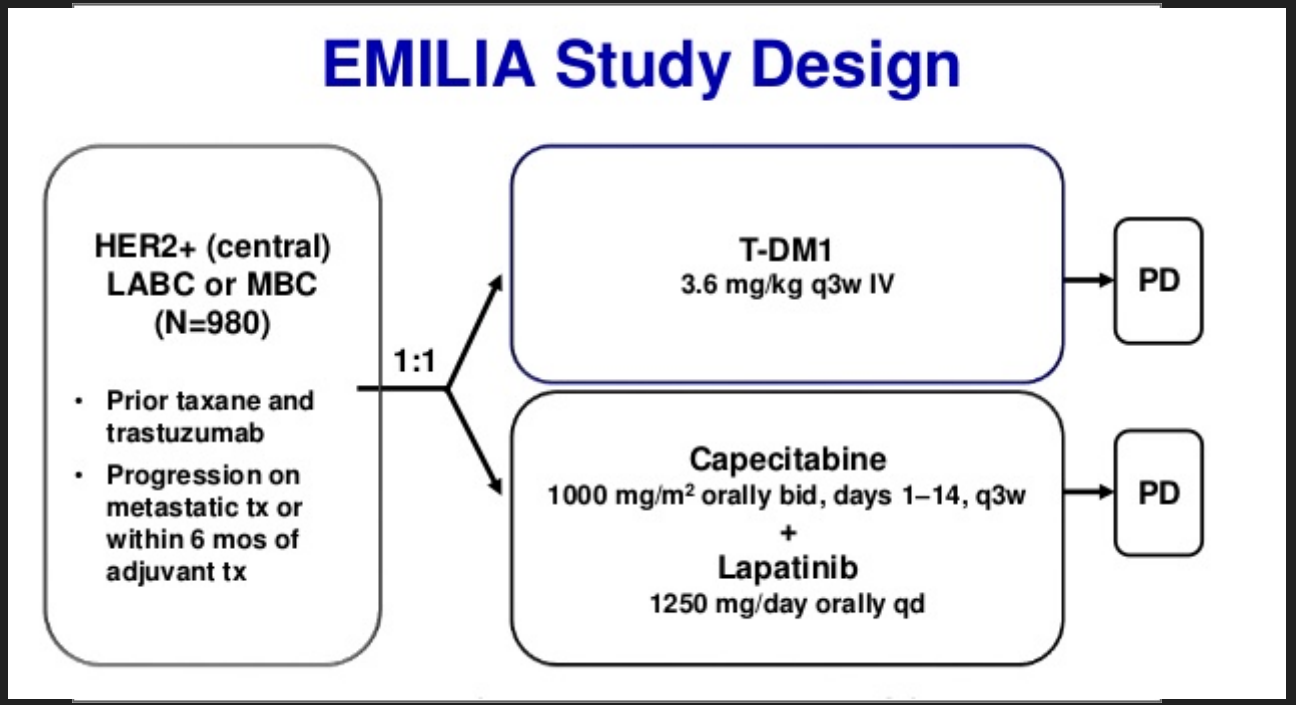
Trastuzumab-like activity by binding to HER2

Targeted intracellular delivery of a potent antimicrotubule agent, DM1



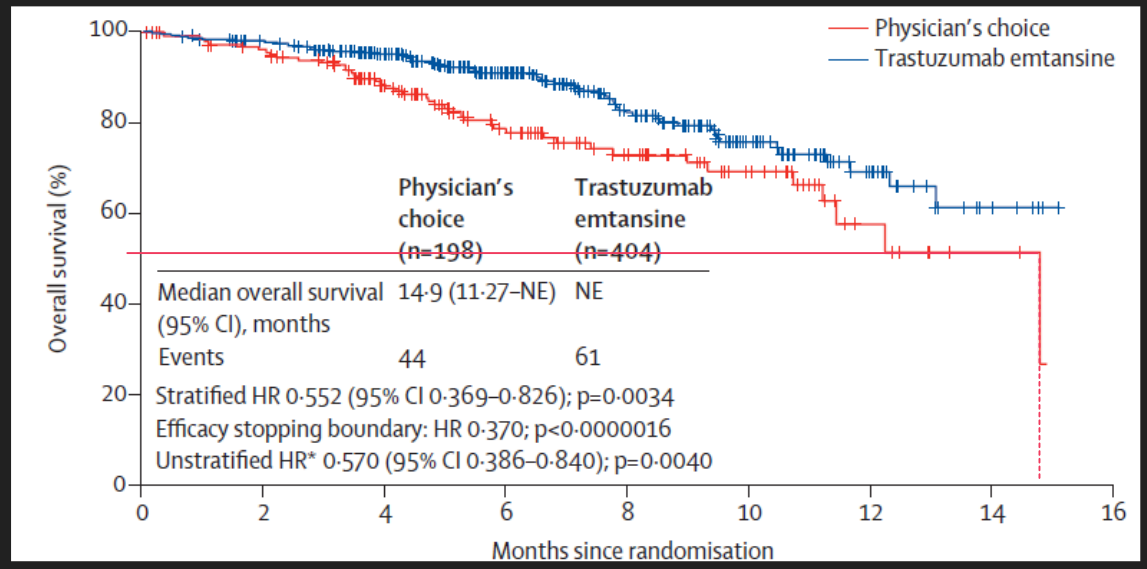
Her-2 targeting agents

- EMILIA
- TDM-1 or Lapatinib/Capecitabine
- After previous treatment with herceptin and a taxane drug
- Published 2012
- Median over all survival by nearly 6 months (from 25 months to nearly 31 months
- Not funded in NZ (is available in private)



Her-2 targeting agents

- Th3resa
- TDM-1 or treatment of doctors choice
- After failure of 2 previous lines of HER2 directed therapy
- Published in 2014, updated in 2015

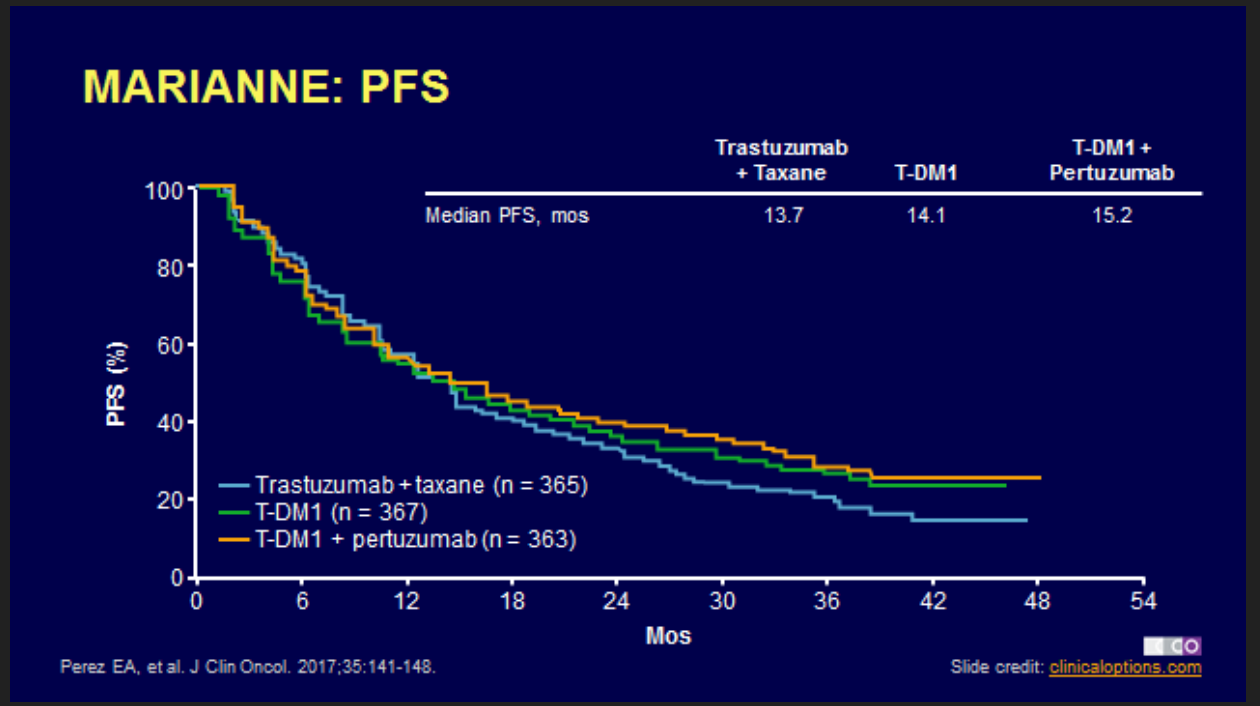


Median OS, Mos	TPC (n = 198)	T-DM1 (n = 404)	Stratified HR (95% CI)	*P* Value
All pts	15.8	22.7	0.68 (0.54-0.85)*	.0007
Sensitivity analysis (pts censored at crossover to T-DM1)	15.6	22.7	0.58 (0.43-0.77)	.0002

Slide credit: clinicaloptions.com

Her-2 targeting agents

- MARIANNE
- Can we combine?
- Pertuzumab + TDM-1
  - Not a useful combination

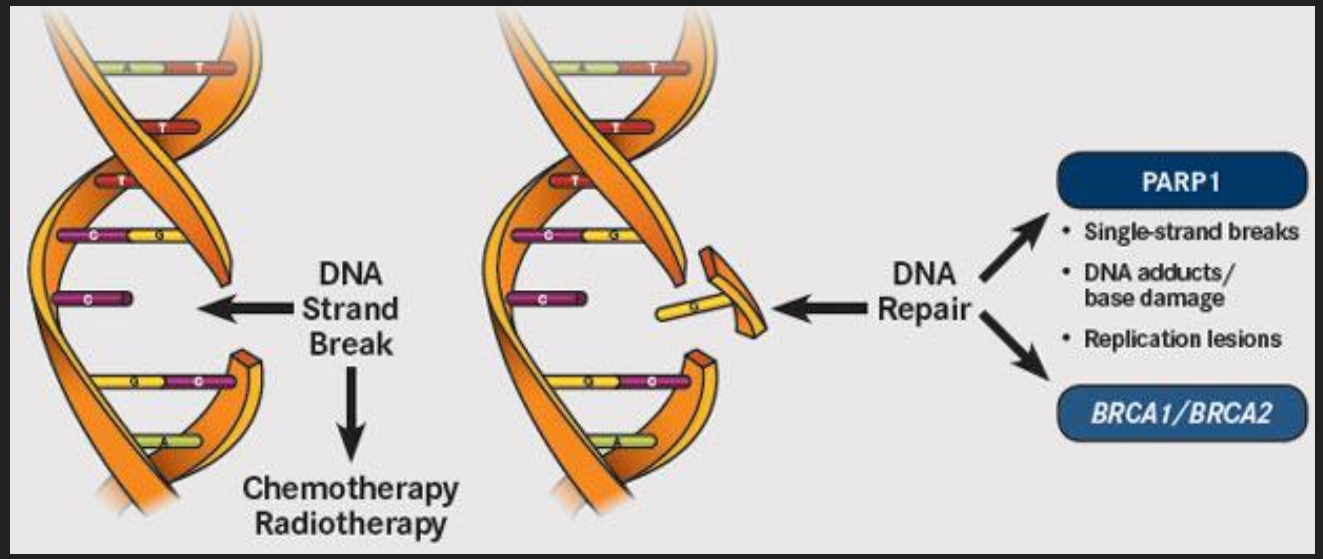


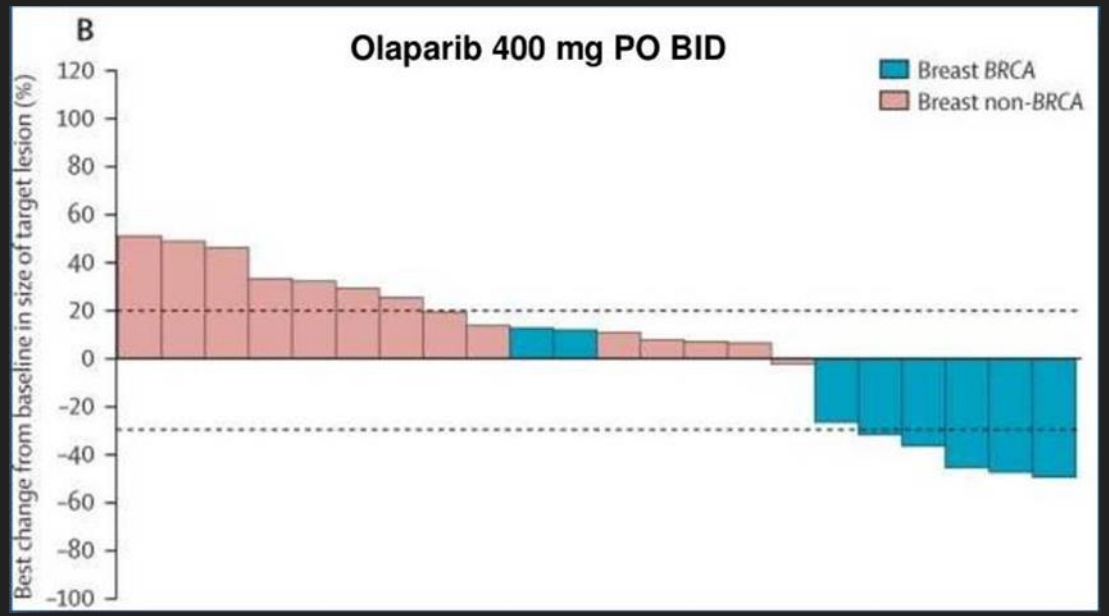
Access

Drug	Mechanism of action	Year of approval			Setting
		USA	Australia	NZ	
Lapatinib	Targeted	2007	2008	(2012 only if unable to use Herceptin)	2nd line +capecitabine
Pertuzumab	Targeted	2012	2014	2017	1st line +herceptin and taxane
TDM-1	Targeted	2013	2014	**Not Funded**	2nd line, After herceptin + taxane
Erubulin	Chemo	2010	2014	**Not Funded**	3rd line of chemo

What about Triple Negative Breast Cancer?

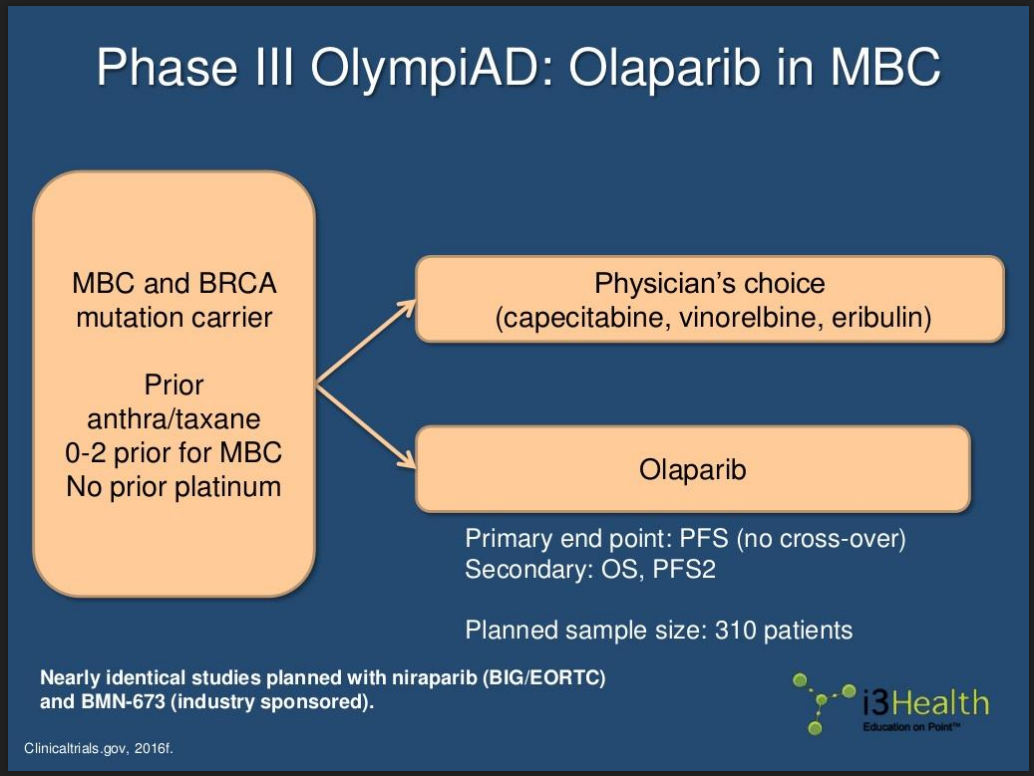
PARP inhibitors





PARP inhibitors

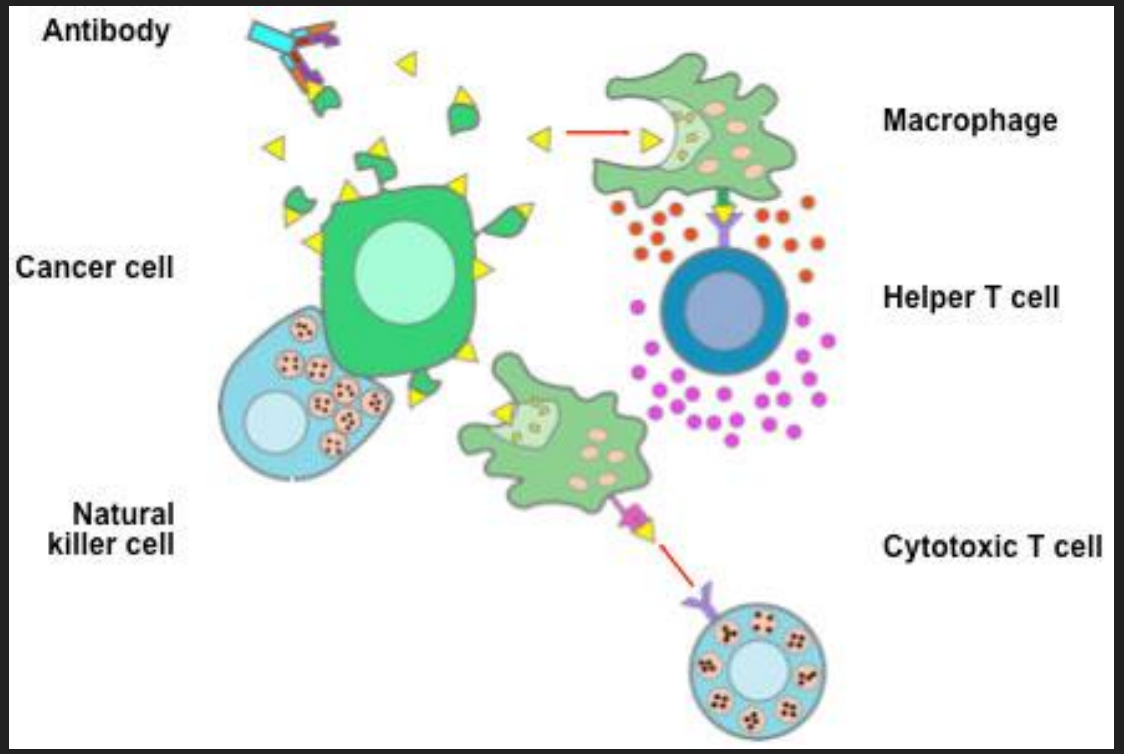
- Have been tested alone and in combination with chemotherapy
- Early studies were sufficiently promising to generate larger confirmatory trials
- Outcomes of the trials in ABC are still accumulating
- Current use is restricted to clinical trials



BREAKING NEWS 17TH Feb: OlymiAD trial has shown improvement in PFS – details awaited

Immunotherapy

- As cancer cells die they release small fragmented proteins called antigens.
- The immune system can recognise these as foreign and initiate an immune response
- Evading the immune system is a hallmark of cancer
- The goal of immune therapies is to kick the immune system into action.

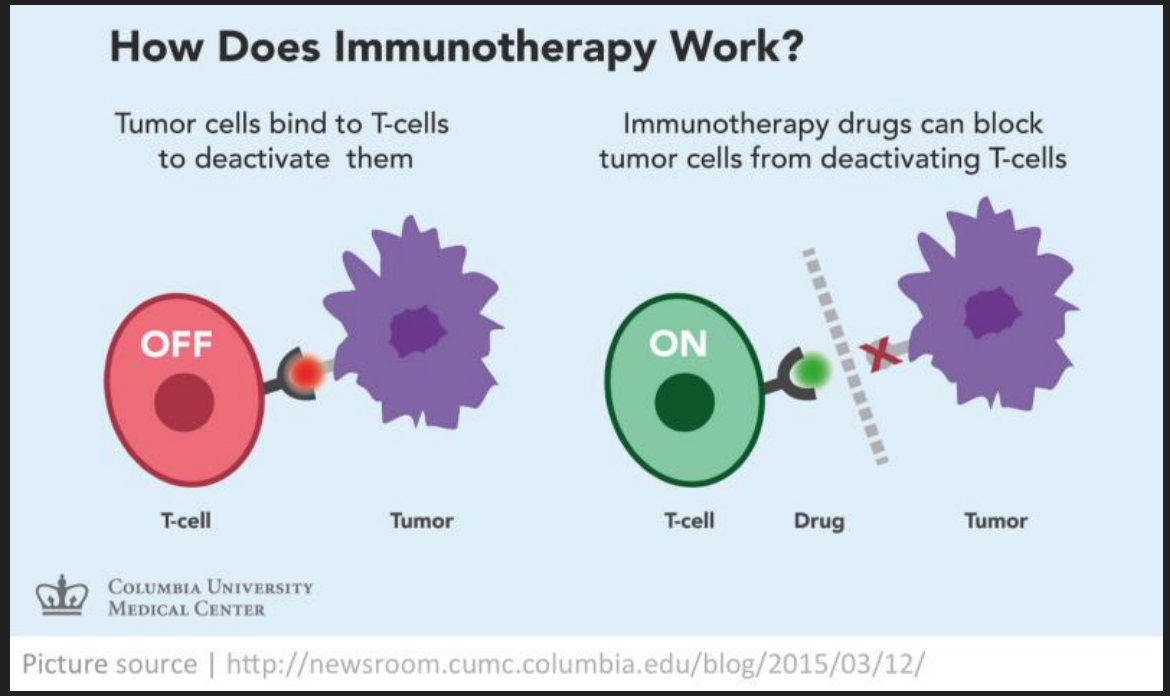


Immunotherapy

- Why focus on immunotherapy in TNBC
  - Higher density of infiltrating immune cells
  - Greater expression of PDL-1- a regulator of immune cells
  - Harbour more mutation which means that the released antigens may be more 'foreign' to the immune system
  - Lack of treatment options for TNBC

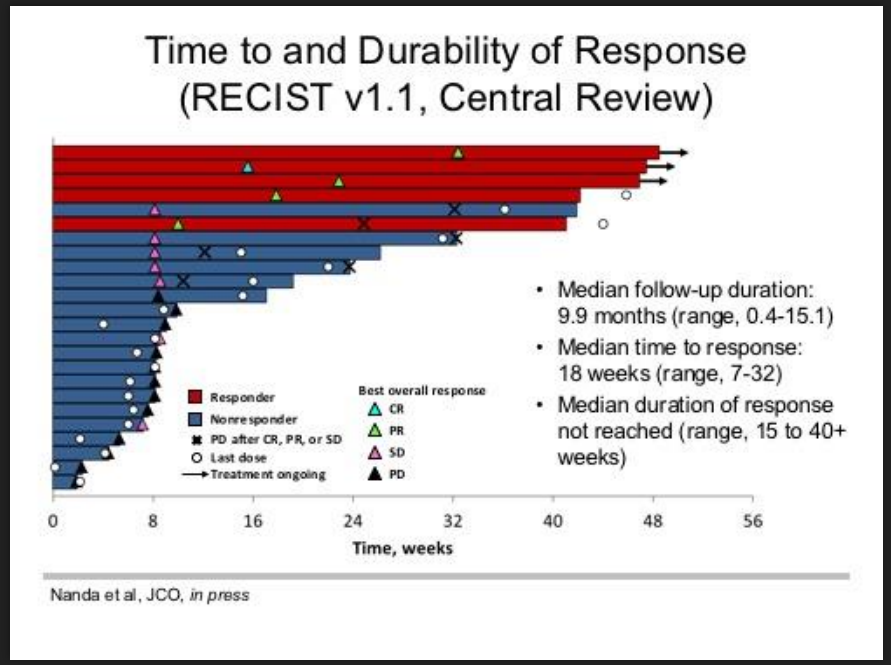
PDL-1 inhibition

- Unleashing the immune system
- PDL-1 inhibitor
  - PD1 is an immune check point receptor
  - When PDL1 attaches to receptor T- cell activation is inhibited and so mutes the immune response
  - Inhibiting PDL-1 allows T cell activation and thus releases the immune system

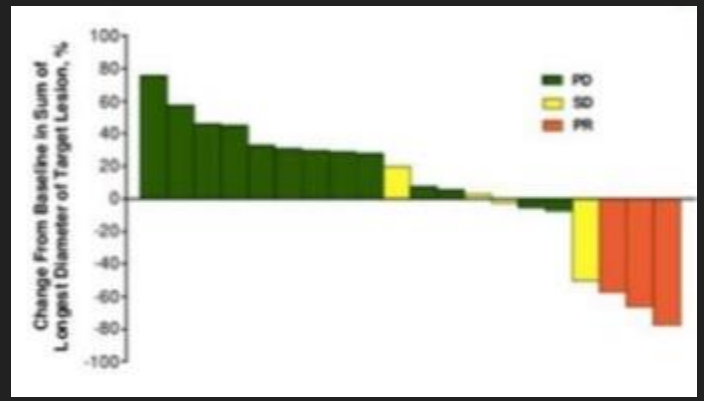


Picture source | http://newsroom.cumc.columbia.edu/blog/2015/03/12/

Keynote-12



Keynote 28

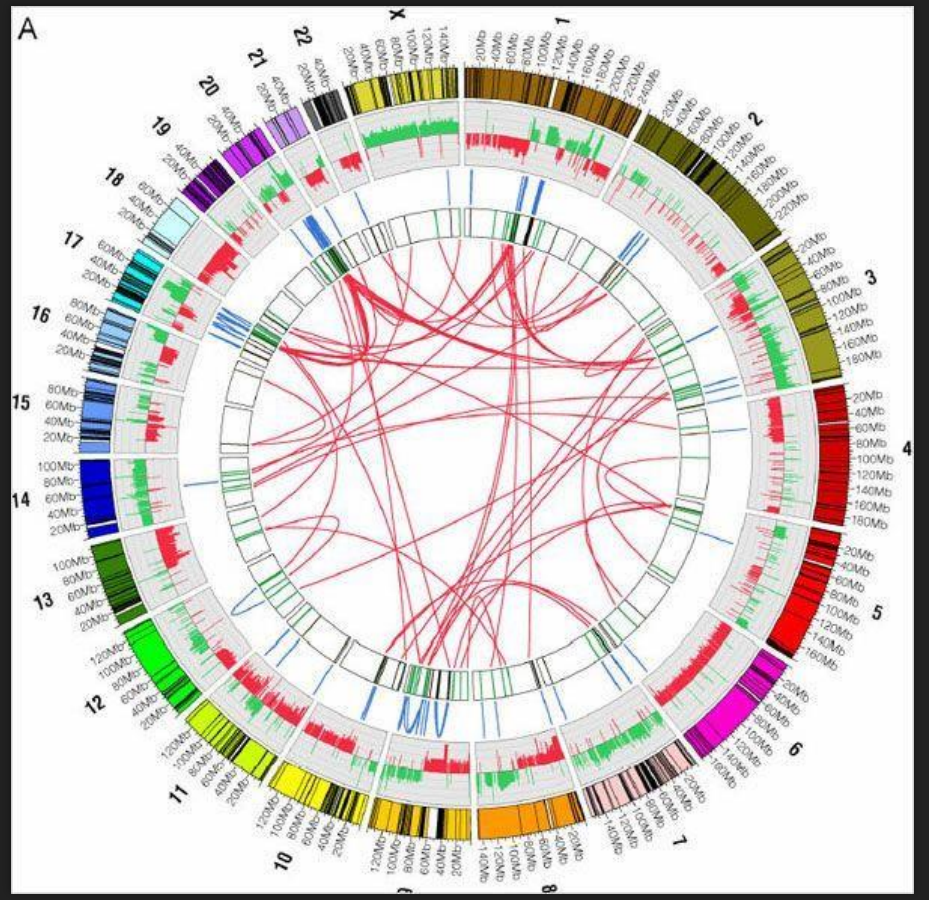


Horizon scanning

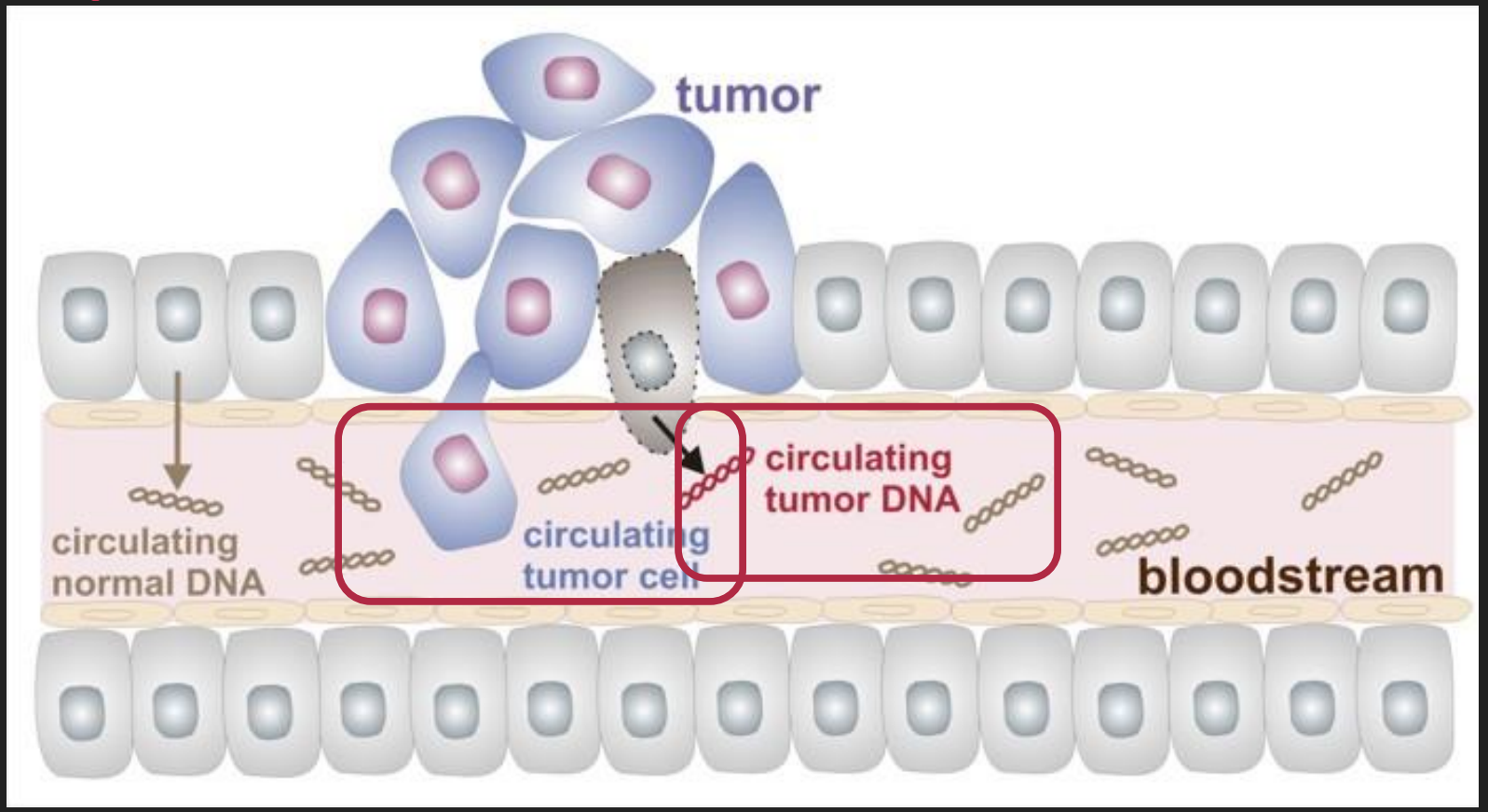
Precision medicine

The use of clinical, pathological , molecular and genomic information to direct the most appropriate treatment for an individual at the most appropriate time

- What is precision medicine?
- The more we know , the more complex we realise it is…
- Most mutations in any given breast cancer are unique and don't represent a target that can be drugged
- Most work is in early breast cancer since tumour tissue is readily available



Circulating tumour cells / cell free DNA



Circulating tumour cells / cell free DNA

- Circulating tumour cells
  - Higher numbers associated with more advanced disease
  - But, not helpful for guiding treatment decisions
- Circulating cell free DNA/ circulating tumour DNA
  - New kid on the block, more work to be done….
  - A liquid biopsy?
- At this time, circulating tumour cell and circulating tumour DNA tests should not be used to guide treatment because they have not been shown to offer benefit

Clinical Trials

BREAST

I3Y-MC-JPBO: A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer or Melanoma

Brain Mets secondary to HR+ Breast Cancer, NSCLC & Melanoma → Screening / Baseline Assessments 28 Days

- **PART A:** HR+ — On HOLD - April 2016
- **PART B:** HR+, HER2- Breast Cancer
- **PART C:** (Surgery) HR+ B — CLOSED - May 2016 — lanoma
- PAR — On HOLD - Oct 2016
- PART — On HOLD - Oct 2016
- **PART F:** HR+ Breast Cancer, NS — CLOSED - May 2016 — eningeal Mets

→ Abemaciclib Single Agent or in Combination with Endocrine Therapy **OR** **Abemaciclib in combination with Trastuzumab, Gemcitabine or Pemetrexed**

→ 21 Day cycles with GD-MRI, CT-CAP, RECIST 1.1 & RANO-BM assessments, Clinical Tumour assessments, MDASI-BT & Trail Making Tests A & B **Refer to Protocol**

CONTACT
CRC: Kathryn Johnstone x 23085; PI: Dr Rosalie Stephens x 23863; Nurses: Angie Li or Anna Ruri x 22139

ZMC-ARX788-101 - Phase 1a: Dose escalation

Advanced cancers with HER2 expression

Email Sanjeev for triaging of potential candidates with sponsor.

Key eligibility criteria:	Washout: *(chemo/RT/*	Triage: Email Sanjeev	Screening: Visits D-28	Treatment cycles: • Treat Q3W, D1 IV
and ISH positive	Washout = 56 days*	CONSENT	If eligible: ENROL	• Weekly visits cycles 2, 4 & onwards.

RECRUITMENT ON HOLD

CONTACT
CRC: Beth Caudwell x 23199; PI: Dr Sanjeev Deva x 23832; Nurse: Angie Li x 22139/25046 or 021 979 568

ARTEMIN: a biomarker for breast cancer

Comparison of serum ARTN levels

Recruiting to **COHORTS B & C**

COHORT A	COHORT B	COHORT C
Healthy volunteers	Early-stage breast cancer (Pre-op)	Advanced or metastatic breast cancer (any time)

CONTACT
For subjects: Janene Biggs, 923 5870, j.biggs@auckland.ac.nz;
UoA PI: Dr Dong-Xu Liu 923 9603;
ADHB PI: Dr Reuben Broom x 23868

ELIMINATE

Stratification by:
1. Menopausal status
2. Clinical Stage 2 vs Stage 3

→ Randomize 2:1

- **Chemotherapy** (≥18 weeks anthracycline + taxane) Letrozole (+ Goserelin if pre/perimenopausal)
- **Chemotherapy** (≥18 weeks anthracycline + taxane)

→ Surgery → **Routine Care** Adjuvant endrocrine therapy & radiotherapy

CONTACT
CRC: Kathryn Johnstone x 23085; PI: Dr David Porter x 23833; Nurse: Anna Ruri x 22139/25046

ALL GROUPS

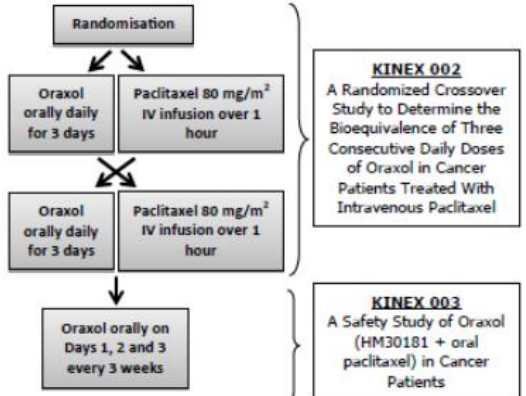
Beigene

A Phase 1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors

Patients continue until PD, unacceptable toxicity or withdrawal

CONTACT
CRC: Andrew Conley x 23921, Joanne Lim x 23381;
PI: Dr Sanjeev Deva x 23832;
Nurse: Elly J Heo 021 913 464 or x 22139/25046

KINEX 002 & 003



KINEX 002
A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel

KINEX 003
A Safety Study of Oraxol (HM30181 + oral paclitaxel) in Cancer Patients

Initially KINEX 003 will be limited to those participants who complete KINEX 002

CONTACT
CRC: Elizabeth Wardrop x 22499
PI: Dr Sanjeev Deva x 23832
Nurse: Georgia Wilson x 22139/25046

Summing up

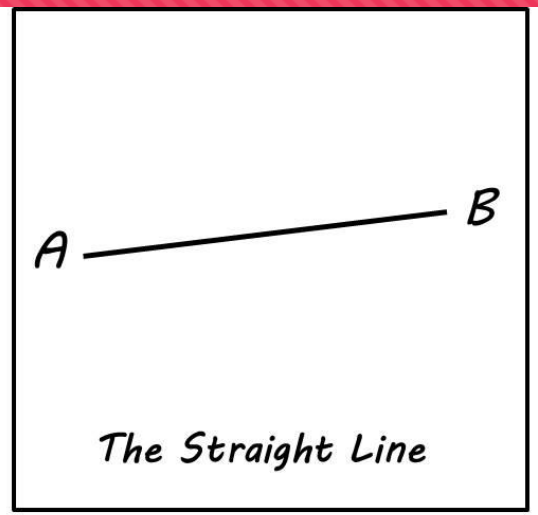
- Advanced breast cancer is a varied disease that cannot be approached or treated in a one-size fits all fashion
- There have been improvements in outcomes over time
- Innovation has not been comparable across all ABC subtypes,

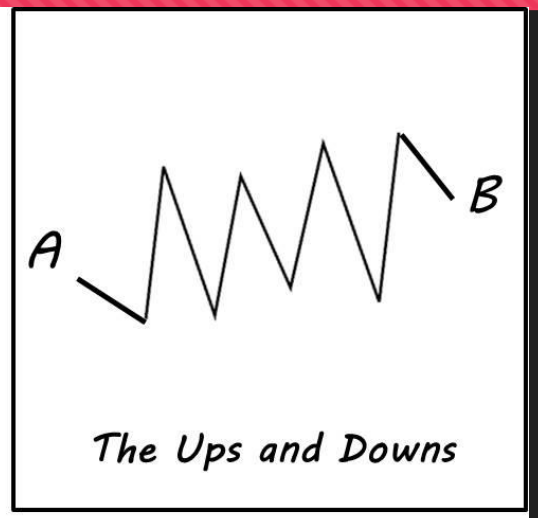
  with greater success occurring in HER2+ ABC and a large unmet need in TNBC
- Access to new treatments is a particular challenge in NZ
- Progress made in the scientific understanding of ABC has

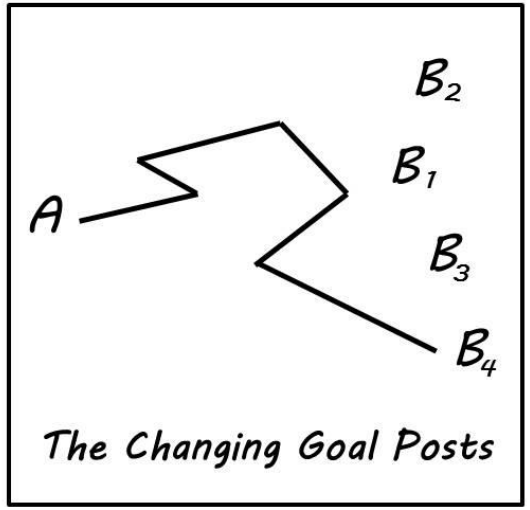
  highlighted the previously unrecognized complexity of

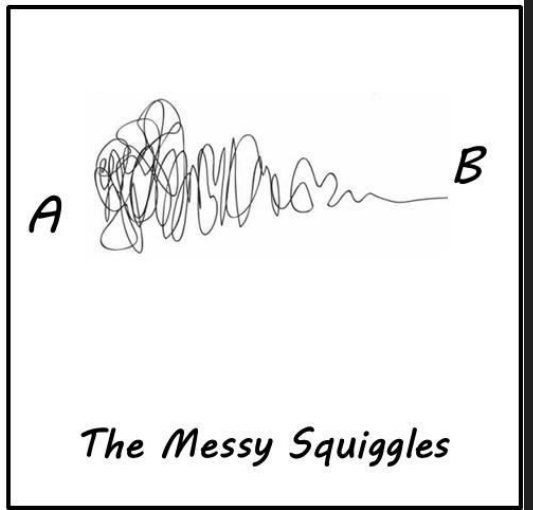
  the disease

The road ahead

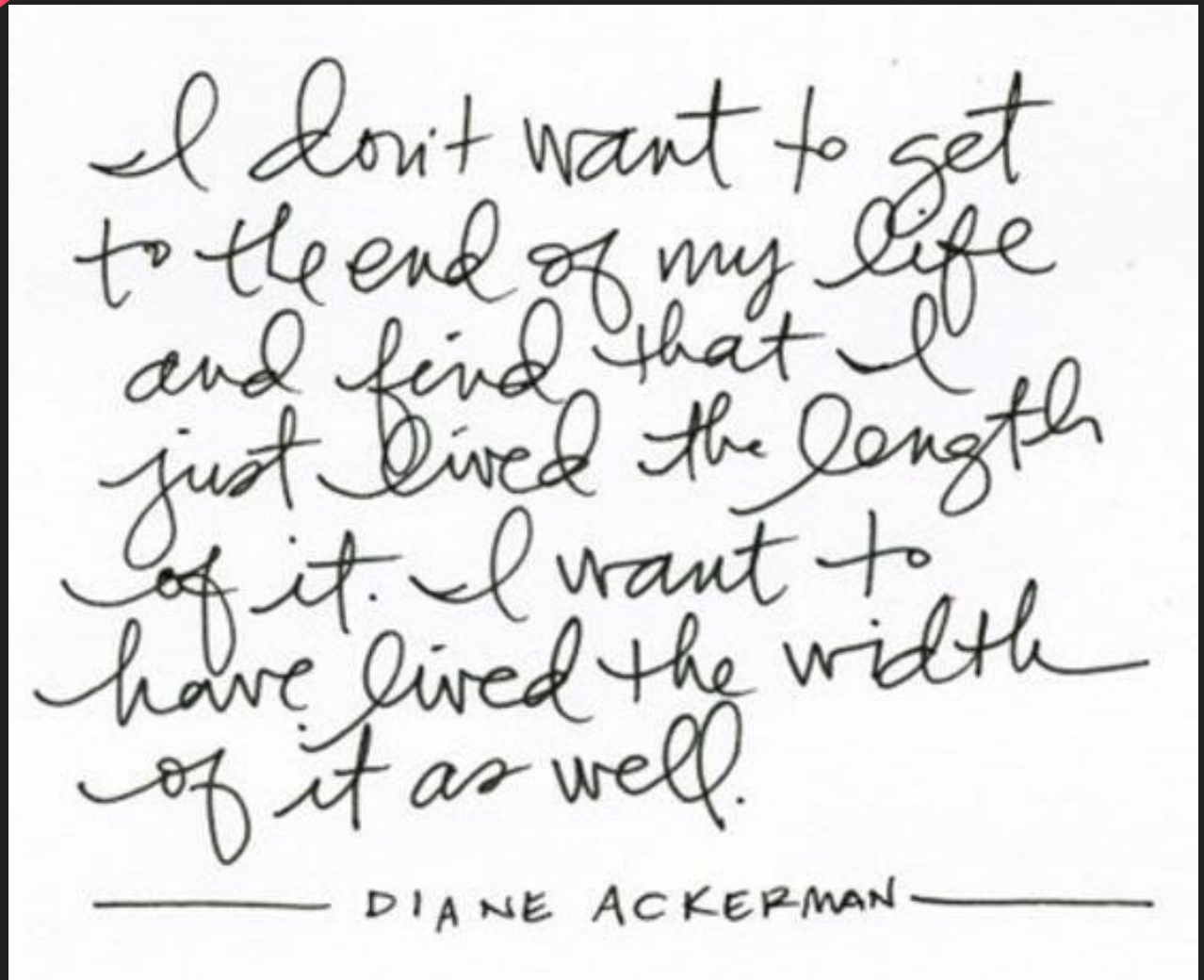








Thank you


I don't want to get
to the end of my life
and find that I
just lived the length
of it. I want to
have lived the width
of it as well.
DIANE ACKERMAN