Breast Cancer – can we call it a chronic disease ?

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Incidence

- In 2016, it was estimated that 15,930 women and 150 men were diagnosed with breast cancer.
- On average, 43 women will be diagnosed with breast cancer every day.
- The number of women and men being diagnosed with breast cancer in Australia is increasing; however the number of deaths from breast cancer is decreasing.
- Breast cancer is the most common cancer diagnosed in Australian women.
- The risk of being diagnosed with breast cancer by age 85 is 1 in 8 for women and 1 in 838 for men.
- Breast cancer can occur in younger women - estimated that 795 women between the ages of 20 and 39 were diagnosed with breast cancer in 2015 - approx 5% of all breast cancers diagnosed in Australia.

Breast Cancer Network Aust 2016

Survival

- Australia has one of the best breast cancer survival rates in the world
- The chance of surviving at least five years (five year relative survival) has increased from 72% in 1982-1987 to 90% in 2015.
- The chance of surviving at least ten years (ten year relative survival) is now 83%.
- Increasing survival is due to earlier diagnosis through screening and improved treatments.
- It is estimated there are over 160,000 women alive who had been diagnosed with breast cancer in the previous 30 years
- Breast cancers in younger (pre-menopausal) women have poorer survival outcomes compared with older women
- There are sub-groups of the population who have lower survival than others including women living in rural and remote areas and Aboriginal and Torres Strait Islander women.

Breast Cancer Network Aust 2016

Mortality

- Breast cancer accounts for 15.5% of all cancer deaths in Australian women and is currently the second leading cause of cancer death in Australian women after lung cancer.

- Approximately 3,040 women and 25 men died from breast cancer in 2015. This means that on average, eight people died from breast cancer every day.

- The risk of being diagnosed with breast cancer increases with age.

- Approximately 75% of new cases of breast cancer develop in women over the age of 50.

- The average age of the first diagnosis of breast cancer in women is 60.

- Approximately 5-10% of breast cancers are due to a strong family history or genetic mutation, such as BRCA1 or BRCA2.

Case –

- 69 yr old female independent, supported by husband

Oxycontin 30 bd and gabapentin 100mg bd “chronic” back pain,

- First diagnosed when she was 47 yrs old (1995)

right 15mm IDC, grade 2 extensive DCIS 0/17 LN ER/PR positive – treated completion mastectomy, then on tamoxifen

- age of 52 yr old (2001)

left breast cancer - with multifocal calcifications on mammography, discussion regarding simple mastectomy and axillary node sampling

Path confirmed extensive high grade DCIS, a small focus of invasion 0.5mm, Paget’s disease of the nipple, 0/1 LN, ER/PR negative

Ceased tamoxifen

- 2009 aged 61

  presented with back pain, symptoms of cord compression – bone biopsy ER weak pos Her 2 positive breast cancer

  commenced on nab-paclitaxel and Herceptin approx 4 months, continued on the Herceptin alone, monthly Zometa

- 2012 aged 64

  noted right chest wall nodule biopsied – path ER diffusely but strongly positive, 50% PR positive, and Her 2 positive,

  Recommenced nab-paclitaxel Herceptin for approx 4 months, commenced on exemestane, Herceptin, monthly Zometa

- 2013 bone pain increased, progression bone metastasis

  changed to Kadcyla 3/52, Zometa 6/52

- 2015 left anterior neck nodal mass biopsied – ER PR positive Her 2 neg

  Continued on Kadcyla, exemestane and everolimus, everolimus poorly tolerated, ceased 2016, with disease stability

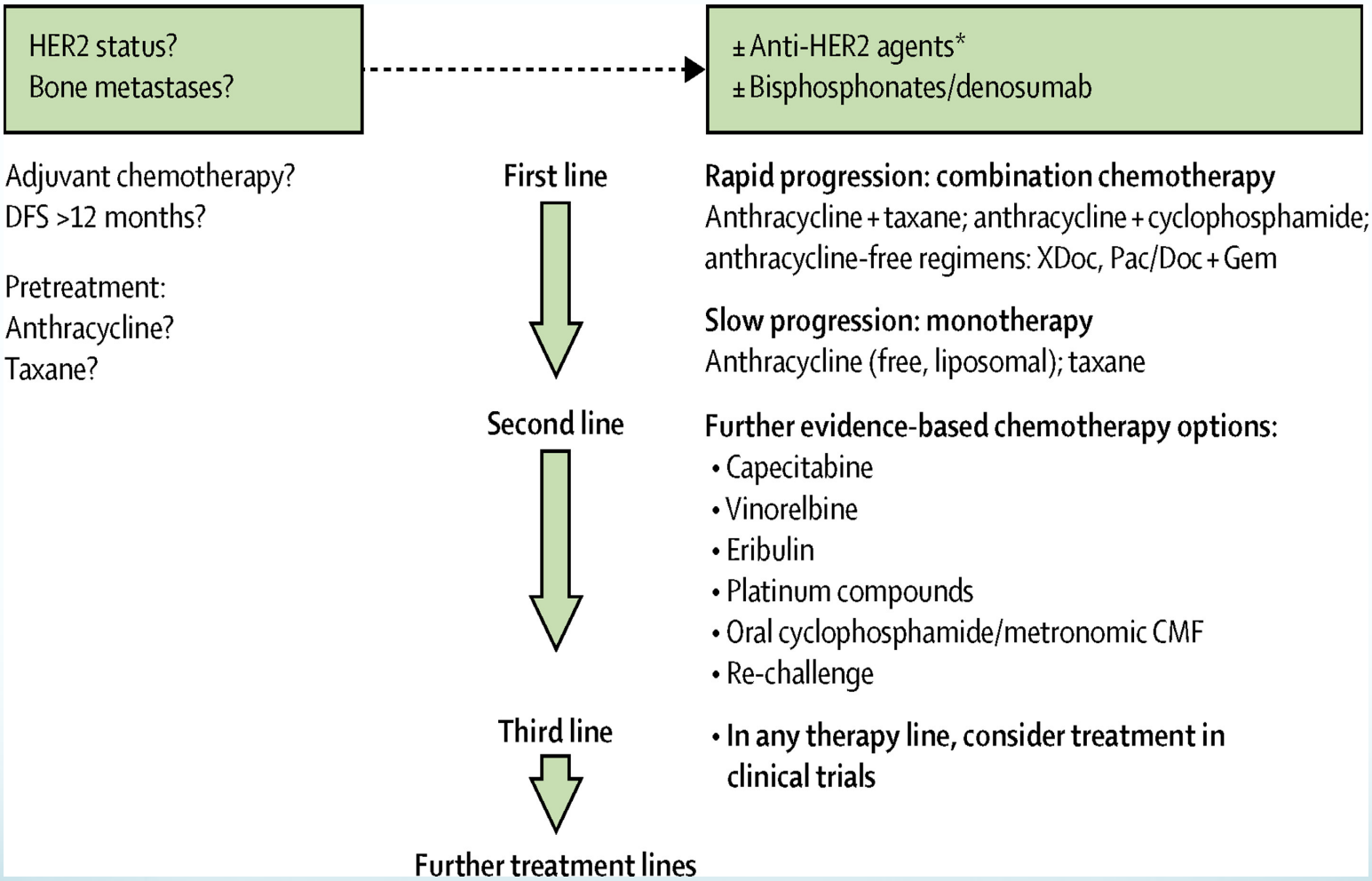
- 2017 new supraclavicular nodal disease, biopsy showed ER moderate positive, Her2 pos disease

  Lapatinib and capecitabine approved

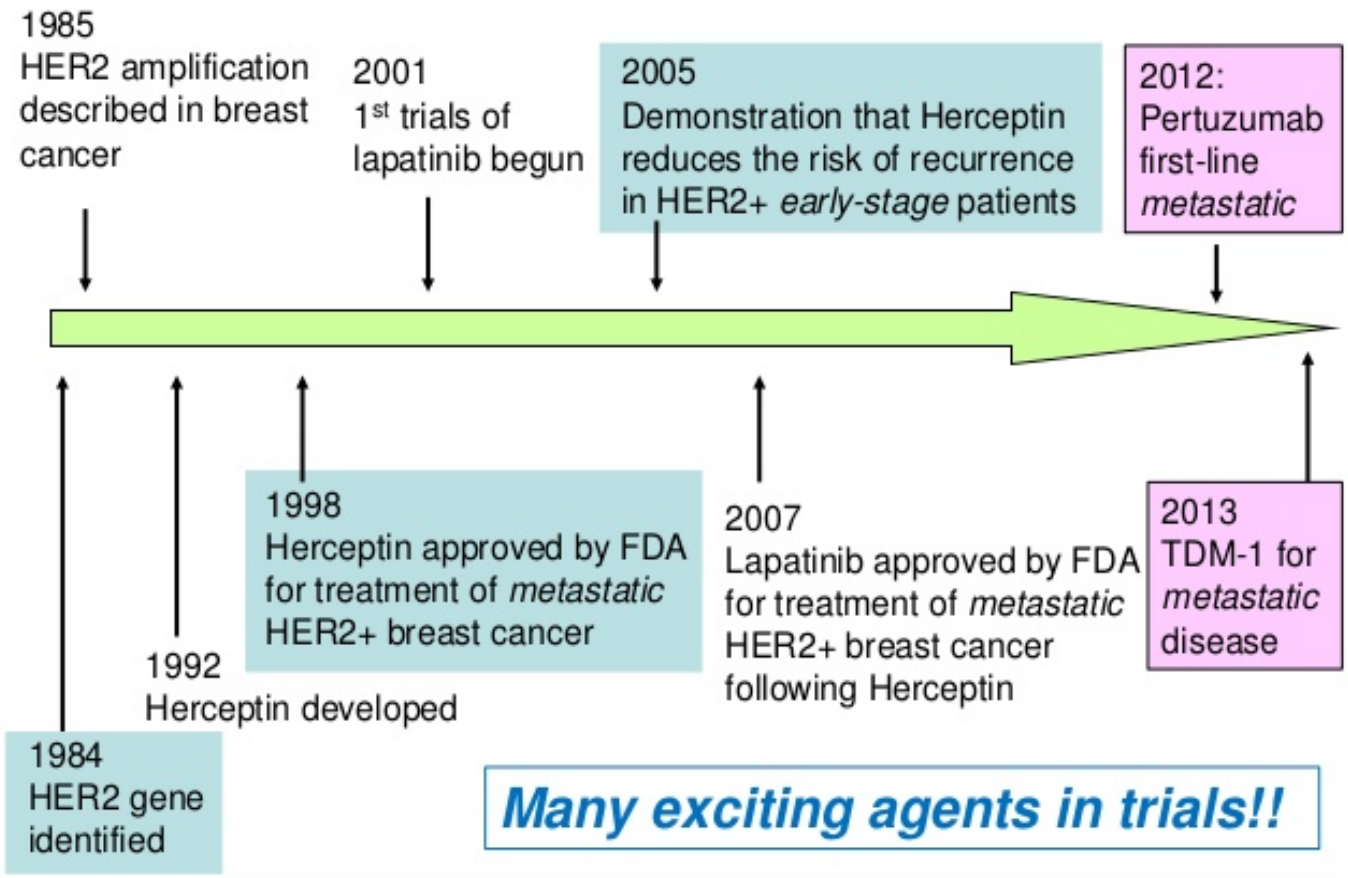
  with reduction clinically in nodal disease

  XRT considered if symptomatic however extensive mediastinal nodal disease

  Still other chemotherapy options


HER2 status?
Bone metastases?
± Anti-HER2 agents*
± Bisphosphonates/denosumab
Adjuvant chemotherapy?
DFS >12 months?
Pretreatment:
Anthracycline?
Taxane?
First line
Second line
Third line
Further treatment lines
Rapid progression: combination chemotherapy
Anthracycline + taxane; anthracycline + cyclophosphamide;
anthracycline-free regimens: XDoc, Pac/Doc + Gem
Slow progression: monotherapy
Anthracycline (free, liposomal); taxane
Further evidence-based chemotherapy options:
• Capecitabine
• Vinorelbine
• Eribulin
• Platinum compounds
• Oral cyclophosphamide/metronomic CMF
• Re-challenge
• In any therapy line, consider treatment in clinical trials

Timeline


1985
HER2 amplification described in breast cancer
2001
1st trials of lapatinib begun
2005
Demonstration that Herceptin reduces the risk of recurrence in HER2+ *early-stage* patients
2012:
Pertuzumab first-line *metastatic*
1984
HER2 gene identified
1992
Herceptin developed
1998
Herceptin approved by FDA for treatment of *metastatic* HER2+ breast cancer
2007
Lapatinib approved by FDA for treatment of *metastatic* HER2+ breast cancer following Herceptin
2013
TDM-1 for *metastatic* disease
Many exciting agents in trials!!

Systemic treatment

- Oral targets –

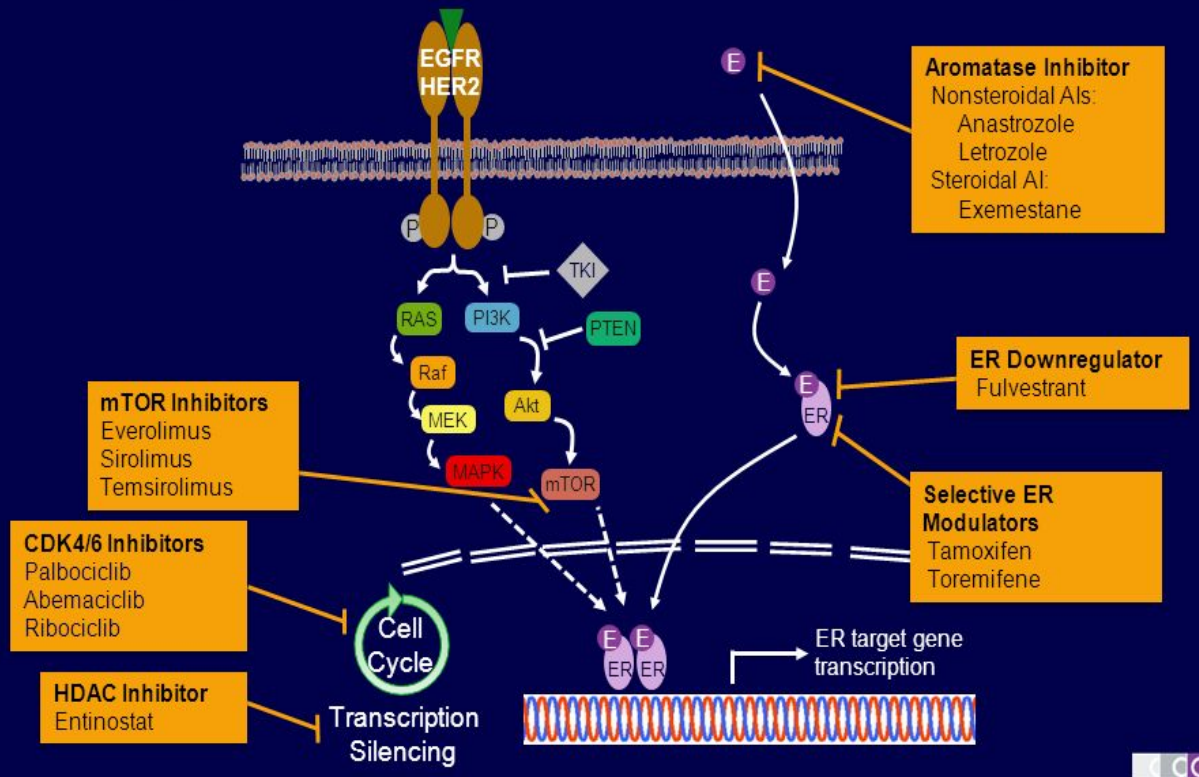
  ER/PR – tamoxifen, aromatase inhibitors

  mTOR – everolimus (on PBS + exemestane)

  cyclin 4/6 – palbociclib/ ribociclib (FDA /non PBS)

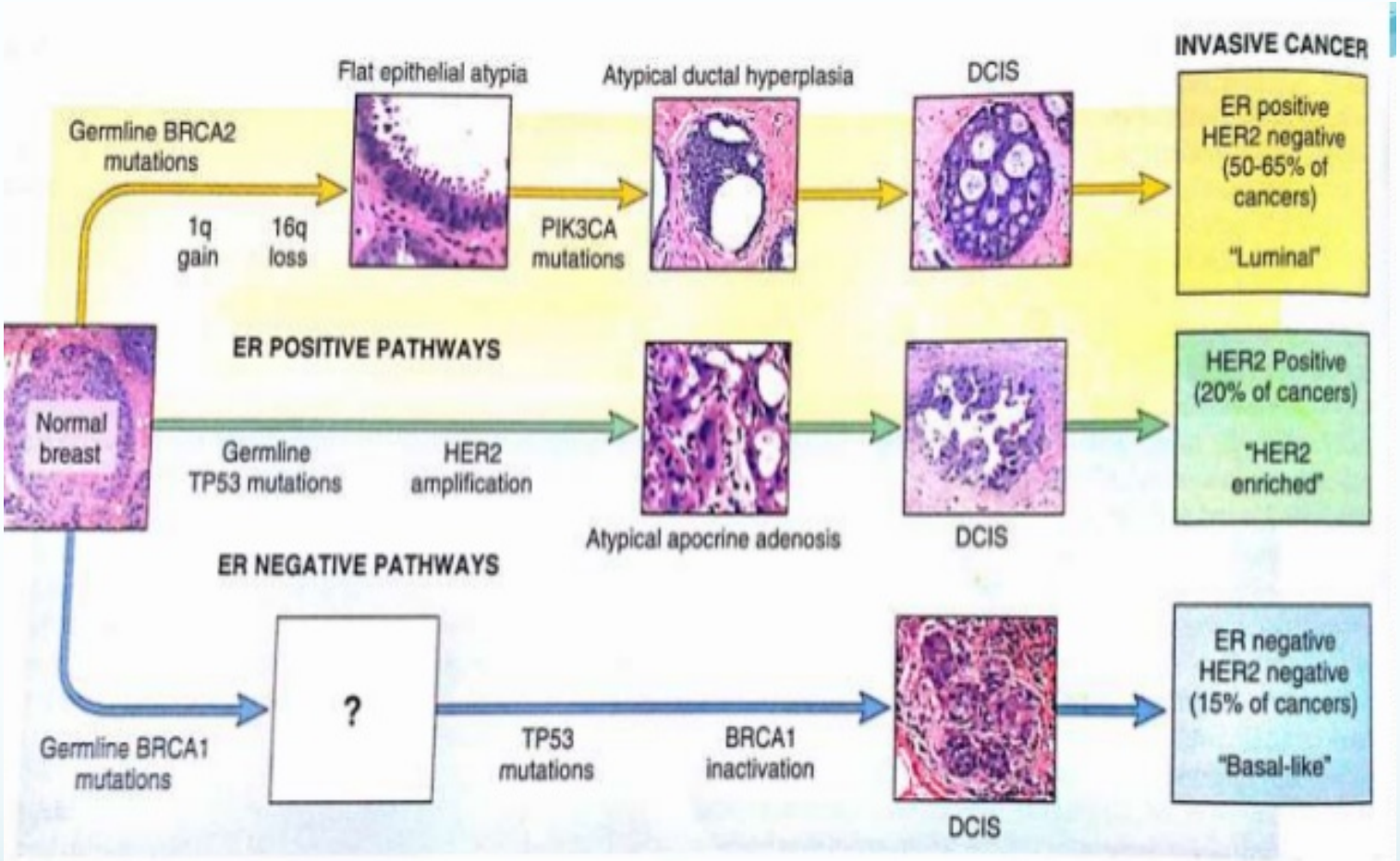
- Oral chemotherapy – capecitabine, vinorelbine
- IV targets – Herceptin®, Perjeta®, Kadcyla®
- IV chemotherapy – anthracycline, taxane , erubilin, platinum, gemcitabine

Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer



Johnston SR. Clin Cancer Res. 2010;16:1979-1987.

Slide credit: clinicaloptions.com



e 23-16 *Major pathways of breast cancer development. Three main pathways have been identified. The most common pathway (yellow arrow) leads to positive carcinomas. Recognizable precursor lesions include flat epithelial atypia and atypical hyperplasia. A less common pathway (blue arrow) leads to nomas that are negative for ER and HER2. The box with the question mark indicates that no precursor lesions have been identified—perhaps because s progress quickly to carcinoma. The third pathway (green arrow) consists of HER2-positive cancers, which may be ER-positive or ER-negative. fication of the HER2 gene is also present in a subset of atypical apocrine lesions, which may represent a precursor lesion. Each molecular subtype has racteristic gene expression profile termed luminal, HER2 enriched, and basal-like, respectively. See text for other details.*

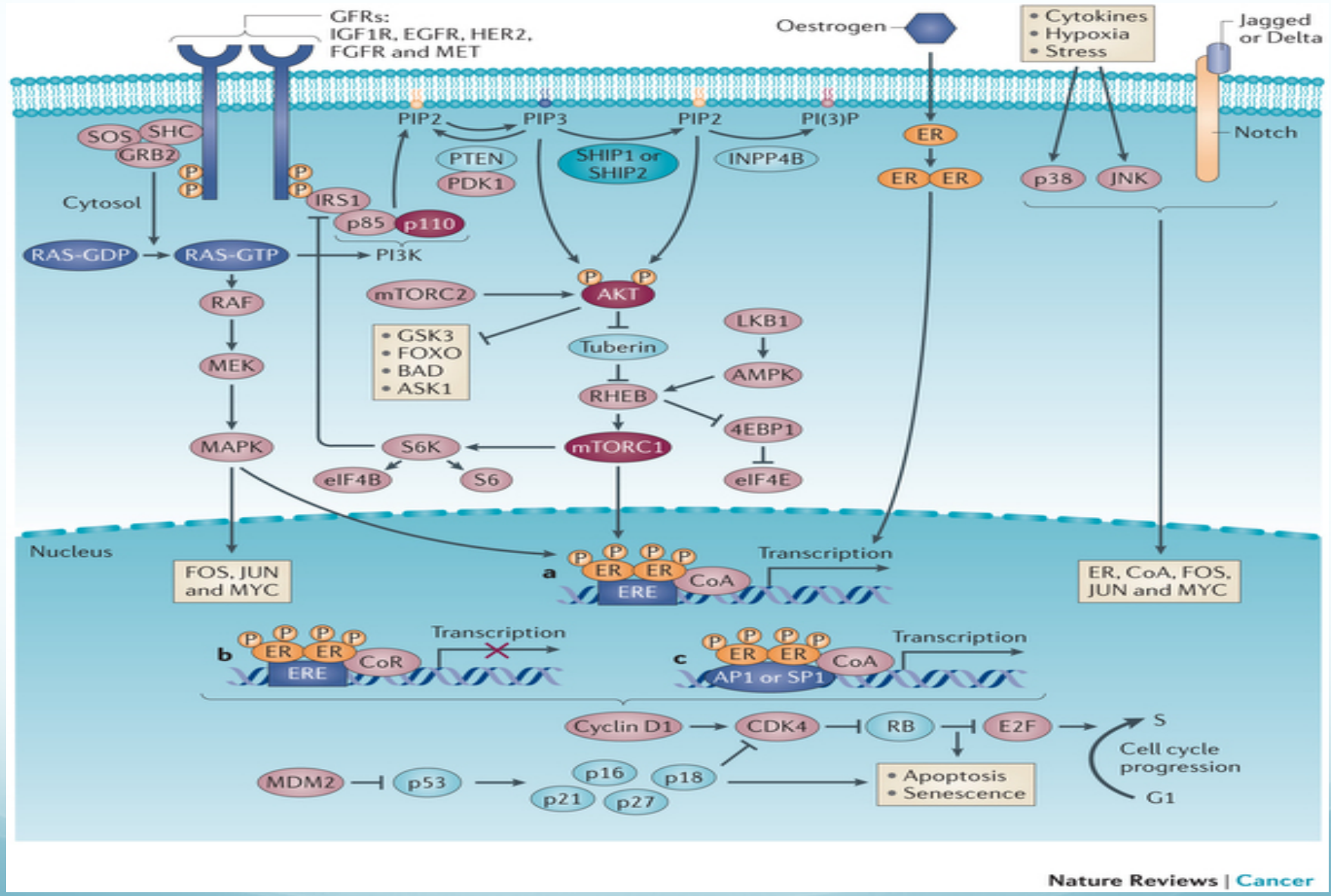
Young ER

- Case 43 yr locally advanced R breast cancer, noticed increasing breast lesion breastfeeding
- US and clinically 4cm upper outer quad, palpable axillary nodes, bx IDC ER/PR pos, Her 2 neg
- Staging clear
- Neoadj TAC X6 (Jan – May 2014) > mastectomy (June 2014)
- Path – fibrosis, but 40mm G2 LVI pos, DCIS high grade within tumor 26/28 LN extranodal spread, ER 3+ 100%, PR 2+20%, Her2 neg.

- Presented to DEM back pain Jan 2015 > bone scan confirmed mets, CT clear of visceral metastasis commenced exemestane and zometa, XRT, > post XRT started everolimus
- clinically stable, CT staging March increased size sacral lesion despite XRT started nab-paclitaxel – stable radiologically and clinically till Aug 2015
- CT staging new uncompromised pleural and pericardial effusion > ECHO/ cardiol review > pericardiocentesis fluid cytology c/w ER/PR pos breast ca > started carboplatin/gemcitabine X4 cycles
- Feb 2016 Clinical progression dyspnoea, confirmed on staging, started capecitabine.....

Her 2

- Dx 76 yr old liver metastasis and R local breast cancer – bx liver and breast Her 2 pos, ER neg breast cancer > started taxol/herceptin 2009, > on off taxol > clear progression 2015 now age 85 years on Kadcyla, treatment breaks
- Dx 80 yr old with L breast cancer, spinocerebellar symptoms (antineuronal Abs pos), bone, liver metastasis Her 2 pos, ER neg > commenced taxol/herceptin 2009 > now age 89 yr on Herceptin alone



Nature Reviews | Cancer

Triple neg

- 65 yr old EBC hx of CRC, and IHD, Adj AC-T very poorly tolerated
- 67 yrs bx proven mets to lungs capectabine 18/12
- 69 yrs > carboplatin/gemcitabine

Triple negative

- Basal like 1 and 2 (BL1 BL2) high expression cell cycle and DNA response genes

  More responsive platinum

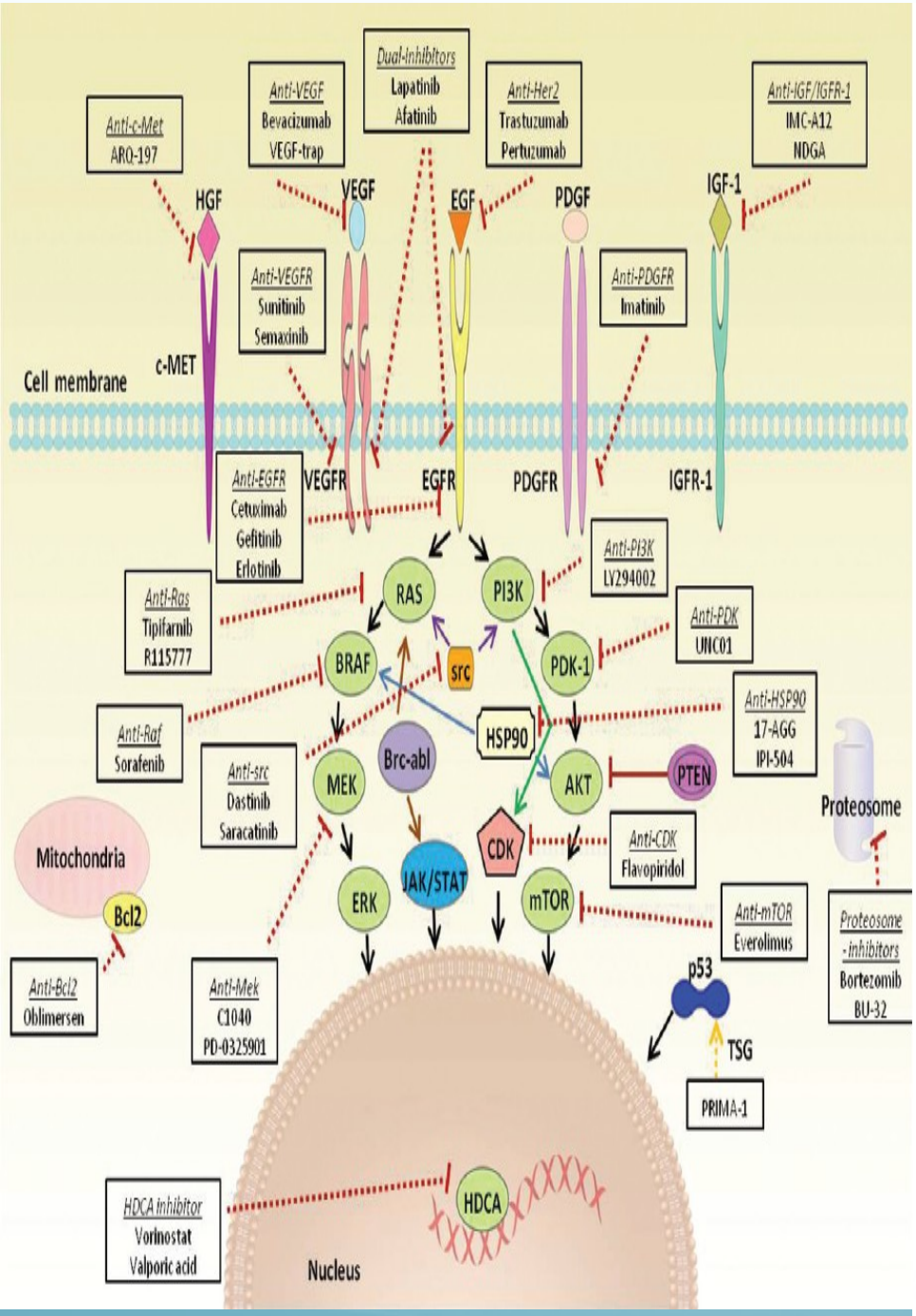
- Immunomodulatory

- Mesenchymal and mesenchymal stem cell like

  responsive to mTOR, PI3K, abl-src pathways

- Luminal androgen receptor (LAR)

  responsive to androgen receptor drugs



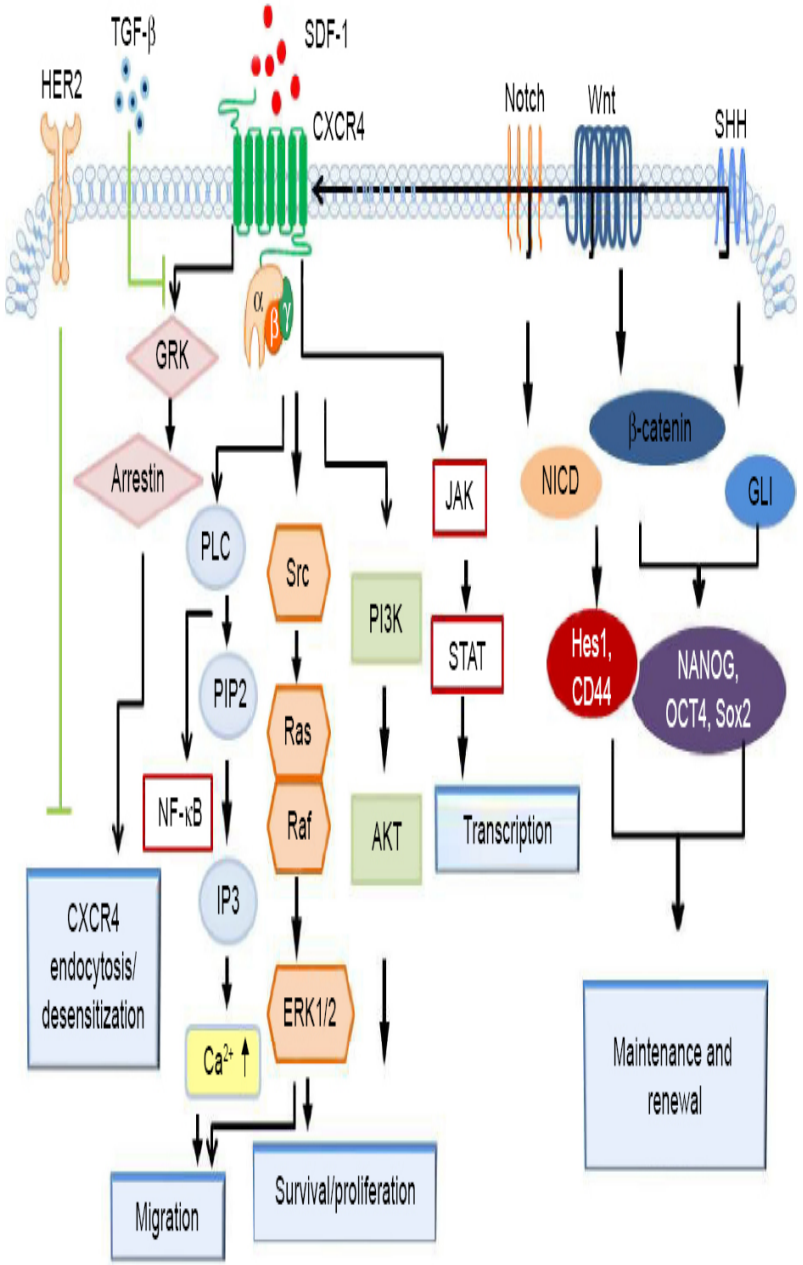
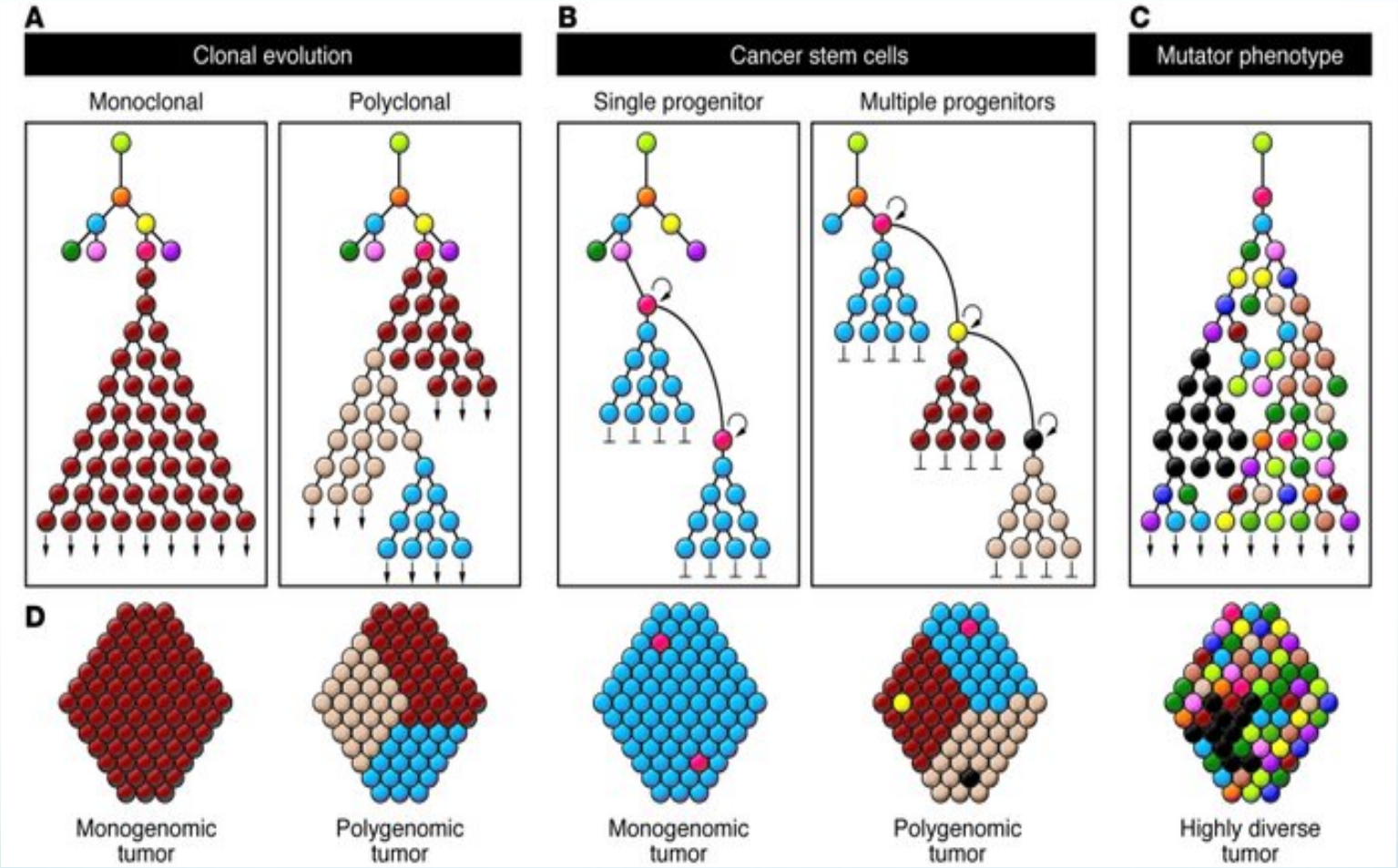


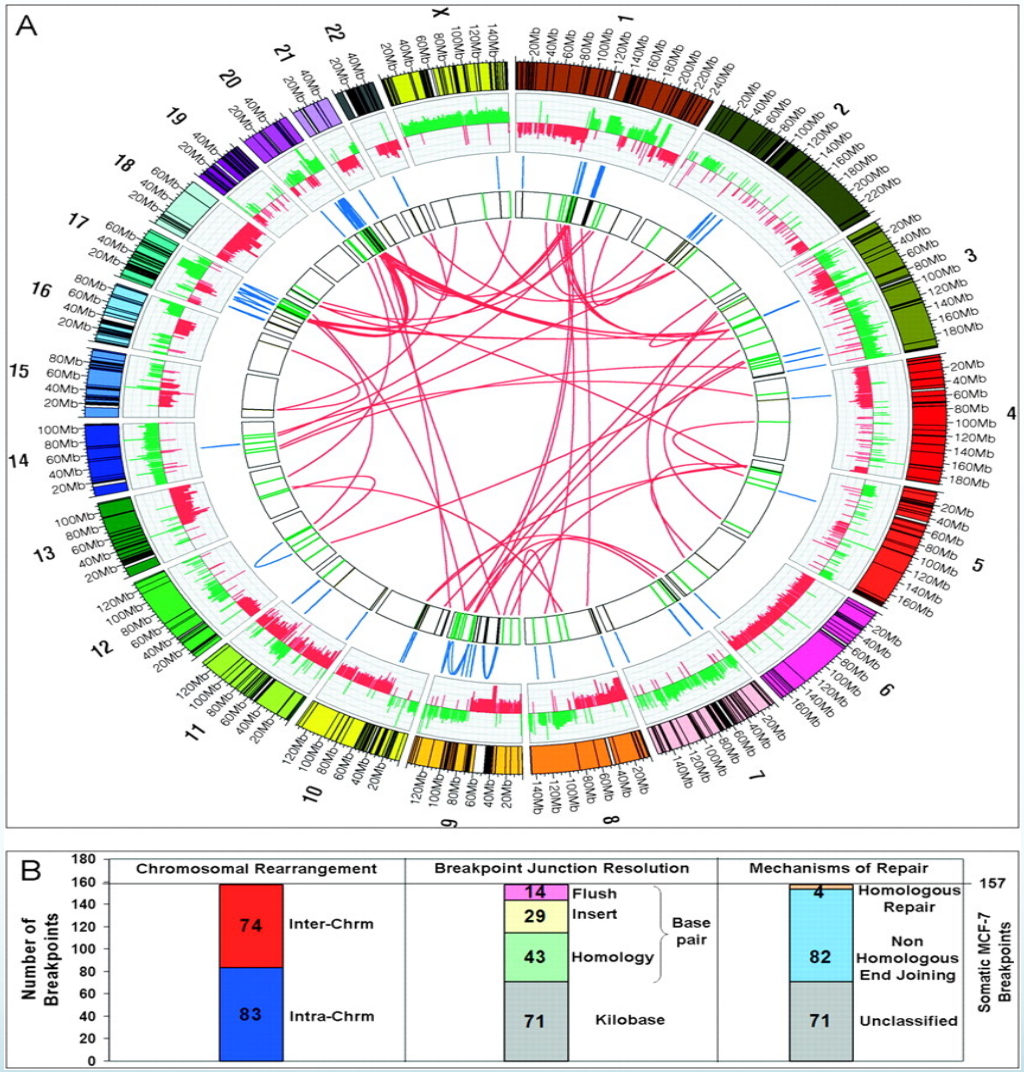
Figure 1 CXCR4-mediated feedback loop of multiple signaling pathways.

Notes: CXCR4 (C-X-C chemokine receptor type 4) expression is positively regulated by the developmental signaling pathways Wnt/β-catenin,[30–32] Sonic hedgehog (SHH)-

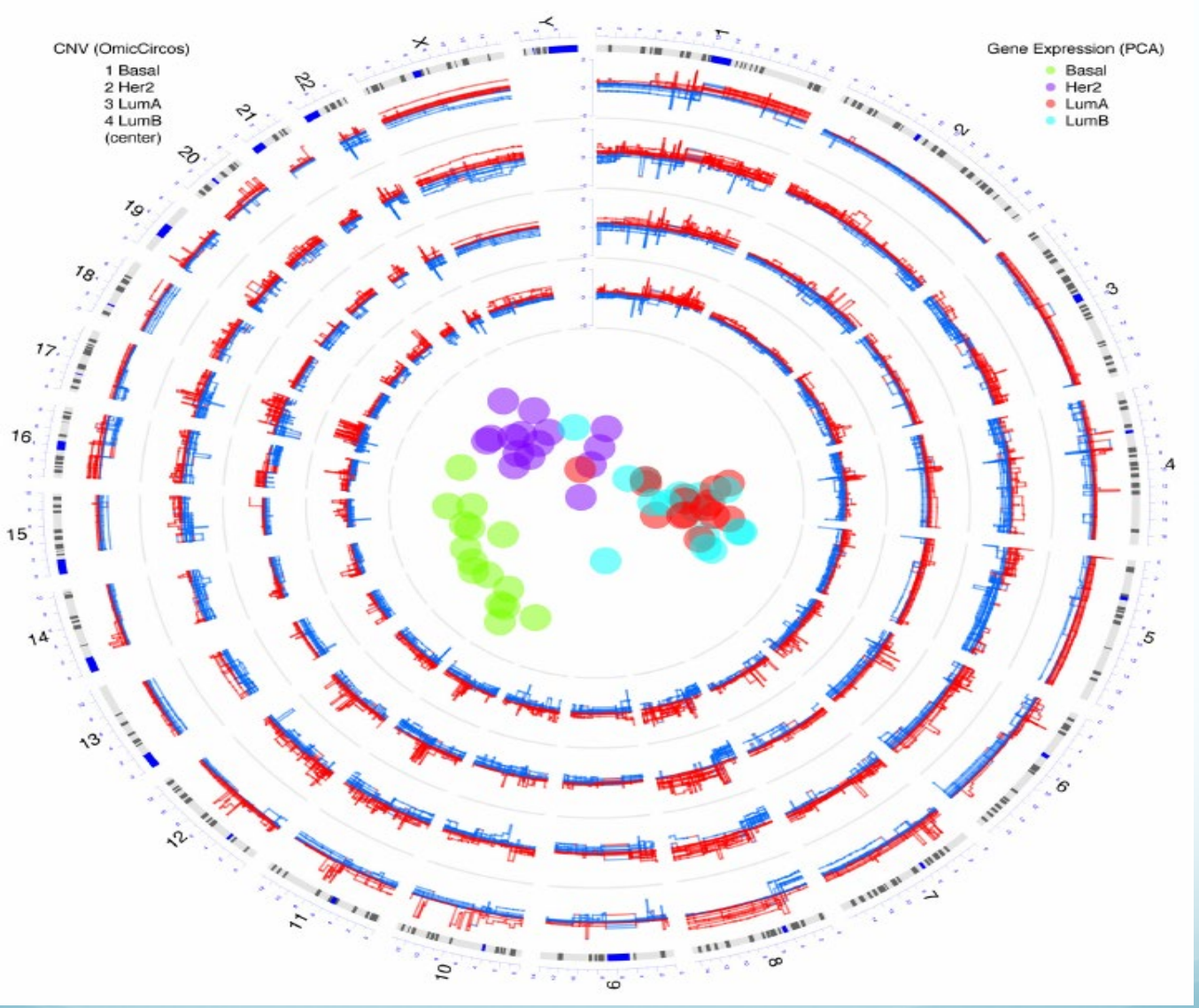
Tumor heterogeneity



(A) Circular visualization of the MCF-7 genome obtained using Circos software.



Oliver A. Hampton et al. Genome Res. 2009;19:167-177


CNV (OmicCircos)
1 Basal
2 Her2
3 LumA
4 LumB
(center)
Gene Expression (PCA)
Basal
Her2
LumA
LumB
X
Y
1
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