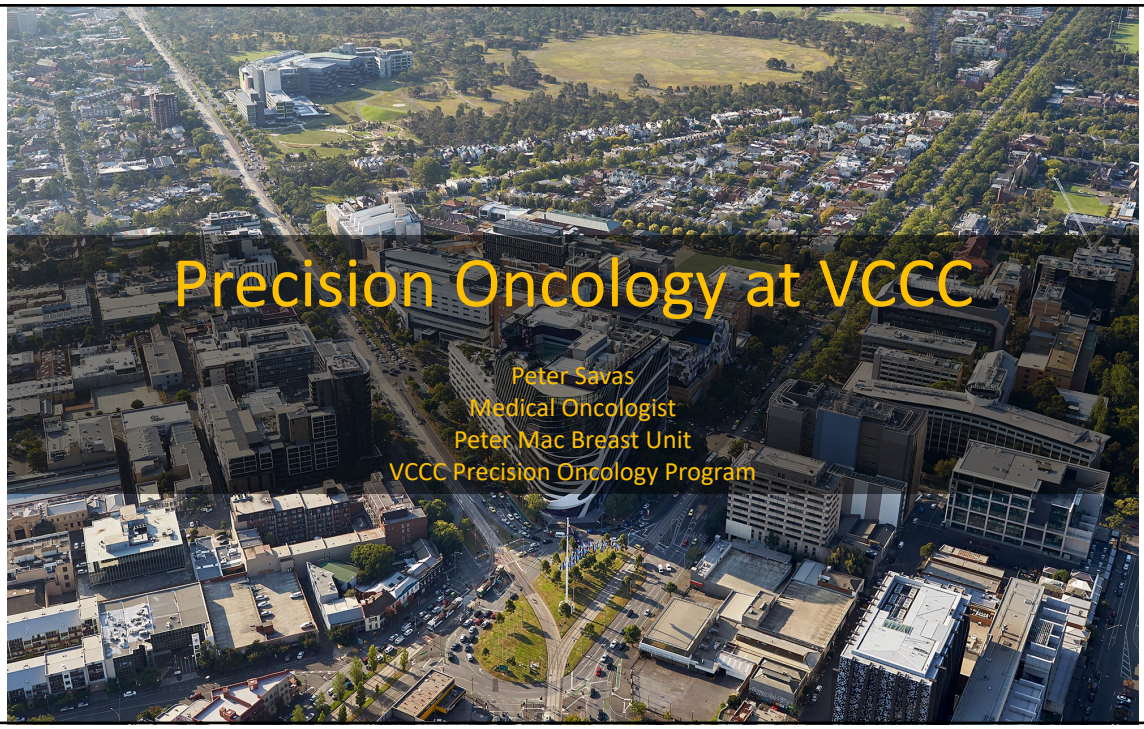
Queensland Molecular Tumour Board Meeting

14th November 2018
Room 2004, TRI, Princess Alexandra Hospital,
Woolloongabba, QLD



Precision Oncology at VCCC

Peter Savas
Medical Oncologist
Peter Mac Breast Unit
VCCC Precision Oncology Program

Case A

- 40 year old woman
- Metaplastic triple negative breast carcinoma 2012
- Neoadjuvant FEC + Docetaxel, poor response

Surgical History

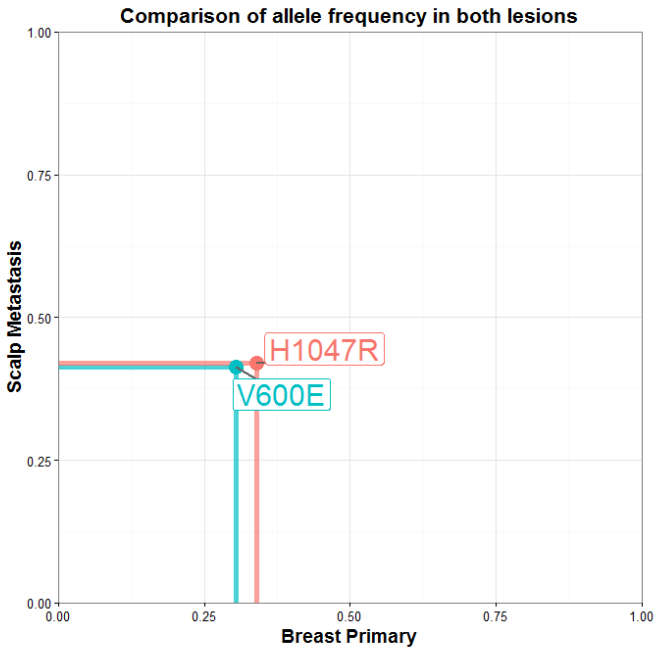
Date	Procedure	
27/1/2012	Left mastectomy and axillary clearance (Post neoadjuvant chemotherapy)	← Sequenced
21/5/2013	Resection of scalp metastasis	← Sequenced
1/5/2014	Wide resection of sternal tumour	'Adjuvant' gemcitabine + carboplatin
4/6/2016	Resection of recurrent chest wall mass involving skin, pericardium, thymus, 4th and 5th ribs.	

SEGMENT

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

MUTATIONS

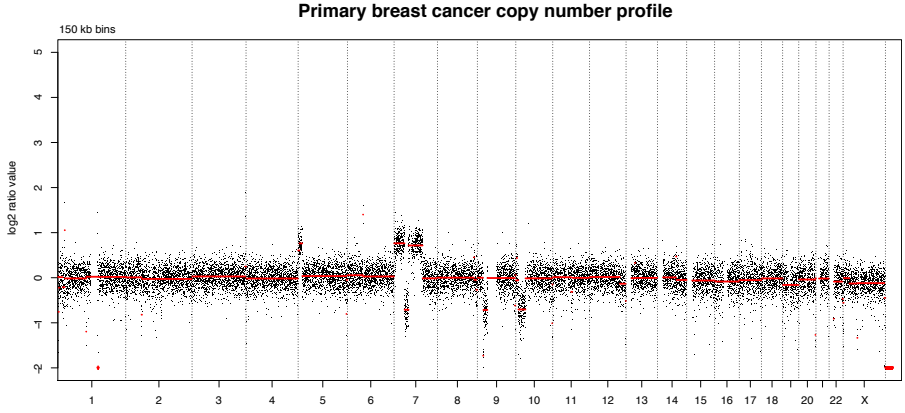
Gene	Type of variant	Protein change	NCBI Gene ID/ RefSeq Transcript	Oncogenic status
BRAF	Missense substitution	p.V600E	673 NM_004333	Oncogenic Previously reported
PIK3CA	Missense substitution	p.H1047R	5290 NM_006218	Oncogenic Previously reported in breast cancer



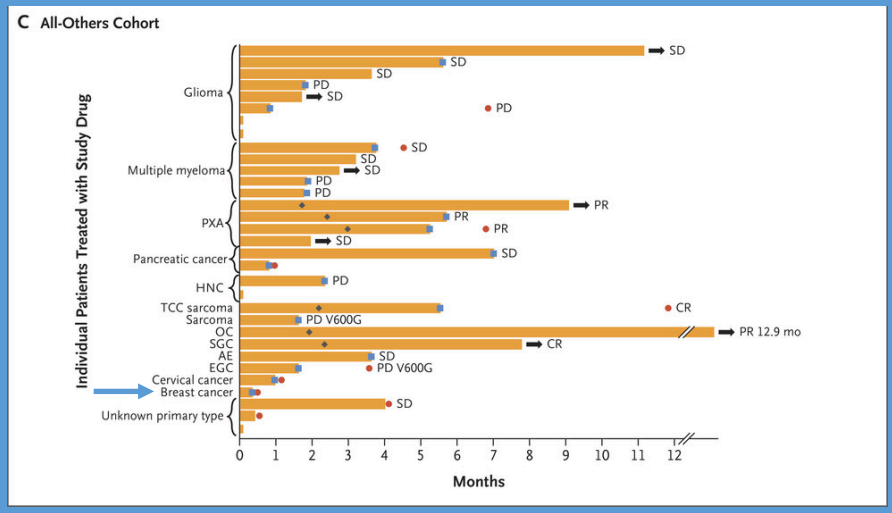
COPY NUMBER VARIANTS

Gene	Type of variant	Location	NCBI Entrez Gene ID	Estimated total copies	Oncogenic status
CDKN2A	Whole gene deletion	9p21	1029	0.2	Oncogenic

Primary breast cancer copy number profile

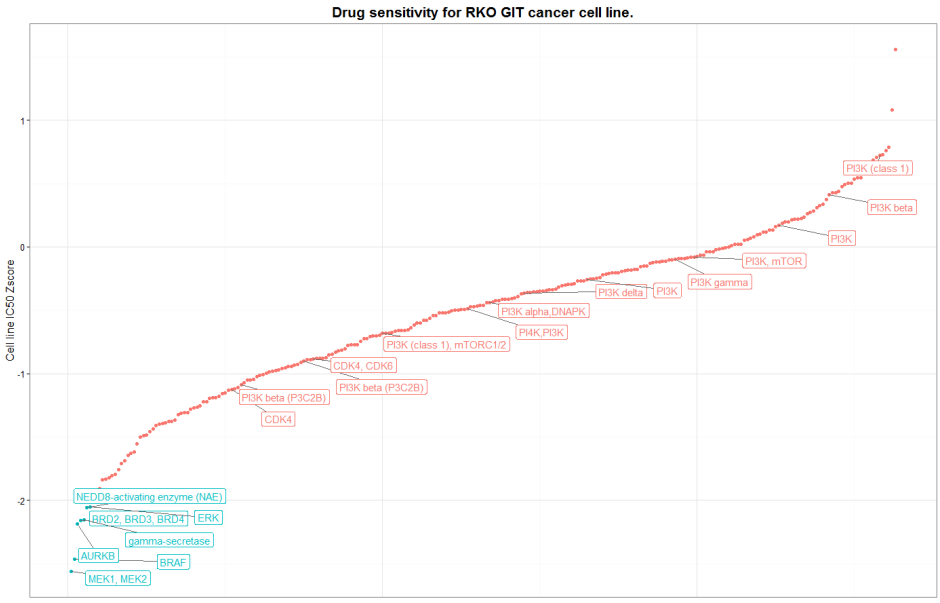


Time to Events in Individual Patients and According to the Best Overall Response.



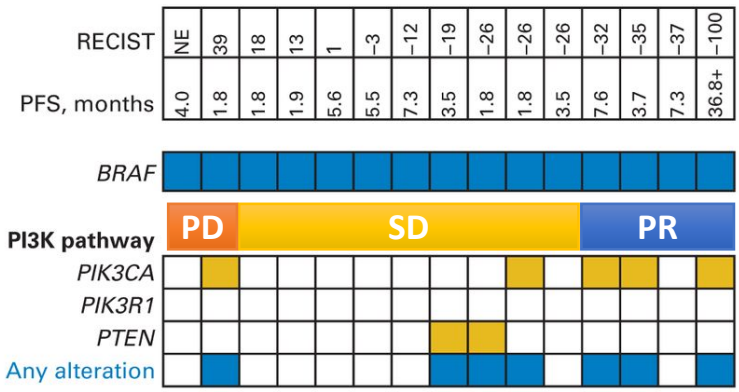
Hyman DM et al. N Engl J Med 2015;373:726-736.

The NEW ENGLAND JOURNAL of MEDICINE



http://www.cancerrxgene.org/translation/CellLine/909698

487-gene mutational analysis of archival tumor specimens available from 15 patients with BRAF mutant colorectal cancer treated with Dabrafenib + Trametinib.



Ryan B. Corcoran et al. JCO 2015;33:4023-4031

Progress

- Reviewed in molecular tumour board
  - Slight preference for targeting BRAF over PIK3CA initially
  - ctDNA testing – negative for BRAF and PIK3CA mutations
- EViCT trial – vemurafenib + erlotinib
  - 5 months of therapy
  - Stable disease, then progression
- Phase I PD-1 inhibitor
  - Progressed at first scan

Progress

- Symptomatic with intractable cough due to lung masses
- Progressive adrenal and bone metastasis
- ctDNA testing (Sarah-Jane Dawson)
  - Negative for PIK3CA H1047R and BRAF V600E despite large disease burden September and October 2017
- Enrolled on Phase II PIKNIC trial with apelisib monotherapy (PI Sherene Loi)
  - PIK3CA alpha-subunit specific inhibitor

Case B

- 59 year old woman
- Locally advanced HER2 positive breast cancer 2009
- ACx4, TCH x6, 12 months Trastuzumab
- Recurrence 2011 skin
- Trastuzumab monotherapy
- Trastuzumab + Vinorelbine
- Trastuzumab + Docetaxel
- Liposomal Doxorubicin
- Capecitabine + Trastuzumab
- Carboplatin + Trastuzumab
- Capecitabine + Lapatinib
- TDM-1
- Eribulin + Trastuzumab

	Start date (mm/yyyy)	Stop date (mm/yyyy)		
AC x 4 TCH x 6 12 months trastuzumab	09/2009	10/2010		Locally advanced primary Neoadjuvant chemo
Trastuzumab	07/2011	11/2011	4 months	Skin recurrence
Vinorelbine + Trastuzumab	11/2011	02/2012	3 months	
Docetaxel + Trastuzumab	02/2012	07/2012	5 months	
Liposomal doxorubicin	09/2012	12/2012	3 months	
Capecitabine + Trastuzumab	12/2012	03/2013	4 months	
Trastuzumab	03/2013	08/2013	5 months	Resection of solitary cerebellar lesion
Carboplatin + Trastuzumab	08/2013	10/2013	2 months	
Capecitabine + Lapatinib	10/2013	04/2014	6 months	
TDM-1	04/2014	06/2014	2 months	
Eribulin + Trastuzumab	10/2014	12/2014	2 months	ctDNA assessment (USA)
Abraxane, Everolimus, Trastuzumab	12/2014	07/2015	7 months	
Abraxane + trastuzumab	07/2015	09/2015	2 months	

Non-Invasive Cancer Sequencing Report

GUARDANT360

POSITIVE: 5 Total Genomic Alterations Detected

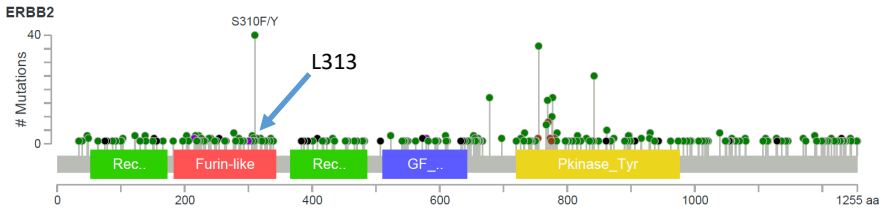
MAJOR ALTERATIONS	**ERBB2** L313I	
MINOR ALTERATIONS	**TP53** V143E	**CSF1R** Y300Y
	AR E32*	**ERBB2** I148I

	Genomic Alteration	Approved Therapies	Approved Therapies in Other Indications	Trials
ASSOCIATED TREATMENTS	AR E32*	No	No	No
	ERBB2 L313I	No	No	No
	TP53 V143E	No	No	NCT01664000, NCT01748825

Table 1. Allele frequency of altered circulating cell-free DNA detected in this patient

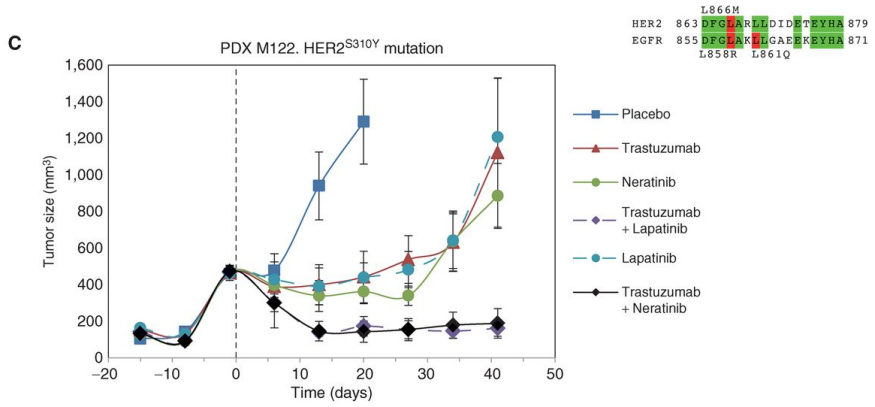
ERBB2 L313I	8.6%
TP53 V143E	0.4%
CSF1R Y300Y	0.3%
AR E32*	0.2%
ERBB2 I148I	0.2%

Recurrent ERBB2 mutations - TCGA



www.cbioportal.org

Drug treatment of HER2- or KRAS-mutant colorectal cancer PDXs. A, HER2 gene–specific sequencing of 48 cetuximab-refractory, quadruple WT PDXs identified 4 PDXs with HER2 mutations.



Shyam M. Kavuri et al. Cancer Discovery 2015;5:832-841

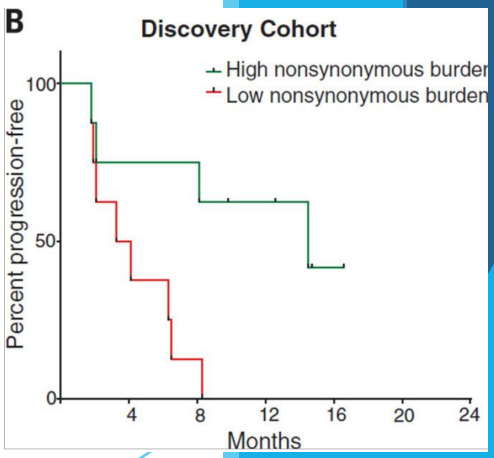
CANCER DISCOVERY

High TMB breast cases

Kate Roberts

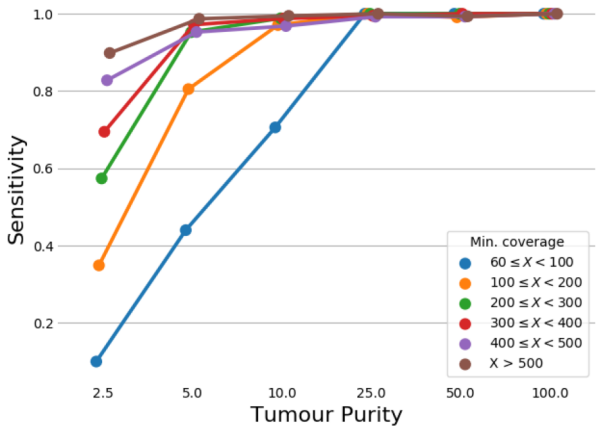
Tumor Burden : Nonsynonymous mutation burden associated with clinical benefit of anti-PD-1 therapy

Fig 1: Based on exome sequencing:
(HR 0.19, 95% CI 0.08–0.47, log-rank P = 0.0004)

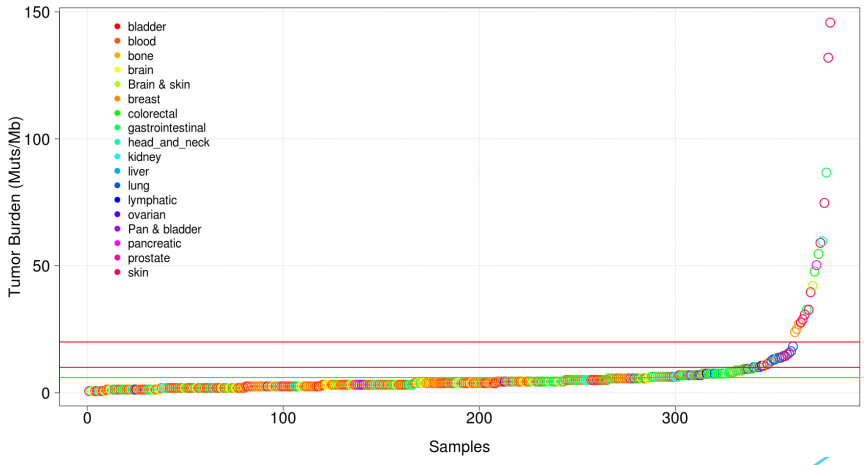


Rizvi et al. Science. Science. 2015 Apr 3; 348(6230): 124-128.

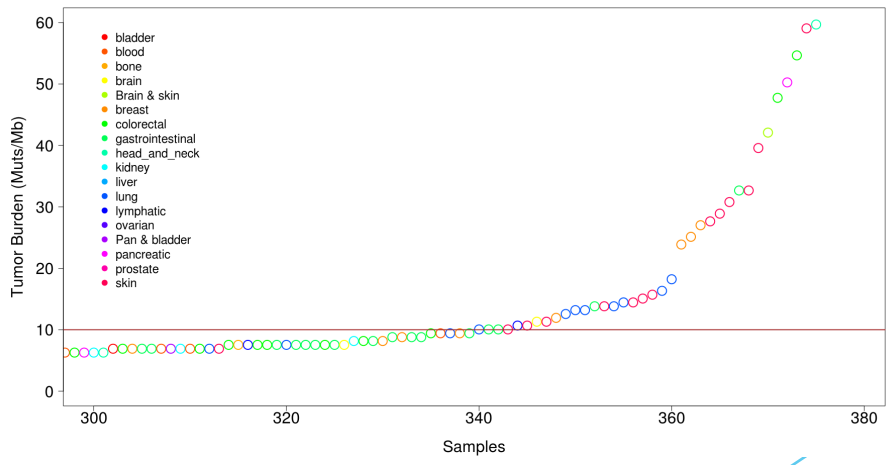
Tumour Burden



High TMB – PAH WES testing



High TMB – PAH WES testing



Case 1
MTB 27.02

- 49 yr old, premenopausal female
- BSQ detected lesion
- Clinically, lesion >4cm. No palpable axillary nodes.
- Bx: Invasive Ca, HER 2 positive.

- PMHx:
  HTN, Hypercholesterolaemia

Case 1 Continued
MTB 27.02

- Pathology of mastectomy/ALND:
  - 45mm invasive carcinoma, NST. 190mm DCIS.
  - 0/29 LN involved
  - Grade 3
  - ER negative, PR negative, HER 2 SISH positive

- Adjuvant TCH

- WES: No clinically actionable somatic mutations identified

Somatic Findings

- TP53 S166* (stop gain) VAF=28.8% COSM44467 (count 14) FATHMM PATHOGENIC (0.984)
- Tumour Purity estimate 37-57%
- Tumour Burden 27 (Muts/Mb) (highest observed so far in breast cancers)
- CNV for Breast Cancer : ERBB2 Whole gene amplification 32 copies

Case 2 Continued
MTB 25.13

- WLE/SLNB
- Path:
  - 15mm Invasive Ductal Ca. Grade 3
  - ER pos (3+, >90%), PR pos (3+, >90%), HER2 SISH neg.
  - Positive margin posteriorly, but excision down to pectoral
- Adjuvant XRT
- Adjuvant hormonal therapy: intolerant of AI and tamoxifen

- WES: No clinically actionable somatic mutations

Case 2
MTB 25.13

- 78 yr female
- Self-palpated L breast lump
- Imaging: 9mm breast lesion. Bx: invasive Ca

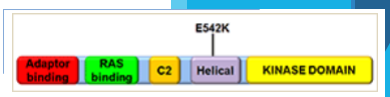
- PMHx:
  - R breast Cancer 2009 (Resected/ Adj XRT/ Adj endocrine not tolerated)

Somatic Findings

- PIK3CA E545K VAF=4.9% COSM763 (count 1708) FATHMM PATHOGENIC (0.973)
- PIK3CA H743R VAF=6.8% VUS – no observed before.

- Tumour Purity estimate 20-40%
- Tumour Burden 25 (Muts/Mb) (second highest observed so far
- No clinically Relevant CNV for Breast Cancer

PI3K E545 IK3CA E545K/E542K are the second most recurrent PIK3CA mutations in breast cancer



Summary

▶PIK3CA E545K action taragetable?
▶Particularly high tumour burden apparent. Actionable in the context of ER+ PR +HER2- ?

Case 3

▶Age 46
▶Patient noticed right breast lump with change in breast shape
▶Mammogram:4cm spiculated mass in LOQ right breast; 2cm mass at 12:00
▶US: 3.7 x 2.8 x 3.6cm mass at 8:00 with skin tethering
▶1.1cm mass at 12:00/8cm - core biopsy = sclerosed fibroadenoma
▶Family History; Negative for breast and ovarian cancer

Examination

- ~5-6cm mass in LOQ right breast with significant distortion and tethering. A few small mobile right axillary nodes(reactive). No left axillary nodes. No supraclavicular nodes. Normal left breast
- Pathology:
  - core biopsy - 9 o clock invasive carcinoma, 12oclock sclerosed fibroadenoma
  - ER 85% 3+, PR 75%, 3+
  - HER negative

- R axillary LN FNA - monoclonal B cell population ? B cell small lymphocytic lymphoma

- Procedure : SLNB July
- Pathology: morphologically normal cells but flow cytometry consistent with CLL & Isolated tumour cells
- PET scan negative
- Haematology – plan for observation of CLL
- Neoadjuvant chemotherapy – Doxorubicin, Cyclophoophomide, Paclitaxel – 7 cycles
- Nil clinical or radiological response on repeat USS so proceeded to Mastectomy
- Mastectomy & axillary sampling

- Pathology; 45mm & 2mm
- 0/4 LNs
- No treatment effect
- No LVI
- Rec ++-
- Post op Radiotherapy - 50Gy/25#s to R CW
- Endocrine Rx
  - On Tamoxifen
  - Plan to swap to AI at 2 yrs

Somatic Findings

- PIK3CA R357Q VAF=14% COSM276751 (count 6) FATHMM PATHOGENIC (0.993)
- PIK3CA H1047R VAF=14% COSM775 (count 2300) FATHMM PATHOGENIC (0.961)
- ERBB2 D769H VAF=28.6% COSM13170 (count 4) FATHMM PATHOGENIC (0.993)

- Tumour Purity estimate 23-43%
- Tumour Burden 9.4 (Muts/Mb)
- No clinically Relevant CNV with Breast Cancer

ERBB2 in HER2+ cancers: rare 1.6-2%

Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov. 2013 Feb;3(2):224-37*

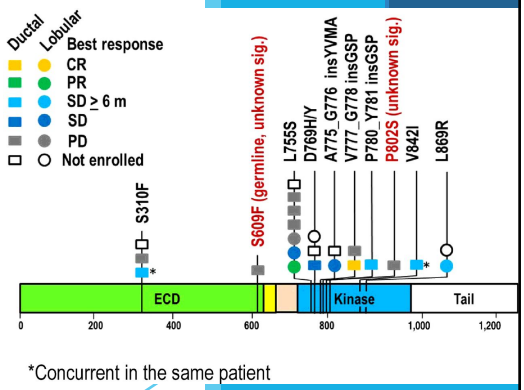
HER2 L755S mutation is a known lapatinib resistance
D769H activated HER2 (increased dimerization)

Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer

Ma et al., 2017, Clin. Cancer Res.

Metastatic breast cancer treated with neratinib monotherapy. Five of the 16 patients achieved clinical benefit including 1 complete response (6%), 1 partial response (6%) and 3 with stable disease >24 weeks (19%). ctDNA contain ERBB2 mutation was reduced.

Frequency lobular 7.8% vs. ductal 1.6%;



PIK3CA finding

- ▶PIK3CA H1047R higly recurrent SNP variants in cancer,
- ▶Especially common breast cancer – accounts for >50% of PIK3CA cases
- ▶Studies inconclusive
  - ▶Meta-analyses - patients positive H1047R worse overall survival
  - ▶Other studies have shown no difference between H1047R and other PIK3CA mutants in terms of prognostic significiance.
  - ▶Targeted therapies for this particular variant are common but still in early clinical trial phases.

▶PIK3/mtor inhibitor in the future?

Discussion

- Most relevant
- PICK3A activation, ERBB2 activation, High Tumour Burden