Queensland Molecular Tumour Board

9th Oct 2019
Room 2004, TRI, Princess Alexandra Hospital,
Woolloongabba, QLD

Clinical Trial finding PA Cohort studies

Methodology:

Match Molecular Mutations to ascertain relevant clinical trials

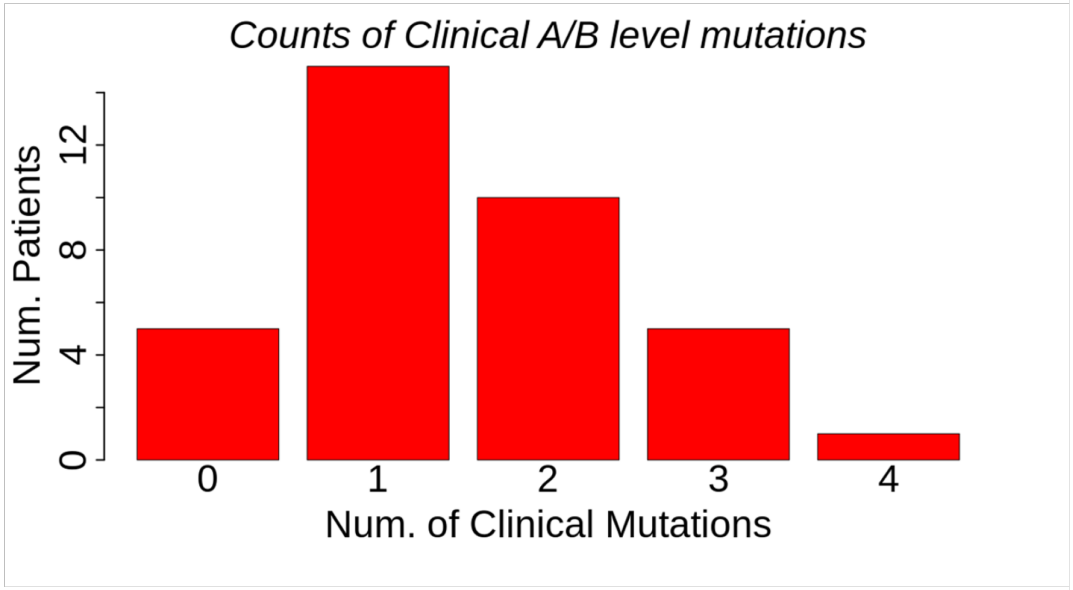
Matching can be done at gene and/or mutation level

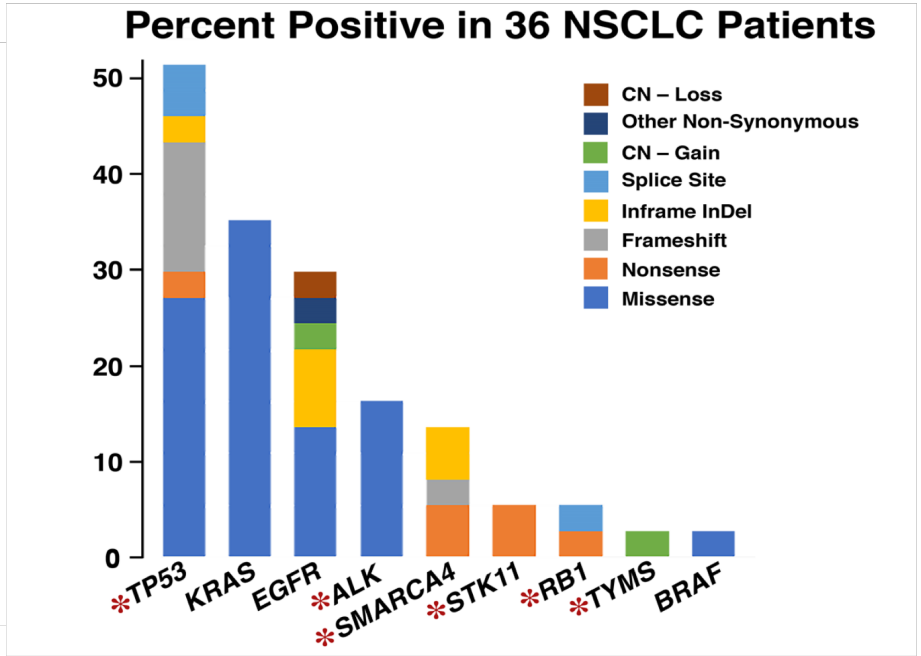
As some somatic mutations maybe be just passengers
Examples
PIK3CA mutated
PIK3CA:p.H1047R (well know activating mutation, appears 2300 times in TCGA cancers)
PIK3CA:p.A345T (mutation never seen in TCGA cancers, unknown significance)

Match with Gene and protein level is preferred!

Examples for PA sequencing Experience in Lung cancers – Data Presented at WCLC 2019 :

N=36 patients. From eBUS and FFPE samples a relevant mutation was found in most samples
There were a variant of different types:





O'Byrne et.al The Clinical Utility and Performance of Whole-Exome Sequencing for NSCLC Patient Care: A Comparison to Standard-of-Care WCLC Poster 2019

Matching at the gene /mutation level, recruiting Australian clinical trials:
(they excluded TMB as an immunotherapy biomarker- 11 out of 36 had a high TMB)

24 % of lung cancer patients matched clinical trails in routinely tested gene *EGFR, KRAS, NRAS, or BRAF* were used

41% is samples could be match if the other large panel gene were included trails below

Gene	Mutations Detected	e.g. Clinical Trial Eligibility (Australia)
ATM	Ser1250Phe, Leu1465Phe, Ser2812ValfsTer3	NCT03330405
BRAF	CN – GAIN	NCT02974725
BRCA1	Arg959Lys	NCT03330405
BRCA2	CN – LOSS	NCT03330405
CDKN2A	CN – LOSS	NCT02857270
CDKN2B	CN – LOSS	NCT02857270
EGFR	CN – GAIN	NCT03974022
FGFR2	Arg61Cys	NCT02052778
MET	CN – GAIN	NCT03539536
NTRK1	CN – GAIN	NCT02568267
PTEN	CN – LOSS	NCT03330405

Examples
Preliminary results for Renal cancers :

In n=30 patients there are no Australian clinical trails specific to RCC
and specific molecular biomarker

There were clinical trials for patients with
“advanced or Metastatic cancers targeting pathways involved in mutation in:
MSH6, SK11, SMARCB1, BRCA2,
TSC1, FBXW7, EGFR, CDK12 , NRAS, BRAF

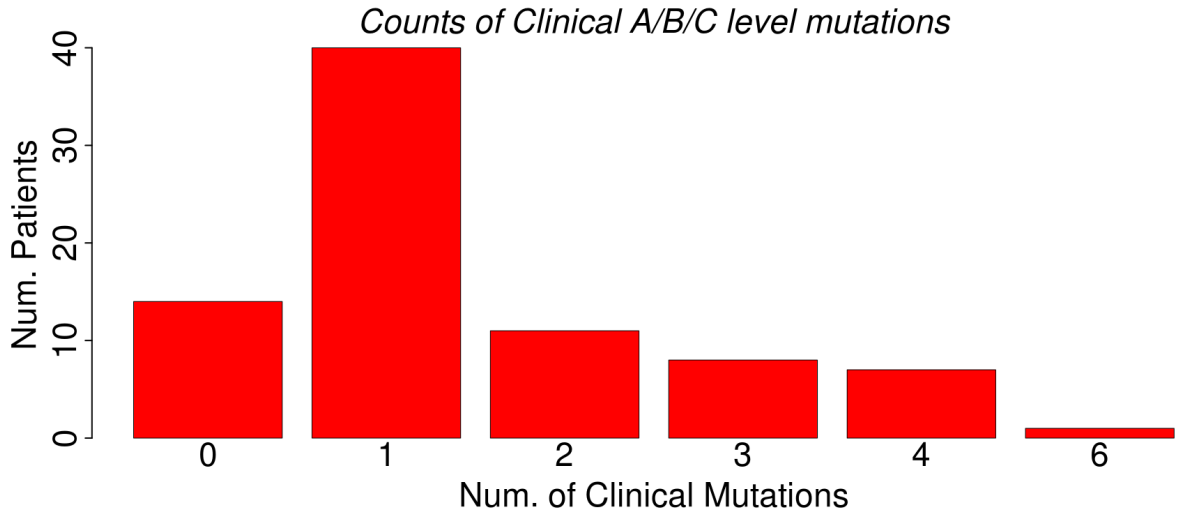
OF which ~ 30% of patients has a mutation

Handoo et al, under preparation

Breast cancers – A similar analysis is underway:

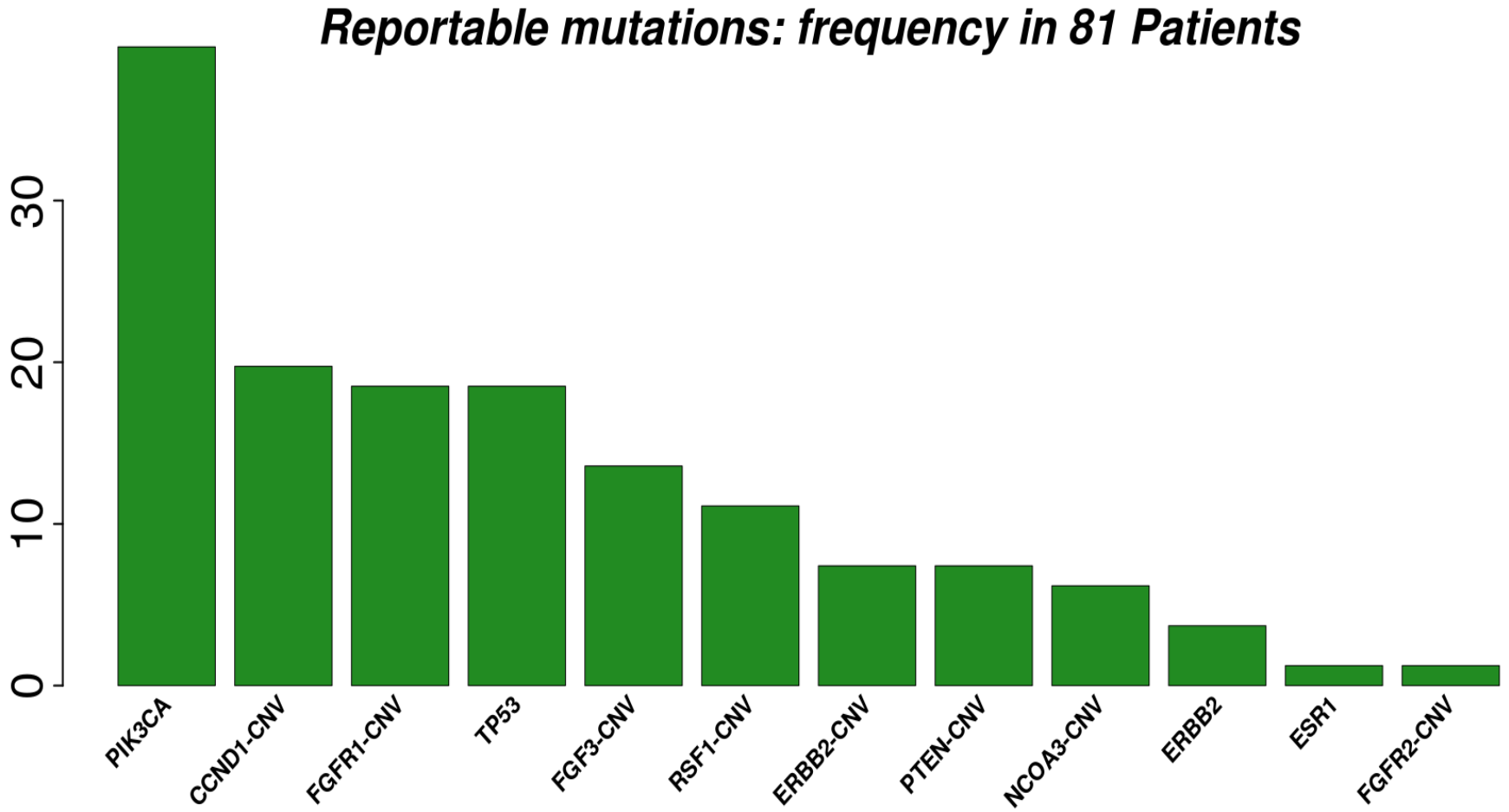
N=81. On average 1.5 somatic variants (Level A-C described in large clinical trails):

ABCC3, AKT1, CCND1, CCNE1, CDKN2A,
ERBB2, ESR1, FGF3, FGFR1, FGFR2, MTOR, NCOA3, NF2,
PIK3CA, PIK3R1, PTEN, RB1, RSF1, SF3B1, TP53



Roberts et.al . Establishing whole-exome sequencing for Breast patient care SABCS 2019 Poster accepted

In Breast Cancer Copy number loss and amplifications are more important

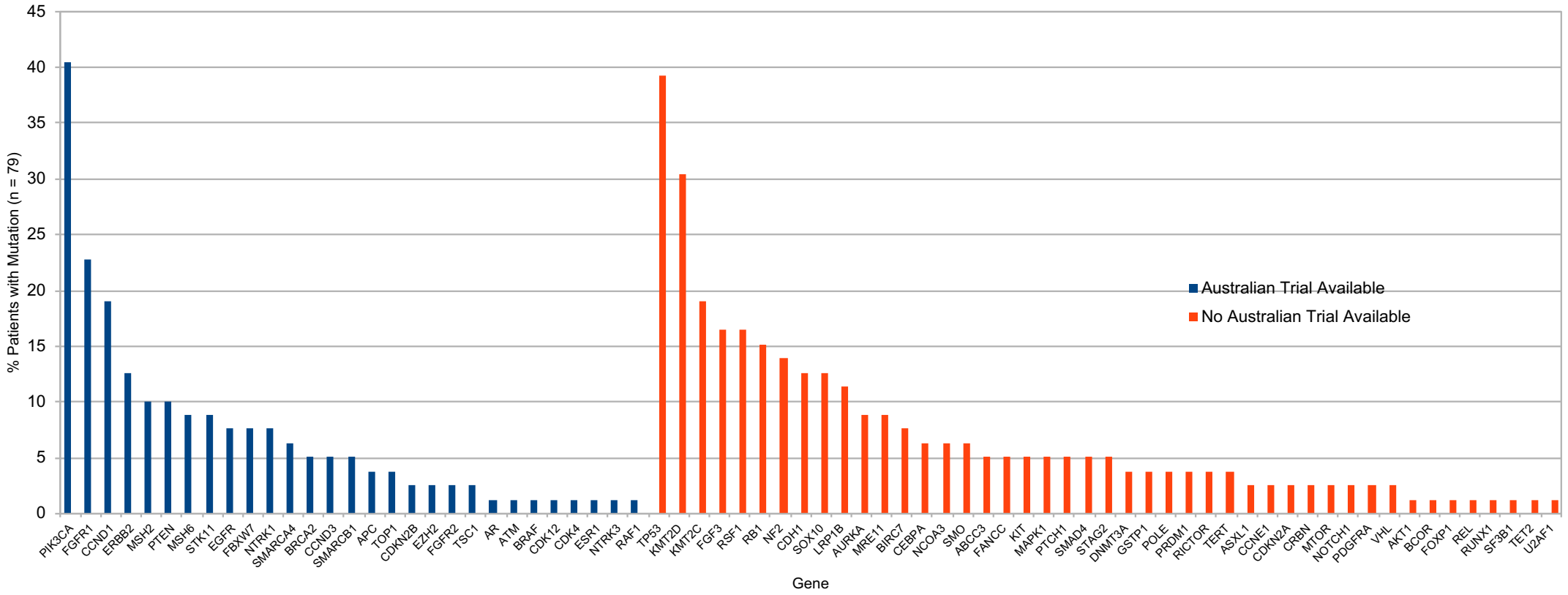


Matching at the gene mutation level

- What trials might capture the largest % of the cohort?
- What are the unmet needs?
- What genes are the most informative?
- Does the profile assist in directing to the most relevant clinical trial?

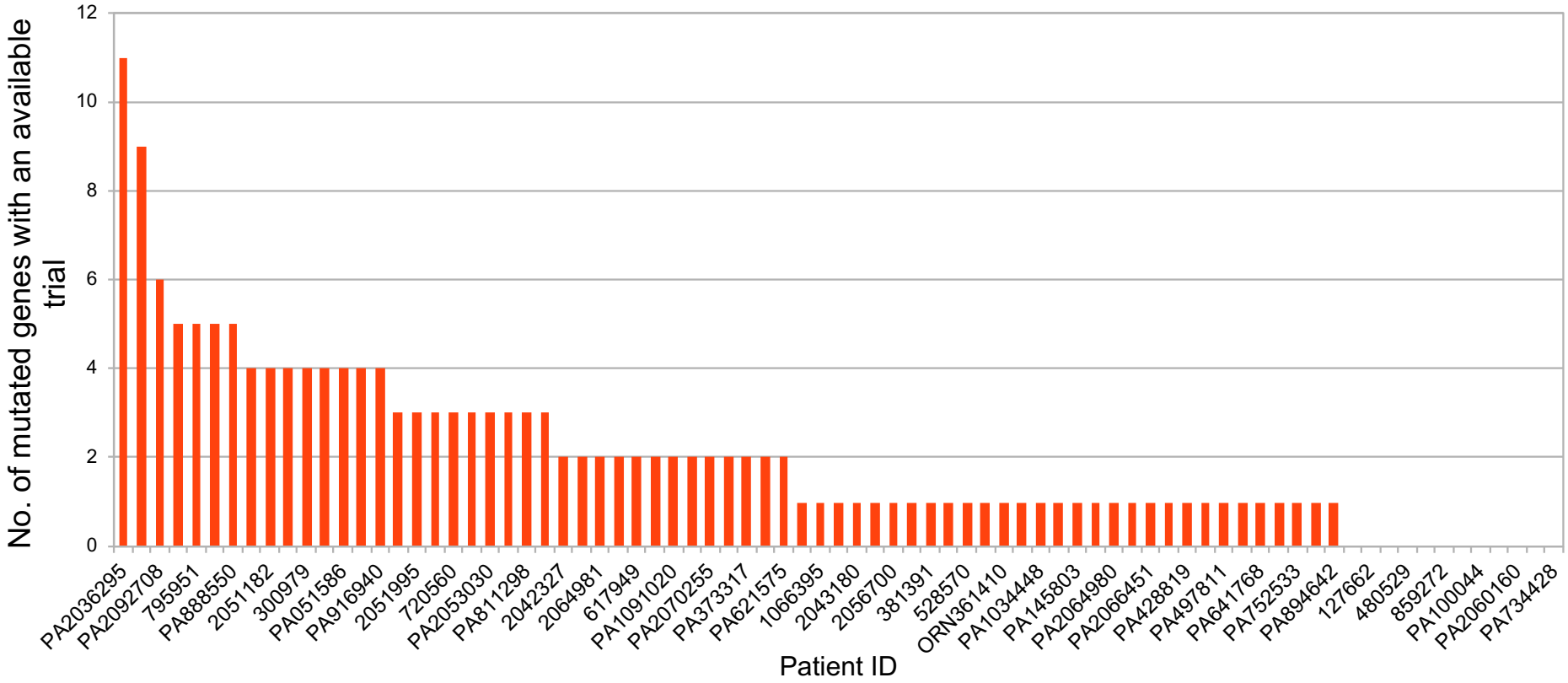
A clinical trial matching tool: *molecular match* was used to assign clinical trials based on molecular profiling reports:
https://app.molecularmatch.com

By taking into account all mutations that might be informative for clinical trails we identify other genes /mutations in these patients:



85% patient had mutations which could potentially be linked to a clinical trial

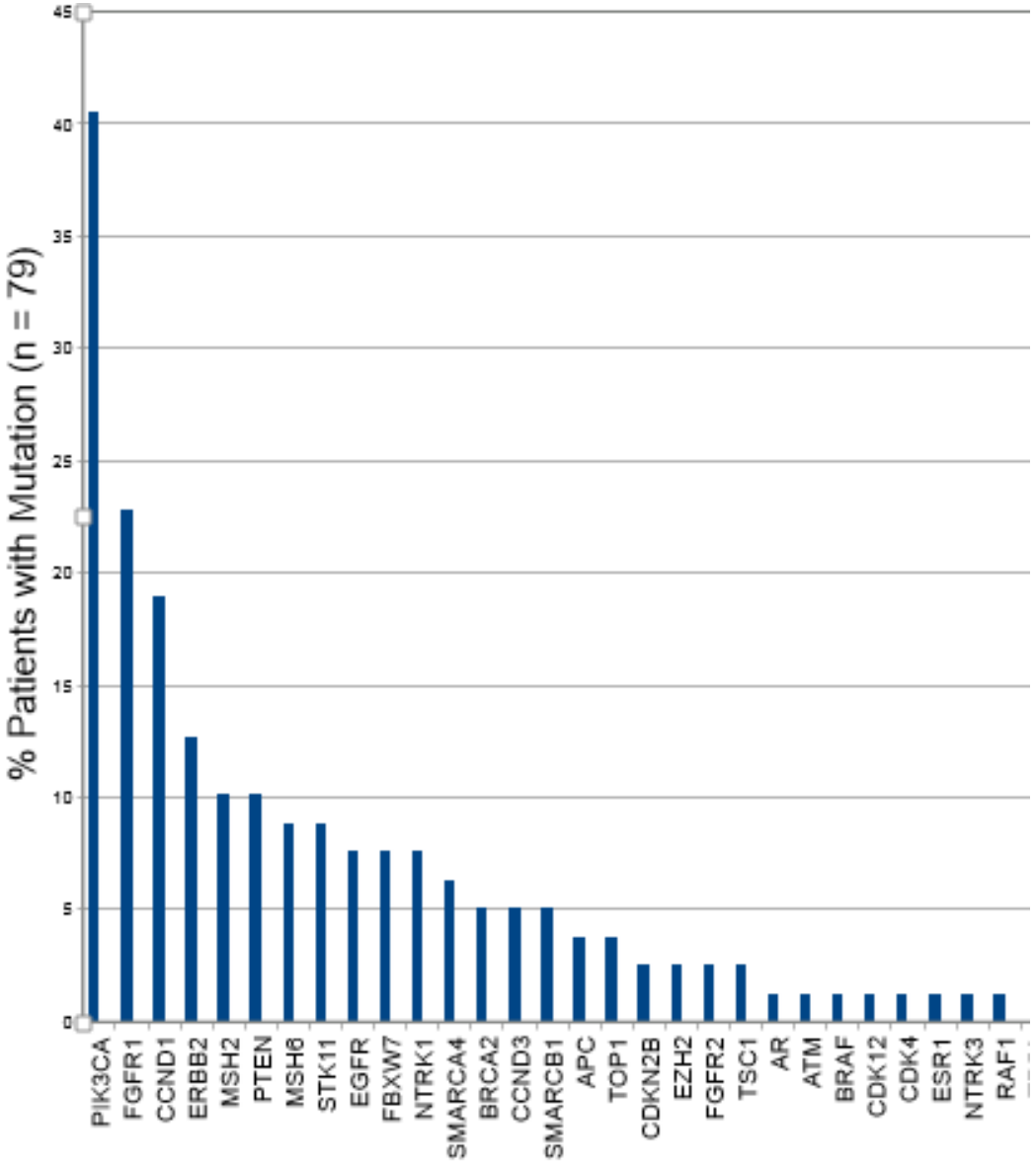
- Some had >1 relevant mutation



The improvement from 77% to 85% came from genes not typically reported for Breast Cancer . But are relevant to trials in metastatic cancer that are accessible to Breast Cancer Patients

Examples

FGFR1 : 22 patients
SMARCB1/EZH2 : 5 patients



Molecular Tumor Board

Suggested strategy: Discuss relevant trials using quick approach utilizing all variants in metastatic patients

Include those of well established clinical utility and those that match to clinical trails in metastatic cancers

UR: [redacted]
DOB: [redacted]
ER.PR.HER.2: 60%/60%/neg
T3N1M1 Grade 3 De novo Met

Gene	Mutation	Trial?	No Trails	Trials	Drugs
CCND1	6x	yes	2	NCT02107703, NCT03701334	Abemaciclib + Fulvestrant
CCNE1	23x	no	0		
FGF3	6x	no	0		
FGFR1	23x	yes	1	NCT02052778	TAS-120
PIK3CA	p.Glu545Lys	yes	1	NCT03337724	Ipatasertib, Paclitaxel
RSF1	7x	no	0		
TP53	p.Arg213Ter	no	0		

Clinical Trial Discussion:

PIK3CA.p.G545L:

NCT03337724 ; A Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Participants With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer (Phase 3 local)

CCND1 6x

NCT02107703 - A Study of Abemaciclib (LY2835219) Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer (Phase 3 local)

NCT03701334 - A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer

NCT02052778 - A Study of TAS-120 in Patients With Advanced Solid Tumors

FGFR1 23x

NCT02052778 - A Study of TAS-120 in Patients With Advanced Solid Tumors (NSW only)