Development of new targeted agents for TNBC

Dr Nicholas Turner

ESMO 2012

The Royal Marsden NHS Foundation Trust

ICR The Institute of Cancer Research 1909 2009

Relevant disclosures

Honoraria and/or Research funding

Novartis
AstraZeneca
Clovis
EOS
Tesaro

Therapeutic strategies for TNBC

- Common genetic events
- Targeting TNBC subtype specific features
- Rare targetable oncogenic events
  - Discussed by Lajos Pustzai

Research article

Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies

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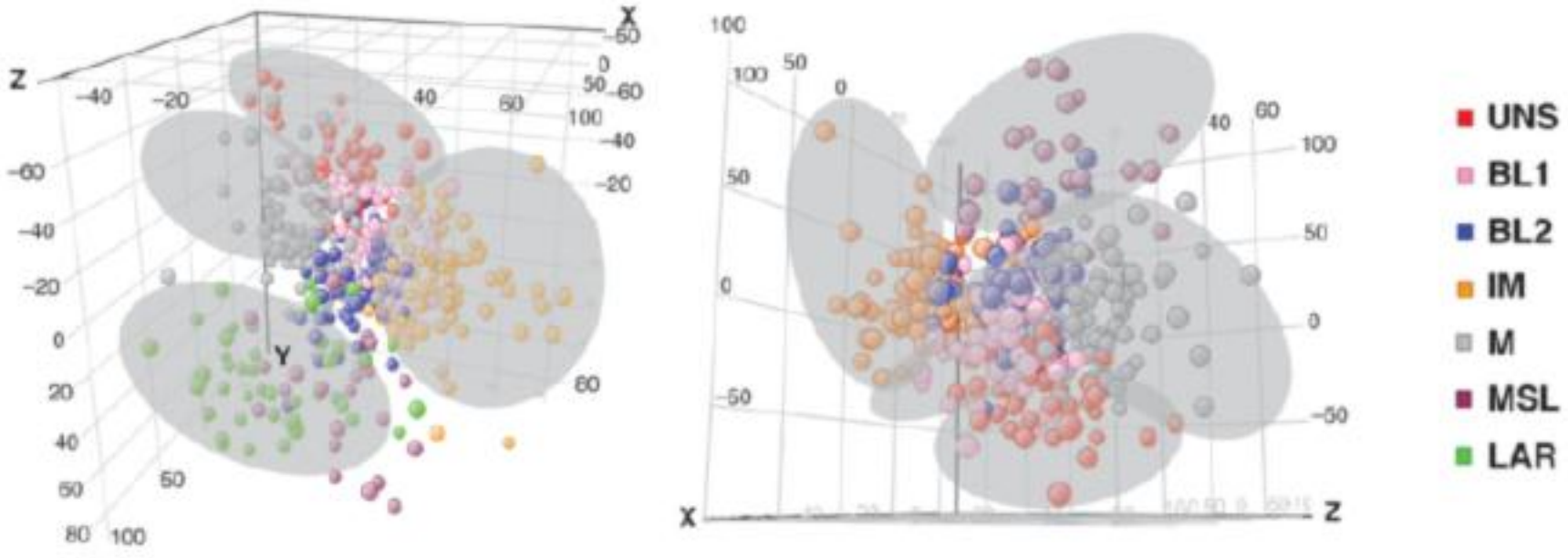
21 publically available gene expression data sets
587 TNBC



Subtypes of Triple negative breast cancer

Basal-like 1 and 2

Immunomodulatory

Mesenchymal-like

Luminal-AR

Subtypes of Triple negative breast cancer

Basal-like 1 and 2

Immunomodulatory

Mesenchymal-like

Luminal-AR

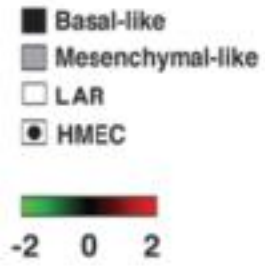
Basal-like

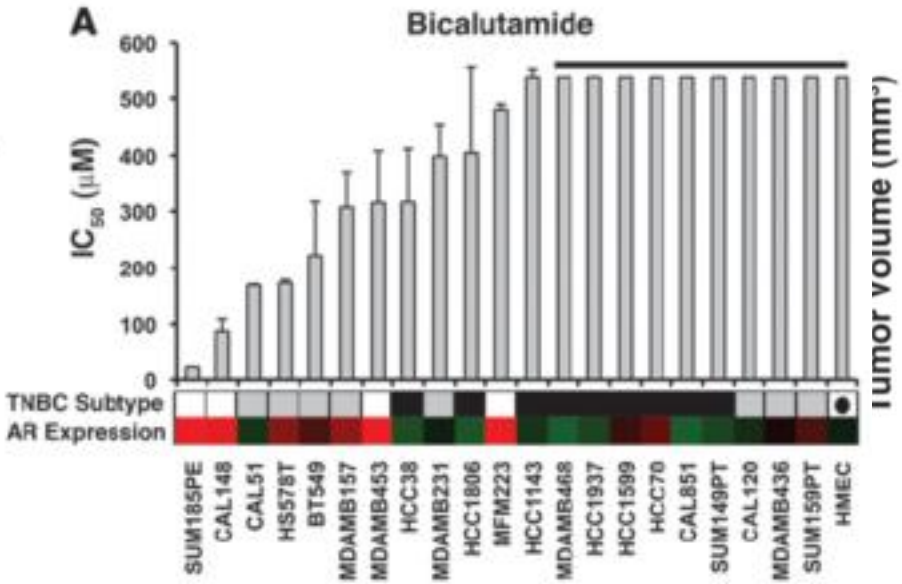
Luminal AR cell lines

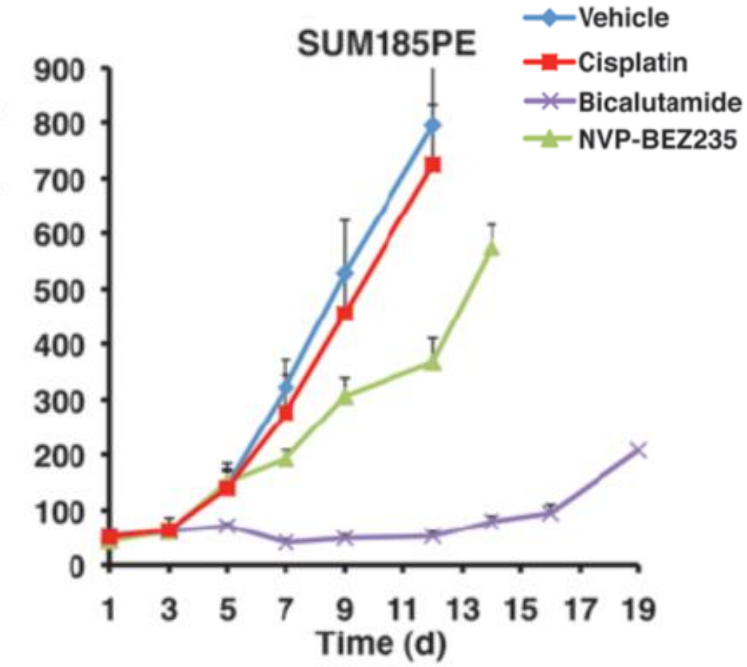
Express androgen receptor

Sensitive *in vitro* to Bicalutamide

High frequency of *PIK3CA* mutations







Targeting the androgen receptor (AR) in women with AR+ ER-/PR- metastatic breast cancer (MBC)

ER/PR negative (<=10% by IHC) but AR positive (>10% IHC)

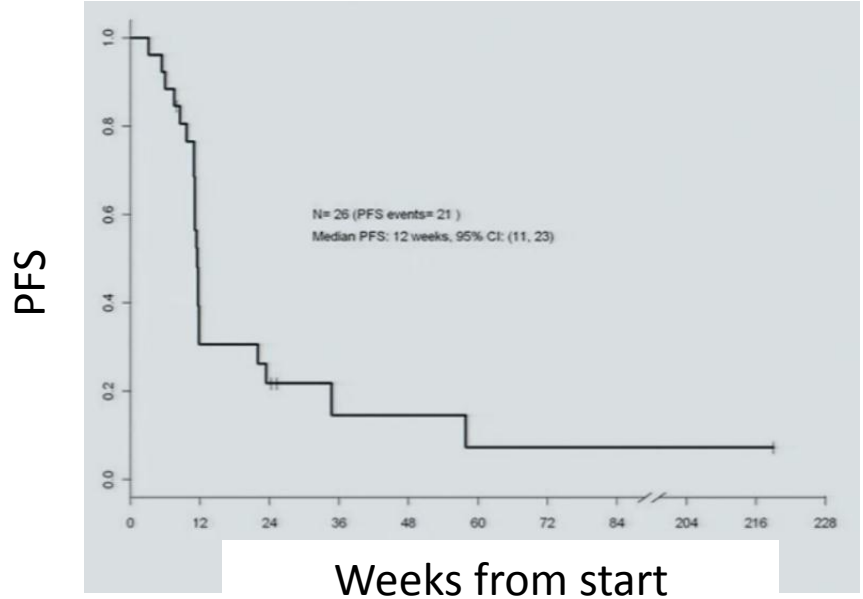
Bicalutamide 150mg qd

Screened 424 patients 12% AR positive – 28 treated on study

0% Response rate

21% (5/24) stable disease >6 months

Trials with Abiraterone and Enzalutamide ongoing



Gucaip et al ASCO 2012

Subtypes of Triple negative breast cancer

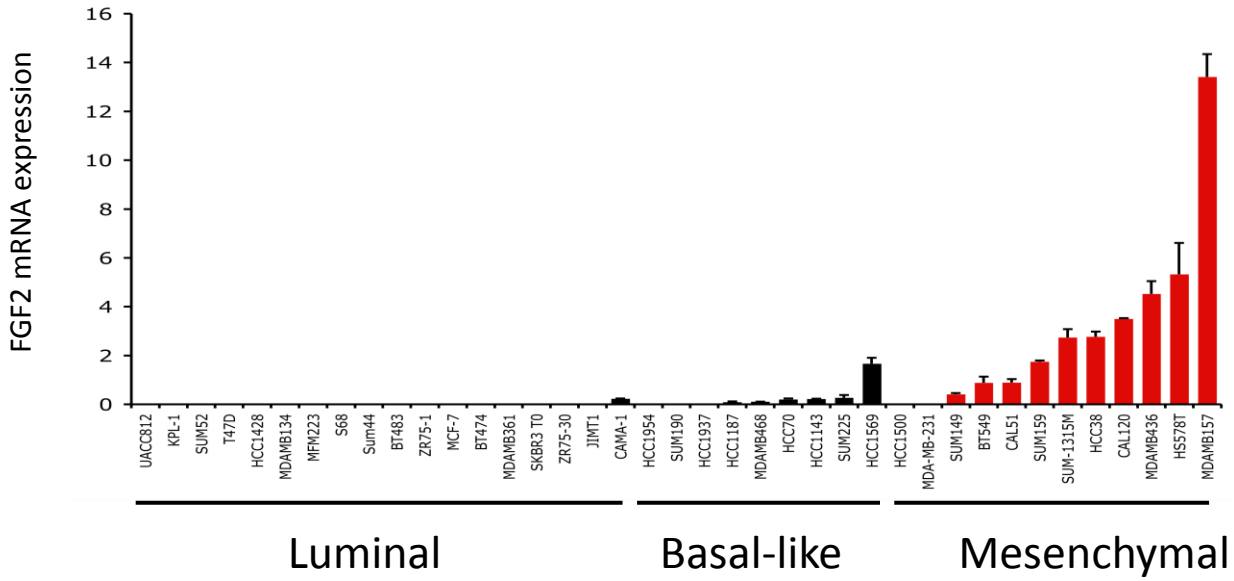
Basal-like 1 and 2

Immunomodulatory

Mesenchymal-like

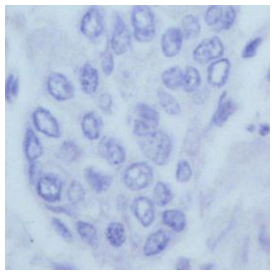
Luminal-AR

FGF2 expression in TN mesenchymal-like cell lines

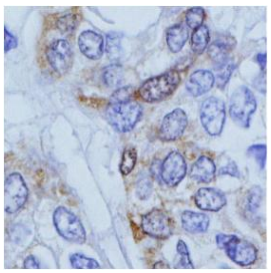


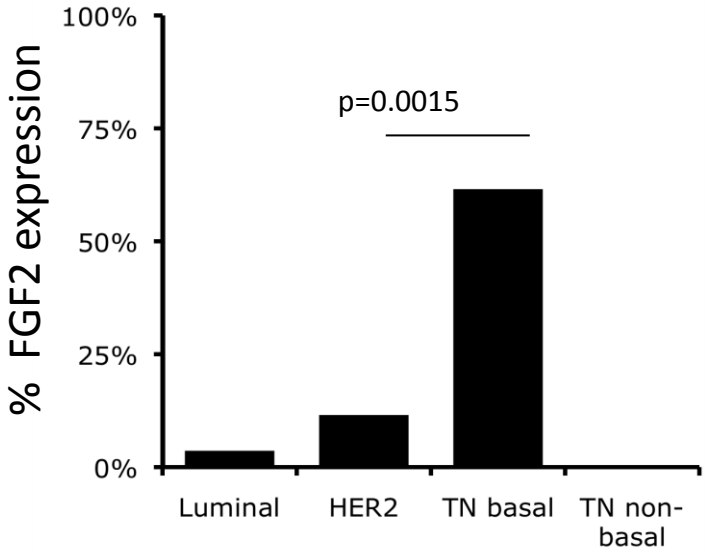
FGF2 IHC

Negative



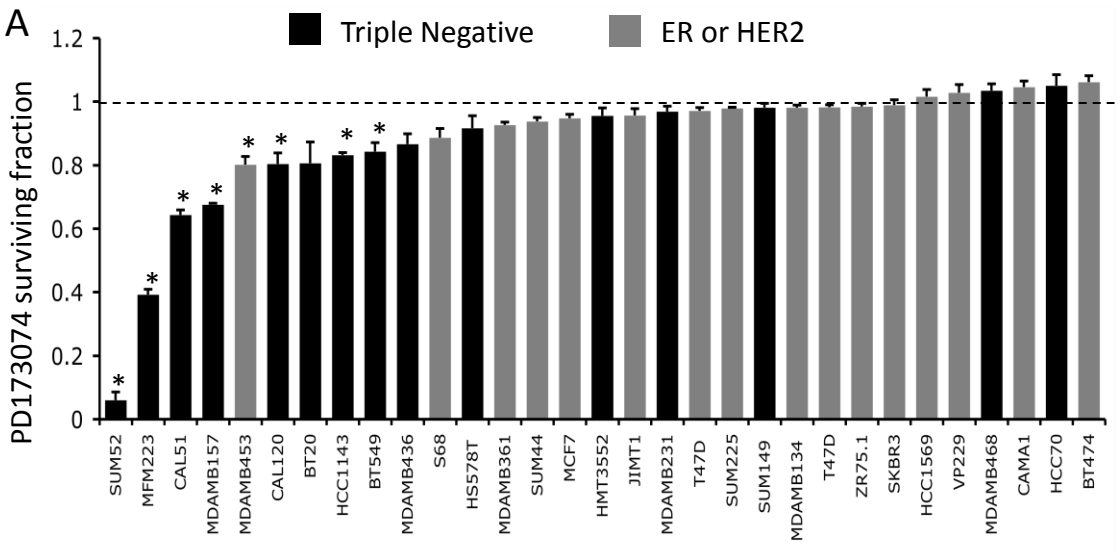
Positive

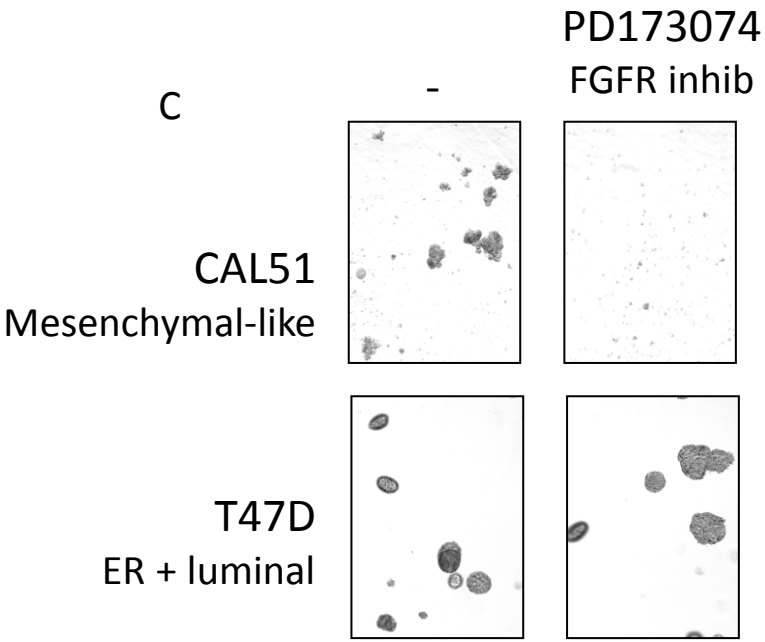


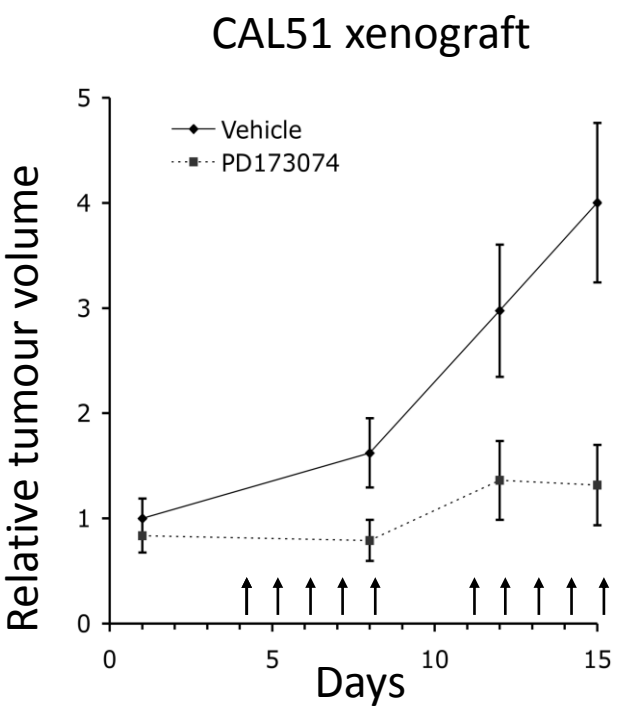


Sharpe et al CCR 2011

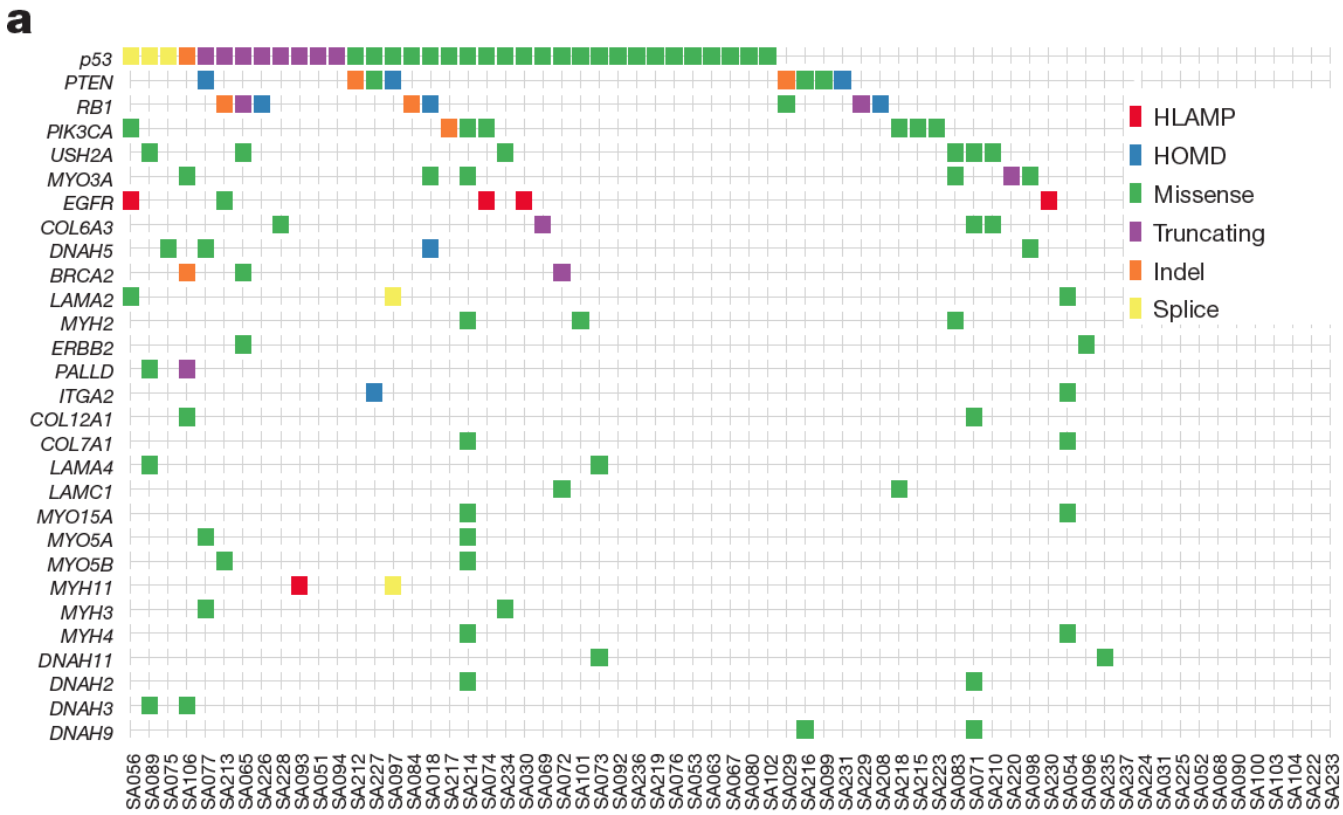
FGF2 cell lines are sensitive to an FGFR inhibitor







TN breast cancer - common genetic events?



Shah et al Nature 2012

Common genetic events

~75% Mutation *TP53*

~40% Myc amplification

~20% Mutation/loss RB

~15-20% Mutation of *BRCA1 or BRCA2*

TCGA Nature 2012

BRCAness in TN breast cancer

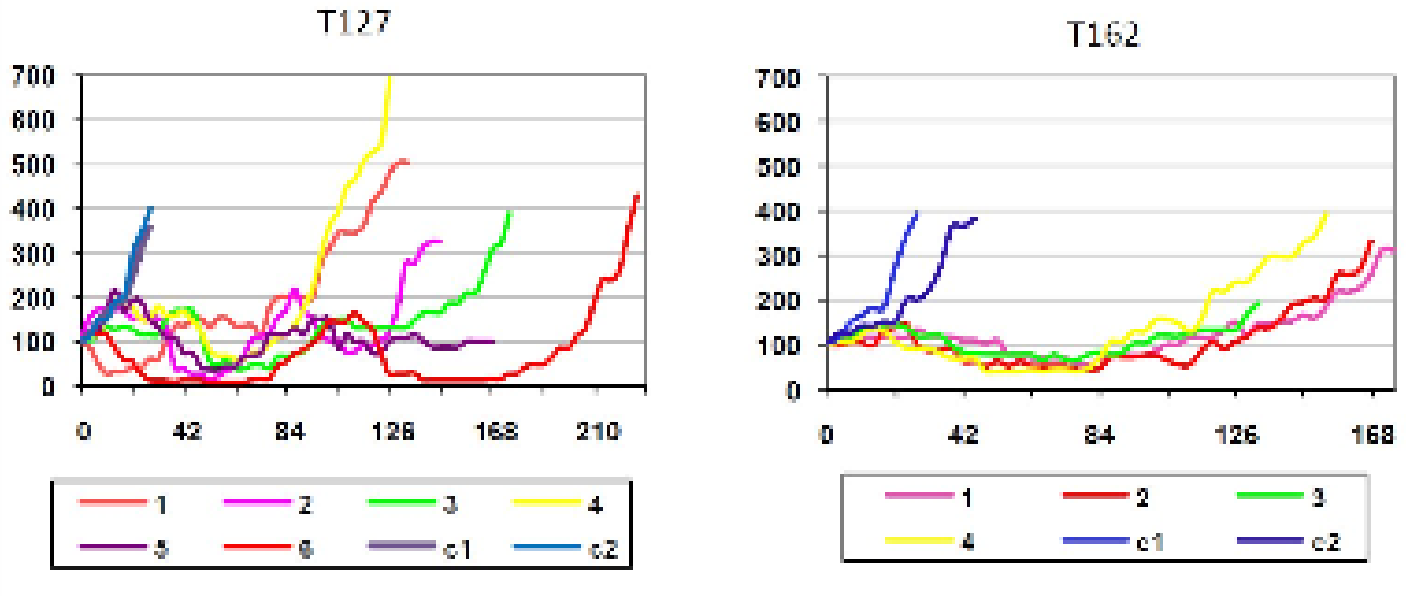
BRCA1 and *BRCA2* mutated in ~15-20% cancers
~60% germline and ~40% somatic

Shah et al Nature 2012, TCGA Nature 2012

BRCA1 promoter methylation in ~15%

Turner et a Oncogene 2012

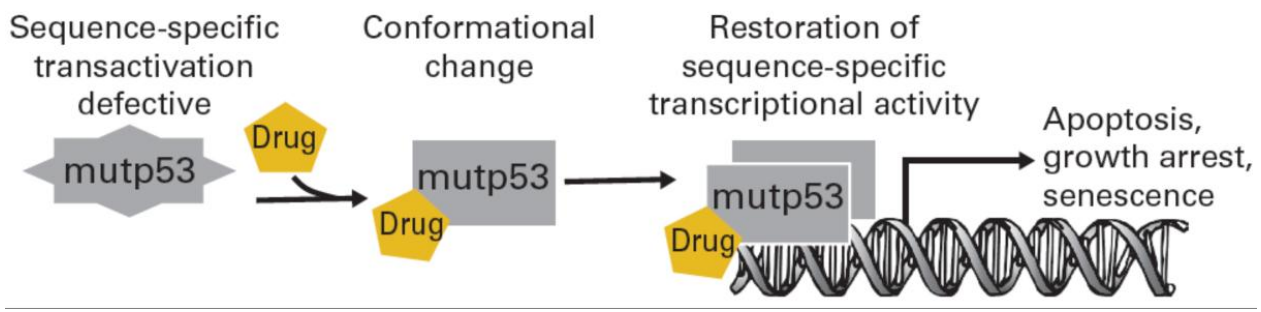
Sensitivity of *BRCA1* methylated primary xenografts to olaparib



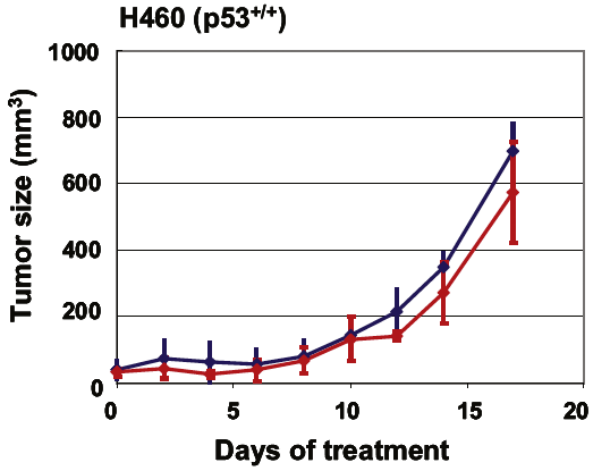
SABCS 2011 Jos Jonkers NKI

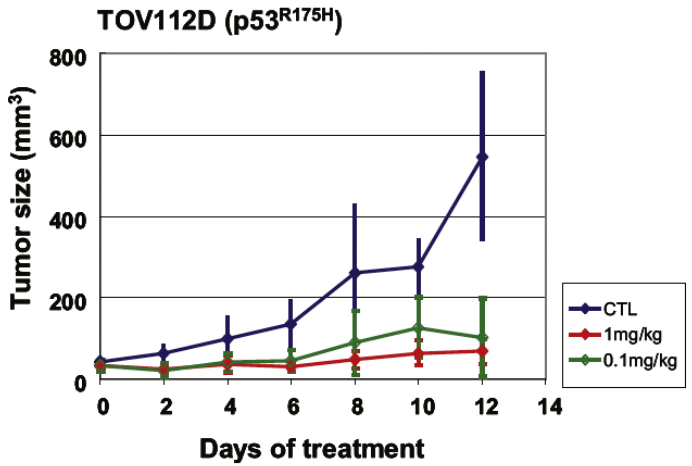
Like all targeted therapies selection is the key

Restoring activity to mutant *TP53*



Lehman and Pietenpol JCO 2012





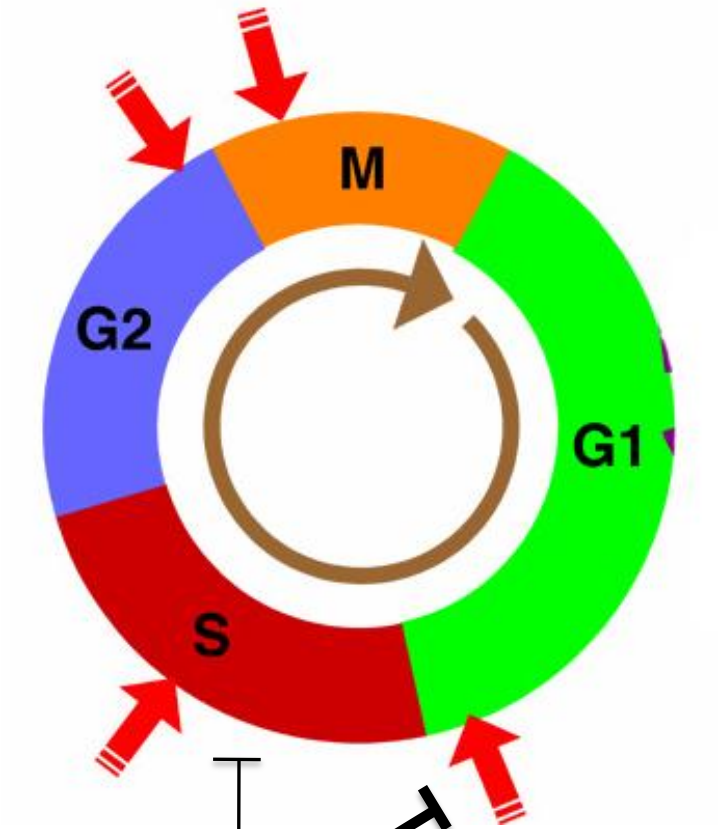
Yu et al Cancer Cell 2012

DNA damage checkpoints

TP53 wild-type

Spindle checkpoint

G2-M

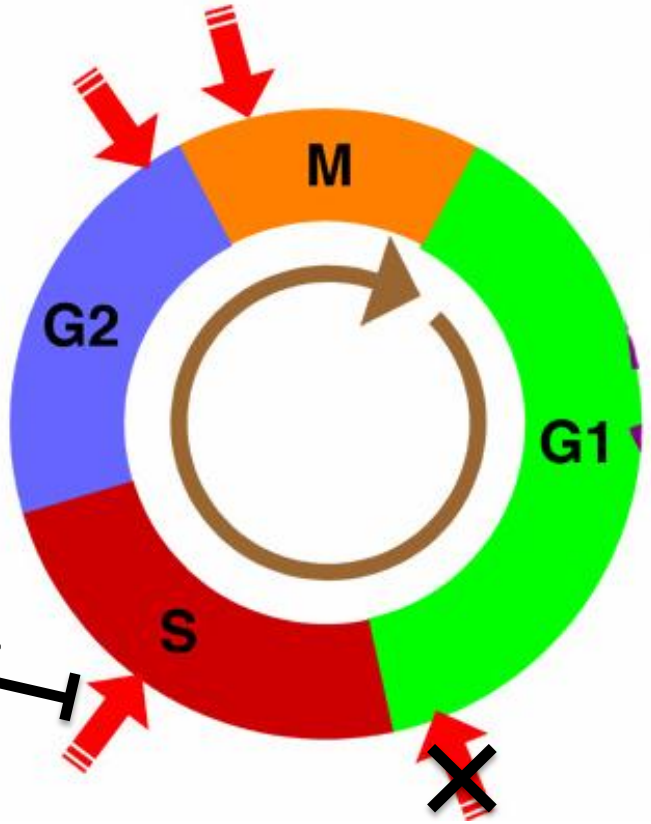


S phase

TP53 mutant

Spindle checkpoint

G2-M

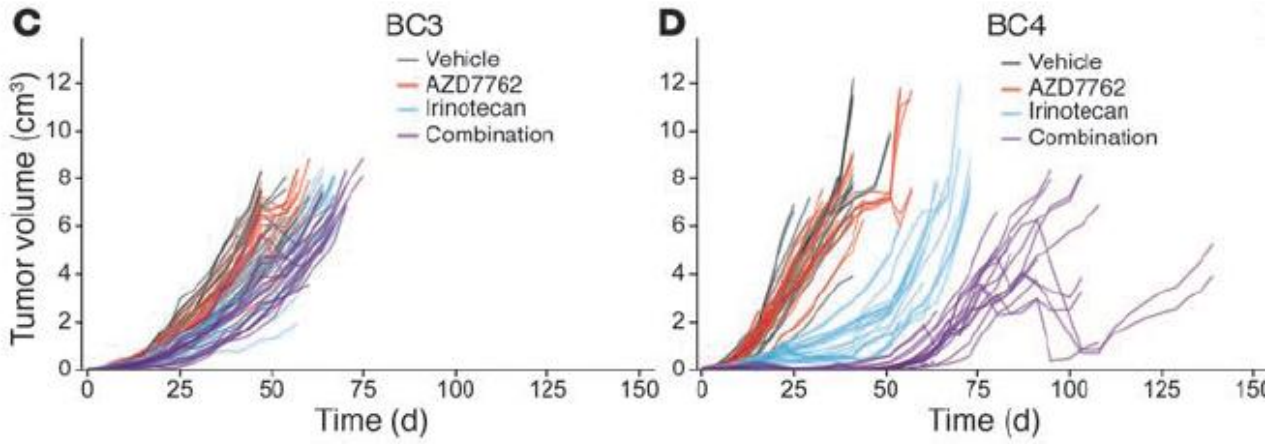


S phase

Targeting cell cycle defects of *TP53* TN breast cancer

TP53 mutant cancer cells rely on *Intra-S phase and G2/M checkpoint m*ediated by ATR-CHK1 access

CHK1 inhibitors sensitize *TP53* mutant cancers selectively to chemotherapy



TP53 wildtype

TP53 mutant

Ma et al JCI 2012

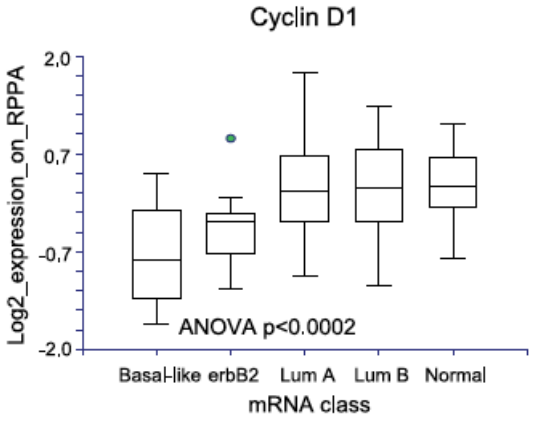
Preliminary evidence of efficacy in TNBC in phase 1 trials

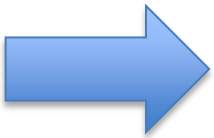
Problems with tolerability

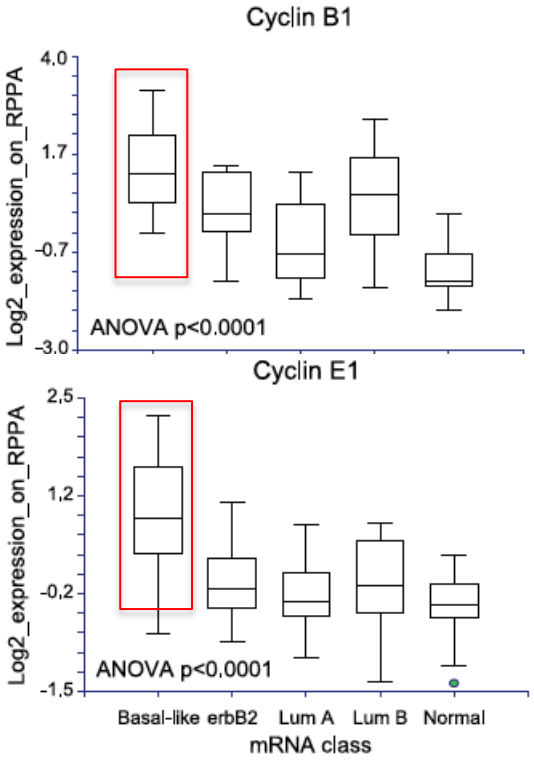
Fracasso et al CCP 2011

Basal-like cancers - primed for mitotic entry

Basal-like cancers use cyclin E and mitotic cyclins to drive proliferation







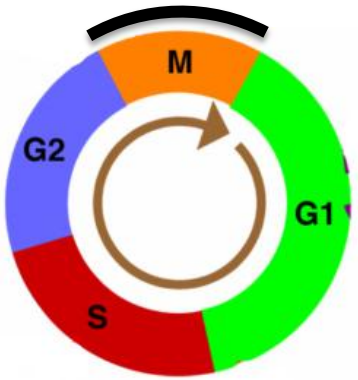
Agarwal et al CCR 2009

Driven by FOXM1 transcription factor

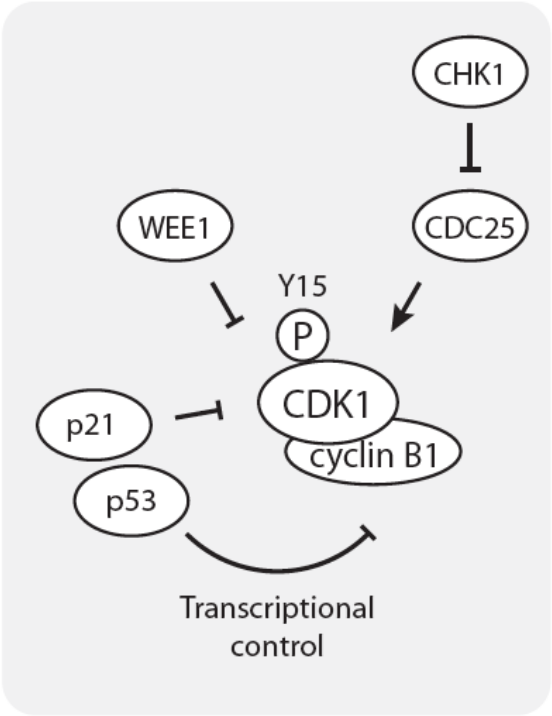
TCGA Nature 2012

Basal-like cancers - primed for mitotic entry

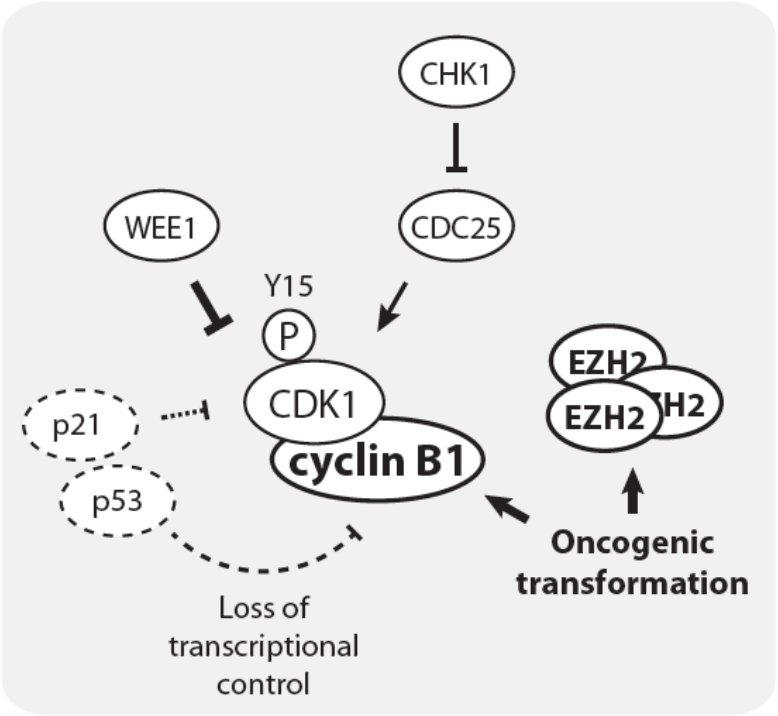
CDK1 active



Normal



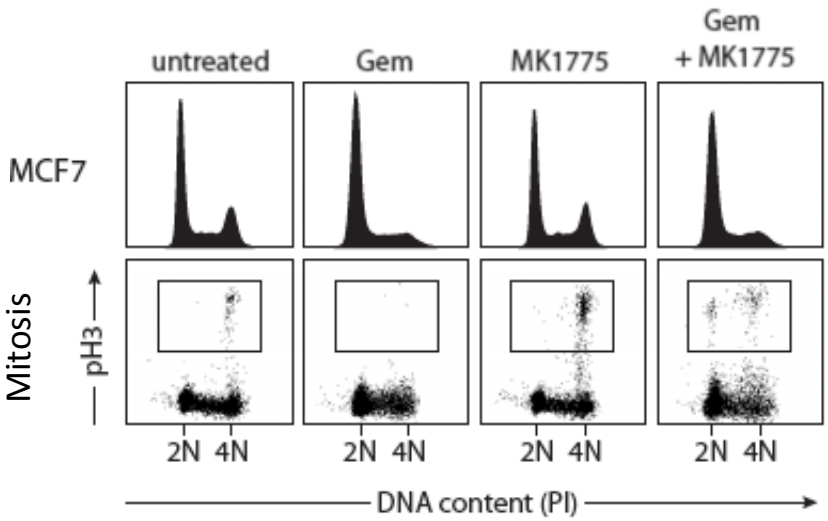
TP53 basal



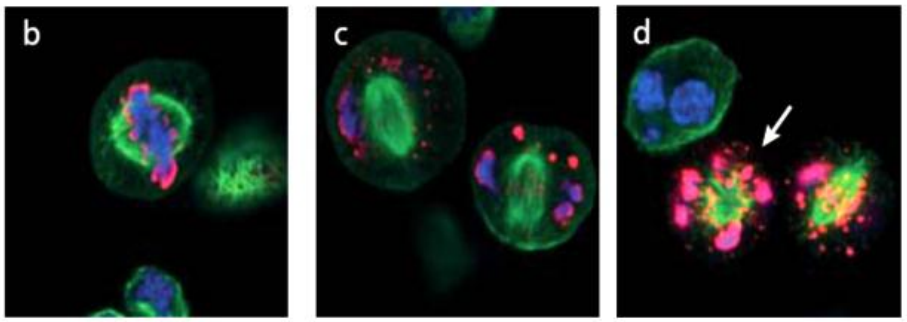
M Aarts *et al* Cancer Discovery 2012

WEE1 inhibition forces premature mitotic entry

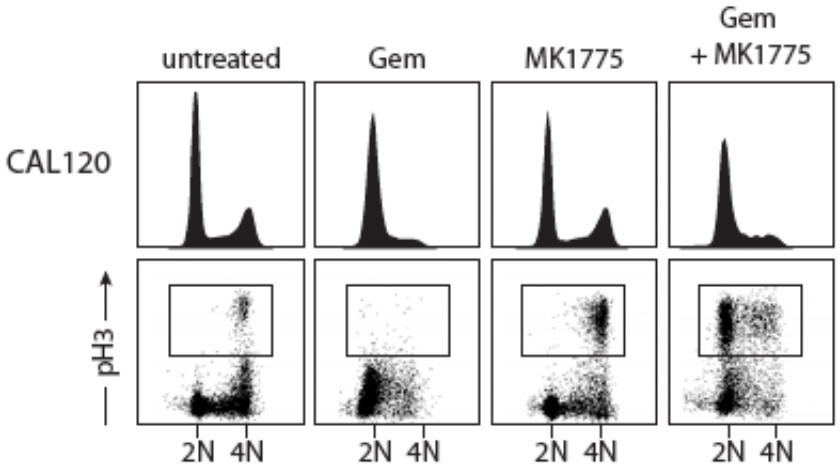
TP53 wild type



Control Gem-WEE1

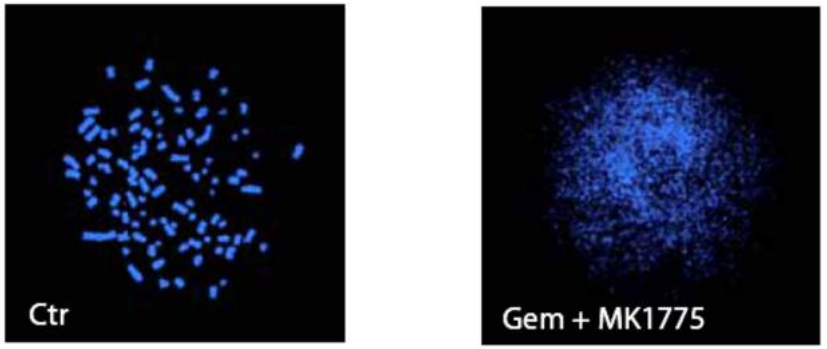


TP53 mutant



Chromosome spreads

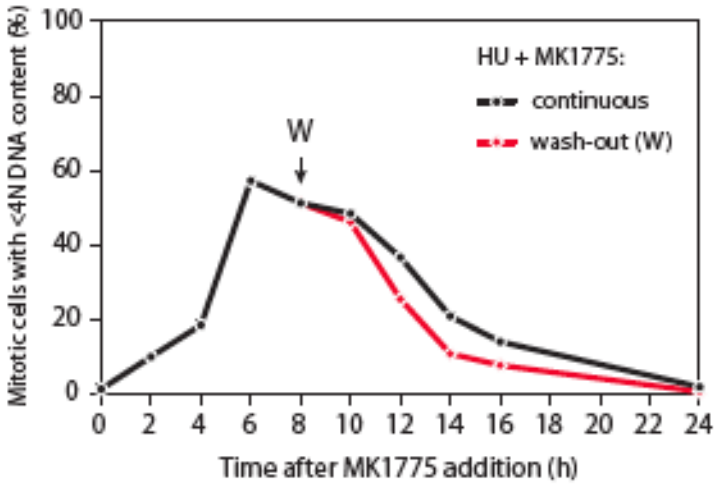
Control Gem-WEE1



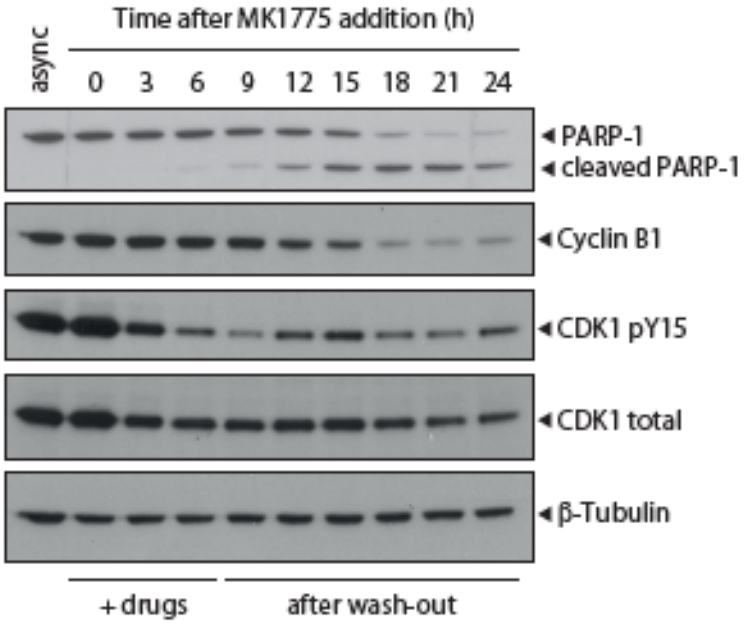
M Aarts *et al* Cancer Discovery 2012

WEE1 as a therapeutic target in *TP53* mutant breast cancer

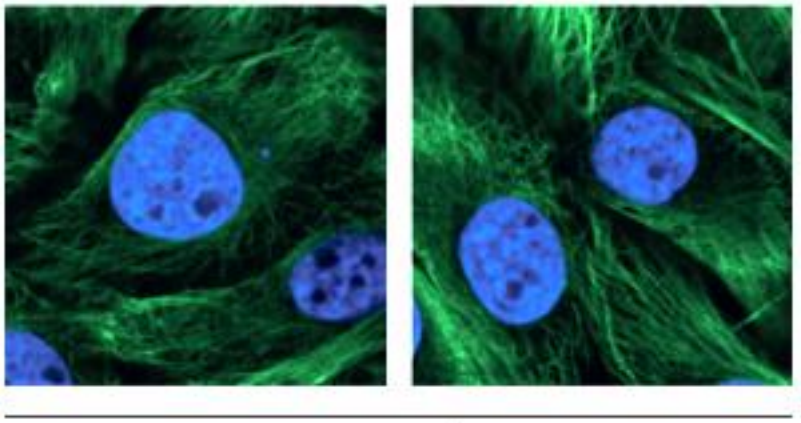
B



C

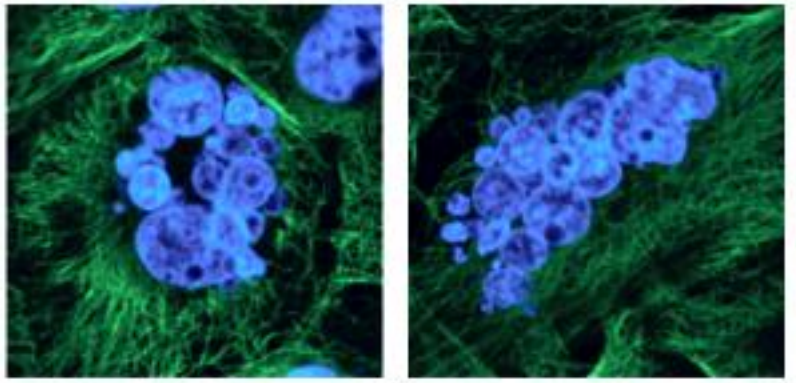


Untreated



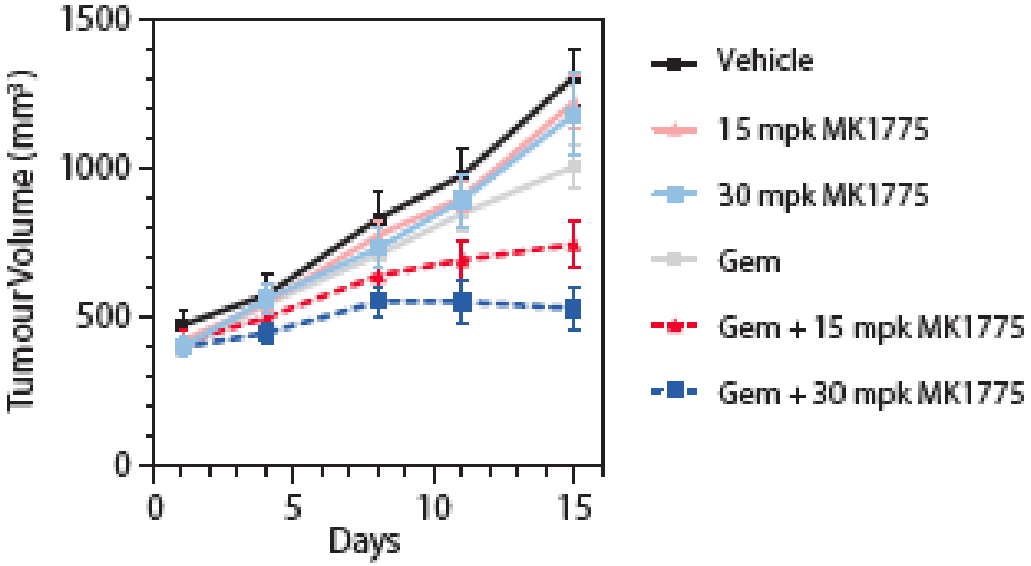
normal

Post forced mitosis

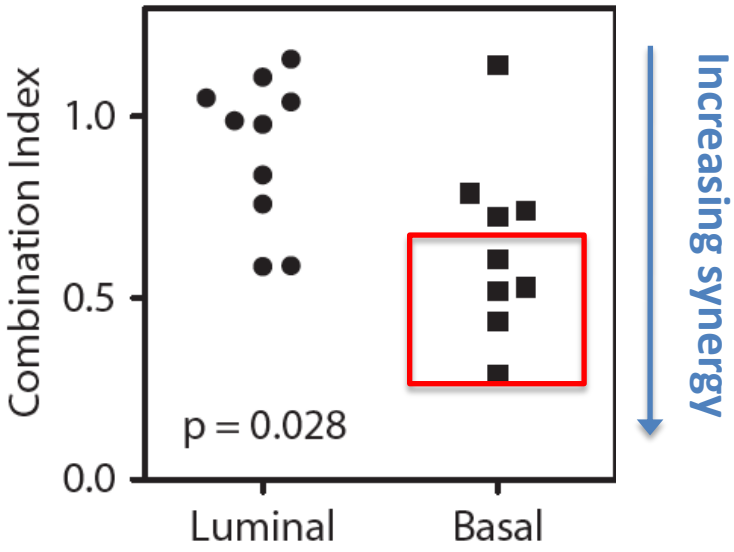


micronucleated

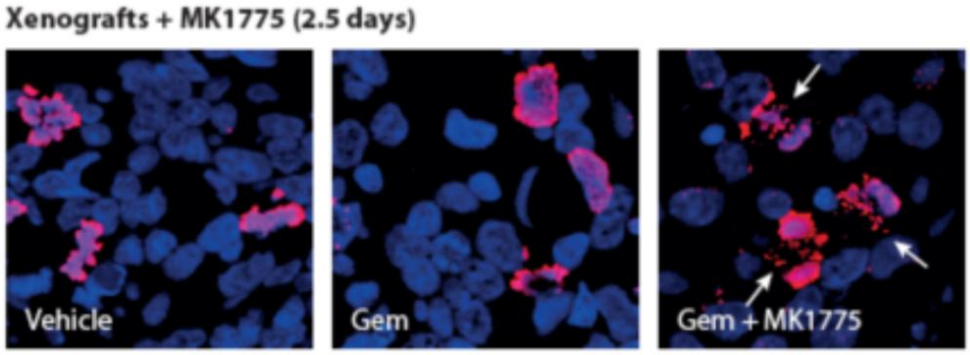
WEE1 inhibitors targets basal-like *TP53* mutant cancer



Synergy with gemcitabine



Forced mitosis *in vivo*



Gemcitabine – WEE1 inhibitor combinations in phase I/II

Common targets for TN breast cancer?

TP53 mutation in basal-like cancers is common and may be targetable

BRCA1/2 loss is a relatively common event

Within subtypes of TN there may be common events

Luminal TN and androgen receptors

Acknowledgments

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