Target validation and early phase clinical trial

Dr Nicholas Turner

IMPAKT training course 2015

The Royal Marsden NHS Foundation Trust

ICR The Institute of Cancer Research

Disclosure relevant to presentation

Nicholas Turner

I am an employee of the Institute of Cancer Research that has a commercial interests in AKT inhibitors

Honoraria

AstraZeneca, Novartis

Target identification, validation and early phase clinical trial

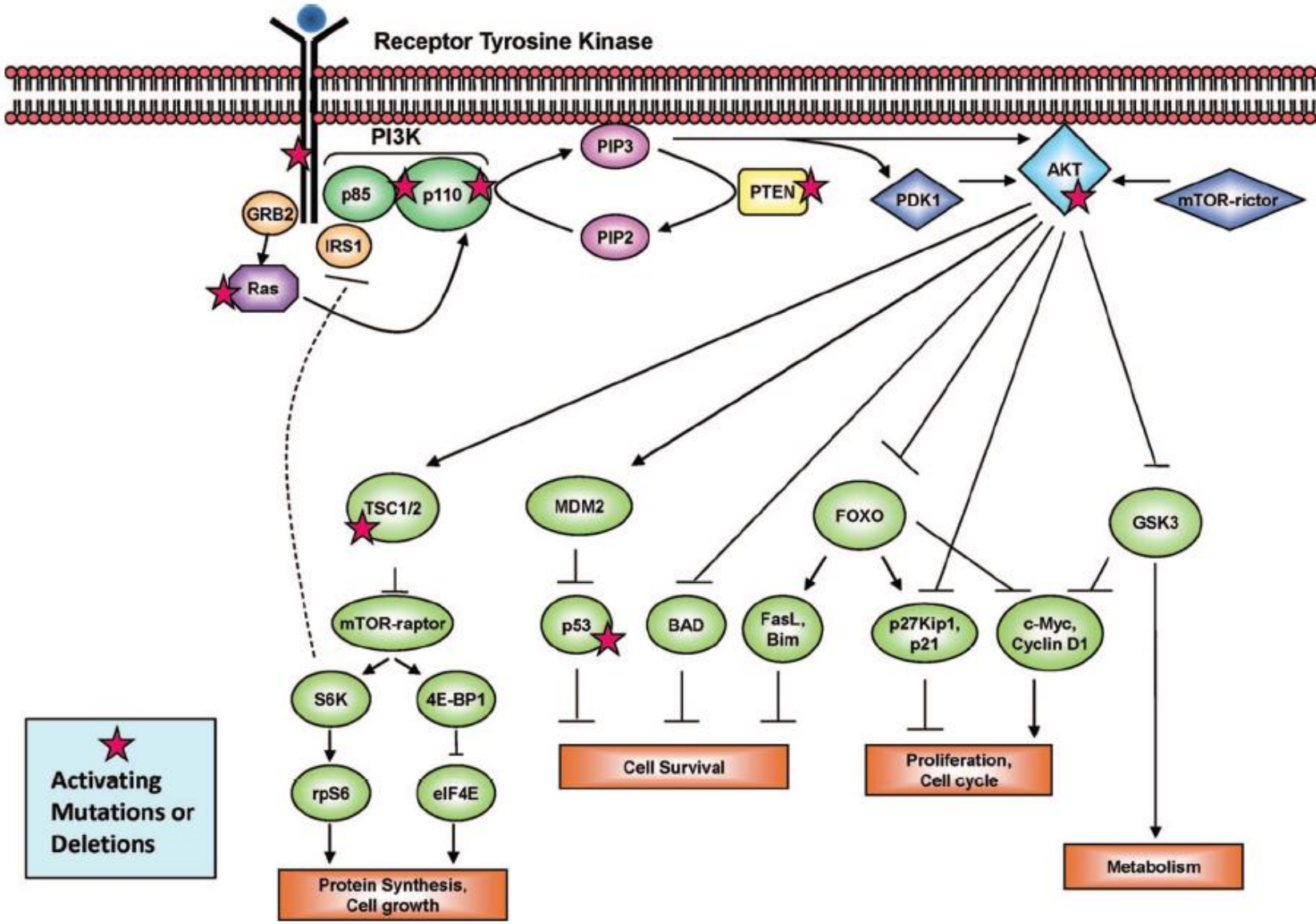
- Basic principles of drug development from target identification through the the early stages of clinical development

- Illustrate principles with the development of an AKT inhibitor

AKT inhibitors in clinical development

AZD5363
MK2206
GDC0068
GSK2141795

Background: PI3K-Akt pathway



Baselga J The Oncologist 2011

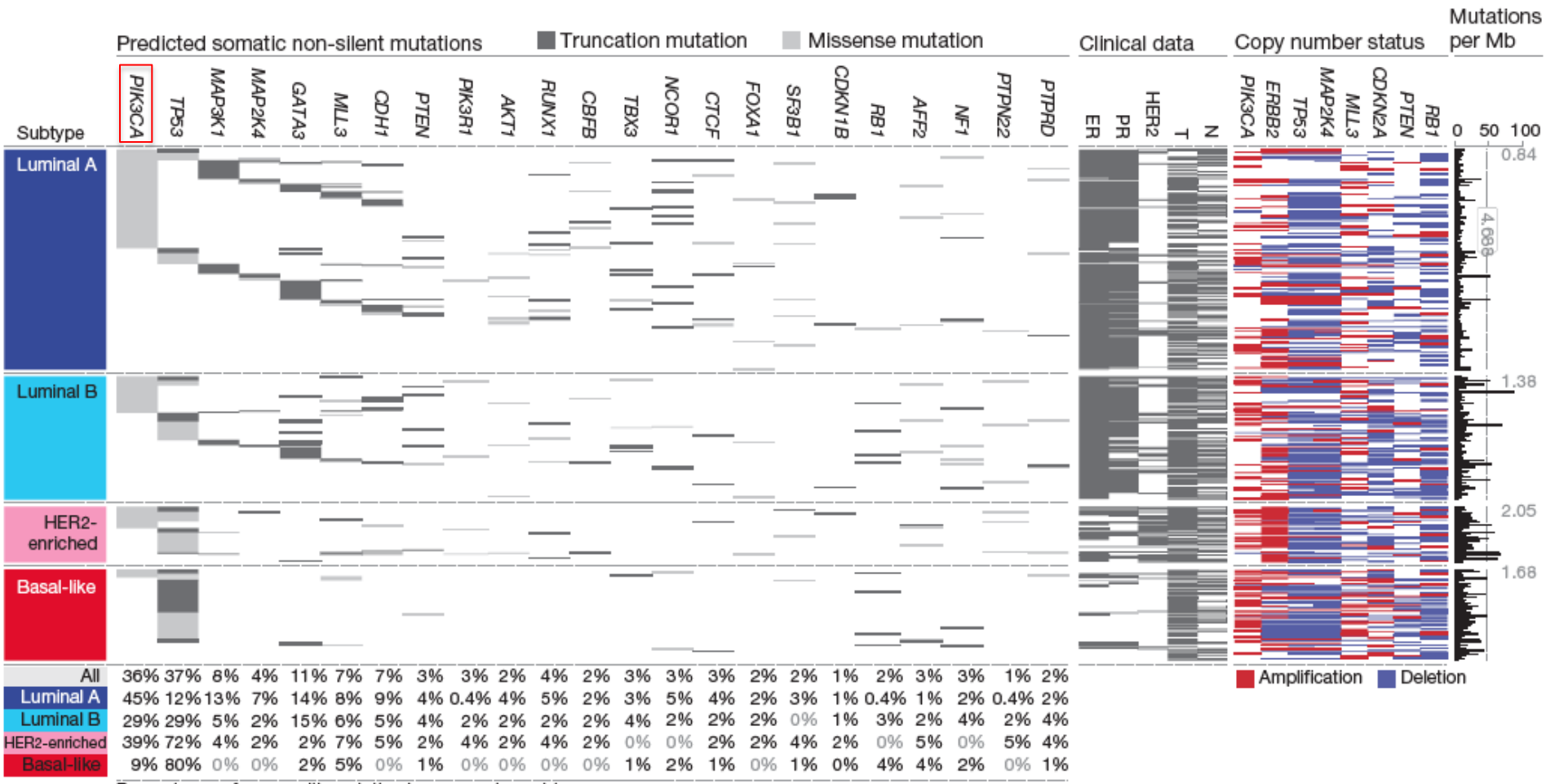
ARTICLE

doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

Targeting genetic events in the PI3K-AKT-mTOR pathway



TCGA Nature 2012

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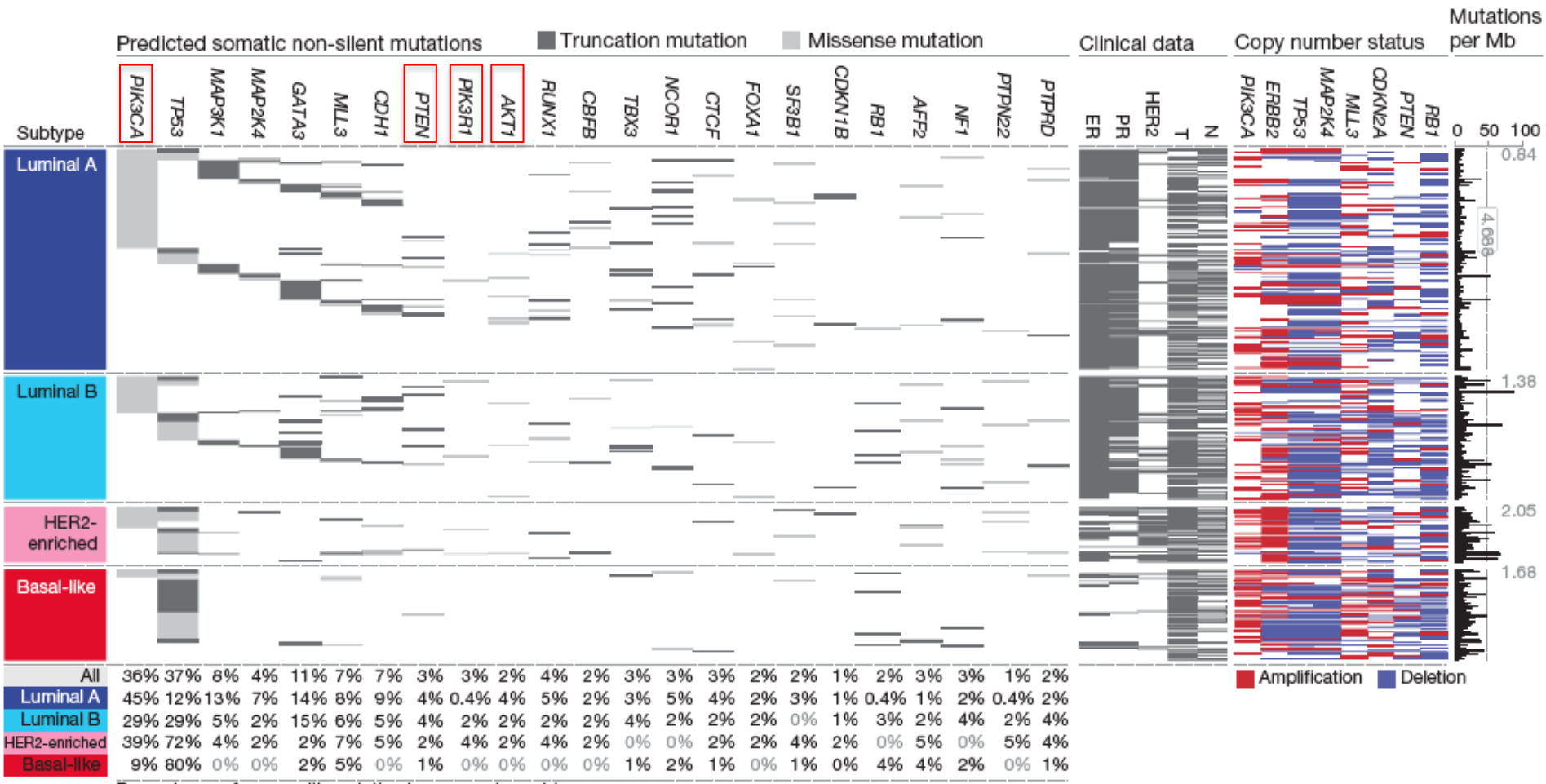


TCGA Nature 2012

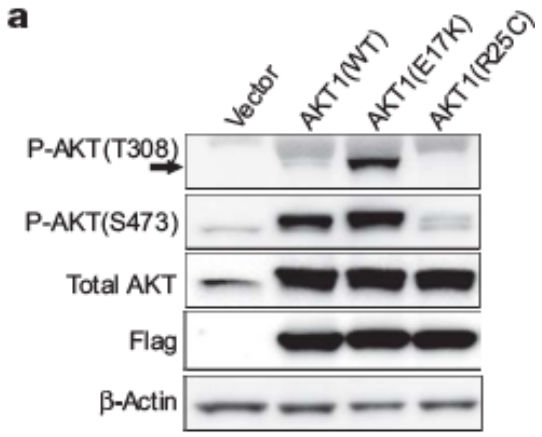
AKT1 mutations in breast cancer

AKT1 mutations are oncogenic

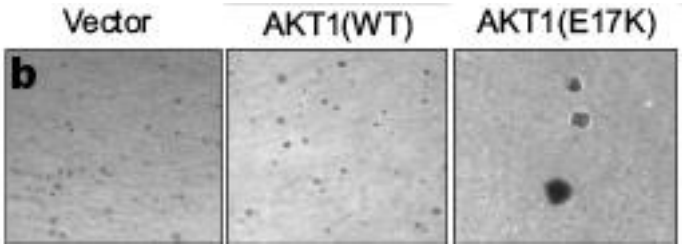
Mutated in ~3% of breast cancer

Luminal subtypes of breast cancer
>90% mutations a single AKT1 E17K mutation

Increases membrane localisation
Conditional activation of AKT



Transforms cells

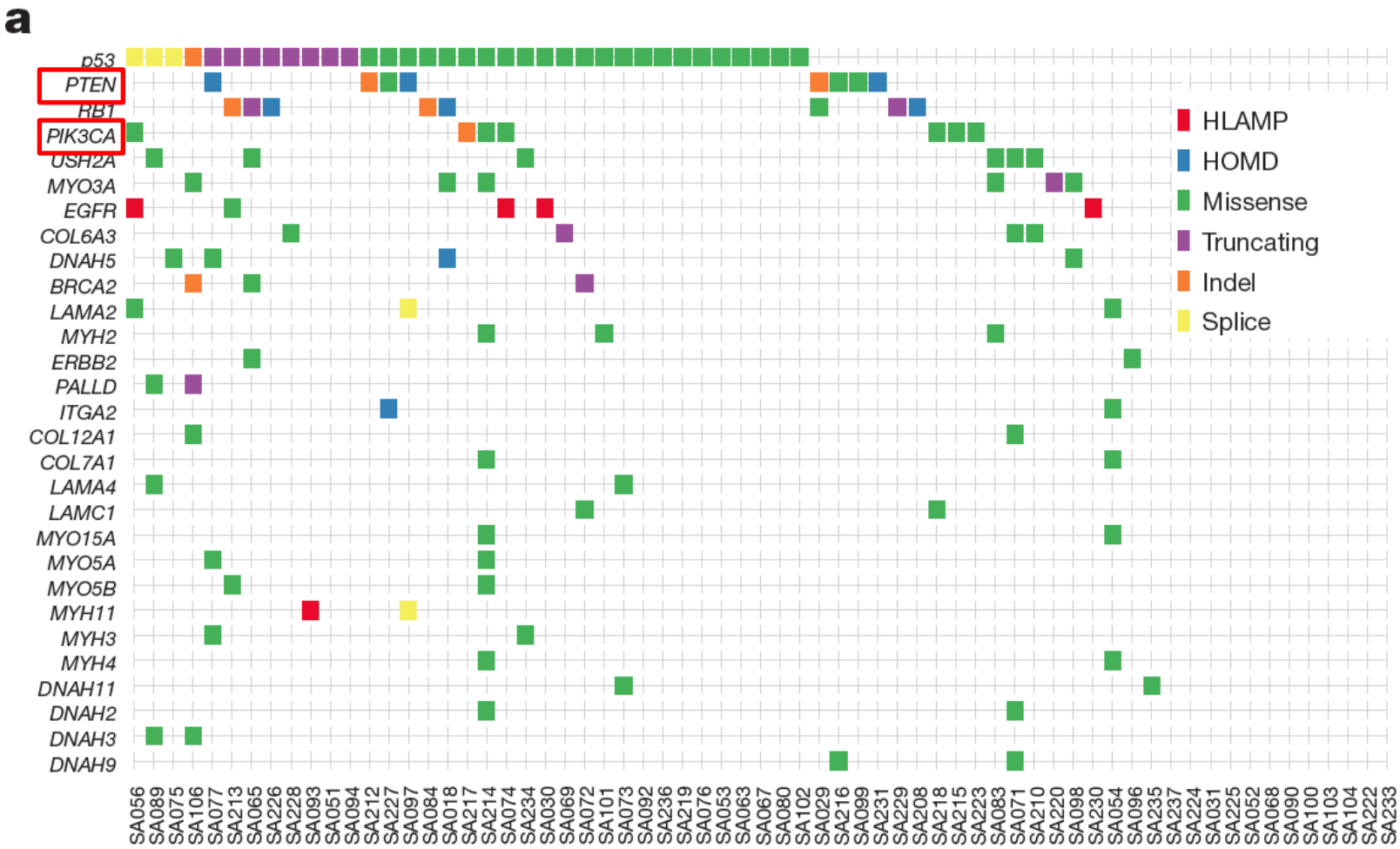


AKT1 mutated cells are sensitive to some AKT inhibitors

Carpten et al Nature 2007

PTEN and Triple negative breast cancer

PI3K alterations in TN breast cancer

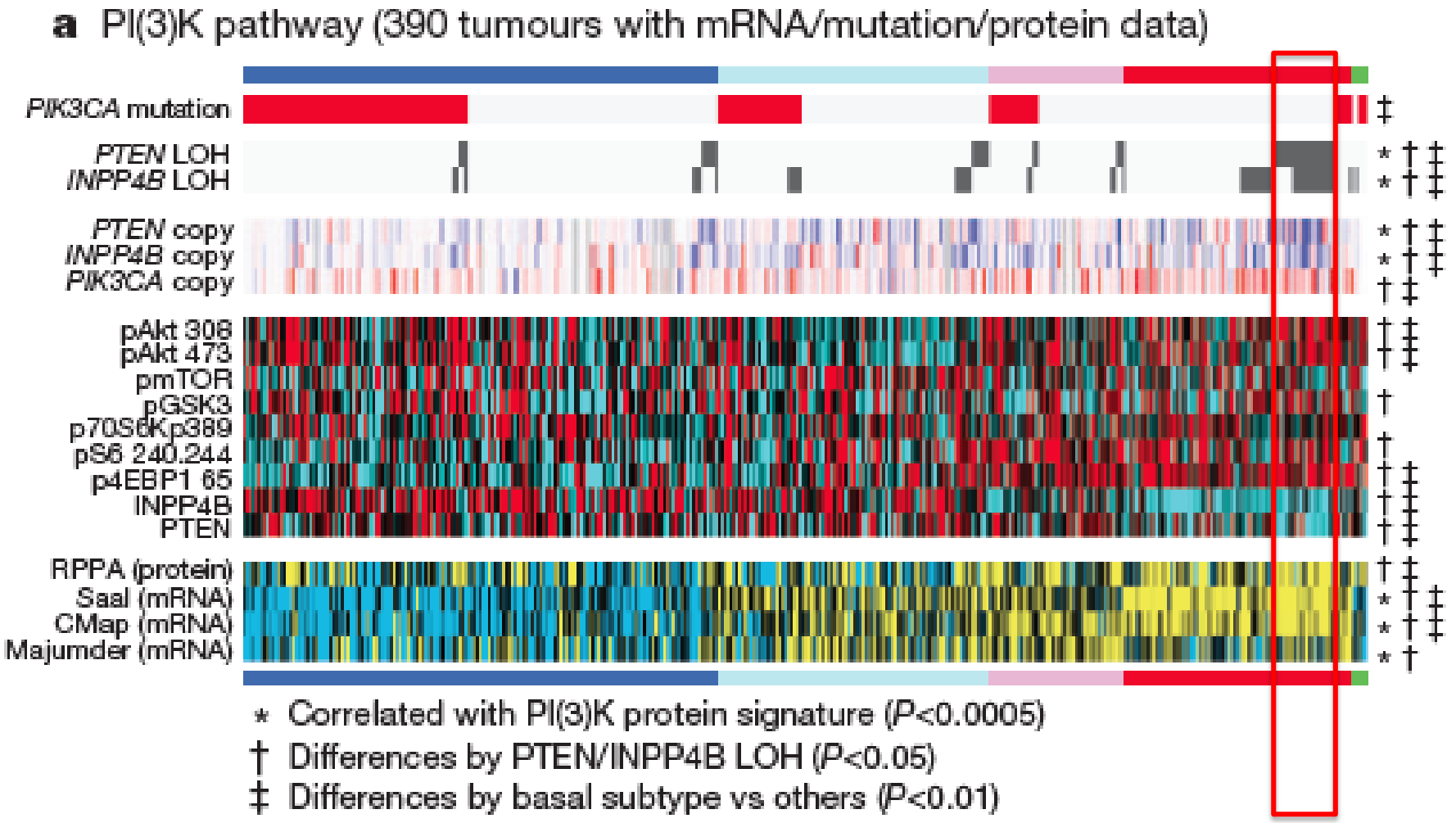


PTEN genetically lost in ~8-10% of TNBC

low/absent by IHC in ~25% of TNBC

Shah et al Nature 2012

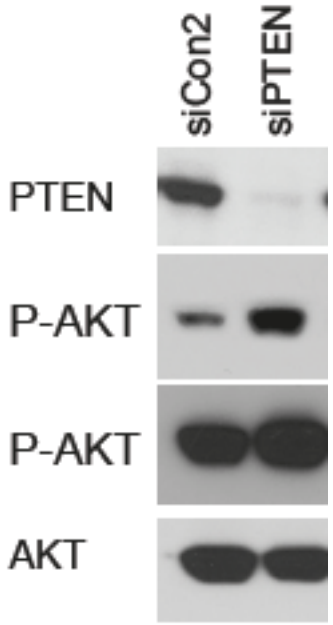
PI3 kinase pathway is active in basal-like breast cancer



Low PTEN in basal-like breast cancer correlates with activation of AKT and mTOR

Loss of PTEN activates AKT in breast cancer

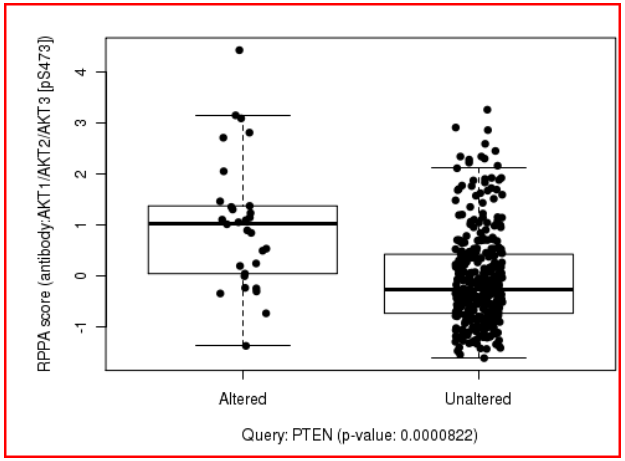
siRNA PTEN in TNBC cell line



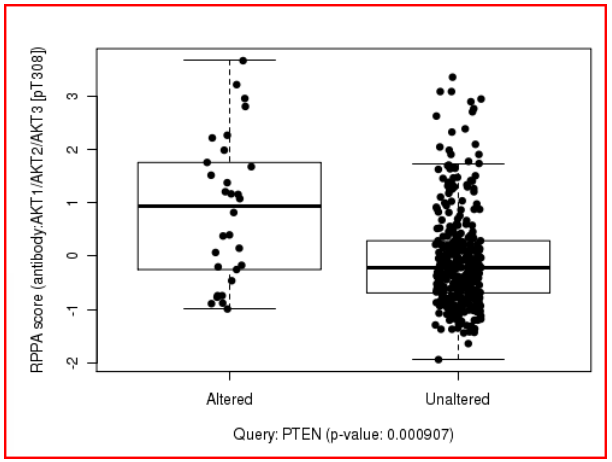
SUM52

PTEN loss correlates with AKT activation

pAKT 473



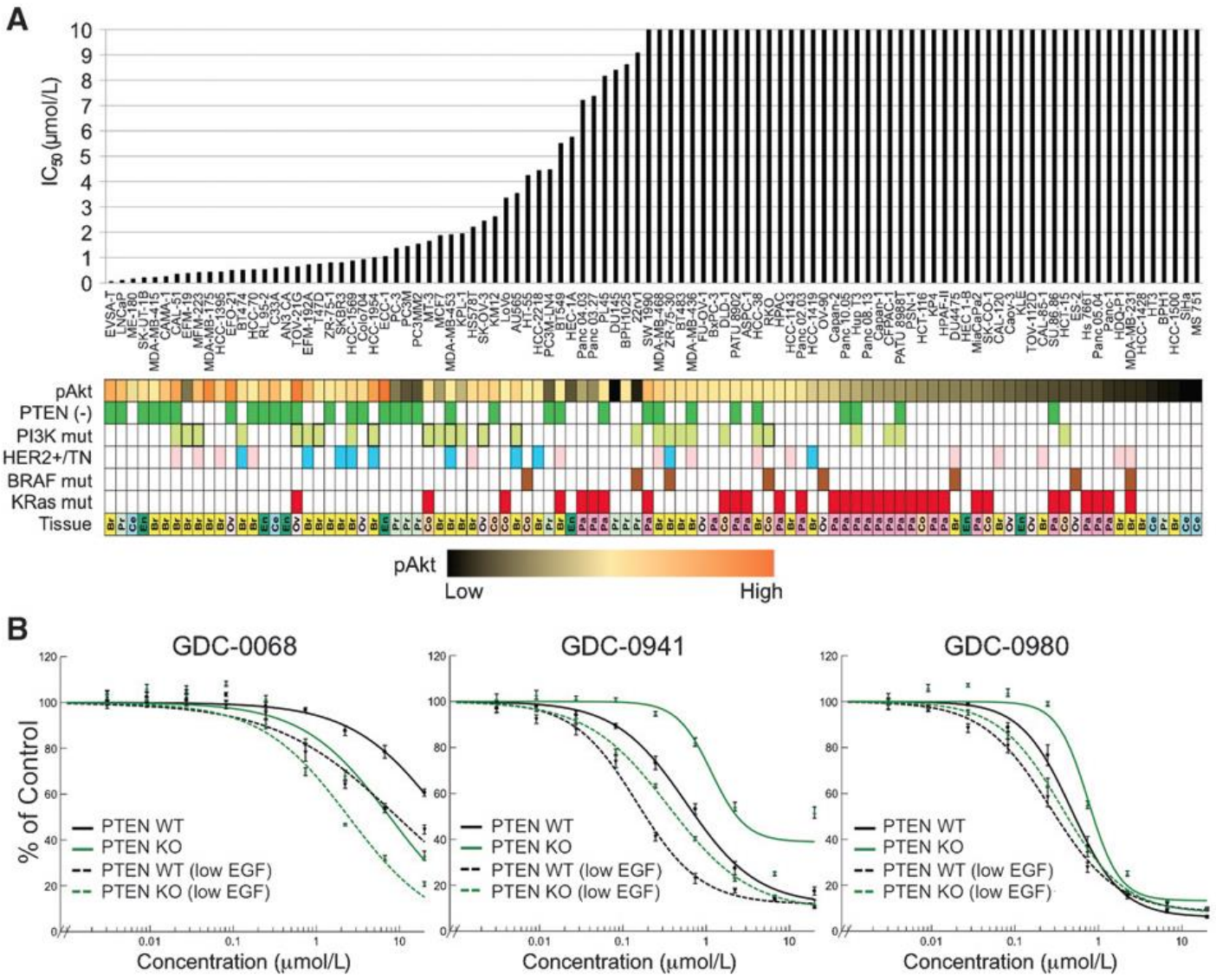
pAKT 308



PTEN Mut/HOMD **PTEN WT**

TCGA Nature 2012

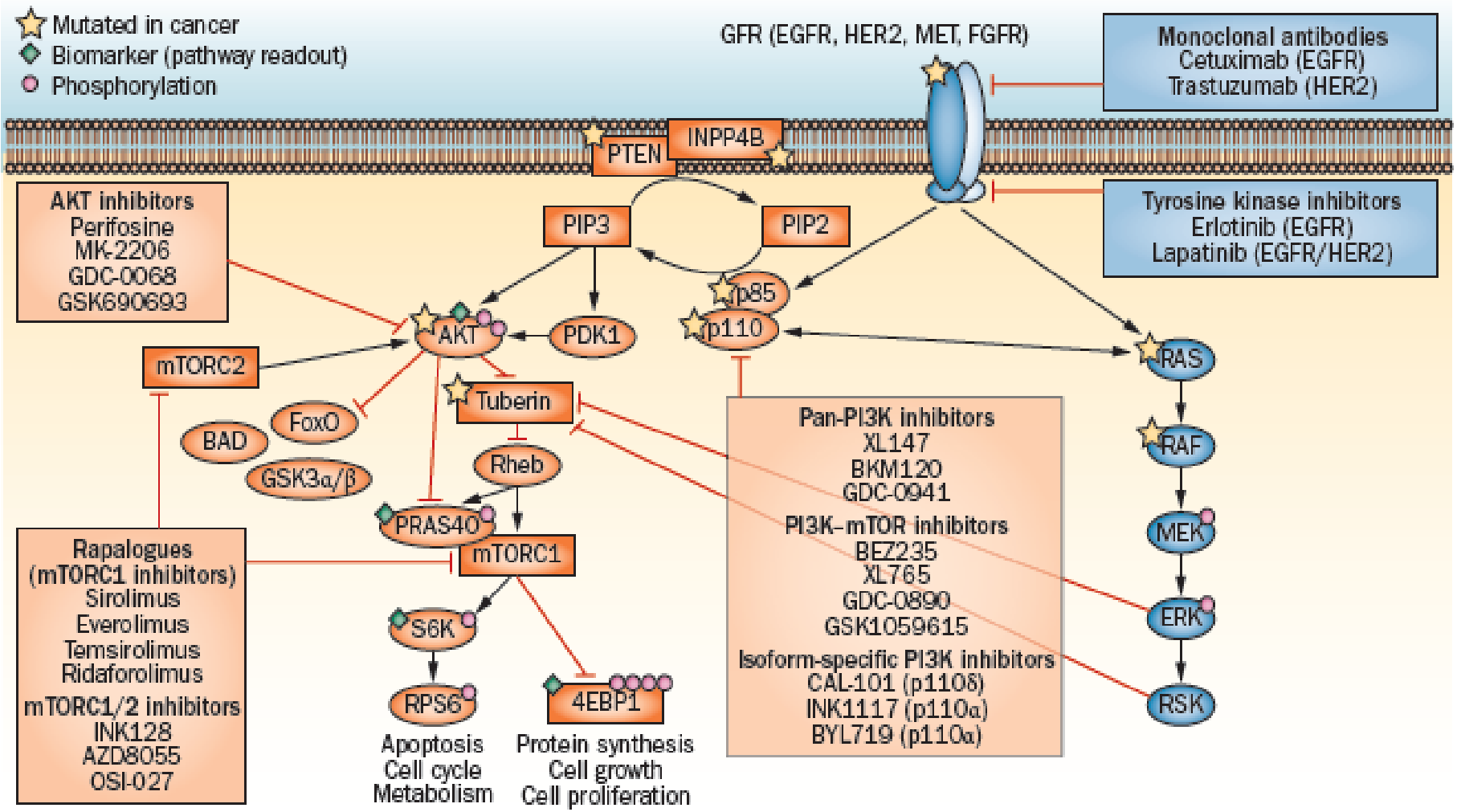
AKT inhibitors – targeting loss of PTEN



Cancer with PTEN loss may be particularly sensitive to AKT inhibitor GDC-0068

Lin et al CCR 2-13

Drugging the PI3K-AKT-mTOR pathway



Target validation

Does inhibiting the target have the predicted biochemical effect?

Does inhibiting the target result in reduced growth?

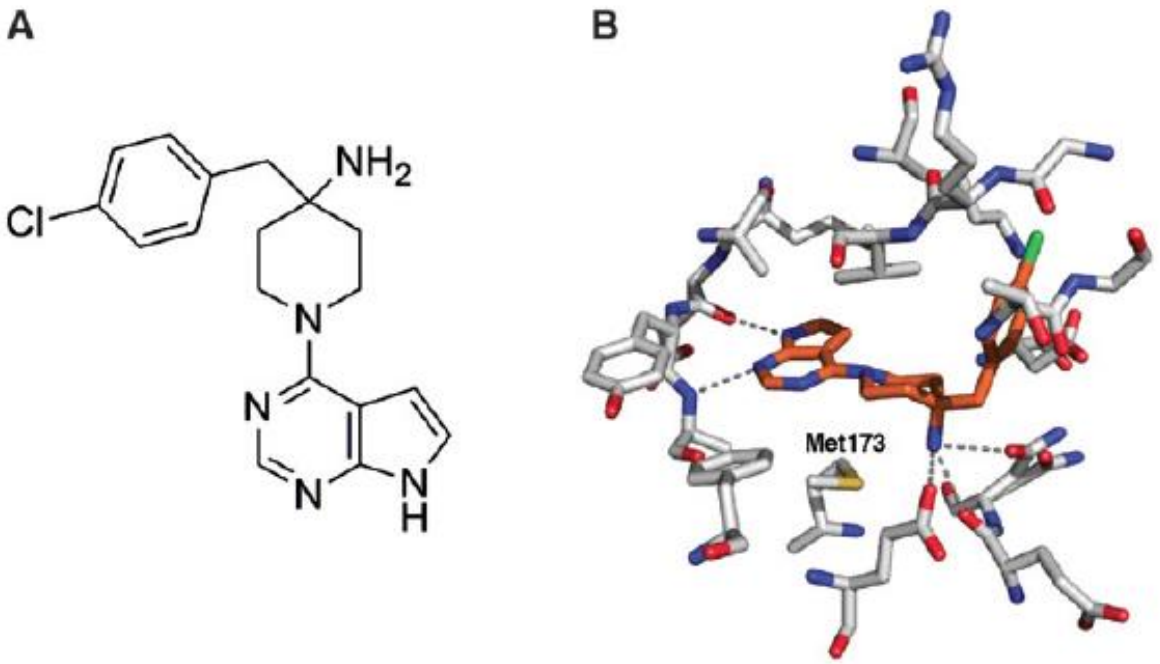
Resources

Cancer cell lines
Patient derived xenografts
(Exogenously manipulated cell lines)

Tools

Tool box inhibitors
RNA interference

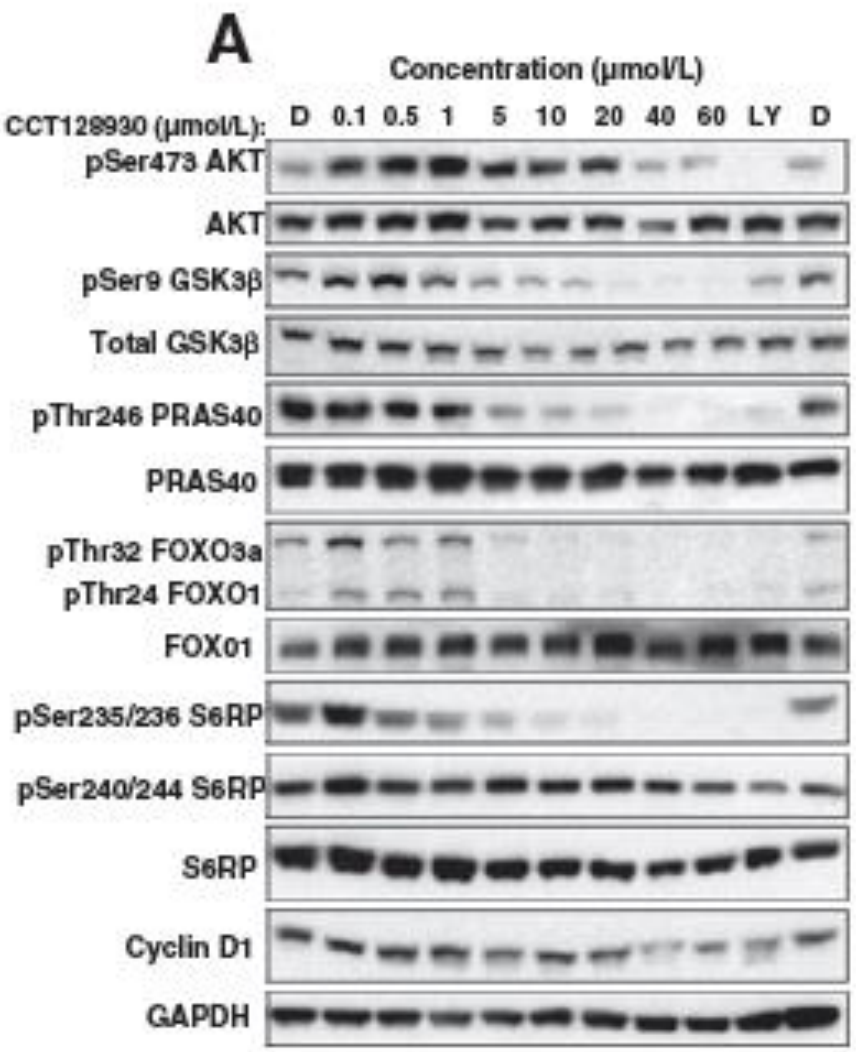
Target validation



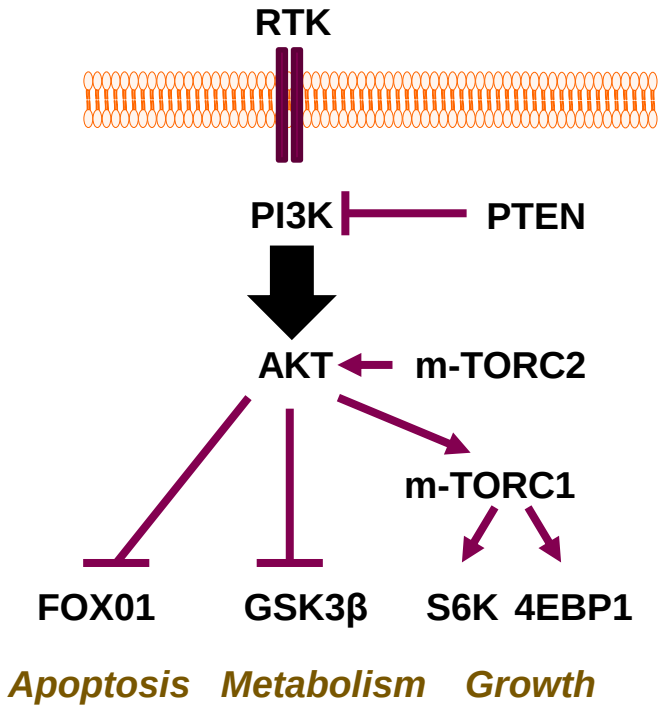
Develop tool box compound to assess the potential of inhibiting AKT

Yap T et al Cancer Res 2011

Target validation



Inhibiting AKT results in loss of down stream signalling

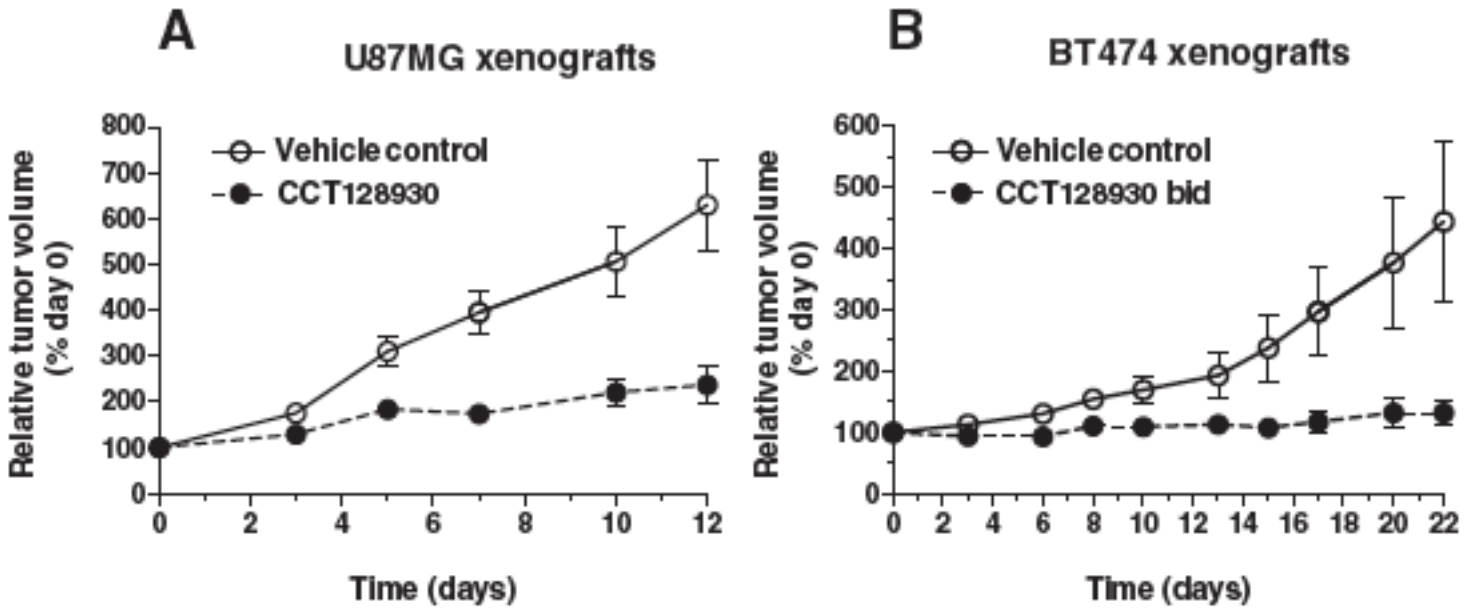


Yap T et al Cancer Res 2011

Target validation

PTEN null

HER2 amp
PIK3CA mutant



Inhibition of AKT reduces tumour growth *in vivo*

Yap T et al Cancer Res 2011

Preclinical development

From tool-box compound to clinical candidate

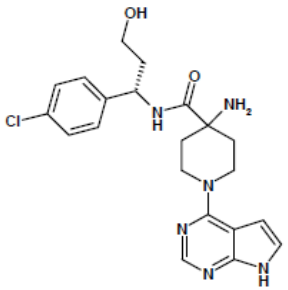
Optimization of chemical structure – iterative process

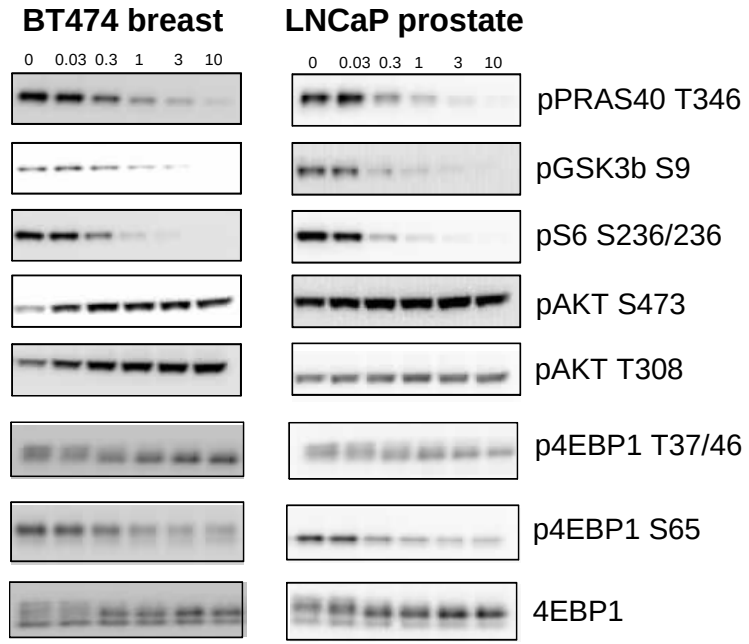
- Increase potency and specificity
- Increase drug like properties
- Reduce potential for non-specific toxic effects

Preclinical toxicology and ADME testing

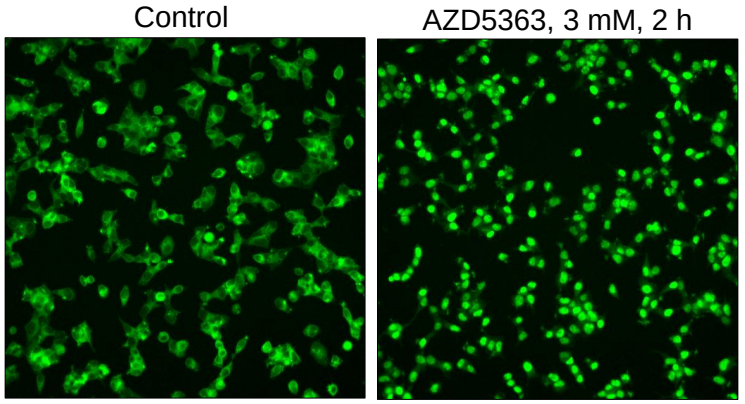
absorption, distribution, metabolism, and excretion

AZD5363: Potent inhibitor of AKT kinases, AKT substrates and downstream pathway proteins

AZD5363 structure		
Enzyme inhibition (nM)	Akt1	3
	Akt2	7
	Akt3	7
	ROCK1	470
	ROCK2	60
	PKA	7
	P70S6K	6
Inhibition of AKT substrates in cells (μM)	pGSK3β	0.76 (BT474c; Western) 0.06 (LNCaP; Western) 0.38 (MDA-MB-468; Acumen)
	pPRAS40	0.31 (BT474c; Western) 0.22 (LNCaP; Western) 0.39 (MDA-MB-468; Acumen)
	pFOXO3a translocation	0.69 (BT474c)



FOXO3a translocation assay (BT474c breast)



Davies BR *et al. Mol Cancer Ther* 2012;11:873–887

Early phase clinical development

First in human – Phase 1 with expansion

Establish side effects and maximum tolerated dose
Establish PK and PD
Preliminary efficacy in expansion

Randomized phase IIb to confirm efficacy

Definitive phase III study

Yap T et al Cancer Res

Results of two Phase I multicenter trials of AZD5363, an inhibitor of AKT1, 2 and 3: biomarker and early clinical evaluation in Western and Japanese patients with advanced solid tumors

Udai Banerji,[1,2] Malcolm Ranson,[3] Jan HM Schellens,[4] Taito Esaki,[5] Emma Dean,[3] Andrea Zivi,[2] Ruud van der Noll,[4] Paul K Stockman,[6] Marcelo Marotti,[6] Michelle D Garrett,[1] Barry R Davies,[6] Paul Elvin,[6] Andrew Hastie,[6] Peter Lawrence,[6] SY Amy Cheung,[6] Christine Stephens,[6] and Kenji Tamura[7]

[1]Division of Cancer Therapeutics, The Institute of Cancer Research, London, UK; [2]The Drug Development Unit, The Royal Marsden NHS Foundation Trust, London, UK ; [3]Department of Medical Oncology, Christie Hospital NHS Trust, Manchester, UK; [4]Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [5]Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan; [6]AstraZeneca R&D, Macclesfield, UK; [7]Breast and Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan

AACR 2013

Defining the dose

Maximum tolerated dose

Generally defined on toxicity in the first cycle

No more than one out of 6 patients having a dose limiting toxicity

Cohort may be expanded to further define whether the does is tolerated

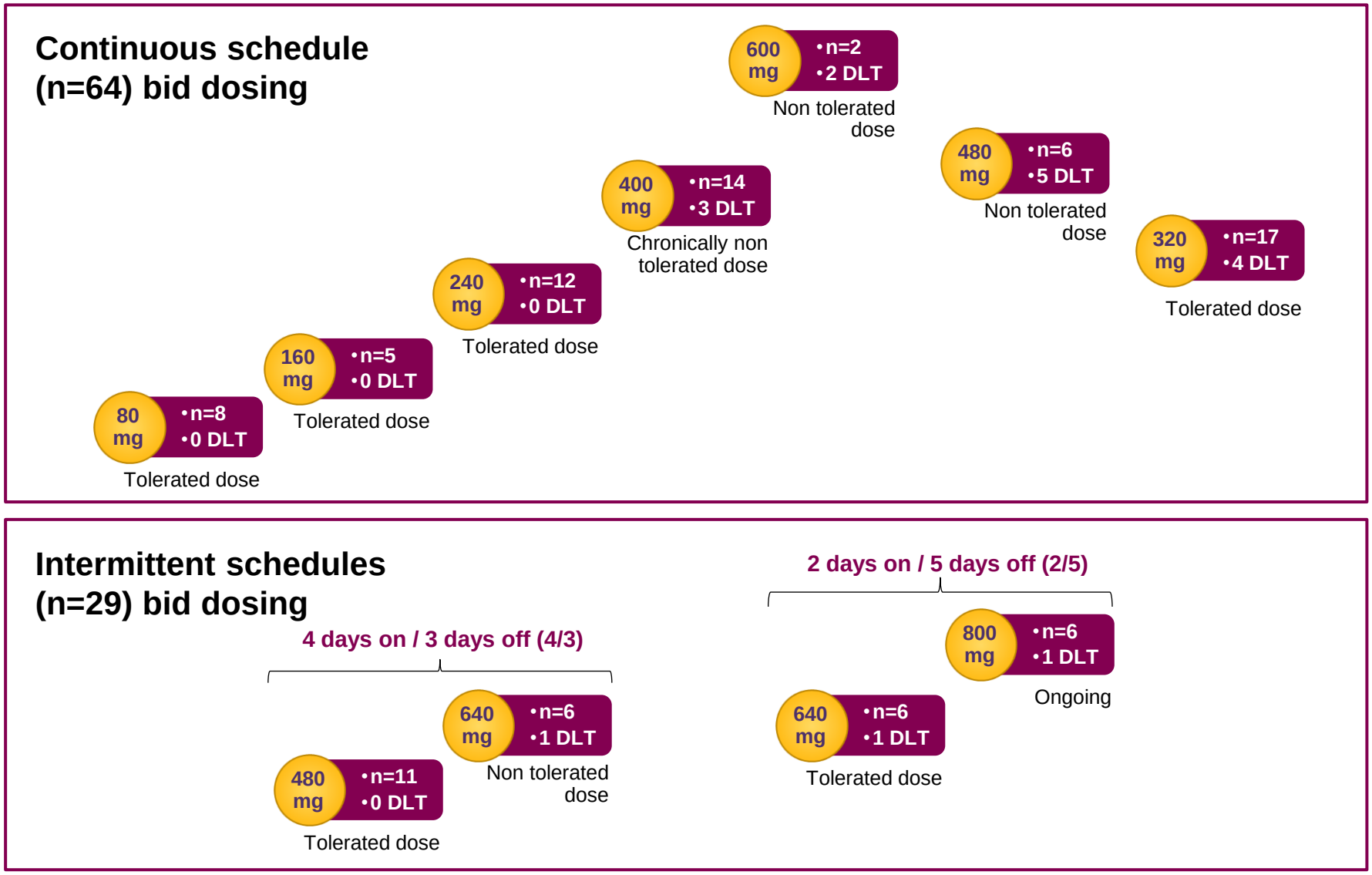
Chronically tolerated dose

Not formally defined

Acceptable chronic toxicity

The dose that is compatible with dosing patients for many cycles

Study flow – European and Japanese patients



DLT: Dose-limiting toxicity

Data cut off: Feb 18 2013
Unvalidated data

Dose-limiting toxicities

Continuous schedule

Dose (mg) bid	Number of patients with DLT	DLT	CTCAE grade	Number of events
80	0/8	-	-	-
160	0/5	-	-	-
240	1/12	Hypoxia (multiple pulmonary metastases)	3	1
320	4/14	Maculo papular rash Diarrhea	2 , 3 3	1 , 1 2
400	3/14	Maculo papular rash Diarrhea	3 3	2 1
480	5/6	Maculo papular rash Diarrhea	3 2	3 2
600	2/2	Maculo papular rash	4	2

Intermittent schedule

Dose (mg) bid	Number of patients with DLT	DLT	CTCAE grade	Number of events
480 *(4 / 3)*	0/11	-	-	-
640 *(4 / 3)*	1/6	Diarrhea	3	1
640 *(2 / 5)*	1/6	Hyperglycemia	3	1
800 *(2 / 5)*	1/6	Hyperglycemia	3	1

Establish PK and PD

Pharmacokinetics (PK)

How the body handles the drug

Pharmacodynamics (PD)

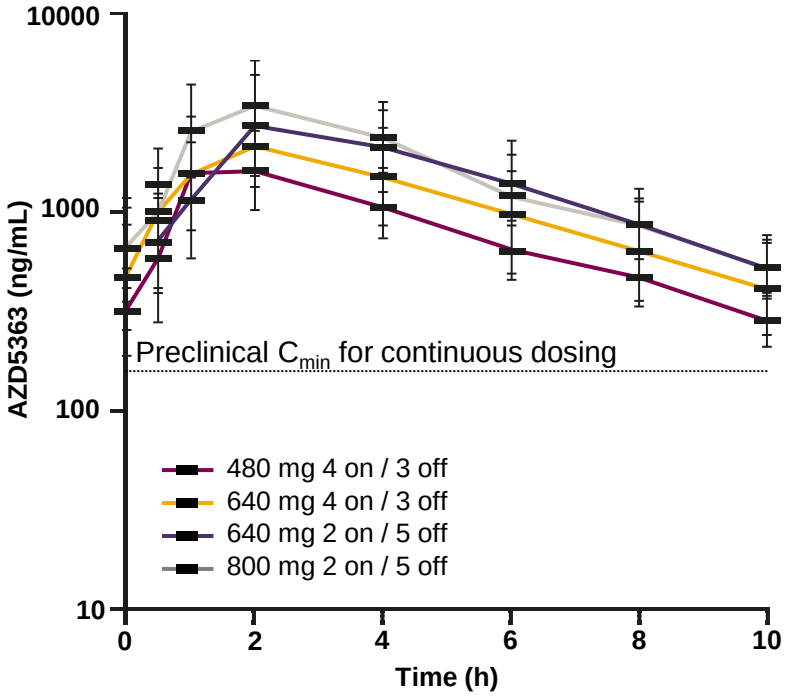
Whether the drug has the desired effect once an adequate dose has been achieved

Surrogate tissues – blood cells, skin, hair

Principally useful if no effect is seen – drug doesn't work

Tumour tissue

AZD5363 PK profile in Western patients receiving intermittent bid dosing



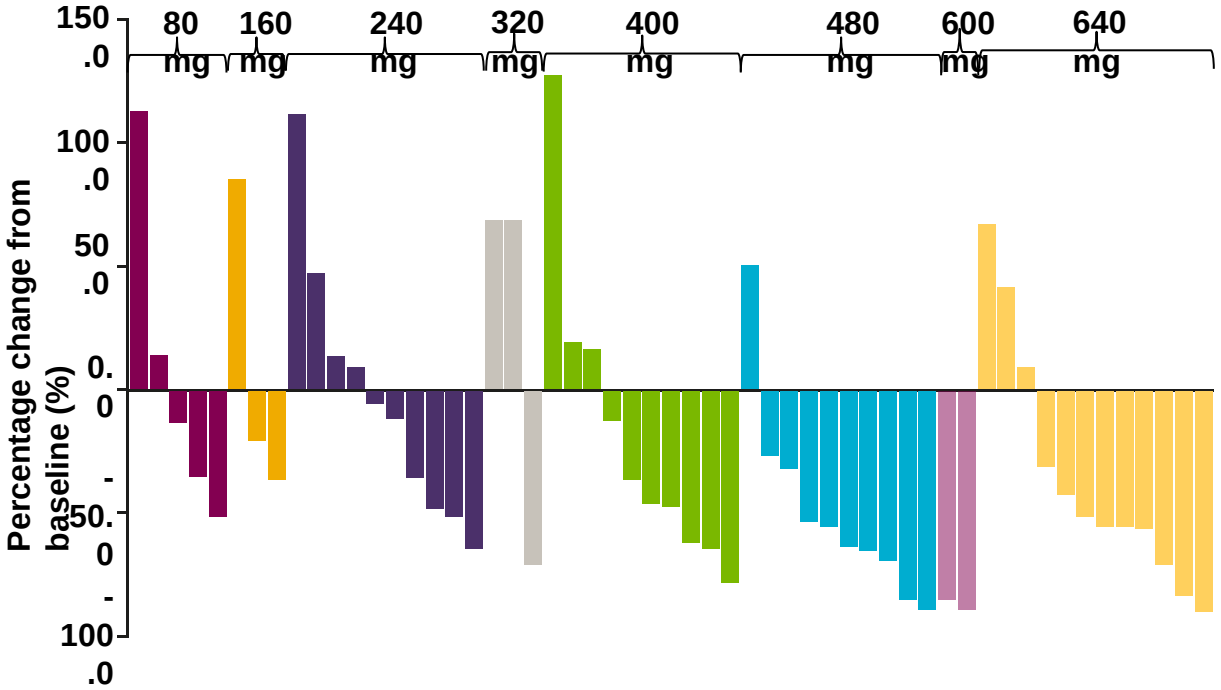
	Single dose			Steady state		
Dose (mg)	t_{max} (h)	C_{max} (ng/mL)	AUC (ng.h/mL)	$t_{ss,max}$ (h)	$C_{ss,max}$ (ng/mL)	AUC_{ss} (0-10h) (ng.h/mL)
480 *4 on / 3 off*	2.0	1,353	7,388	2.0	1,816	8,602
640 *4 on / 3 off*	2.0	2,248	12,000	2.0	2,721	13,759
640 *2 on / 5 off*	1.5	1,213	6,763	2.0	2,484	11,737
800 *2 on / 5 off*	2.0	2,482	13,286	1.5	3,317	16,728

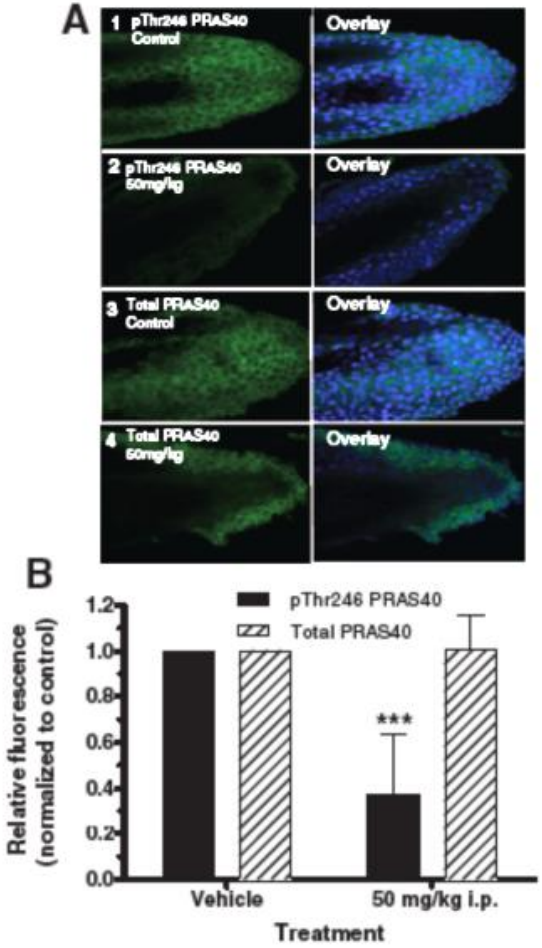
PK following a single dose

- **AZD5363 is rapidly absorbed**
- **Exceeds exposure required for preclinical efficacy based on preclinical modelling**
- **Dose proportional increase in C_{max}/AUC**
- **Half life of approximately 10 hours allow flexible dosing schedules to be explored**

Pharmacodynamic assays: p-PRAS40 inhibition in hair follicles

Each bar represents data averaged from
four hair follicles per patient at 4 hours post-dose

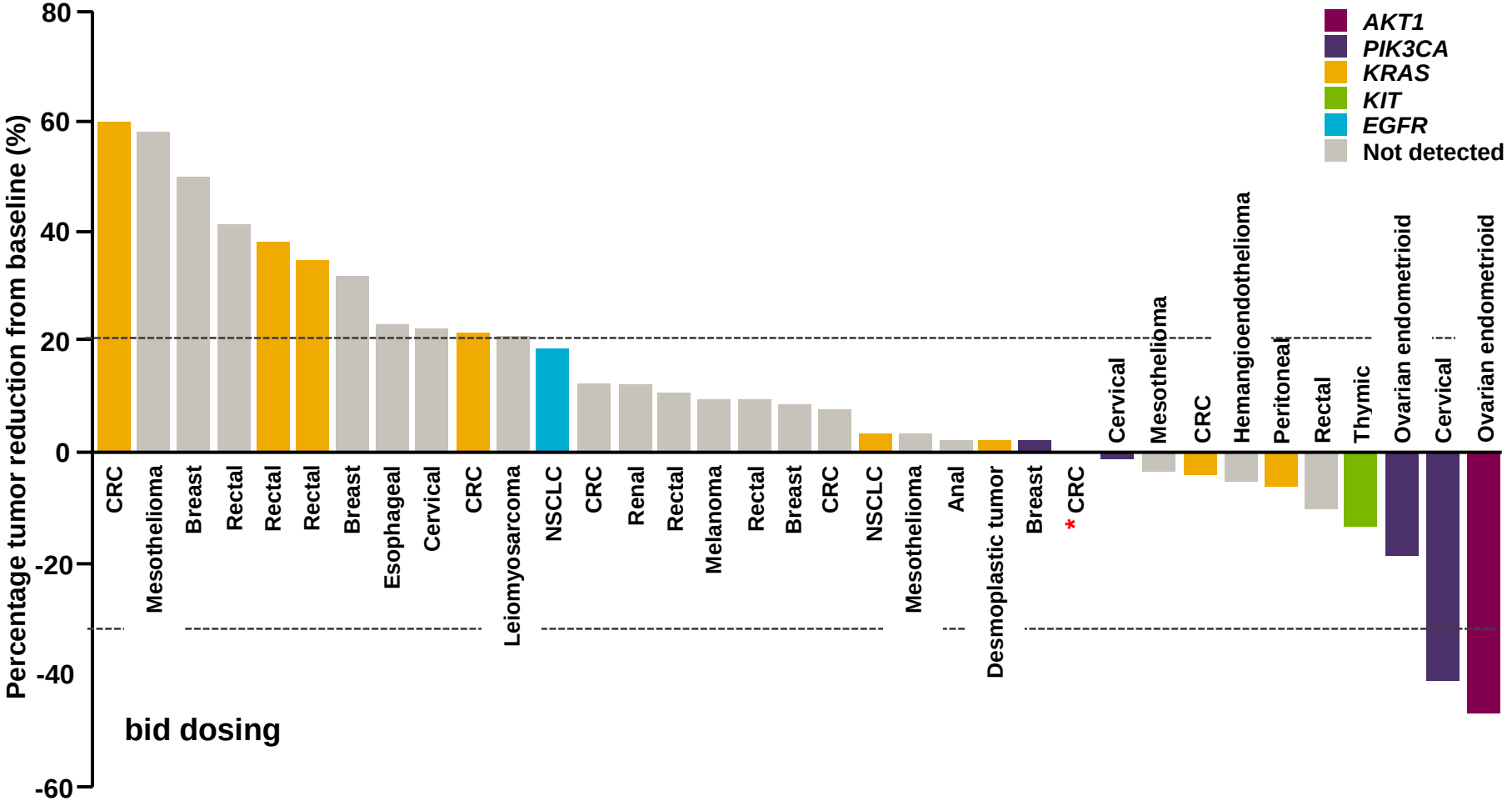




- **Evidence of activity in an extravascular tissue compartment**
- **Dose dependent activity: >50% inhibition at 400mg and above**

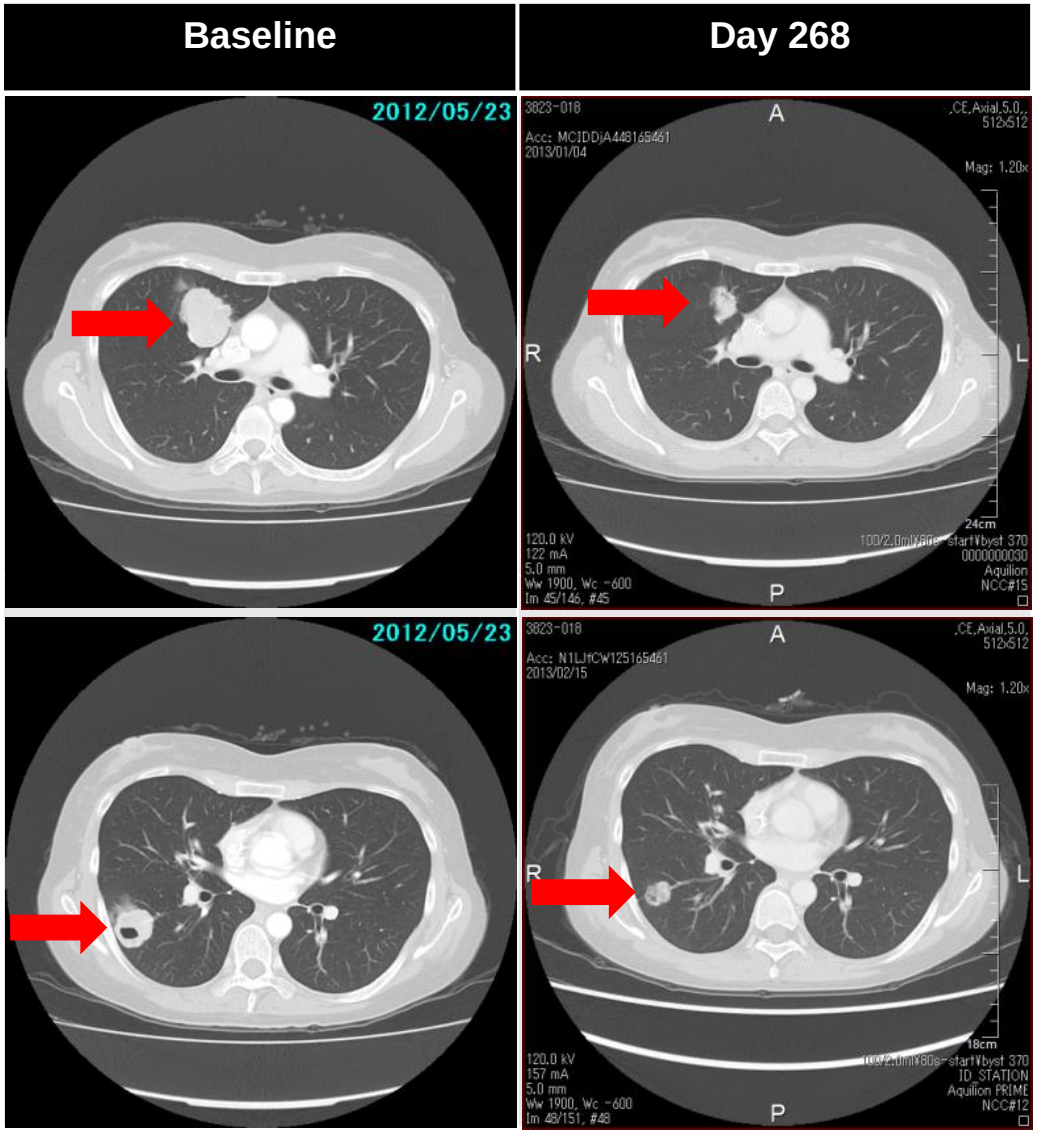
Clinical PD biomarker group, ICR

Efficacy: Best response and gene mutation



- Not all patient samples tested due to lack of tissue availability
- Data shown are across whole dose range
- 3 patients with *PIK3CA* or *AKT1* mutation received doses ≥ 400 mg bid and all achieved tumour shrinkage

Response in *AKT1* mutant cancer to AZD5363



- **A 38-year-old Asian female patient with metastatic endometrioid cancer of the ovary**
- **Eight previous lines of chemotherapy**
- ***AKT1*^{E17K} somatic mutation detected in tumor**
- **AZD5363 480 mg bid (4 days on / 3 days off schedule)**
- **47% decrease in tumor size from baseline**

Banerjii et al AACR 2013

Expansion cohort(s)

Expansion of study at recommended phase II dose

Recruit a set number of biomarker defined patients to establish preliminary efficacy

More efficient than the older strategy of a separate phase II study

Ongoing for AKT1 mutant breast cancers

Moving to randomised phase IIb

What degree of efficacy is seen in expansion cohort(s)

Very high or high in a tumour type with few standard options

↓

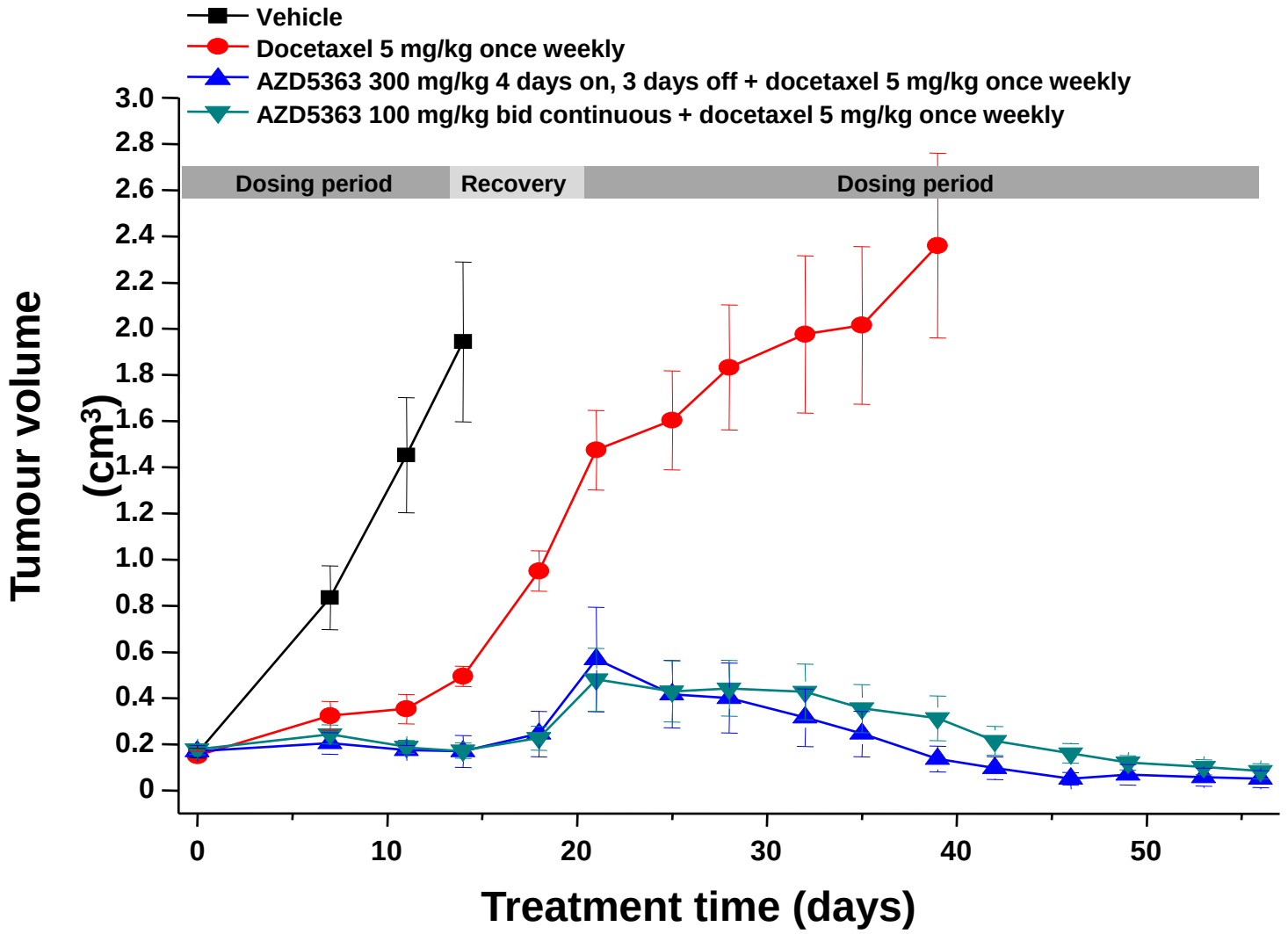
Single agent randomisation against standard of care

Low-high levels of single agent activity

↓

Randomised phase II of addition of new therapy to standard of care

AZD5363 sensitizes HCC-1187 xenografts to docetaxel

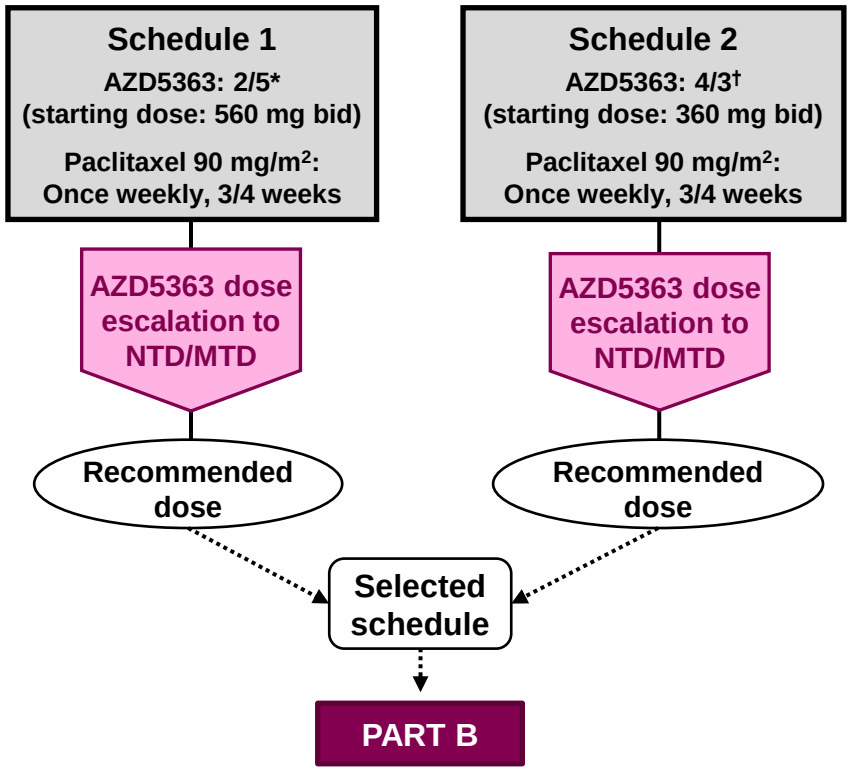


Davies BR *et al. Mol Cancer Ther* 2012;11:873–887

BEECH: International, multicentre, two-part study

Part A

Multiple-ascending-dose evaluation of AZD5363 combined with weekly paclitaxel in females aged ≥18 years with HER2-negative metastatic breast cancer and up to two prior chemotherapy courses for advanced cancer



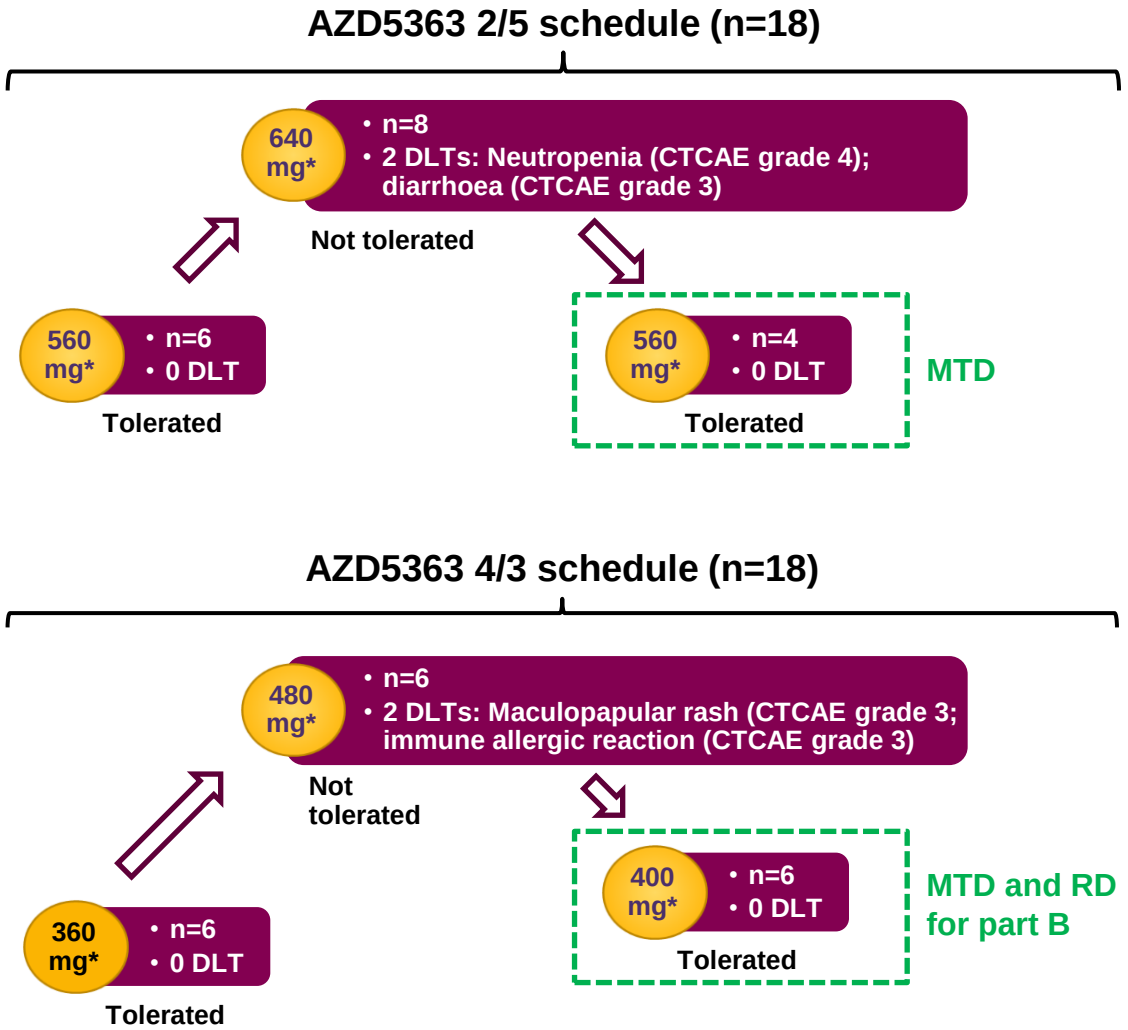
Objectives

- Primary:
  - Safety/tolerability of AZD5363 combined with paclitaxel
  - Recommend dosing schedule for part B
- Secondary:
  - Antitumour activity of AZD5363 in combination with paclitaxel
  - PK of AZD5363 and paclitaxel in combination
  - Changes in the platelet PD biomarker PRAS40
- Exploratory
  - Can ctDNA analysis predict response/resistance earlier than conventional RECIST measurements?

***AZD5363 intermittent dosing, 2 days on treatment, 5 days off; †AZD5363 intermittent dosing, 4 days on treatment, 3 days off AZD5363 commenced 24 hours post-paclitaxel**

ctDNA, circulating tumour DNA; MTD, maximum tolerated dose; NTD, non-tolerated dose; PD, pharmacodynamic; PK, pharmacokinetic; PRAS40, proline-rich AKT substrate 40; RECIST, Response Evaluation Criteria In Solid Tumors

DLTs observed in patients evaluable for toxicity assessment



*In combination with paclitaxel 90 mg/m^2

CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; RD, recommended dose

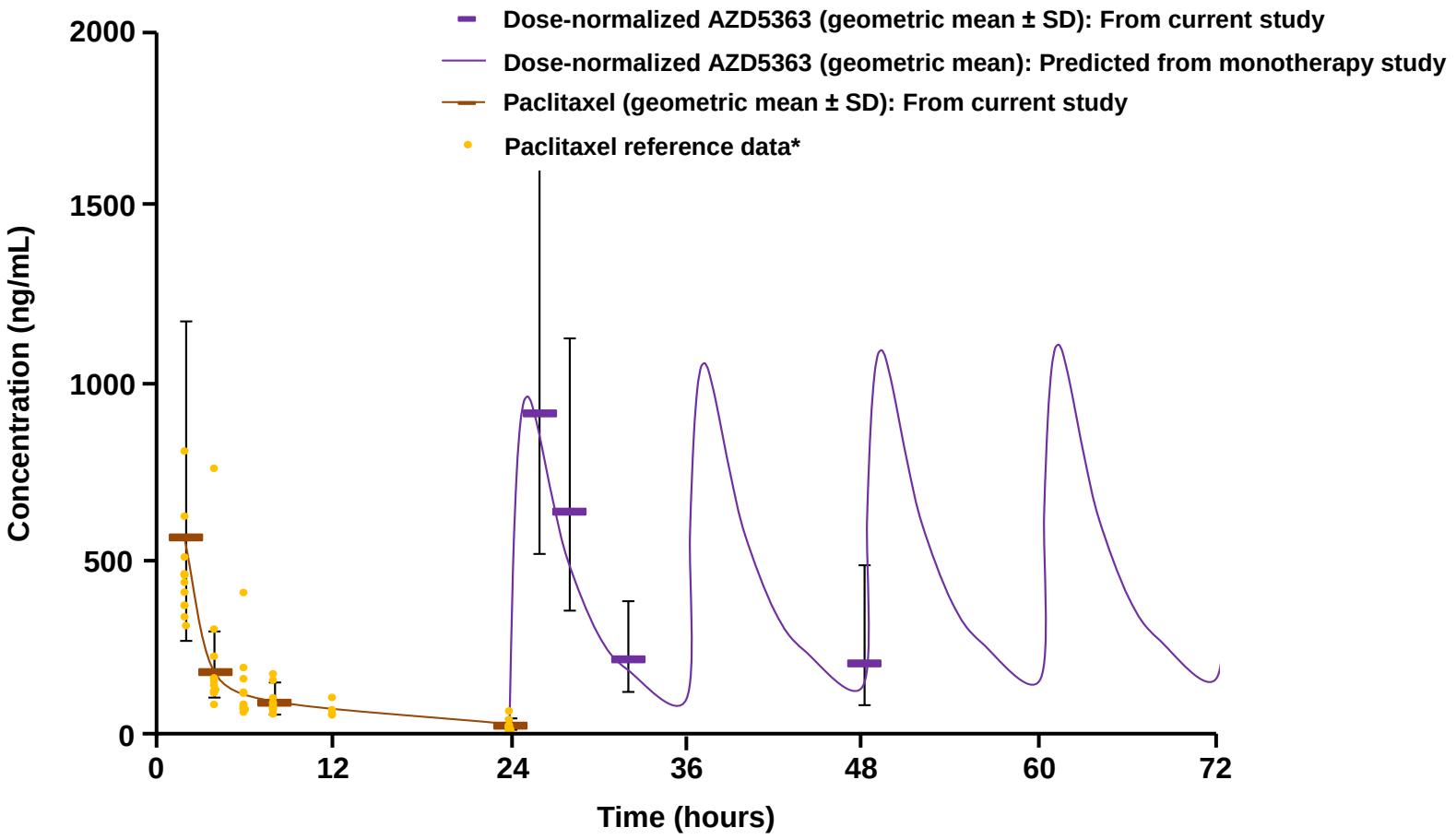
Most common AEs, irrespective of relationship to treatment

	AZD5363 2/5 schedule: Total (n=18)	AZD5363 4/3 schedule: Total (n=18)	Total (n=36)
Patients with AE, n (%)	13 (72.2)	18 (100.0)	31 (86.1)
Diarrhoea	11 (61.1)	17 (94.4)	28 (77.8)
Nausea	9 (50.0)	10 (55.6)	19 (52.8)
Rash*	7 (38.9)	12 (66.6)	19 (52.8)
Asthenia	7 (38.9)	10 (55.6)	17 (47.2)
Neurotoxicity	5 (27.8)	6 (33.3)	11 (30.6)
Vomiting	3 (16.7)	8 (44.4)	11 (30.6)
Alopecia	5 (27.8)	5 (27.8)	10 (27.8)
Anaemia	5 (27.8)	4 (22.2)	9 (25.0)
Decreased appetite	2 (11.1)	7 (38.9)	9 (25.0)
Back pain	5 (27.8)	4 (22.2)	9 (25.0)
Hyperglycaemia	5 (27.8)	3 (16.7)	8 (22.2)

The most common AEs considered to be related to AZD5363 were diarrhoea (23/36, 63.9%), hyperglycaemia and nausea (7/36, 19.4% for both)

Note: Adverse events (AEs) occurring in ≥8 patients overall; *Erythematous, papular, macular, pruritic and maculopapular combined

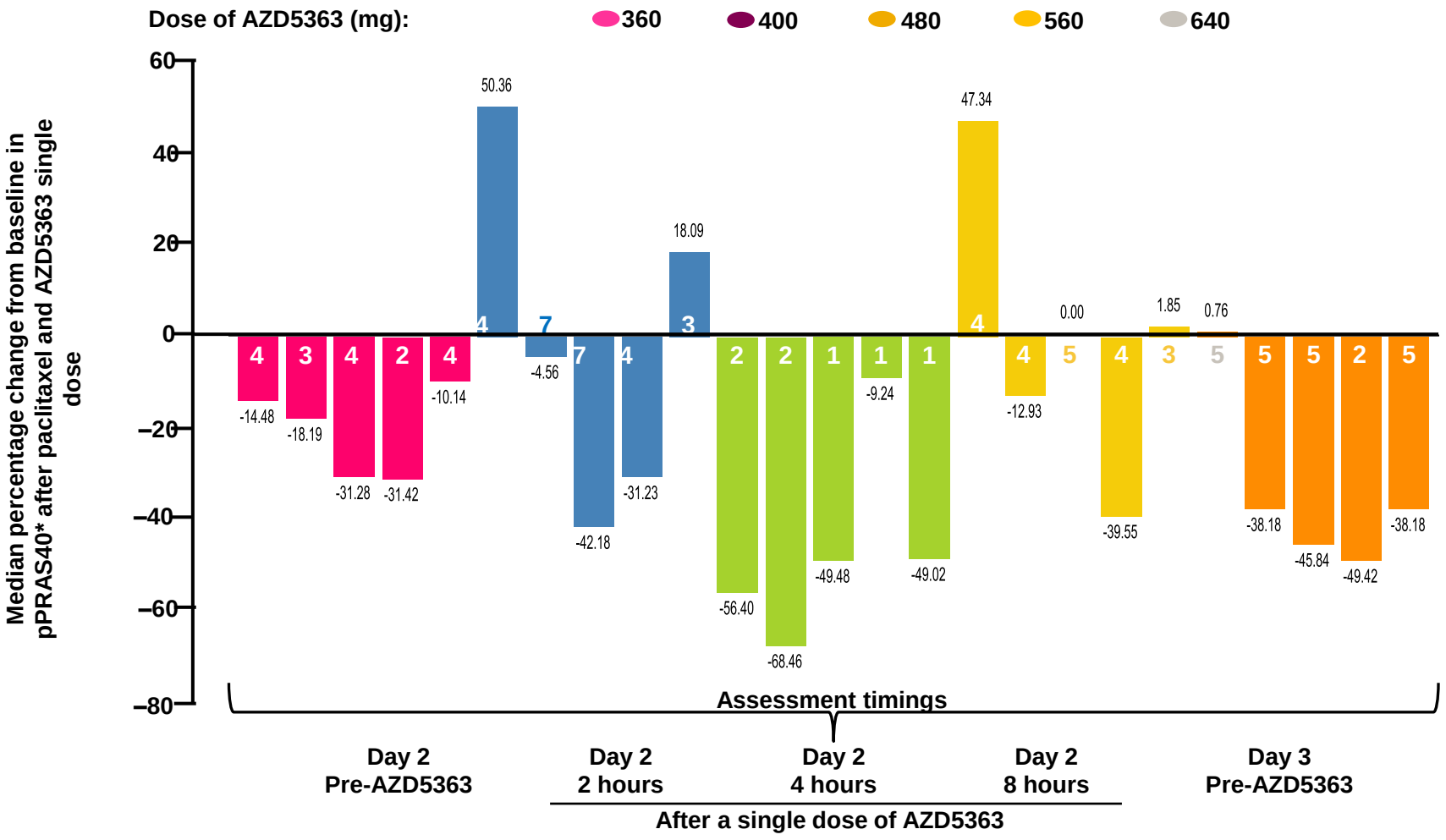
Dose-normalized AZD5363 and paclitaxel PK profiles



Paclitaxel administered 24 hours before AZD5363 dosing had no apparent effect on AZD5363 exposure
The observed PK profile of AZD5363 was in line with monotherapy data

*From study D0102C00003 (Phase I/II study of AZD8931 in combination with paclitaxel; NCT00900627)

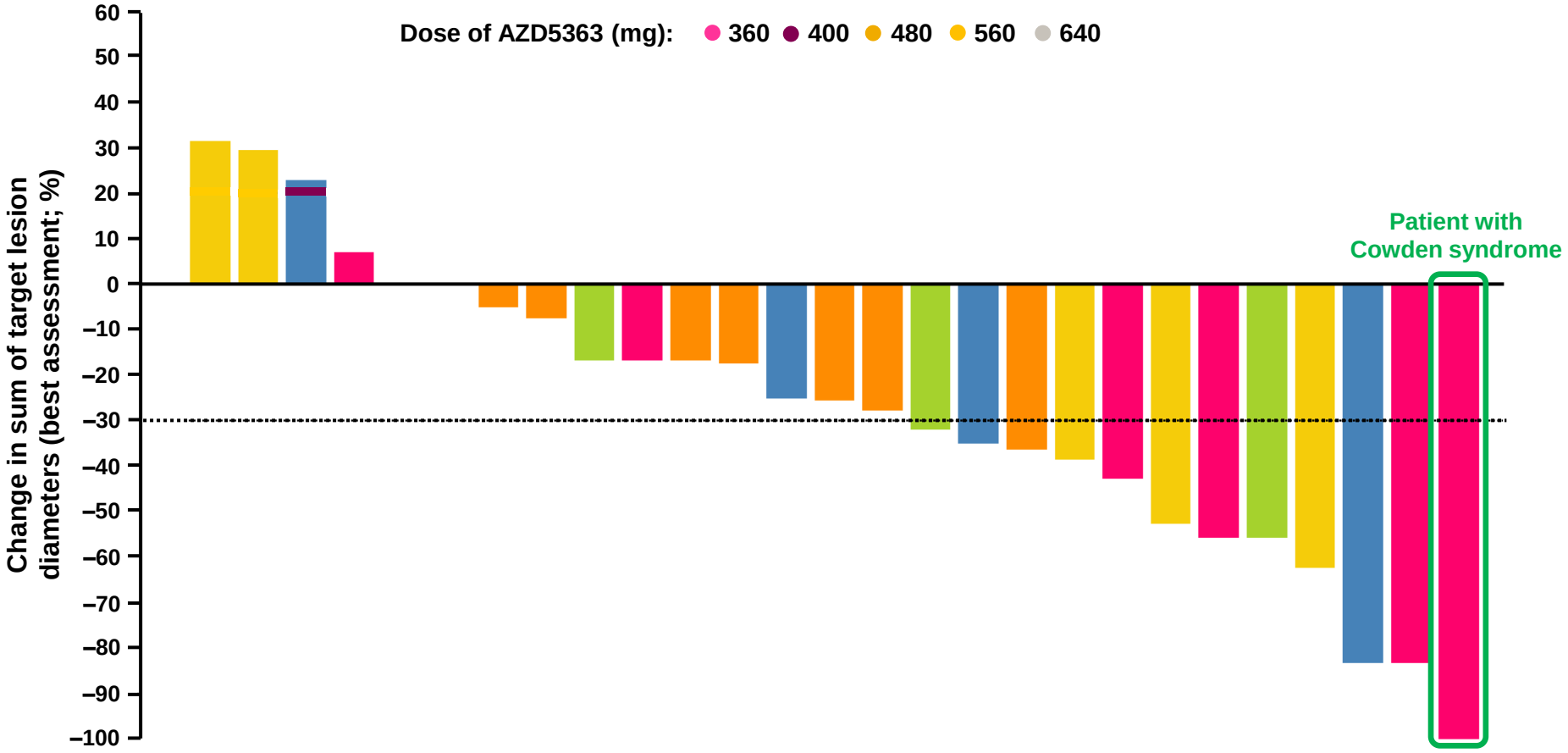
Changes in pPRAS40 in platelet-rich plasma



*Measured in platelet-rich plasma

pPRAS40, phospho-PRAS40

Best percentage change in tumour size



Subject ID	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
PIK3CA status	ND	Unk	ND	ND	ND	Unk	ND	ND	Unk	Unk	PIK3+	PIK3+	Unk	ND	PIK3+	ND	PIK3+	ND	PIK3+	PIK3+	PIK3+	ND	ND	ND	PIK3+	ND	ND
Receptor status	TNBC	TNBC	TNBC	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+	HR+

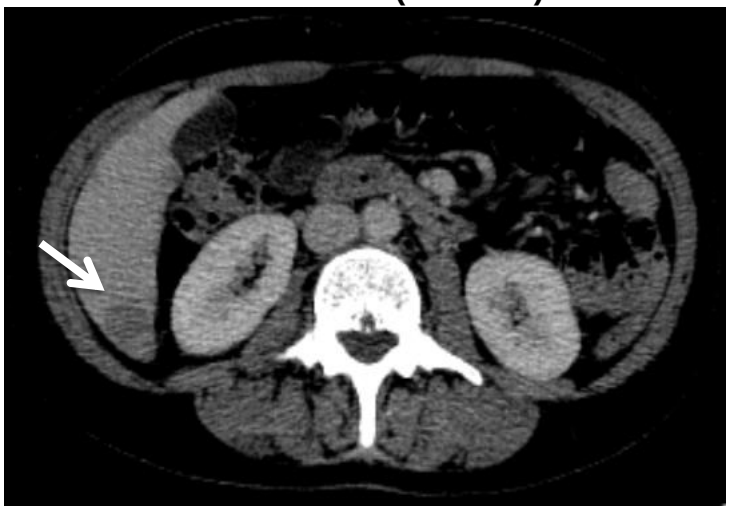
Note: Dotted line represents the threshold for partial response

ND, not detected; PIK3+, *PIK3CA* mutation detected; Unk, unknown

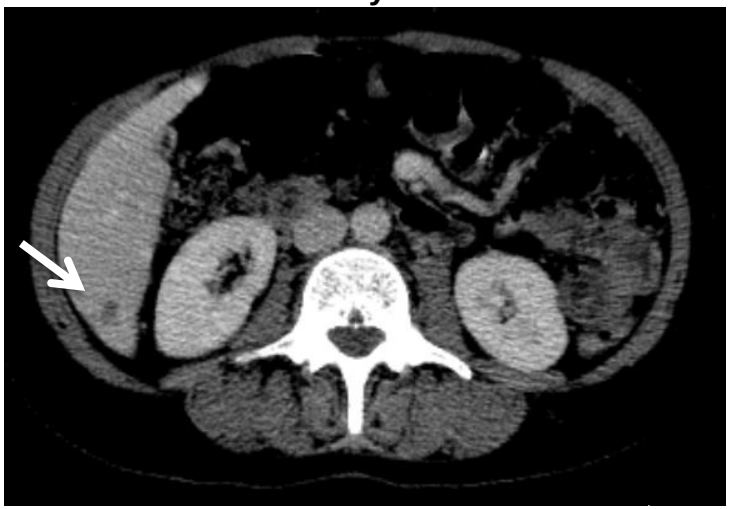
PIK3CA mutation assayed in tumour biopsy and in baseline plasma DNA

Durable complete response in a patient with Cowden syndrome

October 2012 (baseline)



January 2013



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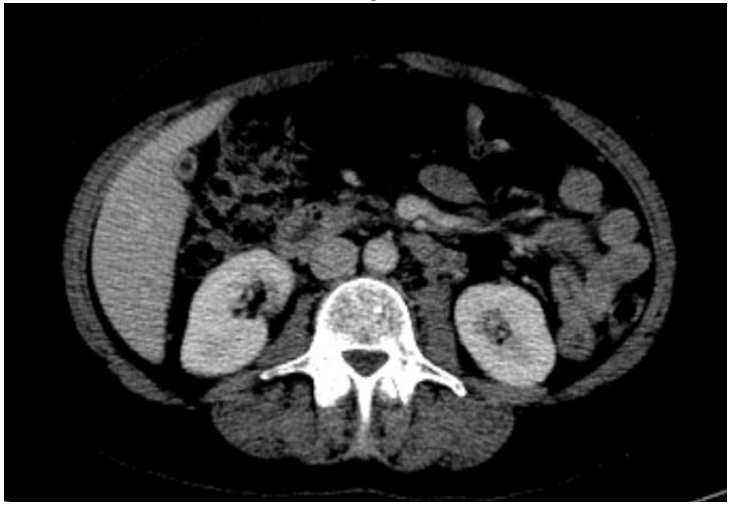
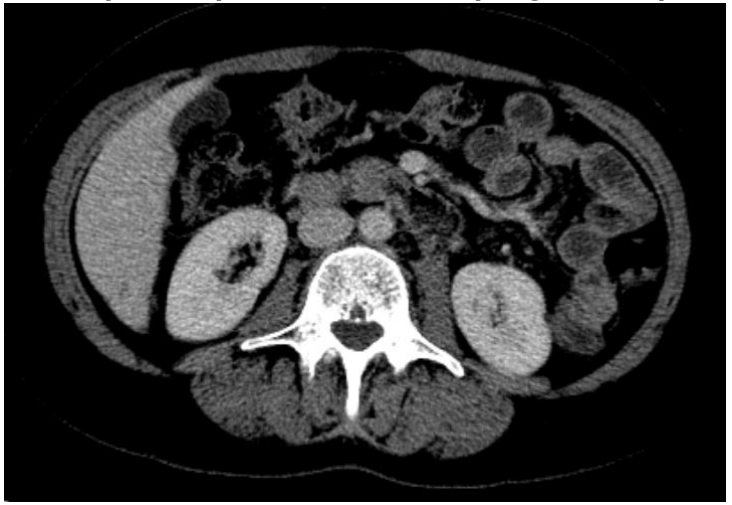


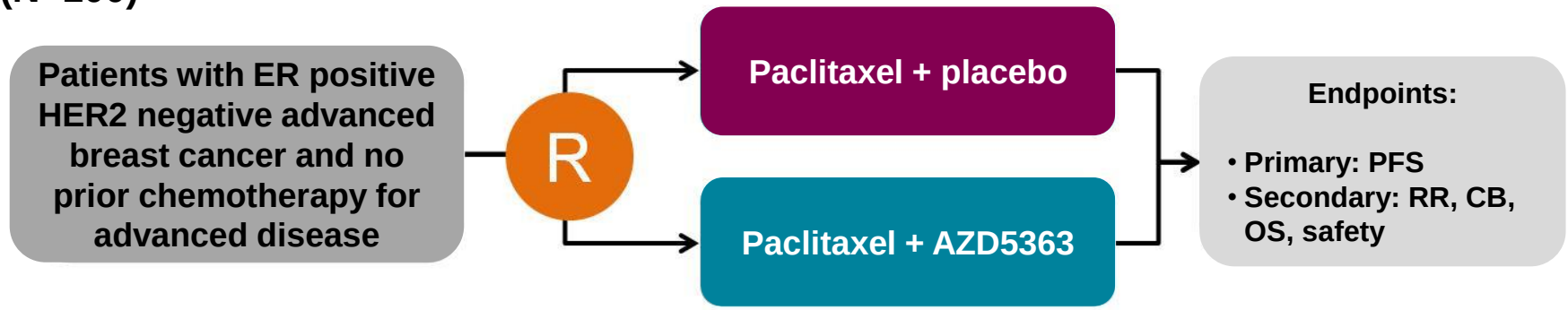
May 2014 (last scan before progression)



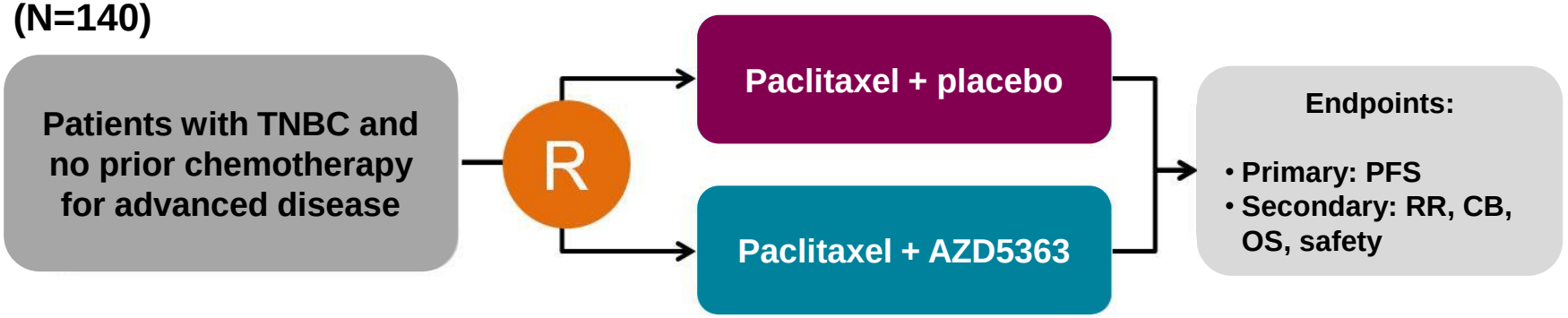
Response maintained for 378 days on AZD5363 alone

Ongoing, randomized Phase II trials: Paclitaxel ± AZD5363

BEECH part B, CI Nick Turner (N=100)



PAKT, CI Peter Schmid (N=140)



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