Target validation and early phase clinical trial

Dr Nicholas Turner

IMPAKT training course 2015
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

Receptor Tyrosine Kinase

PI3K

GRB2

IRS1

Ras

mTOR-raptor

S6K

4E-BP1

rpS6

eIF4E

Cell Survival

Protein Synthesis, Cell growth

p85

p110

PI3K

PIP3

PTEN

PIP2

PDK1

AKT

mTOR-riCTOR

MDM2

p53

BAD

FasL, Bim

FOXO

p27Kip1, p21

c-Myc, Cyclin D1

GSK3

QSK3

Cell Proliferation, Cell cycle

Metabolism

Activating Mutations or Deletions

TSC1/2

Baselga J The Oncologist 2011
### Targeting genetic events in the PI3K-AKT-mTOR pathway

#### Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

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#### Predicted somatic non-silent mutations

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PIK3CA</th>
<th>TP53</th>
<th>MAP3K1</th>
<th>MAP2K4</th>
<th>GATA3</th>
<th>ML3</th>
<th>CDH1</th>
<th>PTEN</th>
<th>PIK3R1</th>
<th>AKT1</th>
<th>RUNX1</th>
<th>CBFB</th>
<th>MCR1</th>
<th>CTCF</th>
<th>FOXA1</th>
<th>SRB1</th>
<th>CARK1</th>
<th>RB1</th>
<th>AUR</th>
<th>NF1</th>
<th>PTEN</th>
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#### Clinical data

- ER
- PR
- HER2
- T
- N

#### Copy number status

- Amplification
- Deletion

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#### Mutations per Mb

<table>
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<th>Subtype</th>
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</tbody>
</table>

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**Percentages of cases with mutation by expression subtype**

- PIK3CA
- TP53
- MAP3K1
- MAP2K4
- GATA3
- ML3
- CDH1
- PTEN
- PIK3R1
- AKT1
- RUNX1
- CBFB
- MCR1
- CTCF
- FOXA1
- SRB1
- CARK1
- RB1
- AUR
- NF1
- PTEN

---

TCGA Nature 2012
Comprehensive molecular portraits of human breast tumours

Targeting genetic events in the PI3K-AKT-mTOR pathway

The Cancer Genome Atlas Network*
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

PTEN loss correlates with AKT activation

PTEN loss correlates with AKT activation

TCGA Nature 2012
AKT inhibitors – targeting loss of PTEN

Cancer with PTEN loss may be particularly sensitive to AKT inhibitor GDC-0068
Drugging the PI3K-AKT-mTOR pathway

- Mutated in cancer
- Biomarker (pathway readout)
- Phosphorylation

AKT inhibitors
- Perifosine
- MK-2206
- GDC-0068
- GSK690693

mTORC1 inhibitors
- Rapalogues: Sirolimus, Everolimus, Temsirolimus, Ribafosum
- mTORC1/2 inhibitors: INK128, AZD8055, OSI-027

mTORC2
- FoxO
- GSK3α/β

PI3K
- PDK1
- AKT

Rheb
- Tuberin
- PRAS40
- mTORC1

S6K
- RPS6
- 4EBP1

mTORC2
- BAD
- PRAS40
- Tuberin

AKT
- PDK1
- PIP3
- PIP2

GFR (EGFR, HER2, MET, FGFR)

INPP4B
- PTEN

Monoclonal antibodies
- Cetuximab (EGFR)
- Trastuzumab (HER2)

Tyrosine kinase inhibitors
- Erlotinib (EGFR)
- Lapatinib (EGFR/HER2)

Pan-PI3K inhibitors
- XL147
- BKM120
- GDC-0941

PI3K-mTOR inhibitors
- BEZ235
- XL765
- GDC-0890
- GSK1059615

Isoform-specific PI3K inhibitors
- CAL-101 (p110δ)
- INK1117 (p110α)
- BYL719 (p110α)
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 downstream signalling

Yap T et al Cancer Res 2011
Inhibition of AKT reduces tumour growth *in vivo*
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

<table>
<thead>
<tr>
<th>AZD5363 structure</th>
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<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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</table>

<table>
<thead>
<tr>
<th>Enzyme inhibition (nM)</th>
<th>Akt1</th>
<th>Akt2</th>
<th>Akt3</th>
<th>ROCK1</th>
<th>ROCK2</th>
<th>PKA</th>
<th>P70S6K</th>
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<td>3</td>
<td>7</td>
<td>7</td>
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<td>7</td>
<td>6</td>
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</table>

<table>
<thead>
<tr>
<th>Inhibition of AKT substrates in cells (µM)</th>
<th>pGSK3β</th>
<th>pPRAS40</th>
<th>pFOXO3a translocation</th>
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<tbody>
<tr>
<td>BT474 breast</td>
<td>0.75</td>
<td>0.31</td>
<td>0.69</td>
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<tr>
<td>0.03 (BT474c; Western)</td>
<td>0.06</td>
<td>0.22</td>
<td>(BT474c)</td>
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<tr>
<td>0.3 (LNCaP; Western)</td>
<td>0.38</td>
<td>0.39</td>
<td>(MDA-MB-468; Acumen)</td>
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</table>

<table>
<thead>
<tr>
<th>LNCaP prostate</th>
<th>pPRAS40 T346</th>
<th>pGSK3b S9</th>
<th>pS6 S236/236</th>
<th>pAKT S473</th>
<th>pAKT T308</th>
<th>p4EBP1 T37/46</th>
<th>p4EBP1 S65</th>
<th>4EBP1</th>
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<td>0.03 (BT474c)</td>
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</table>

FOXO3a translocation assay (BT474c breast)

Control

AZD5363, 3 mM, 2 h

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
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 Tamura7

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

Continuous schedule (n=64) bid dosing

- **80 mg**
  - Tolerated dose
  - n=8
  - 0 DLT

- **160 mg**
  - Tolerated dose
  - n=5
  - 0 DLT

- **240 mg**
  - Non tolerated dose
  - n=12
  - 0 DLT

- **400 mg**
  - Chronically non tolerated dose
  - n=14
  - 3 DLT

- **600 mg**
  - Non tolerated dose
  - n=2
  - 2 DLT

Intermittent schedules (n=29) bid dosing

- **480 mg**
  - Tolerated dose
  - n=6
  - 0 DLT

- **640 mg**
  - Non tolerated dose
  - n=6
  - 1 DLT

- **800 mg**
  - Ongoing
  - n=6
  - 1 DLT

- **1600 mg**
  - 2 days on / 5 days off (2/5)
  - n=6
  - 1 DLT

- **2400 mg**
  - 4 days on / 3 days off (4/3)
  - n=11
  - 0 DLT

DLT: Dose-limiting toxicity

Data cut off: Feb 18 2013
Unvalidated data
## Dose-limiting toxicities

<table>
<thead>
<tr>
<th>Dose (mg) bid</th>
<th>Number of patients with DLT</th>
<th>DLT</th>
<th>CTCAE grade</th>
<th>Number of events</th>
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<tbody>
<tr>
<td>80</td>
<td>0/8</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>160</td>
<td>0/5</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>240</td>
<td>1/12</td>
<td>Hypoxia (multiple pulmonary metastases)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>320</td>
<td>4/14</td>
<td>Maculo papular rash Diarrhea</td>
<td>2 , 3 3</td>
<td>1 , 1 2</td>
</tr>
<tr>
<td>400</td>
<td>3/14</td>
<td>Maculo papular rash Diarrhea</td>
<td>3 3</td>
<td>2 1</td>
</tr>
<tr>
<td>480</td>
<td>5/6</td>
<td>Maculo papular rash Diarrhea</td>
<td>3 2</td>
<td>3 2</td>
</tr>
<tr>
<td>600</td>
<td>2/2</td>
<td>Maculo papular rash</td>
<td>4</td>
<td>2</td>
</tr>
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### Continuous schedule

### Intermittent schedule

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<thead>
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<th>Dose (mg) bid</th>
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<tbody>
<tr>
<td>480 (4 / 3)</td>
<td>0/11</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>640 (4 / 3)</td>
<td>1/6</td>
<td>Diarrhea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>640 (2 / 5)</td>
<td>1/6</td>
<td>Hyperglycemia</td>
<td>3</td>
<td>1</td>
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<tr>
<td>800 (2 / 5)</td>
<td>1/6</td>
<td>Hyperglycemia</td>
<td>3</td>
<td>1</td>
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</table>

**Continuous schedule**

**Intermittent schedule**
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

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

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
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 \textit{PIK3CA} or \textit{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

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?

**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

**Schedule 1**
AZD5363: 2/5*  
(starting dose: 560 mg bid)  
Paclitaxel 90 mg/m²: Once weekly, 3/4 weeks

AZD5363 dose escalation to NTD/MTD

Recommended dose

Selected schedule

**Schedule 2**
AZD5363: 4/3†  
(starting dose: 360 mg bid)  
Paclitaxel 90 mg/m²: Once weekly, 3/4 weeks

AZD5363 dose escalation to NTD/MTD

Recommended dose

**Part B**

*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

cDNA, 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

**AZD5363 2/5 schedule (n=18)**

- **640 mg***
  - n=8
  - 2 DLTs: Neutropenia (CTCAE grade 4); diarrhoea (CTCAE grade 3)

- **560 mg***
  - n=6
  - 0 DLT
  - Tolerated

- **560 mg***
  - n=4
  - 0 DLT
  - MTD

**AZD5363 4/3 schedule (n=18)**

- **480 mg***
  - n=6
  - 2 DLTs: Maculopapular rash (CTCAE grade 3); immune allergic reaction (CTCAE grade 3)

- **360 mg***
  - n=6
  - 0 DLT
  - Tolerated

- **400 mg***
  - n=6
  - 0 DLT
  - MTD and RD for part B

*In combination with paclitaxel 90 mg/m²

CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; RD, recommended dose
## Most common AEs, irrespective of relationship to treatment

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

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

Dose of AZD5363 (mg):
- 360
- 400
- 480
- 560
- 640

Median percentage change from baseline in pPRAS40* after paclitaxel and AZD5363 single dose

Day 2
- Pre-AZD5363
- Day 2
  - 2 hours
  - 4 hours
  - 8 hours
- Day 3
  - Pre-AZD5363

*Measured in platelet-rich plasma
pPRAS40, phospho-PRAS40
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 ND ND ND Unk PIK3+ PIK3+ Unk ND PIK3+ ND PIK3+ ND PIK3+ PIK3+ PIK3+ PIK3+ PIK3+ ND ND ND PIK3+ ND ND 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+ HR+ HR+ HR+
Durable complete response in a patient with Cowden syndrome

Response maintained for 378 days on AZD5363 alone
Ongoing, randomized Phase II trials: Paclitaxel ± AZD5363

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

- Patients with ER positive HER2 negative advanced breast cancer and no prior chemotherapy for advanced disease
  - Paclitaxel + placebo
  - Paclitaxel + AZD5363

Endpoints:
- Primary: PFS
- Secondary: RR, CB, OS, safety

**PAKT, CI Peter Schmid (N=140)**

- Patients with TNBC and no prior chemotherapy for advanced disease
  - Paclitaxel + placebo
  - Paclitaxel + AZD5363

Endpoints:
- Primary: PFS
- Secondary: RR, CB, OS, safety
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