ASCO 2018 investor event; breakout 3:
Next-gen DNA damage response and
tumour drivers

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04 June 2018
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DNA damage response: *Lynparza* and beyond

Developing chemo-free regimens, extending survival

- Establish *Lynparza* leadership as monotherapy
- Launch *Lynparza* combinations (VEGF, IO)
- Expand *Lynparza* beyond *BRCA* (Study 08, prostate cancer)
- Launch AZD1775 (WEE1) / AZD6738 (ATR) *Lynparza* combinations
- Deliver next-generation DDR medicines: AZD0156, AZD1390 (ATM inhibitors), AZD2811 (aurora kinase B inhibitor), DNA-PK

**Scientific leadership in DDR**

|-------------|-------------|-------------|

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AstraZeneca portfolio targets distinct aspects of DDR

Deep development portfolio from preclinical to launch

One launched medicine, four clinical and two preclinical projects: uniquely placed to exploit the full range of therapeutic opportunities afforded by DDR

ATM = ataxia-telangiectasia mutated; ATR = ataxia-telangiectasia and Rad3-related; DNA-PK = DNA-dependent protein kinase; DSB = double strand break; PARP = poly ADP-ribose polymerase; SSB = single-strand break.
**Lynparza: IO and DDR**

Next-generation combinations underway

**Lynparza + Imfinzi**
MEDIOLA Phase II trial

- **Ovarian cancer n=30**
  (3rd-line and later platinum-sensitive, gBRCAm)

- **Breast cancer n=38**
  (1st to 3rd-line HER2-negative, non-platinum refractory, gBRCAm)

- **Small-cell lung cancer n=34**
  (Relapsed 3-6 months post 1st-line platinum chemo)

- **Gastric cancer n=37**
  (2nd-line)

- **Potential additional indication (future)**

**Lynparza + novel DDR**
VIOLETTE Phase II trial

- **Lynparza + ATR (AZD6738)**
  (n=150)

- **Lynparza + WEE1 (AZD1775)**
  (n=150)

- **Lynparza**
  (n=150)

**Triple-negative breast cancer**
- HRR’m (BRCA)
- HRRm (non-BRCA)
- Non-HRRm

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Broad DDR portfolio; deep scientific understanding is driving combination approach

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Capivasertib (AZD5363): targeting AKT

**AKT pathway**

- AKT is a key node in the PI3K-AKT network: common oncogenic pathways converge
- AKT is key driver of resistance to multiple therapies, including hormonal therapies and chemotherapy
- Genetic alterations in the PI3K-AKT network are common in a number of tumours

**Hypothesis**

- Inhibition of AKT to prevent early adaptation and feedback responses
- AKT is key driver of resistance to multiple therapies, including hormonal therapies and chemotherapy
- Genetic alterations in the PI3K-AKT network are common in a number of tumours

**Combinations:**

- inhibition of AKT to prevent early adaptation and feedback responses

**Patient selection:**

- genetic alterations in the network (AKT1, PTEN, PIK3CA, etc.)
Capivasertib: PAKT randomised Phase IIb; 1st-line TNBC

PAKT overall survival: ITT population

Median OS (95% CI) 19.1m vs. 12.6m
HR (95% CI) 0.61 (0.37, 0.99)

PAKT progression-free survival: PI3KCA/AKT/PTEN altered (aberrations by NGS on FFPE)

Median PFS (95% CI) 9.26m vs. 3.75m
HR (95% CI) 0.30 (0.11, 0.79)

1. Triple-negative breast cancer.
Source: ASCO 2018, abstract #1007.
Q&A
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