Meet AZN management: ASCO 2019
Breakout 3: early-stage pipeline

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Rich early to mid-stage pipeline

Tumour drivers and resistance

- **capivasertib** (AKT\(^1\) inhibitor)
  - breast, prostate cancers, Phase III to start
- **AZD9833** (SERD\(^2\), oral)
  - breast cancer, Phase I
- **AZD5991** (MCL1\(^3\) inhibitor)
  - haematologic cancers, Phase I
- **savolitinib** (cMET\(^4\))
  - NSCLC, Phase II

DNA damage response (DDR)

- **adavosertib** (WEE1\(^5\) inhibitor)
  - solid cancers, Phase II
- **ceralasertib** (ATR\(^6\) inhibitor)
  - solid cancers, Phase II
- **AZD2811** (aurora kinase B inhibitor)
  - solid cancers, Phase II
- **AZD1390** (ATM\(^7\) inhibitor)
  - solid cancers, Phase I
- **AZD7468** (DNA-PK\(^8\))
  - solid cancers

Immuno-oncology (IO)

- **monalizumab** (NKG2A\(^9\) mAb\(^{10}\))
  - head & neck, colorectal, Phase II ongoing
- **MEDI5752** (PD-1/CTLA-4 bispecific mAb)
  - solid cancers, Phase I
- **olecumab** (CD73\(^{11}\) mAb)
  - lung, pancreatic cancers, Phase I/II
- **AZD4635** (A2aR\(^{12}\) inhibitor)
  - solid cancers, Phase II
- **AZD9150** (STAT3\(^{13}\) inhibitor)
  - solid cancers, Phase II
- **AZD2811** (aurora kinase B inhibitor)
  - solid cancers
- **AZD7468** (DNA-PK\(^8\))
  - solid cancers

Tumour drivers and resistance: early breast
Building on an established franchise

Capivasertib (AZD5363): targeting AKT

AZD9833 (SERD, oral)

Early evidence of enhanced benefit with capivasertib + paclitaxel in altered metastatic TNBC

ASCO 2019 data on Tuesday 4 June 2019, abstract #1005:
- OS HR 0.57 in the ITT population

Phase III to initiate

Phase I ongoing
Phase II in planning

1. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha  2. Phosphatase and tensin homolog.

Source: ASCO 2018.
Tumour drivers and resistance: cell death
Haematologic cancers the next wave of innovation

Targeting distinct nodes of cell death

AZD5991 (MCL1)\(^1\): novel macrocyclic chemistry
AZD4573 (CDK9)\(^2\): distinct mechanism of targeting MCL1
AZD0466 (Bcl2\(^3\)/xL\(^4\)): nanomedicine to improve therapeutic margin

AZD5991 (MCL1 inhibitor)

Single dose of AZD5991 achieves tumour regression in haematological cancer preclinical models


AZD5991 in Phase I

1. Inhibitor.
2. Cyclin-dependent kinase 9.
DNA damage response: *Lynparza* and beyond

Developing chemo-free regimens, extending survival

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Initiative</th>
</tr>
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<tbody>
<tr>
<td>2016 - 2018</td>
<td><strong>Establish <em>Lynparza</em> leadership as monotherapy</strong></td>
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<td></td>
<td><strong>Launch <em>Lynparza</em> combinations (VEGF(^1), IO)</strong></td>
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<td><strong>Expand <em>Lynparza</em> beyond BRCA (prostate cancer, ovarian cancer)</strong></td>
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<td>2019 - 2021</td>
<td><strong>Launch adavosertib (WEE1) / ceralasertib (ATR) <em>Lynparza</em> combinations</strong></td>
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<td><strong>Deliver next-generation DDR medicines:</strong></td>
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<tr>
<td></td>
<td>AZD1390 (ATM inhibitor), AZD2811 (aurora kinase B inhibitor)</td>
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<td></td>
<td>AZD7648 (DNA-PK)</td>
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<td>2022 - 2025</td>
<td><strong>Launch adavosertib (WEE1) / ceralasertib (ATR) <em>Lynparza</em> combinations</strong></td>
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<td><strong>Launch adavosertib (WEE1) / ceralasertib (ATR) <em>Lynparza</em> combinations</strong></td>
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1. Vascular endothelial growth factor.
DNA damage response: pipeline

The next wave of potential DDR medicines

A broad pipeline targeting complementary aspects of DNA damage repair and cell cycle regulation

AZD2811: targeting Aurora Kinase B

Monotherapy activity in SCLC\(^1\) model *in vivo*

Phase I ongoing
Phase II start in planning

1. Poly (ADP-ribose) polymerase.
# Broad IO pipeline: enhancement of antitumour immunity

Fully harnessing immune system to eliminate tumours

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Example</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No effective antitumour immunity</td>
<td>'Cold' tumour</td>
<td>PD-L1/CD40L, IL-12 mRNA, NDV-GMCSF, HPV Vaccine</td>
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<td>2</td>
<td>Suboptimal or exhausted antitumour immunity</td>
<td>Example: PD-L1+ tumour</td>
<td>PD-L1, CTLA-4, PD-1/CTLA-4, NKG2A</td>
</tr>
<tr>
<td>3</td>
<td>Antitumour immunity suppressed by TME</td>
<td>Example: CD73+ tumour</td>
<td>CD73, A2aR, CD39, STAT3</td>
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</table>

**Goal:** highly-active antitumour immunity

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1. Tumour micro environment  
2. Cluster of differentiation 40 ligand  
3. Interleukin-12  
4. Messenger RNA  
5. Recombinant Newcastle disease virus  
6. granulocyte-macrophage colony-stimulating factor  
Developing an adenosine franchise
Reversing tumour immunosuppression

Targeting adenosine pathway

IMMUNE RESPONSE

Pro-inflammatory

Immunosuppressive

Cancer therapy

↑ Dendritic cell
↑ Macrophage
↓ Tregs

↑ MDSC\(^1\)
↑ Tregs\(^2\)
↑ Fibroblast
↑ Angiogenesis

T effectors
↓ NK\(^3\) cells
↓ Tregs
↑ Suppressive TAM\(^4\)
↑ Angiogenesis

Cell death

↑ Dendritic cell
↑ Macrophage
↓ Tregs

↑ MDSC\(^1\)
↑ Tregs\(^2\)
↑ Fibroblast
↑ Angiogenesis

T effectors
↓ NK\(^3\) cells
↓ Tregs
↑ Suppressive TAM\(^4\)
↑ Angiogenesis

Cancer therapy

P2X7

P2Y2

CD73

CD39

AMP\(^6\)

Adenosine triphosphate

Adenosine monophosphate

AZD4635: targeting A2aR

Phase I ongoing
Phase II in planning

Multiple projects aimed at full suppression

1. Myeloid-derived suppressor cells
2. Regulatory T cells
3. Natural killer cells
4. Tumour-associated macrophages
5. Adenosine triphosphate
6. Adenosine monophosphate

RCC: renal cell carcinoma.
H&N: head and neck cancer.
Next-generation checkpoints
Utilising the innate and adaptive immune system

Monalizumab: targeting NKG2A

MEDI5752: PD-1/CTLA-4 bispecific

Tumour: increased efficacy
Periphery: increased safety

Internalisation and degradation of PD-1 leads to complete and durable blockade of PD-1 and CTLA-4 in the TME
Mitigated toxicity due to reduced binding to CTLA-4+ peripheral T cells

Phase II ongoing
Phase III in planning

Phase I ongoing
Phase II in planning

Source: Cohen et al ESMO 2018.
Oncolytic viruses offer multiple mechanisms of action
Leveraging internal and external expertise

**MEDI5395: NDV-GMCSF**

- Not a select agent; suitable for world-wide development
- F-Protein Cleavage site modification
- Transgene insertion
- Incorporation of intergenic stretch sequence (198nt)
- MEDI5395 (ICPI <0.2)

**Collaboration with Transgene**

1. IFN\(^\gamma\) production, Th\(^2\)1 education
2. T cell memory and homeostasis
3. Activation of APC\(^3\)s
4. Immune priming and APC activation
5. Increase lysis & Type I IFN response

**Collaboration of five oncolytic viruses**

- Intracerebral pathogenicity index scale (ICPI): <0.4 is non-pathogenic

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