Combinations of targeted therapies in oncology – an industry view

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Disclosures

- I am a full time employee of AstraZeneca UK
- I hold AstraZeneca shares
- I will mention non-approved use of investigational agents, olaparib, selumetinib (AZD6244, ARRY-142886), AZD9291, AZD5363, AZD2014, AZD8186, AZD8835
Approach to Prioritising Combinations

- Start where one agent has anti-tumour activity
  - Lineage matters – understand how ‘lineage marker’ eg AR, ER, BCR interacts with target mechanism
- Understand mechanisms of pathway reactivation and resistance mechanisms which emerge *clinically* under clonal selection pressure
- Schedule matters
  - Continuous inhibition not necessarily optimal
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Established 1\textsuperscript{st} line therapy for mutant EGFR NSCLC - reversible EGFR inhibitors (Active vs ‘sensitising’ EGFR mutations Exon19 deletion and L858R substitution.)

Iressa (gefitinib)  
Tarceva (erlotinib)

Recently developed irreversible EGFR inhibitors eg. afatinib and dacomitinib

- potently inhibit EGFRm+ and WT EGFR but DLTs of rash and diarrhea limit ability to target EGFR T790M clinically.

No currently approved therapies to specifically address T790M acquired EGFR-TKI resistance.
Resistance mechanisms - gefitinib / erlotinib

Clinical data

- **T790M** 60%
- **HER2 + T790M** 4%
- **Unknown** 18%
- **Small cell** 1%
- **Small cell + MET** 1%
- **Small cell + T790M** 2%
- **MET + T790M** 3%
- **MET amplification** 3%

Pre-clinical data

- EGFR T790M mutation
- HER2 amplification
- MET amplification
- SCLC transformation
- EMT/AXL activation
- IGFR pathway activation
- Autophagy
- BIM deletion polymorphism
- MAPK amplification
- CRKL over expression
- NRAS mutation
- NFkB signalling
- N-cadherin overexpression
- JAK/stat pathway activation
- miR-214 / PTEN/AKT signalling
- FGFR pathway activation
- Activated stroma / TGFβ signalling
AZD9291: Irreversible selective inhibitor of sensitising and T790M EGFR mutations

Designed to inhibit EGFR Exon19 del, L858R, T790M

Differentiation

- Increased potency towards dual EGFRm+/T790M
- Large selectivity margin vs. wild-type EGFR / IGFR
- Exon 19 del/L858R potency equivalent to current TKIs

- Potential to prevent emergence of T790M resistance mutations
- Potential to sustain longer efficacy
- Reduced EGFR wt toxicity, no hyperglycemic effect
AZD9291: Response rate* 64% in T790M+; Longest response > 9 months and ongoing

Best percentage change from baseline in target lesion
T790M+ evaluable patients, expansion cohorts only (n=107)

Overall disease control rate (CR+PR+SD) = 94%


*Includes confirmed responses and responses awaiting confirmation; # represents imputed values.
Population: all dosed centrally confirmed T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD or PD), N=107 (from 120 T790M+ patients, 13 patients with a current non-evaluable response are not included). QD, once daily; D, Discontinued
Generating EGFR TKI resistant cell populations

In vitro acquired resistance frequently associated with increased sensitivity to MAPK pathway inhibition

Parental cell lines

PC9 (EGFR<sub>exon19del</sub>)

PC9 gefitinib resistant (EGFR<sub>exon19del / T790M</sub>)

PC9 gefitinib resistant (EGFR<sub>L858R / T790M</sub>)

NCI-H1975

Chronic treatment with escalating or single concentration s of an EGFR inhibitor

afatinib (1.5µM)

gefitinib (1.5µM)

WZ4002 (1.5µM)

azinib (1.5µM)

AZD9291 (160nM)

EC<sub>50</sub> µM

<table>
<thead>
<tr>
<th></th>
<th>AZD5363 (AKT)</th>
<th>AZ_6592 (cMET)</th>
<th>selumetinib (MEK1/2)</th>
<th>AZD9291 (EGFR)</th>
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<tbody>
<tr>
<td>PC9</td>
<td>5.661</td>
<td>1.972</td>
<td>6.475</td>
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<td>PC9 GR_1</td>
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<td>PC9 AZDR_1</td>
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<td>PC9 AZDR_2</td>
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<td>0.874</td>
<td>0.641</td>
<td>1.637</td>
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<td>NCI-H1975</td>
<td>1.576</td>
<td>2.582</td>
<td>4.094</td>
<td>0.011</td>
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<tr>
<td>NCI-H1975 AZDR_1</td>
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<td>2.064</td>
<td>0.024</td>
<td>2.506</td>
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<tr>
<td>NCI-H1975 AZDR_2</td>
<td>0.455</td>
<td>1.799</td>
<td>0.110</td>
<td>2.196</td>
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<tr>
<td>NCI-H1975 AZDR_3</td>
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<td>2.608</td>
<td>10.000</td>
<td>3.021</td>
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<td>NCI-H1975 AZDR_5</td>
<td>0.590</td>
<td>2.103</td>
<td>0.033</td>
<td>2.548</td>
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</table>

> than 5 fold increase in sensitivity

> than 5 fold decrease in sensitivity
Combination of AZD9291 with selumetinib may prevent or delays resistance

Selumetinib combination restores tumour growth inhibition following progression on AZD9291
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PIK3CA is the second most commonly mutated gene in breast cancer (TCGA dataset)

- Shown are all genes with total mutation frequency >= 1.5%
- Most commonly mutated gene is the tumour suppressor p53
- The third most commonly mutated gene is TITIN – a very large gene that accumulates a high number of random mutations by chance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Frequency</th>
<th>Hotspot Mutations (mostly missense; excludes hotspot deleterious)</th>
<th>Other Mutations</th>
<th>Deleterious Mutations (frameshift/nonsense)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>30-40%</td>
<td>Proportion of ER+ BrCa tumours with mutations in the PIK3CA gene</td>
<td>Encodes the catalytic domain of phospho-inositol 3-kinase (PI3K)</td>
<td></td>
</tr>
</tbody>
</table>
Cell lines with PIK3CA mutations preferentially sensitive to PI3Kα inhibitor

**PIK3CA Mutation**
MCF7: ER+ Breast Cancer
PIK3CA mutation (E545K)

AZD8835 (PI3Kα inh.) with sensitivity in cell lines with PIK3CA mutations

Using cut off of 1 μM:
- PIK3CA mutation associated with sensitivity
  \( p = 0.00000012, \text{OR} = 12.1 \)

AZD8835 (PI3Kα inh.) with sensitivity in PIK3CA mutant

**PIK3CA Mutation**
MCF7: ER+ Breast Cancer
PIK3CA mutation (E545K)

**Graphs:**
- Tumour volume (cm³) vs. Days dosing
- Control vs. Novartis BYL719 vs. AZD8835 (PI3Kα)
AZD8835 inhibits PI3K pathway in mPIK3CA cells
…but pathway can be reactivated (feedback)

- Pathway suppressed but then reactivated at later timepoints despite continued presence of compound
- Feedback is widely observed with agents targeting PI3K pathway

BT474 cells: ER+ HER2+ mPIK3CA (K111N)
Exposed to 2.5μM AZD8835 throughout time-course
Transient pathway inhibition with AZD8835 (PI3Kα)

Imaging based analysis of FoxO3A cytoplasmic-nuclear translocation

BT474 cells: ER+ HER2+ mPIK3CA (K111N)

Feedback
- On treatment, FoxO3A initially partitions from cytoplasm to nucleus
- FoxO3A activates gene transcription leading to reactivation of growth factor signalling (feedback)
- This reactivation of the pathway, despite the continued presence of AZ8835, re-phosphorylates FoxO3A with re-partitioning into the cytoplasm
Combination of AZD8835 (PI3Kα) + AZD5363 (AKT) induces apoptosis in vivo

Cleaved Caspase-3 end point, BT474 xenograft model - ER+ HER2+ mPIK3CA (K111N)
AZD8186 inhibits growth of PC346C following castration and induces PSA and TMPRSS gene expression.

In castrated animals AZD8186 treated tumour remain dormant after removal of therapy - tumour growth only occurs when testosterone pellets are implanted.

PC346C induction of AR responsive genes in tumours upon inhibition of Pi3K signalling.

Van Weerden and Marques, Erasmus
Inhibiting Pathway Reactivation Increases Cell Kill Combination - PI3Kα and PI3Kβ inhibitor

...which reduces feedback leading to increased apoptosis

Neal Rosen MSKCC collaboration

The combination achieves...
- Greater pathway inhibition at 2h
- Less reactivation of the pathway at 24h

Note that the PI3Kα inhibitor is by itself ineffective in this PTEN null line

The combination achieves...
- Greater inhibition of cell growth
- Much greater apoptosis

Greater inhibition Less reactivation
Endocrine Resistance – Lineage Matters: Hormonal therapy + Dual PI3K blockade

PI3Kβ + PI3Kα + enzalutamide in transgenic model PTEN null prostate cancer
Intermittent dosing *increases* target engagement (hyperglycaemia) with *reduced* diarrhoea & rash

AZD5363 (AKT) clinical data supports intermittent dosing
AZD2014 (Dual TORC1/2): Tumour response and AE profile in TAX-TORC study

Ph I solid tumours, paclitaxel (80mg/m²) + TORC1/2 (AZD2014) dosed 3 days each week

- 93% Disease Control Rate (14/15 patients)
- 47% Partial Response (7/15 patients)
- 0% grade 3 toxicities at 50 mg bid

- 2/2 PRs squamous NSCLC
- Both progressed on prior taxane therapy
- One heavily pretreated patient ongoing (>7 m)

Dr Udai Banerji, Institute of Cancer Research UK, ASCO abstract 2607
AZD2014 (Dual TORC1/2) down-regulates HR genes

Olaparib combination (ER+ HER2+ breast cancer)
BKM120 + Olaparib
Overall Response rates (Based on n = 42 pts$^1$)

<table>
<thead>
<tr>
<th>Response</th>
<th>Ovarian cancer pts (n= 32)</th>
<th>Breast cancer pts (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (22%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (47%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>PD</td>
<td>7 (22%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (9%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
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ASCO 2014 - Phase I of Oral BKM120 and Oral Olaparib for High Grade Serous Ovarian Cancer or Triple Negative Breast Cancer
Ursula Matulonis et al
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  Paul Smith

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  Sarit Schwarz

- MD Anderson
  Gordon Mills

- Vanderbilt
  William Pao

- Erasmus
  Van Weerden Marques

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