Targeted agents in Gynecologic Cancer

Amit M. Oza
Professor of Medicine,
Princess Margaret Hospital,
University of Toronto

Co-Chair Gynecology, NCIC CTG
Targeted Therapies

Incorporation of novel targeted therapies

- Biologic rationale
- Prevalence of target
- Characteristics of the target
  - Amenable to modulation
- Availability of inhibitor
- Effect of target inhibition in patients – activity of inhibitors
Therapies for intracellular targets

Virtue of promiscuity over fidelity?
- Complexity of signal transduction pathways
- Value of single target

Combined approaches due to synergy
- Eg target EGFR + Chemo
- Sequential or concurrent therapy
- Combinations of targeted agents

Aberrations in multiple inter-related pathways
- Develop clinical and translational studies
Molecular Pathways of Interest

- **Angiogenesis**
  - Ovarian, Endometrial, Cervical

- **PI3 Kinase – AKT – mTOR**
  - Endometrial, Ovarian

- **Epigenetic mechanisms**
  - Ovarian, Endometrial

- **EGFR targeting**
  - Ovarian, Cervical, endometrial

- **Poly (ADP-ribose) polymerase inhibition (parp inhibition)**
  - Ovarian
Rationale for Anti-angiogenic therapy

- As tumours increase in size, become dependent on vasculature
- Exploitable differences between normal and tumour vasculature
- Affecting one blood vessel effects large numbers of tumour cells
- Endothelial cells are less likely to develop drug resistance due to slower rates of division
- May actually be synergistic with cytotoxic chemotherapy and radiotherapy
The Angiogenic Switch and Antiangiogenic Therapy

Somatic mutation → Small avascular tumor

Tumor secretion of angiogenic factors stimulates angiogenesis

Rapid tumor growth and metastasis

Angiogenic inhibitors may reverse this vascularization

Angiogenesis is involved throughout tumour formation, growth and metastasis.

Stages at which angiogenesis plays a role in tumour progression

Tumour vasculature differs from normal vasculature

Normal blood vessels  Tumour blood vessels

- Maturation factors
  - No growth factors
  - Tight
  - Support cells

- Growth factors (VEGF)
  - Integrins
  - Leaky
  - Fewer supporting cells

Carmeliet P. Nat Med 2003;9:653–60
VEGF

- Key mediator of angiogenesis
- Controls tumour growth by
  - Stimulating tumour angiogenesis
  - Maintaining tumour vasculature
  - Increasing vascular permeability
  - Affecting the normal immune response
  - Possible direct effect on tumour cells

Ovarian cancer:
High VEGF secretion and expression
  - Latter related to stage/mitotic activity - prognosis
  - VEGF angiogenic and permeability factor: ascites
VEGF

- Key mediator of angiogenesis
  - Stimulating tumour angiogenesis
    - Proliferation and migration of endothelial cells
  - Maintaining tumour vasculature
    - Survival of endothelial cells
  - Increasing vascular permeability
    - Increases interstitial fluid pressure
      - Impairs delivery of $O_2$, nutrients and drugs
      - Hypoxic loop set up causing further production of VEGF
    - May allow tumour cells to enter the circulation and metastasize

Konerding et al. BJC 1999, 80; 724-32
Agents Targeting the VEGF Pathway

- Antibodies inhibiting VEGF receptors (e.g. bevacizumab)
- Soluble VEGF receptors (VEGF-TRAP)
- Antibodies inhibiting VEGF receptors
- Cation channel
- Small-molecules inhibiting VEGF receptors (TKIs) (e.g. PTK-787)
- Ribozymes (Angiozyme)
- Migration, permeability, DNA synthesis, survival
- Angiogenesis
- Lymphangiogenesis
### Single Agent Bevacizumab in Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Bevacizumab Dosing</th>
<th>Number of Patients</th>
<th>Previous Chemotherapy</th>
<th>Platinum Resistance</th>
<th>Response Rate (CR + PR)</th>
<th>6-month PFS</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 170D (Burger ASCO 2005)</td>
<td>Bevacizumab 15mg/kg q 3/52</td>
<td>N=64</td>
<td>1 or 2 previous chemotherapy courses, 55% platinum resistant</td>
<td>55% platinum resistant</td>
<td>RR 18% (CR 5%) SD 55%</td>
<td>6month PFS 38.7%</td>
<td>Median PFS 4.7months</td>
<td>Median OS 17months</td>
<td>Emesis, constipation, TE</td>
</tr>
<tr>
<td>Cannistra et al (ASCO 2006)</td>
<td>Bevacizumab 15mg/kg q 3/52</td>
<td>N=44</td>
<td>Up to 3 prior chemotherapy courses, 100% platinum resistant</td>
<td>100% platinum resistant</td>
<td>RR 16% (CR 0%) SD 25%</td>
<td>6 month PFS 27%</td>
<td>Median PFS 4.3months</td>
<td>Median OS not reached</td>
<td>Arterial TE, GI perforation, HT</td>
</tr>
</tbody>
</table>
## Combination Bevacizumab Regimens in Ovarian Cancer

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin Paclitaxel (n=43, Penson, ASCO 2006)</th>
<th>Cyclophosphamide (N=70) (Garcia JCO 2007)</th>
<th>Erlotinib (n=13) Friberg ASCO 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab</strong></td>
<td>15 mg/kg q3w (+maintenance)</td>
<td>10 mg/kg q2w</td>
<td>15 mg/kg q3w</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td>Carboplatin AUC5 Paclitaxel 175 mg/m² q3/52</td>
<td>Cyclophosphamide 50 mg/d</td>
<td>Erlotinib 150 mg/d</td>
</tr>
<tr>
<td><strong>Prev. regimens</strong></td>
<td>0</td>
<td>≤3</td>
<td>≤3</td>
</tr>
<tr>
<td><strong>Pt sensitivity</strong></td>
<td></td>
<td>Pt Refractory</td>
<td>4 refractory, 2 resistant, 7 sensitive</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Neuro, HT, PE, Wound healing (No GI perf, ATE)</td>
<td>III/IV (&gt;5%): HT, fatigue, Na↓, pain</td>
<td>Diarrhoea, GI perforation (2/13), HT</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>CT: CR 56%, PR 22%</td>
<td>CR 0%, PR 25%, SD 50%</td>
<td>CR 1 (8%), PR 1 (8%) SD 7 (54%)</td>
</tr>
<tr>
<td><strong>Median PFS (m)</strong></td>
<td>7</td>
<td>7</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Progression-Free Survival
By Treatment Group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PF</th>
<th>Failed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical Controls</td>
<td>2</td>
<td>330</td>
<td>332</td>
</tr>
<tr>
<td>PI vs GOG 1700</td>
<td>14</td>
<td>48</td>
<td>62</td>
</tr>
</tbody>
</table>

Log-Rank P < .0001
Bevacizumab
ICON-7 Design

Stratification factors: stage, residual disease status, country

Treatment:
Carboplatin AUC = 6
Paclitaxel 175 mg/m²
Bevacizumab 7.5 mg/kg
(All treatments q 3 weeks)

1520 stage IIB-IV patients

Carboplatin/paclitaxel

6 cycles (4.5 months)

Carboplatin/paclitaxel + bevacizumab

12 cycles (7.5 months)

observation

bevacizumab
Current Trials

First Line
- ICON 7: TC +/- Bevacizumab 7.5mg/kg
  - Concurrent and maintenance – 12 cycles
  - Max: 12 months
- GOG 218: TC +/- B 15mg/kg
  - Concurrent
  - Maintenance
  - Max: 15 months

Second Line
- TC +/- AZD 2171
  - Concurrent
  - Maintenance

Maintenance
- sorafenib
Anti-angiogenics in OVCA

Anti VEGF

- MoAB: Bevacizumab
- AMG 386 + paclitaxel
- VEGF Trap – Sanofi - Aventis
- Oral TKIs –
  - Sorafenib (Bay 43-9006)
    - In combination
    - Maintenance post chemotherapy
  - Sunitinib
  - AZD 2171
    - Single agent
    - ICON 6 in platinum sensitive ovarian cancer recurrence
PI3 Kinase-AKT-mTOR

The PI3-kinase (PI3K) and mTOR pathways

- key growth factor-mediated signal transduction pathways that regulate cell growth
- Regulates cell growth and proliferation in response to metabolic signals and cellular stress

PI3K and mTOR cooperate to activate downstream targets that regulate the translation of cell cycle regulatory proteins

mTOR Inhibitors

- inhibits translation of proteins regulating G1 phase
Metabolic programming of cells

- PI3K/AKT
- Cell proliferation
- Nutrients
- Energy
- Biosynthetic activity
- DNA Viruses
- Viral replication
- Glycolysis
- Lipid biosynthesis
- Signal transduction
- Gene expression

- mTOR
- pS6 kinase
- 4EBP1
- HIF 1A
- VEGF
- CYCLIN A
- CDK ½
- CDK INHIB
- Rb protein
- eIF4G

TRANSLATION
PTEN and mTOR in endometrial cancer

PTEN
- Tumour suppressor gene
- Encodes PI3-phosphatase which antagonizes PI3 kinase signaling
- Negative regulator of PkB/Akt signaling

PTEN mutations common in endometrial cancer
- enhanced PkB/Akt phosphorylation and presumably activation
  - cycle turnover (angiogenesis and protein synthesis)
PTEN mutations
Common in endometrial ca

PTEN

Ras

PI3K

PI4,5P3

PTEN

PI4,5P2

G-protein receptor

RTK

Integrin

Nutrients

PTEN

Akt

P

Rapamycin

Temsiorlimus

Everolimus

Deforolimus

mTOR

P70s6k

S6

Ribosome Synthesis

4E-BP1

EIF-4E

Translation Initiation

G1 Arrest

Increased protein synthesis, G1 progression and cell growth
Waterfall plots of response – chemo naïve and chemo treated.

**IND.160a**
(n = 28 evaluable patients)

**IND.160b**
(n = 24 evaluable patients)
**Temsirelimus in Endometrial Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Chemo Naïve Population (N=28 evaluable)</th>
<th>Chemo treated patients (N=24 evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (25%)</td>
<td>5.6 (2.8-20.2)</td>
</tr>
<tr>
<td>SD</td>
<td>16 (57%)</td>
<td>9.5 (3.1-13.4)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (18%)</td>
<td>10 (42%)</td>
</tr>
</tbody>
</table>
Correlative Studies in Archival Tissue: Response or SD

No correlation
- PTEN loss of expression (61%)
- PTEN mutations (55%)
- Cytoplasmic AKT
- Nuclear AKT
- pmTOR
- pS6 expression

BUT: archival tissue
- Expression at time of metastatic disease?

Histology
- Grade 1 = 5/5 and 2/2
- Grade 2 = 7/12 and 0/3
- Grade 3 = 10/13 and 8/17
- Serous = 5/6 and 5/8
Single agent relevance

- Single agent activity seen.
  - Chemo naïve patients
  - Chemo treated patients
  - High grade and serous histologies
  - Not isolated to patients with PTEN mutations or PTEN loss

- Level of activity encouraging.
  - Temsirolimus
  - Deforolimus
Deforolimus

NCIC CTG
Single agent Phase II
Chemo-naïve patients
N=30

Ariad/Merck
Randomized Phase II
Chemo-treated
Deforolimus vs Hormones
N=150

Randomized Phase III clinical trial
Deforolimus vs Hormones
?Chemo-naïve or chemo-treated
N=380
Combination Studies

Chemotherapy
- NCIC CTG – with carboplatin and paclitaxel
- Phase I with Topotecan
  - Temsirolimus
  - Everolimus

Hormonal Therapy
- GOG: Temsirolimus +/- Hormones
  - Randomized Phase II

Targeted Agents
- GOG: Temsirolimus + bevacizumab
Future Strategies

- **Phase II/III**
  - Carbo/paclitaxel+mTOR inhibitor
  - Maintenance therapy following chemotherapy
    - Advanced stage disease
- **Synergy with other targeted agents**
  - VEGF
  - EGFR
  - HDAC inhibitors
- **Synergy with radiation**
Novel Agents

- Antiangiogenics
  - Active in Ovarian Ca
  - Phase III underway
  - Agent/schedule
  - indication

- mTOR inhibition
  - Active in Endo Ca
  - Random Phase II – III
  - Agent/schedule
  - indication

Combinations with other targeted agents

Radiation?

Indications?
**GOG 218 Proposal (US)**

**Primary endpoint:** OS

**Secondary endpoint:** PFS

**Arm A**
- Carboplatin AUC6
- Paclitaxel 175 mg/m²
- Placebo

**Arm B**
- Placebo
- Avastin 15 mg/kg
- Carboplatin AUC6

**Arm C**
- Avastin (15 mg/kg)
- Paclitaxel 175 mg/m²
- Placebo

1:1:1 Randomization

Cycles (q3wk)*

15 months*

Stratification variables: PS (0-1 vs 2), stage (III vs IV)

Sub-optimally debulked Stage III/IV OC N=2000

* Taxane consolidation therapy prohibited
New Drugs in Ovarian Cancer

- Anti VEGF
  - VEGF Trap – Sanofi - Aventis
  - Oral TKIs –
    - Sorafenib (Bay 43-9006)
    - Sunitinib
    - AZD 2171 – ICON 6 in platinum sensitive ovarian cancer recurrence
**ICON 6 Design schema**

**2:3:3 RANDOMISATION**

**Arm A**
Reference arm
6 cycles of chemotherapy
plus Placebo

**Arm B**
Chemotherapy
Plus
AZD2171
during Chemotherapy

**Arm C**
Chemotherapy
plus
AZD2171
during Chemotherapy

No Progressive disease
Placebo
Maximum 18 months from randomisation

No Progressive disease
Placebo
Maximum 18 months from randomisation

No Progressive disease
Maintenance
AZD2171 after chemotherapy
Maximum 18 months from randomisation