BEYOND BEVACIZUMAB
NOVEL TARGETS IN NEW SIGNALING PATHWAYS IN EPITHELIAL OVARIAN CANCER

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Conflict of Interest Disclosure

I herewith declare that I have potential conflicts of interest with several pharmaceutical companies, the drugs of which will be mentioned during my presentation, predominantly in form of unrestricted research grants donated to the research institutes directed by me, but also as honoraria for consulting.
Non-Target or Pathway Driven Approaches

- **New cytostatic / cytotoxic agents with**
  - New formulations:
    - Lurbinectedin (PM01183)
    - Nab-paclitaxel
    - Etirinotecan Pegol (NKTR-102)

- **Deletion of old / new ineffective cytotoxic agents**
  - Topotecan
  - Patupilone (EPO 906)
  - Vintafolide (MK-8109)
  - Phenoxodiol
Impact on Outcome has / will come from:

- **New insights into the patho-physiology of the disease**
  - Implementing a molecular classification based on underlying patho-mechanisms
  - Responding therapeutically to these new categorizations
  - Pre-selecting patients and antitumoral agents accordingly based on pre-established biomarkers

- **Development of substances interfering with these newly identified patho-mechanisms**
Target / Pathway Driven Approaches

Endothelial cell

- VEGF
  - Bevacizumab
  - VEGF trap

VEGFR
- Cediranib
- Pazopanib
- Sorafenib
- Sunitinib
- Nintedanib
- Cabozantinib
- Brivanib

FGFR
- Nintedanib
- Pazopanib
- Sorafenib
- Sunitinib

PDGFR
- Nintedanib
- Sorafenib
- Sunitinib

Tie2 receptor
- Angiopoietin
- AMG 386

Angiogenesis

Ovarian cancer cell

- PI3K/AKT/mTOR inhibitors
  - MK-2206
  - AZD2014

Folate receptor
- Pertuzumab
- Vinfludine

EGFR/HER2/her3 inhibitors
- Erlotinib
- Gefitinib
- Trastuzumab
- Pertuzumab
- MM-121

IGFR inhibitors
- AMG 479
- Linotinib

PI3K/AKT/mTOR

mTOR

Ras/Raf/MEK inhibitors
- Selumetinib
- Trametinib
- MEK162

Src inhibitor
- Saracatinib

Cell-cycle inhibitors
- Aurora kinase inhibitor-
  - alisertib
- Wee1 inhibitor-MK-1775

Nucleus

PARP inhibitors
- Olaparib
- Rucaparib
- Veliparib
- Niraparib
- BMN-673

DNA replication

Normal cell
- HR-mediated DNA repair
- Cell survival

Tumor cell (BRCA-deficient)
- Impaired HR-mediated DNA repair
- Cell death

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Targeting Angiogenesis / Vascularity

- VEGF: (Bevacizumab), VEGF-Trap
- VEGFR: Sorafenib, sunitinib
- PDGFR: Cediranib, pazopanib, imatinib
- FGFR: Nintedanib, brivanib, dovitinib
- c-MET: Cabozantinib
- Angiopoietin-1/2: Trebananib (AMG 386)
- Vascular disruption: Combretastatin (fosbretabulin)
Academic-Led, Industry-Supported Gynecologic Cancer Intergroup (GCIG) Randomized, Double-Blind Phase III Trial of Cediranib (AZD 2171) in Relapsed Platinum Sensitive Ovarian Cancer (ICON6)

Survival benefit demonstrated

**Maintenance Cediranib vs Chemotherapy only**

**Progression-free survival (primary)**
- PFS increased by 3.1 months with maintenance cediranib, from 9.4 to 12.5 months*

**Overall survival (secondary)**
- OS increased by 2.7 months with maintenance cediranib, from 17.6 to 20.3 months*

* Restricted means analysis due to non-proportional hazards

Courtesy of Stark et al on behalf of the ICON6 Collaborators (NCRI, NCIC-CTG, ANZGOG, GEICO)
Anti-Angiopoietin Therapy with Trebananib for Recurrent Ovarian Cancer (TRINOVA-1): A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase III Trial

Monk et al; Lancet Oncol 2014 (http://dx.doi.org/10.1016/S1470-2045(14)70244-X)

Median PFS
7.2 months
5.4 months

HR 0.66 (95%CI 0.57-0.77); p<0.0001
Target / Pathway Driven Approaches

VEGFR
- Cediranib
- Pazopanib
- Sorafenib
- Sunitinib
- Nintedanib
- Cabozantinib
- Brivanib

FGFR
- Nintedanib
- Pazopanib
- Sorafenib
- Sunitinib

PDGFR
- Nintedanib
- Sorafenib

VDAs
- Combrertatin
- Forskhatulin
- Ombrabulin

PI3K/AKT/mTOR inhibitors
- MK-2206
- AZD2014

Angiogenesis
- MET
- Cabozantinib

Folat receptor
- Farnetuzumab
- Vintafoide

Ras/Raf/MEK inhibitors
- Selumetinib
- Trametinib
- MEK182

Src inhibitor
- Saracatinib

Cell-cycle inhibitors
- Aurora kinase inhibitor
- alsetenb
- Wee1 inhibitor-MK-1775

PARP inhibitors
- Olaparib
- Rubucaparib
- Veliparib
- Niraparib
- BMN-673

Normal cell
- HR-mediated DNA repair
- Cell survival

Tumor cell (BRCA-deficient)
- Impaired HR-mediated DNA repair

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## Dualistic Model of Carcinogenesis in Ovarian Cancer

No Common Precursor of Epithelial Ovarian Cancer Identified

<table>
<thead>
<tr>
<th>Type I Tumors</th>
<th>Type II Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development stepwise from precursor lesions; potentially from fallopian tube epithelium (borderline tumors, endometriosis)</td>
<td>Development from serous tubal intra-epithelial lesions (STILs) p53 signatures</td>
</tr>
<tr>
<td>Low-grade serous cancer (LGSC)</td>
<td>High-grade serous cancer (HGSC)</td>
</tr>
<tr>
<td>Low-grade endometrioid cancer</td>
<td>High-grade endometrioid cancer</td>
</tr>
<tr>
<td>Clear cell cancer</td>
<td>Malignant mixed mesodermal tumors (carcinosarcomas)</td>
</tr>
<tr>
<td>Mucinous cancer</td>
<td>Undifferentiated cancer</td>
</tr>
<tr>
<td>Large mass</td>
<td>Presentation in advanced stage (II-IV)</td>
</tr>
<tr>
<td>Confined to ovary (stage Ia)</td>
<td>Growth rapid and aggressive</td>
</tr>
<tr>
<td>Indolent</td>
<td>Dismal prognosis</td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Genetically unstable</td>
</tr>
<tr>
<td>Genetically relatively stable</td>
<td>Preponderance of TP53 mutation and BRCA inactivation (mutation or hypermethylation)</td>
</tr>
<tr>
<td>Variety of somatic mutations</td>
<td></td>
</tr>
</tbody>
</table>

Kurmann & Shih; Human Pathology 42:918-931, 2011
Prevalence of Histologic Types of Epithelial Ovarian Cancer and Their Associated Molecular Genetic Changes

Type I

- ARID1A
- CTNNB1
- PTEN
- PIK3CA
- PPP2R1A Mutation

Type II

- TP53 mutation
- Chromosomal instability

Inactivation of BRCA 1/2 (Mutation or hypermethylation)

Kurmann & Shih; Human Pathology 42:918-931, 2011
Mechanism of Synthetic Lethality between BRCA Deficiency and PARP Inhibition

DNA damage (SSBs)

PARP inhibition
Impairs base excision repair

DNA replication (DNA DSBs or replication fork collapse)

Normal cell with functional HR pathway

HR-mediated DNA repair
Cell survival

Tumor-selective cell death (synthetic lethality)

HR-deficient tumor cell (BRCA deficient)

Cell death
Impaired HR-mediated DNA repair

Banerjee et al; Nat Rev Clin Oncol 7:508-519, 2010
Homologous Recombination (HR) Deficiency, Platinum Sensitivity and Capacity to Evolve

- Genomic instability +/-
- Platinum sensitivity (+) or resistance
- Capacity to evolve +/-

- BRCA1 Germline 8%
- BRCA2 Germline 6%
- BRCA1 Somatic 3%
- BRCA2 Somatic 3%
- BRCA1 Methylation 11%
- EMSY Amplification 6%
- PTEN Loss 5%
- Other HRD 7%
- Other 34%

- Genomic instability ++
- Platinum hypersensitivity ++
- Capacity to evolve ++

Not HR deficient Homologous recombination (HR) deficient

Adapted from The Cancer Genome Atlas 2011 and modified acc to Gourley 2014 ESMO-Congress Madrid
Poly(ADP-Ribose)Polymerase (PARP) - Inhibitors

PARP-inhibitors exploit synthetic lethality to target DNA-repair defects

- Olaparib (AZD2281): oral
- Veliparib (ABT-888): oral
- Rucaparib (PF 0136738): iv / oral
- Niraparib (MK 4827): oral
- BMN 673 (BioMarin): oral
- INO-1001 (Inotek): iv
- GP1201 (Eisai): oral
- CEP 9722 (Cephalon): oral
Olaparib (AZD2281)

Double-blind, placebo-controlled phase II-study
High-grade serous ovarian cancer patients with PR or CR from platinum-containing therapy
(22% BRCA mutated, 64% BRCA status unknown)

Randomization

Maintenance therapy vs Placebo

8.4 months Median PFS 4.8 months
HR 0.35 (95%CI 0.25 to 0.49); p<0.001

Overall survival
HR 0.94 (95%CI 0.63 to 1.39); p=0.75

Olaparib Maintenance Therapy in Patients with Platinum-Sensitive Relapsed Serous Ovarian Cancer: Randomized Phase II Trial

Ledermann et al; Lancet Oncol 15:852-861, 2014

<table>
<thead>
<tr>
<th>BRCAm N=136</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/total patients (%)</td>
<td>26/74 (35%)</td>
<td>46/62 (74%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.2 (8.3–NC)</td>
<td>4.3 (3.0–5.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.18 (0.10–0.31); p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Progression-free Survival in Relation to BRCA Mutation

Ledermann et al; Lancet Oncol 15:852-861, 2014
Cediranib and Olaparib vs Olaparib Alone in Recurrent Platinum-Sensitive Ovarian Cancer: A Randomized Phase II Study

Liu et al; Lancet Oncol 15:1207-1214, 2014

Months

Progression-free survival (%)

Olaparib Cediranib/Olaparib Olaparib Cediranib/Olaparib

16.5 months 19.4 months 5.7 months 16.5 months

p=0.16 p=0.008

HR 0.55 (95% CI 0.24-1.27) HR 0.32 (95% CI 0.14-0.74)

A Germline BRCA1/2 mutated

B Germline BRCA1/2 wild-type or unknown

Number at risk

Olaparib group 24
Cediranib plus olaparib group 23

18 9 5 1 0

26 15 7 3 0

18 9 4 1 0

18 9 4 1 0

Liu et al; Lancet Oncol 15:1207-1214, 2014
p53 Pathway

- Ribonucleotide depletion
- Hypoxia
- Nitric oxide
- Oxidative stress
- Mitotic apparatus dysfunction
- Oncogene activation
- DNA replication stress
- Double-strand breaks
- Telomere erosion

MDM2 - p53

Regulation of p53 target genes
- Metabolic homeostasis
- Antioxidant defence
- DNA repair

Growth arrest

Senescence

Apoptosis

Mild and physiological stress

Severe stress

Levine & Oren; Nature Reviews Cancer 9:749-758,2009
Schematic Illustration of Pathway Alterations Involved in the Development of Low-Grade Serous Cancer (LGSC)

Kurmann & Shih; Human Pathology 42:918-931, 2011
Selumetinib in Women with Recurrent LGSC of the Ovary or Peritoneum: An Open-Label, Single-Arm, Phase II Study

- **Primary endpoint:** Proportion of patients with ORR (acc. to RECIST)
- **Pretreatment:** ≥ 3 previous chemotherapies in 58% of patients
- **Activity:** 8 (15%) ORR: 1 CR, 7 PR; 34 (65%) SD
- **Toxicities (G4):** cardial (1), pain (1), pulmonary (1)
- **Toxicities (G3):** GI (13), skin (9), metabolic (7), fatigue (6), anemia (4), pain (4), constitutional (3), cardiac (2)
- **Median PFS/PFS 6:** 11.0 months / 63%
- **Median OS:** not yet reached
- **No correlation between ORR and BRAF/KRAS mutational status**

Farley et al; Lancet Oncol 14:134-140,2013
Histologic Subtypes of Epithelial Ovarian Carcinoma and Associated Mutations / Molecular Aberrations

Ovarian cancer

Epithelial

High-grade serous
- TP53
- BRCA1 and 2
- NF1
- RB1
- CDK12
- Homologous recombination repair genes*

Low-grade serous
- BRAF
- KRAS
- NRAS
- ERBB2

Mucinous
- KRAS
- HER2 amplification

Clear cell
- ARID1A
- PIK3CA
- PTEN
- CTNNB1
- PPP2R1α

Endometrioid
- ARID1A
- PIK3CA
- PTEN
- PPP2R1α

Sex cord-stromal
- Granulosa cell
- FOXL2

Others, including germ cell
- Sertoli-Leydig cell
- DICER1

Pathway alterations:
- PI3K/RAS/NOTCH/FOXM1

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HER2 as Target in Ovarian Cancer

- Trastuzumab in recurrent / refractory ovarian cancer with overexpression of HER2: Phase II GOG trial (Bookman et al; J Clin Oncol 21:283-290, 2003)
  - Old taxonomy
  - No patient with mucinous histology
  - ORR 7.3% (1 CR, 2 PR)
  - Median PFS: 2 months

- Lapatinib in persistent or recurrent epithelial ovarian cancer or primary peritoneal carcinoma: A GOG study (Garcia et al; Gynecol Oncol 124:569-574, 2012)
  - N=28 patients
  - PFS 6: 8%
  - No objective response
  - Unselected population
  - Minimal activity
HER2 as Target in Ovarian Cancer

  - Median PFS:
    - $p=0.14$ HER2 positive patients (N=8) 20.9 weeks
    - HER2 negative patients (N=20) 5.8 weeks
    - HER2 unknown patients (N=27) 9.1 weeks
  - ORR: 4.3%

- Randomized phase II: Pertuzumab plus carboplatin vs carboplatin in relapsed, platinum-sensitive ovarian cancer (Kaye et al; Ann Oncol 24:145-152, 2013)
  - No histology detailed
  - No prolongation of PFS in unselected patients
Target / Pathway Driven Approaches

![Diagram showing target/pathway driven approaches in cancer therapy]

**Endothelial cell**
- VEGFR
  - Cediranib
  - Pazopanib
  - Sorafenib
  - Sunitinib
  - Nintedanib
  - Cabozantinib
  - Brivanib
- MET
  - Cabozantinib
- Tie2 receptor
  - Angiopoietin
  - AMG 386

**Ovarian cancer cell**
- VEGF
  - Bevacizumab
  - VEGF trap
- PI3K/AKT/mTOR inhibitors
  - MK-2206
  - AZD2014
- Folate receptor
  - Farnetuzumab
  - Vintafolide
- Ras/Raf/MEK inhibitors
  - Selumetinib
  - Trametinib
  - MEK182
- Src inhibitor
  - Saracatinib
- Cell-cycle inhibitors
  - Aurora kinase inhibitor- alisertib
  - Wee1 inhibitor-MK-1775
- EGFR/HER2/HER3 inhibitors
  - Erlotinib
  - Gefitinib
  - Trastuzumab
  - Pertuzumab
  - MM-121
- IGFR inhibitors
  - AMG 479
  - Linotinib

**PARP inhibitors**
- Olaparib
- Rucaparib
- Veliparib
- Niraparib
- BMIN-673

**Gene-replication**
- Normal cell
  - HR-mediated DNA repair
  - Cell survival
- Tumor cell (BRCA-deficient)
  - Impaired HR-mediated DNA repair

**CCR New Strategies**
Randomized Phase III Study of Erlotinib versus Observation in Patients with No Evidence of Disease Progression after First-Line Platin-Based Chemotherapy for Ovarian Carcinoma

Vergote et al; J Clin Oncol 32:320-326, 2014
Folate Transport

- Folate receptor α is a membrane-bound protein with high affinity for binding and transporting folate into cells.
- Folate receptor α expression is up-regulated in ~90% ovarian cancers.
- Farletuzumab is a humanized MoAb targeting folate receptor α.
Folate Transport
Farletuzumab – Study Results

- Phase I:
  (Konner et al; CCR 2010)
  No MTD at 400 mg/m² weekly iv
t₁/₂ 120-260 hrs; dose proportional PK

- Phase II:
  (Armstrong et al; Gynecol Oncol 2013)
  Platinum-sensitive patients
  Farletuzumab + carboplatin/paclitaxel
  Combination:
  CA125 normalization in 81%
  ORR: 75%;
  PFS Int2 > PFS Int1: 21%
  Toxicities: pyrexia, headache, flushing

- Phase III:
  (Weil, AACR 2012)
  (Morphotek Press Release 2013)
  Platinum-sensitive patients
  Carboplatin/paclitaxel + farletuzumab
  Primary endpoint (PFS significantly ↑) not met
Immune Therapy

- Interferon gamma (IFNγ)
- Oregovomab (anti-CA125 MoAb)
- Abagovomab (anti-idiotypic CA125 MoAb)
- Catumaxomab (anti-EpCAM / anti-CD3 MoAb)
- Ontak (anti-CD25 MoAb)
- Ipilimumab (anti-CTLA-4 MoAb)
- Nivolumab (anti-PD-1 MoAb)
- MDX 1105 (anti-PD-L1 MoAb)
Potential Future Therapeutic Consequences Based upon New Classifications and Molecular Characteristics

- **High-grade serous ovarian cancer**
  - BRCAness ↔ PARP inhibitors
  - mut p53 ↔ HSP 90 inhibitors (17AAG, ganetespib)
    - HDAC inhibitors
  - Mitotic checkpoint aberrations ↔ Aurora kinase A inhibitor
    - (alisertib (MLN 8237))
    - Wee-1 kinase inhibitor (MK-1775)
  - PI3K amplification ↔ PI3K inhibitors

- **Low-grade invasive serous ovarian cancer**
  - Aberrations in the Ras-Raf-MEK-MAPK pathway ↔ inhibitors
    - (e.g. MEK 1/2 inhibitor selumetinib (AZD6244))
  - DNA hypermethylation ↔ demethylation (decitabine, azacitidine)
Potential Future Therapeutic Consequences Based upon New Classifications and Molecular Characteristics

- **Clear cell ovarian cancer**
  - Angiogenesis ↑ ↔ angiogenesis inhibitors
  - PI3K mutation ↔ PI3K-Akt-mTOR inhibitors

- **Endometrioid ovarian cancer**
  - PTEN loss/mutation ↔ PI3K-Akt-mTOR inhibitors

- **Mucinous ovarian cancer**
  - HER2 overexpression/amplification ↔ HER2-targeted agents (trastuzumab, pertuzumab) ERBB3-directed AB (MM-121)
  - KRAS mutation ↔ inhibitors of MEK