New promising antineoplastic agents for Pancreatic Cancer

ZK 304709 (MTGI)
L19-IL2
Presentation overview

- Treatment barriers and options in cancer therapy
- Molecular and pharmacodynamic profile of ZK304709 (MTGI)
  => Blockade of cell cycle and neoangiogenesis
- Mode of action and pharmacodynamic efficacy of L19-IL2
  => Activation of immune response in the tumor microenvironment by targeted delivery of IL2
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Pathophysiology of solid tumors

Clinical observations

Molecular and cellular heterogeneity of tumor cell population (Chromosomal instability)

Pre-existing drug resistant cellular clones or selected cellular clones resistant to standard treatment modalities (Multi drug resistance)

To escape immune defence tumors develop a immuno-suppressive microenvironment (Anergy of cellular immunity)

Tumor growth needs

Solid tumor growth is driven by constitutively active aberrant signalling pathways

Every tumor cell needs a functional cell cycle (which may be aberrantly activated) for division dependence on cell cycle

Solid tumor growth above 2-5 mm diameter is dependent on neo-angiogenesis aberrant vascular network
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Rationale for Inhibition of Angiogenesis

Tumor induced neo-angiogenesis
- a critical step for tumor growth and metastasis formation
- mediated by VEGF / VEGF-receptor tyrosine kinase system

Anti-angiogenic therapies
- Avastin (Genentech), humanized Ab neutralizing VEGF A, approved
- VEGF-RTKI’s, clinical studies phase III
Mode of action of Avastin and VEGF-RTKIs

VEGF-RTKIs inhibit multiple VEGF receptor tyrosine kinases and the PDGF-receptors
Hypothesis:
Combination of anti neo-angiogenesis and inhibition of cell cycle progression should be superior to respective monotherapies.

The novel oral Multi-target Tumor Growth Inhibitor™

- Rationale
- Mode of action of ZK304709
- Efficacy of ZK304709 in tumor xenograft models
Cyclin-dependent kinases (CDK): The key drivers of a cell through the cell division cycle.

Deregulation of the cell division cycle in tumor cells by

- overexpression / amplification of cell cycle activators (D- or E-type cyclins, CDK4, cdc25)
- inactivation of cell cycle inhibitors (p53, p16, Rb)

CDK2 and CycE k.o. mice:
- CDK2 and CycE largely dispensable for proliferation of most normal cells, but
- cells were relatively resistant to oncogenic transformation
ZK 304709: Multi-Target Tumor Growth Inhibitor™
Simultaneous Blockade of Tumor and Vessel Growth

- Inhibition of cell cycle progression (proliferation)
- Induction of tumor cell apoptosis
- Inhibition of tumor angiogenesis
- Reduction of interstitial pressure (reduced risk of metastasis)
**ZK304709: A pyrimidine based nanomolar inhibitor of CDK1/2, VEGF-R1,2,3 and PDGF-Rβ**

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC50 [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK2/CycE</td>
<td>4</td>
</tr>
<tr>
<td>CDK1/CycB</td>
<td>60</td>
</tr>
<tr>
<td>CDK4/CycD</td>
<td>100</td>
</tr>
<tr>
<td>CHK1</td>
<td>500</td>
</tr>
<tr>
<td>GSK3β</td>
<td>9,000</td>
</tr>
<tr>
<td>Akt2/PDK1</td>
<td>1,300</td>
</tr>
<tr>
<td>PKC</td>
<td>6,000</td>
</tr>
<tr>
<td>PKA</td>
<td>1,000</td>
</tr>
<tr>
<td>MK2</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>PI3K</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>T-Fyn</td>
<td>10,000</td>
</tr>
<tr>
<td>EGF-R</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Insulin-R</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>VEGF-R1,2,3</td>
<td>~30</td>
</tr>
<tr>
<td>PDGF-Rβ</td>
<td>55</td>
</tr>
<tr>
<td>Ckit</td>
<td>1,000</td>
</tr>
</tbody>
</table>

**Blockade of cell cycle progression followed by tumor cell apoptosis**

Inhibition of tumor cell proliferation in 6 tumor cell lines:

IC$_{50}$ = 100-300 nM

**Blockade of neoangiogenesis followed by tumor cell starvation and apoptosis**
### ZK-304: Inhibitor of CDK1/2, VEGF-R1,2,3 and PDGF-Rβ

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC50 [nM]</th>
</tr>
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<tbody>
<tr>
<td>CDK2/CycE</td>
<td>4</td>
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<td>100</td>
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<tr>
<td>CHK1</td>
<td>500</td>
</tr>
<tr>
<td>GSK3β</td>
<td>9,000</td>
</tr>
<tr>
<td>Akt2/PdK1</td>
<td>1,300</td>
</tr>
<tr>
<td>PKC</td>
<td>6,000</td>
</tr>
<tr>
<td>PKA</td>
<td>1,000</td>
</tr>
<tr>
<td>MK2</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Plk1</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>T-Fyn</td>
<td>10,000</td>
</tr>
<tr>
<td>EGF-R</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Insulin-R</td>
<td>&gt; 10,000</td>
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<tr>
<td>VEGF-R1,2,3</td>
<td>~30</td>
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<tr>
<td>PDGF-Rβ</td>
<td>55</td>
</tr>
<tr>
<td>Ckit</td>
<td>1,000</td>
</tr>
</tbody>
</table>

**Perfect fit into ATP-pocket of CDK2 and VEGF-R2**

- **Hydrophobic pocket**
- **Ribo site**
- **Phosphate site**

(Structure of co-crystal) (fitted into crystal structure)
Dual specificity of ZK-304709

Blockade of neoangiogenesis

Blockade of cell cycle
### ZK304709: G1 arrest and apoptosis induction in MCF7 cells stimulated to enter S phase from quiescence

<table>
<thead>
<tr>
<th>Control (DMSO)</th>
<th>0.3 µM</th>
<th>1 µM</th>
<th>3 µM</th>
<th>10 µM</th>
<th>30 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Histogram" /></td>
<td><img src="image2" alt="Histogram" /></td>
<td><img src="image3" alt="Histogram" /></td>
<td><img src="image4" alt="Histogram" /></td>
<td><img src="image5" alt="Histogram" /></td>
<td><img src="image6" alt="Histogram" /></td>
</tr>
</tbody>
</table>

- **G0/G1**: Quiescent state
- **S-phase**: DNA synthesis phase
- **G2/M**: Transition to mitosis
- **Apoptosis**: Programmed cell death

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 µM</td>
<td>30, 60, 90</td>
</tr>
<tr>
<td>1 µM</td>
<td>40, 70, 100</td>
</tr>
<tr>
<td>3 µM</td>
<td>50, 80, 110</td>
</tr>
<tr>
<td>10 µM</td>
<td>60, 90, 120</td>
</tr>
<tr>
<td>30 µM</td>
<td>70, 100, 130</td>
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</tbody>
</table>
Linear relationship between dose, serum level and response

MaTu human mammary tumor model

**Time course of tumor growth**

<table>
<thead>
<tr>
<th>Days [after tumor transplantation]</th>
<th>Tumor area [mm²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>vehicle</td>
</tr>
<tr>
<td></td>
<td>ZK304709 30mg/kg po 1xdaily</td>
</tr>
<tr>
<td></td>
<td>ZK304709 50mg/kg po 1xdaily</td>
</tr>
<tr>
<td></td>
<td>ZK304709 75mg/kg po 1xdaily</td>
</tr>
</tbody>
</table>

**Tumor weight at day 21**

<table>
<thead>
<tr>
<th>Tumor weight [mg]</th>
<th>Vehicle</th>
<th>ZK304709 30mg/kg po 1xdaily</th>
<th>ZK304709 50mg/kg po 1xdaily</th>
<th>ZK304709 75mg/kg po 1xdaily</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>vehicle</td>
<td>30 mg/kg po 1xdaily</td>
<td>50 mg/kg po 1xdaily</td>
<td>75 mg/kg po 1xdaily</td>
</tr>
</tbody>
</table>

**Serum concentration of ZK 304709 2h after last p.o. application**

<table>
<thead>
<tr>
<th>Dose per application</th>
<th>Serum concentration [µM, ± SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg/kg</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>50 mg/kg</td>
<td>3.7 ± 1.2</td>
</tr>
<tr>
<td>75 mg/kg</td>
<td>4.7 ± 2.0</td>
</tr>
</tbody>
</table>
Reduction of large tumor masses without body weight loss

Hormone independent p53 unknown (MaTu model)

treatment schedule: 100 mg/kg po 1x daily

body weight [g]

vehicle
treatment start: d3
treatment start: d7
treatment start: d11
treatment start: d15
VEGF antagonism *in vivo*(1): Reduction of tumor blood supply

vehicle  ZK304709

(MaTu mammary tumor xenograft, 4 treatment days)
VEGF antagonism *in vivo* (2): Inhibition of VEGF-induced vascular permeability

This study provides direct evidence that ZK304709 inhibits the VEGF-system *in vivo*.

**Miles assay:**
ZK304709 given po 2 h prior sc VEGF injection, extravasation of dye measured 30 min after VEGF injection.
**CDK antagonism: Inhibition of Rb Phosphorylation**

**In vitro:** pRb level treated MCF7 cancer cells stimulated to enter S phase from quiescence - concentration dependence.

These studies provide direct evidence that ZK304709 inhibits CDK in vivo within the tumor tissue (biomarker Rb phosphorylation).

**In vivo:** pRb level treated MaTu xenograft tumors

<table>
<thead>
<tr>
<th>Study No.</th>
<th>no treatment</th>
<th>ZK 304709 100 mg/kg po 1xdaily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4x</td>
</tr>
<tr>
<td>EO2002.0143</td>
<td><img src="image1.png" alt="Image of pRb and ppRb" /></td>
<td><img src="image2.png" alt="Image of pRb and ppRb" /></td>
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<tr>
<td>EO2002.0455</td>
<td><img src="image5.png" alt="Image of pRb and ppRb" /></td>
<td><img src="image6.png" alt="Image of pRb and ppRb" /></td>
</tr>
</tbody>
</table>

- pRb (S612)
- actin
Massive induction of apoptosis

MaTu mammary tumor xenograft, 4 treatment days

vehicle                        ZK304709

(Tunel stain)
MIA PaCa-2 human pancreatic tumor model

**Tumor weight at day 25 (subcu.):**

- Vehicle
- Gemcitabine 250mg/kg ip d3, d16
- ZK304709 100mg/kg po d3-d25

**Tumor weight at day 63 (orthotop.):**

- Vehicle
- ZK304709 60 mg/kg po 1xdaily d29-d63
- ZK304709 100 mg/kg po 1xdaily d29-d63

**Tumor weight [mg ± SD]:**

- **T/C**
  - 0.48 0.04
  - 0.36 0.11

**ZK 304709 similarly efficacious in subcu. and orthotop. MIA PaCa-2 model**
Capan-1 human pancreatic tumor model

Tumor weight at day 23 (subcu.)

- **Vehicle**: Control
- **Doxorubicin**: 10mg/kg iv 1xd3,d14
- **Paclitaxel**: 12mg/kg ip 1x250mg/kg ip 1xd3-d7, 1x1d14
- **Gemcitabine**: 5mg/kg po 1xdaily 1xd3,d14
- **Flavopiridol**: 100mg/kg po 1xdaily
- **ZK 304709**: 100mg/kg po 1xdaily

<table>
<thead>
<tr>
<th>Drug</th>
<th>T/C</th>
<th>Tumor weight (mg +/- SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.26</td>
<td>0.26 0.58 0.37 0.18</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavopiridol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZK 304709</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tumor weight at day 91 (orthotop.)

- **Vehicle**: Control
- **ZK 304709**: 60 mg/kg po d14-d91
- **ZK 304709**: 100 mg/kg po d14-d91

<table>
<thead>
<tr>
<th>Drug</th>
<th>T/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.23</td>
</tr>
<tr>
<td>ZK 304709</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**ZK 304709 similarly efficacious in subcu. and orthotop. Capan-1 model**
Capan-1 human pancreatic tumor model

Tumor weight at day 90 (orthotop.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tumor Weight (mg ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>700 ± 50</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>600 ± 40</td>
</tr>
<tr>
<td>ZK 304709</td>
<td>400 ± 30</td>
</tr>
</tbody>
</table>

T/C 0.80 0.20

Metastases

- with metastases
- without metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Animals</th>
<th>Tumor Weight (mg ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>100</td>
<td>700 ± 50</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>75</td>
<td>600 ± 40</td>
</tr>
<tr>
<td>ZK 304709</td>
<td>25</td>
<td>400 ± 30</td>
</tr>
</tbody>
</table>

**ZK 304709:**
complete blockade of metastasis growth

Treatment schedules
- Mono treatments
- Gemcitabine: 250 mg/kg ip once every 2 weeks
- ZK 304709: 100 mg/kg po once daily
- Vehicle
- Treatments started at d16 after tumor inoculation when tumors had established

Klaus Bosslet
Corporate Research Oncology
Schering AG, Berlin

FALK-Symposium No.150, Berlin Oct, 3-4 05
**ZK 304709: inhibition of tumor growth and reduction of microvessel density in a human pancreatic tumor model**
BON human neuroendocrine pancreatic tumor model

Tumor weight at day 61 (orthotop.)

Metastases

ZK 304709: inhibition of primary tumor growth and metastasis growth of a human neuroendocrine pancreatic tumor model
**BON human neuroendocrine pancreatic tumor model**

**Apoptosis (tunel stain)**

- Vehicle
- ZK 304709

**Microvessel density (CD34 stain)**

- Vehicle
- ZK 304709

---

**ZK 304709: induces apoptosis and reduces microvessel density in a human neuroendocrine pancreatic tumor model**
Superior efficacy of ZK304709 in various xenograft models

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>ZK304709</th>
<th>Doxorubicin</th>
<th>Paclitaxel</th>
<th>Flavopiridol</th>
<th>CYC 202</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MaTu</td>
<td>0.01</td>
<td>0.43</td>
<td>0.02</td>
<td>0.19</td>
<td>0.62</td>
<td>n.d.</td>
</tr>
<tr>
<td>MX-1</td>
<td>0.01</td>
<td>0.19</td>
<td>n.d.</td>
<td>0.38</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>MaTu/MDR</td>
<td>0.08</td>
<td>0.53</td>
<td>&gt;1</td>
<td>0.17</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>NCI/ADR-RES</td>
<td>0.03</td>
<td>0.37</td>
<td>0.75</td>
<td>0.54</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>Prostate</td>
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<tr>
<td>DU145</td>
<td>0.19</td>
<td>0.57</td>
<td>0.80</td>
<td>0.49</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>CWR-22</td>
<td>0.16</td>
<td>0.35</td>
<td>0.46</td>
<td>0.55</td>
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<td>n.d.</td>
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<tr>
<td>Pancreas</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MIA PaCa-2</td>
<td>0.06</td>
<td>0.26</td>
<td>n.d.</td>
<td>0.63</td>
<td>n.d.</td>
<td>0.48</td>
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<tr>
<td>Capan-1</td>
<td>0.18</td>
<td>0.26</td>
<td>0.26</td>
<td>0.37</td>
<td>0.58</td>
<td></td>
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<tr>
<td>Kidney</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Caki-1</td>
<td>0.17</td>
<td>0.41</td>
<td>0.77</td>
<td>0.65</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Caki-2</td>
<td>0.23</td>
<td>0.34</td>
<td>0.26</td>
<td>&gt;1</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>786-O</td>
<td>0.43</td>
<td>0.43</td>
<td>1</td>
<td>&gt;1</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>Glioblastoma</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>U-87 MG</td>
<td>0.04</td>
<td>0.04</td>
<td>0.55</td>
<td>0.39</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>Melanoma</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>A375</td>
<td>0.19</td>
<td>0.36</td>
<td>&gt;1</td>
<td>0.36</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>Hematol. Tumors</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>RL (non-Hodgkin)</td>
<td>0.31</td>
<td>n.d.</td>
<td>n.d.</td>
<td>0.34</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>RAMOS (Burkitt’s)</td>
<td>0.03</td>
<td>n.d.</td>
<td>n.d.</td>
<td>0.01</td>
<td>n.d.</td>
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<tr>
<td>KG-1 (AML)</td>
<td>0.03</td>
<td>0.19</td>
<td>n.d.</td>
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<td>n.d.</td>
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<td>Colon</td>
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<td>HCT-116</td>
<td>0.16</td>
<td>0.58</td>
<td>0.39</td>
<td>0.4</td>
<td>n.d.</td>
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<td>0.45</td>
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<td>n.d.</td>
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<td>NSC Lung</td>
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</tr>
<tr>
<td>A549</td>
<td>0.35</td>
<td>0.39</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>NCI-H460</td>
<td>0.49</td>
<td>0.38</td>
<td>0.91</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>
ZK 304709: Multi-Target Tumor Growth Inhibitor™
Simultaneous Blockade of Tumor and Vessel Growth

- Inhibition of cell cycle progression (proliferation)
- Induction of tumor cell apoptosis
- Inhibition of tumor angiogenesis
- Reduction of interstitial pressure (reduced risk of metastasis)
Summary of ZK 304709

• ZK304709 is the Multi-target Tumor Growth Inhibitor that induces apoptosis via
  • inhibition of cell cycle progression (inhibition of CDK2&1)
  • plus inhibition of tumor-induced angiogenesis
    (inhibition of VEGF and PDGF receptor tyrosine kinases).

• ZK304709 shows a very encouraging anti-tumor efficacy and tolerability in various human tumor xenograft models: particularly efficacious in slowly growing, hormone-independent, p53 negative, and multidrug-resistant tumors.
Presentation overview

- Treatment barriers and options in cancer therapy
- Molecular and pharmacodynamic profile of ZK304709 (MTGI)
  => Blockade of cell cycle and neoangiogenesis
- Mode of action and pharmacodynamic efficacy of L19-IL2
  => Activation of immune response in the tumor microenvironment by targeted delivery of IL2
L19-IL2: A RECOMBINANT FUSION PROTEIN FOR THE TREATMENT OF SOLID TUMORS

Human IL2

scFv L19

Linker: (Ser$_4$-Gly)$_3$
ED-B - Fibronectin

- Highly specific oncofetal antigen
- Associated with tumor growth/angiogenesis
- Highly conserved
- Function of ED-B unknown
Therapeutic efficacy of L19-IL2 in pancreatic carcinoma
Overexpression of ED-B Fibronectin in pancreatic cancer

Pancreas

Chronic Pancreatitis

Pancreatic cancer

ED-B Fibronectin

CD31
L19-IL2 selectively localizes in ED-B expressing human tumor xenograft

scFv L19-IL2 cyanine dye conjugate (ED-B-FN targeting)
Animal: mouse, F9 teratocarcinoma

irrelevant scFv cyanine dye conjugate (non-specific control)
Animal: mouse, F9 teratocarcinoma
A pancreatic cancer model representative for human disease

Orthotopic transplantation of MPS cell line
MPS model shows clinical complications comparable to human pancreatic cancer

hemorrhagic ascites

gall bladder

jaundice

biliary obstruction

D. choledochus

Duod.

liver

TM

small intestine

TM

liver
Typical metastatic spread into mesenterial lymph nodes
liver and abdomen

- mesenterium
- small intestine
- liver
- spleen
- kidney
- vena cava

Klaus Bosslet
Corporate Research Oncology
Schering AG, Berlin

FALK-Symposium No.150, Berlin Oct, 3-4 05
Destructive and invasive growth of orthotopically implanted pancreatic cancer in stomach and liver
Treatment regimen of established tumor mass

Tumorimplantation:
Day -48 => fully established orthotopic tumor

Treatment schedule:

- Daily i.v. injections for 5 consecutive days
- No treatment for 2 days
- Daily i.v. injections for 5 consecutive days
Therapeutic effect after 2 treatment cycles with L19-IL2 in orthotopic MPS pancreatic cancer model in nu/nu

High-dose IL2 Therapy: 2.16 MIU/kg BW/day
Low-dose IL2 Therapy: 3-24 MIU/m²/BSA/day (~70,000-553,000 IU/kg BW/day)
NK-cell accumulation within L19-IL2 targeted tumor mass

Effect of L19-IL2 on Serum Lipase as a surrogate-marker of pancreatitis

No deleterious effect on normal pancreas function
Therapeutic efficacy of L19-IL2 in Hepatocellular Carcinoma (HCC)
Overexpression of ED-B Fibronectin in HCC

Liver

Liver cirrhosis

HCC
Development of an orthotopic hepatocellular carcinoma model

ED-B Fibronectin
Therapeutic effect after 2 treatment cycles using L19-IL2 in the orthotopic HuH7-model for HCC

Tumor implantation: Day -40

Klaus Bosslet
Corporate Research Oncology
Schering AG, Berlin

FALK-Symposium No.150, Berlin Oct, 3-4 05
No deleterious effects on normal liver function using L19-IL2 therapy, but significant reduction of tumor mass.

**Effect of L19-IL2 on serum AST / ALT as surrogate-parameters of Hepatitis**

- **NK 1.1**
- **control**
- **L19-IL2**

**AST: Aspartate amino transferase**

**ALT: Alanine amino transferase**
L19-IL2: MOA
Expected clinical benefit of L19-IL2

- Targeted delivery of IL2 leads to the specific accumulation and retention of IL2 at the tumor site
- Preclinical data indicate that L19-IL2 has
  - improved efficacy
  - improved side effect profile
- We expect L19-IL2 to be superior over PROLEUKINE (non targeted IL2) and it may open new treatment options in addition to renal cell cancer such as pancreatic and hepatocellular carcinoma
Acknowledgements

L19-IL2

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Angela Bieseke
Kai Licha
Andreas Menrad
Pancreatic Cancer: Facts

incidence 10 / 100,000
appr. 11,000 deaths annually (Germany)
appr. 35,000 deaths annually (USA)
fifth leading cause of cancer-related death
25% of all GI-malignancy-related deaths
worst prognosis of all solid tumors
### Therapeutic options for pancreatic cancer
- *the therapeutic dilemma*

<table>
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<th>year</th>
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<td>42</td>
<td>Steptozotocin+MitomycinC+5-FU Cisplatin+Cytoxin+Caffein</td>
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<td>5-FU + Doxorubicin 5-FU + Doxo + Ftorafur</td>
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Prognosis of HCC

Survival rates of patients with HCC

5-year survival rate < 5%
Surgical / local therapy < 8%
Transplantation < 1%