Integrating Anti-Angiogenesis Therapy In The Management Of Metastatic Colorectal Cancer:

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David Geffen School of Medicine at UCLA
Disclosures

Speakers Bureau:

- Genentech
- Roche
- Pfizer
- BMS
- Sanofi-Aventis
Altuzan: Proposed Mechanism of Action

- Altuzan may act against tumours in three ways
  - Regression of existing microvasculature
  - Normalisation of surviving microvasculature
  - Inhibition of vessel regrowth and neovascularisation
Effects of VEGF inhibition: regression of microvasculature

Inai T, American Journal of Pathology, Vol. 165, No. 1, July 2004
Effects of VEGF inhibition: inhibition of new vascular development

- Neovascularisation in a ‘vascular window’ mouse model following implantation of tumour cells and induction of ischaemia

Potential effects of VEGF inhibition on tumour vasculature: clinical consequences

**Early effects**
1. Regression of existing microvasculature
   - Increase in tumour response across treatment regimens

**Late and continued effects**
2. Normalisation of surviving mature vasculature
   - Potential to effectively combine anti-VEGF therapy with other anticancer agents
3. Inhibition of new and recurrent vessel growth
   - Extended survival and delay of disease progression
   - Maintenance of stable disease through sustained inhibition of tumour growth
• Evaluation included measurements of tumor physiology, systemic response, and tumor response

• Tumor physiology measurements included
  – blood perfusion, blood volume, permeability-surface area product, microvascular density, perivascular coverage, interstitial fluid pressure, and 18-fluorodeoxyglucose (18-FDG) uptake

Tumor vascular density was significantly reduced in patients with rectal cancer treated with a single dose of bevacizumab
(2) Tumor Vasculature Normalization

- Normalization occurred in patients with rectal cancer when treated with a single dose of bevacizumab, indicated by
  - Decreased microvascular density, Increased pericyte coverage
  - Decreased IFP (Mean decrease: 15.4 to 4.8 mm Hg)
Response to Bevacizumab in Rectal Cancer

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
<th>Patient #3</th>
<th>Patient #4</th>
<th>Patient #5</th>
<th>Patient #6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 days post Altuzan Infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 weeks post treatment: Surgical specimen</td>
<td>Ulcer</td>
<td>Ulcer</td>
<td>Ulcer</td>
<td>Ulcer</td>
<td>Ulcer</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairooz Kabbinavar, M.D.

Primary endpoint: survival

- Bolus IFL + placebo (n=412)
  - No bevacizumab past disease progression
- Bolus IFL + bevacizumab (n=403)
  - May receive bevacizumab past disease progression
- 5-FU/LV + bevacizumab (n=110)
  - May receive bevacizumab past disease progression

IFL
- bolus 5-FU 500mg/m²
- leucovorin 20mg/m²
- irinotecan 125mg/m given 4/6 weeks

5-FU/LV
- bolus 5-FU 500mg/m²
- leucovorin 500mg/m given 6/8 weeks

Bevacizumab
- 5mg/kg every 2 weeks
Altuzan – 1st-line superior PFS + OS with irinotecan - 2107

Median progression-free survival
6.2 vs 10.6 months
HR=0.54 (p<0.0001)

Median survival
15.6 vs 20.3 months
HR=0.66 (p<0.001)

## Phase III Trial of Altuzan + IFL as First-Line Therapy for MCRC (AVF2107g): Efficacy Summary

<table>
<thead>
<tr>
<th></th>
<th>Placebo + IFL (n=411)</th>
<th>Altuzan + IFL (n=402)</th>
<th>P Value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS (mo)</strong></td>
<td>15.6</td>
<td>20.3</td>
<td>&lt;0.001*</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>PFS (mo)</strong></td>
<td>6.2</td>
<td>10.6</td>
<td>&lt;0.001*</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>35</td>
<td>45</td>
<td>&lt;0.01†</td>
<td></td>
</tr>
<tr>
<td><strong>DOR (mo)</strong></td>
<td>7.1</td>
<td>10.4</td>
<td>0.001</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*By stratified log-rank test.
†By chi² test.

Altuzan® (bevacizumab) PI. December 2004.
Effect of Bevacizumab on PFS

**PFS-gain in months per 10% gain in RR**

- Conventional Chemo
- Altuzan

*P = 0.04*

Months Gained per 10%RR

First-Line Regimen
Clinical benefit of Altuzan in responding and non-responding patients: overall survival

Median OS for responders: 27.7 vs 21.8 months
Hazard ratio = 0.60, P = 0.014

Median OS for nonresponders: 14.7 vs 12.6 months
Hazard ratio = 0.76, P = 0.019

Mass R, et al. J Clin Oncol 2005;23(June 1 Suppl.):249s (Abstract 3514)
Clinical benefit of Altuzan in responding and non-responding patients:

progression-free survival

Median PFS for responders: 14.0 vs 10.6 months
Hazard ratio = 0.53, P = 0.0002

Median PFS for non-responders: 7.0 vs 4.4 months
Hazard ratio = 0.63, P = 0.0001

Mass R, et al. J Clin Oncol 2005;23(June 1 Suppl.):249s (Abstract 3514)
Response-Independent Survival Benefit with Altuzan-containing First-Line Treatment

- Regardless of response, patients treated with Altuzan received a significant survival benefit compared to controls
  - Non-Responder risk of death ↓ 24%
  - Non-Responder risk of progression ↓ 37%

- For patients with Stable Disease for 12 weeks as “best outcome”, Altuzan-treated patients experienced a significant decrease in risk of progression (↓ 45%)*

- This exploratory analysis suggests objective response may not be an appropriate criterion for stopping treatment
  - Disease progression may be a more appropriate criterion

- This issue merits investigation in prospective trials

Effects of VEGF inhibition: inhibition of new and recurrent vessel growth
Effects of VEGF inhibition: inhibition of new and recurrent vessel growth

A. Epithelial tumour cells (green) and endothelial cells (red) in a heavily vascularised tumour

B. After 6 weeks of anti-VEGF therapy, vessel regression is observed in the tumour

C. Three weeks after discontinuing anti-VEGF therapy, large and highly vascularised tumour areas have reformed

# Altuzan + IFL Increases Survival in Poorly Responding Subgroups

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Bolus IFL + Placebo</th>
<th>Bolus IFL + Altuzan</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td>813</td>
<td>15.6</td>
<td>20.3</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td><strong>Age ≥65 years</strong></td>
<td>271</td>
<td>14.9</td>
<td>24.2</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td><strong>Sex Male</strong></td>
<td>485</td>
<td>15.4</td>
<td>21.2</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG PS ≥1</strong></td>
<td>352</td>
<td>12.1</td>
<td>14.9</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td><strong>Location of primary tumor Rectum</strong></td>
<td>169</td>
<td>14.9</td>
<td>24.2</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>&gt;1 metastatic disease sites</td>
<td>507</td>
<td>14.6</td>
<td>19.9</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

Overall Hazard Ratio = 0.66 (34% reduction in likelihood of death in IFL + Altuzan group)

Fyfe et al. ASCO 2004; Abstract 3617.
Addition of Bevacizumab to Bolus Fluorouracil and Leucovorin in First-Line Metastatic Colorectal Cancer: Results of a Randomized Phase II Trial

Fairooz F. Kabbinavar, Joseph Schulz, Michael McCleod, Taral Patel, John T. Hamm, J. Randolph Hecht, Robert Mass, Brent Perrou, Betty Nelson, and William F. Novotny

JOURNAL OF CLINICAL ONCOLOGY
Comparison of Altuzan Treatment Effect Across 5-FU/LV Studies

Median Survival

- 780 (small phase II) 17.7 mos
- 2192 (large phase II) 16.6 mos
- Arm 3, 2107 (phase III) 18.3 mos

- The effect of Altuzan on median survival is reproducible across different 5-FU/LV studies (approximately 17-18 mos)
Combined Analysis of Efficacy: The Addition of Bevacizumab to Fluorouracil/Leucovorin Improves Survival for Patients With Metastatic Colorectal Cancer

Fairooz F. Kabbinavar, Julie Hambleton, Robert D. Mass, Herbert I. Hurwitz, Emily Bergsland, and Somnath Sarkar
5-FU/LV + Altuzan in First-Line MCRC: Overall and Progression-Free Survival

Median survival: 14.6 vs 17.9 mo
HR=0.74
P=0.0081

Median PFS: 5.6 vs 8.8 mo
HR=0.63
P=0.0001

Quality of Life (QoL) in Patients with MCRC Treated with Altuzan + CT: Results

<table>
<thead>
<tr>
<th></th>
<th>Median TDQ (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCS</td>
</tr>
<tr>
<td><strong>Pivotal Trial</strong></td>
<td></td>
</tr>
<tr>
<td>IFL + Placebo</td>
<td>2.73</td>
</tr>
<tr>
<td>IFL + Altuzan</td>
<td>2.89</td>
</tr>
<tr>
<td><strong>Phase II Trial</strong></td>
<td></td>
</tr>
<tr>
<td>FL + Placebo</td>
<td>3.02</td>
</tr>
<tr>
<td>FL + Altuzan</td>
<td>3.12</td>
</tr>
</tbody>
</table>

- Altuzan did not affect QoL but increased OS and PFS when added to IFL
- Altuzan combination with 5-FU/LV appears to delay the decline in QoL while increasing PFS in frail or elderly patients

TDQ: Time to QoL Deterioration; FACT-C: Functional Assessment of Cancer Therapy-Colorectal; CCS: Colon Cancer Subscale of FACT-C; TOI-C: Trial Outcome Index
Phase II trial of bevacizumab plus irinotecan (AVIRI): study design

Patients with previously untreated metastatic CRC (n=209)

Bevacizumab 5mg/kg every 2 weeks + FOLFIRI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n=209 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>88 (42.1)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>95 (45.5)</td>
</tr>
<tr>
<td>Overall response</td>
<td>92 (44)</td>
</tr>
<tr>
<td>Disease control</td>
<td>188 (90.0)</td>
</tr>
<tr>
<td>6-month progression-free survival (%)</td>
<td>82</td>
</tr>
</tbody>
</table>

Period 1: Treatment Regimens

**FOLFIRI**
- Irinotecan: 180 mg/m² (D1)
- LV: 400 mg/m² over 2 h (D1)
- 5-FU: 400 mg/m² (bolus) (D1)
- 5-FU: 2400 mg/m² (46-h infusion) (D1)
- q2wks

**mIFL**
- Irinotecan: 125 mg/m² (D1, 8)
- 5-FU: 500 mg/m² (bolus) (D1, 8)
- LV: 20 mg/m² (D1, 8)
- q3wks

**CapeIRI**
- Irinotecan: 250 mg/m² (D1)
- Capecitabine: 1000 mg/m² bid (D1-14)
- q3wks

**Stratification:**
- Age (≤ 70 vs > 70)
- PS (0 vs 1)
- Low dose aspirin use (≤ 325mg every day): yes vs no
**BICC-C Period I**

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI</th>
<th>mIFL</th>
<th>CapeIRI</th>
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</thead>
<tbody>
<tr>
<td>FU=22</td>
<td>FU=31 m</td>
<td>FU=22 m</td>
<td>FU=31 m</td>
</tr>
<tr>
<td>PFS</td>
<td>8.2 m</td>
<td>7.6 m</td>
<td>6.0 m</td>
</tr>
<tr>
<td>(mon)</td>
<td>23.1 m</td>
<td>23.1 m</td>
<td>17.6 m</td>
</tr>
</tbody>
</table>
Period 2: Treatment Regimens

FOLFIRI
- Irinotecan: 180 mg/m² (D1)
- LV: 400 mg/m² over 2 h (D1)
- 5-FU: 400 mg/m² (bolus) (D1)
- 5-FU: 2400 mg/m² (46-h infusion) (D1)
  q2wks
- + 5 mg/kg bevacizumab q 2wks

mIFL
- Irinotecan: 125 mg/m² (D1, 8)
- 5-FU: 500 mg/m² (bolus) (D1, 8)
- LV: 20 mg/m² (D1, 8)
  q3wks
- + 7.5 mg/kg bevacizumab q 3wks

CapeIRI
- Irinotecan: 250 mg/m² (D1)
- Capecitabine: 1000 mg/m² bid (D1-14)
  q3wks

Stratification: Age, PS, Low dose aspirin use

BICC-C Study Design
# BICC-C Period II

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI N=57</th>
<th>+Bev</th>
<th>mLFL N=60</th>
<th>+Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU=22 m</td>
<td>FU=22 m</td>
<td>FU=31 m</td>
<td>FU=22 m</td>
<td>FU=31 m</td>
</tr>
<tr>
<td>PFS (mon)</td>
<td>9.9 m</td>
<td>11.2 m</td>
<td>8.3 m</td>
<td>8.3 m</td>
</tr>
<tr>
<td>OS (mon)</td>
<td>NR</td>
<td>NR</td>
<td>18.7 m</td>
<td>19.2 m</td>
</tr>
<tr>
<td>Iyr Survival</td>
<td>87%</td>
<td>87%</td>
<td>61%</td>
<td>61%</td>
</tr>
</tbody>
</table>
### Phase II Trial of Cetuximab/Bevacizumab/Irinotecan versus Cetuximab/Bevacizumab in Irinotecan-Refractory CRC

**BOND 2**

<table>
<thead>
<tr>
<th></th>
<th>Altuzan/cetuximab/irinotecan (n=41)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, %</td>
<td>37</td>
<td>0.03</td>
</tr>
<tr>
<td>TTP, months</td>
<td>7.9</td>
<td>&gt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Altuzan/cetuximab (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, %</td>
<td>20</td>
<td>0.05</td>
</tr>
<tr>
<td>TTP, months</td>
<td>5.6</td>
<td>&gt;0.01</td>
</tr>
</tbody>
</table>

Saltz et al. ASCO 2005
## Phase II Trial of Cetuximab/Bevacizumab/Irinotecan versus Cetuximab/Bevacizumab in Irinotecan-Refractory CRC

<table>
<thead>
<tr>
<th></th>
<th>BOND 1</th>
<th>BOND 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cetuximab/irinotecan (historical)</td>
<td>Altuzan/cetuximab/irinotecan (n=41)</td>
<td></td>
</tr>
<tr>
<td>RR, %</td>
<td>23</td>
<td>37</td>
<td>0.03</td>
</tr>
<tr>
<td>TTP, months</td>
<td>4</td>
<td>7.9</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td></td>
<td>Cetuximab alone (historical)</td>
<td>Altuzan/cetuximab (n=40)</td>
<td></td>
</tr>
<tr>
<td>RR, %</td>
<td>11</td>
<td>20</td>
<td>0.05</td>
</tr>
<tr>
<td>TTP, months</td>
<td>1.5</td>
<td>5.6</td>
<td>&gt;0.01</td>
</tr>
</tbody>
</table>

Saltz et al. ASCO 2005
BRiTE: study overview

- Previously untreated metastatic, locally advanced and unresectable CRC (n=1968)

- Chemotherapy regimen and Altuzan dose / schedule at investigator discretion

- Patients are followed for up to 3 years and clinical data updated every 3 months

- Objectives
  - safety: incidence of adverse events possibly related to Altuzan
  - efficacy: time to progression, response rate and OS

Hedrick E, et al. J Clin Oncol (Meeting Abstracts) 2006;24(June 20 suppl):155s(abs 3536)
BRiTE: first-line chemotherapy regimens used on study

- Median PFS is 10.2 months (95% CI: 9.9–10.9)
- Median PFS was comparable in the two groups of patients

FLOX = 5-FU/LV + oxaliplatin

First-BEAT: most commonly used chemotherapy regimens

# BRiTE: PFS

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Median PFS (months)</th>
<th>95% CI (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>10.2</td>
<td>9.9-10.9</td>
</tr>
<tr>
<td><strong>Chemotherapy regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan-containing (n=477)</td>
<td>10.4</td>
<td>9.5-11.3</td>
</tr>
<tr>
<td>Oxaliplatin-containing (n=1226)</td>
<td>10.2</td>
<td>9.9-11.2</td>
</tr>
<tr>
<td>Neither (n=204)</td>
<td>9.5</td>
<td>8.1-11.3</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years (n=1062)</td>
<td>10.4</td>
<td>9.9-11.3</td>
</tr>
<tr>
<td>&gt;65 years (n=898)</td>
<td>10.1</td>
<td>9.5-10.8</td>
</tr>
</tbody>
</table>

Kozloff M, et al. J Clin Oncol (Meeting Abstracts) 2006;24(June 20 suppl):155s(abs 3537)
Altuzan: Safety Overview

- Altuzan has now been studied in > 5000 patients
- Phase II safety profile
  - Hypertension
  - Proteinuria
  - Thromboembolic events
  - Bleeding: minor mucosal (epistaxis) and major hemorrhage (nonsmall cell lung cancer)
- Phase III: 3 additional safety signals emerged
  - Gastrointestinal (GI) perforation
  - Arterial thromboembolic events
  - Wound healing/postoperative bleeding

Hurwitz H et al. NEJM 2004;350:2335–42
First-BEAT: selected serious adverse events

<table>
<thead>
<tr>
<th>Type</th>
<th>Related serious adverse event* n=1,789 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATEs</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>17 (1.0)</td>
</tr>
<tr>
<td>GI perforation</td>
<td>12 (0.7)</td>
</tr>
<tr>
<td>Wound healing</td>
<td>3 (0.2)</td>
</tr>
</tbody>
</table>

*Investigator assessment

BRiTE: bevacizumab-related serious adverse events

<table>
<thead>
<tr>
<th>Serious adverse events possibly related to bevacizumab</th>
<th>No. of patients (%) (n=1,960)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI perforation</td>
<td>1.7</td>
</tr>
<tr>
<td>Postoperative bleeding or wound-healing complication</td>
<td>1.4</td>
</tr>
<tr>
<td>Arterial thromboembolic events</td>
<td>1.5</td>
</tr>
<tr>
<td>Grade 3/4 bleeding</td>
<td>2.2</td>
</tr>
<tr>
<td>Other</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Safety Conclusions:

- Altuzan does not alter the safety profile of chemotherapy.
- Hypertension is the most common Altuzan-associated side effect requiring intervention – manageable using oral medication.
- The most serious adverse events in colorectal cancer patients treated with Altuzan are:
  - GI perforation: ~2% of patients
  - arterial thrombosis: ~5% of patients
Combining Altuzan with chemotherapy results in a consistent clinical benefit

Overall survival (months)

Improvement observed when Altuzan is added to standard chemotherapy

Patients were treated 2nd line

*Patients were treated 2nd line

Conclusions

- Combining Altuzan with standard chemotherapy or Erbitux results in a consistent clinical benefit, even in patients with relapsed CRC.

- Altuzan-based therapy has a manageable toxicity profile in combination with 5-FU/LV +/- oxaliplatin or irinotecan.

- Administration of Altuzan with chemotherapy or Erbitux is feasible with no clear indication of synergistic toxicity.

- **Bevacizumab + Chemotherapy should be the first line option for patient with mCRC.**