The Challenge of Cancer Cachexia

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Disclosures

- **Advisory Board/Consultant:** Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Hospira, Ono Pharmaceuticals

- **DSMB Member:** Celgene, Hoffman LaRoche, Merrimack, Sanofi

- **Principal Investigator/Research Funding:** Amgen, AstraZeneca, GTx, MedImmune
International Consensus Definition of “Cancer Cachexia”

“Multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.”

Loss of muscle mass impairs physical function and metabolic & immunologic health

- **Weakness**
  - Muscle strength

- **Mobility Disability**
  - Physical performance

- **Anorexia Fatigue**
  - QOL

**Disease**
- Muscle mass

**Protein Stores**
- Changes in enzymes, peptide hormones, antibodies and cytokines, etc...

**Metabolism**
- Insulin resistance

**Immunity**
- Impaired immunity and ineffective antitumor response

- **Independence**
- Hospitalization
- **Response to chemo**
- **Tolerability to chemo**
- **Mortality**
Prevalence of Low Muscle Mass in Patients with Solid Tumors of the Lung or Gastrointestinal Tract, N = 1476

Consecutive patients referred to a medical oncology service in a regional cancer center in Alberta, Canada.
Couldn't find the exact article this may have come from. Closest I found was this:
(http://www.ncbi.nlm.nih.gov/pubmed/18539529)
Sara Fagerlie; 25/06/2014
Distribution of Pre-Diagnosis Weight Loss in Patients Presenting with NSCLC III/IV Among a Population Cohort in Northern Alberta

Mean weight loss at presentation 6%

### Clinical Practice Guidelines on Cancer Cachexia

<table>
<thead>
<tr>
<th>Treatment Approach</th>
<th>Consensus Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral nutritional therapy</td>
<td>Yes</td>
</tr>
<tr>
<td>Parenteral nutritional therapy</td>
<td>No</td>
</tr>
<tr>
<td>Supplements</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Non-pharmacologic therapy</td>
<td>Yes</td>
</tr>
<tr>
<td>Nutritional counseling</td>
<td>Yes</td>
</tr>
<tr>
<td>Psychotherapeutic interventions</td>
<td>Yes (QOL)</td>
</tr>
<tr>
<td>Physical training</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacologic Therapy</th>
<th>Consensus Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>May increase appetite</td>
</tr>
<tr>
<td>Omega-3-fatty acids</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Megestrol/progestins</td>
<td>Stimulate appetite + increase weight, but not muscle</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes (short term)</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Little benefit</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>Yes, for GI symptoms</td>
</tr>
</tbody>
</table>

1. Interfere with atrophy signaling
   - Myostatin /activin inhibitors
   - Anti-TNFα
   - Anti- IL-6

2. Stimulate hypertrophy signaling
   - Ghrelin mimetics/GH secretagogues
   - Androgenic anabolic steroids / SARMs

SARM - Selective Androgen Receptor Modulator

The AR is a ligand-dependent transcription factor

Benefits and risks of androgens

Benefits
• Increase muscle mass and strength
• Increase bone mass
• Positive effects on mood, energy level, sense of well being and libido

Risks
• Hirsutism and virilization (women)
• Prostate hyperplasia (men)
• Polycythemia
• Decrease in serum HDL cholesterol
• Elevations in transaminases (oral androgens)


Crawford; MASCC 2014.
Enobosarm Increased Lean Body Mass and Improved Physical Function in Three Efficacy Clinical Trials

Phase IIb cancer cachexia trial:
159 subjects with cancer cachexia, 4 months tx

Phase II POC clinical trial:
120 elderly men and postmenopausal women, 3 months tx

Phase Ib sarcopenia trial:
88 postmenopausal women, 3 months tx


Crawford; MASCC 2014.
International Pivotal Phase III Clinical Trials: G300504 and G300505

Indication: Prevention and treatment of muscle wasting in patients with NSCLC
Stage III/IV NSCLC patients at initiation of 1st line chemotherapy

Primary endpoints @ Day 84
- Lean body mass DEXA
- Physical function SCP

G300504
- Enobosarm 3 mg
- Platinum + taxane
  - 150 patients
- Placebo
  - 150 patients

G300505
- Enobosarm 3 mg
- platinum + non-taxane
  - 150 patients
- Placebo
  - 150 patients

Efficacy Assessments
- SCP: screening, baseline (Day 0), Day 42, Day 84 and Day 147
- DEXA: baseline (Day 0), Day 42, Day 84 and Day 147

Secondary endpoints
- Durability of effect @ Day 147
- Overall survival (safety analysis)

Day 84
- Day 147
- Observation for vital status

Crawford; MASCC 2014.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Power 1 Platinum + Taxane (N=321)</th>
<th>Power 2 Platinum + Non-Taxane (N=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=161)</td>
<td>Placebo (n=161)</td>
</tr>
<tr>
<td></td>
<td>Enobosarm (n=160)</td>
<td>Enobosarm (n=159)</td>
</tr>
<tr>
<td>≥5% weight loss prior 6 months</td>
<td>49.1%</td>
<td>42.5%</td>
</tr>
<tr>
<td>Baseline LBM (kg/m²) Adjusted for height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14.2 (11.6 to 19.1)</td>
<td>14.8 (12.7 to 17.5)</td>
</tr>
<tr>
<td>Male</td>
<td>17.1 (11.9 to 21.5)</td>
<td>17.3 (13.3 to 24.9)</td>
</tr>
<tr>
<td>Baseline Power (watts)</td>
<td>158.3 (25.7 to 435.0)</td>
<td>161.6 (65.2 to 458.3)</td>
</tr>
<tr>
<td></td>
<td>156.5 (46.7 to 449.8)</td>
<td>164.8 (30.1 to 485.2)</td>
</tr>
</tbody>
</table>

Crawford; MASCC 2014.
**G300504 Lean body mass efficacy endpoint**

Slope analysis through Day 84 visit

- GTx-024
- Placebo

Day 84 visit window (day 63-105)

Slope analysis through Day 147

- GTx-024
- Placebo

Day 147 visit window (106-188)

**G300504 Stair climb test (% power change) efficacy endpoint**

Slope analysis through Day 84 visit

- GTx-024
- Placebo

Slope analysis through Day 147

- GTx-024
- Placebo

Crawford; MASCC 2014
G300505 Lean body mass efficacy endpoint

Slope analysis through Day 84 visit

![Graph showing LBM (kg) vs. Time (d)]

Control: n = 139
Experimental: n = 134
Between Arm Difference P Value: Slope = 0.0011

G300505 Stair climb test (% power change) efficacy endpoint

Slope analysis through Day 84 visit

![Graph showing SCP % Change vs. Time (d)]

Control: n = 139
Experimental: n = 134
Between Arm Difference P Value: Slope = 0.0057

Slope analysis through Day 147

![Graph showing LBM (kg) vs. Time (d)]

Control: n = 140
Experimental: n = 138
Between Arm Difference P Value: Slope = 0.0028

![Graph showing SCP % Change vs. Time (d)]

Control: n = 139
Experimental: n = 134
Between Arm Difference P Value: Slope = 0.0018

Crawford; MASCC 2014.
Placebo: n=161  Enobosarm: n=160
Between-Arm Difference P Values Slope= 0.0530

Placebo: n=161  Enobosarm: n=160
Between-Arm Difference P Values Slope= 0.0388

Placebo: n=161  Enobosarm: n=159
Between-Arm Difference P Values Slope= 0.7025

Placebo: n=161  Enobosarm: n=161
Between-Arm Difference P Values Slope= 0.7825

Crawford; MASCC 2014.
Change in Lean Body Mass (observed cases)

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment 1 (N)</th>
<th>Treatment 2 (N)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 84</td>
<td>118; 132</td>
<td>111; 115</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 147</td>
<td>105; 108</td>
<td>96; 96</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Crawford; MASCC 2014.
Further Efficacy Analyses

Stair climb power percent change by lean body mass response

Survival by lean body mass response

Quality of Life by LBM Response
LBM Response is Associated with Improved Stair Climb Power (SCP)

Crawford; MASCC 2014.
Quality of Life

Maintenance of Quality of Life Measurements from Baseline to Day 84

- IAACI (p < 0.0101)
- CJS0501 (p < 0.0351)
- IAACI (p < 0.1148)
- CJS0505 (p = 0.8889)

- LBM Responder = increase or maintenance of lean body mass from baseline
- LBM Non-Responder

Crawford; MASCC 2014.
LBM Response is Associated with Longer Survival

- **POWER 1 Survival by LBM Response**
  - Day 84 Landmark Analysis
  - HR = 0.557
  - P = 0.0115

- **POWER 2 Survival by LBM Response**
  - Day 84 Landmark Analysis
  - HR = 0.545
  - P = 0.0069

Hazard ratios and p values from Cox proportional hazards model

Crawford; MASCC 2014.
Conclusions

- These trials confirm that patients with advanced NSCLC have severe muscle loss and physical function impairment at diagnosis that decline further with platinum-based chemotherapy treatment.
- Enobosarm treatment was associated with an increase in lean body mass compared with a decline in LBM in the placebo group in both studies.
- In G300504, enobosarm treatment was associated with better stair climb performance compared with placebo. These results were not clearly seen in G300505.
- LBM response, regardless of treatment arm, was associated with an improvement in both physical function and survival, as well as maintenance of QOL.
- Enobosarm was very well tolerated in both trials.
The Role of Ghrelin in Anorexia-Cachexia Syndromes

- Ghrelin – The “hunger hormone”
- Stimulates food intake
- Stimulates release of GH/IGF-1 increase
- Decreases inflammatory cytokines
**Trial Design**

- ROMANA 1 (NCT01387269) is one of two international, double-blind, Phase 3 trials
- Patients with unresectable stage III or IV NSCLC and cachexia (≥5% weight loss within prior 6 months or BMI <20 kg/m²)
- Randomized (2:1) to receive either 100 mg ANAM or placebo, administered daily orally for 12 weeks
- Assess ANAM efficacy and safety

*ANAM*, anamorelin HCl; *BMI*, body mass index; *NSCLC*, non-small cell lung cancer; *QD*, once a day.

Bonomi, et al. 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
Endpoints

• **Co-Primary Endpoints**
  - Change from baseline over 12 weeks in:
    - LBM (measured by DXA)
    - HGS of the non-dominant hand
  - 477 patients per study
    - 90% power to detect 2 kg difference in lean body mass and hand grip strength between treatment arms

• **Secondary Endpoints**
  - Included changes from baseline over time in:
    - Body weight
    - Quality of life as assessed by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT)\(^1\) and Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)\(^2\) questionnaires
    - Overall survival
    - Assessment of safety and tolerability of ANAM

**ANAM**, anamorelin HCl; **DXA**, dual-energy X-ray absorptiometry; **HGS**, hand grip strength; **LBM**, lean body mass.


Bonomi, et al. 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
### Patient Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 161)</th>
<th>ANAM 100 mg (N = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>121 (75.2)</td>
<td>247 (76.5)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>119 (73.9)</td>
<td>218 (67.5)</td>
</tr>
</tbody>
</table>

### Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ANAM 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV</td>
<td>114 (70.8)</td>
<td>256 (79.3)</td>
</tr>
<tr>
<td>Median time from initial diagnosis to enrollment, months</td>
<td>6.30</td>
<td>8.45</td>
</tr>
</tbody>
</table>

### Concomitant Cancer Therapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 161)</th>
<th>ANAM 100 mg (N = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy, n (%)</td>
<td>139 (86.3)</td>
<td>288 (89.2)</td>
</tr>
<tr>
<td>Active therapy</td>
<td>134 (83.2)</td>
<td>275 (85.1)</td>
</tr>
</tbody>
</table>

- **ANAM**, anamorelin HCl; **BMI**, body mass index; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **SD**, standard deviation.

Bonomi, et al. 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
Lean Body Mass and Body Weight over 12 Weeks

- **Mean change in body weight from baseline (kg)**
  - ANAM: not statistically different in the ANAM arm compared with placebo
  - ANAM, anamorelin HCl; HGS, hand grip strength; LBM, lean body mass.

Bonomi, et al. 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
Observed Changes in Lean Body Mass and Body Weight

Lean Body Mass

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156</td>
<td>127</td>
<td>101</td>
</tr>
<tr>
<td>ANAM</td>
<td>319</td>
<td>257</td>
<td>199</td>
</tr>
</tbody>
</table>

Body Weight

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 6</th>
<th>Week 9</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>141</td>
<td>140</td>
<td>139</td>
<td>126</td>
<td>120</td>
</tr>
<tr>
<td>ANAM</td>
<td>284</td>
<td>281</td>
<td>276</td>
<td>247</td>
<td>230</td>
</tr>
</tbody>
</table>

Mean change from baseline (kg)

-1 0 1 2 3

Data shown for LBM graph are observed values only; data shown for body weight graph are from mixed-effects pattern-mixture model.

ANAM, anamorelin HCl.

Bonomi, et al. 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
Hand Grip Strength

**ROMANA 1**

<table>
<thead>
<tr>
<th>Median change from baseline non-dominant hand (kg)</th>
<th>N.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-1.45</td>
</tr>
<tr>
<td>ANAM</td>
<td>-1.00</td>
</tr>
</tbody>
</table>

**ROMANA 2**

<table>
<thead>
<tr>
<th>Median change from baseline non-dominant hand (kg)</th>
<th>N.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.95</td>
</tr>
<tr>
<td>ANAM</td>
<td>-1.15</td>
</tr>
</tbody>
</table>

Median change:
- ANAM: -1.00 kg (95% CI: -1.60, -0.30)
- Placebo: -1.45 kg (95% CI: -2.69, -1.05)

- ANAM: -1.15 kg (95% CI: -2.05, -0.45)
- Placebo: -0.95 kg (95% CI: -1.60, 0.00)
**Patient-Reported Outcomes**

**FAACT Anorexia/Cachexia Domain**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 6</th>
<th>Week 9</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>141</td>
<td>139</td>
<td>137</td>
<td>125</td>
<td>119</td>
</tr>
<tr>
<td>ANAM</td>
<td>283</td>
<td>279</td>
<td>271</td>
<td>244</td>
<td>227</td>
</tr>
</tbody>
</table>

- ANAM, anamorelin HCl; FAACT, Functional Assessment of Anorexia/Cachexia Treatment.

**FACIT-F Fatigue Domain**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 6</th>
<th>Week 9</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>140</td>
<td>136</td>
<td>137</td>
<td>123</td>
<td>116</td>
</tr>
<tr>
<td>ANAM</td>
<td>281</td>
<td>278</td>
<td>269</td>
<td>243</td>
<td>226</td>
</tr>
</tbody>
</table>

- Mean change from baseline in FAACT anorexia/cachexia domain score
- Mean change from baseline in FACIT-F fatigue subscale score
- ANAM, anamorelin HCl; FAACT, Functional Assessment of Anorexia/Cachexia Treatment.

Bonomi, et al. 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
Is Romano 1 a practice changing study?

**PRO**
- Anamorelin treatment is associated with an increase in LBM and body weight, along with significant improvements in patient reported outcomes in an advanced lung cancer population
- No significant safety concerns have been identified.
- Existing therapies are inadequate.
Is Romano 1 a practice changing study?

**CON**
- Despite significant improvement in LBM with anamorelin, no difference was seen in functional assessment (HGS).
- Body weight and PROs were secondary outcomes.
- Regulatory authorities prefer quantitative endpoints (functional improvement) to qualitative endpoints (patient reported outcomes).
Is Romano 1 a practice changing study?

Clinical Question:
If you had a drug that improved appetite with resultant improvement in body weight and lean body mass with minimal toxicity, would you prescribe it for patients with cancer cachexia?
Is Romano 1 a practice changing study?

Clinical Question:
If you had a drug that improved appetite with resultant improvement in body weight and lean body mass with minimal toxicity, would you prescribe it for patients with cancer cachexia?

YES!
Conclusions

1) The Romano trials provide a rich database for better understanding the impact of weight loss and muscle wasting on outcomes in patients with lung cancer.

2) A pathway to regulatory approval of anamorelin will be a major step forward in the treatment of cancer cachexia.

3) Further studies of anamorelin and enobosarm, as well as other agents in development will help us dissect the complex biology and therapy of muscle wasting in patients, not only with cancer cachexia, but with heart failure, COPD, renal dialysis and chronic infections, as well as age related sarcopenia.