HOW TO MAKE ADVERSE EVENTS LOOK PRETTY

Robert Snijder
DISPLAY OF ADVERSE EVENTS

TRADITIONAL
## ADVERSE EVENTS OVERVIEW (A FIRST IMPRESSION)

<table>
<thead>
<tr>
<th>Post Randomization</th>
<th>Treatment A (N=156)</th>
<th>Treatment B (N=157)</th>
<th>Placebo (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event (MedDRA V 13.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects Experiencing Adverse Events</td>
<td>105 (67.3%)</td>
<td>109 (69.4%)</td>
<td>75 (48.4%)</td>
</tr>
<tr>
<td>Subjects Experiencing Serious Adverse Events</td>
<td>20 (12.8%)</td>
<td>13 (8.3%)</td>
<td>15 (9.7%)</td>
</tr>
<tr>
<td>Subjects Experiencing Adverse Events Leading to Permanent Discontinuation of Study/Study Drug</td>
<td>7 (4.5%)</td>
<td>8 (5.1%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>2 (1.3%)</td>
</tr>
</tbody>
</table>
AND WITH A BIT MORE DETAIL

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA V 13.1)</th>
<th>Treatment A (N=156)</th>
<th>Treatment B (N=157)</th>
<th>Placebo (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site erythema</td>
<td>12 (7.7%)</td>
<td>14 (8.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Application site pain</td>
<td>44 (28.2%)</td>
<td>46 (29.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>8 (5.1%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (2.6%)</td>
<td>9 (5.7%)</td>
<td>8 (5.2%)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>8 (5.1%)</td>
<td>3 (1.9%)</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Glycosylated haemoglobin increased</td>
<td>9 (5.8%)</td>
<td>5 (3.2%)</td>
<td>7 (4.5%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (5.1%)</td>
<td>5 (3.2%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>8 (5.1%)</td>
<td>14 (8.9%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td>15 (9.6%)</td>
<td>15 (9.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (1.9%)</td>
<td>10 (6.4%)</td>
<td>6 (3.9%)</td>
</tr>
</tbody>
</table>
HEAD TO HEAD COMPARISON – PART 1

Most Frequent On-Therapy Adverse Events
Sorted by Relative Risk

Percent

Relative Risk with 95% CL

Drug A (N=xx) ▲ Drug B (N=xx)
HEAD TO HEAD COMPARISON – PART 2

Grade 3 Treatment Emergent Adverse Events with incidence of at least 1 percent

- Urinary Tract Obstruction
- Urinary Tract Infection
- Urinary Retention
- Syncope
- Spinal Cord Compression
- Pathological Fracture
- Nausea
- Metastatic Pain
- Hypertension
- Hyperglycemia
- Hypersensitivity
- Hypotension
- Fatigue
- Fall
- Cataract
- Bone Pain
- Back Pain
- Anemia

% patients with AE

% More in Placebo

% More in Active

Creation date: 12DEC13
HEAD TO HEAD COMPARISON - MORE THEN TWO TREATMENTS

Most Frequent On-Therapy Adverse Events

- Headache
- Respiratory Disorder
- Weight Decrease
- Dyspepsia
- Vomiting
- Insomnia
- Hematuria
- Anorexia
- Nausea
- Arthralgia

Percent

Drug A (N=xx) ▲ Drug B (N=xx) ▼ Drug C (N=xx)
TIME TO EVENT

- Fatigue
- Fractures
- Hypertension
- Neutropenia

Cumulative percentage of patients vs. nr of days since first treatment for both active and placebo treatment arms.
COMBINING ADVERSE EVENTS WITH LAB DATA

Patient ID = XXXXXXXXXX, Age = 52 Years, Female

- DBP (Stand)
- DBP (Supine)
- Pulse (Stand)
- Pulse (Supine)
- SBP (Stand)
- SBP (Supine)

Value

- ODBP
- OPulse
- OSBP

Value

Arthralgia

Study Day

Grade 1 2 3 4 5
COMBINING AE’S WITH DOSE LEVELS

Dose level and trough values:

- Dose Increased: diarrhea
- Dose Reduced: leukopenia
- Dose Reduced: allergy to metronidazole

Date:
- Skin closure Date
- Dosing Dates
- 01AUG2010 to 01MAR2011

Dose level and trough levels:
- Basiliximab Dose (mg)
- MMF Dose (g)
- Dose (mg)
- Trough Level

Graph showing changes in dose levels and trough values over time.
BURDEN OF THERAPY
On each day (day 1 to day 55) the number of AE's present in a single patient are counted, colored by severity.
EXAMPLE PATIENTS – TREATMENT B
GENERAL IDEA

The presence of TEAEs was plotted against study day, such that if a patient reported a TEAE from Days 3 to 5, this TEAE was considered present on Days 3, 4 and 5. If that patient reported TEAEs of differing severity on a single day, the worst severity was taken into account in the analysis.

If an end date was not present in the database, or a TEAE was ongoing, the last study day of the patient was taken as the end day of the TEAE.
WEIGHTING

In order to visually represent the safety burden experienced by a patient, varied weighting was applied to TEAE severity in each arm in a consistent manner. The presented graph therefore displays the weighted TEAEs per day. For the purposes of example graphs presented in this Presentation, TEAEs that were recorded as mild, moderate, and severe were weighted to represent 1x, 2x, and 3x TEAEs per event per day, respectively.
Other weighting tools might include Utility functions estimated with discrete choice experiments.
Combined graph:
Time to response and % patients with a RELATED AE per day

Severity of the AEs

Date April 2, 2014
Difference in percentage of Related Treatment Emergent Adverse Events

% patients with AE per day

% More in A % More in B

Study day

Treatment A

Treatment B
By summing up the burden of each day for each patient, with or without the weighting of events, one can derive an Area Under Curve (AUC) per patient. This will give a burden estimate for each patient (Supplementary Appendix).
ADVERSE EVENTS

% patients with an AE per day

Application site pain or dermal changes

<table>
<thead>
<tr>
<th>Placebo</th>
<th>No</th>
<th>Active</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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Percentage of Patients with an Adverse Event per Day, multiple periods
A novel standard to evaluate the impact of therapeutic agents on patient safety – The BURDEN OF THERAPY™

Ayad K. Abdulahad, Robert J. Snijder, Moeen K. Panni, Faysal K. Riaz, Andreas J. Karas
SIMILAR THOUGHTS

Longitudinal adverse event assessment in oncology clinical trials: the Toxicity over Time (ToxT) analysis of Alliance trials

Gita Thanarajasingam, Pamela J Atherton, Paul J Novotny, Charles L Loprinzi, Jeff A Sloan, Axel Grothey