Patient Reported Outcomes in an Era of Immunotherapy Drug Development

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Disclosures

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Board member/Officer:
FACIT.org, PROMIS Health Organization
Treatment Benefit

May be measured as:

– **Comparative efficacy**

  An improvement or delay in the development of symptoms or decrements in function compared to placebo or an active comparator

– **Comparative safety**

  *Reduction or delay in treatment-related toxicity compared to placebo or an active comparator*
Imatinib (Glivec) Registration Trial (Phase III, Multicenter, Open Label)

1,106 pts. with newly diagnosed CML

Imatinib

Ifn-α + LDAC

Crossover for:
- Lack of response
- Loss of response
- Intolerance of treatment
Estimated Mean FACT-BRM (with crossover)

- **Imatinib no crossover** ($n=517$)
- **IFN crossover** ($n=312$)
- **IFN no crossover** ($n=207$)

1st row: imatinib VS. IFN+LDAC (crossover)
2nd row: IFN+LDAC (no crossover) VS. IFN+LDAC (crossover)

$p < 0.05$
$+ p < 0.01$
$\ ▽ p < 0.0001$

Months After Randomization
Patient reported outcomes in oncology

- Disease symptoms
- Side effect burden
- Tolerability

Response rate and progression free survival

Patient treatment experience

Treatment preference

OS, overall survival.

Clinical Benefit in Hematology-Oncology

• Overall survival considered gold standard
  • Surrogate endpoints like progression-free survival often used

• Traditional endpoints do not fully address treatment responses experienced by the patient
  • Symptom relief, functional improvement

• *Patient-reported outcomes* can complement traditional efficacy measures

• Once we know the patient-reported outcomes, how do we incorporate them into risk-benefit analysis

Starting with the end in mind: Possible messages from trial results

- **PFS benefit** of “x” relative to “y” was associated with:
  - Disease-related symptom benefit (efficacy)
  - Improved physical function (efficacy)
  - Improved quality of life (efficacy)
  - Reduced toxicity (safety)

- Relative to “y,” “x” provided superior **CBR**. That is:
  - Longer PFS, reduced symptoms, and comparable safety
  - Longer PFS, no difference in symptoms, better safety
  - No difference in PFS with better symptom control
  - etc
Composite endpoints can be intuitive or conceptually appealing

• Takes into account multiple traditional endpoints:
  – Response rate
  – Survival
  – Toxicity
  – PROs

• Help health-care providers, patients, and decision-makers to understand the total clinical benefit of a particular intervention.

• When survival or QOL measures alone do not adequately define the clinical effects of treatment
Symptom Indexing

• Nesting of tumor-specific or treatment-specific symptoms within larger, often multidimensional questionnaires creates opportunity to derive targeted symptom scales:
  – EORTC; FACT/FACIT; etc
  – PRO-CTCAE
  – PROMIS

• Functional status reported by patient) can offer cross-cutting information
  – Physical Functioning (EORTC; SF-36; FACT PWB; FACT FWB; PROMIS PF)
### Advanced Kidney Cancer Symptom Index – Long Form

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have bone pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel fatigued</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have been short of breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have a good appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have been coughing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by fevers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to work (includes work from home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by blood in my urine</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

AXIS Trial: Disease-related symptoms

Overall, disease-related symptoms did not change while on treatment

- However, disease-related symptoms were worse when patients came off treatment due to disease progression or AEs
FKSI-15 # 2: I Am Bothered by Side Effects of Treatment

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Axitinib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>327 285 260 219 212 179 166 148 127 112 93 82 63 54 48 37 30 21 15 164</td>
<td></td>
</tr>
<tr>
<td></td>
<td>317 302 249 226 206 181 162 139 121 98 89 73 61 57 41 36 28 22 14 12 7 193</td>
<td></td>
</tr>
</tbody>
</table>

Side effect bother by diarrhea grade, combined Treatments

FDA Perspective: Key contributors to Quality of Life

Core Concepts Measures Individually

- Disease Symptoms
- Symptomatic Adverse Events
- Physical Function

- Use existing until something better comes along

Kluetz et al, *Clin Cancer Res*, published Online Jan 12, 2016; DOI: 10.1158/1078-0432
Umbrellas and Baskets

**Umbrella**
- Single tumor type or histology
- PRO considerations
  - Small N
  - Single-arms opening and closing
  - Common disease symptoms
  - Physical function unifying endpoint
  - Safety/side effect variability

**Basket**
- Multiple tumor types
- PRO considerations
  - Small N
  - Single-arms opening and closing
  - Disease symptoms highly variable
  - Physical function unifying endpoint
  - Safety/side effect variability
Some PRO issues with MATCH

• Small N, single-arm searches for efficacy signals among pts with common molecular profile
• Discovery valued over hypothesis testing
• PS = 0/1, variable primary sites, 6 month f/u
  – disease symptom assessment unlikely to be informative
• Variability in patient preferences and tolerability
  – Willingness to undergo testing with unknown benefit
  – Comprehension of testing results, risks and benefits
  – Preferences regarding decision-making... and family impact
• How to measure treatment toxicity
  – “On-target” versus “off-target” and relationship to efficacy
  – Which ones?

Cella & Wagner, J Comm and Supp Onc, 2015
Which Treatment Symptoms? A proposal

Based on available monotherapy data:

- $\geq 40\%$ all grade
- $\geq 2\%$ grade 3/4

First 4 MATCH Substudies: How might PROs look?  
(Cella & Wagner, 2015)

<table>
<thead>
<tr>
<th>MATCH Substudy</th>
<th>Agent</th>
<th>Patient population</th>
<th>Sample size</th>
<th>Key disease symptoms,¹ Functional status and patient preferences</th>
<th>Expected PRO-relevant toxicity²</th>
<th>Likely number of questions (minutes per assessment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F</strong></td>
<td>Crizotinib</td>
<td>ALK translocations, except lung adeno and anaplastic large cell lymphoma</td>
<td>35</td>
<td>Various Physical Function Tolerability/preference</td>
<td>Constipation Diarrhea Nausea Fatigue Dyspnea Visual disturbances</td>
<td>20 (4)</td>
</tr>
<tr>
<td><strong>G</strong></td>
<td>Crizotinib</td>
<td>ROS1 translocations, except non small cell lung cancer</td>
<td>35</td>
<td>Various Physical Function Tolerability/preference</td>
<td>Constipation Diarrhea Nausea Fatigue Dyspnea Visual disturbances</td>
<td>20 (4)</td>
</tr>
<tr>
<td><strong>H</strong></td>
<td>Dabrafenib and Trametinib</td>
<td>BRAF V600E and V600K mutations, except melanoma and thyroid</td>
<td>35</td>
<td>Various Physical Function Tolerability/preference</td>
<td>Hand foot syndrome Pyrexia Chills Fatigue Rash Nausea Vomiting Back pain Constipation Diarrhea Dehydration</td>
<td>30 (6)</td>
</tr>
<tr>
<td><strong>R</strong></td>
<td>Trametinib</td>
<td>BRAF fusions, or non V600E, non V600K BRAF mutations</td>
<td>35</td>
<td>Various Physical Function Tolerability/preference</td>
<td>Nausea Vomiting Fatigue Diarrhea Rash</td>
<td>18 (4)</td>
</tr>
</tbody>
</table>

¹ For Substudy F: in addition to symptoms of interest, patient-reported functional status and patient preferences.  
² For Substudy F: Constipation Diarrhea Nausea Fatigue Dyspnea Visual disturbances

**Notes:**
- Each MATCH Substudy evaluates a specific agent and patient population, focusing on the expected PRO-relevant toxicity and likely number of questions (in minutes per assessment).
- The table summarizes key aspects of each MATCH Substudy, including the agent, patient population, sample size, key disease symptoms, functional status, and expected PRO-relevant toxicity.
Attributing and Selecting Symptoms

- Many of the most important symptoms are caused by both disease and treatment
- Treatments induce MANY symptoms
  - Which to select?
  - Who selects?

- A proposal: Use existing questionnaires, supplemented with:
  - Trial-specific, transparent, pre-specified and externally-adjudicated subset of most likely PRO-relevant side effects
  - Careful planning of assessment timing and acuity/chronicity
  - Valuation exercise (within or outside of trial) aimed at providing patient preferences for each of the outcomes in the composite relative to each other
Some Questions: Where do you stand?

• Can disease symptoms be separated from treatment symptoms?
  – By patients?
  – By investigators or data reviewers?

• Can one “pick and choose” symptoms for use in a precision medicine (or any other) study?
  – If so, how does minimize or remove bias?
  – What validity information is needed?
Potential benefits of successful blinding

**Participants**
- Less likely to have biased psychological or physical responses to intervention
- More likely to comply with trial regimens
- Less likely to seek additional adjunct interventions
- Less likely to leave trial without providing outcome data, leading to lost to follow-up

**Trial investigators**
- Less likely to transfer their inclinations or attitudes to participants
- Less likely to differentially administer co-interventions
- Less likely to differentially adjust dose
- Less likely to differentially withdraw participants
- Less likely to differentially encourage or discourage participants to continue trial

**Assessors**
- Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest
Impact of Blinding on Trial Results

- Unblinded investigators may report treatment effects not reported by blinded investigators

- More subjective endpoints create greater opportunity for bias

- Some studies cannot be fully blinded
  - Lack of blinding does not necessarily make a weak trial

- Those blinded versus unblinded should be explicated for best review and interpretation
  - Beyond single-, double-, triple-blind