Surrogate Marker: CMV Viremia

• Endpoint that is reasonably likely to predict clinical outcome, although not validated

• In the U.S. this type of endpoint allows for the possibility of Accelerated Approval of a CMV antiviral using CMV viremia as a primary endpoint

• Accelerated Approvals require confirmatory trials that demonstrate an effect on a true clinical endpoint
Validating a Surrogate Criteria (Fleming 2005)

• The biological marker must be correlated with the clinical endpoint
  – Literature supports correlations of baseline CMV viremia and disease progression and, to a lesser extent, correlations of decreases in CMV viremia and reductions in clinical disease endpoints

• The marker must fully capture the net effect of the intervention on the clinical efficacy endpoint
  – Where we need to focus further investigation
• All mechanisms of action of the intervention on the true endpoint are mediated through the surrogate.

Example: HIV-RNA Validation

• 1996 Surrogate Marker Working Group
  – Industry, academia, and government
• Sponsors, FDA, NIH analyzed data to assess:
  – Correlations between viral load and clinical outcome
  – Correlations between short-term viral load suppression and durability of viral load response
• July 1997 Antiviral Advisory Committee
• Also conducted a Meta-analysis of clinical trials in the literature
## HIV RNA and Clinical Benefit

5 Analyses (1996), >5000 patients

<table>
<thead>
<tr>
<th>ANALYSES</th>
<th>N</th>
<th>REGIMENS</th>
<th>CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Abbott Single Study (subset)</td>
<td>159</td>
<td>PI + NRTIS</td>
<td>21</td>
</tr>
<tr>
<td>2) NIH AIDS Clinical Trial Group Multiple Studies</td>
<td>1000</td>
<td>Many</td>
<td>218</td>
</tr>
<tr>
<td>3) Glaxo-Wellcome Studies Multiple Studies</td>
<td>1581</td>
<td>ZDV +3TC (others)</td>
<td>209</td>
</tr>
<tr>
<td>4) Pharmacia &amp; Upjohn Studies: Two Studies</td>
<td>1842</td>
<td>DLV+ZDV DLV+DDI ZDV, DDI</td>
<td>230</td>
</tr>
<tr>
<td>5) Roche Study Single Study</td>
<td>940</td>
<td>SQV+DDC SQV, DDC</td>
<td>170</td>
</tr>
</tbody>
</table>
Association of Viral Load Reduction and Clinical Benefit (3 slides)

- Magnitude of Reduction
- Nadir of Reduction
- Duration of Reduction
Clinical Progression vs. HIV RNA Reduction

POOLED ACTG STUDIES

ADJ. RR (natural log)

WEEK 24 HIV RNA Reduction

Stratifying factors:
- study and treatment
- none
- study
- treatment

- >1.0 log
- 0.5-1.0 log
- 0-0.5 log
- no reduction
Progression vs. Viral Load Nadir

GSK Analyses

Viral Load Nadir (copies/mL)

Incidence

<Median  >Median

<400  <500  <20,000  >20,000
# Clinical Hazard by Duration of Reduction

## Pharmacia-Upjohn Analyses

<table>
<thead>
<tr>
<th>Response Duration #DAYS</th>
<th>Hazard ratio</th>
<th>95% CI for HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>1-29</td>
<td>0.68</td>
<td>(0.43, 1.04)</td>
</tr>
<tr>
<td>30-57</td>
<td>0.72</td>
<td>(0.41, 1.27)</td>
</tr>
<tr>
<td>58-113</td>
<td>0.55</td>
<td>(0.32, 0.95)</td>
</tr>
<tr>
<td>114-141</td>
<td>0.26</td>
<td>(0.128, 0.528)</td>
</tr>
<tr>
<td>&gt;142</td>
<td>0.29</td>
<td>(0.145, 0.564)</td>
</tr>
</tbody>
</table>
Analyses: Summary of Findings

• HIV RNA decreases (> 0.5 log) are associated with lower risks of disease progression
• Greater Reductions associated with lower risks of progression
• More Sustained Reductions (> 8-12 weeks) in HIV RNA are associated with lower risks of disease progression
• Suppression of HIV-RNA below assay quantification is associated with longer duration of virologic suppression and less emergence of HIV resistance
• Validation process took several years and concurrently the working group investigated how HIV-RNA would be incorporated into all phases of drug development and clinical trial designs.
Forum CMV Working Group
Future Directions

How do we use CMV viremia in clinical investigations?

• Need to define CMV viremia thresholds for initiating pre-emptive therapy:
  – Could one randomize subjects according to initiation thresholds, (500, 1000, 5000 copies, etc.?) in a pre-emptive therapy trial?

• Defining a level of viremia that is considered “safe” would be helpful for conducting proof-of-concept trials (phase 1 and 2). In effect, can we see the PD effect of a new antiviral in a CMV viremic patients that don’t require approved treatment?
Future Directions
CMV Viremia Issues

• Do we know enough about CMV viral kinetics across a range of treatment to design all phases of trials?
  – For Phase 1 proof of concept or phase 2 dose finding: What is the minimum amount of time needed to discern important dose related PD effects (3 days, 2 weeks)?
  – For phase 2 and 3 trials: What is the median time to undetectable or acceptable virus levels? How does this differ by baseline patient characteristics (SOT, HSCT)?

• What activity data is needed for investigators to feel comfortable substituting ganciclovir with an investigational drug? For Treatment? For Pre-emptive therapy? For Prophylaxis?
Future Directions
CMV Viremia Issues

• Will CMV viremia be useful as a surrogate endpoint for the treatment of CMV disease, in that clinical resolution occurs in the same time frame as resolution of CMV viremia? Or will it be a necessary part of a primary clinical endpoint? When do we measure treatment success?
Future Directions
Other Issues/Questions

• Define control arms for various indications and the historical data to support non-inferiority margins in active controlled trials

• Explore openness to investigating different prophylaxis durations (e.g., 100 or 200 days)—duration-response can support efficacy

• Are trials feasible in ganciclovir resistant (or intolerant) populations (enough subjects)?

• Is there a bias against studying combination therapy at this time?