Obstacles to Dose Optimization in Early Stage Cancer Drug Development

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Outline

• Oncology drug development and dose selection
• A drug-disease modeling framework
  – Longitudinal tumor size models
  – Survival models
• New proposed endpoints based on continuous tumor growth inhibition metrics for early oncology studies
• Conclusions
Oncology drug development and dose selection

- Expedited programs, huge competition
- Empirical selection of dose and dosing schedules in Phase I
  - Maximum tolerated dose (MTD)
    - Not appropriate for dose selection with targeted therapies?
  - Pharmacologically active dose based on biomarker responses specific to the mechanism of action
    - Fine to establish proof of mechanism …
      - i.e. is the target impacted, is there some tumor growth inhibition…
    - … but not mature for dose selection

- Phase II program not informative
  - Design
    - Limited to establish proof of concept
    - Very few randomized Phase IIb dose-ranging studies
  - Primary clinical endpoints poorly informative (ORR, PFS) and somewhat subjective (PFS)
- Phase III: High failure rate
  - > 50%
Modeling Framework
Tumor Growth Inhibition Metrics
A modeling framework to support the Phase II-III transition

Figure 1 Tumor growth inhibition as a biomarker to predict clinical benefit in oncology studies.

Tumor growth inhibition (TGI) metrics to assess exposure-response in early clinical studies and predict expected OS

Drug-specific tumor size models

- Semi-mechanistic exposure-driven tumor growth inhibition (TGI) models
  - Tumor growth, exposure driven drug effect, resistance appearance\(^1\)-\(^6\)

- Empirical models
  - Simplified TGI model (assumes constant exposure)\(^7\)-\(^8\)
  - Linear growth plus exponential shrinkage\(^9\)-\(^10\)
  - Exponential growth and shrinkage\(^11\)

\(^1\)Claret et al. PAGE 2006;
\(^4\)Stein et al. BMC Cancer 12:311, 2012
\(^5\)Ribba et al. Clin. Cancer Res. Published online (Jul-03, 2012)
\(^6\)Hansson et al. CPT:PSP, 2, e84, 2013
\(^7\)Claret et al. PAGE 2012;
\(^8\)Claret et al. J. Clin. Oncol. 31:2110-14, 2013
Models for clinical endpoints (overall survival)

- Survival time distribution is estimated (parametric model) as a function of prognostic factors and treatment effect
- Drug independent, disease specific model
  - TGI metric is used as a biomarker to capture treatment effect
  - Historical Phase III studies can be used to develop the models
  - Overall survival models have been developed for MBC\(^1\), CRC\(^2,3\), pancreatic cancer, ovarian cancer\(^4\), H&N carcinoma, multiple myeloma\(^5\), non-hodgkin lymphoma, gastric cancer\(^6\), renal cell carcinoma\(^7\) (Pharsight collaborators)
  - and NSCLC\(^8-10\) (FDA, Pharsight)
- A few cases of external evaluations are available\(^2,5,11\)
  - More are needed

4. Lindborn et al. ACoP, 2009
6. Quartino et al. PAGE 2013
7. Mercier et al. ESMO 2014

Tumor growth inhibition metrics

Optimal endpoint for randomized phase II trials

Sharma et al, JCO 2014: Resampling the N9741 Trial to Compare Tumor Dynamic Versus Conventional End Points in Randomized Phase II Trials
Optimal endpoint for randomized phase II trials

- N9741, a randomized phase III trial of chemotherapy for metastatic colorectal cancer
- Compared the power of various endpoints to detect the superior therapy
  - In this 3 arm study FOLFOX demonstrated longer OS than IROX or IFL
- Simulated two-arm, randomized phase II trials of 20 to 80 patients per arm
- Resampled (1002 patients, 5000 replications):
  - Week 6, 12, and 18 ECTS (observed)
  - TTG (model-based)
  - PFS
Resampling simulation results

Power of randomized phase II trials of:

(A) FOLFOX vs. IFL
(B) FOLFOX vs. IROX
with various endpoints

Log ratio = ECTS

Sharma et al, JCO, 33, 36-41, 2015
Conclusions

• Supports the consideration of TTG estimated from nonlinear mixed-effects modeling of tumor measurements as a powerful endpoint for randomized phase II trials
  – Should be measured as a secondary endpoint
  – More studies should compare TGI metrics with PFS (or even ORR)
    • Which phase II endpoint will most often lead to the correct go/no-go decision?

• TGI metrics
  – Might show a distinct advantage when treatment benefit is smaller (e.g. FOLFOX vs. IROX)
  – Might benefit from optimized study designs (e.g. in term of tumor size observation schedule)
Clinical Trial Simulations to Support to Phase II Decisions: Metastatic Renal Cell Carcinoma Framework

Mercier et al, ESMO 2014; Claret et al, ASCPT 2015
A model relating overall survival to tumor growth inhibition in renal cell carcinoma patients treated with sunitinib, axitinib or temsirolimus
**Metastatic renal cell carcinoma (mRCC) OS model**

- **Historical Phase II-III studies with a variety of treatments**
  - **Over 2500 patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Line</th>
<th>N*</th>
<th>N_eval**</th>
<th>Treatment groups</th>
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<tbody>
<tr>
<td>Temsirolimus 1098</td>
<td>III</td>
<td>1st, poor prognosis</td>
<td>501</td>
<td>496</td>
<td>Temsirolimus, interferon, temsirolimus+interferon</td>
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<tr>
<td>Sunitinib 1006</td>
<td>III</td>
<td>2nd, refract²</td>
<td>106</td>
<td>105</td>
<td>Sunitinib 50 mg qd 4/2</td>
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<tr>
<td>Sunitinib 1034</td>
<td>III</td>
<td>1st</td>
<td>725</td>
<td>709</td>
<td>Interferon, Sunitinib 50 mg qd 4/2</td>
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<tr>
<td>Sunitinib 1065</td>
<td>II</td>
<td>1st</td>
<td>289</td>
<td>267</td>
<td>Sunitinib 50 mg qd 4/2, and 37.5 mg qd cont</td>
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<tr>
<td>Sunitinib 1072</td>
<td>II</td>
<td>1st and 2nd</td>
<td>51</td>
<td>51</td>
<td>Sunitinib 50 mg qd</td>
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<tr>
<td>Sunitinib 1110</td>
<td>NA</td>
<td>Long term extension</td>
<td>118</td>
<td>113</td>
<td>Sunitinib long term safety and tolerability</td>
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<tr>
<td>Axitinib 1012</td>
<td>II</td>
<td>2nd refract²</td>
<td>52</td>
<td>48</td>
<td>Axitinib 5 mg bid</td>
</tr>
<tr>
<td>Axitinib 1023</td>
<td>II</td>
<td>2nd, refract¹</td>
<td>62</td>
<td>50</td>
<td>Axitinib 5 mg bid</td>
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<tr>
<td>Axitinib 1032 (AXIS)</td>
<td>III</td>
<td>2nd</td>
<td>714</td>
<td>651</td>
<td>Axitinib 5 mg bid, Sorafenib 400 mg bid</td>
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<tr>
<td>Axitinib 1035</td>
<td>II</td>
<td>2nd, refract²</td>
<td>64</td>
<td>62</td>
<td>Axitinib 5 mg bid</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>2628</td>
<td>2552 (97.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Metastatic renal cell carcinoma (mRCC) OS model

- OS model incorporates 7 baseline prognostic factors
  - Drug effect captured by week 8 ETS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>8.07 (0.270)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 8 ETS</td>
<td>-1.99 (0.135)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>0.133 (0.111)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG=1</td>
<td>-0.400 (0.048)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG=(2, 3)</td>
<td>-0.163 (0.077)</td>
<td>0.033</td>
</tr>
<tr>
<td>Corrected calcium (mg/dL)</td>
<td>-0.104 (0.019)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log(# metastases)</td>
<td>-0.209 (0.032)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from diagnosis (days)</td>
<td>8.0E-5 (1.7E-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline LDH (U/L)</td>
<td>-3.7E-4 (9.2E-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung metastases (yes)</td>
<td>-0.138 (0.046)</td>
<td>0.002</td>
</tr>
<tr>
<td>Log(scale)</td>
<td>-0.107 (0.020)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SE: standard error, p: wald test ($\chi^2$)
+ sign favorable; - sign not favorable

Metastatic renal cell carcinoma (mRCC) OS model

- Model qualification
  - Predictive check of the sunitinib to INF-α HR in the first-line sunitinib study (1034)

Metastatic renal cell carcinoma (mRCC) OS model

- Model simulation
  - Predictive distribution of HR comparing an investigational treatment to sunitinib in a 600 patient study (300 per arm) as a function of difference in tumor growth inhibition (delta in week 8 ECTS)

  ![Graph showing HR distribution](Image)

- According to the simulations
  - An investigational treatment that would induce a 20% week 8 ETS difference from reference may result in an improved OS with a HR of \( \sim 0.75 \)
  - A 300 patients per arm Phase III study would have an 80% probability of success to show a HR < 0.80 (target product profile)

Discussion - Conclusions
Value of new endpoints and model-based simulations

- New endpoints based on continuous longitudinal tumor size data may offer powerful alternatives
  - To establish proof of concept based on early clinical data (cohort extensions in Phase I or Phase II studies)
  - To assess dose-response by enabling randomized dose-ranging Phase II studies

- Combined with model-based simulations, expected survival (PFS) probability distribution for an investigational treatment (and possibly HR vs. SOC) can be predicted, bridging Phase II TGI data to Phase III outcome\(^1,2\)

- Phase III clinical trials can be simulated to assess probability of success in support of
  - Go-no go decision
  - Trial design
  - Interim analyses

- Predictions of expected outcome can also be made for unstudied doses and schedules

\(^1\)Claret et al. J. Clin. Oncol. 27:4103-8, 2009
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References (cont.)


