Dose Optimization by Safety Guided Titration Approaches: Axitinib as a Case Example

Yazdi K. Pithavala, PhD
Axitinib

- Axitinib, a potent, selective, second-generation vascular endothelial growth factor (VEGF) receptor inhibitor
- Approved for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy, based on randomized Phase 3 head-to-head AXIS trial comparing it with sorafenib
I. INLYTA DOSE TITRATION: WHY?
   1. Justification for axitinib 5mg BID starting dose
   2. Axitinib dose titration rationale: retrospective analysis of phase II mRCC data

II. INLYTA DOSE TITRATION: HOW?
   1. Dose titration algorithm, timing, metrics
   2. Design of prospective study to evaluate benefit of dose titration
   3. Results from prospective study
Justification for axitinib 5 mg BID starting dose

• Phase I study in 36 patients receiving axitinib at doses ranging from 5 to 30 mg by mouth twice daily\(^1\):
  - Maximum-tolerated dose of axitinib was 5 mg, twice daily

• Axitinib dosing needs to be twice a day based on the plasma half-life range of 2.5–6.1 hours\(^1\)
  - 5 mg BID resulted in approximately 1.4-fold accumulation compared with administering a single dose

• Therefore, the recommended starting dose of INLYTA\(^\circ\) is 5 mg BID, with titration as required\(^2\)

2. INLYTA\(^\circ\) USPI 2012
Justification for axitinib 5 mg BID starting dose

• **Pharmacodynamics**
  – AUC at 5 mg BID resulted in near maximal decrease in blood flow/permeability and soluble VEGFR-2 in plasma

• **Efficacy**
  – 5 mg BID associated with robust clinical response (44% ORR) in Phase 2 RCC study A4061012

<table>
<thead>
<tr>
<th>Setting</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine-refractory¹,²</td>
<td>44%</td>
<td>13.7 months</td>
</tr>
</tbody>
</table>

Axitinib-Related Changes in Blood Flow/Permeability: Phase 1 (FIH) Study

Representative DCE-MRI images from a patient with adenoid cystic carcinoma showing a decline in tumor perfusion after exposure to axitinib.

Axitinib-Related Changes in Blood Flow/Permeability: Phase 1 (FIH) Study

Near-maximal reduction in blood flow/permeability at 5 mg BID dose


Mean steady state plasma exposures obtained in patients at 5 mg BID with Form XL1 are overlaid with vertical lines.
Higher AUC Associated with Longer PFS using pooled data from Ph 2 mRCC Studies

Studies | Median PFS, weeks (95% CI) | Hazard Ratio (95% CI) | P-value
--- | --- | --- | ---
A4061012 | low AUC (< median) | high AUC (≥ median) | | |
A4061023 | n=86, 60 | n=87, 49 | 0.608 | 0.00926 |
A4061035 | 33 (32, 48) | 64 (48, 102) | (0.416, 0.888) | |

n=number of patients meeting AUC criterion, number of PFS events assessed by investigator
AUC cycle1 refers to average AUC across first cycle of treatment

Higher AUC Associated with Longer OS in Ph 2 mRCC Patients

All RCC Patients
median AUC_{cycle1} = 367 h.ng/mL

Studies | Median OS, weeks (95% CI) | Hazard Ratio (95% CI) | P-value
--- | --- | --- | ---
low AUC (< median) | high AUC (≥ median) | | |
A4061012 | 72 (64, 118) | 131 (95, NA) | 0.54 (0.347, 0.842) | 0.00579 |
A4061023 | n=86, 53 | n=87, 31 | | |
A4061035 | | | |

n=number of patients meeting AUC criterion, number of OS events
AUC cycle1 refers to average AUC across first cycle of treatment

Axitinib dose titration rationale: Retrospective analysis of phase II mRCC data

- **All patients before titration**

<table>
<thead>
<tr>
<th>Median AUC_{12} ng·hr/mL (range)</th>
<th>5 mg BID n=129</th>
<th>7 mg BID n=30</th>
<th>10 mg BID n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEFORE titration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFTER titration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Before titration**: variable level of drug exposure and significant percentage of patients below the therapeutic threshold (AUC_{12} <150 ng·h/mL)

  
  \[
  \text{AUC}_{12} = \text{area under the plasma concentration-time curve from 0 to 12 hr}
  \]

Rini et al. ASCO 2012 Abstract 4503
Axitinib dose titration rationale: Retrospective analysis of phase II mRCC data

Patients who could not be titrated based on clinical criteria
(BP increase or other AE)

<table>
<thead>
<tr>
<th>Median AUC₁₂ ng·hr/mL (range)</th>
<th>5 mg BID n=129</th>
<th>7 mg BID n=30</th>
<th>10 mg BID n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BEFORE titration</strong></td>
<td></td>
<td>231 (42–931)</td>
<td></td>
</tr>
<tr>
<td><strong>AFTER titration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Sub-therapeutic exposure defined as AUC₁₂ <150 ng·h/mL

- These patients were largely although not entirely above the therapeutic threshold (AUC₁₂ 150 ng·h/mL) with an average value of 231

BP = blood pressure; AE = adverse event

Rini et al. ASCO 2012 Abstract 4503
Axitinib dose titration rationale:
Retrospective analysis of phase II mRCC data

• Before titration, many if not most patients were below what is considered to be therapeutic exposure

<table>
<thead>
<tr>
<th>AUC_{12} (ng·hr/mL)</th>
<th>BEFORE titration</th>
<th>AFTER titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg BID</td>
<td>231 (42–931)</td>
<td>160 (32.8–443)</td>
</tr>
<tr>
<td>7 mg BID</td>
<td></td>
<td>129 (31.9–304)</td>
</tr>
<tr>
<td>10 mg BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median AUC_{12} ng·hr/mL (range)

ALL patients before titration (n=175)

Before titration
- 5 mg BID
- 7 mg BID
- 10 mg BID

After titration

Sub-therapeutic exposure defined as AUC_{12} <150 ng·h/mL

Rini et al. ASCO 2012 Abstract 4503
Axitinib dose titration rationale: Retrospective analysis of phase II mRCC data

- After axitinib dose titration (7 or 10mg BID), most patients achieved therapeutic drug levels

**Axitinib dose titration rationale:**
Retrospective analysis of phase II mRCC data

**Median AUC\textsubscript{12} ng·hr/mL (range)**

<table>
<thead>
<tr>
<th></th>
<th>5 mg BID</th>
<th>7 mg BID</th>
<th>10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n=129</td>
<td>n=30</td>
<td>n=16</td>
</tr>
<tr>
<td><strong>BEFORE titration</strong></td>
<td>231 (42–931)</td>
<td>160 (32.8–443)</td>
<td>129 (31.9–304)</td>
</tr>
<tr>
<td><strong>AFTER titration</strong></td>
<td>225 (45.9–620)</td>
<td>258 (63.9–608)</td>
<td></td>
</tr>
</tbody>
</table>

Sub-therapeutic exposure defined as 
AUC\textsubscript{12} <150 ng·h/mL

**ALL patients before titration**
(n=175)

- No titration
- 5 mg BID
- 7 mg BID
- 10 mg BID

**Patients who did titrate (after titration)**
Pharmacokinetic data confirm normalization of plasma exposures with dose titration in patients who tolerate 5 mg BID

Median AUC$_{12}$ ng·hr/mL (range)

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>BEFORE titration</th>
<th>AFTER titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>231 (42–931)</td>
<td>225 (45.9–620)</td>
</tr>
<tr>
<td>7</td>
<td>160 (32.8–443)</td>
<td>258 (63.9–608)</td>
</tr>
<tr>
<td>10</td>
<td>129 (31.9–304)</td>
<td></td>
</tr>
</tbody>
</table>

Sub-therapeutic exposure defined as AUC$_{12}$ <150 ng·h/mL

- Pharmacokinetic data confirm normalization of plasma exposures with dose titration in patients who tolerate 5 mg BID

Rini et al. ASCO 2012 Abstract 4503
Dose Escalation Algorithm in Ph 3

- Patients may have their dose increased by one dose level to maximum of 10 mg BID if they meet the following criteria within a consecutive 2-week period:
  
  i. patient has no adverse events > CTCAE Grade 2 related to study drug, and
  
  ii. patient is normotensive (BP < 150/90 mm Hg), and
  
  iii. Patient is not taking any anti-hypertensive medication

- Clinical judgment of the treating physician should be exercised in titrating axitinib dose.

<table>
<thead>
<tr>
<th>Axitinib Dose Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>+2</td>
<td>10 mg BID</td>
</tr>
<tr>
<td>+1</td>
<td>7 mg BID</td>
</tr>
<tr>
<td>0 (Starting Dose)</td>
<td>5 mg BID</td>
</tr>
<tr>
<td>-1</td>
<td>3 mg BID</td>
</tr>
<tr>
<td>-2</td>
<td>2 mg BID</td>
</tr>
</tbody>
</table>
Dose titration in the axitinib Phase 3 study

Percentage of patients with dose modifications

STARTING Dose
5mg BID
100% pts
(n=359)

Dose Reduction
<5mg BID
34% pts
(n=121)

No Dose Change
5mg BID
28% pts
(n=102)

Dose-escalation
>5mg BID
38% pts
(n=136)

Titration based on tolerability vs. therapeutic drug monitoring (TDM)

- Phase 3 study implemented dose titration based on individual patient tolerability
- Titration based on TDM not been prospectively studied for axitinib
- No data to indicate whether concentration-driven dose-escalation would be better than current schema based on tolerability
- Due to short plasma half-life, axitinib concentrations rise and fall significantly during a dosing interval. Also, there is minimal accumulation at steady-state. Hence unlikely that a PK sample collected at a single time will be adequate to make dosing decisions.
- Specific plasma concentration to be targeted for TDM need to be validated
Dose titration allowed after **at least 2 consecutive weeks** of dosing at the 5 mg BID starting dose

- With 2.5-6.1 hour plasma half-life, steady state expected in 2-3 days of dosing
- Intent is to optimize drug exposure prior to first on-treatment study scan, usually ~ 6-8 weeks after study start
- Pts could come off study (due to disease progression) by week 6, and in an attempt to facilitate adequate drug exposure prior to this, dose-titration permitted as early as 2 weeks after initiation of treatment.
- Many AEs emerge within first cycle of treatment, and dose-reduction permitted **at any time** in response to drug-related AEs
Prospective study

• A prospective, randomized, double-blind, study (N=200) in 1st line RCC patients was initiated to evaluate the benefit of dose-titration
Study Design

Figure 1. Schema for axitinib front-line mRCC dose-titration study.

Randomization criteria

BP ≤150/90 mmHg and no grade 3 or 4 axitinib-related toxicities and no dose reduction during lead-in period and no more than 2 concurrent antihypertensive medications

Yes

RANDOMIZE 1:1

Arm A (n = 35)
axitinib 5 mg BID + axitinib dose titration (blinded treatment)

Arm B (n = 35)
axitinib 5 mg BID + placebo dose titration (blinded treatment)

No

Arm C (n = 130)
axitinib 5 mg BID or reduced dose prn (no dose titration)

Randomization stratified by Eastern Cooperative Oncology Group performance status. BID = twice daily; BP = blood pressure.
Prospective Phase II study on axitinib dose titration, blood pressure and exposure in mRCC

• Primary objective
  – To compare the ORR in patients receiving axitinib plus dose titration (Arm A) vs. axitinib plus placebo (Arm B)
    ▪ 80% power to detect ≥ 25% improvement in ORR

• Secondary objectives
  – PFS, OS, safety, duration of response, axitinib plasma pharmacokinetics, BP measurements, biomarker and pharmacogenetic analyses

Rini et al. ASCO 2012 Abstract 4503; Rini et al. ASCO GU 2013 Abstract LBA349
Patients who get dose-escalated have lower exposures initially at the starting dose.

<table>
<thead>
<tr>
<th></th>
<th>Arms A + B</th>
<th>Arm C</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{24}$ ng•h/mL (n)</td>
<td>198 (n=28)</td>
<td>467 (n=23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C$_{max}$ ng/mL (n)</td>
<td>25.5 (n=32)</td>
<td>40.3 (n=25)</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Axitinib pharmacokinetic parameters on Cycle 1 Day 15

AUC$_{24}$ = area under the plasma concentration-time curve from 0 to 24 hr; C$_{max}$ = maximum observed plasma concentration

Grünwald et al. ECCO ESMO 2011 Abstract 7140
Results: Primary Endpoint (ORR)

- Patients with axitinib dose titration had a significant increase in ORR vs. patients with placebo dose titration.

- Patients not eligible for dose titration (Arm C) based on randomisation criteria had similar ORR than patients with dose axitinib titration (Arm A).

*R value is from a 1-sided Cochran-Mantel-Haenszel test stratified by ECOG PS from randomization system.
†Includes 10 patients who withdrew during lead-in period.

Rini et al. ASCO GU 2013 Abstract LBA349
## Results: PFS and OS (secondary endpoints)

<table>
<thead>
<tr>
<th></th>
<th>Active Titration (Arm A)</th>
<th>Placebo Titration (Arm B)</th>
<th>Non-randomized (Arm C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=56)</td>
<td>(n=56)</td>
<td>(n=91)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>14.5</td>
<td>15.7</td>
<td>16.6</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(9.2, 24.5)</td>
<td>(8.3, 19.4)</td>
<td>(11.2, 22.5)</td>
</tr>
<tr>
<td>HR (95% CI)†; P §</td>
<td>0.85 (0.54, 1.35); P=0.244</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>42.7</td>
<td>30.4</td>
<td>41.6</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(24.7, NE)</td>
<td>(23.7,45.0)</td>
<td>(33.0, NE)</td>
</tr>
<tr>
<td>HR (95% CI)†; †; P §</td>
<td>0.785 (0.485-1.272); P=0.1616</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Although study wasn’t powered to show statistical differences in PFS or OS for dose titration, there was a trend in favor of dose titration for both.

---

*Includes 10 patients who withdrew during lead-in period; NE = not estimable
† Assuming proportional hazards, HR <1 indicates a reduction in favor of active titration; HR >1 indicates a reduction in favor of placebo titration.

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival

Rini et al. ASCO GU 2013 Abstract LBA349
## Results: Safety

<table>
<thead>
<tr>
<th>Adverse Events, (%)†</th>
<th>Total* (N=213)</th>
<th>Active Titration (n=56)</th>
<th>Placebo Titration (n=56)</th>
<th>Non-randomized (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65</td>
<td>30</td>
<td>61</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60</td>
<td>8</td>
<td>61</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>7</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>40</td>
<td>1</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>36</td>
<td>3</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>35</td>
<td>0</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>2</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>32</td>
<td>4</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>30</td>
<td>1</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>

* Includes 10 patients who withdrew during lead-in period.
† Treatment-emergent, all-causality adverse events reported in >30% of treated patients.
Prospective Study: Conclusions

• Patients titrated with active axitinib
  – Experienced a significant improvement in ORR (54% vs. 34%; \( P=0.019 \))
  – Experienced a 15% reduction in the risk of disease progression/death and 21% reduction in risk of death
    ▪ This study was not powered to compare PFS or OS between treatment arms

• Patients with presumed optimal drug dose (Arm C):
  ▪ Demonstrated 59% ORR

• Increases in the dose of INLYTA in patients in Arm A were not correlated with any new or unexpected adverse events

• Clinical parameters for dose titration based on individual tolerability are useful for identifying pts with sub-therapeutic axitinib exposure at 5-mg BID starting dose
Acknowledgments

• Patients and families for their participation in clinical trials

• Study personnel at participating clinical sites

• All investigators who participated in axitinib trials, and in particular, Dr Brian Rini

• Axitinib Clinical Development team
  – In particular, Glen Andrews, Angel Bair, Ying Chen, May Garrett, Sinil Kim, Kourosh Parivar, Alison Russell, Jamal Tarazi, Michael Tortorici
Axitinib dose titration rationale: Retrospective analysis of phase II mRCC data

- **Pts with AUC_{12} ≥ 150 ng·hr/mL before titration**
- **Pts with AUC_{12} < 150 ng·hr/mL before titration**

**AUC_{12} = area under the plasma concentration-time curve from 0 to 12 hr**

**Pooled RCC Patients AUC_{12} after Dose Titration**

<table>
<thead>
<tr>
<th>mPFS, wks (95% CI)</th>
<th>AUC_{12}</th>
<th>AUC_{12}</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 150 ng·hr/mL</td>
<td>≥ 150 ng·hr/mL</td>
<td></td>
</tr>
<tr>
<td>32 (24, 48)</td>
<td>n=36, 26</td>
<td>n=139, 83</td>
<td>0.56 (0.359, 0.874)</td>
</tr>
</tbody>
</table>

n=number of patients meeting AUC criterion, number of PFS events assessed by investigator.

*Rini et al. ASCO 2012 Abstract 4503*
### Prospective Dose Titration Study
### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Axitinib (N=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (range)</td>
<td>61 (28-87)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male / Female</td>
<td>143 (67) / 70 (33)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>162 (76)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Asian</td>
<td>46 (22)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Rini et al, ASCO 2012, abstract 4503
### Clinical Outcome According to Diastolic Blood Pressure on Cycle 1 Day 15

<table>
<thead>
<tr>
<th>Blood pressure parameter</th>
<th>mPFS, mo</th>
<th>ORR</th>
<th>AUC&lt;sub&gt;12&lt;/sub&gt;, ng·h/mL&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆dBP ≥10 mmHg, n=39</td>
<td>16.7</td>
<td>59%</td>
<td>176</td>
</tr>
<tr>
<td>∆dBP &lt;10 mmHg, n=22</td>
<td>8.3</td>
<td>45%</td>
<td>63</td>
</tr>
<tr>
<td>∆dBP ≥15 mmHg, n=20</td>
<td>19.3</td>
<td>60%</td>
<td>235</td>
</tr>
<tr>
<td>∆dBP &lt;15 mmHg, n=41</td>
<td>11.1</td>
<td>51%</td>
<td>93</td>
</tr>
<tr>
<td>dBP ≥90 mmHg, n=17</td>
<td>22.5</td>
<td>65%</td>
<td>195</td>
</tr>
<tr>
<td>dBP &lt;90 mmHg, n=46</td>
<td>13.7</td>
<td>50%</td>
<td>110</td>
</tr>
</tbody>
</table>

<sup>a</sup> Geometric mean

dBP = diastolic blood pressure (per ambulatory blood pressure monitoring); ∆dBP = change in dBP from baseline; mPFS = median progression-free survival; ORR = objective response rate

Rini et al, ASCO 2012, abstract 4503