Dose-finding of Small Molecule Oncology Drugs

May 18-19, 2015

Washington Court Hotel, Washington DC
Day 2:
Welcome and Workshop Objectives

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Division of Oncology Products 1 (DOP1), OHOP, OND, CDER, FDA

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Director, Lowe Center for Thoracic Oncology
Scientific Director, Belfer Institute for Applied Cancer Science
Senior Physician, Dana Farber Cancer Institute
Professor of Medicine, Harvard Medical School
Session III:  
Dose-Exposure Exploration

Oncology Drugs Dose Selection – What Have We Learned?
Qi Liu, PhD  
Clinical Pharmacology Team Leader, Division of Clinical Pharmacology V, OCP, OTS, CDER, FDA

Dose Optimization: Ceritinib
Dan Howard, PhD  
VP, Oncology Clinical Pharmacology, Novartis

Dose Optimization: Axitinib as a Case Example for Dose Titration
Yazdi Pithalva, PhD  
Senior Director, Clinical Pharmacology, Pfizer
Oncology Drugs Dose Selection
-What Have We Learned?

Qi Liu
Team Leader, Division of Clinical Pharmacology V
Office of Clinical Pharmacology
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The views of this presentation represent my personal opinion, do not necessarily reflect any position of the Food and Drug Administration
Overview

• Current status

• Lessons Learned at FDA
  o Case studies

• Goals of Session 3
Current Status

From 2011 to 2015

- 26 out of 44 NMEs approved in OHOP are small molecule anticancer targeted therapies
  - 14/26 selected MTD for dose

- Increased interest in alternatives to MTD approach*
  - optimize effectiveness
  - minimize toxicity
  - promote patients adherence

Lessons Learned at FDA Related to Oncology Drug Dose Selection

- Test more than one dose in Phase 2/3 trials
- Use dose/exposure-response models to integrate all available data
- Consider target inhibition data when MOA is clear
- Different doses may be needed in different disease settings
- Evaluate the dose(s) throughout drug development
  (nonclinical, phase 1 → phase 4)

Case 1: Nilotinib
Lessons Learned at FDA Related to Oncology Drug Dose Selection (Cont.)

- Consider long term (beyond 1\textsuperscript{st} cycle) safety/tolerability for chronic use
- Consider food-drug interaction
- Allowing up and down titration maybe helpful
  - Axitinib case (stay tuned for Dr. Pithavala’s presentation)

Case 2 & 3: Olaparib Ceritinib
Case Study 1: Nilotinib

a kinase inhibitor indicated for:

– Chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to imatinib (US approval in 2007)
  
  Recommended dose: 400 mg BID

– Newly diagnosed adult patients with Ph+ CML in CP (US approval in 2010)
  
  Recommended dose: 300 mg BID
Case Study 1: Nilotinib (Cont.)

Selection of Phase 2 dose in original NDA (2nd line CML):

- In phase 1, MTD = 600 mg BID
- 400 mg BID selected for Phase 2
  - Safety of 400 mg BID was better than 600 mg BID
  - No increase in PK when the dose increases from 400 to 600 mg
  - Phase 1 dose/concentration-response suggest that higher systemic exposure was related to better efficacy
  - Trough concentrations at 400 mg BID are in the concentration range predicted to inhibit the targets based on nonclinical data

Case Study 1: Nilotinib (Cont.)

2nd line CML:

• Phase 2 trial in was conducted using 400 mg BID dose

• Overall benefit-risk assessment supported the approval of 400 mg BID dose in this disease setting
Case Study 1: Nilotinib (Cont.)

Important safety findings at the time of initial approval:

- QT prolongation and sudden deaths resulted in Box Warning
- QT prolongation is exposure-dependent

Case Study 1: Nilotinib (Cont.)

Moving to the Frontline CML setting:

Selection of Phase 3 doses:

Two nilotinib doses (300 and 400 mg BID) were tested

- 400 mg BID was selected as it was approved for 2\textsuperscript{nd} line.

- 300 mg BID was selected in the hope of reasonably maintaining efficacy while improving safety based on the E-R relationship identified in the 2\textsuperscript{nd} line CML

Phase 3 data supported 300 mg BID for this indication:

- 300 mg BID had similar efficacy but better safety compared to 400 mg BID.

EMA/CHMP Assessment Report

Lessons Learned from the Nilotinib case:

• Test more than one dose in Phase 2/3 trials
  – Other examples: dasatinib, sonidegib

• Use dose/exposure-response models to integrate all available data
  – Other examples: axitinib, dasatinib

• Consider target inhibition data when MOA is clear
  – Other examples: temsirolimus, everolimus

• Different dose(s) may be needed in different disease settings
  – Other examples: dasatinib, everolimus

• Evaluate the dose(s) throughout the drug development (nonclinical, phase 1 through phase 4)
  – Other examples: dasatinib, sutent, vandetanib
Case Study 2: Olaparib

- A PARP inhibitor approved for gBRCA mutated advanced ovarian cancer after ≥ 3 prior lines of chemotherapy
- Indication as proposed by the applicant: Maintenance treatment for platinum-sensitive relapsed gBRCA mutated ovarian cancer
  - unfavorable vote from ODAC
    - One of the main reasons: Toxicity of therapy and risk of MDS/AML for patients not otherwise undergoing treatment

FDA review: [http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000TOC.cfm)
Case Study 2: Olaparib (Cont.)

Labeling related to food

– Many ODAC members were concerned over the prolonged GI tolerability issue in the maintenance setting
– In the patients with gBRCA-mutated ovarian cancer who received 3 or more prior lines of chemo, 64% had nausea, 43% had vomiting, 31% had diarrhea
– Olaparib was taken under fasting conditions in the trials.
– Food effect on PK was minimal
– We recommended allowing the drug to be taken without regards to food, for patients convenience and potential improvement in the GI tolerability
Case Study 3: Ceritinib

- a kinase inhibitor approved for ALK(+) metastatic NSCLC progressed on or intolerant to crizotinib
- 750 mg once daily on empty stomach (i.e., do not administer within 2 hours of a meal)

-------------------------WARNINGS AND PRECAUTIONS-------------------------

- Severe or Persistent Gastrointestinal Toxicity: Dose modification due to diarrhea, nausea, vomiting or abdominal pain occurred in 38% of patients. Withhold if not responsive to anti-emetics or anti-diarrheals, then dose reduce ZYKADIA. (2.2, 5.1)

FDA review: [http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000TOC.cfm)
Case Study 3: Ceritinib (Cont.)

• Food increases the drug exposure
  – Low-fat meal ↑ AUC by 58%
  – High-fat meal ↑ AUC by 73%

• Food may improve GI tolerability and compliance

• A PMR trial to compare the systemic exposure and safety of
  – 750 mg in the fasted state
  – Lower dose(s) with food

FDA review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000TOC.cfm
Lessons Learned from the Olaparib and Ceritinib cases:

- Consider long term (beyond 1st cycle) safety/tolerability for chronic use
  - Other examples: panobinostat, cabozantinib

- Consider food-drug interaction
  - Other examples: abiraterone, palbociclib, bosutinib

- Food for thought:
  - What if we study the food effect early on, and use the information to help the dosing strategy in the registration trials?
  - Will it improve the benefit/risk profile and compliance?
Conclusion

- Careful balance of benefit and risk is critical in oncology dose selection
- Improvement can be made to the traditional MTD approach
  - optimize effectiveness
  - minimize toxicity
  - promote patient adherence
Goals of Session 3

• To share dose selection/optimization experiences

• To discuss the different dose finding approaches, their successes, limitations and challenges
  – e.g., MTD and optimal biological dose

• To discuss tools that can be utilized, including their strengths and limitations
  – e.g., modeling and simulation, target inhibition data

• To discuss what we should do differently in the future
  – e.g., number of doses in the phase 2 and 3 trials, long term (beyond 1st cycle) safety/tolerability, food effect, individualized dosing (titration)
Dose Optimization – Ceritinib and More

Dan Howard, PhD
Novartis Oncology Business Unit
East Hanover, New Jersey
FDA-AACR May 18-19, 2015
#### Molecular Target of Ceritinib (Zykadia™)

**ALK in NSCLC**

- Anaplastic lymphoma kinase (ALK) rearrangements are present in 2% to 7% of patients with NSCLC\(^1\)
- \textit{EML4-ALK} fusion protein can activate multiple signalling pathways involved in cell transformation and tumorigenesis\(^2\)

\[\text{Ceritinib}\] is a potent and selective oral ALK inhibitor. It is 20-fold more potent and has greater specificity for ALK than \textit{crizotinib} (1\(^{st}\) approved ALK inhibitor) based on enzymatic assay\(^3,4\)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Ceritinib IC(_{50}) (μM)</th>
<th>Crizotinib IC(_{50}) (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>0.00015</td>
<td>0.003</td>
</tr>
<tr>
<td>IGF1R</td>
<td>0.008</td>
<td>0.4</td>
</tr>
<tr>
<td>MET</td>
<td>3.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Cell-based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>0.027</td>
<td>0.11</td>
</tr>
<tr>
<td>MET</td>
<td>1.3</td>
<td>0.028</td>
</tr>
</tbody>
</table>

ASCEND-1 First-in-Man Global Phase 1 Trial (NCT01283516)
An open-label dose-escalation and expansion study in adult patients with tumors characterized by genetic abnormalities in ALK

Any advanced ALK+ cancer Progression on standard therapy

50 mg QD (n = 2)
100 mg QD (n = 2)
200 mg QD (n = 3)
300 mg QD (n = 3)
400 mg QD (n = 14)
500 mg QD (n = 10)
600 mg QD (n = 10)
700 mg QD (n = 5)
750 mg QD (n = 10) MTD

Dosing under fasted condition

Additional 245 pts treated

ALK+ NSCLC
Prior ALKi therapy

≤2 months after prior ALKi
>2 months after prior ALKi

ALK+ NSCLC Naive to ALKi

ALK+ tumors other than NSCLC

• Primary objective: determination of MTD
• Secondary objectives: characterize safety, pharmacokinetics and antitumor activity
Determination of the Maximum Tolerated Dose

- MTD was based on probability of Cycle 1 DLT using Bayesian logistic regression model and clinical assessment.
- In the dose-escalation phase, 59 patients were treated at 50-750 mg. 8 DLTs at Cycle 1 were observed in 6 patients.
- Predicted chance of overdose (> 25% probability that DLT rate ≥ 33%) was 3.3% at 750 mg and 13.6% at 900 mg. BLRM permitted dose escalation to 900 mg.
- Clinical input from all investigators was incorporated into the MTD declaration of 750 mg.
  - Increasing frequency of Gr 1-2 GI disturbances including nausea, vomiting and diarrhea precluded escalation above 750 mg.

Data on file
ASCEND-1 First-in-Man Global Phase 1 Trial (NCT01283516)

Tumor responses to ceritinib for patients with ALK+ NSCLC

Change in tumor size after patients received ceritinib at doses of 400 to 750 mg per day

- Among 114 patients with ALK+ NSCLC who received ≥ 400 mg of ceritinib per day, the ORR was 58% (95% CI: 48 to 67)

- Strong early clinical evidence is the driver for ceritinib accelerated development

Analyses includes all the patients who received ceritinib by 19-Oct-2012. The data cut-off date was 2-Aug-2013
Preclinical Data Support Selection of Highest Exposures

Higher exposures are required in crizotinib-resistant models

PK data in crizotinib-resistant model

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AUC$_{0-24h}$ (h*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>12503</td>
</tr>
<tr>
<td>50</td>
<td>29744</td>
</tr>
<tr>
<td>100</td>
<td>57796</td>
</tr>
</tbody>
</table>

Clinical PK data

<table>
<thead>
<tr>
<th>clinical dose</th>
<th>AUC$_{0-24}$ (ng*h/mL), C2D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>750 (n=23)</td>
<td>23800</td>
</tr>
</tbody>
</table>

NOTE: Immature clinical DOR data precluded time-to-event E-R analyses prior to RD determination

Selected Event Timeline for Ceritinib (Zykadia™)

- **2010**
  - **October:** Ceritinib IND was filed

- **2011**
  - **March:** Ceritinib first patient first treatment in phase 1 first-in-man (FIM) study
  - **August:** FDA approved Crizotinib, first ALK+ NSCLC therapy

- **2012**
  - **April:** Ceritinib FIM study reached Proof of Concept, showing ceritinib is active in ALK+ NSCLC patients
  - **May:** MTD/RD declared to be 750 mg qd, expansion phase enrollment started
  - **November:** FDA end-of-phase 1 / pre-phase 3 meeting; FDA agreed with Novartis proposal to submit data from single-arm FIM study in ALK+ NSCLC patients as the basis for NDA under Subpart H; FDA agreed with the proposed design of confirmatory phase 3 study; FDA agreed with the proposed overall clinical pharmacology strategy; FDA encouraged Novartis to request BTD

- **2013**
  - **March:** Ceritinib receives Break-Through Therapy Designation from FDA
  - **May:** FDA agrees to accept 9 months of registration stability data for drug substance and 6 months of registration stability for drug product in the NDA
  - **November:** FDA Pre-NDA meeting
  - Ceritinib regulatory application is submitted to the FDA on a rolling basis in 3 parts

- **2014**
  - **April:** Zykadia™ is approved by the FDA for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib

Lau YY. Ceritinib: Breakthrough Treatment for ALK-Positive Non-small Cell Lung Cancer. ASCPT, 2015
The Impact of Break-Through Therapy Designation

- Our first-in-man study was now our pivotal registration study
  - Safety, efficacy, pharmacokinetics, dose-selection and justification, exposure-response
  - Significant attention was focused on quality, completeness and speed of study

- Our first-in-man formulation required immediate evaluation for commercial feasibility

- Priority clinical pharmacology studies required acceleration
Efficacy and Safety in Patients Treated With Ceritinib (Zykadia™)

Key efficacy results at 750 mg daily by Investigator assessment\(^1,2\)

<table>
<thead>
<tr>
<th>Efficacy Parameter (RECIST 1.0)</th>
<th>ALKi Pre-treated (N = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate [95% CI]</td>
<td>54.6% [47, 62]</td>
</tr>
<tr>
<td>CR</td>
<td>1.2%</td>
</tr>
<tr>
<td>PR</td>
<td>53.4%</td>
</tr>
<tr>
<td>Duration of Response, median (months) [95% CI]</td>
<td>7.4 [5.4, 10.1]</td>
</tr>
</tbody>
</table>

Safety:

- Dose reductions due to AEs occurred in 59% of patients treated with ceritinib. The most frequent adverse reactions, reported in at least 10% of patients, that led to dose reductions or interruptions were: increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%).
- Discontinuation of therapy due to AEs only occurred in 10% of patients treated with ceritinib.

\(^1\)Kim D-W, et al. Dong-Wan Kim et al; Poster 8003 presented at the 50\(^{th}\) ASCO, 2014; analyses based on 31-Oct-2013 cut-off date
\(^2\)Zykadia® Prescribing Information 2014.
Exposure–Response Relationship for Efficacy

$C_{\text{tough,ss}}$ versus ORR

Proportion of patients with tumor response status (%) vs. Average steady state trough concentration (ng/mL)

Data on file
No DOR/OR difference for daily doses of <750 mg and 750 mg

Panel A: Duration of response (DOR, days)

Panel B: Overall Survival (OS, days)

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib 750mg (n=246)</th>
<th>Ceritinib &lt;750mg (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>144 (58.5%)</td>
<td>22 (50.0%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(52.1%, 64.8%)</td>
<td>(34.6%, 65.4%)</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI), in months</td>
<td>9.7 (7.0, 11.4)</td>
<td>8.2 (5.9, 18.1)</td>
</tr>
<tr>
<td><strong>BIRC assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>121 (49.2%)</td>
<td>17 (38.6%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(42.8%, 55.6%)</td>
<td>(24.4%, 54.5%)</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI), in months</td>
<td>NE (7.1, NE)</td>
<td>8.3 (7.0, 18.6)</td>
</tr>
</tbody>
</table>

Taken from FDA Clinical Pharmacology Biopharmaceutics Review, 2014-3-25: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf
Higher exposure is associated with earlier dose reduction and interruption.

No clear association between $C_{\text{trough,ss}}$ and time to permanent discontinuation of ceritinib.

Data on file.
E–R Relationship for Safety
Positive trends noted for grade 2+ ALT/AST, grade 2+ glucose and QTc prolongation

- Similar trend for AST
- No trend for Gr 2+ TB

C\text{trough,ss} versus grade 2+ ALT

C\text{trough,ss} versus grade 2+ glucose elevation

C\text{trough,ss} versus grade 1+ GI AEs

\Delta\text{QTcP} from baseline versus time-matched PK conc

Estimated mean (90% CI) \(\Delta\text{QTcP} at C_{\text{max}, SS} = 13.6 \text{ ms (11.7; 15.5)}\)

Data on file
Confirmation of Ceritinib Dose Selection

1. There was no clear E-R relationship for efficacy
   - The range of exposures studied were driven by the predominance of data in the 750 group. Insufficient data were available in the lower part of the dose-response curve to draw clear conclusions regarding its shape, and hence the efficacy of lower exposures.

2. The efficacy results from the pivotal FIM study demonstrate that the recommended dose of 750 mg induces a high rate of early and durable responses.

3. Non-clinical data supported the selection of higher exposures to maximize efficacy and confer a more durable response in the setting of crizotinib resistance.

4. The safety profile was manageable via dose modification, with a low rate of AEs leading to discontinuation (10%).
   - Relative dose intensity at 750 mg daily was above 80% of the planned dose.
   - Dose reductions occurred throughout the dosing period, not limited to the first 2 cycles.
   - High frequency, low-grade AEs can be effectively managed with SoC including anti-emetics and anti-diarrheals.
Additional Tumor Modeling was Inconclusive

Effective concentration for tumor shrinkage of 30%-50% from baseline ranged: ~250-800 ng/ml
A High-frequency GI Toxicity was Observed

- At the recommended 750 mg dose under fasted conditions, the majority of patients experienced GI AEs:

<table>
<thead>
<tr>
<th>US Prescribing Information</th>
<th>Ceritinib N = 255</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>GI disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>86</td>
</tr>
<tr>
<td>Nausea</td>
<td>80</td>
</tr>
<tr>
<td>Vomiting</td>
<td>60</td>
</tr>
</tbody>
</table>

- No apparent relationships between systemic plasma exposure and GI AEs
  - Possibly due to high drug concentration in the GI tract which leads to GI track AEs directly

- It was postulated that taking ceritinib with food could improve GI tolerability, however, it could also lead to increased non-GI exposure-related effects through increased variability or increased drug exposure
Positive Food Effect of Ceritinib Observed in Healthy Volunteers

Compared with the fasted state, exposure of ceritinib after a single dose was increased by 58% after the intake of a low-fat meal and 73% after the intake of a high-fat meal.

Zykadia® Prescribing Information 2014; Lau YY et al; Abstract PII-043 presented at ASCPT, 2015
Ceritinib (Zykadia™) Dose and Regimen Optimization

- The preclinical data support the selection of highest tolerable exposures to maximize efficacy
- The clinical efficacy results demonstrate the recommended dose of 750 mg induces a high rate of early and durable responses
- Permanent discontinuation due to AEs occurred in only 10% of patients
- Coadministration of food increases exposure, and may increase GI tolerability
- The high rate of GI events suggest regimen optimization with food is warranted
  - Novartis is conducting a clinical study to explore doses of 450 mg and 600 mg daily with food to determine if GI tolerability can be improved at matching fasted drug exposures
Dose Optimization
Axitinib: case example for Dose Titration

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

Co-crystal Structure Modeling for Axitinib Binding to JM Domain-containing VEGFR-2 Kinase

Solowiej J. et al, Biochemistry 2009;48:7019
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
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\(^\circledR\) is 5 mg BID, with titration as required\(^2\)

2. INLYTA\(^\circledR\) USPI 2012
Justification for axitinib 5mg 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 XLI are overlaid with vertical lines.
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>
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</tbody>
</table>

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

AUC_{12} = 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 AUC$_{12}$ (ng·hr/mL)</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>231 (42–931)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFTER titration</td>
<td></td>
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</table>

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

- These patients were largely although not entirely above the therapeutic threshold (AUC$_{12}$ 150 ng·h/mL) with an average value of 231

BP = blood pressure; AE = adverse event

Rini et al. ASCO 2012 Abstract 4503
Before titration, many if not most patients were below what is considered to be therapeutic exposure.
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

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

<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>231 (42–931)</td>
<td>160 (32.8–443)</td>
<td>129 (31.9–304)</td>
</tr>
<tr>
<td>AFTER titration</td>
<td>225 (45.9–620)</td>
<td>258 (63.9–608)</td>
<td></td>
</tr>
</tbody>
</table>

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

**AUC** = area under the plasma concentration-time curve from 0 to 12 hr

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

**Table:**

<table>
<thead>
<tr>
<th>AUC\textsubscript{12}</th>
<th>mPFS, wks (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150 ng·hr/mL</td>
<td>32 (24, 48)</td>
<td>0.56 (0.359, 0.874)</td>
</tr>
<tr>
<td>≥ 150 ng·hr/mL</td>
<td>52 (43, 69)</td>
<td></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
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)

- Titration based on TDM not been prospectively studied for axitinib
- Phase 3 study implemented dose titration based on individual patient tolerability
- No data to indicate whether concentration-driven dose-escalation is 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
**Time to Initiation of Dose-Titration**

Dose titration allowed after *at least 2 consecutive weeks* of dosing at the 5 mg BID starting dose

- 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 PD) 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

- With 2.5-6.1 hour plasma half-life, steady state expected in 2-3 days of dosing
Prospective study

- A prospective, randomized, double-blind, study (N=200) in 1\textsuperscript{st} 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

Lead-in period (Cycle 1) N = 200
axitinib 5 mg BID (4 weeks)

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

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

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.

Rini et al, ASCO 2012, abstract 4503
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
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Axitinib (N=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, yr (range)</strong></td>
<td>61 (28-87)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male / Female</td>
<td>143 (67) / 70 (33)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></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
**Results: Pharmacokinetics**

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>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible for dose titration</td>
<td>Not eligible for dose titration</td>
<td></td>
</tr>
<tr>
<td>AUC$_{24}$ (ng·h/mL) (n)</td>
<td>198 (n=28)</td>
<td>467 (n=23)</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/mL) (n)</td>
<td>25.5 (n=32)</td>
<td>40.3 (n=25)</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$_{\text{max}}$ = maximum observed plasma concentration

Grünwald et al. ECCO ESMO 2011 Abstract 7140
<table>
<thead>
<tr>
<th>Blood pressure parameter</th>
<th>mPFS, mo</th>
<th>ORR</th>
<th>AUC_{12}, ng·h/mL⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>DdBP ≥10 mmHg, n=39</td>
<td>16.7</td>
<td>59%</td>
<td>176</td>
</tr>
<tr>
<td>DdBP &lt;10 mmHg, n=22</td>
<td>8.3</td>
<td>45%</td>
<td>63</td>
</tr>
<tr>
<td>DdBP ≥15 mmHg, n=20</td>
<td>19.3</td>
<td>60%</td>
<td>235</td>
</tr>
<tr>
<td>DdBP &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>

⁴ Geometric mean

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

Rini et al, ASCO 2012, abstract 4503
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).

*P 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 (secondary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Total* (N=213)</th>
<th>Active Titration (Arm A) (n=56)</th>
<th>Placebo Titration (Arm B) (n=56)</th>
<th>Non-randomized (Arm C) (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS from first dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>14.6 (11.5, 17.5)</td>
<td>14.5 (9.2, 24.5)</td>
<td>15.7 (8.3, 19.4)</td>
<td>16.6 (11.2, 22.5)</td>
</tr>
<tr>
<td>HR (95% CI)†</td>
<td>0.85 (0.54, 1.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*P §</td>
<td></td>
<td></td>
<td></td>
<td>0.244</td>
</tr>
</tbody>
</table>

- Although study was not powered to show statistical difference in PFS between axitinib dose titration and placebo dose titration, there was a trend in favor of axitinib dose titration (HR 0.85)

---

*Includes 10 patients who withdrew during lead-in period.
† 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 (Arm A)
  - Experienced a significant improvement in ORR
    • 54% vs. 34%; \( P=0.019 \)
  - Experienced a 15% reduction in the risk of disease progression or death
    • HR=0.85 (95% CI: 0.54, 1.35; \( P=0.244 \))
    • This study was not powered to compare PFS or OS between treatment arms

- Patients with presumed optimal drug dose (Arm C):
  • Demonstrated 59% ORR and median PFS of 16.6 months

- 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

Rini et al, ASCO 2012, abstract 4503
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
Session III: Dose-Exposure Exploration

Dose Optimization: Vandetanib
Eric Masson, PharmD
Executive Director, Quantitative Clinical Pharmacology, AstraZeneca

Dose Optimization for Small Molecule Combinations in Oncology
Jin Jin, PhD
Associate Director, Head of Modeling and Simulation, Genentech
Dose Optimization for Small Molecule Combinations in Oncology

Jin Y. Jin, Ph.D.
Associate Director
Head of Modeling and Simulation
Clinical Pharmacology
Genentech
Outline

Small Molecule Combination Therapy in Oncology

- Overview
  - Challenges and opportunities
  - Dose optimization strategy

- Case Examples for Dose Optimization of Small Molecule Combinations
  - PBPK – assessment of PK drug-drug interaction
  - Translational PKPD – animal/human translation
  - Clinical PKPD – dosing optimization
  - Biomarkers – assessment of target inhibition
  - Tolerability – benchmarking with single agent

- Summary and Future Direction
**Overview**

**Vision and Scientific Rationale for Combination Therapy in Oncology**

**Vision:**
Simultaneous inhibition of multiple targets to enhance activity in broader population with less resistance

**Scientific Rationales:**
- Multiple pathways downstream of validated oncology drug targets (HER2, EGFR, KIT)
- Prominent mutational activation of multiple targets in multiple tumor types
- Extensive pathway cross-talk leading to primary or acquired resistance to single agent-single pathway therapy

⇒ Combination therapy in oncology (NME + SOC; NME + NME)

*NME: new molecular entity; SOC: standard of care*
Overview

Combination Therapies in Oncology

- **NME + SOC:**
  - Dose and regimen for the SOC is generally known
  - Optimize dose and/or regimen for the NME

- **NME + NME:**
  - New area with accumulating knowledge
  - Optimal dose and/or regimen for both agents are unknown
  - Innovative clinical development

**Novel Challenges in Co-development of 2NME:**

- Preclinical efficacy
- Preclinical safety
- Clinical development
  - Overall development plan
  - Optimize dosing strategy for both NMEs
  - PK drug-drug interaction
  - PD drug-drug interaction
  - Dosing conditions
- CMC
- Regulatory

*NME: new molecular entity; SOC: standard of care*
Overview

Dose Optimization Strategy in Oncology

Preclinical-to-clinical translation
- Homogeneous xenograft vs. heterogeneous patients
- Resistance development
- Safety: challenging

Early-to-late clinical translation
- Predictive biomarkers
- Translation of early tumor response to long-term efficacy
- Chronic safety: challenging

- **PK:**
  - High PK variability in oncology patients
  - Dose adjustment based on intrinsic/extrinsic factors
  - Poly-pharmacy for co-mobility

- **Biomarker:**
  - Demonstration of pathway inhibition
  - Dosing justification based on target-specific or indication-specific biomarkers

- **Clinical efficacy/safety:**
  - Optimize therapeutic window

Complexity double/triple with combination therapy!
Case Example: PK

Assessment of PK Drug-Drug Interaction

Potential reasons for PK DDI in SM Combination:
- Metabolic enzyme
- Transporter
- Absorption

PBPK approach can provide critical input on dose selection and inclusion/exclusion criteria for clinical trials, especially for combination therapies in oncology (SOC+NME, NME+NME)

Physiologically-Based PK (PBPK)
is a M&S tool by integrating patient-specific and drug-specific factors to quantitatively predict PK and assess the effect of intrinsic/extrinsic factors.

Predicted AUC change: ≤ 2-fold ~ low DDI risk; 2-to 5-fold ~ moderate DDI risk; ≥ 5-fold ~ high DDI risk
**Case Example: PK (NME+SOC)**

**PBPK Application:** Paclitaxel Combo Phase Ib Dose Selection

**Challenge:** DDI risk for compound with narrow therapeutic window

**Opportunity:** Use of PBPK (prospective) and Population PK (retrospective) modeling

- Available *in vitro* data suggested that PI3K theoretically may inhibit CYP2C8 ([I]/Ki < 1).
- Paclitaxel is a CYP2C8 substrate, suggesting its PK may be affected by PI3K co-administration.
- In spite of the low PK DDI risk, the clinical impact may be high given the narrow therapeutic window of paclitaxel.

- Overall PBPK simulation predicted low PK DDI risk for PI3K + paclitaxel at the starting dose in Phase Ib.

- Observed PK data in Phase Ib confirmed no PK DDI between PI3K and paclitaxel:
  - Paclitaxel PK in the presence of PI3K is consistent with historical paclitaxel alone PK (PopPK)
  - No change of 6-OH-paclitaxel/paclitaxel ratio
  - PI3K PK in the presence of paclitaxel is consistent with historical PI3K alone PK (PopPK)

---

### Impact of PI3K on Rosiglitazone PK (Rosi as surrogate CYP2C8 substrate)

<table>
<thead>
<tr>
<th>PI3K Dose</th>
<th>Rosi AUC Ratio Median (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase Ib starting dose</td>
<td>1.1 (1.0 – 1.2)</td>
</tr>
<tr>
<td>Efficacy target dose</td>
<td>1.3 (1.1 – 1.7)</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrate</th>
<th>$K_i$ (μM)</th>
<th>SE</th>
<th>Likely Mechanism of Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Phenacetin</td>
<td>58</td>
<td>6</td>
<td>Competitive</td>
</tr>
<tr>
<td>2B6</td>
<td>Bupropion</td>
<td>&gt;40</td>
<td>NA</td>
<td>No inhibition</td>
</tr>
<tr>
<td>2C8</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>0.2</td>
<td>Non-competitive</td>
</tr>
<tr>
<td>2C9</td>
<td>Diclofenac</td>
<td>4.5</td>
<td>0.5</td>
<td>Competitive</td>
</tr>
<tr>
<td>2C19</td>
<td>S-Mephenytoin</td>
<td>42</td>
<td>4</td>
<td>Non-competitive</td>
</tr>
<tr>
<td>2D6</td>
<td>Bufuralol</td>
<td>18</td>
<td>2</td>
<td>Competitive</td>
</tr>
<tr>
<td>3A4</td>
<td>Midazolam</td>
<td>25</td>
<td>5</td>
<td>Competitive</td>
</tr>
<tr>
<td>3A4</td>
<td>Testosterone</td>
<td>5</td>
<td>1</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

---

Case Example: PK (NME+NME)

PBPK Application: 2NME Combo Phase Ib Study Design

**Challenge:** “Bi-directional” PK DDI risk

**Opportunity:** Use of PBPK (prospective) to de-risk without single agent lead-in

![NME1:](CYP3A and UGT2B7 substrate (in vitro) CYP3A and CYP2D6 inhibitor (in vitro)]

![NME2:](CYP3A and CYP2D6 substrate (in vitro) CYP3A inhibitor (in vitro)]

- The *in vitro* data suggested PK DDI potential for this 2NME combination.
- PBPK simulations suggested that the DDI potential is low-to-moderate.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitor</th>
<th>PBPK Predicted AUC Ratio - Median (Min/Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Minimal PBPK model</td>
</tr>
<tr>
<td>NME1 (low dose)</td>
<td>NME2</td>
<td>1.02 (1.00/1.43)</td>
</tr>
<tr>
<td>NME1 (high dose)</td>
<td>NME2</td>
<td>1.01 (1.00/1.21)</td>
</tr>
<tr>
<td>NME2</td>
<td>NME1 (low dose)</td>
<td>1.14 (1.01/3.53)</td>
</tr>
<tr>
<td>NME2</td>
<td>NME1 (high dose)</td>
<td>1.17 (1.02/4.78)</td>
</tr>
</tbody>
</table>

- These PBPK results supported the starting dosing of NME1 and the 2NME Phase Ib study design without single agent lead-in phase (ethical and time-saving in dose-escalation).

**PBPK Application:** 2NME Combo Phase Ib Study Design

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</table>

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Case Example: Translational PKPD

Oncology Translational PKPD Strategy

STAGE 1 – Fitting (Mouse)
Mouse PK

Mouse Efficacy

Conc. vs. Effect

STAGE 2 – Simulation (Human)
Human PK

%TGI at Clinical Exposures

TGI: tumor growth inhibition

Mouse PKPD model to correlate drug concentration and anti-tumor response

Use of human PK to correct for inter-species difference in drug exposure

Correction for inter-species difference in protein binding or target binding

Assume same PD parameters in mouse and human

Adapted from Harvey Wong
Rational for the Translational PKPD Approach

- Retrospective analysis of 8 anti-cancer agents suggested good correlation between simulated xenograft TGI driven by human PK and clinical response.
- This analysis suggests >60% TGI in preclinical models, at clinically relevant exposures, are more likely to lead to clinical response.

Table 1. Tumor growth inhibition at maximum tolerated dose in mouse, human simulated tumor growth inhibition using xenograft/allograft PK-PD model, and clinical response for 8 anticancer agents

<table>
<thead>
<tr>
<th>Anticancer agent</th>
<th>Xenograft/Allograft</th>
<th>Mouse %TGI at MTD</th>
<th>Human simulated %TGI on day 21</th>
<th>Clinical disease</th>
<th>Clinical response (overall response) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>Fibroblast NR6-Del (748-752)</td>
<td>99</td>
<td>102</td>
<td>NSCLC, exon 19 del</td>
<td>71</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>786-O (renal cell adenocarcinoma)</td>
<td>106</td>
<td>81</td>
<td>Metastatic renal cell carcinoma</td>
<td>47</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Colo205 (colorectal)</td>
<td>104</td>
<td>63</td>
<td>Colorectal cancer</td>
<td>1.2</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>K-562 (chronic myeloid leukemia)</td>
<td>117</td>
<td>104</td>
<td>Chronic myeloid leukemia</td>
<td>90</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>KPL-4 (HER2+ Breast)</td>
<td>80</td>
<td>73</td>
<td>HER2+ Breast</td>
<td>15</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Medulloblastoma, mutational driven tumor</td>
<td>115</td>
<td>104</td>
<td>Advanced basal cell carcinoma</td>
<td>55</td>
</tr>
<tr>
<td>Vismodegib (GDC-0449)</td>
<td>D5123 (colorectal, ligand-driven tumor)</td>
<td>49</td>
<td>40</td>
<td>Ovarian cancer/colorectal with FOLFOX or FOLFIRI</td>
<td>No signal</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Cal151x1.1s (triple negative breast)</td>
<td>90</td>
<td>88</td>
<td>Metastatic breast cancer</td>
<td>33</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>MX-1 (triple negative breast)</td>
<td>97</td>
<td>88</td>
<td>Advanced breast cancer</td>
<td>31</td>
</tr>
<tr>
<td>5-FU</td>
<td>Colo205 (Colorectal)</td>
<td>116</td>
<td>75</td>
<td>Colorectal cancer</td>
<td>10.3</td>
</tr>
</tbody>
</table>

This analysis suggests >60% TGI in preclinical models, at clinically relevant exposures, are more likely to lead to clinical response.
**Case Example: Translational PKPD (NME+NME)**

**Translational PKPD Application: 2NME Combo Phase Ib Dose Selection**

**Challenge:** How do we test 2NME combo?

**Opportunity:** Stepwise dose escalation with different degrees of tumor inhibition

---

**2NME Translational PKPD**

**MEK PK**

**PI3K PK**

**Challenge:** How do we test 2NME combo?

**Opportunity:** Stepwise dose escalation with different degrees of tumor inhibition

---

**2NME Phase 1b Design**

<table>
<thead>
<tr>
<th>MEK Dose</th>
<th>PI3K Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>a</td>
</tr>
<tr>
<td>B</td>
<td>b</td>
</tr>
<tr>
<td>C</td>
<td>c</td>
</tr>
</tbody>
</table>

**Tumor Growth**

- **TGI ≥ 80%** (Optimal Target)
- **TGI ≥ 60%** (Minimal Target)
- **TGI < 60%** (Below Target)

**Translational PKPD suggested good probability of anti-tumor activity during 2NME PhIb dose escalation.**

---

**Jin JY, Budha N, Choo E, Salphati L, Musib L, Ware J, Dresser M, et al.**

©2015, Genentech
Case Example: Clinical PKPD (NME+SOC)

Clinical PKPD Application: Optimization of Dose and Schedule

**Challenge:** Potential loss of efficacy for alternate dose/schedule  
**Opportunity:** Use longitudinal tumor response modeling to optimize dose/schedule

Clinical PKPD of longitudinal tumor response suggested low risk of losing efficacy with intermittent PI3K dosing, which can be investigated as alternative dosing option to potentially mitigate safety risk.

Lu T, Claret L, Bruno R, Ware J, Dresser M, Jin J et al.
Case Example: Biomarker

Assessment of Clinical Target Inhibition Using Biomarkers and PKPD

**Challenge:** Demonstration of target inhibition

**Opportunity:** Dose justification based on target specific biomarker response and PKPD

---

**Growth Factors**

- RTK
- PI3K
- PTEN
- GDC-0068
- AKT
- mTORC2
- TSC1/2
- PRAS40
- PRP
- mTORC1
- PTEN
- mTORC2
- TSC1/2
- PRAS40
- PRP
- 40 phospho-proteins

**Dose Justification Base on Biomarker PKPD**

- 200mg 400mg 600mg

**PpGSK3b Ratio**

- 0.2
- 0.4
- 0.6
- 0.8
- 1.0

**AUC (μM·hr)**

- 0 to 30

---

Yan Y et al. CCR. 2013

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**Case Example: Tolerability (NME+SOC)**

**Benchmarking with Single Agent Tolerability**

**Challenge:** Interpretation of combo tolerability w/o control arm

**Opportunity:** Maximize learning from historical single agent data

Neutropenia incidence rate and neutrophil counts time profiles in NME+PAC combo was consistent with historical Paclitaxel monotherapy based on literature database MBMA and PKPD.

Lu D et al. CPT:PSP. 2014

Lu T, Lu D, Ware J, Dresser M, Jin JY et al. 2013 ACoP

Friberg L et al. JCO. 2002
Quantitative Systems Pharmacology Model for Mechanism-Based Exploration of Combo Rx and Regimens

**Growing Opportunity**

**Quantitative Systems Pharmacology Model**

- **Dose** → **Exposure**
- **Biomarkers** → **Tumor Size Dynamics** → **Outcome**

**Systems Model**

1. **Target Modulation**
   - PI3Ki
   - PI3K
defining  \( f(x) \)

2. **Downstream Biology & Markers**
   - BRAF
   - PIK3CA
   - MEKi
   - RAFi

3. **Tumor Growth**
   - Prolif
   - Apop

**Outcome**

- **PFS/OS**

**PK Model**

- **PK> Model**
- **Safety**
- **Efficacy**

Quantitative system pharmacology integrating pathways, cells, tissues, physiology/pathology, patient heterogeneity

Conduct mechanism based exploration of combo Rx & regimens, including effects of:

- Feedbacks, synergies, and redundancies
- Alternate biological contexts
  - different mutations
  - baseline biomarkers/diagnostics

Courtesy of Saroja Ramanujan

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Summary

Combination Therapy in Oncology

Unique challenges:
- Trial design
  - How do we efficiently study drug combinations with potentially multiple doses and schedules?
  - Challenge the MTD paradigm?
- Translation from preclinical to clinical, from early to late
- Combo PK, efficacy, and tolerability
- ......

Unique opportunities:
- Innovative study design – preclinical and clinical
- Effective measurements – PK, biomarker, imaging, efficacy, safety
- Application of Modeling and Simulation throughout the development cycle
  - PK DDI – PBPK and PopPK
  - PD DDI – translational PKPD, clinical PKPD, E-R, C-QT
  - Literature database meta-analysis
- ......

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Growing Complexities in Combination Therapy

- Poly-combinations
  - Triplet, quadruplet ......

- Combination of multiple molecule types
  - SM + LM, SM + ADC, LM + ADC ......

- Combination of multiple novel mechanisms
  - CIT+kinase, CIT+CIT ......

- Dosing sequence, dosing titration ......
# Acknowledgements

## Clinical Pharmacology/M&S
- Nageshwar Budha
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- Dan Lu
- Joseph Ware
- Luna Musib
- SMCP Group

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- Yuan Chen (DMPK)
- Harvey Wong (DMPK)
- Edna Choo (DMPK)
- Laurent Salphati (DMPK)
- Yibing Yan (OBD)
- Saroja Ramanujan (QSP)

## Project Team Members
- Mark Dresser
- Bert Lum
- Amita Joshi
Panel Discussion
Session III: Dose-Exposure Exploration

Moderators:
Qi Liu, PhD
FDA
Julie Bullock, PharmD
d3 Medicine

Panelists:
• Yazdi Pithavala, PhD, Pfizer
• Eric Masson, PharmD, AstraZeneca
• Dan Howard, PhD, Novartis
• Jin Jin, PhD, Genentech
• Akintunde Bello, PhD, Executive Director, Clinical Pharmacology Oncology and Immuno Oncology, Bristol-Myers Squibb
• Mark Ratain, MD, Associate Director for Clinical Sciences, Comprehensive Cancer Center, University of Chicago
• Eric Rubin, MD, Merck
• Vivek Kadambi, PhD, Blueprint Medicines
• Stuart Bailey, PhD, Novartis
• Nam Atiqur Rahman, PhD, Director, DCPV, OCP, OTS, CDER, FDA
Session IV: Integrating Dose Optimization in Clinical Development

Integrative Approach to Dose-finding
Geoffrey Kim, MD
Director, Division of Oncology Products 1 (DOP1), OHOP, OND, CDER, FDA

Feasibility of an Integrative, Adaptive Dose-finding Trial
Rajeshwari Sridhara, PhD
Director, DBV, OB, OTS, CDER, FDA

Barriers to Implementing Integrative, Adaptive Dose-finding Trials
Lilli Petruzzelli, MD, PhD
Global Head, Translational Clinical Oncology, Novartis
An Integrative Approach to Dose Finding

Geoffrey Kim, MD
DOP1/OHOP/CDER/FDA
Scope of the Problem

• High rate of dose reductions and discontinuations in clinical trials
• Adherence to therapy in the “real world”
• Redundant drug development process with inefficiencies
  – Kinase inhibitors in thyroid cancer
My Naive Observations

• Appears to be room for interdisciplinary discussions

• Findings from each discipline could be informative throughout the entire lifecycle of drug development

• Sponsor’s have far more internal data than what they submit

• Those who do not learn from the past are doomed to repeat it
What Era Are We In

- Kinase Inhibitor Era?
- Genomic Era?
- Omics Era?
- Immunotherapy Era?

Information Era!
Progress in the Information Era

• So much data!
  – All in different formats
  – Difficult to filter out the noise
  – Difficult to weigh importance
  – Difficult to integrate

• Still, the Data is all related
  – And may be useful
In an Ideal World
Pharmacology Matters

Neurons at **Kinase** layer

Neurons at **AE** layer

1

2

3

P

Q

BCPNN
Identify Kinase Specific Safety

**Aim**
Predict the association between adverse events (AEs) and kinase targets

**Method**
Combined population PK modeling, systems pharmacology and association analysis based on the databases of *in vitro* kinase inhibition and AEs frequency by KIs

**Results**

 Association score: \[ F \times K = \sum (f_{zx}) \times \left( C_{ave} \div k_{xy} \right) = A \]
Goals

• Move away from 3+3
• DLT definitions beyond 1st 28 days of dosing
• More doses studied
• Identify discipline specific “best practices”
• Evaluate novel approaches to data integration
  – Including modeling and simulation
• Lifecycle integration of data
• Envision better outputs
  – Efficient dose finding trial designs
  – Efficient dose finding for combinations
  – Accurate drug labeling
Goals

• Address barriers in implementing novel dose finding strategies
• Discuss tenable strategies to reduce inefficiencies in the development of novel kinase inhibitors
Feasibility of an integrative, adaptive dose finding trial

Rajeshwari Sridhara, Ph.D.
Division Director, OB, CDER, FDA
# Current Product Development Process

<table>
<thead>
<tr>
<th>Phase</th>
<th>Activities</th>
</tr>
</thead>
</table>
| Pre-Clinical | • Assess DLT within 28-day cycle  
• Cumulative Toxicity Unknown                                      |
| Phase I   | • Assess DLT within 28-day cycle  
• Determine MTD  
• Cumulative Toxicity Unknown                                      |
| Phase II  | • Use MTD  
• Multiple cycles of treatment  
• Frequent dose modifications  
• Soft efficacy endpoint (ORR)                                   |
| Phase III | • Use MTD or a modified MTD  
• Multiple cycles of treatment  
• Frequent dose modifications  
• Clinical endpoint (OS)                                            |
| Phase IV  | • Dose Finding                                                            |
Current Product Development Process – Outdated

- Dose-finding uses old cytotoxic therapy paradigm
- Cytotoxic paradigm:
  - 28-day cycles, finite number of treatment cycles
  - Dose based on BSA, a substitute for exposure based dosing
  - Toxicity observed in short time
  - More is better
  - Good animal models
  - Well characterized toxicities (hematologic, GI, neurologic, etc.) with CTCAE grading criteria
  - DLT defined based on these toxicities
Current Products

• Example: Kinase Inhibitors
  – Oral formulation of fixed doses
  – Administered beyond 28-day 6 cycles – until disease progression
  – Cumulative toxicity
  – Delayed toxicity, that is not observed in pre-clinical or dose-finding studies
  – Type of toxicities different from typical cytotoxic products: example, rash
Questions:

• Do we have adequate animal model?
  – Maybe not. Current study design unable to predict some toxicities
  – Replication in different animal models useful

• Is the definition of DLT appropriate?
  – No
  – Define BED (Biologically effective dose) or minimum effective dose (MED)?

• Are we using all the data we have?
  – No

• How can we learn from past observations?

• How can we account for limitations and uncertainties?
Can We Be More Efficient?

Yes,
But there is cost
Product Life-cycle Adaptive Process

- Phase I Dose Finding Trial Data
- Phase II Trial Data
- Phase III Trial Data
- In-vitro Data
- Pre-clinical Data
What can we do now?

• **We have many approved Kinase inhibitors**

➢ Review data from Phase III studies to:

1. Characterize ‘unacceptable’ toxicities
   1. Go back to pre-clinical testing
2. Redefine DLT based on this information
   1. Go back to dose-finding trial
3. Record when these toxicities occurred
4. Estimate exposure – how long treatment was received
5. Develop statistical model based on observed dose modifications
What can we do now? – Contd.

- Review data from Phase II studies to:
  1. Understand limitations and uncertainties in the PK-PD modelling
  2. What is the missing piece of information that we should have assessed in order to make better decisions?

- Review data from Phase I studies
  1. What happened to patients beyond the first cycle?
  2. What dose modifications were made?
  3. What toxicities were observed beyond the first cycle?
  4. Do we have the right PD marker?

- Any in-vitro data that were not used in the pre-clinical or Phase I studies
What can Statisticians do?

- Incredible amount of data is generated
  - Can be used for priors in the statistical models
- Simulate multiple clinical trial scenarios
- Think beyond 28-day cycle
- Use new definition of DLT
- MTD? May be use BED or MED
- Model both toxicity and efficacy?
- Model with dose as a function of time?
- Use what you learn
Product Life-cycle Adaptive Process

- **Phase I Dose Finding Trial Data**
- **Phase II Trial Data**
- **Phase III Trial Data**
- **Pre-clinical Data**
- **In-vitro Data**
Summary

- 3 + 3 Designs are inefficient – no memory; **Model based dose-finding trials** are more efficient
  - Feasible? – computing and statistical expertise, buy-in from investigators and scientists, operational logistics, upfront investment necessary
  - Allows to characterize the uncertainty in the estimates
- Use all the available data to make informed trial design changes
- Therapeutic index vs. MTD
Summary

• There are best practices to improve efficiency
  – Use pre-clinical models and phase I results to make go/no-go decisions
  – Pre-clinical models to manage toxicity post-hoc
  – Randomized phase II with two or more doses, to explore schedule and sequencing of drugs, food effect, combinations, etc.

• Continuous learning and improvement is essential – product life-cycle process.

• Data and experience sharing among sponsors would greatly improve efficiency – more importantly patients will benefit
Session IV:
Integrating Dose Optimization in Clinical Development

Practical Considerations of Implementing Dose Optimization Strategies in the Clinic
Alice Shaw, MD, PhD
Associate Professor, Department of Medicine, Harvard Medical School
Attending Physician, Thoracic Cancer Program, Massachusetts General Hospital

Approaches to Integrative, Adaptive Dose-finding Combination Studies
Pasi Jänne, MD, PhD
Dana Farber Cancer Institute
Approaches to integrative, adaptive dose-finding combination studies

Pasi A. Jänne, M.D., Ph.D.
Lowe Center for Thoracic Oncology
Dana Farber Cancer Institute
Disclosure Information
Pasi A. Jänne

Consultant for: Astra Zeneca, Boehringer Ingelheim, Pfizer, Genentech, Roche, Sanofi-Aventis, Clovis Oncology, Chugai Pharmaceuticals, Merrimack Pharmaceuticals

Research Support: Astellas, AstraZeneca

Stockholder in: Gatekeeper Pharmaceuticals

Other: LabCorp - post-marketing royalties from DFCI owned intellectual property on EGFR mutations
Combinations of Kinase Inhibitors

• Single agents unlikely to cure cancer
• Rationale biologically based combinations have been identified
  - PI3K/MEK
  - EGFR/MET
  - EGFR/MEK
  - BRAF/MEK
• Many work in preclinical models; few are successful in the clinic
Challenges of Developing Combinations of Kinase/Signal transduction inhibitors

- Combinations are toxic
  - Many single agents developed on an MTD model
  - Administered continuously
  - Long half life drugs are often prioritized
  - Overlapping toxicities with other TKIs
  - Therapeutic window may not exist
Balancing Dose and Overlapping Toxicity

Drug 1

Intolerable Toxicity

Rash
Diarrhea
Transaminitis
Pneumonitis

Drug 2

Intolerable Toxicity

Rash
Diarrhea
Transaminitis
Pneumonitis

Combination of Drug 1 & 2

Intolerable Toxicity

Rash
Diarrhea
Transaminitis
Pneumonitis

Adrian Sacher
Dual EGFR Inhibition – Combination of Afatinib and Cetuximab is effective against EGFR T790M

Regales et al. JCI 2009
Afatinib/Cetuximab in EGFR TKI resistant EGFR mutant NSCLC

Janjigian et al. ESMO 2012

RR: 30%
PFS: 4.7 months
Duration of PFS for individual patients with respect to best response and T790M status

Grade 3 Treatment related AEs: 44%
Grade 4 Treatment related AEs: 2%

**Phase I study of dacomitinib & crizotinib**

**Dose-Escalation**
- N = 33; RE = 31
  - DL1: Dacomitinib 30 mg qD, Crizotinib 200 mg BID
    - N = 14
  - DL2: Dacomitinib 45 mg qD, Crizotinib 200 mg BID
    - N = 6
    - DLT: diarrhea, elevated ALT
  - DL3: Dacomitinib 30 mg qD, Crizotinib 250 mg BID
    - N = 7
    - DLT: mucositis
  - DL4: Dacomitinib 45 mg qD, Crizotinib 250 mg BID
    - N = 6
    - DLT: hypoxia

**Expansion Cohort 1**
- N = 24; RE = 21
  - NSCLC
  - Acquired Resistance to gefitinib or erlotinib
  - Dacomitinib 30 mg qD, Crizotinib 200 mg BID
    - (dose adjustment permitted if necessary)

**Expansion Cohort 2**
- N = 9; RE = 9
  - NSCLC
  - Acquired Resistance to gefitinib or erlotinib
  - Single Agent Dacomitinib 30 or 45 mg qD until disease progression
    - N = 9
  - Dacomitinib 30 mg qD, Crizotinib 200 mg BID
    - (dose adjustment permitted if necessary)
    - N = 3 with immature efficacy data

---

\(^a\)Defined as progression following either initial response (complete or partial) or stable disease (for 6 months) on single-agent erlotinib or gefitinib; no intervening therapy allowed
ALT: alanine aminotransferase; BID: twice daily; DL: Dose Level; DLT: dose-limiting toxicity; qD: once daily; RE: response evaluable

## Treatment-Related Adverse Event (≥15%)

<table>
<thead>
<tr>
<th></th>
<th>Expansion Cohort 1 Combination N=23, n (%)</th>
<th>Expansion Cohort 2 Single Agent Dacomitinib N=8, n (%)</th>
<th>Expansion Cohort 2 Combination N=3, n (%)</th>
<th>Overall total Combination N=39*, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AEs</strong></td>
<td>Grade 1/2 15 (65) Grade 3 7 (30) Grade 4 5 (63)</td>
<td>Grade 1/2 5 (63) Grade 3 2 (25) Grade 4 3 (100)</td>
<td>Grade 1/2 31 (53) Grade 3 24 (41) Grade 4 3 (5)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (35) 1 (13)</td>
<td>1 (33)</td>
<td>24 (41) Grade 4 1 (2)</td>
<td></td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>8 (35) 1 (4) 1 (13)</td>
<td>1 (13)</td>
<td>18 (47) Grade 4 1 (2)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>6 (26) 2 (25)</td>
<td></td>
<td>18 (31)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14 (60) 2 (9) 8 (100) 1 (13)</td>
<td>1 (33)</td>
<td>38 (64) Grade 4 9 (15)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (30) 2 (9) 3 (38) 1 (13) 1 (33)</td>
<td></td>
<td>21 (36) Grade 4 4 (7)</td>
<td></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>6 (26) 3 (38) 2 (67) 1 (33)</td>
<td></td>
<td>12 (20) Grade 4 1 (2)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (39) 3 (38) 2 (67) 1 (33)</td>
<td></td>
<td>33 (56) Grade 4 2 (3)</td>
<td></td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>5 (22) 1 (4)</td>
<td></td>
<td>19 (32) Grade 4 1 (2)</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>8 (35) 4 (50) 1 (33)</td>
<td></td>
<td>19 (32) Grade 4 3 (5)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4 (17) 3 (38) 1 (13)</td>
<td></td>
<td>17 (29) Grade 4 5 (9)</td>
<td></td>
</tr>
<tr>
<td>Visual impairment</td>
<td>2 (9) 1 (13)</td>
<td></td>
<td>12 (20)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (30) 1 (13) 3 (100)</td>
<td></td>
<td>27 (46)</td>
<td></td>
</tr>
</tbody>
</table>

- Table includes all common TRAEs ≥15% of the overall population during combination therapy (Crizotinib + Dacomitinib) period.
- Overall Total includes patients from dose-escalation group (source of Grade 4 AE)
- There were no treatment related grade 5 AEs
- Reflects AE which arose only during combination treatment period.
Skin Toxicity from EGFR Inhibitors from Inhibiting Wild Type EGFR

Acneiform Rash

Paronychia, Trichomegaly & Skin fissure

http://www.managecrc.com
Combination of PI3K & MEK inhibitor is effective in KRAS G12D NSCLC

Engelman and Wong, Nature Medicine 2008
### PI3K and MEK Inhibitor Combinations

<table>
<thead>
<tr>
<th>PI3K Inhibitor</th>
<th>MEK Inhibitor</th>
<th>Phase</th>
<th>NCT</th>
<th>Toxicty</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-05212384</td>
<td>PD-0325901</td>
<td>I</td>
<td>NCT01347866</td>
<td>-</td>
</tr>
<tr>
<td>BKM120</td>
<td>MEK162</td>
<td>I</td>
<td>NCT01363232</td>
<td>-</td>
</tr>
<tr>
<td>BEZ235</td>
<td>MEK162</td>
<td>I</td>
<td>NCT01337765</td>
<td>-</td>
</tr>
<tr>
<td>XL765 (SAR245409)</td>
<td>Pimasertib (MSC1936369B)</td>
<td>I</td>
<td>NCT01390818</td>
<td>Rash (62%, 13% Gr 3), diarrhea (56%, 4% Gr 3), fatigue (51%, 2% Gr 3), nausea (49%, 2% Gr 3), vomiting (45%, 2% Gr 3), peripheral edema and pyrexia (34%, each) and visual impairment with underlying serous retinal detachment (21%).</td>
</tr>
<tr>
<td>WX-037</td>
<td>WX-554</td>
<td>I</td>
<td>NCT01859351</td>
<td>-</td>
</tr>
<tr>
<td>BKM120</td>
<td>Trametinib (GSK1120212)</td>
<td>I</td>
<td>NCT01155453</td>
<td>Dermatitis acneiform, diarrhea (51% each); nausea (41%); vomiting (37%); rash (33%); asthenia (31%); CK increase, decreased appetite, pyrexia or stomatitis (29% each) and hyperglycemia (27%). AEs led to treatment discontinuation, 17 pts (35%) and interruptions/dose reductions, 25 pts (51%).</td>
</tr>
<tr>
<td>Copanlisib (BAY80-6946)</td>
<td>Refametinib (BAY86-9766)</td>
<td>I</td>
<td>NCT01392521</td>
<td>-</td>
</tr>
<tr>
<td>BYL719</td>
<td>MEK162</td>
<td>I</td>
<td>NCT01449058</td>
<td>Rash (88%, 17.5% Gr 3), diarrhea (85%, 10% Gr 3), nausea (58%), fatigue (45%, 8% Gr 3), CK increase (45%, 5% Gr 3), vomiting (33%), edema (13%), anemia (13%), GERD (13%), AST increase (10%)</td>
</tr>
<tr>
<td>GDC-0941</td>
<td>XL518 (GDC-0973)</td>
<td>I</td>
<td>NCT00996892</td>
<td>-</td>
</tr>
<tr>
<td>GSK2126458</td>
<td>GSK1120212</td>
<td>I</td>
<td>NCT01248858</td>
<td>Rash (68%, 3% Gr 3), diarrhea (42%, 6% Gr 3), nausea (29%), vomiting (23%, 3% Gr 3), decreased appetite (19%), stomatitis (13%, 3% Gr 3) and fatigue (13%, 3% Gr 3)</td>
</tr>
</tbody>
</table>
Potential Strategies for Combination Treatment

• Alternative dosing schedules
  - May reduce/minimize overlapping toxicities
Different ways of dosing erlotinib

150 mg daily continuous

25 mg daily continuous

Clinical responses have been observed in EGFR mutant NSCLC patients

1500 - 2000 mg once per week

Costa et al. JTO 2010; Milton et al. Cancer 2006
Phase 1 Trial of Low-Dose Daily in Combination With High-Dose Twice Weekly Erlotinib in EGFR-Mutant Lung Cancer

Hypothesis: Daily low dose and twice weekly high dose erlotinib will be well-tolerated, and will delay emergence of EGFR T790M.

| Conventional Dosing | | | | | | |
|---------------------|---|---|---|---|---|
| 150 | 150 | 150 | 150 | 150 | 150 | 150 |

Dose Level 1

| 600 | 600 | | | | |
| 25 | 25 | 25 | 25 | 25 |

Dose Level 3

| 750 | 750 | | | | |
| 50 | 50 | 50 | 50 | 50 |

Dose Level 5

| 1050 | 1050 | | | | |
| 50 | 50 | 50 | 50 | 50 |

1° Endpoint: MTD/Safety
2° Endpoints: RR, PFS

EGFR mut NSCLC
EGFR TKI naïve

PI: Helena Yu, MSKCC IRB #12-278, Clinicaltrials.gov NCT01967095
Different pharmacokinetics of MEK inhibitors

**GSK - trametinib**
- \(t_{1/2} = 5.5\) days

**AZ - selumetinib**
- \(t_{1/2} = 5\) hrs
Dose Escalation Schema for MEK inhibitor GDC-0973 and the pan-PI3K inhibitor GDC-0941

<table>
<thead>
<tr>
<th>Dose Escalation Schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDC-0973 (mg)</td>
</tr>
<tr>
<td>QD 21/7</td>
</tr>
<tr>
<td>80 60 40 20</td>
</tr>
<tr>
<td>1 → 3 → 4 → 5 → 6 → 6a</td>
</tr>
<tr>
<td>GDC-0941 (mg)</td>
</tr>
<tr>
<td>QD 21/7</td>
</tr>
<tr>
<td>80 100 130</td>
</tr>
</tbody>
</table>

21/7 Dosing

Intermittent MEK Dosing

3+3 study design
PK sample collection
Serial FDG-PET scans
Tumor assessments q8 weeks
Archival tumor tissue collection

Shapiro et al. ASCO 2011
Potential Strategies for Combination Treatment

• Alternative dosing schedules
  - May reduce/minimize overlapping toxicities

• Selective inhibitors
  - Mutant selective or target selective
Properties of Mutant Selective EGFR Inhibitors

Increased potency in T790M bearing models compared to current clinical agents

Less effective against WT EGFR

Potent and Mutant Selective in vivo
Relative potencies of EGFR inhibitors on different forms of EGFR

- Gefitinib
- Afatinib
- AZD9291

- T790M
- EGFRm
- Wt

Selectivity

Mutant
## Next Generation EGFR Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Clinical Stage</th>
<th>Covalent</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>WZ4002</td>
<td>DFCI</td>
<td>Tool compound</td>
<td>Yes</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>AP26113</td>
<td>Ariad</td>
<td>Phase I/II</td>
<td>No</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>CO-1686*</td>
<td>Clovis</td>
<td>Phase II/III</td>
<td>Yes</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>AZD9291*</td>
<td>Astra Zeneca</td>
<td>Phase II/III</td>
<td>Yes</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>HM61713</td>
<td>Hanmi</td>
<td>Phase I</td>
<td>Yes</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>ASP8273</td>
<td>Astellas</td>
<td>Phase I</td>
<td>Yes</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>EGF816</td>
<td>Novartis</td>
<td>Phase I</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Avitinib</td>
<td>Acea Bio</td>
<td>Phase I</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PF-06747775</td>
<td>Pfizer</td>
<td>Phase I</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*FDA Breakthrough designation*
AZD9291 Phase I study design

Phase I, open-label, multicenter study of AZD9291 administered once daily in Asian and Western patients with advanced NSCLC who have documented radiological progression while on prior therapy with an EGFR-TKI (AURA; NCT01802632)

Objectives
Primary: safety and tolerability in EGFR-TKI-refractory patients
Secondary include: define maximum tolerated dose, pharmacokinetics, preliminary efficacy

Escalation
Not preselected by T790M status

Expansion
Enrollment by local testing followed by central laboratory confirmation* of T790M status or by central laboratory testing alone

Rolling six design

Cohort 1
20 mg

Cohort 2
40 mg

Cohort 3
80 mg

Cohort 4
160 mg

Cohort 5
240 mg

T790M+

T790M+

T790M+

T790M+

T790M+

1st-line EGFRm+

1st-line EGFRm+

Biopsy

Biopsy

*cobas® EGFR Mutation Test (Roche Molecular Systems)
AZD9291 in EGFR T790M NSCLC – Multiple efficacious doses

Best percentage change from baseline in target lesion

DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

<table>
<thead>
<tr>
<th></th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>240 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (157)</td>
<td>10</td>
<td>32</td>
<td>61</td>
<td>41</td>
<td>13</td>
<td>157</td>
</tr>
</tbody>
</table>

ORR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>240 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>59%</td>
<td>66%</td>
<td>51%</td>
<td>54%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>(19, 81)</td>
<td>(41, 76)</td>
<td>(52, 77)</td>
<td>(35, 67)</td>
<td>(25, 81)</td>
<td>(51, 66)</td>
<td></td>
</tr>
</tbody>
</table>

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

Jänne et al. NEJM 2015
## AZD9291 - Summary of All Adverse Events

<table>
<thead>
<tr>
<th>Patients with an AE, n (%)</th>
<th>20 mg (N=21)</th>
<th>40 mg (N=58)</th>
<th>80 mg (N=103)</th>
<th>160 mg (N=80)</th>
<th>240 mg (N=21)</th>
<th>Total (N=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>21 (100)</td>
<td>56 (97)</td>
<td>102 (99)</td>
<td>78 (98)</td>
<td>21 (100)</td>
<td>278 (98)</td>
</tr>
<tr>
<td>Any AE, drug-related*</td>
<td>15 (71)</td>
<td>40 (69)</td>
<td>88 (85)</td>
<td>72 (90)</td>
<td>21 (100)</td>
<td>236 (83)</td>
</tr>
<tr>
<td>Any AE ≥ Grade 3</td>
<td>6 (29)</td>
<td>25 (43)</td>
<td>40 (39)</td>
<td>33 (41)</td>
<td>9 (43)</td>
<td>113 (40)</td>
</tr>
<tr>
<td>Any AE ≥ Grade 3, drug-related*</td>
<td>3 (14)</td>
<td>3 (5)</td>
<td>14 (14)</td>
<td>23 (29)</td>
<td>4 (19)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Any AE leading to death</td>
<td>2 (10)</td>
<td>2 (3)</td>
<td>5 (5)</td>
<td>0</td>
<td>1 (5)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Any AE leading to death, drug-related*</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Any AE leading to dose interruption</td>
<td>4 (19)</td>
<td>7 (12)</td>
<td>24 (23)</td>
<td>23 (29)</td>
<td>6 (29)</td>
<td>64 (23)</td>
</tr>
<tr>
<td>Any AE leading to dose reduction</td>
<td>0</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>18 (23)</td>
<td>10 (48)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>3 (14)</td>
<td>4 (7)</td>
<td>7 (7)</td>
<td>8 (10)</td>
<td>2 (10)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation, drug-related*</td>
<td>2 (10)</td>
<td>0</td>
<td>1 (1)</td>
<td>7 (9)</td>
<td>1 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>5 (24)</td>
<td>13 (22)</td>
<td>26 (25)</td>
<td>20 (25)</td>
<td>5 (24)</td>
<td>69 (24)</td>
</tr>
<tr>
<td>Any serious AE, drug-related*</td>
<td>4 (19)</td>
<td>1 (2)</td>
<td>5 (5)</td>
<td>6 (8)</td>
<td>1 (5)</td>
<td>17 (6)</td>
</tr>
</tbody>
</table>

Population: pre-treated, capsule-dosed patients (excluding Japanese cytology cohort)
Data cut-off 2 Dec 2014
*As assessed by the investigator
AE, adverse event
As of 19th March 2015, of more than 1000 patients across all studies dosed with AZD9291, ILD grouped term events reported in approx 2.7% of patients (27 events): 12 grade 1–2; 13 grade ≥3; 2 currently ungraded. Of these, a total of 3 patients are reported to have died due to ILD (Grade 5).

CTCAE, Common Toxicity Criteria for Adverse Events; Gr, Grade

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<th>20 mg (N=21)</th>
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<tbody>
<tr>
<td></td>
<td>Any Gr Gr ≥3</td>
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<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>29 0</td>
<td>47 2</td>
<td>36 1</td>
<td>68 3</td>
<td>76 5</td>
<td>50 2</td>
</tr>
<tr>
<td>Rash, grouped terms</td>
<td>24 0</td>
<td>33 0</td>
<td>38 0</td>
<td>63 3</td>
<td>76 5</td>
<td>46 1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>38 10</td>
<td>19 0</td>
<td>26 3</td>
<td>24 0</td>
<td>33 0</td>
<td>25 2</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 5</td>
<td>17 0</td>
<td>18 1</td>
<td>34 1</td>
<td>43 0</td>
<td>24 1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14 0</td>
<td>16 0</td>
<td>15 0</td>
<td>36 0</td>
<td>24 0</td>
<td>22 0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>14 0</td>
<td>9 0</td>
<td>21 2</td>
<td>29 4</td>
<td>38 5</td>
<td>22 2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 0</td>
<td>21 0</td>
<td>19 0</td>
<td>20 0</td>
<td>38 0</td>
<td>21 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 5</td>
<td>26 0</td>
<td>16 0</td>
<td>19 0</td>
<td>19 5</td>
<td>19 1</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 0</td>
<td>26 0</td>
<td>21 0</td>
<td>18 0</td>
<td>14 0</td>
<td>19 0</td>
</tr>
<tr>
<td>Cough</td>
<td>19 0</td>
<td>17 0</td>
<td>13 0</td>
<td>21 0</td>
<td>0 0</td>
<td>16 0</td>
</tr>
</tbody>
</table>

Select AEs of interest

<table>
<thead>
<tr>
<th></th>
<th>20 mg (N=21)</th>
<th>40 mg (N=58)</th>
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<tbody>
<tr>
<td></td>
<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
<td>Any Gr Gr ≥3</td>
</tr>
<tr>
<td>Hyperglycaemia (n=8)</td>
<td>0 0</td>
<td>3 0</td>
<td>4 0</td>
<td>3 0</td>
<td>0 0</td>
<td>3 0</td>
</tr>
<tr>
<td>QT prolongation (n=10)</td>
<td>0 0</td>
<td>2 0</td>
<td>4 1</td>
<td>5 0</td>
<td>5 0</td>
<td>4 0.4</td>
</tr>
<tr>
<td>ILD-like events* (n=8)</td>
<td>0 0</td>
<td>0 0</td>
<td>3 2</td>
<td>6 4</td>
<td>0 0</td>
<td>3 2</td>
</tr>
</tbody>
</table>


*All ILD-like events are undergoing full investigation and subject to change

Jänne et al. ELCC 2015
# Ongoing & planned combination studies with mutant selective EGFR inhibitors

<table>
<thead>
<tr>
<th>EGFR Inhibitor</th>
<th>AZD9291</th>
<th>CO-1686</th>
<th>EGF816</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>MEDI4736</td>
<td>Trametinib</td>
<td>INC280 (MET)</td>
</tr>
<tr>
<td>Volitinib (MET)</td>
<td></td>
<td>Pembrolizumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Selumetinib</td>
<td></td>
<td>PDL1 (TBD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aurora Kinase</td>
<td></td>
</tr>
</tbody>
</table>

Which combination therapy should be used and when?

Should combination strategies be in EGFR TKI naïve patients, those with EGFR T790M or in other biomarker positive populations?
**Future Considerations**

- **Mutant selective inhibitors**
  - ? Applicable to other targets
    - FGFR, HER2, RET etc.

- **Combination strategies**
  - Intermittent dosing
    - How much and for how long does a target need to be inhibited?
      - Virtually no data in humans......
Considerations for Toxicity

- The hope is that combinations will lead to long term efficacy
- Typical DLT window (21 or 28 days) may not be applicable
- Need to address long term toxicity
  - Fraction of patients completing X months of therapy
  - Fraction of patients requiring dose reductions/interpretations
Potential Strategies to maximize clinical benefit but reduce/minimize long term toxicity

Interruption:
- Single Agent
- Combination A
- Single Agent

Sequential:
- Single Agent
- Combination A
- Combination B

Alternating:
- Combination A
- Combination B
- Combination A
Future Considerations and Moving Forward

Moderators:
Geoffrey Kim, MD  
FDA

Alice Shaw, MD, PhD  
Massachusetts General Hospital

Panelists:
• Pasi Jänne, MD, PhD, Dana Farber Cancer Institute
• Lilli Petruzzelli, MD, PhD, Novartis
• Amy McKee, MD, FDA
• Mark Ratain, MD, University of Chicago
• Jeffrey Barrett, PhD, Vice-president, Interdisciplinary Pharmacometrics Group, Sanofi
• James Yates, PhD, Principal Scientist, AstraZeneca
• Jin Jin, PhD, Genentech
• Stuart Bailey, PhD, Novartis Oncology
• Donna Dambach, VMD, PhD, Genentech