Opportunities for healthy volunteer clinical pharmacology studies in oncology drug development: targeted agents, immunomodulatory agents and beyond

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Quantitative Clinical Pharmacology

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Evolution of cancer therapy
A shift from life-prolonging to potentially curative therapies

Chemotherapeutics

- Methotrexate
- Vinca alkaloids
- Camptothecin
- Anthracyclines & Platinum based agents
- Paclitaxel
- irinotecan

Targeted anti-cancer agents

- imatinib, 1st approved small molecule targeted agent
- ipilimumab 1st approved checkpoint inhibitor
- pembrolizumab

Targeted small molecules + biologics

- Tisagenlecleucel, 1st approv CAR-T
- Axicaptagene ciloleucel

- rituximab, 1st approved mAb
- brentuximab vedotin
- ado-trastuzumab emtansine

- gemtuzumab ozogamicin, 1st approved ADC
- Intron-A

- gefitinib
- erlotinib
- sorafenib
- sunitinib
- dasatinib
- lapatinib
- nilotinib
- pazopanib

- blinatumomab, 1st approved bispecific

Why Healthy Volunteers?

- Improved equipoise through exposure of fewer end-of-life patients to compounds of undetermined efficacy

<table>
<thead>
<tr>
<th>Richer Data</th>
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<tbody>
<tr>
<td>• Lower drop-out rates among HVs</td>
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<td>• Allows for a longer wash-out between doses</td>
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<td>• Allows for “inconvenient” sampling</td>
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<thead>
<tr>
<th>Cleaner Data</th>
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<tbody>
<tr>
<td>• Homogenous study population</td>
</tr>
<tr>
<td>• Better compliance among HVs</td>
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<td>• Lower risk of study deviations</td>
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<td>• HV studies require fewer sites</td>
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<td>• “In-house” stay allows for better safety monitoring and quicker response time</td>
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<tr>
<th>Operational Efficiency</th>
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<tr>
<td>• Patient studies take longer to enroll</td>
</tr>
<tr>
<td>• Reduced burden on drug supply</td>
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<tr>
<td>• High quality data helps make quicker decisions</td>
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<td>• Lower cost per subject</td>
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HV studies can accelerate development by helping make timely, well informed, quality decisions

**Phase-1**
- food effect

**Phase-2**
- Guide dosing conditions during Ph1/2, gather safety experience with fed dosing
- DDI (pH or metabolic)
  - Allow/restrict/prohibit use of pH modifying agents, metabolic inhibitors/inducers
- Human ADME + ABA
  - Inform the need for clinical DDI studies/type of study
  - Inform I/E and timing/design of organ impairment studies
  - Build & qualify PBPK models
  - Use PBPK M&S to de-risk additional DDI scenarios and support waiver applications

**Phase-3**
- Rel BA/BE (Formulation comparison)
  - Earlier introduction of Ph2/3 or to-be-marketed formulation
Clinical Pharmacology package at NDA, most extensive for oncology drugs that could be evaluated in HVs

- Small molecules still represent a large proportion (38/56) of NMEs that were approved in last 6 years
- 26 NMEs had used healthy volunteers to conduct clinical pharmacology studies
- Food effect > DDI > QT > Special population (Organ impairment)

Faucette et al, CPT, 2017
# Study Design Considerations

<table>
<thead>
<tr>
<th>Type of Clinical Pharmacology study</th>
<th>Number of doses if dosed to HVs</th>
<th>Dose of investigational agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADME</td>
<td>1 dose</td>
<td>May be conducted at a dose lower than the clinical dose depending upon dose-linearity &amp; potential for saturation of metabolic pathways</td>
</tr>
<tr>
<td>QTc</td>
<td>1 dose</td>
<td>Preferably @clinical dose, rarely supratherapeutic</td>
</tr>
<tr>
<td>BA/BE/comparability</td>
<td>2 doses</td>
<td>Preferably @clinical dose</td>
</tr>
<tr>
<td>Food Effect</td>
<td>2 doses</td>
<td>Preferably @clinical dose</td>
</tr>
<tr>
<td>DDIs</td>
<td>2 doses</td>
<td>@clinical dose (for induction DDI), lower dose may be considered if large DDI expected (for inhibition DDI)</td>
</tr>
<tr>
<td>Organ impairment</td>
<td>1 dose</td>
<td>Lower dose may be considered</td>
</tr>
<tr>
<td>Ethnicity bridging</td>
<td>1 dose</td>
<td>Preferably @clinical dose, lower dose may be considered</td>
</tr>
</tbody>
</table>
Targeted agents: Most studies used the approved dose in HVs

- **TKI**
  - Alectinib
  - Axitinib
  - Bosutinib
  - Dasatinib
  - Neratinib
  - Gefitinib
  - Lapatinib
  - Lenvatinib
  - Everolimus
  - Temsirolimus

- **Dual TKI**
  - Sorafenib
  - regorafenib

- **Lipid KI**
  - Idelalisib

- **Serine threonine KI**
  - Palbociclib

- **mAb**
  - trastuzumab
  - bevacizumab

- **Hormonal**
  - exemestane
  - Fulvestrant
  - enzalutamide

- Up to 2 doses of the investigational agent administered with a reasonable wash-out (typically ~5 t₁/₂) between doses
- Most common AEs: headache, nausea, vomiting, diarrhea
- No SAEs, except in Idelalisib study in which idelalisib administered as multiple dose (150 mg BID)
Immunomodulators: Mifamurtide (liposomal MTP-PE)

• Stimulates innate immune response to elicit anti-tumor effects (activator of macrophage tumoricidal activity)
• Approved in the EU, Switzerland and other regions indicated in children, adolescents and young adults for treatment of high-grade resectable non-metastatic osteosarcoma (an orphan disease indication), post surgical resection in combination with multiagent chemotherapy
• Approved dose 2 mg/m² (approx. 4 mg), IV infusion

A pharmacokinetic, pharmacodynamic, and electrocardiographic study of liposomal mifamurtide (L-MTP-PE) in healthy adult volunteers

Karthik Venkatakrishnan, William G. Kramer, Timothy W. Synold, Daniel B. Goodman, Evin Sides III, Cristina Oliva

Pharmacokinetics and pharmacodynamics of liposomal mifamurtide in adult volunteers with mild or moderate hepatic impairment

Karthik Venkatakrishnan, Yi Liu, Dennis Noe, Jaime Mertz, Michael Bergfrede, Thomas Marbury, Kamble Farbakhsh, Cristina Oliva, Ashley Mitton

Pharmacokinetics and pharmacodynamics of liposomal mifamurtide in adult volunteers with mild or moderate renal impairment

Karthik Venkatakrishnan, Yi Liu, Dennis Noe, Jaime Mertz, Michael Bergfrede, Thomas Marbury, Kamble Farbakhsh, Cristina Oliva, Ashley Mitton
## Safety profile of mifarmutide in HVs and Associated Risk Mitigation Strategy

<table>
<thead>
<tr>
<th>AEs</th>
<th>RI (n=33)</th>
<th>HI (n=37)</th>
<th>QTc (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Grade 3 AEs</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(syncope)</td>
</tr>
<tr>
<td>Chills</td>
<td>70%</td>
<td>70%</td>
<td>71%</td>
</tr>
<tr>
<td>Headache</td>
<td>58%</td>
<td>73%</td>
<td>86%</td>
</tr>
<tr>
<td>hypotension</td>
<td>48%</td>
<td>16%</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>42%</td>
<td>27%</td>
<td>29%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>39%</td>
<td>35%</td>
<td>43%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>39%</td>
<td>32%</td>
<td>67%</td>
</tr>
<tr>
<td>Nausea</td>
<td>36%</td>
<td>41%</td>
<td>52%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>30%</td>
<td>38%</td>
<td>-</td>
</tr>
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### Risk Mitigation and Safety Management

- **Inclusion/Exclusion:**
  - excluded subjects with rheumatoid arthritis
  - excluded subjects with atherosclerosis

- IV fluids to treat/manage dehydration/ hypotension

- Close monitoring of BP

- Tylenol for headache (couldn’t use ibuprofen since it would interfere with PD)
Immunomodulators: Lenalidomide and Pomalidomide

- Lenalidomide: 25 mg QD; Pomalidomide: 4 mg QD
- These agents are not free of certain severe AEs (embryo-fetal tox, hematologic toxicity and venous and arterial thromboembolism) and yet with appropriate I/E criteria, and risk mitigation these agents have been evaluated in HVs

Evaluation of Pharmacokinetic and Pharmacodynamic Interactions when Lenalidomide is Co-administered with Warfarin in a Randomized Clinical Trial Setting

Daniel Weiss, Robert Knight, Simon Zhou, Maria Palmisano, Nianhang Chen

Distribution of Lenalidomide Into Semen of Healthy Men After Multiple Oral Doses

Nianhang Chen, PhD, Henry Lau, PhD, Somesh Choudhury, PhD, Xiaomin Wang, PhD, Mahmoud Assaf, MS, and Oscar L. Laskin, MD, FCP

A Phase 1, double-blind, 4-period crossover study to investigate the effects of pomalidomide on QT interval in healthy male subjects

Sabina A. Mondal, Mahmoud Assaf, Liangang Liu, Edward O'

Lenalidomide at Therapeutic and Supratherapeutic Doses Does Not Prolong QTc Intervals in the Thorough QTc Study Conducted in Healthy Men

Nianhang Chen, Vicky Tsao, Josephine Reyes, Mahmoud S. Assaf, Claudia Kasserra, Simon Zhou and Maria Palmisano

Pomalidomide: Evaluation of Cytochrome P450 and Transporter-Mediated Drug–Drug Interaction Potential In Vitro and in Healthy Subjects

Claudia Kasserra, PhD, Mahmoud Assaf, MS, MBA, Matthew Hoffmann, PhD, Yan Li, PhD, Liangang Liu, PhD, Xiaomin Wang, PhD, Gondi Kumar, PhD, and Maria Palmisano, MD
Immunomodulators: recombinant interferon-α (IFN-α)

- IFN-α is a potent immunocytokine, approved for treatment of Hep C, hairy cell leukemia, malignant melanoma, follicular lymphoma
- Key Mitigations:
  - Excluded pts wit immunologic disorders: RA, psoriasis, sarcoidosis
  - Prior IFN treatment, exposure to live vaccines, active viral or bacterial infection
  - Oral temp, HR and BP measured every 2h

AEs and safety management
- Flu-like symptoms (severe) → close monitoring of body temp
- Pyrexia, chills and headache → Tylenol
- Back and abdominal pain → Tylenol
- No AEs or lab findings resulted in significant sequelae

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Corssitt et al, Clinical and Experimental Immunology, 1997
NHV Task force: Systematic evaluation via cross-functional collaboration to make an informed decision

1. Drug Safety Research Evaluation
   1. Not genotoxic or mutagenic
   2. Low risk for QTc prolongation
   3. No permanent damage to tissues, organs

2. Oncology Clinical Research
   1. Safety profile @MTD and RP2D
   2. Provide input on study design (Inclusion/exclusion)+ safety monitoring plan

3. Pharmacovigilance
   1. Ensure AEs are manageable, reversible and monitorable
   2. Design a safety monitoring and risk mitigation plan based upon known and expected AEs

4. Quantitative Clinical Pharmacology
   1. Study design and assessments (# of doses, duration of in-house stay & wash-out, sample collection and analysis plan)

5. Clinical Operations
   1. Site selection based upon study parameters (in-house vs. furlough, single v. multi-site, ability to handle emergencies)
Illustration of this approach: TAK117

- Investigational PI3Kα inhibitor
- High PK variability (>100%CV) in cancer patients
- Urgent need to understand the sources of PK variability/FE
- Three part study (abstract# PII-110, ASCPT Annual Meeting 2017):
  - Part 1: relative BA (formulation bridging)
  - Part 2: Food effect
  - Part 3: pH DDI
- Projected timelines (FPI to top line data)
  - Cancer patients: 2-3 yr
  - NHVs: ~6 months
- Actual timelines in NHV: 4.5 months
- Food ↑ oral BA and ↓ PK variability supporting the use of fed dosing condition for future TAK117 studies
- No SAEs, all AEs were mild (Gr 1) and resolved within 2-3 days

Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Non-mutagenic</td>
<td>✓</td>
</tr>
<tr>
<td>Non-genotoxic</td>
<td>✓</td>
</tr>
<tr>
<td>Low risk for QT prolongation (hERG + telemetry data)</td>
<td>✓</td>
</tr>
<tr>
<td>Does not cause hemolysis</td>
<td>✓</td>
</tr>
<tr>
<td>AEs manageable, reversible and monitorable</td>
<td>✓</td>
</tr>
<tr>
<td>Safety profile @MTD &amp; RP2D</td>
<td>✓</td>
</tr>
<tr>
<td>Single dose safety profile</td>
<td>X</td>
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One approach to collecting single dose safety profile of an investigational anti-cancer agent

FIH dose escalation in patients (repeat dose safety evaluation)

- Multiple dose safety/tolerability
- Development of a safety monitoring and risk mitigation strategy
- Consider collecting single dose safety profile in patients if feasible

Conduct a single dose “mini” escalation in healthy volunteers

- Collect safety/PK, biomarker in all dose levels
- Assess duration & reversibility of AEs
- Define a safe dose for healthy volunteers

Dose level 1
0 DLTs/3 treated

Dose level 2
0 DLTs/3 treated

Dose level 3
≤1 DLT/6 treated

Dose level 4

Dose level 5
MTD

Dose level minus 2
Target dose level

Dose level minus 3
Key Takeaways

• Utilizing HVs provide benefit across dimension of quality, cost and time; however prospective planning and cross functional collaboration is key to success

Some options to consider:
• Adjusting IND enabling GLP tox/safety pharmacology studies + conducting single dose tox studies to understand reversibility and monitorability of AEs
• Collecting single dose safety data in patients in early clinical studies
• Conduct a “mini” single dose escalation in HVs to understand the risk and safety profile (duration and reversibility of AE), when uncertainty exists regarding single dose safety/tolerability profile
• For next generation IO agents, modality, MoA, duration/extent of immune activation need to be considered
• Develop a risk mitigation and safety management plan and ensure it is appropriately communicated to HVs
Acknowledgements

Healthy Volunteer Task Force @Takeda

- Heather Stein (Global Patient Safety Evaluation)
- Karthik Venkatakrishnan (Quantitative Clinical Pharmacology)
- Alice Choi (Early Clinical Operations)
- Sean Ottinger (Drug Safety Evaluation)