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

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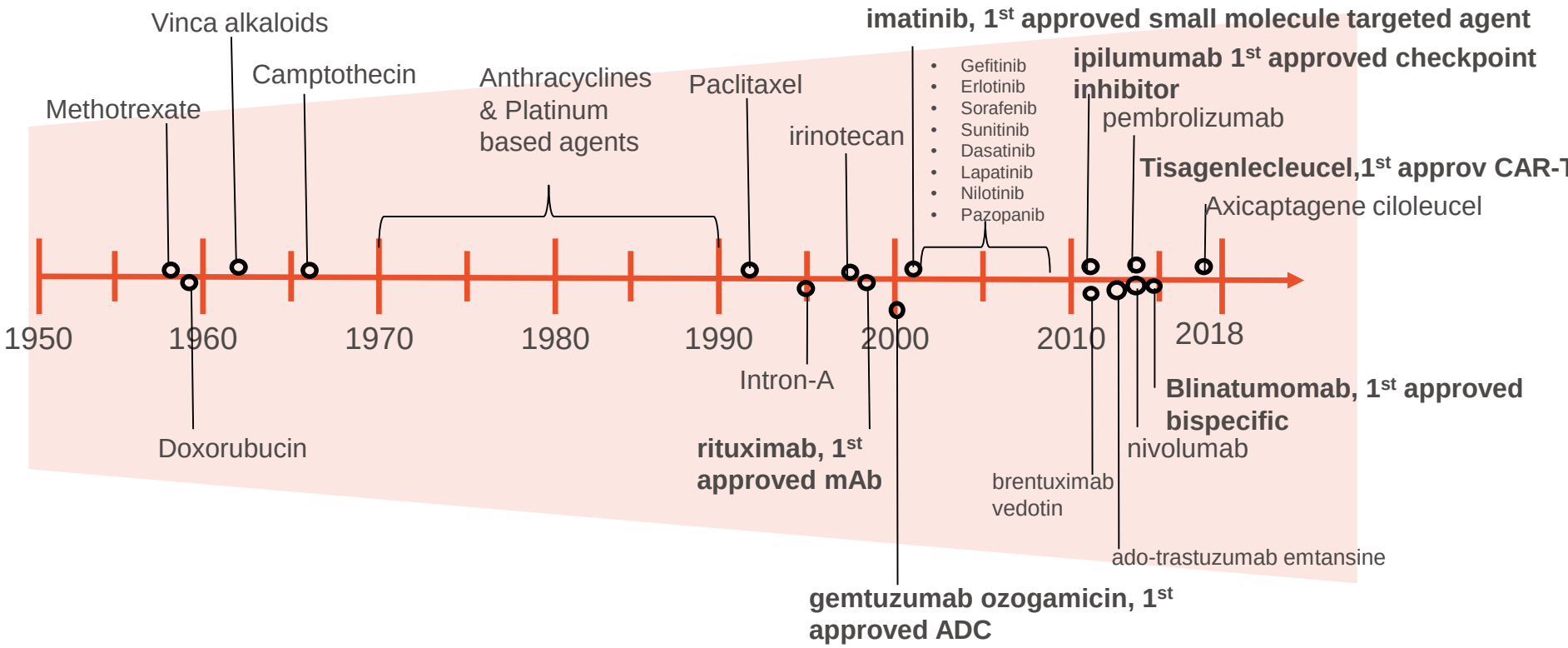
23rd March 2018

Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics 2018

Evolution of cancer therapy

A shift from life-prolonging to potentially curative therapies

Chemotherapeutics	Targeted anti-cancer agents	Targeted small molecules + biologics



Why Healthy Volunteers?

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

Richer Data	• **Lower drop-out rates among HVs** • **Allows for a longer wash-out between doses** • **Allows for "inconvenient" sampling**
Cleaner Data	• **Homogenous study population** • **Better compliance among HVs** • **Lower risk of study deviations** • **HV studies require fewer sites** • "In-house" stay allows for **better safety monitoring and quicker response time**
Operational Efficiency	• **Patient studies take longer to enroll** • **Reduced burden on drug supply** • **High quality data helps make quicker decisions** • **Lower cost per subject**

HV studies can accelerate development by helping make timely, well informed, quality decisions

Takeda ONCOLOGY

Phase-1 → Phase-2 → Phase-3

food effect	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
Rel BA/BE (Formulation comparison)	• Earlier introduction of Ph2/3 or to-be-marketed formulation

Use of Healthy Volunteers Drives Clinical Oncology Drug Development Decision Making

M Iwamoto[1], R Iannone[2] and JA Wagner[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 92 NUMBER 5 | NOVEMBER 2012

Clinical Pharmacology package at NDA, most extensive for oncology drugs that could be evaluated in HVs

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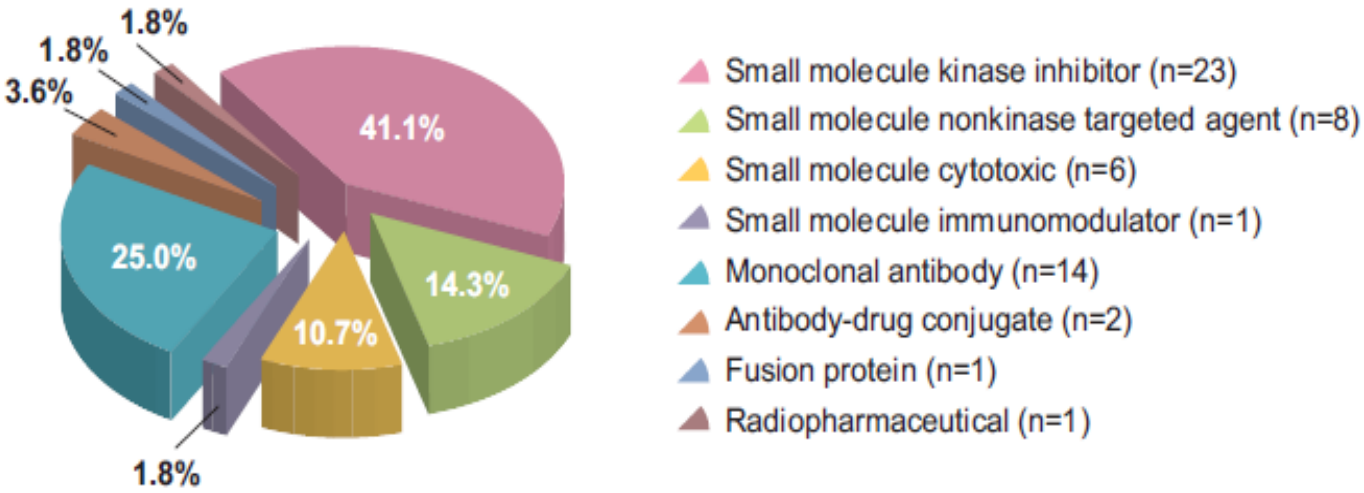


- Small molecules still represent a large proportion (38/56) of NMEs that were approved in last 6 years
- 26 NMEs had used healthy volunteers to conduct clinical pharmacology studies
- Food effect >DDI >QT >Special population (Organ impairment)

Faucette et al, CPT, 2017

Study Design Considerations

Type of Clinical Pharmacology study	Number of doses if dosed to HVs	Dose of investigational agent
ADME	1 dose	May be conducted at a dose lower than the clinical dose depending upon dose-linearity & potential for saturation of metabolic pathways
QTc	1 dose	Preferably @clinical dose, rarely supratherapeutic
BA/BE/comparability	2 doses	Preferably @clinical dose
Food Effect	2 doses	Preferably @clinical dose
DDIs	2 doses	@clinical dose (for induction DDI), lower dose may be considered if large DDI expected (for inhibition DDI)
Organ impairment	1 dose	Lower dose may be considered
Ethnicity bridging	1 dose	Preferably @clinical dose, lower dose may be considered

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

Serine threonine KI

Palbociclib

Lipid KI

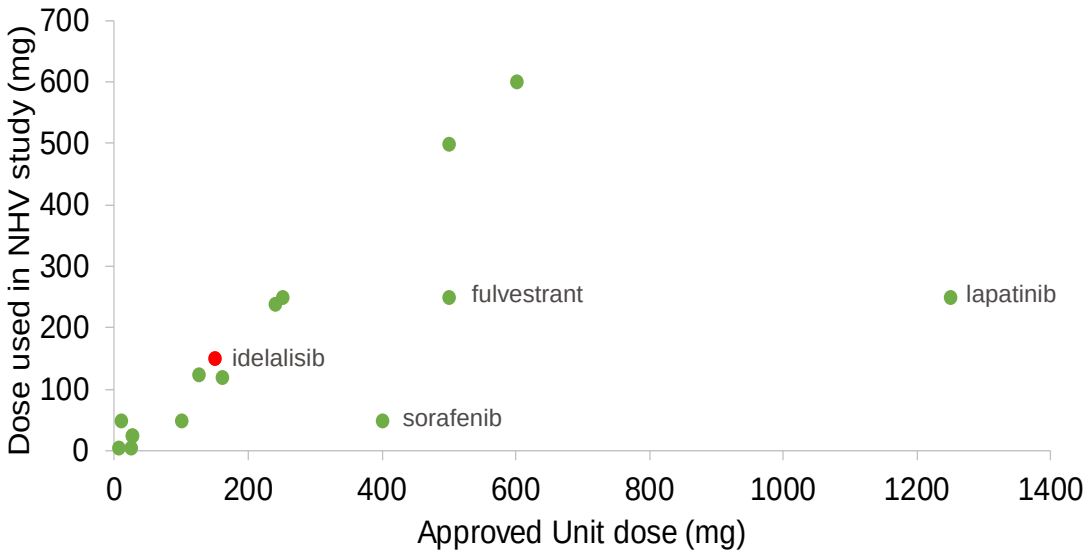
Idelalisib

Hormonal

exemestane
Fulvestrant
enzalutamide

mAb

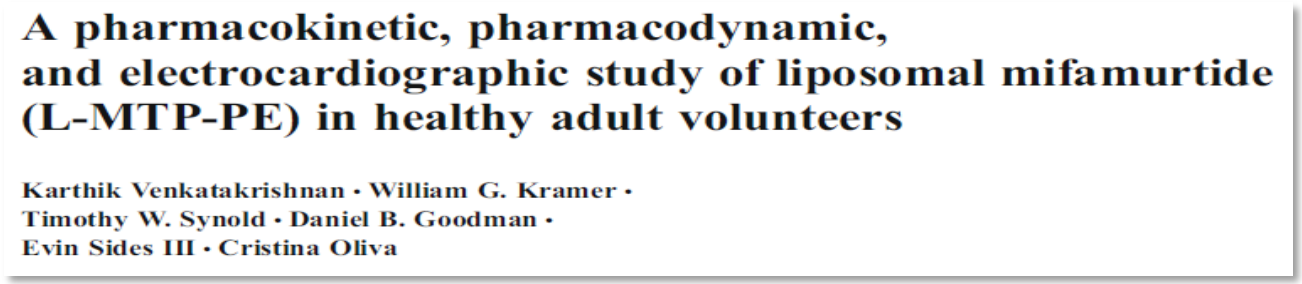
trastuzumab
bevacizumab



- Up to 2 doses of the investigational agent administered with a reasonable wash-out (typically ~5 $t_{1/2}$) 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/m^2 (approx. 4 mg), IV infusion

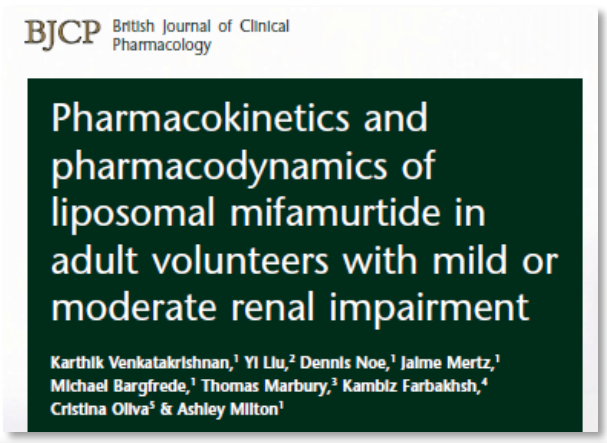

A pharmacokinetic, pharmacodynamic, and electrocardiographic study of liposomal mifamurtide (L-MTP-PE) in healthy adult volunteers

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


BJCP British Journal of Clinical Pharmacology

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

Karthik Venkatakrishnan,[1] Yi Liu,[2] Dennis Noe,[1] Jaime Mertz,[1] Michael Bargfrede,[1] Thomas Marbury,[3] Kambiz Farbakhsh,[4] Cristina Oliva[5] & Ashley Milton[1]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Pharmacokinetics and pharmacodynamics of liposomal mifamurtide in adult volunteers with mild or moderate renal impairment

Karthik Venkatakrishnan,[1] Yi Liu,[2] Dennis Noe,[1] Jaime Mertz,[1] Michael Bargfrede,[1] Thomas Marbury,[3] Kambiz Farbakhsh,[4] Cristina Oliva[5] & Ashley Milton[1]

Safety profile of mifarmutide in HVs and Associated Risk Mitigation Strategy

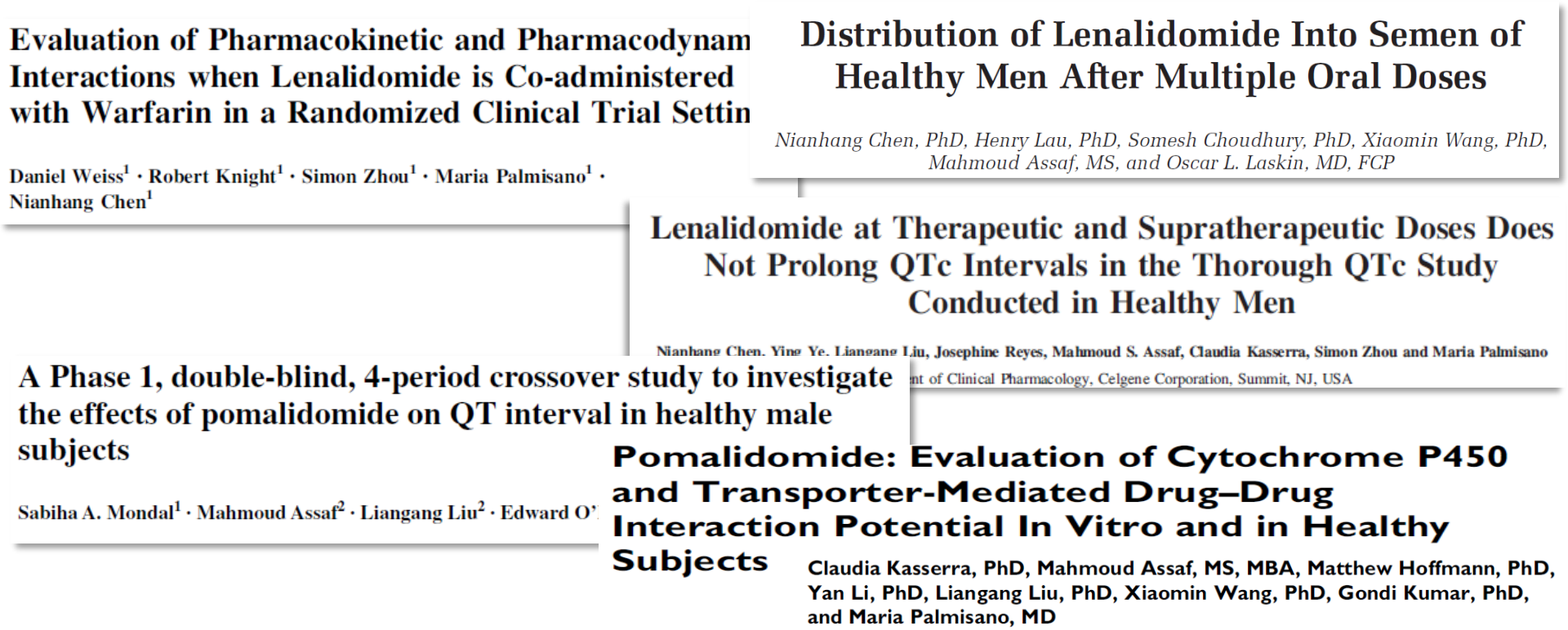
AEs	RI (n=33)	HI (n=37)	QTc (n=21)
#Grade 3 AEs	0	0	1 (syncope)
Chills	70%	70%	71%
Headache	58%	73%	86%
hypotension	48%	16%	-
Vomiting	42%	27%	29%
Pyrexia	39%	35%	43%
Tachycardia	39%	32%	67%
Nausea	36%	41%	52%
Orthostatic hypotension	30%	38%	-

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



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

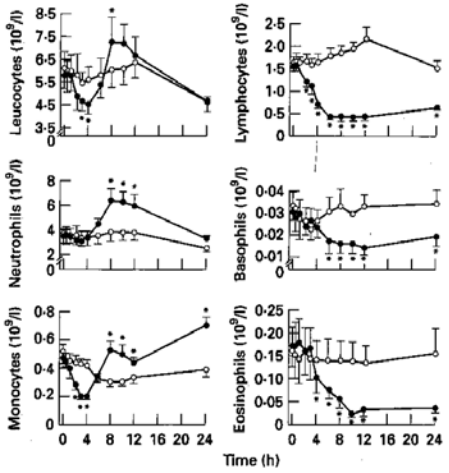


Fig. 1. Effects of IFN-α (5×10^6 U/m²) (●) or saline (○) on differential leucocyte counts. Values are mean ± s.e.m. *$P < 0.05$ *versus* the corresponding value of the control study.

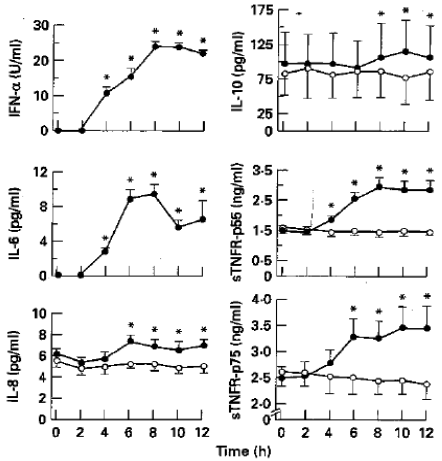
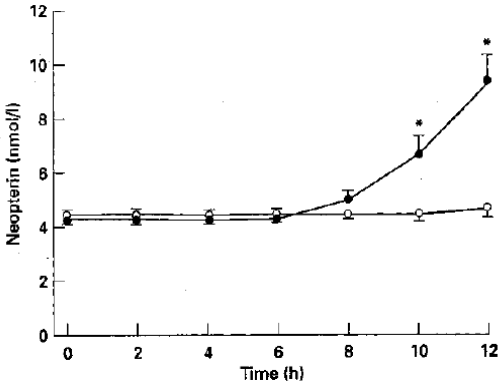


Fig. 4. Effects of IFN-α (5×10^6 U/m²) (●) or saline (○) on plasma concentrations of cytokines (IFN-α, IL-6, IL-8, IL-10, sTNFR-p55, sTNFR-p75). Values are mean ± s.e.m. On the control day, concentrations of IFN-α and IL-6 were below the detection limit in all subjects. *$P < 0.05$ *versus* the corresponding value of the control study.



Corsmitt et al, Clinical and Experimental Immunology, 1997

- 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

NHV Task force: Systematic evaluation via cross-functional collaboration to make an informed decision

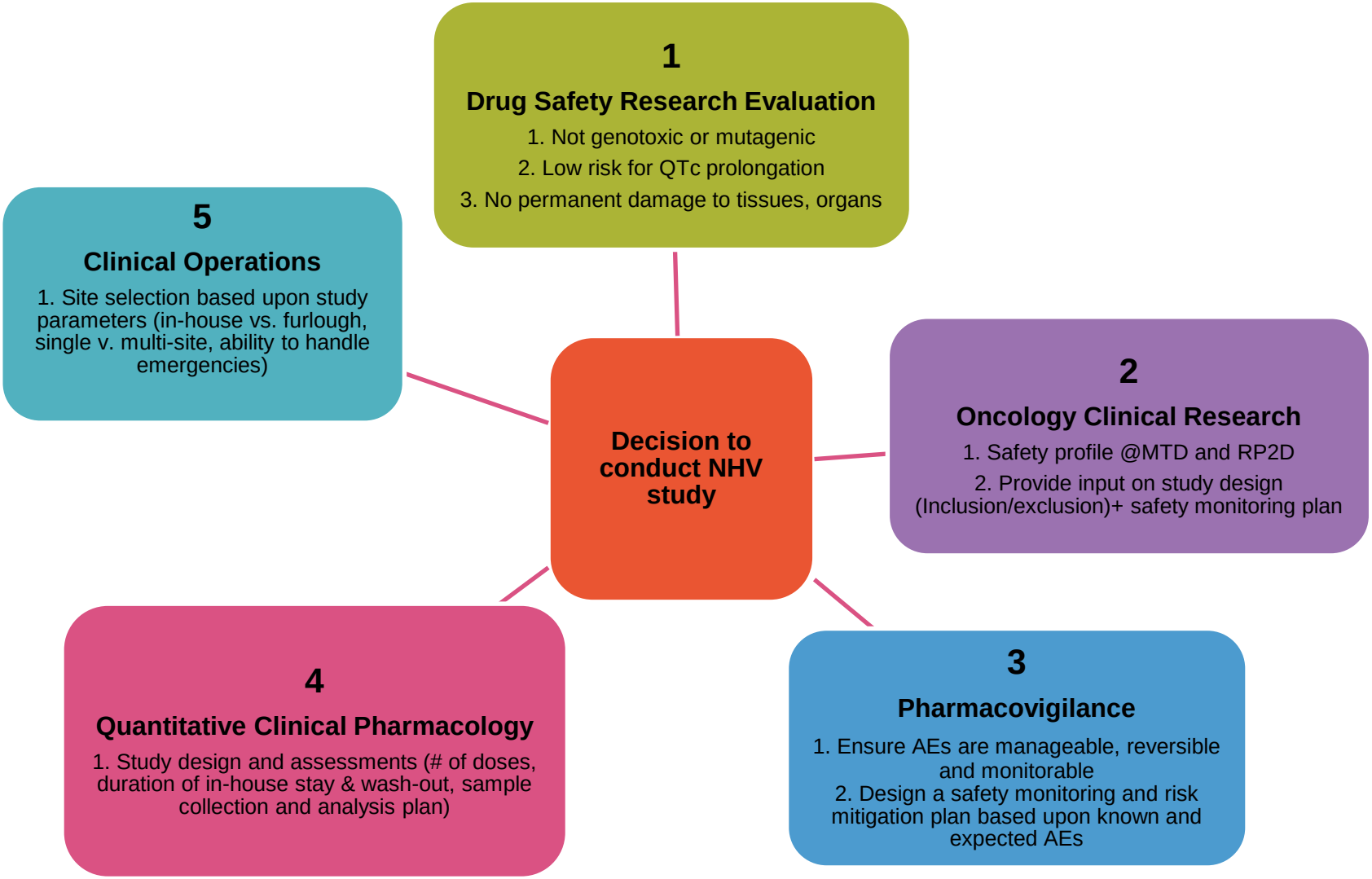


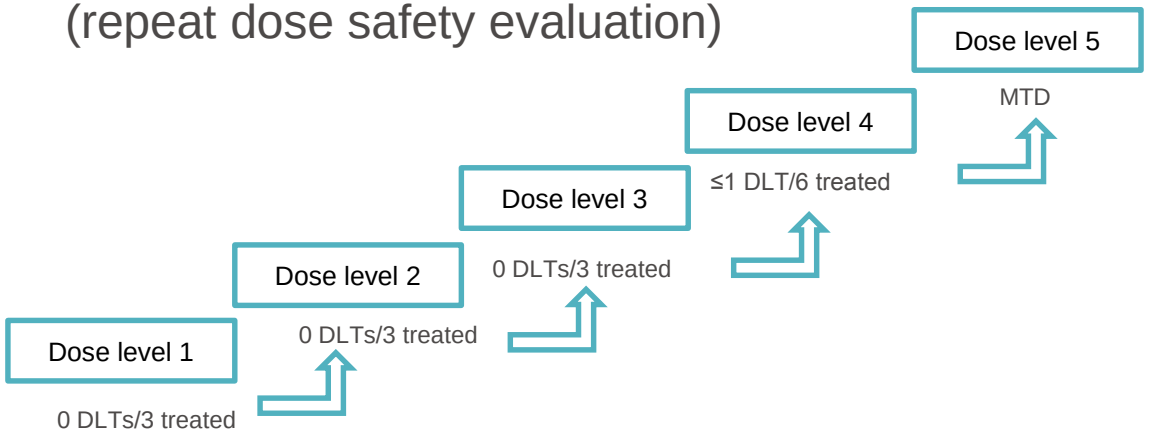
Illustration of this approach: TAK117

- 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	
Non-mutagenic	√
Non-genotoxic	√
Low risk for QT prolongation (hERG + telemetry data)	√
Does not cause hemolysis	√
AEs manageable, reversible and monitorable	√
Safety profile @MTD & RP2D	√
Single dose safety profile	X

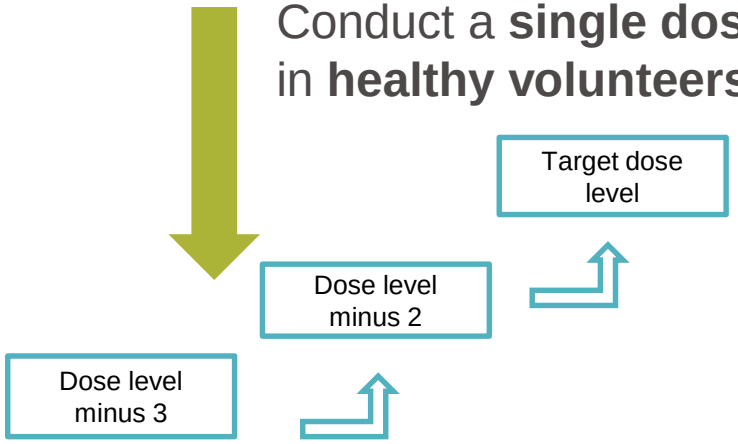
One approach to collecting single dose safety profile of an investigational anti-cancer agent

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

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)

Takeda Pharmaceuticals International Co.