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Applied Translational Medicine

Can Small Molecule Oncology Drugs Be Tested in Healthy Subjects?

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Executive Summary

- Compare safety profile for today's small molecule oncology products vs. yesterday's chemotherapeutic agents
- Opportunity to test early in healthy subjects vs. patients at considerable cost and time savings
- Some common Adverse Events which can potentially be mitigated/managed
- Common physical-chemical properties
- Opportunity to evaluate critical clinical pharmacology properties to inform transition to patients early in development

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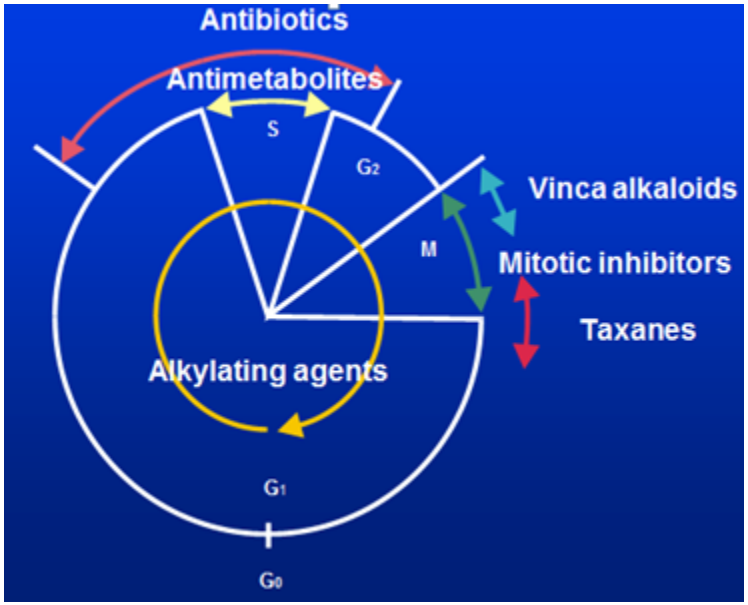
Yesterday's Traditional Chemotherapy

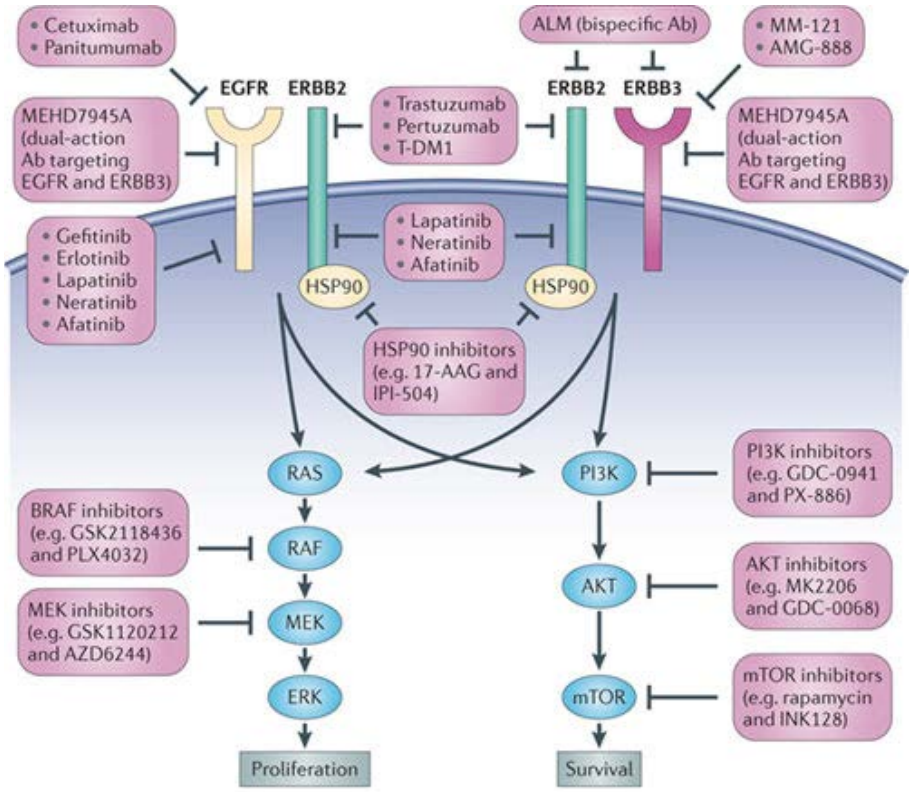


- Non-specifically target healthy and cancer cells
- Can produce secondary malignancies
- Serious dose- and duration-limited Adverse Events
- Typically parenteral administration

American Cancer Society http://www.cancer.org/acs/groups/cid/documents/webcontent/002995-pdf.pdf
http://howmed.net/pharmacology/cancer-chemotherapy-an-introduction/
Accessed June 8, 2015

Today's Treatment: Kinase Inhibitor

- Inhibit Tyrosine/ Serine/ Threonine Kinases
- Orally bioavailable (most)
- More specifically targeting overexpressed receptors and/or enzymes
- More selective for cancer cells vs. healthy cells
- Not without Adverse Event concerns



The ERBB network: at last, cancer therapy meets systems biology
Yosef Yarden & Gur Pines
Nature Reviews Cancer 12, 553-563 (August 2012)

AE: Adverse Events

Example Drugs Targeting Receptor and Intracellular Kinases (Tyrosine, Serine, Threonine)

Kinase Type	Name	Trade/Code Name	Selective Target	FDA Approved	Cancer (Examples)
Receptor	Crizotinib	Xalkori	MET	+	NSCLC, anaplastic large cell lymphoma, neuroblastoma
Receptor	Erlotinib	Tarceva	EGFR	+	NSCLC, pancreatic cancer
Receptor	Gefitinib	Iressa	EGFR	+	NSCLC, AML
Receptor	Icotinib	Conmana	EGFR	+	NSCLC
Receptor	Lapatinib	Tykerb	HER-2, EGFR	+	Breast cancer
Receptor	Lenvatinib	E7080	VEGFR2, 3	+	Approved for thyroid cancer in Japan
Receptor & Intracellular	Cabozantinib (XL184)	Cometriq	VEGF, RET, MET, NTRKB, TIE2, AXL	+	Medullary thyroid cancer, progressive metastatic medullary thyroid cancer
Receptor & Intracellular	Dasatinib	Sprycel	BCR-ABL, SRC, KIT, PDGFRs, EPH, CSK	+	CML, ALL
Receptor & Intracellular	Imatinib	Gleevec	ABL, KIT, PDGFRs	+	Gastrointestinal stromal tumor, leukemias
Receptor & Intracellular	Nilotinib	Tasigna	BCR-ABL, KIT, LCK, EPHA3, 8, DDR1, 2	+	CML
Receptor & Intracellular	Sunitinib	Sutent	VEGFR2, PDGFRβ, KIT, RET, CSF1R, FLT3	+	Renal cell carcinoma, gastrointestinal stromal tumor

Developing Oncology Products: Phase I Timeline/Cost

- Estimates range from at least 12-18 months for n=25 oncology patients*
- Compared to 4-6 months for healthy normal subjects (HNS)
- Patients studies can cost into the millions
- Targeted therapies alter the risk vs. benefit ratio relative to cytotoxic agents
- Unless compound causes direct DNA damage, FDA typically allows dosing in HNS

*Hughes et. Al. 2012. Assay Guidelines
Early Drug Discovery and Development Guidelines:
For Academic Researchers, Collaborators, and Start-up

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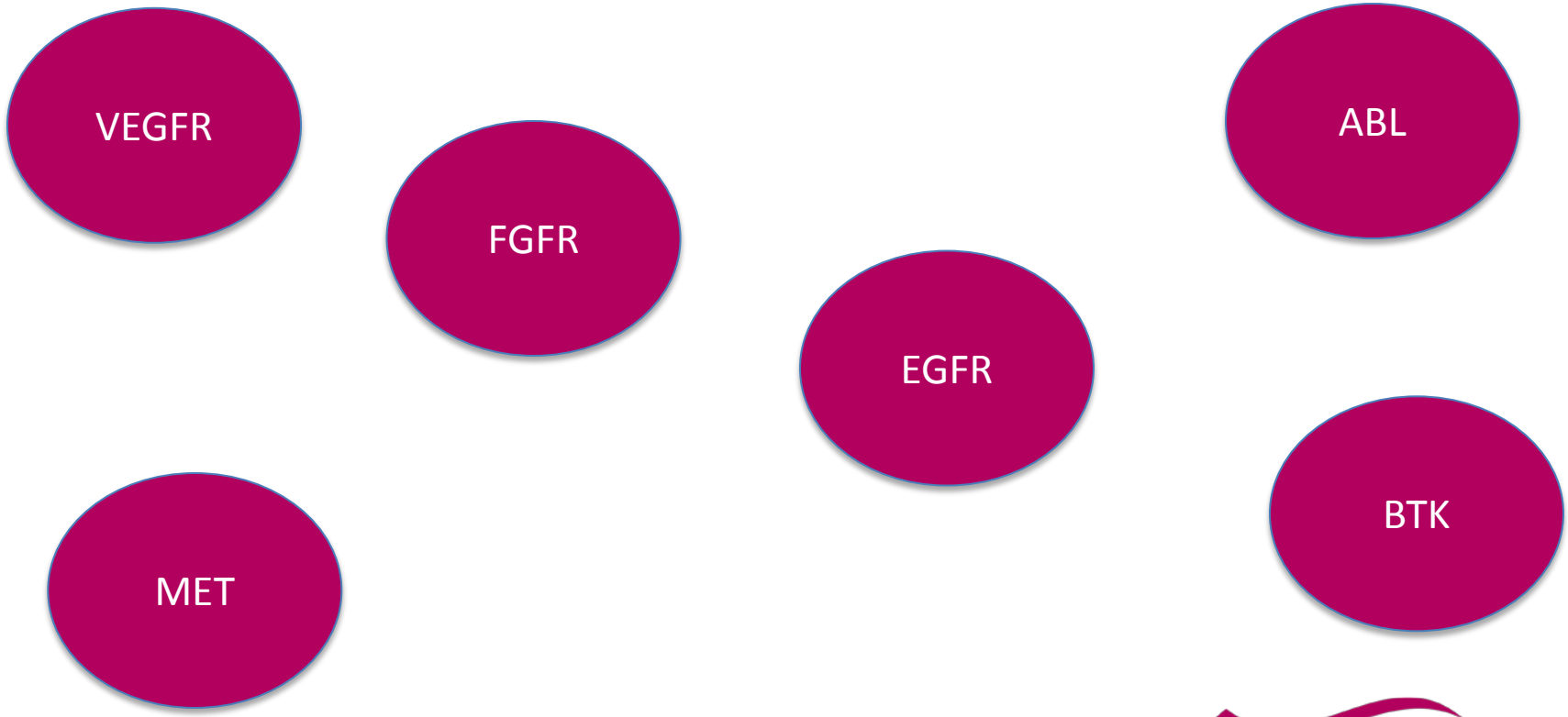
Celerion's Oncology Small Molecule Experience in Healthy Volunteers

- >45 studies (Since 2011) across variety of targets



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Considerations Before Testing Oncology Drugs in Healthy Subjects

General

- Mutagenicity/carcinogenicity
- Reproductive toxicity

Class Specific Concerns

- Skin rashes and other cutaneous reactions
- Hepatotoxicity
- Cardiovascular safety
- Gastrointestinal irritation (nausea/vomiting)

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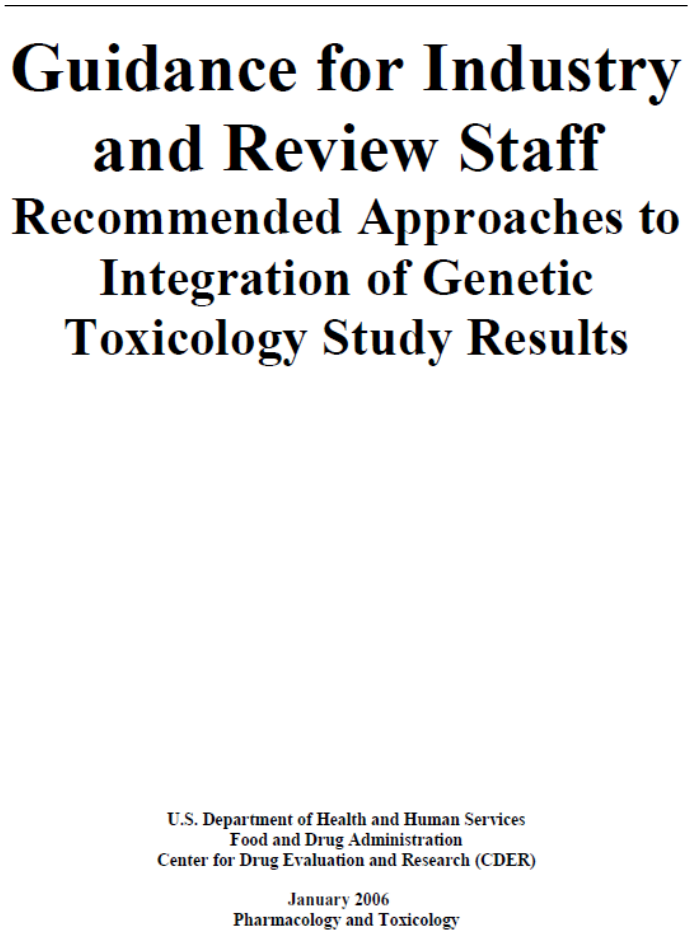
Carcinogenicity & Mutagenicity Concerns

- Previous paradigm for oncology didn't warrant such scrutiny as not using HNS
- Genotoxicity which causes direct DNA damage, not good candidate for HNS study
  - 3 negative assays before dosing in HNS
- ICH M3: need at least Ames test for single-dose
- ICH M3: also need test for DNA damage for multiple-dose



Guidance for Industry and Review Staff

Recommended Approaches to Integration of Genetic Toxicology Study Results

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2006
Pharmacology and Toxicology

HNS: Healthy Normal Subjects
ICH: International Conference on Harmonization

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Reproductive Toxicity Considerations

- Sperm cycle is ~70 days – males must use barrier method until impact on sperm expected to be nil
- Absence of testing or positive effect may require excluding women of child bearing potential – regardless of contraception
- Females not of child-bearing potential can be employed
  - For repeat-dose ICH M3 suggests toxicity testing on reproductive organs should be conducted first

ICH: International Conference on Harmonization

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Skin Reactions and Risk Mitigation

- Cutaneous reactions among most common AEs in oncology:
  - Skin eruptions
  - Xerosis (dryness)
  - Fissures
  - Hair changes (alopecia, depigmentation)
- EGFR inhibitors produce dose-dependent effects >75% patients within 1-2 weeks
- Difficult to mitigate risk, mostly supportive management if these effects occur in clinical studies

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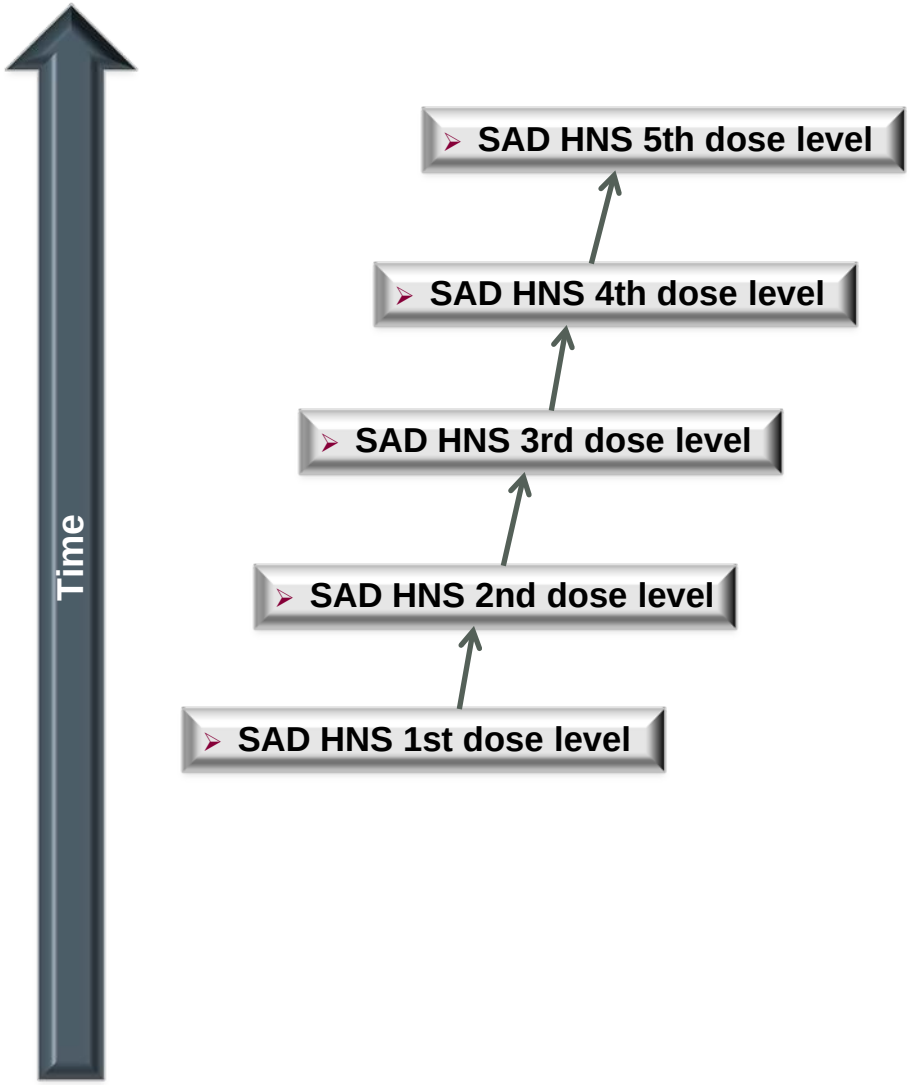
Integrate Intensive ECG Monitoring for Early QT liability



Each Cohort

- ECG Extractions
- Single 24 hr Holter monitoring session
- Three triplicate baseline timepoints
- 6-9 triplicate post-dose timepoints
- Proactively plan for extended supine periods

HNS: Healthy Normal Subjects

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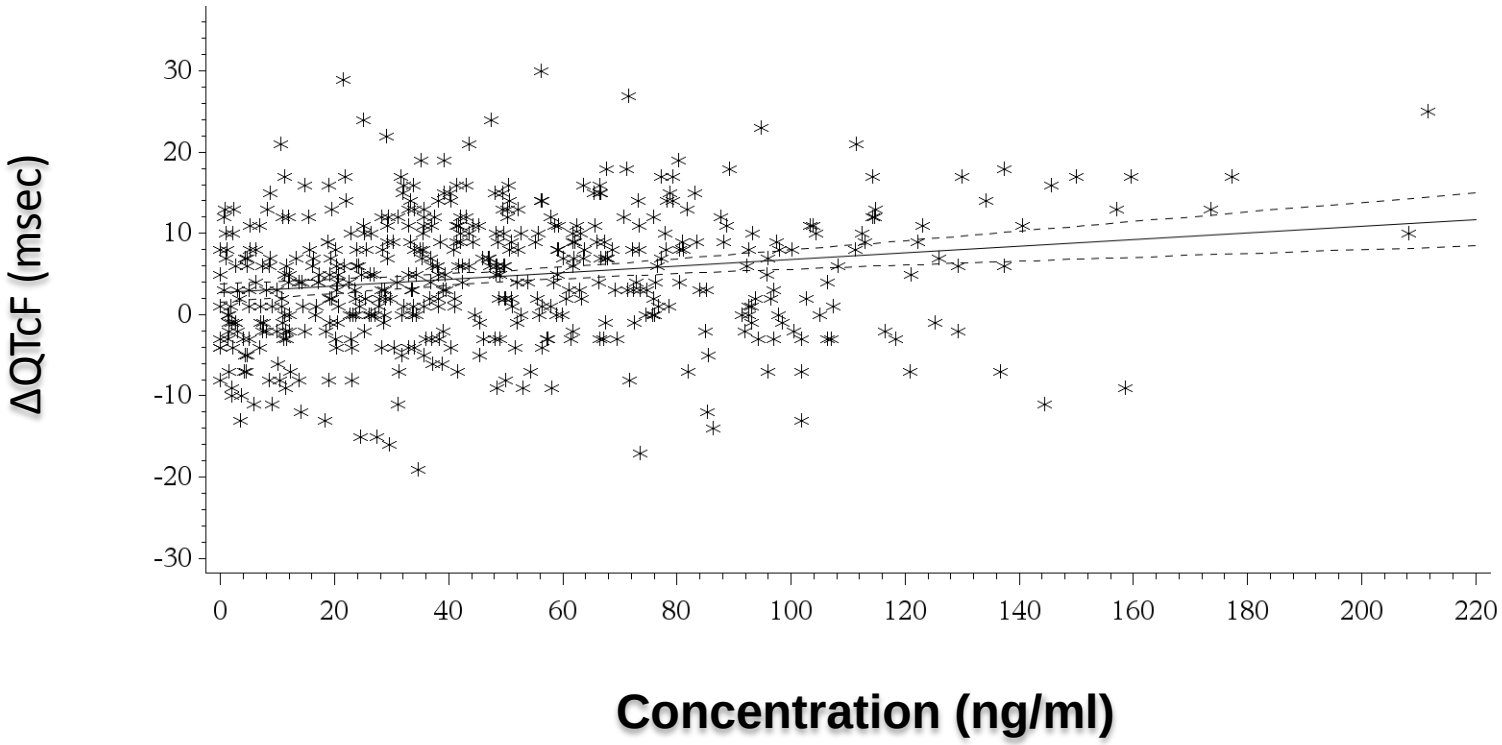
SAD Allows for Evaluation of Potentially Supra-Therapeutic Exposure



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Mitigating GI Risk

- Nausea and vomiting common with TKIs, especially with EGFR inhibitors
- TKI tested in dose escalation (FIH SAD) in patients with Most frequently reported adverse events were:
  - Nausea
  - Vomiting
  - Diarrhea
  - Abdominal pain
  - Clear gastrointestinal-related adverse event profile

FIH: First-in-Human
SAD: Single-Ascending Dose Study

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Mitigation of GI Effects for Healthy Subject Studies

- In healthy subject studies, consider prophylactic antiemetics in highly emetogenic drugs (based on the initial studies in cancer patients)
- IM diphenhydramine (mild CYP2D6 inhibitor)
- Oral ondansetron (Zofran, not likely interact with metabolism but may impact GI motility) – consider for rescue
- Pre-treatment with 16 mg 30-45min pre-dose: 0 emesis events in one group of n=24 HNS

HNS: Healthy Normal Subjects
GI: Gastrointestinal
Min: Minute

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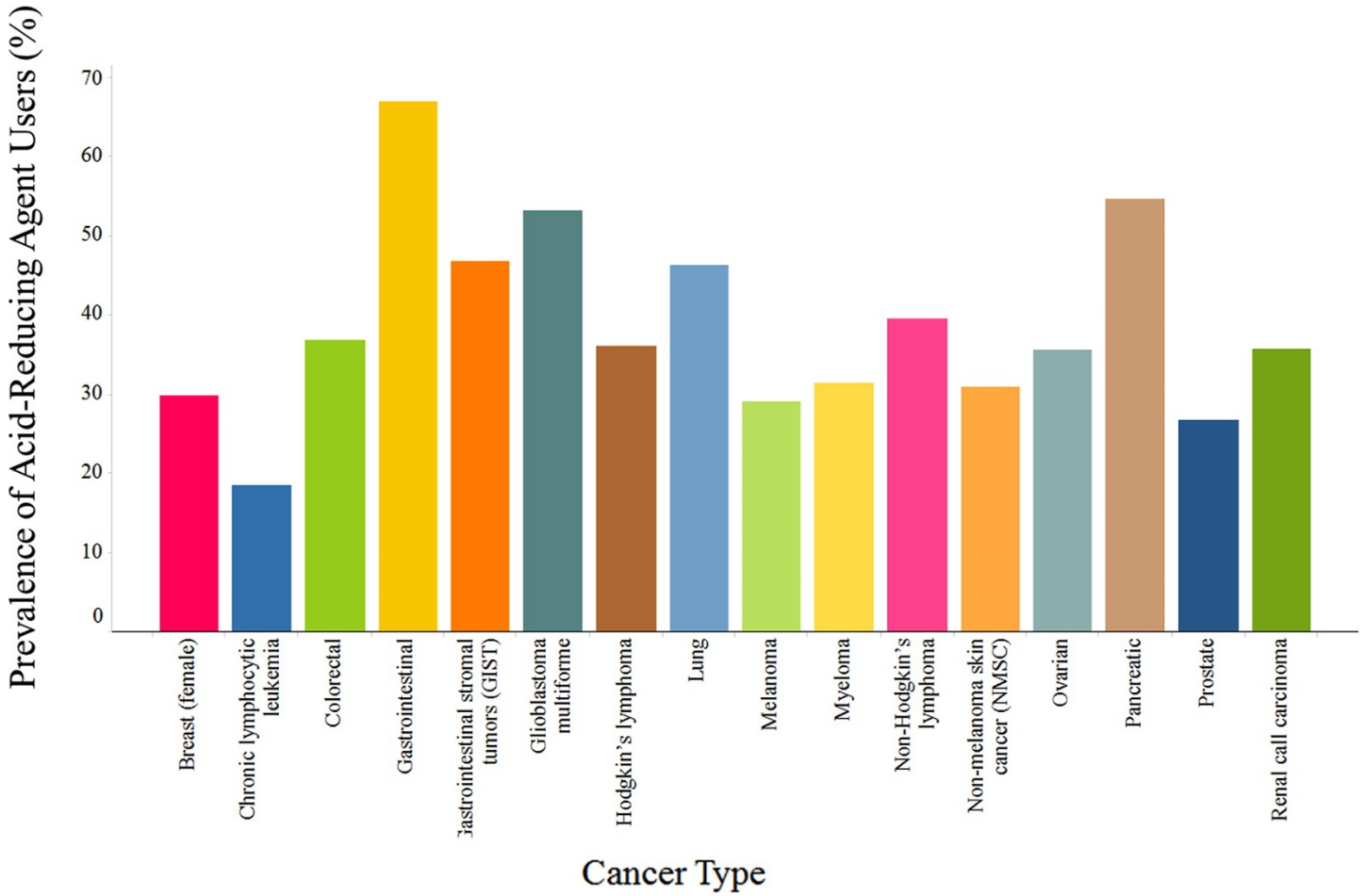
Use of Acid-Reducing Agents in Cancer Patients

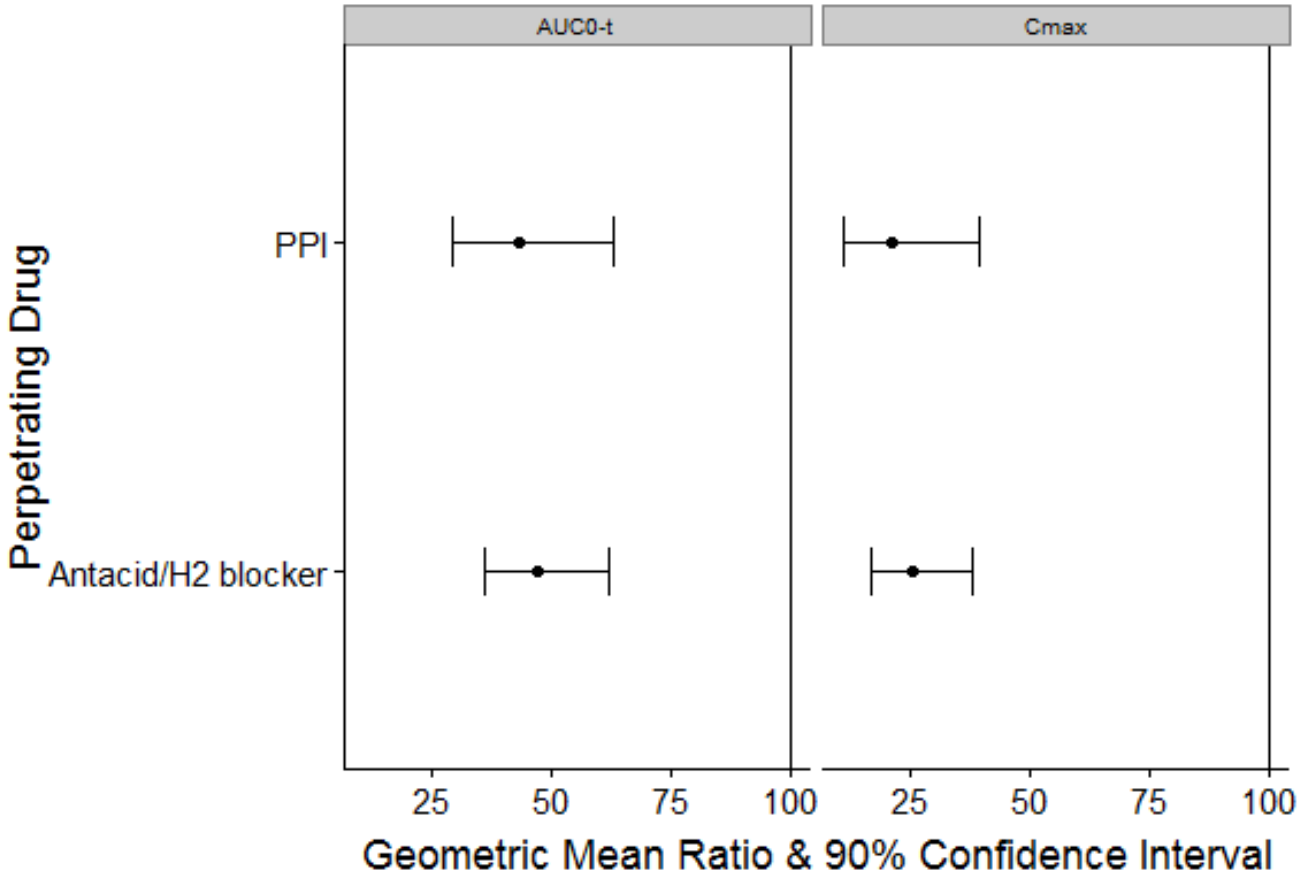


Gillian S. Smelick; Timothy P. Heffron; Laura Chu; Brian Dean; David A. West; Scott L. DuVall; Bert L. Lum; Nageshwar Budha; Scott N. Holden; Leslie Z. Benet; Adam Frymoyer; Mark J. Dresser; Joseph A. Ware; *Mol. Pharmaceutics* **2013,** 10, 4055-4062.
DOI: 10.1021/mp400403s

Kinase Inhibitor DDIs with Acid-Reducing Agents?

- Most of these compounds are weak bases, so more acidic environment ionizes drug improving solubility, but…
- ↑pH with gastric acid-reducers ↓ ionization and ↓ solubility – potentially ↓ bioavailability
- pH dependent solubility observed in vitro doesn't always translate to in-vivo
- Efficient testing can be performed using strong acid suppressors (e.g. Proton Pump Inhibitors (PPI)), then if an effect is observed, consider weaker (H2 antagonists, antacids)

Example Magnitude of Acid-Reducing Agents on PK of TKI Class Compound



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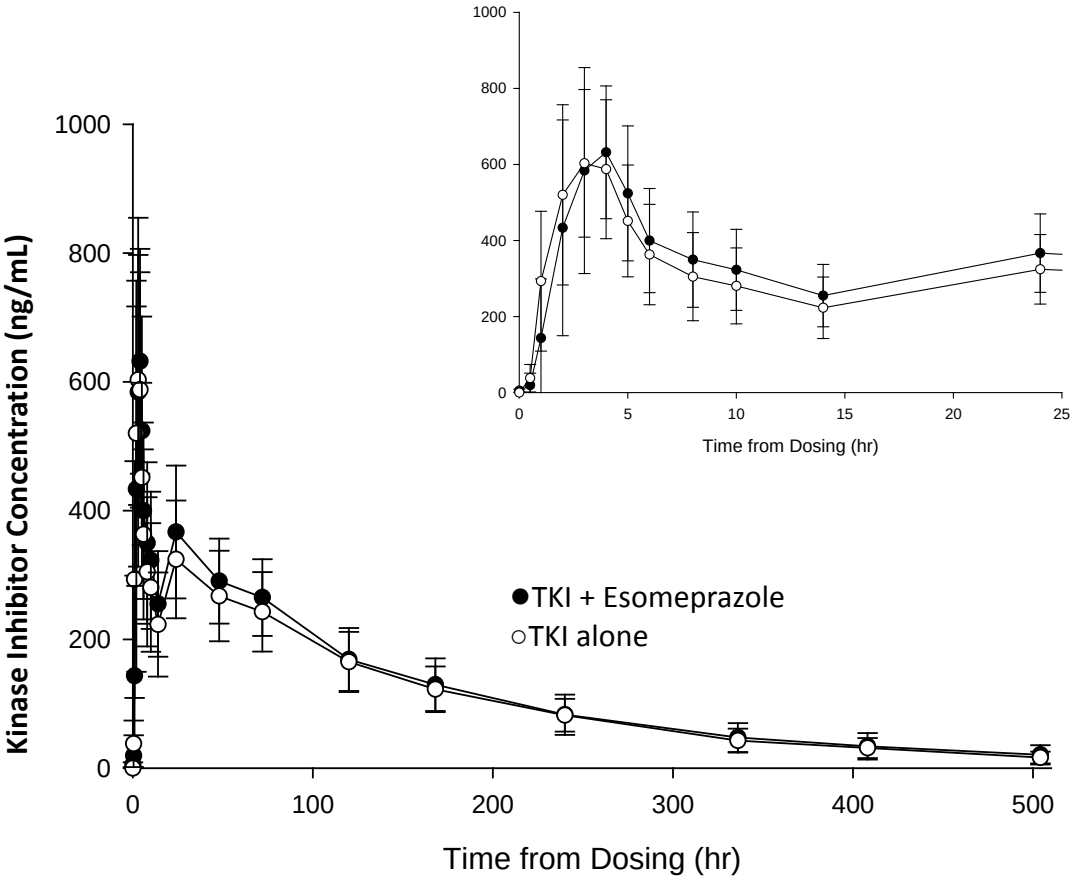
Lack of Significant Effect of Acid Reducer on Another TKI – Not a Class Effect?



TKI: Tyrosine Kinase Inhibitor

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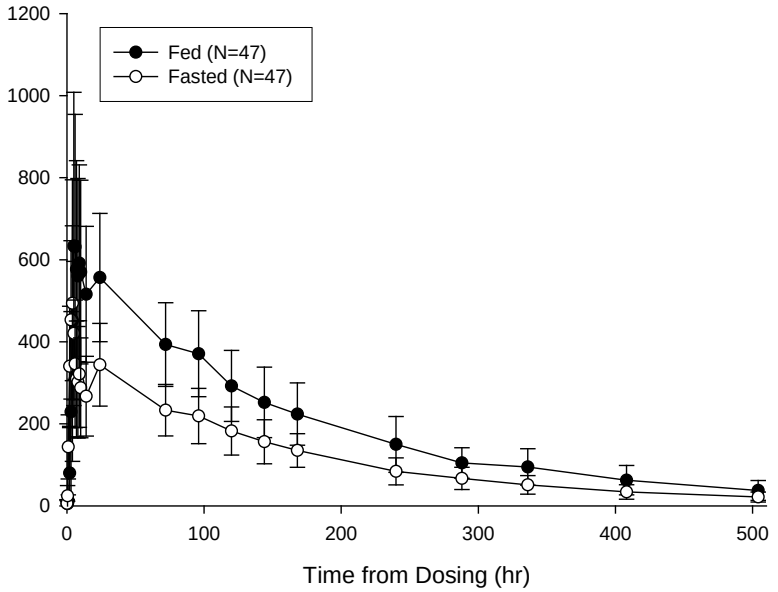
What about Food-Effect?

- Similar principles apply as for the PPI interaction
  - pH dependent solubility can be influenced by meal
  - Important to test impact of meal early on when moving quickly into patient studies



PK Parameter	GMR%	90% CI
C_{max}	141	118-167
AUC0-t	157	136-182
AUC0-inf	157	135-182

PPI: Proton Pump Inhibitor
PK: Pharmacokinetic
GMR: Geometric Mean Ratio
CI%: Confidence Interval
C_{max}: Maximum Concentration
AUC: Area Under the Curve

Impact of Tobacco Use

- Tobacco induces CYP1A
- Constitutive activity of CYP1A low in normal individuals, however substantially upregulated
- If preclinical testing suggests CYP1A catalyzed metabolism:
  - Consider testing in vivo, impact of smoking status on PK in early clinical pharmacology study before Phase II/III
  - Mitigates risk of treatment failure in cancer patients who continue to smoke during treatment

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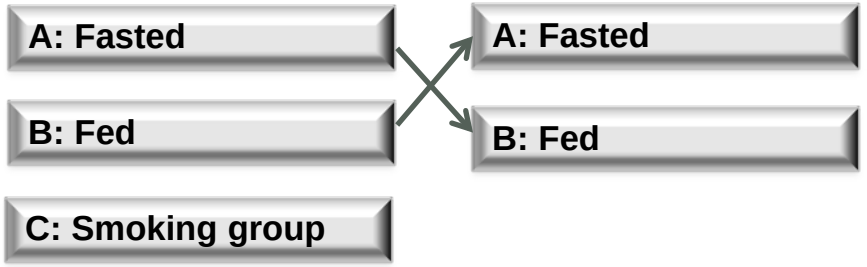
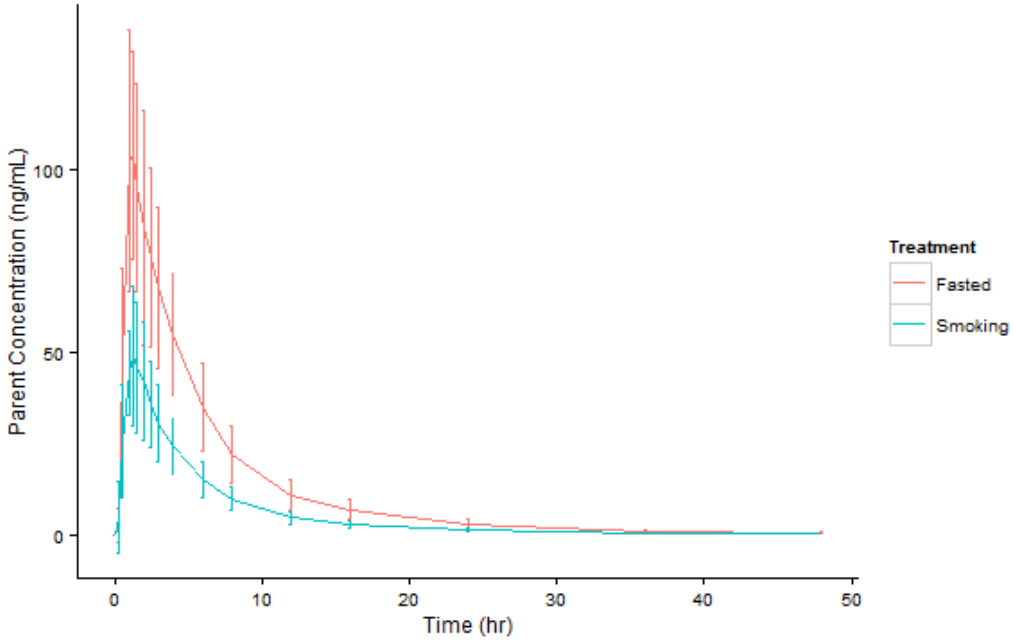
Study 1: Food-effect + Effect of Smoking (CYP1A induction)

Study 1

- 2-period single-dose x-over in HNS
  - Fasted
  - Fed
- Parallel group comparison to HNS moderate-heavy cigarette smokers





HNS: Healthy Normal Subjects
X-over: Crossover Design

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Other DDIs

- Many of the TKIs are metabolized by the CYP3A4 system
- Many potential interactions
- Consider testing for effect of CYP3A4 early on in Phase I (FDA has commented to either test or avoid certain concomitant medication in patient studies)
- Fewer inducers in clinical practice, if cost/time a factor consider deferring induction effect until after Phase II

TKI: Tyrosine Kinase Inhibitor

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How Do I Know if I Should Plan for a DDI Study and When?

- FDA guidance considers the [I]/Ki ratio where:
  - [I] is the Cmax at steady-state of the inhibitor
  - Ki is the concentration of the inhibitor which reduces the rate of the in-vitro reaction by half
  - Ratio >0.1 suggest possible interaction
  - Ratio >1 suggest likely
- If drug is a substrate for CYP3A4, possibly also for p-glycoprotein, consider testing in-vitro and in-vivo before patient studies in a human Drug-Drug Interaction

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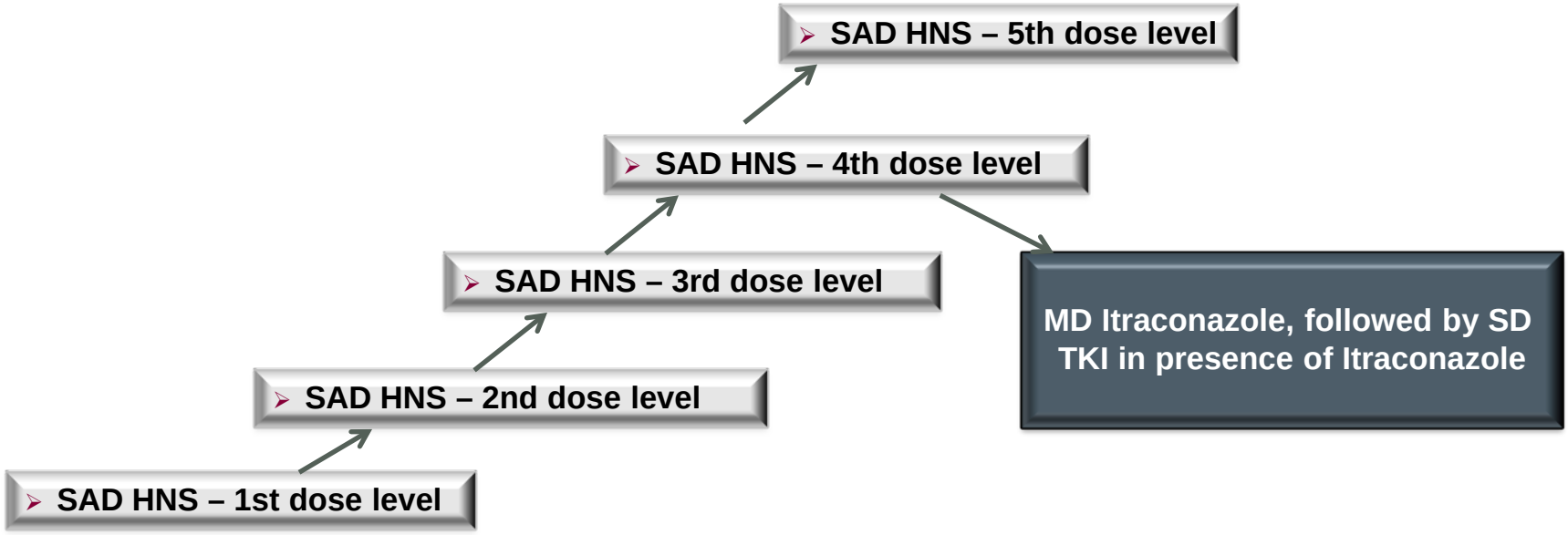
Options For Testing CYP3A4 Inhibition of TKI in Early Clinical Research

Option 1

- Fixed-sequence test of itraconazole (strong CYP3A4 inhibitor) as part of SAD



SD: Single-dose
SAD: Single Ascending Dose
MD: Multiple-dose
DDI: Drug-Drug Interaction
HNS: Healthy Normal Subject

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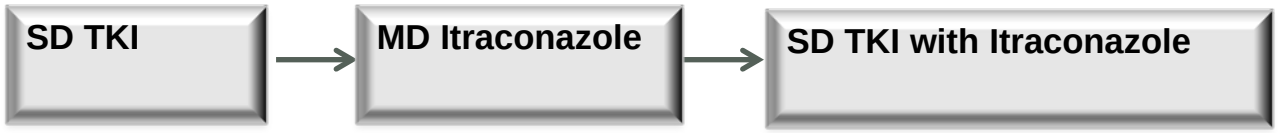
Options For Testing CYP3A4 Inhibition of TKI in Early Clinical Research

Option 2

- Dedicated standalone study
- Fixed-sequence test of itraconazole (strong CYP3A4 inhibitor)



SD: Single-dose
MD: Multiple-dose
DDI: Drug-Drug Interaction

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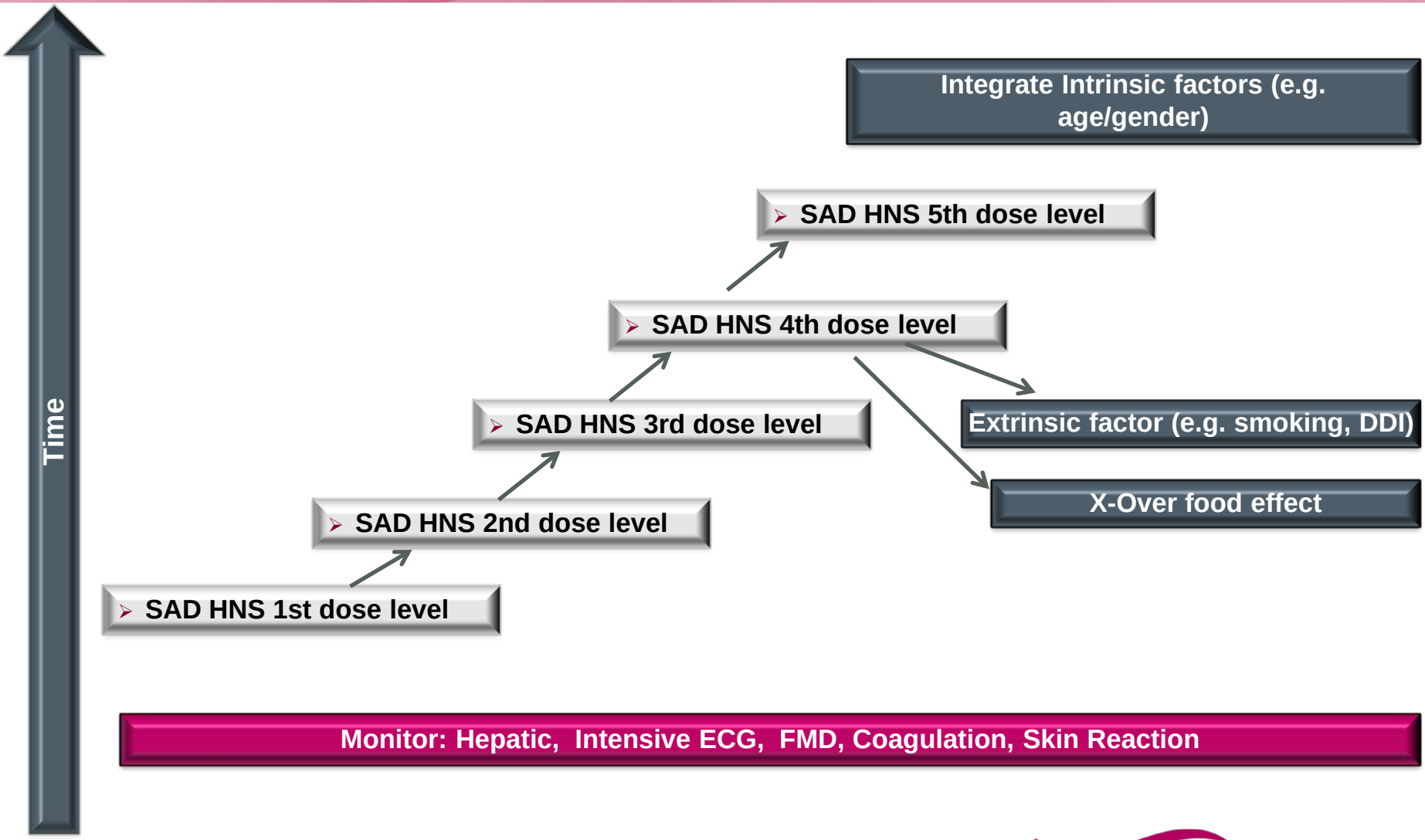
Integrate Intrinsic/Extrinsic Factors into SAD with Intensive Safety Monitoring



SAD: Single Ascending Dose
HNS: Healthy Normal Subject

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Summary

- Consideration of using HNS in non-cytotoxic small molecule oncology not different from other therapeutic classes
- Time/cost savings and speed of start-up of a FIH in HNS to be weighed against safety concerns and benefits of doing trials in cancer patients.
- Some AEs (emesis may be mitigated by anti-emetics)
- Common physical-chemical characteristics suggest food-effects, GI acid effects
- CYP3A4 inhibition victim

AE: Adverse Effects
GI: Gastrointestinal
FIH: First-in-Human
HNS: Healthy Normal Subjects

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Thank you
Questions?