Use of Healthy Volunteers in Oncology Drug Development: A Case Study

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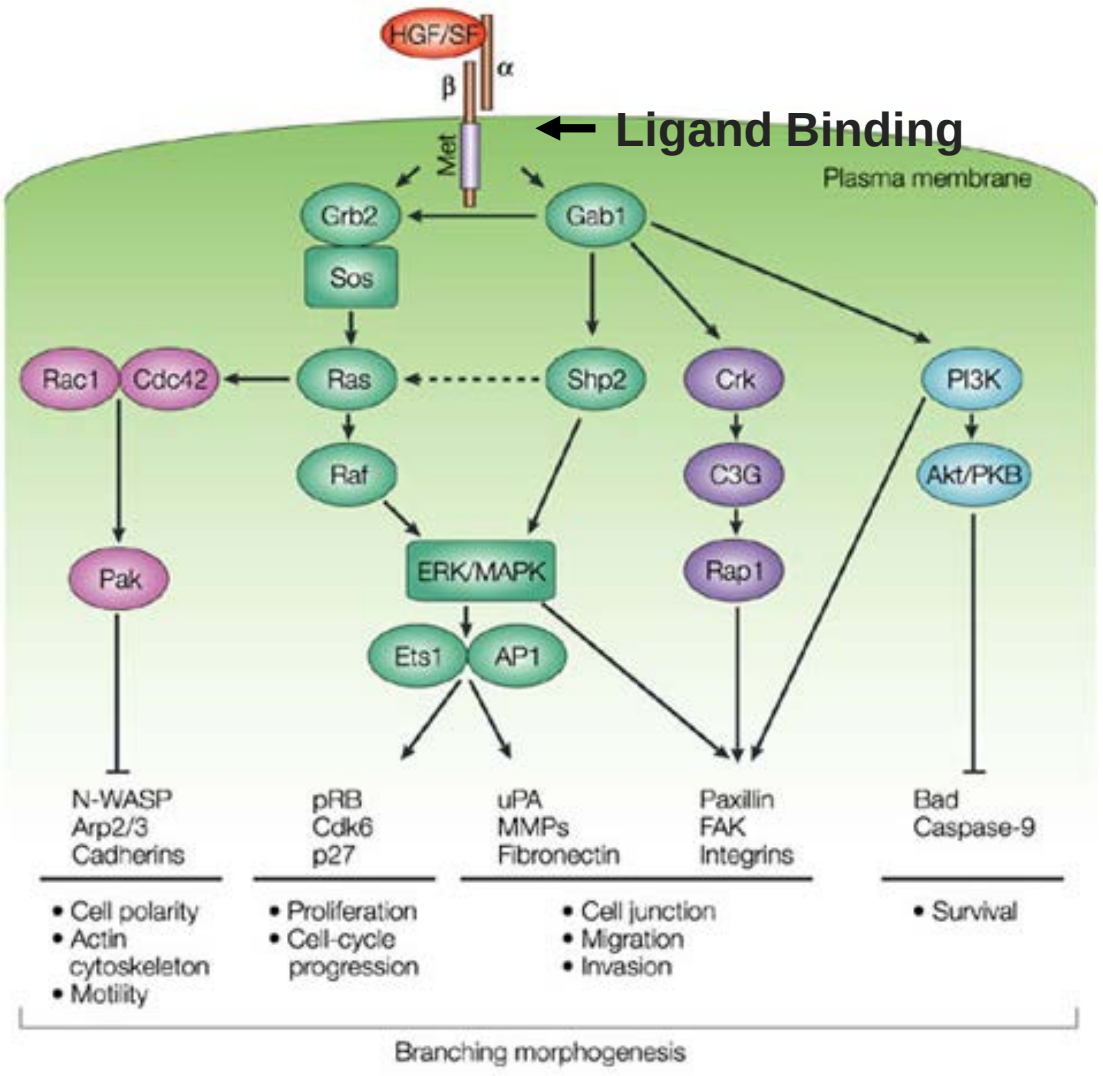
Introduction

- Phase 1 first-in-human dose-escalating studies with investigational oncology drugs are typically conducted in patients with advanced cancer.
- Development of molecularly targeted, non-cytotoxic anticancer therapeutics offers scope for clinical investigation in healthy volunteers.
- Trials in these populations can provide useful safety, PK, DDI, Food Effect and possibly PD data to help guide further clinical development.

PF-04217903: c-Met/HGFR Inhibitor



- PF-03 is a small molecule, selective, ATP-competitive inhibitor of the c-Met/HGFR.
- PF-03 was not genotoxic based on a standard battery of assays for mutagenicity and clastogenicity.

C. Birchmeier, et al Nature Reviews (2003) **4:** 915-25

Clinical Studies

- Study 1001
  - A Phase 1, Double-Blind, Escalating Single Dose, Safety, Tolerability, and Pharmacokinetic Study of PF-03 in Healthy Adult Volunteers

    (Tan W et al, ASCPT Poster 2009)

- Study 1002 [NCT00706355]
  - A Phase 1, Escalating Multiple Dose, Safety, Tolerability, and Pharmacokinetic Study of PF-03 in Patients with Advanced Solid Tumors

    (Diamond JR et al, JCO v31, 2013)

Study 1001 in Healthy Volunteers

- To evaluate the safety and tolerability of escalating single doses of PF-03 when administered to healthy adult subjects.

- To evaluate the PK of PF-03 and its metabolite (if present) after escalating single doses of PF-03, administered to healthy adult subjects under fed and fasted conditions.

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Study Design

- Randomized, placebo-controlled, double-blind, single-dose escalation study with a parallel-group design.
- Subjects within each cohort were randomly assigned to receive one dose of either PF-03 (n=6) or placebo (n=2).
- Dosing in subsequent cohorts began at least 7 days after dosing in the prior cohort, in the absence of dose-limiting AEs in two or more subjects.
- All subjects were fasted except that the 6 subjects in the food effect cohort
- Blood and urine samples were collected and analyzed for concentrations of PF-03 and its metabolite.

Starting Dose and Stopping Dose

- Starting dose: 1 mg
  - EC_{10} = 2.2 nM (free concentration) or 4.9 ng/mL (total concentration)
  - EC_{10} dose = 0.7 mg (rounded to 1 mg) using predicted human PK parameters
  - Expected to produce no or minimal pharmacologic effect

- Stopping dose: 700 mg
  - NOAEL exposure in the 7-day dog toxicity study: 3.3 μg/mL (C_{max}) and 13 μg·h/mL (AUC)
  - Stopping dose was determined to be 717 mg (rounded to 700 mg)

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Dose Escalations

Cohort	Number of Subjects	Treatment					
		A	B	C	D	E	F (Food Effect)
1	6	1 mg					
	2	Placebo					
2	6		4 mg				
	2		Placebo				
3	6			8 mg			
	2			Placebo			
4	6				… …		
	2				Placebo		
5	6					240 mg	
	2					Placebo	
6	8						X mg *

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Study Subjects

A total of **70** subjects: 16 received placebo and 54 received escalating doses of PF-03 ranging from 1 mg to 240 mg

Inclusion Criteria:

- Healthy men or women of non-childbearing potential
- Age: 18–55 years.
- Body mass index: 18–30 kg/m^2; body weight: ≥50 kg
- Normal creatinine clearance during screening
- Plasma troponin I concentration <0.04 ng/mL, due to microscopic changes in the heart from a preclinical toxicology study in dogs

Exclusion Criteria:

- History of clinically significant disease (hepatitis B or C)
- Male subjects with conditions that might affect fertility
- QTc >450 ms
- Regular consumption of alcohol or tobacco products
- Investigational drug within 30 days
- Prescription or non-prescription drugs within 7 days

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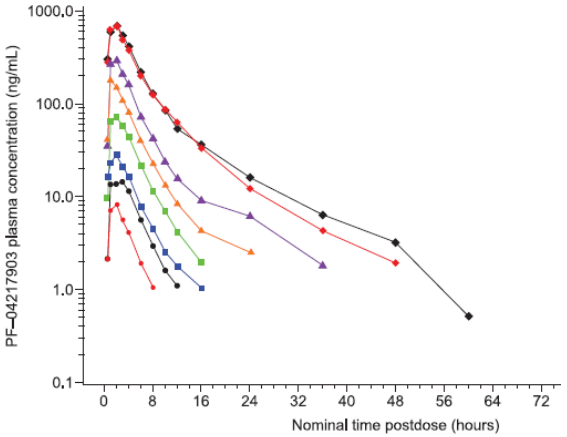
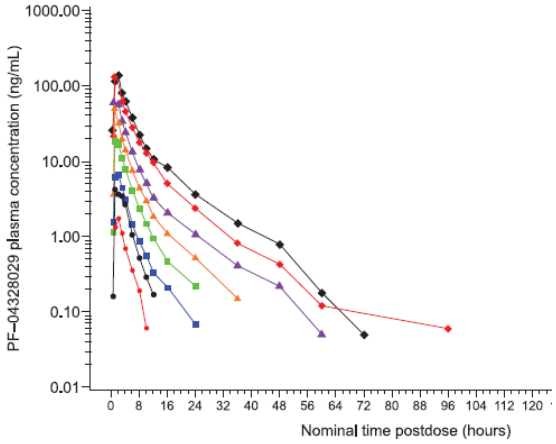
Pharmacokinetic Results

- PF-03 absorption was rapid, median T_{max} of 1-2 hrs.
- PF-03 C_{max} and AUC_{inf} appeared to increase proportionally with dose ranging from 4 mg to 120 mg.
- $T_{1/2}$ ~8 hrs
- Formation of metabolite PF-029 was rapid, median T_{max} of 1-2.5 hrs.
- M/P ratio ranged from 0.16 to 0.24.
- High-fat meal increased C_{max} and delayed median T_{max} by ~3 hrs, but did not change AUC_{inf}.
- The urinary excretion of PF-03 was negligible (1%).





Safety Results

- There were no deaths, SAEs, or withdrawals due to AEs reported in this study and no subject had a severe AE.
- No laboratory abnormalities seemed to be dose-dependent and some abnormalities were noted in placebo-treated subjects.
- No consistent trends by dose or by time point were noted for mean changes from baseline in vital signs, BP, and ECG results.
- PF-03 doses up to 120 mg were safe and well tolerated.
- Clinically significant elevations in ALT/AST were reported for 2 subjects in the 240 mg fasted group. These dose-limiting AEs, in conjunction with PK data from the 120 and 240 mg doses, led to a decision that dose escalation would not be continued beyond 240 mg.

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Study 1002 in Advanced Cancer Patients

- Determine the safety profile of PF-03
  - Identify MTD
  - Identify RP2D
- Determine the multiple-dose PK profile of PF-03
- Determine any evidence of anti-tumor activity of PF-03
- Perform exploratory evaluations of c-Met/HGFR genotyping and expression, PD endpoints and biomarkers of PF-03

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Starting Dose Selection in Patients

- **Starting dose = 280 mg daily (DeGeorge algorithm)**
  - One-sixth of the highest dose evaluated in dogs that did not cause severe, irreversible toxicity.

- **Starting dose = 50 mg BID (Using data from Study 1001)**
  - Exceeding the predicted efficacious drug concentration of 83 ng/mL for at least 50% of the dosing interval.
  - Below the lowest observed AUC from 0 to 24 hours and C_{max} at which dose-limiting AEs were observed in HVs

- In Study 1002, MTD = 100 mg BID and MAD = 150 mg BID

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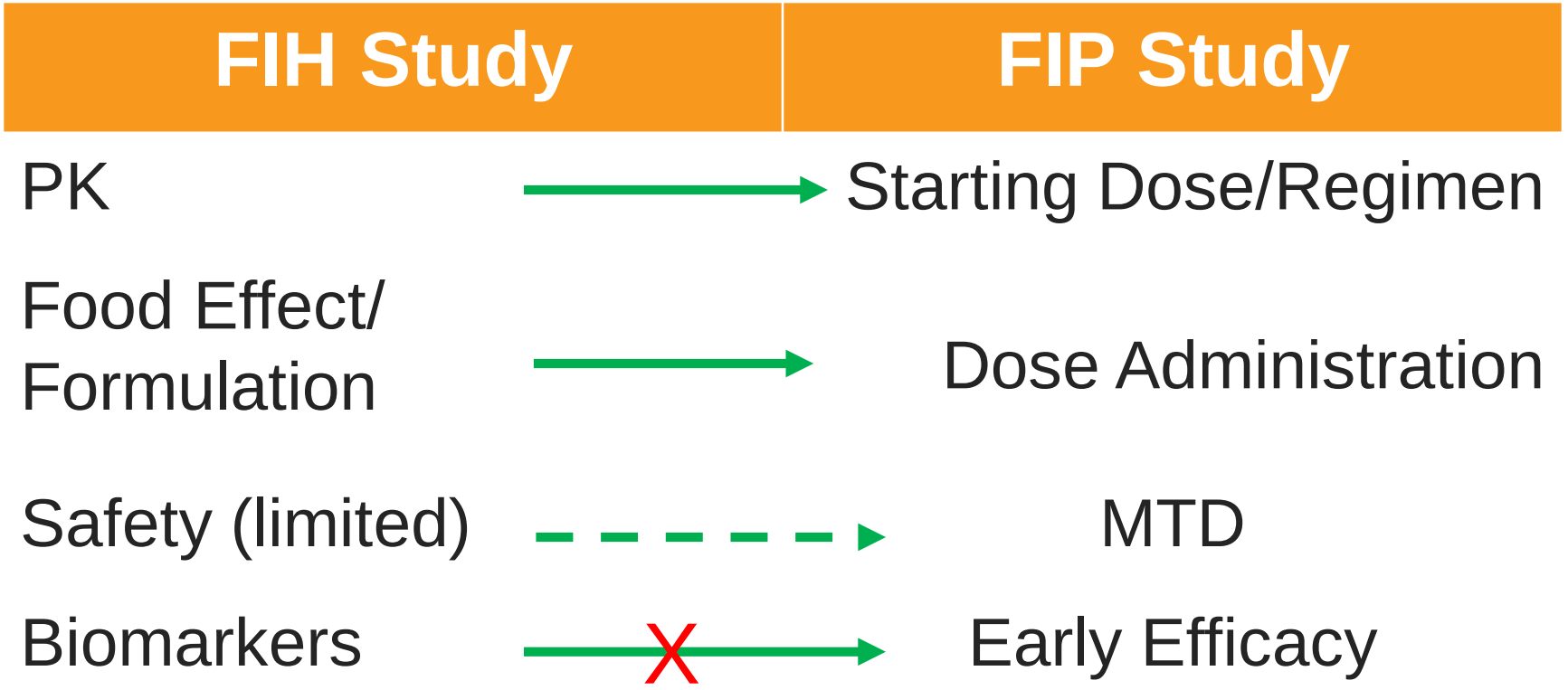
Data from Healthy Volunteer Study to Support Cancer Patient Study



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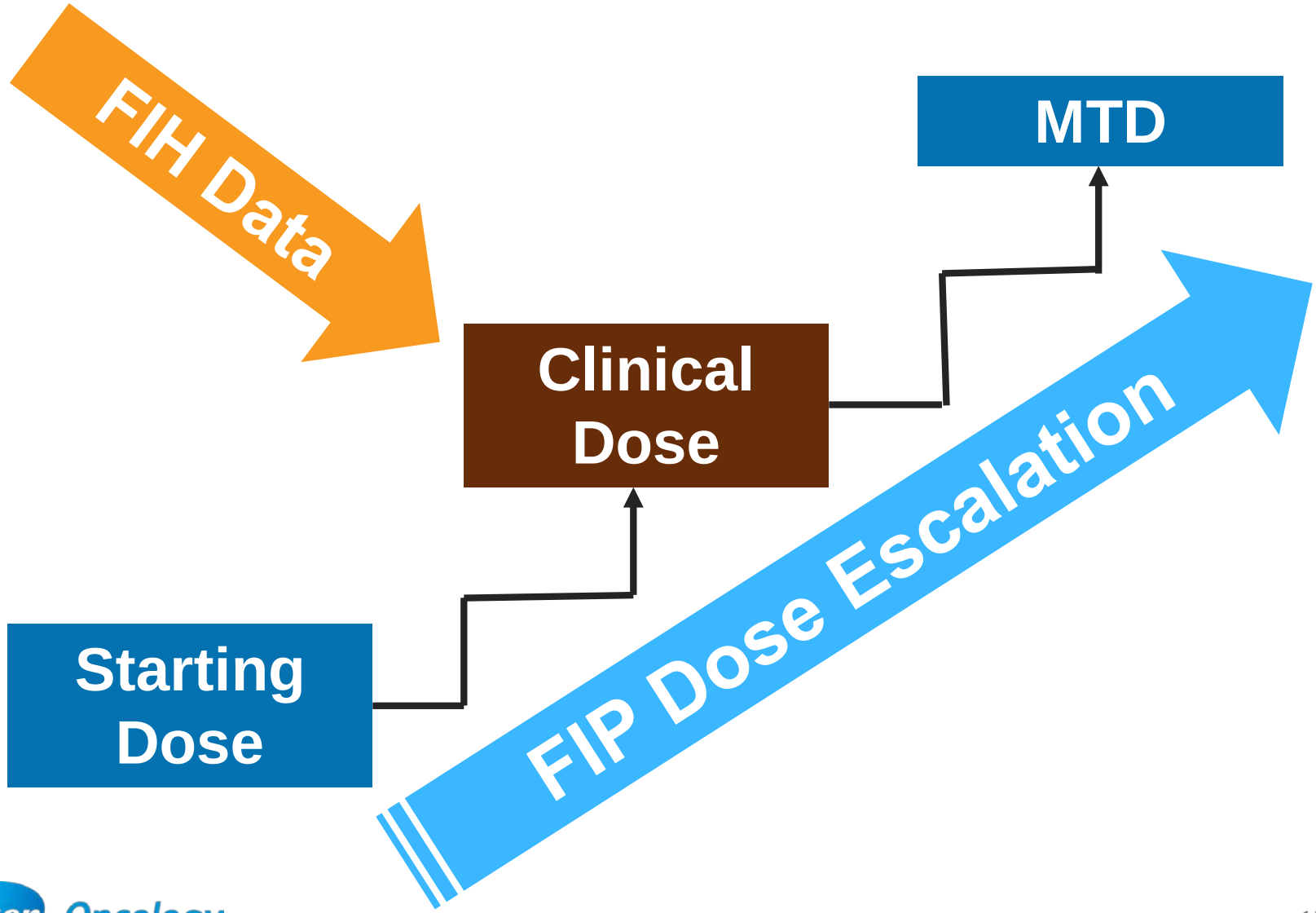
First-in-Human to First-in-Patient



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Thank You!

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