



PHASE 1 DEVELOPMENT ONCOLOGY- INVESTIGATOR'S PERSPECTIVE

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DISCLOSURES



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What is a Phase I Trial?

- Phase I trials can be truly “first-in-humans” of a new molecular entity
 - Can also be of a new drug combined with a “standard” therapy
- Designed to test the safety, side effects, best dose, and formulation method for a drug
- Normally, a small group of 2–100 healthy volunteers recruited
- Usually conducted in a clinical trial clinic, where the subject can be observed by full-time staff
- In the non-oncology setting, these clinical trial clinics are often run by contract research organizations (CROs) on behalf of industrial or other sponsors
- The subject who receives the drug is usually observed to assess safety, pharmacokinetics (how the body eliminates the drug), sometimes pharmacodynamics (what the drug does to the body or body component)
- Phase I trials normally study escalating doses to assure a dose with likely value in treating a disease
 - Usually not proceed to a dose at which the compound is poisonous to administer; usually a fraction of the dose causing harm in animals
- Non – oncology Phase I trials most often include healthy volunteers.

Adapted from Wikipedia, October 8, 2018

How are oncology Phase I trials different?

- Since cancer treatments (also true for other life-threatening conditions e.g., historically HIV) have toxic side effects or are used at doses likely to cause adverse events in healthy individuals, clinical patients are generally subjects of oncology phase I studies
- These studies are usually conducted in specialized units, potentially in-patient where participants receive 24-hour medical attention and oversight.
- Phase I oncology subjects have co-morbidities from the cancer or prior treatments for cancer; therefore distinguishing effects of the drug from the disease or its prior treatment can be challenging
- Phase I oncology subjects have typically already tried and failed to improve on the existing standard therapies.
- While endpoints are similar to other phase I studies, observing any clinical effects on the cancer is usually a secondary endpoint.

Adapted from Wikipedia, October 8, 2018

Are Oncology Phase I trials “therapeutic research” ?

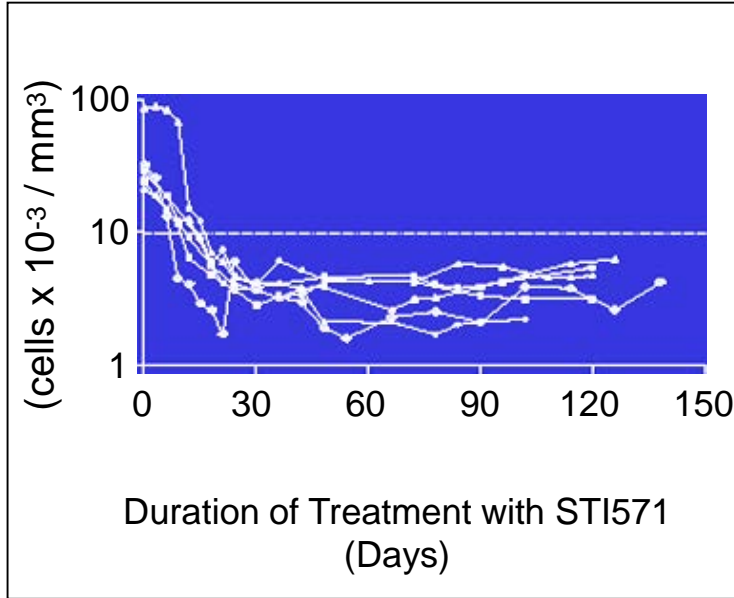
- Historically, not considered “therapeutic”, as endpoint was not “treatment” of a specific disease
- Declaration of Helsinki proposed “a fundamental distinction. . . between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific”
- Important implications for certain sponsors’ coverage of routine clinical costs of phase I trials

EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

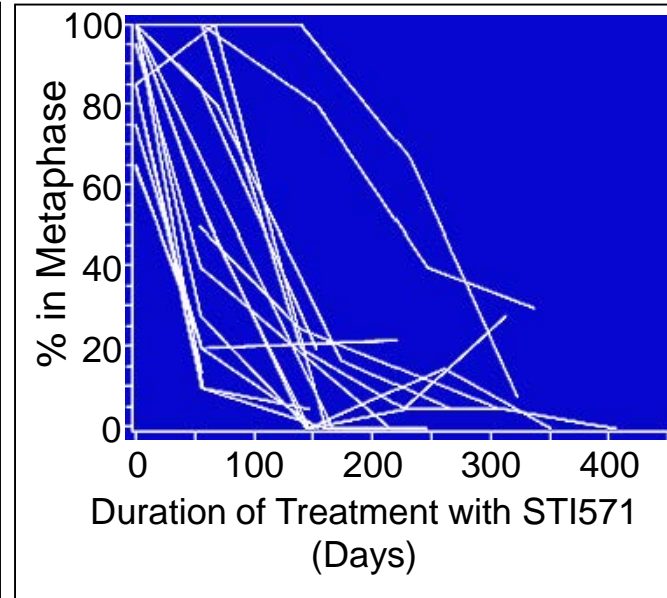


“We conducted a phase 1, dose-escalating trial of STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase. STI571 was administered orally to 83 patients with CML in the chronic phase in whom treatment with interferon alfa had failed”.

White Cell Count



Ph Chromosome + Cells





Critique of the prior example

- Imatinib specifically developed as a bcr – abl inhibitor, with abundant evidence of pathogenic basis for CML
- BUT Horstmann et al analyzed 460 trials involving 11,935 participants from NCI sponsored non-pediatric Phase I studies conducted from 1991-2002, all of whom were assessed for toxicity and 10,402 of whom were assessed for a response to therapy
- The overall response (CR+PR) was 10.6 percent
- “Classic” phase 1 of single agent chemotherapeutic (20% of trials) had a response rate of 4.4 percent
- Studies that included at least one anticancer agent approved by the Food and Drug Administration constituted 46.3 percent of the trials and had a response rate of 17.8%
- An additional 34.1 percent of participants had stable disease or a less-than partial response
- The overall rate of death due to toxic events was 0.49 percent
- Of 3465 participants for whom data on patient-specific grade 4 toxic events were available, 14.3 had at least one episode of grade 4 toxic events

Horstmann et al. N Engl J Med 352:895, 2005

CFR 21 312.21 Rev April 1, 2018

- “Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, ***and, if possible,*** to gain early evidence on effectiveness”.

Patient decision making in entering Phase I oncology trials

- In a series of 163 patients considering entry into phase I oncology clinical trials
 - 88% were white, 96% had health insurance, and 51% were college
 - 81% were aware of hospice, but only 6% had seriously considered hospice for themselves; 84% were aware of palliative care and 10% seriously;
 - 7% considered getting no treatment at all. Overall, 75% reported moderate or a lot of pressure to participate in the phase I study because their cancer was growing
- 7% reported such pressure from the study investigators 9% felt pressure from their families
- For 63% of patients, the most important information for decision making was that the phase I drug killed cancer cells; only 12% reported that the adverse effects of the drug(s) was the most useful information.
- More than 90% of patients said they would still participate in the study even if the experimental drug caused serious adverse effects, including a 10% chance of dying.
- Conclusion: Patients main goal is to fight their cancer, and almost no adverse effect, including death, would dissuade them from enrolling.

Agrawal et al, J Clin Oncol 24:4479, 2006

But do patients really understand phase I trial goals / limitations?

- Of 118 advanced cancer patients consented for phase I trials, only 45 % recalled physician disclosure of Phase I purpose after 10 days
- Neuro-cognitive testing better in patients with correct recall
- Elderly patients performed less well
- Raise question of whether more detailed cognitive testing should precede phase I consent process

Hlubocky et al J Clin Oncol 36: 2483, 2018

Design of oncology phase I trials: Objectives-I

- If toxicity expected from the drug based on activity in animal models, Phase I usually designed as a dose escalation study to define the maximum tolerable dose (MTD), which may or may not equal the recommended phase II dose (RP2D).
- MTD has an “acceptable” occurrence of expected dose limiting toxicity (DLT)
 - Toxicities observed within 29 days of initial dose of drug graded according to a defined set of criteria, e.g. NCI-CTC, WHO, etc.

Dose Escalation Designs

- Classic
 - Dose Limiting Toxicity(DLT) = Toxicity actually or potentially life-limiting conventionally \geq grade 3 non-hematologic toxicity; \geq Grade 2 CNS toxicity; can be higher Grade heme toxicity
 - If 2 of 3 patients at a dose level show DLT, 90% confidence that the true probability of DLT is $>20\%$.
 - If 0 of 3 patients show DLT 90% confidence that the true probability of DLT is $<55\%$

TABLE 21.1. Dose escalation rules for the standard phase I trial

<i>Outcome:</i> No. DLT Among No. Patients	<i>Action:</i> Escalate, suspend, or halt dose escalation
0 DLT among 3 patients	Escalate dose for next cohort of 3 patients
1 DLT among 3 patients	Treat next cohort of 3 patients at the same dose
>1 DLT among 3 patients	Halt dose escalation: treat total of 6 patients at previous dose to determine MTD ^a
1 DLT among 6 patients	Escalate dose for next cohort of 3 patients
>1 DLT among 6 patients	Halt dose escalation: treat total of 6 patients at previous dose to determine MTD ^a

^a MTD: highest dose for which no more than 1 of the 6 treated patients exhibits dose-limiting toxicity (DLT).

Issues with MTD as phase I endpoint focus-I

- Derive from era when cytotoxic agent anticipated to be use at of just shy of a dose causing toxicity
 - Relevance to targeted agents?
- Anticipate not focusing on a population with a particular disease or in some cases measurable disease
 - Relevance to receptor or antigen directed agents?

Issues with MTD as phase I endpoint focus-II

- “..The fundamental conflict in Phase I trials is between escalating too fast to expose patients to excessive toxicity and escalating too slow so as to deny patients the opportunity to be treated at potentially efficacious dose levels”

Collins et al. Cancer Treat Repts 70: 73, 1986

Dose Escalation Schedule, Classic MTD Phase I

- Decrease in Fibonacci dose level increments (100%, 67%, 50%, 40% and 33% subsequent) from a starting dose defined as 1/6 to 1/10 of most sensitive of two animal species MTD.
- Initial algorithms assumed human MTD to be the dose (mg/M²) which caused lethality in 10% of treated mice, but mice alone not adequate as toxicity predictor

Rubinstein LV & Simon RM Phase I Clinical Trial Design in Budman DR, Calvert AH, Rowinsky EK Handbook of Anti Cancer Drug Development Lippincott Williams & Wilkins Philadelphia 2003 pp 297-308

Example of “Classic” Phase I: 24 hr Paclitaxel



Table 2. Patient Characteristics (N = 26)

Male/female	11/15
Median age (range)	55 (21-83)
Median performance status (range)	1 (0-2)
Primary tumor type	
Melanoma	12
Renal cell	5
Adenocarcinoma of colon	3
Adenocarcinoma of lung	1
Ovarian	1
Squamous cell of nasopharynx	2
Neurofibrosarcoma	1
Adenocarcinoma of unknown primary	1
Prior treatment*	
None	2
Surgery only	7
Radiotherapy	8
Chemotherapy	13
1-2 Regimens	11
> 2 Regimens	2
Hormonal therapy	2
Immunotherapy	2

*Some patients are included in more than one category.

Table 3. Dose Escalation Schedule

Dose (mg/m ²)	No. of Patients	No. of Courses
125*	1	3
150	5	9
190*	1	1
200	6	22
250	10	21
275	5	10

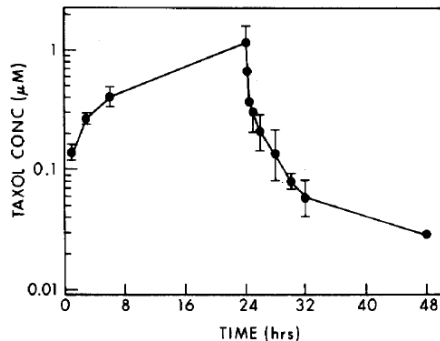
*Patient initially entered and treated at 250 mg/m², then at 190 mg/m². Dose reduced again by 25% because of peripheral neuropathy.

Table 4. Toxicity

Symptom	Dose (mg/m ²)*			
	150	200	250	275
Acute hypersensitivity reaction	0/5	0/6	1/10	0/5
Rash/pruritis/flushing	0/5	2/6	2/10	3/5
Neutropenia	5/5	6/6	9/9	5/5
	Gr 2 (1)		Gr 3 (1)	Gr 3 (1)
	Gr 3 (1)		Gr 4 (8)	Gr 4 (4)
	Gr 4 (3)	Gr 4 (6)		Gr 4 (4)
WBC nadir × 10 ³ /μL median (range)	1.5 (0.8-3.4)	1.6 (0.8-4.7)	2.4 (0.7-3.4)	2.0 (1.1-2.3)
Peripheral neuropathy	0/5	3/6	4/10	4/5
		Gr 1 (3)	Gr 1 (1)	Gr 1 (1)
			Gr 2 (2)	Gr 2 (3)
			Gr 3 (1)	

Abbreviation: Gr, grade.

*Number in parentheses indicates number of patients.



-Identify dose without hypersensitivity reactions
 -Emergence of neuropathy as DLT

Wiernik et al J Clin Oncol 5: 1232, 1987

Design of oncology phase I trials: Objectives-II

- If drug NOT expected to be toxic in the dose range associated with activity in preclinical models; dose escalation to MTD not usually appropriate. Approaches taken:
 - Pharmacokinetic: assume effective steady state concentration or AUC (C x T curve) estimable from preclinical studies (problem: need good assay with acceptable coefficient of variation)
 - Minimum Biologically Active Dose: in surrogate or tumor tissue (problem: need good assay of pharmacodynamics effect)

Rubinstein LV & Simon RM Phase I Clinical Trial Design in Budman DR, Calvert AH, Rowinsky EK Handbook of Anti Cancer Drug Development Lippincott Williams & Wilkins Philadelphia 2003 pp 297-308



Conundrum: Suppose you really don't know toxicity likelihood?

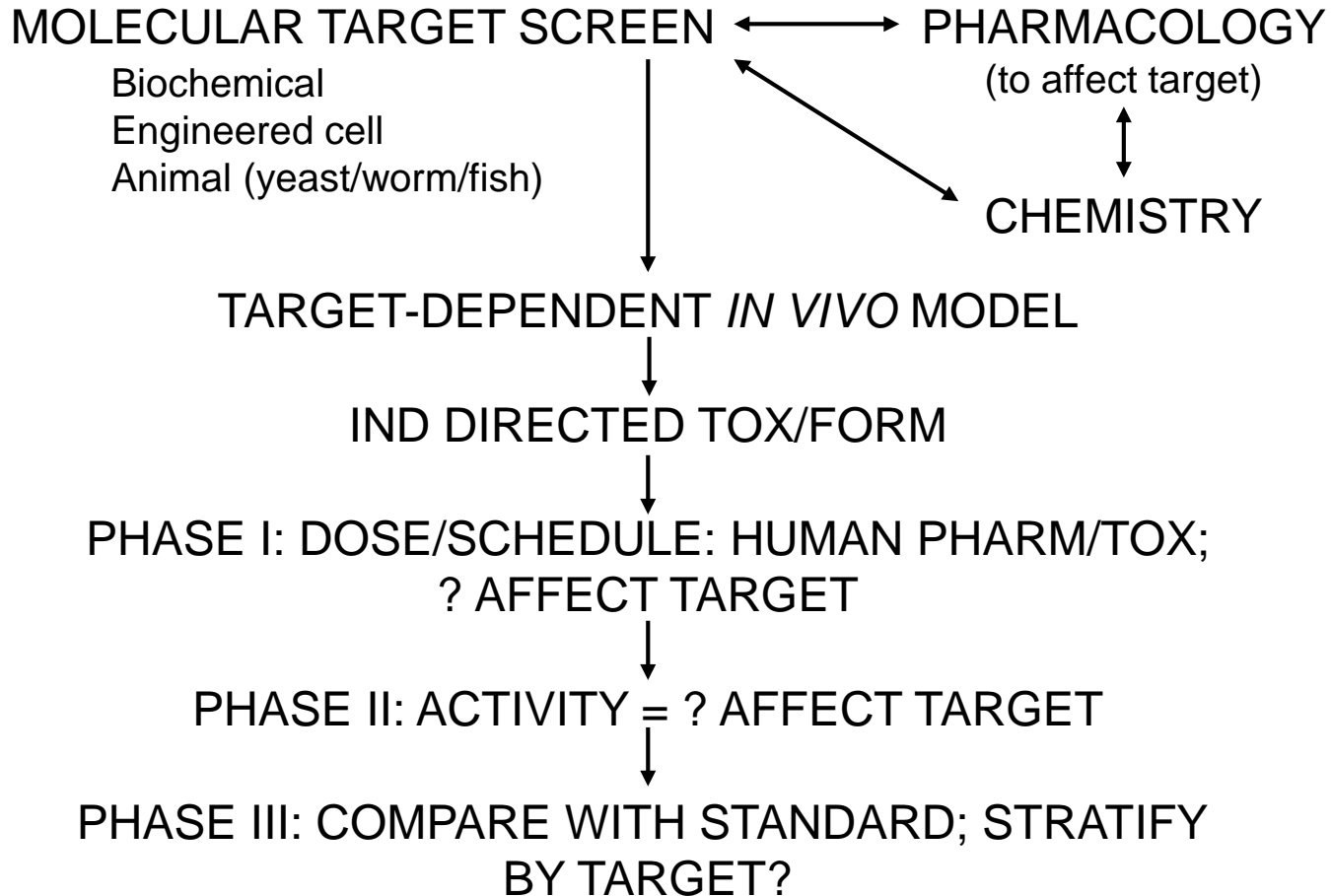
- Hybrid approach: Dose escalation with attention to toxicity
- Pharmacology information in real time with declaration of endpoints in relation to tolerability in expansion cohorts
- Recent example: Pembrolizumab / KEYNOTE-001 (Kang et al., Ann Oncol 28:1388, 2017)

PROBLEMS WITH “MTD” DRIVEN ENDPOINTS

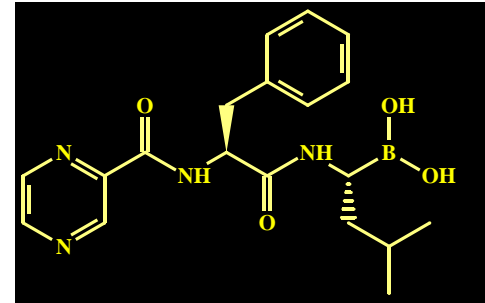
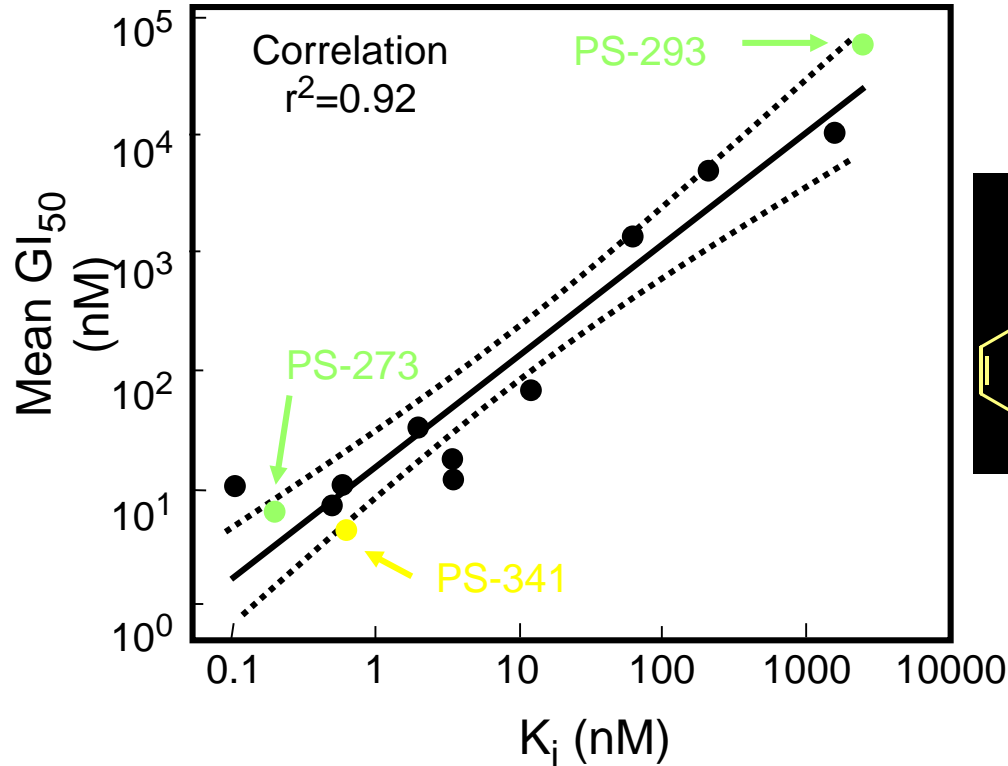


- Drugs regulating pathways important in oncogenesis are effective by combining with high affinity binding sites; therefore must distinguish “targeted” vs “non-targeted” toxicity related to these binding sites
- Whether dosing beyond effect on desired target “buys” therapeutic value not clear
- Therefore must define in pre-clinical studies “*BIOLOGICALLY EFFECTIVE DOSE*” and “*MAXIMUM TOLERATED DOSE*”
- *Use BIOLOGIC rather than TOXIC endpoints in Phase I?*

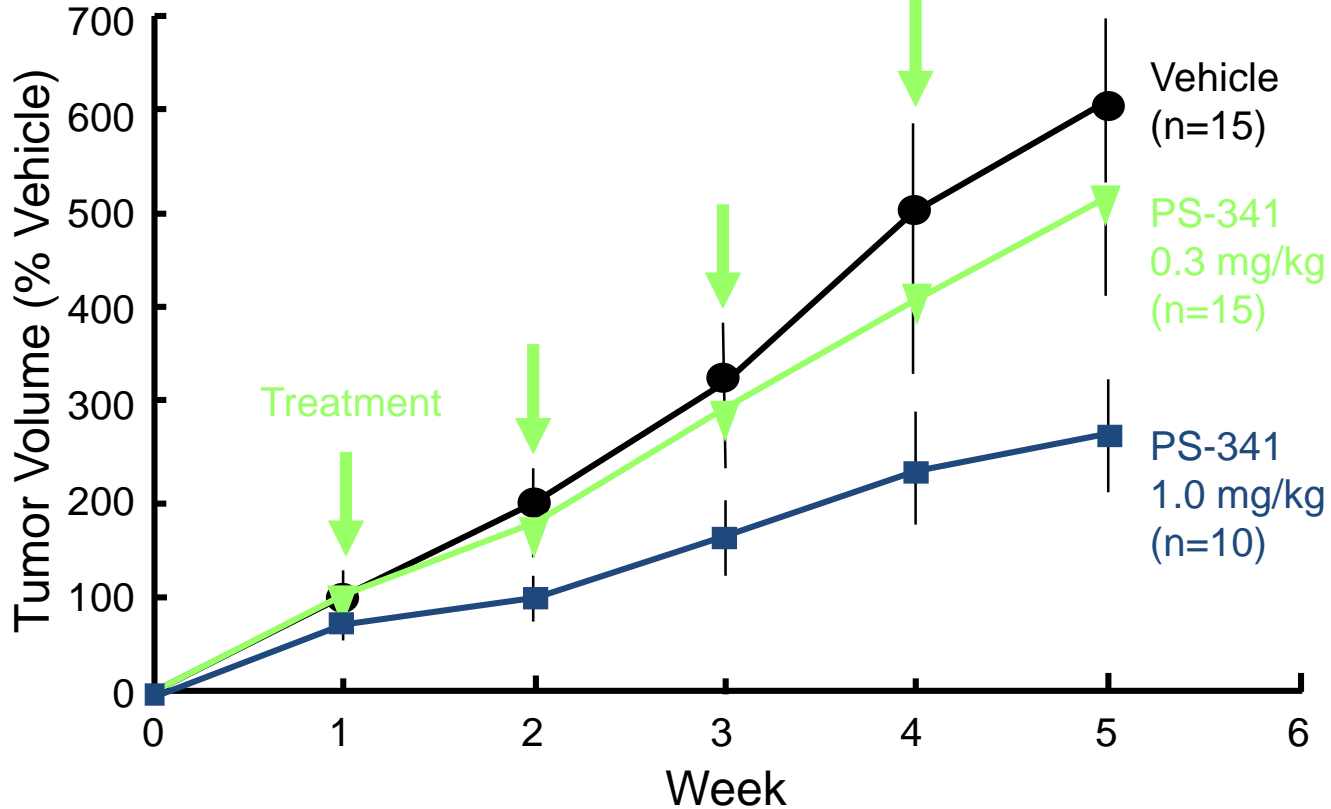
“RATIONAL” DRUG DISCOVERY



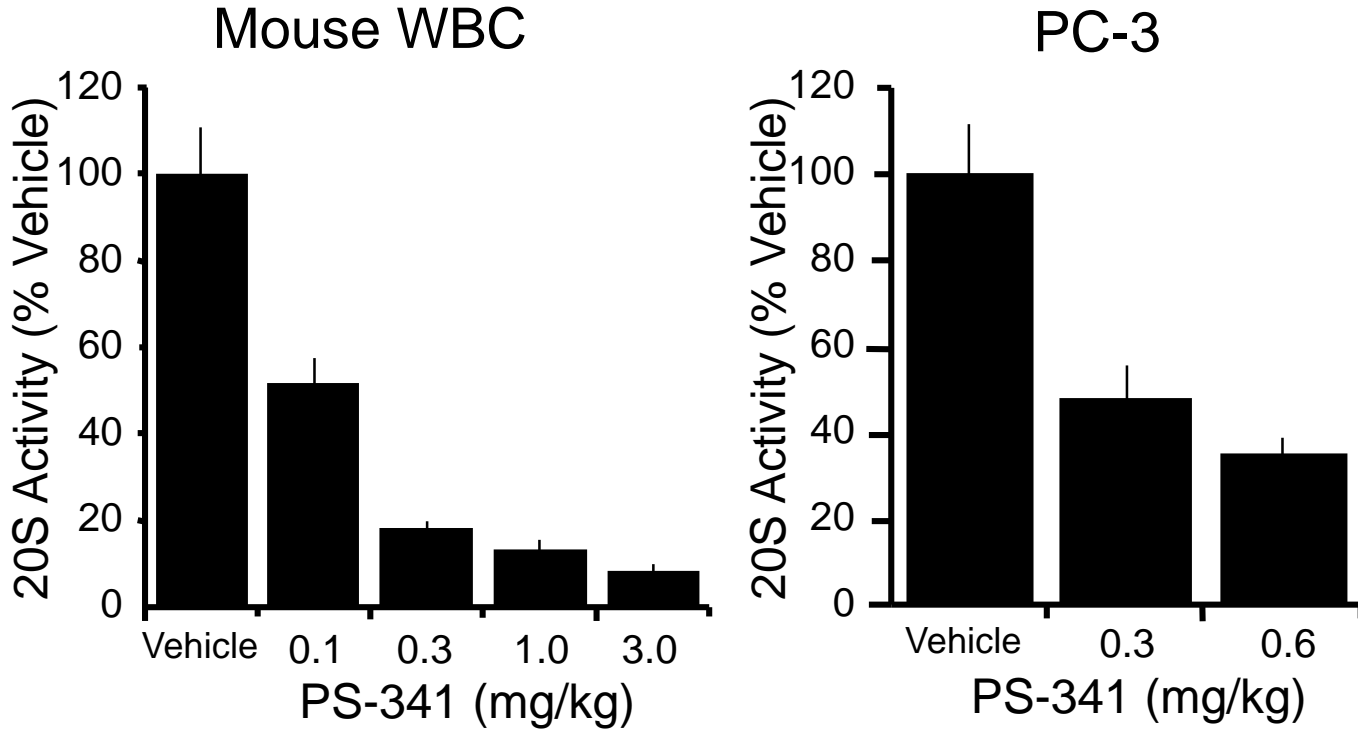
CORRELATION BETWEEN 20S PROTEASOME INHIBITORY POTENCY & GROWTH INHIBITION FOR 13 DIPEPTIDE BORONIC ACIDS



Effect of PS341 on PC3 Tumor growth in mice



EFFECT OF PS-341 ON 20S PROTEASOME ACTIVITY



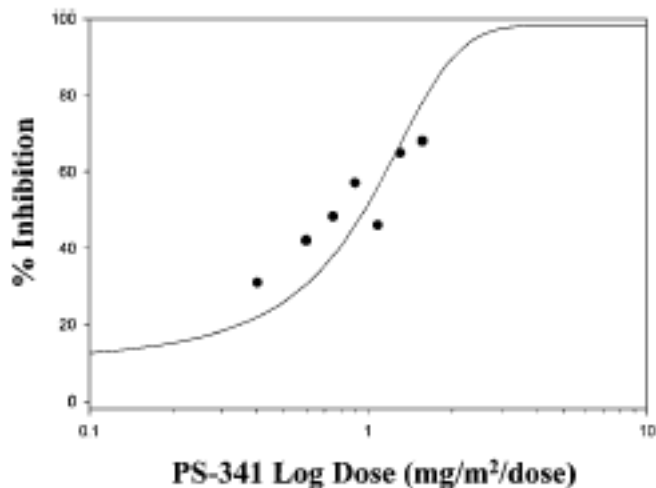
PS-341: INTERSPECIES DOSE RELATIONSHIP

Q: Is the 'safe' dose in animals in the efficacy range for man?

Species	Dose (mg/kg)	Dose (mg/m ²)	% 20S Proteasome Inhibition*
Mouse	1.0	3.0	80
Rat	0.25	1.5	80
NHP	0.067	0.8	70

***In white blood cells at 1.0 h, post-dose**

Bortezomib Phase I in solid tumors



- DLT = neuropathy, diarrhea at 1.56 mg/M2 twice weekly for two weeks of every three
- Associated with ~60% inhibition of proteasome in whole blood lysate

Aghajanian et al Clin Cancer Res 8: 2505, 2002

Alternative Phase I Designs

- Continual Reassessment , Pharmacologically guided, *Accelerated Titration*
 - *Fixed dose increment with 1 patient per cohort if no toxicity > Grade 1 (can have exceptions); If 1 patient have DLT in first course OR 2 patients in a dose level have grade 2, revert to “3+3”*

Simon et al. J Natl Cancer Inst 89:1138, 1997

Phase I study of KRN 5500 using AT

Table 2. Toxicities by KRN5500 dose level

Dose (mg/m ²)	#Patients ^a in cohort	#Cycles	Grade of toxicity experienced																	
			Nausea/emesis			Diarrhea			Liver				Fatigue			Other ^b				
			1	2	3	1	2	3	2	3	4	5	1	2	3	1	2	3		
0.8	1	1											1					1		
1.12	2	3	1			1								1						
1.56	1	1		1			1													
2.18	4	4	1	3		1	1	1					2					1		
3.00	3	3	1	1									2					1		
4.30	6	9	3	1		1	1	1	1		1		4	1	1			1		
6.00	5	5	1	1	2	2					1		2					2	1	
8.40	6	11	2	4		4			1	2			1	3	1			2	1	1

^aThe number of patients per dose sums to 28 (more than the 23 treated patients) due to intra-patient dose-escalation in 5 patients.

^bOther toxicities included fatigue, weight loss, rash, loss of appetite, and instance of increased creatinine and DVT.

“It is noteworthy that the RP2D of 4.3 mg/M2/d x 5 is 35-fold below the dose level of 150 mg/M2/d x5 with notable activity in the COLO205 xenograft model”

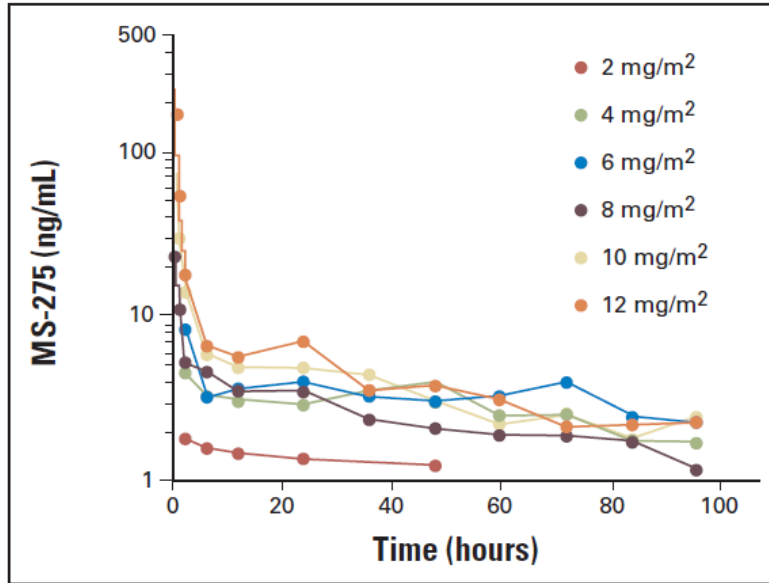
Gadgeel et al. Invest New Drugs 21: 63, 2003

Chronic Issues in Phase I design / implementation

- Humans are not mice
 - Lack of correspondence of human to tolerated mouse pharmacology
- Small numbers of subjects to draw generalizable conclusions about future dose performance
- Medical / past treatment related co-morbidities
- Conclusions about toxicities based on initial treatment (usually 28 day period)
 - How to account for late emerging “cumulative” toxicities
 - Idiosyncratic patient related toxicities (“itis” incidence in checkpoint inhibitor trials)

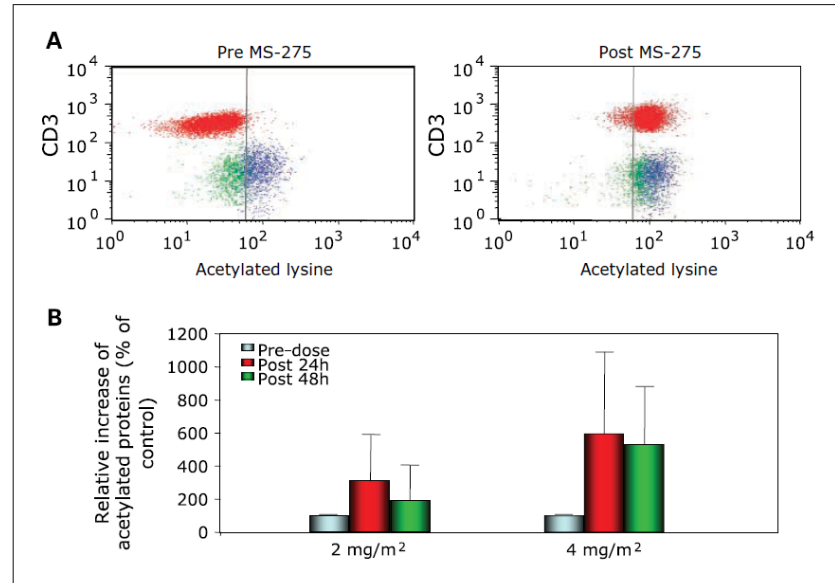
MS-275 have unexpected prolonged half life in humans

PK



Ryan et al. J Clin Oncol 23:3912, 2005

Acetylated lysine in normal T cells



Kummar et al. Clin Cancer Res 13: 5411, 2007

Points to consider in implementing a P1 Oncology Trial

- If multisite, frequent communication between treating physicians
- Patient selection: Patients don't ever "need" a Phase I trial
 - Performance status, co-morbidities in view of expected toxicities, concomitant needed medications and side effects variables to take into account.
 - Specify adverse event/toxicity relatedness to study agent in dose escalation; allow "replacement" patients to avoid confounding issues from being scored as toxicity.
- Phase I trial design should be based on a preclinical model's active schedule and method of administration
 - Human study should ideally be informed by animal model C x t curve data imparting activity and real time PK information

Why do drugs fail in Oncology P1s?

AZD7762 + Gemcitabine

- Unpredictable / new toxicity in humans across dose levels (e.g., AZD7762)
- Discordance between animal and human pharmacology
- Formulation not adequate to achieve needed drug concentrations

Summary of adverse events grade ≥ 3 during cycle 0 (AZD7762 monotherapy) and cycle 1 onwards (AZD7762 + gemcitabine), irrespective of causality

AZD7762 dose (mg)/ gemcitabine dose (mg/m ²)	Cycle 0: AZD7762 monotherapy		Cycle 1: AZD7762 plus gemcitabine ^{b,c}	
	Patients, n (%)	Grade ≥ 3 , term	Patients, n (%)	Grade ≥ 3 , term
6/750 ^a (n = 6)	2 (33)	Decreased appetite INR increased	5 (83)	Anemia (n = 3) Cerebrovascular accident Deep vein thrombosis Device occlusion Endocarditis Hyponatremia Infection Pericardial effusion Thrombocytopenia Neutropenia
6/1,000 ^a (n = 1)	0	–	1 (100)	Neutropenia (n = 2)
6/1,000 (n = 2)	0	–	1 (50)	ALT/AST increased Muscular weakness ALP increased
9/1,000 (n = 3)	0	–	1 (33)	Thrombocytopenia
14/1,000 (n = 6)	0	–	2 (33)	Neutropenia Hyperbilirubinemia Upper GI hemorrhage
21/1,000 (n = 3)	0	–	1 (33)	Atrial thrombosis Febrile neutropenia
30/1,000 (n = 7)	0	–	4 (57)	Neutropenia Hyperglycemia Hypophosphatemia (n = 2) Chest pain Diarrhea
32/1,000 (n = 6)	3 (50)	Hyponatremia Peripheral neuropathy Troponin I increased	3 (50)	Neutropenia Flank pain Nausea Vomiting
40/1,000 (n = 8)	3 (38)	Device-related infection Myocardial ischemia Hyperglycemia	4 (50)	Neutropenia (n = 3) Hyperglycemia Thrombocytopenia Hyperbilirubinemia Blood bilirubin increased Device-related infection Fatigue Leucopenia Small intestine obstruction
Total (n = 42)	7 (17)		22 (52)	

Sausville et al, Cancer Chemotherapy Pharmacology 73:539, 2014



And thanks to:

NCI Developmental Therapeutics Program 1994-2004: (esp J Johnson, J Tomaszewski)

NCI Developmental Therapeutics Program Clinical Trials Unit and Intramural Research Program 1994 – 2004:
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NCI Cancer Therapy Evaluation Program 1994-2004
(especially S Arbuck, L Grochow, M Christian)

University of Maryland Greenebaum Comprehensive Cancer Center Clinical Research Management Office 2004 – present
(especially M Quinn, J Carter, J Nacario)



