Future for Research in CardioOncology: FDA perspective

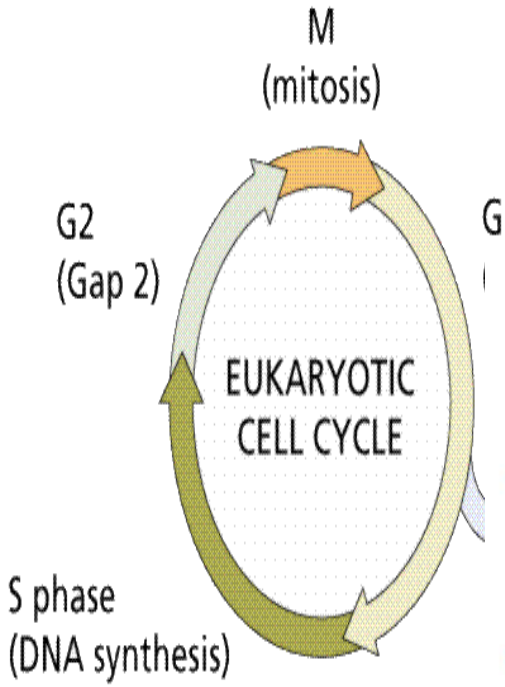
How do we integrate upcoming research into oncology drug development?

Gideon Blumenthal, MD
Medical Officer
Division of Oncology Products 1
Office of Hematology Oncology Products/CDER/FDA

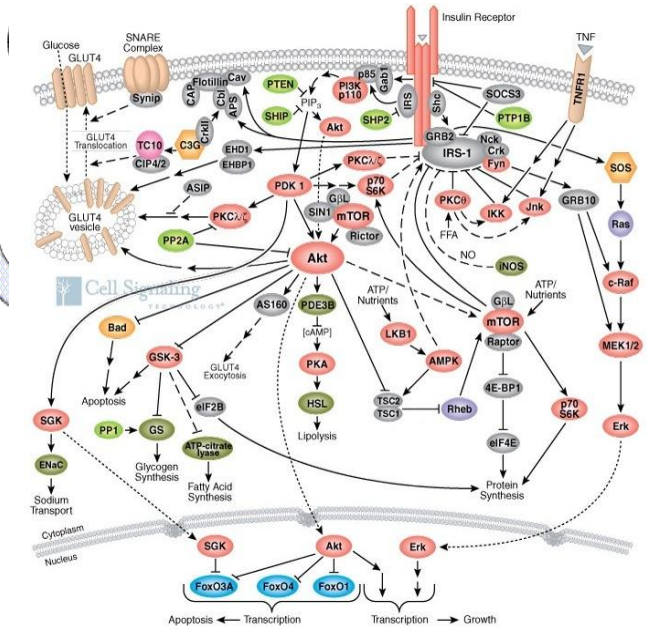
Oncology Drug Development: General Observations

- Greater risk tolerance in treating advanced cancer than other therapeutic areas.
- Pre-clinical/ phase 1-2 toxicity signals in oncology (e.g. prolonged QT, cardiomyopathy) might halt development in other areas.
- Novel molecularly targeted therapies may have unanticipated ‘on’ or ‘off’ target effects.
- Molecularly targeted drugs are likely perturbing pathways critical to cardiac function and survival.
- There are hundreds of molecularly targeted oncology drugs in development, tested in a variety of cancers and combinations.
- Combinations/cocktails of targeted agents will likely increase risk of cardiotoxicity.

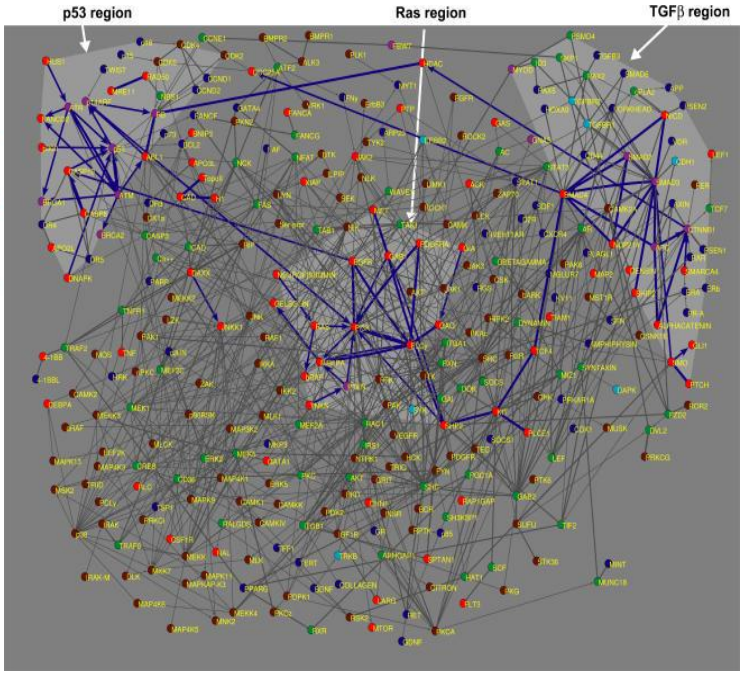
Oncology Drug Development



Then



Now



Cui Q et al Mol Syst Biol 2007

Future?

Tyrosine Kinase Inhibitors approved in U.S.

Drug	Year	Target(s)	Indication(s)	CV toxicity (per label)
Imatinib	2001	ABL,PDGFR (α/β), KIT	CML, GIST, B-ALL, CMML, CEL	CHF, LVEF decline, CM, arrhythmia, cardiac death
Erlotinib	2004	EGFR	NSCLC, pancreatic	MI/ ischemia
Sorafenib	2005	BRAF, VEGFRs, PDGFR (α/β), FLT3, KIT	RCC, HCC	Cardiac ischemia, HTN
Sunitinib	2006	BRAF, VEGFR2, PDGFRβ, csf1R, FLT3, KIT	RCC, GIST, PNET	LVEF decline, QT prolongation, htn
Dasatinib	2006	ABL, PDGFR, KIT, SRC	CML	QT prolongation
Nilotinib	2007	ABL, KIT, PDGFR	CML	QT prolongation
Lapatinib	2007	EGFR, HER2	HER2+ breast cancer	LVEF decline, QT prolongation
Pazopanib	2009	VEGFR, PDGFR, KIT	RCC	QT prolongation, torsades, MI, HTN
Vandetanib	2010	VEGFR, EGFR	Medullary Thyroid	QT prolongation, torsades, sudden death, ischemia, heart failure
Vemurafenib	2011	BRAF	BRAF + Melanoma	QT prolongation, MI, Afib
Crizotinib	2011	ALK, MET	ALK+ NSCLC	QT prolongation

Challenges in assessing cardiotoxicity in early oncology drug development

- Patients with advanced cancer enrolled on early clinical trials are often sick: malnutrition, cachexia, declining performance status, fatigue/asthenia, dyspnea
- Many patients have co-morbid conditions (i.e. htn, tobacco, dm, cad, etc.) and on concomitant supportive medications
- High risk patients are excluded so trial data may not mimic “real world”
- Refractory metastatic patients on drug for short periods of time, may not reflect long-term cardiac risk, risk in earlier settings
- Current methods often detect cardiac toxicity too late
- Paucity of data on proper patient selection, risk mitigation strategies

Oncology Drug Life Cycle from an FDA perspective

Pre-clinical toxicology: histopathology (necropsy), hERG, ECG (non-rodents), KO Mice, tissue cross-reactivity (biologics), troponins

Additional Safety Pharmacology studies (as needed): Purkinje Fibers, ECG telemetry

First in human: Phase 1a in **advanced cancer**: dose escalation, cardiac inclusion/ exclusion criteria; monitoring: vital signs, PhEx, LVEF, ECG, serum biomarkers? (troponins, bnp), dose modification/delay/rechallenge

Phase 1b (combination)

Human QT study

Phase 2a/2b

Phase 3a/3b: DSMB structure; cardiac monitoring: LVEF, ECG, cardiac safety endpoints, stopping rules, long-term f/u

NDA

Phase 4, post-marketing surveillance, novel indications: earlier disease settings, **adjuvant, novel combinations**

Areas of opportunity: Genetic markers of Cardiac Risk

- **Retrospective data** in the literature:
  - Wojnowski *et al* Circulation 2005: genetic variants in doxorubicin transport and NADPH oxidase associated with risk of anthracycline cardiotoxicity in 1,697 patients with NHL.
  - Beauclair *et al* Ann Oncol 2007: Trastuzumab induced toxicity associated with Ile/Val Her2 genotype in 61 patients with advanced breast ca.
- **Feb 2011 Draft Guidance: "Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies"**
  - Identify pts at high risk for adverse drug reaction (ex: abacavir, HLAB*5701 and hypersensitivity)
- Recommend **prospective DNA sample collection** in early and late phase clinical studies

Areas of opportunity: Improved biomarkers

- **Biochemical markers**
  - Troponin
  - Natriuretic peptides
- **ECG**
  - T wave alternans
  - QRS score (myocardial scar); QRS-T angle (abnormal repolarization)
- **Novel Imaging Modalities**
  - Targeted cardiac imaging
  - Cardiac MRI
  - Doppler echocardiography, diastolic measurments
- **CDER Biomarker Qualification**
  - Qualifies a given biomarker within a specific context of use to aid in drug development
  - **October 2010 Draft Guidance: "Qualification Process for Drug Development Tools"**

FDA effort: Develop Knowledge Management database to catalogue key design features and preliminary safety/ PD signals in oncology phase 1a/b trials

	Target	Pre-clinical activity	Pre-clinical Toxicology	Primary Endpoint	Cancer Types	Ph1 Design	Molecularly enriched expansion cohort?	PD assay	DLT/ Significant treatment-related AEs reported	MTD reported
Agent 1	PI3K	Xenograft: breast, GBM, prostate, NSCLC, CRC, melanoma, RCC. Combination data with trastuzumab, MEKi, temozolamide, docetaxel	Hematologic, lymphoid, increased triglycerides, disrupted insulin/glucose homeostasis, diarrhea	Toxicity/ MTD	Solid	Bayesian	Yes- molecular alteration in PI3K and/or PTEN	Surrogate: Skin and blood Tumor: FDG-PET	hyperglycemia, abdominal pain, rash, mood alteration	Yes
Agent 2	PI3K	Xenograft combination with docetaxel NSCLC	GI, hematologic, lymphoid	Toxicity/ MTD	Solid	3+3	N/A	Surrogate: PBMC	Nausea, vomiting, diarrhea	Yes
Agent 3	PI3K	Primary tumor and cell lines hematologic malignancies	Hematologic, GI, liver, lymphoid	Toxicity/ MTD	Heme	3+3	N/A	Surrogate: Chemokines Tumor: pAKT	Pneumonia, AST/ALT	No
Agent 4	PI3K and mTOR	Xenograft: GBM, prostate, breast, NSCLC, CRC including Pik3CA and erbb2 amplified models	Increase in insulin and glucose, GI, bone marrow, testes, lymphoid	Toxicity/ MTD	Solid	Bayesian	Yes- molecular alteration in PI3K and/or PTEN; and/or EGFR	Surrogate: c-peptide Tumor: FDG-PET	fatigue, rash, uveitis	No
Agent 5	PI3K and mTOR	Xenograft: prostate, breast, ovarian, combination with anti-HER2 and with docetaxel	Increase insulin and glucose, Hematologic, GI, lymphoid, testes	Toxicity/ MTD	Solid and Heme	3+3	Yes- molecular alteration in Pi3K	Surrogate: plasma	hyperglycemia	No
Agent 6	PI3K and mTOR	Xenograft: Prostate, breast, GBM, NSCLC, ovarian, including PIK3CA, KRAS, LKB1, and PTEN mutant	Liver, reproductive, cataracts, GI, lymphoid	Toxicity/ MTD	Solid and Heme	3+3	N/A	Surrogate: plasma, insulin, PBMC, hair follicle, skin Tumor: biopsy	anorexia, hypophosphatemia, vomiting, rash, ALT, dyskinesia	Yes

Blumenthal, Charlab Orbach, Zineh, Cortazar, Justice, Pazdur ASCO 2011