Cardiac Toxicity, Risk Management, and Oncology Drug Development

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Is cardiovascular toxicity with cancer therapy a reason to stop development of an effective cancer drug?

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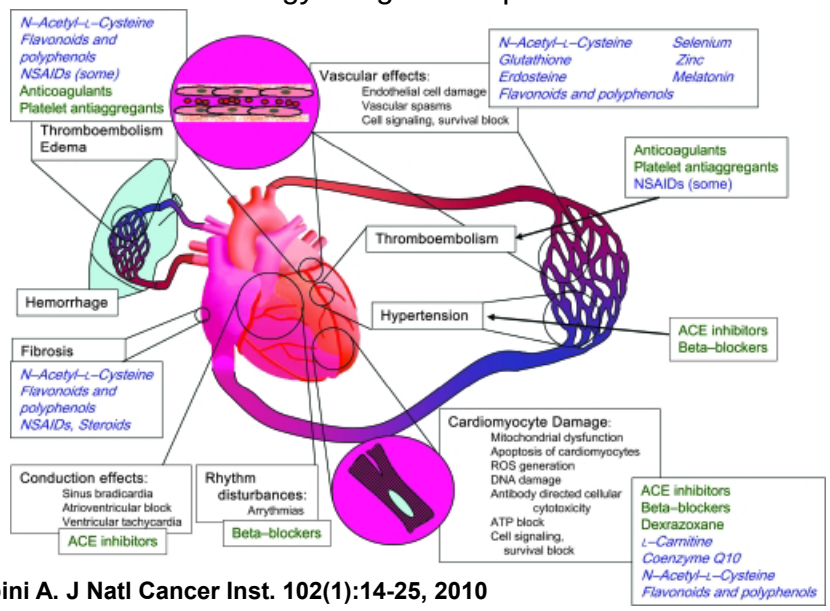
Diverse Mechanisms for Cardiac Safety Issues in Oncology Drug Development



Albini A. J Natl Cancer Inst. 102(1):14-25, 2010

Diverse Cardiac Safety Issues in Oncology Drug Development

QTc Prolongation	Coronary Syndromes	CHF	Hypertension
Arsenic trioxide	5FU; Capecitabine)	Doxorubicin	Cisplatin
Depsipeptide	Bevacizumab	Trastuzumab	Bevacizumab
VDAs	Sorafenib	Lapatinib	Sorafenib
Sunitinib Nilotinib, Dasatinib	VDAs (CA4P, ZD6126, MN-029)	Alemtuzumab	Sunitinib Axitinib
Geldanamycin analogues (17AAG; 17DMAG)			VDAs

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Cardiovacular Safety Issues in Oncology Drug Development

Major Categories

- Vascular; Hyper/Hypotension, Vasospasm; thrombotic effects
- Cardiomyocyte damage
- Conduction abnormalities; Arrhythmias
- Renal or Metabolic effects

Cardiovacular Safety Issues in Oncology Drug Development

Major Categories

- **Vascular; Hyper/Hypotension, Vasospasm; thrombotic effects**

1. Is toxicity a reason to stop development?

2. Can successful Risk Management strategies be developed and employed?

3. Will the patient be toxicity-free if instead treated with current Standard of Care?

Risk Management of Hypertension in the Development of Axitinib

Bedside rules for monitoring & management

- Home BP testing
- For systolic BP >150 mm Hg or diastolic BP >100 mm Hg:
- NO dose reduction or termination from protocol treatment
- New or additional antihypertensive treatment was initiated.
  - For patients on maximum antihypertensive treatment with continued hypertension, the axitinib or placebo dose was reduced one level.
- For systolic BP >160 mm Hg or diastolic BP >105 mm Hg, antihypertensive treatment was adjusted if appropriate
  - Axitinib or placebo dosing was interrupted and resumed at one lower dose level once the BP was < 150/100 mm Hg
- ***Given successful management, starting dose of 5 mg escalated to 10 mg in patients who tolerate***

Kindler H et a ***Lancet Oncol 2011; 12: 256–62***

Axitinib Phase 3 Study in RCC

Frequencies of Hypertension and Discontinuation due to Adverse Event

Phase III Design:
Patients with renal cell cancer randomized to Axitinib or Sorafenib
36.8 % of patients on Axitinib able to escalate dose

Regimen	Gr-3-4 BP	Discontinue due to AE
Sorafenib	**11%**	**8.2%**
Axitinib	**15%**	**3.9%**

Rini B et al, ASCO, 2011

Axitinib Phase 3 Study in RCC

Frequencies of Hypertension and Discontinuation due to Adverse Event

Phase III Design:
Patients with renal cell cancer randomized to Axitinib or Sorafenib
36.8 % of patients on Axitinib able to escalate dose

Regimen	Response Rate	Progression - Free Survival
Sorafenib	**9.4%**	**4.7 months**
Axitinib	**19.9%**	**6.7 months***

*Hazard Ratio 0.665; p < 0.0001

Rini B et al, ASCO, 2011

Axitinib Phase 3 Study in Pancreatic CA

Frequencies of Hypertension with SOC

Phase III Design: Randomized, Double Blind
632 patients with pancreatic cancer randomized to standard Gemcitabine + Placebo or Gemcitabine + Axitinib

Regimen	All Grades	Grades 3-4
Gem + Placebo	**22 (7%)**	**5 (2%)**
Gem + Axitinib	**65 (21%)**	**20 (7%)**

Kindler H et a ***Lancet Oncol 2011; 12: 256–62***

Vascular toxicity associated with common anticancer SOC
5 Fluoro-uracil

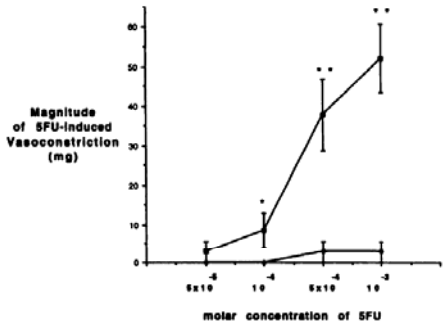


Fig. 3. Dose-response curves indicating the magnitude of vasoconstriction induced by increasing concentrations of 5-FU before (■) and after (◆) exposure to 3×10^{-8} M staurosporine. *, $P < 0.05$; **, $P < 0.001$; statistical significance for differences observed at 10^{-4}, 5×10^{-4}, and 10^{-3} M 5-FU.

Mosseri, Fingert et al Ca Res 53: 3028-3033, 1993

Axitinib-associated hypertension and clinical outcomes

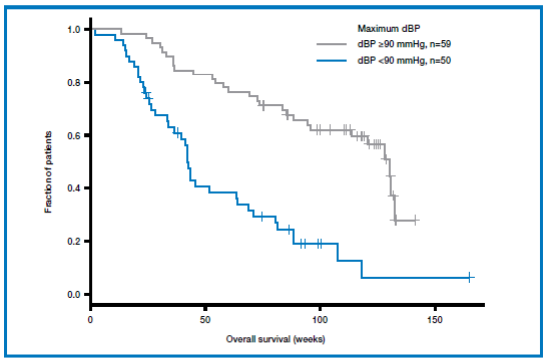
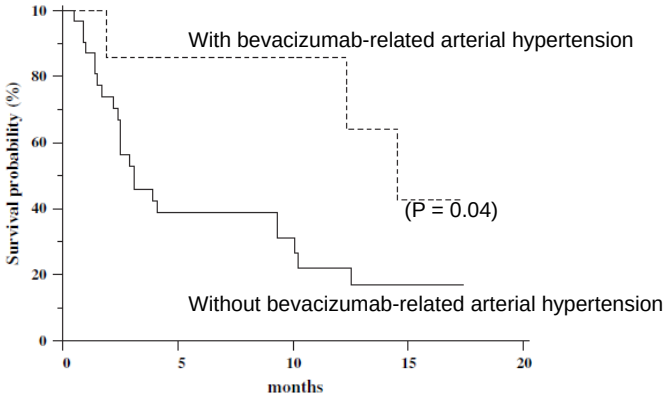


Figure 4. Analysis of overall survival. Patients were grouped into diastolic blood pressure (dBP) ≥90 mmHg or dBP <90 mmHg based on the maximum dBP.

Rixe O et al, ASCO, 2011 Abstract 5045

Bevacizumab-induced hypertension and clinical outcomes in Colon Cancer



Scartozzi M, et al. Ann Oncol 20:227-30, 2009.

Axitinib hypertension & clinical outcomes Lack of relationship to AUC

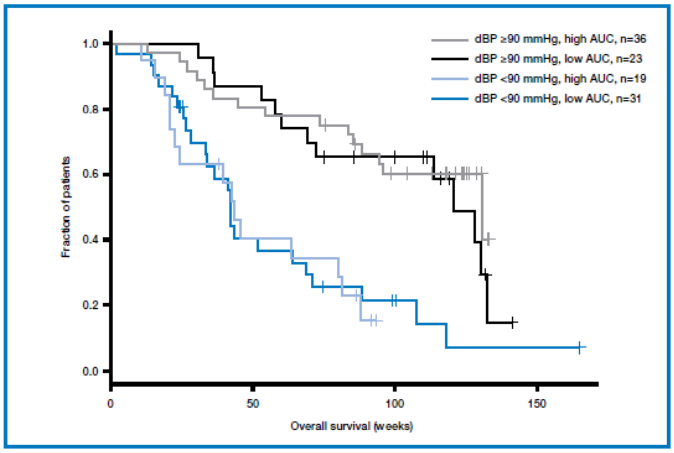


Figure 6. Analysis of overall survival. Patients were classified as being above or below the median steady-state area under the plasma concentration–time curve (AUC_{ss}; end of cycle 1) and having a diastolic blood pressure (dBP) above or below 90 mmHg.

Rixe O et al, ASCO, 2011 Abstract 5045

QTc – Growing Impact on Oncology

Oncology Drug	Impact on Development & Marketing
Romidepsin® (Depsipeptide)	>>$100K vendor costs & major logistic burden for the National Cancer Institute
ZD6474 (AZ)	QTc determines DLT
SR271425 (Sanofi)	QTc determines DLT Dvlpmnt Terminated
Sprycel™ (dasatinib)	Product Label w ECG monitoring and special precautions
Zolinza® (vorinostat)	Product Label w ECG monitoring and special precautions
Tasigna® (nilotinib)	Product Label w Boxed Warning for QTc prolongation & sudden death

Cardiovacular Safety Issues in Oncology Drug Development

Major Categories

Conduction abnormalities;
Arrhythmias

1. Is toxicity a reason to stop development?

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ZD6474 - adding QTc as Phase 1 Substudy

avoiding unintended consequences

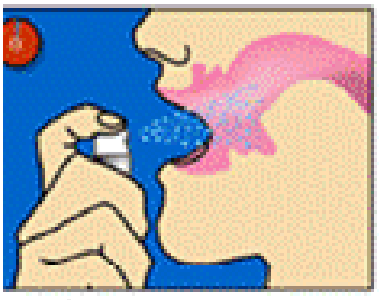
- **Phase 1 adds multiple ECGs without qualified protocol language to manage 'unintended consequences' from these results**
- **QTc prolongation in 4 patients dosed up to 300 mg**
  → *dose reduced 50% in 2 pts who then tolerate wout QTc toxicity*
  - ***These same pts then discontinue protocol due to PD***
- **Exposures predicted sub-therapeutic after same dose reduction**
  - **Doses ≥ 300 mg provide most reliable therapeutic exposures**
- **Nausea, anti-emetics in 15 patients (20%) on study**
  - **No analysis to correlate QTc with nausea**
  - **No consideration of QTc effects from antiemetics, other con meds**

Reference: Holden SN et al, Annals of Oncology, May 19, 2005

Impact of Con Meds on QTc

and spurious findings for experimental anticancer agents

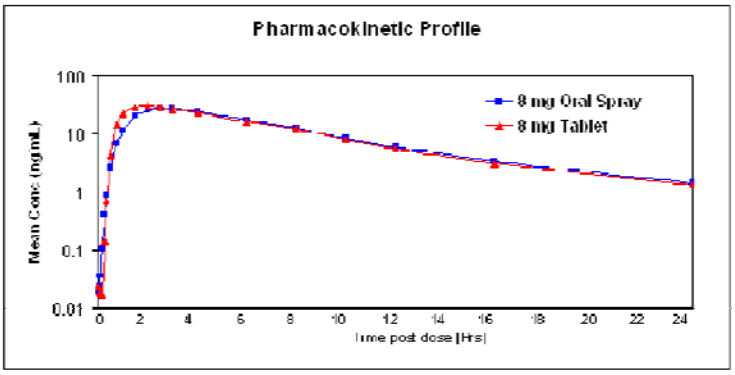
Example:
Ondansetron now
> off-patent
> wider uses likely



Zensana™ (Ondansetron)
Oral Spray – NDA planned

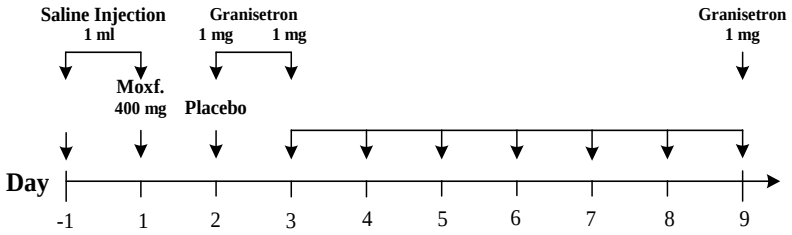
June 23, 2008 H.Fingert 18

Ondansetron PK Profile of 8 mg Zensana (Oral Spray) vs. Tablet



Oncologists use higher doses of conventional ondansetron (e.g. 16-32 mg) in clinical practice

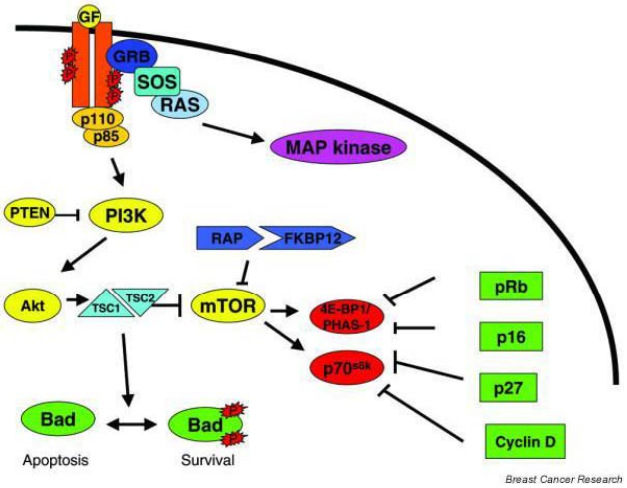
Cardiac Safety Study
Early Development Protocol



- **Goal to characterize QTc after high exposures expected post-approval.**
- ***Similar to* TQT: moxifloxacin; quality ECG & PK conditions, all subjects receive all treatments similar to a crossover**
- ***Different from* TQT: Broader eligibility; 1-day placebo; uniform granisetron; re-dosing & extended treatment; analysis employs mean change and categorical outliers**
- **Opportunities for research about QTc effects of uniform granisetron dose & schedule to prevent nausea**

Roadmaps to Rational Combination Therapies for Breast Cancer

Carraway, et al. Breast Cancer Res. 2004;6(5):219-224.



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Managing CV and Metabolic Risks in Oncology Clinical Development

- MTOR- and PI3K-targeted agents developed by Dr. Josep Tabernero and colleagues at Vall dHebron Hospital, Barcelona & other Hospitals
- Hyperglycemia and -cholesterolemia recognized metabolic toxicities
- Risk management strategies successfully evaluated in early development programs

Reference: Tabernero J et al, J Clin Oncol. 2008 Apr 1;26(10):1603-10

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Novel Combinations and Improved Clinical Outcomes

- MTOR inhibitors show modest single agent activity in women with progressive breast cancer after 1st line hormone treatment.
- Phase 3 'BOLERO-2' Study of Everolimus+Exemestane vs Placebo+Exemestane
- Planned to require 724 pts; stopped early by DSMB
- Significant efficacy advantage at first interim analysis:

Median PFS 11 v 4 months

"…clinical development … will require a change from the current large, randomized trials in unselected patient populations to smaller trials in groups with a molecularly defined tumor type. Combinatorial approaches that act on the secondary mutations and/or compensatory pathways in resistant tumors may markedly improve on the effects of targeted agents used alone.
Ref: Higgins and Baselga, J Clin Invest. 2011 Oct 3;121(10):3797-803.

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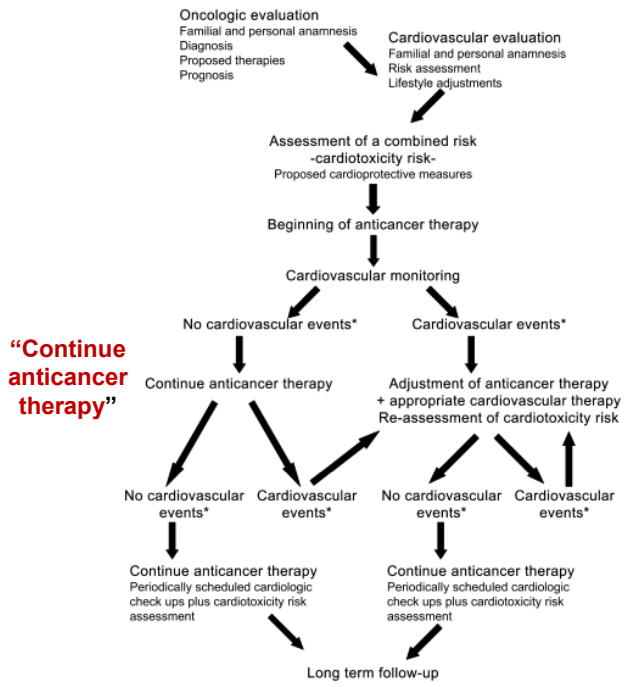

CV risk management within Oncology Drug Development

Reference:
Albini A. J Natl Cancer Inst. 102(1):14-25, 2010

Lessons Emerging about CV Events in Oncology Drug Development

Associations with:

- Control agents used as Standard of Care (SOC)
- Agents targeting new MOA
- Concomitant medications

Why perform cardiac safety–directed research with products designed to treat advanced malignancy?

- **Expanded uses of oncology products**
  - **Different risk-benefit for early or adjuvant settings**
- **Growing combinations, *Novel-Novel* regimens**
  - **Which agent should be adjusted if CV events are identified?**
- **Poly-pharmacy, incl. generic 5HT3 antiemetics, metformin for hyperglycemia**

• Its not simply about NDA approval
• Value of close collaboration with cardiovascular specialists
• Must understand & mitigate risk *appropriately*
…and avoid unintended consequences
• Scientific investigations and validation of safety biomarkers remain an important question in clinical research & practice

Lessons

- More frequent & sensitive monitoring for CV events requires thoughtful protocol designs
  - Engagement of cardiologists/adjudication
  - Avoid unintended consequences
  - Preserve access to treatment & proper dosing
- Be prepared for CV events even with SOC
- Expanding development of novel combinations predicted to further increase possible CV risks
- Safety Risk Management is an alternative to…
  - Premature termination of development programs
  - Premature dose reduction/discontinuation for individual patients

Conclusions

- **Cardiovascular liability is not a "no go" for oncology development, patient benefit, and regulatory approval**
- **Advantages to start in early development**
- **Expanding novel combinations will likely present more challenges about CV safety and risk management**
- **Need to recognize and avoid unintended consequences**
  - **including adverse impact on treatment access, dose modification, development timelines, burden to clinical sites**
  - **Appropriate use of safety markers, e.g. ECGs, troponin, BNP, MUGA, KIM-1, etc.**
- **Opportunities for research, innovation, dialogue:**
  - **Risk Management**
  - **New approaches to clinical/protocol development**
  - **Open dialogue with regulators, sponsors, clinicians, patient advocacy & professional organizations**