
Assessing QT Liability in Oncology Drug Development

1st Worldwide Internet Symposium on Drug-Induced QT Prolongation

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Agenda

- **Drug-induced Torsade de Pointes (TdP)
Impact on drug development and
Regulatory Evolution**
 - QT Prolongation and TdP in oncology
 - Oncology drug development implications
 - Oncology “Nuts and Bolts”
 - Summary
-

Drug-Induced TdP: Implications for Drug Development

- Incidence usually too low to demonstrate with typical approval package of a few thousand patients and healthy volunteers (1:10,000 to 1:1,000,000)
 - In any compound, the developer must weigh risk of compound, of which TdP may be a small part, and potential benefit of compound
 - Risk of a symptomatic treatment for a cold must have an extremely low risk
 - Obviously, drugs that save lives are measured by that benchmark
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Regulatory Timeline: A Decade To Date

Points to Consider



Policy Conference



Joint Health Canada/FDA
Concept Paper

FDA & CHMP

Adopt E14

Health Canada
Adopts E14

1997 1998 1999 2000 2001 2002 2003 2004 2005 2006

FDA Working
Group



Health Canada
Concept Paper



Health
Canada Santé
Canada

ICH issues
S7B
Preclinical
Guidance



Japan Not
Yet Adopted

ICH issues
E14

ICH E14 Implications

- Attempt to assess risk for QT prolongation prior to extensive patient exposure
 - Advocates “Thorough QT/QTc Study” (TQTS) to do this
 - ❑ Early enough in development to minimize risk
 - ❑ Late enough in development to understand metabolism and metabolites
 - ❑ Extrapolate small changes in QTc in healthy volunteers to potential changes in patients
 - Notes potential exceptions like oncology, but provides little guidance
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Oncology Drugs and TdP: Case in Point

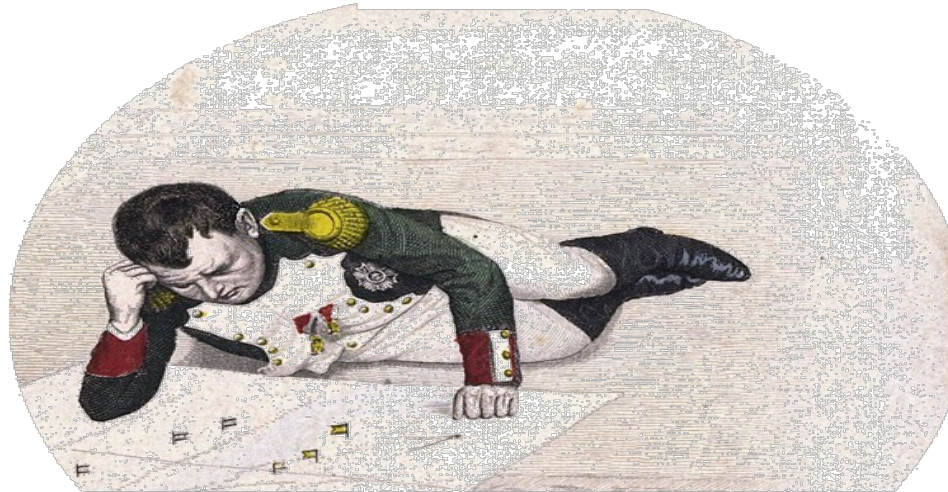
- 52 year-old male whose autopsy ultimately revealed fungating gastric carcinoma presents with nausea, vomiting and diarrhea
 - Treated with multiple medications, some of which worsen gastrointestinal symptoms
 - Although chronically ill, he was alert and awake until he suddenly collapsed and died
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Oncology Drugs and TdP: Case in Point

- “Perfect storm” scenario
 - Multiple medications
 - Arsenic
 - Tartar emetic (contains antimony-associated with TdP)
 - Jesuit bark (contains quinine-prolongs QT)
 - Calomel (contains mercury)
 - Electrolyte imbalances related to vomiting and diarrhea
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Oncology Drugs and TdP: Case in Point

- Napoleon died of arsenic poisoning
 - But was TdP the terminal event?



Arsenic QTc effects

- Review of 1,000 ECGs for 99 patients receiving IV arsenic trioxide
 - Gradual prolongation of QT until steady state
 - Peak effect 47 ms +/- 5 ms at 6 +/- 2 days
 - QT prolongation resolved with discontinuation
- 40% patients with at least 1 QT > 500 ms
- Most TdP with compounded arsenic trioxide

Torsade in Oncology Compounds

- TdP has been associated with following compounds used to treat oncology patients
 - ❑ Arsenic trioxide
 - ❑ Sunitinib*
 - ❑ Depsipeptide
 - ❑ S9275756
 - ❑ LAQ824
 - ❑ Cesium chloride (alternative therapy)
- Prolonged QTc
 - ❑ Anthracyclines
 - ❑ Bolus 5FU/folinic acid

*Mentioned in label but no further documentation found

Molecularly Targeted Oncology Compounds: QT Prolongation

- Histone deacetylase inhibitors
- Multitargeted tyrosine kinase inhibitors
- Farnesyl protein transferase inhibitors
- Vascular disruption agents
- Src/Abl kinase inhibitor
- Protein kinase C inhibitor

Molecularly Targeted Oncology Compounds: QT Prolongation

- Histone deacetylase (HDAC) inhibitors

Drug	Preclinical	Clinical
Depsipeptide	QT/QTc ↑	DR ↑QTc, 6 SCD
LBH589	HERG inhibition	DR ↑QTc
LAQ824	HERG inhibition	DR ↑QTc, 1 TdP

Molecularly Targeted Oncology Compounds: QT Prolongation

- Multi-targeted tyrosine inhibitors

Drug	Preclinical	Clinical
Subitinib malate	HERG inhibition, APD ↑ monkey QTc ↑	Asymptomatic QTc ↑
ZD6474	HERG inhibition	Asymptomatic QTc ↑
ZL647	Unknown	Asymptomatic QTc ↑

Molecularly Targeted Oncology Compounds: QT Prolongation

- Farnesyl protein transferase inhibitors

Drug	Preclinical	Clinical
L-778123	Unknown	Asymptomatic QTc ↑, syncope
Lonafarnib	Unknown	Asymptomatic QTc ↑, syncope

Molecularly Targeted Oncology Compounds: QT Prolongation

Class	Compound	Preclinical	Clinical
Vascular disruption agent	CA4P	HERG, ↑APD	Asymptomatic QTc ↑, syncope
Src/Abl kinase inhibitor	Dasatinib	HERG	Asymptomatic QTc ↑
Protein kinase C inhibitor	Enzastaurin	Unknown	Asymptomatic QTc ↑

ZD6474: Case in Point

- Phase 1 study
 - ❑ Dose limiting toxicity set with ICH E14 criteria Not CTC AE grade
 - ❑ Bazett's correction overestimated QTc change
 - ❑ Dose reduced by 50%
- 7 of 77 patients with QTc prolongation, but only 2 at 300 mg dose
 - ❑ Both patients at 300 mg had dose reduction and withdrew after disease progression
- Dose reduction criteria based upon QT changes and not clinical outcomes
 - ❑ Therapeutic dose subsequently determined to be 300 mg
- “QTc prolongation was also noted in this study, but was not associated with any clinical sequelae, aside from prophylactic interruption or reduction of treatment doses per protocol.”
- “Potential” problem with QTc resulted in subtherapeutic dosing

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The TQTS: Design

- Healthy volunteers
 - ECG safety criteria pertains to this population
 - Normal ECG minimizes variability
 - Randomized, double-blind
 - Placebo/active controlled
 - Active control to demonstrate study sufficiently sensitive to detect QT prolongation of regulatory concern
 - Multiples of therapeutic dose
 - Mimics “worst case” scenario where patient might be on other QT prolonging compounds or metabolic inhibitors
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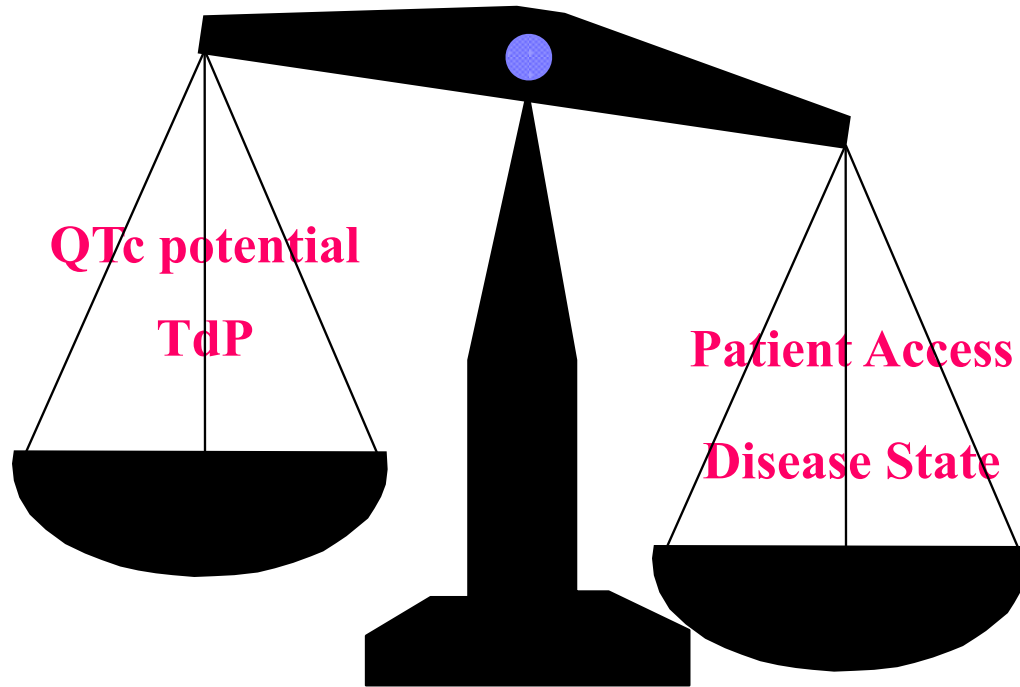
TQTS Not Possible for Many Oncology Compounds

- Compounds too toxic for healthy volunteers
 - Ethical issues
 - Patients expect active treatment
 - Can not delay treatment
 - Toxicity and bone marrow reserve limit supratherapeutic dose
 - Often administered at maximal tolerated dose
 - **Inability to perform a TQTS is not a plan**
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Patients Expect Treatment

- Very high mortality ~100%
- Phase 1 response rate ~1-5%
 - 60% compounds with at least one response
 - >30% with greater than 5% response
 - Dramatic Phase 1 responses do occur
 - Cisplatin for testicular cancer >50%
 - Imatinib mesylate for chronic myeloid leukemia 98%
- Though risk of QT prolongation real, it must be weighed against higher probability of benefit from compound

QTc Risk Benefit in Oncology



QTc Risk Benefit in Oncology

- Disease risk and risk of no treatment does not mean that there is no risk from TdP
- Risk adaptive strategies have been suggested where the extent of the QTc assessment is dependent upon the survival potential
 - QTc prolongation less important when survival in months
 - Further evaluation of QTc prolongation more important when survival in years

QT Impact on Oncology Programs

- Regulatory response to Oncology development still evolving
 - Several approaches have been applied
 - Modified TQTS
 - Sub-studies
 - Labeling
 - Early attempts at complying with E14 have been difficult
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E14 Alternative Proposals

“D. Clinical Development When the “Thorough QT/QTc Study” Cannot Be Performed in Healthy Volunteers (2.4)

There are some drugs that cannot be studied in a “thorough QT/QTc study” in healthy volunteers due to safety or tolerability concerns (e.g., cytotoxic cancer drugs). In such cases, the “thorough QT/QTc study” can often be conducted in patient populations. When this is not possible, the importance of detecting and modifying this safety risk means that other ways of detecting effects on the QT/QTc interval need to be developed. These might include the collection of ECGs at multiple time points under tightly controlled settings that target a broad range of doses early in development.”

Oncology QT obstacles: FDA Statement

- Despite obstacles, FDA requires some QT assessment
- "In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development."

Oncology QT Obstacles

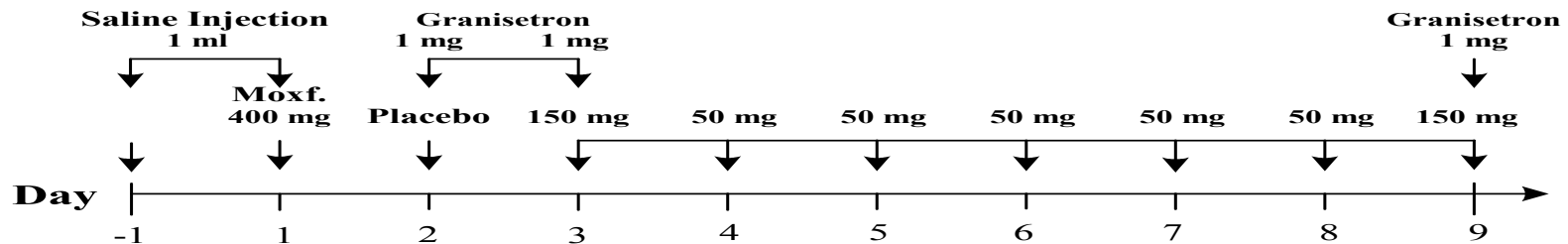
- E14 gives little guidance for “alternative proposals”
 - Oncology patients require special evaluations
 - High incidence of abnormal ECGs
 - High incidence of baseline QT prolongation
 - Studies often have to be done at centers whose expertise is not ECG acquisition
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Alternative Design Schema

- Sequential study
- ?Blind placebo vs active control baseline
- ?Randomize placebo vs active control baseline periods
- Single dose, maximal tolerated
- Placebo baseline on antiemetics that may cause QTc prolongation on their own
- Only a day or two treatment delay
- Analyze exposure/response

Alternative Study Design Schema Example

- Drug with long $t_{1/2}$



- ECG collection must bracket peak effects of study drug, positive control, and antiemetic

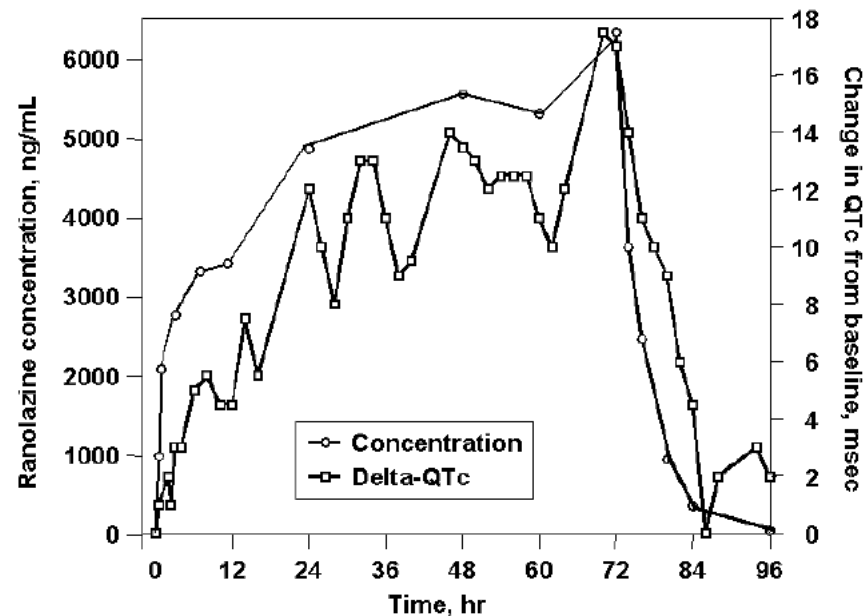
QT Impact on Oncology Programs

Agent	Impact
Depsipeptide	>>\$100K vendor costs & major logistic burden for the National Cancer Institute
ZD6474	QTc determines DLT
SR271425	QTc determines DLT Program terminated
Vorinostat	Product Label advocates ECG monitoring and special precautions
Lapatinib	Product Label includes QTc prolongation, "consider" ECGs, special precautions
AMG 706	> 1500 ECGs in single Phase 1 study

Analyze Exposure Response

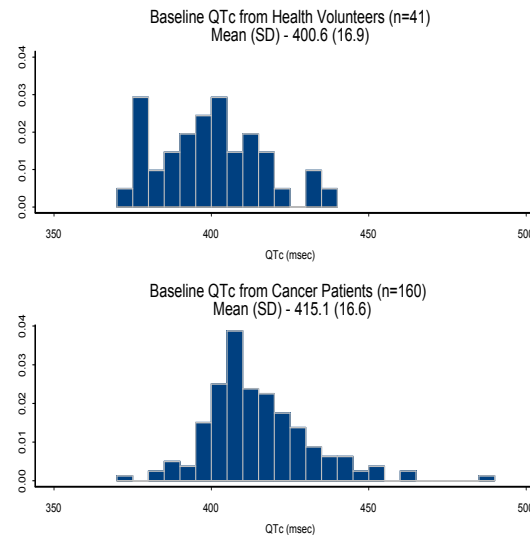
- Provides more information
- Puts individual measurement into perspective

Figure 6-3 Plasma Ranolazine Concentration and QTc Change in Parallel in Study CVT 3111



Other considerations

- No standards on QTc exclusion criteria
 - ❑ QTc longer in oncology patients
 - ❑ Approximately 15% would not meet E14 criteria
 - ❑ Exclusion limits availability of potential life saving therapy



Alternative Eligibility Criteria

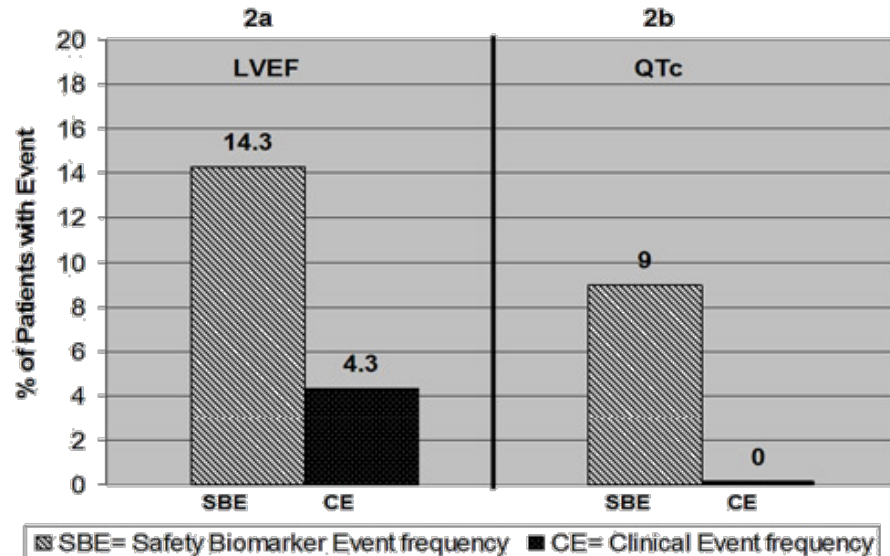
- Alternative eligibility criteria based upon pre-clinical risk assessment

Product's Torsade Risk*	QTc Requirement for eligibility and treatment
<i>Increased</i>	≤ 470 msec so \geq CTC Grade 2 excluded
<i>Standard</i>	≤ 500 msec so \geq CTC Grade 3 excluded

*Based upon pre-clinical findings
Suggested by Fingert

Other considerations

- Dose limiting toxicity should be carefully evaluated
 - QT prolongation not very predictive of risk of clinical event



Alternative approach to Dose Limiting Toxicity

- Use CTCAE criteria levels for QTc as applied to other AEs
- Restart at same dose, rather than reduce dose to what might be an ineffectual dose for life threatening disease

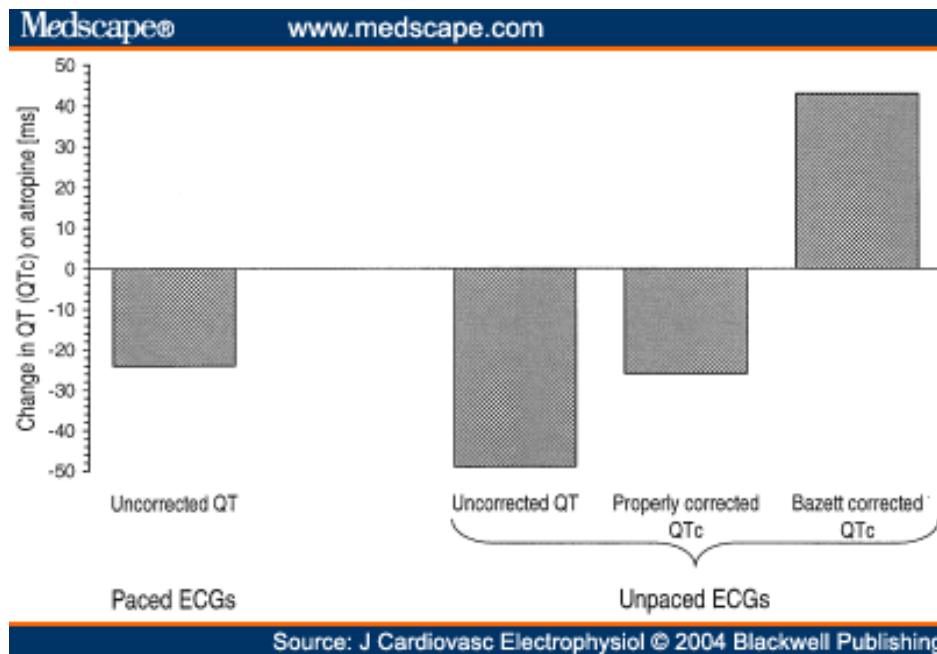
QTc Severity Grade by CTC	Definition
1 = <i>Mild</i>	> 450 to 470 msec
2 = <i>Moderate</i>	> 470 to 500 msec or increase by ≥ 60 msec
3 = <i>Severe</i>*	> 500 msec
4 = <i>Life-threatening</i>*	> 500 with life-threatening signs or symptoms, or torsade

High % Abnormal ECGs Increase QT Variability

- ❑ Variance can preclude <10 ms 95%CI endpoint
 - Abnormal ECG tracings more variable
 - ECG abnormalities exaggerate QT response
 - Comorbid conditions
 - Prior chemotherapy/radiation
 - Malnutrition
 - ❑ Concomitant medications
 - Antiemetics
 - Methadone
 - Antibiotics
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QTc Complicated by Febrile/Anemic Tachycardia

- Bazett's correction inappropriate
 - But often used as primary correction



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Oncology Nuts and Bolts

- Oncology sites not QT-quality
 - ❑ Must understand importance of quality ECG
 - “Clinical ECG” not good enough
 - ❑ Training
 - Onsite
 - Personnel attrition and retrain as needed over extended study duration
 - Appropriate equipment
 - ❑ Oncology sites often with older generation machines
-

Oncology Nuts and Bolts

- Adequate sampling
 - PK
 - Replicates to decrease variability
- Consider Holter technology
 - Easier for site
 - Allows retrospective PK correlation
 - Requires integration into protocol
 - Activity must be restricted just as it would be for a standard ECG
 - Potential electrical interference from cell phones, iPods, chargers

Oncology Nuts and Bolts

- **USE Central ECG laboratory**
 - ❑ QT measurement difficult in abnormal ECG
 - ❑ Central Laboraotry provides standardized
 - ECG machines
 - Communication protocol
 - Measurement approaches
 - ❑ Appropriate heart rate correction
 - ❑ ECG submission to FDA ECG Warehouse

Oncology Nuts and Bolts: Retrospective Paper ECGs

- ECG tracings often “after thought”
 - Manufacturer differences
 - ❑ QT measurement/Heart rate corrections
 - ❑ Generational differences in QT algorithms within single manufacturer
 - Printer fidelity loss/Paper deterioration
 - Limited data
 - If it is all you have, centralize, digitize and measure consistently
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Summary

- Drug-induced TdP is a problem in Oncology
 - Regulatory agencies require a plan to assess
 - Inability to do a TQTS is not a plan
 - Alternative study designs are being explored
 - Oncology drug development presents unique problems due to sites, patients and drugs
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