QTc MONITORING DURING CHEMOTHERAPY: CAN WE REALISTICALLY EXPECT TO LEARN ANYTHING?

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European Institute of Oncology

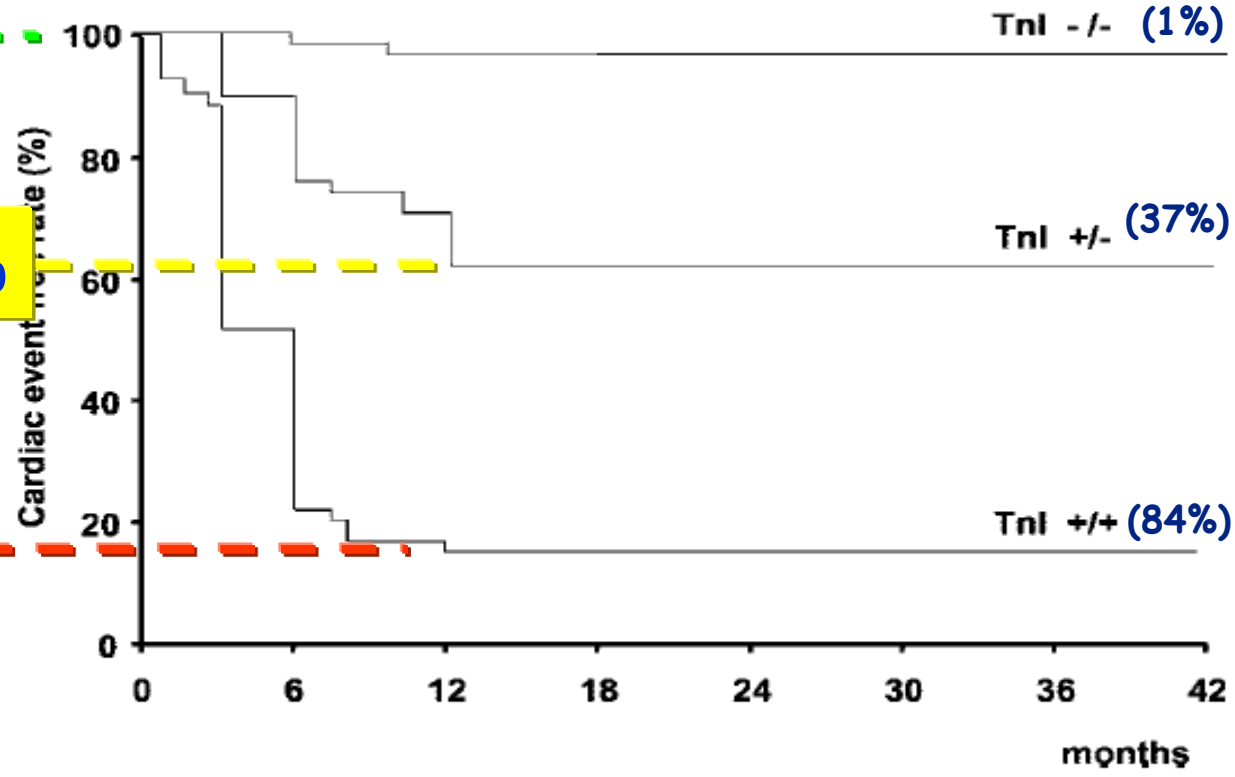
- Admissions 32.000
- Surgical Interventions 15.250
- Chemotherapy courses 22.000
- Radiation Treatment 140.000 + IntraOperative RT 900
- Radiodiagnostic Examinations 15.000
- Nuclear Medicine Examinations 12.000
- Endoscopic Procedures 10.000
- Outpatient visits 113.000
- Hystological Examinations 30.000
- Laboratory Tests 900.000

Pattern of TnI release identifies pts at different risk

Low risk: 70%

Intermediate risk: 21%

High risk: 9%



Positive predictive value = 84%

Negative predictive value = 99%

Circulation 2004

Predictors of cardiotoxicity

Univariate analysis of predictors of cardiotoxicity

Variable	Cardiotoxicity		p Value (Prediction of Cardiotoxicity)	Odds Ratio	95% Confidence Interval
	No (n = 34)	Yes (n = 9)			
Change in the LVEF at 3 months (%)	1.2 ± 9	5.6 ± 8	0.19	5.5	0.45–100
Change in longitudinal strain at 3 months (%)	3 ± 10	15 ± 8	0.01	500	6.7–110,000
Change in radial strain at 3 months (%)	2 ± 23	22 ± 22	0.02	250	4–40,000
Change in NT-proBNP at 3 months (%)	46 ± 240	56 ± 190	0.91	1	0.65–1.4
Elevation hsTnI at 3 months	6 (18%)	6 (67%)	0.006	9	1.8–50

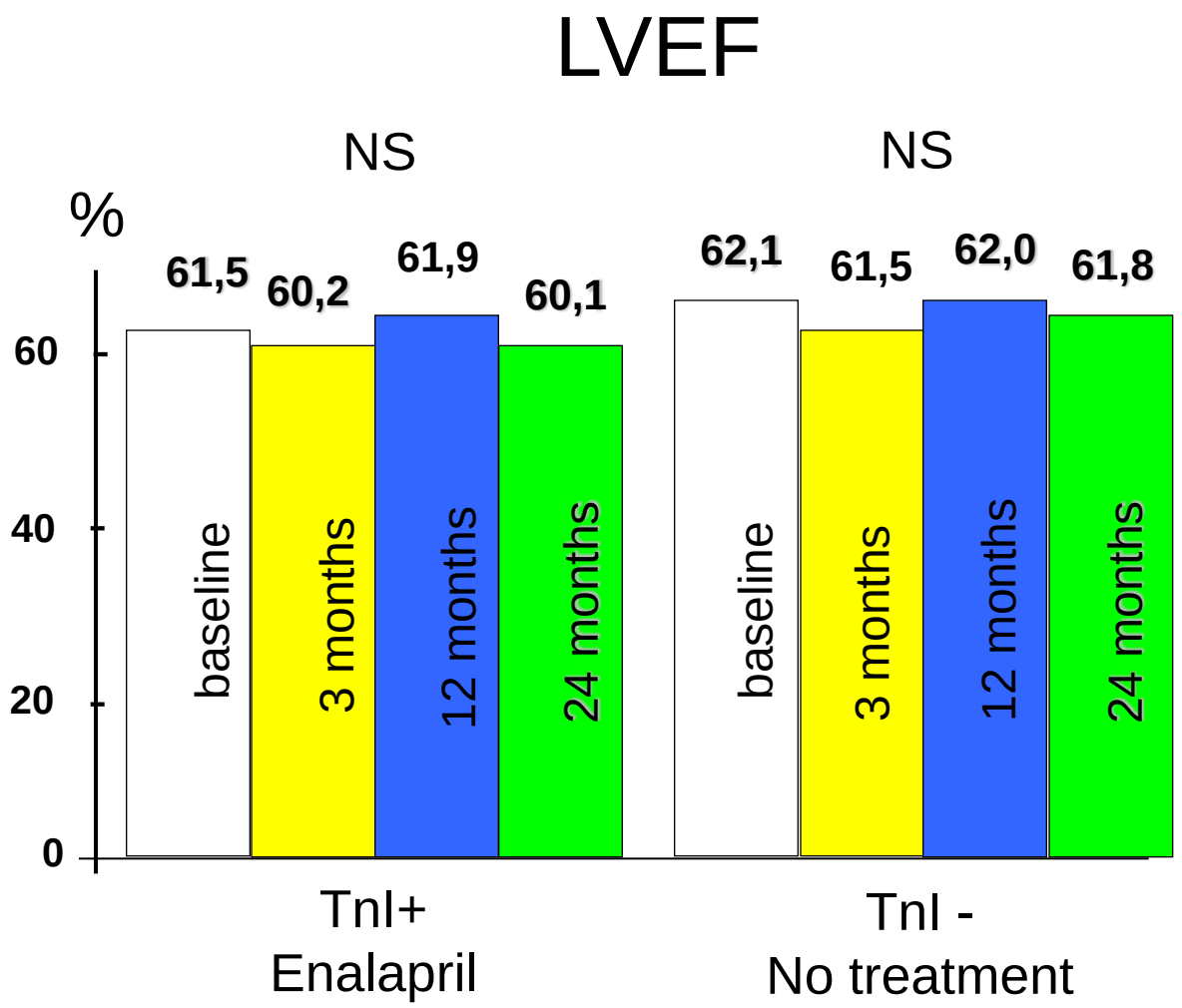
Sensitivity, specificity, and positive and negative value of the predictors of cardiotoxicity

Predictor	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
10% decrease in longitudinal strain	7/9 (78%)	27/34 (79%)	7/14 (50%)	27/29 (93%)
Elevated hsTnI at 3 months	6/9 (67%)	28/34 (82%)	6/12 (50%)	28/31 (90%)
10% decrease in longitudinal strain and elevated hsTnI at 3 months	5/9 (55%)	33/34 (97%)	5/6 (83%)	33/37 (89%)
10% decrease in longitudinal strain or elevated hsTnI at 3 months	8/9 (89%)	22/34 (65%)	8/20 (40%)	22/23 (97%)

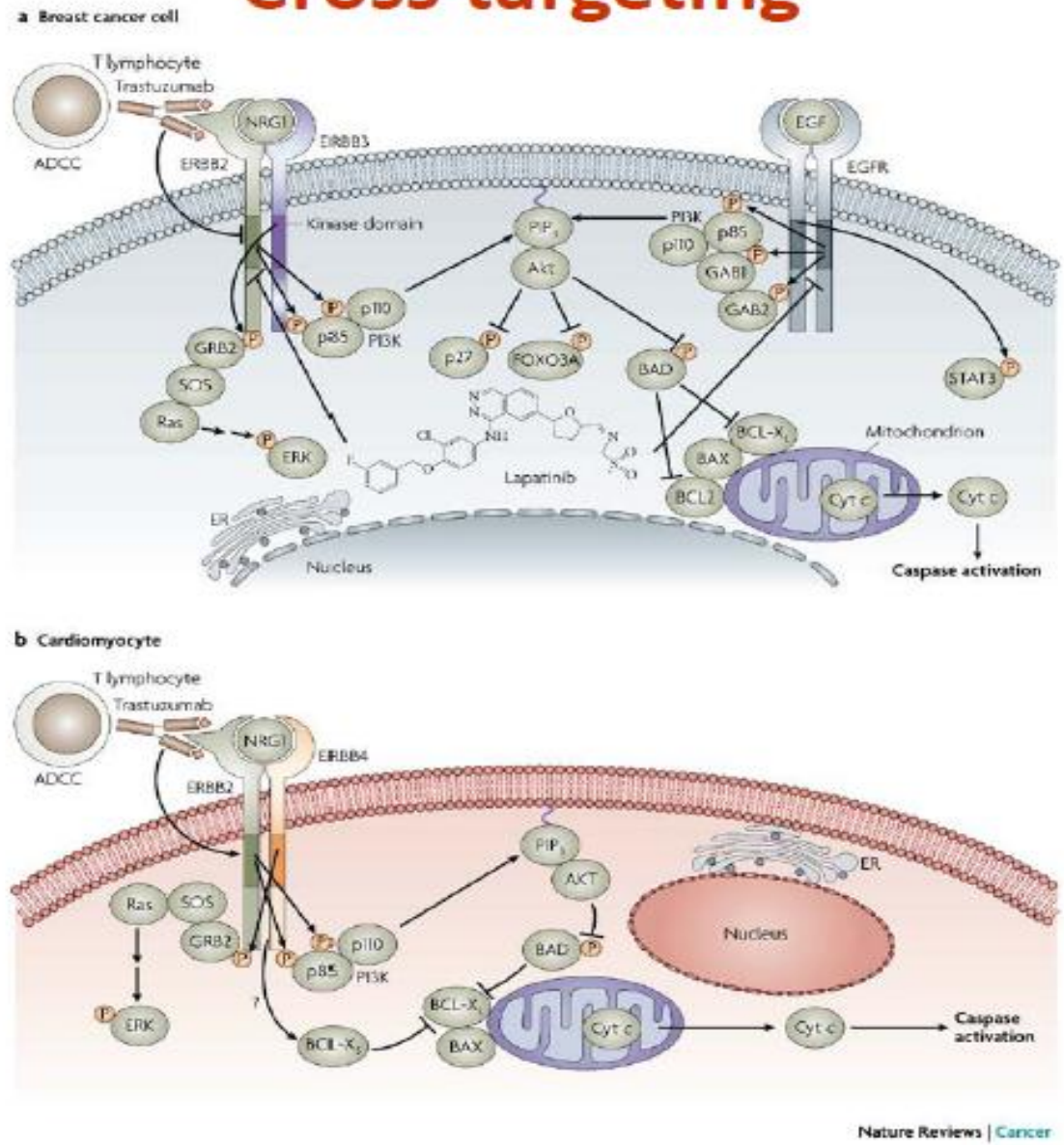
Sawaya et al. Am J Cardiol 2011

Our real world experience

- **1147 post-study pts**
- **Different kind of tumors**
- **Different oncologic treatments**
- **TnI before and after every CT cycle**
- **TnI + = n. 172 (15%)**
- **Enalapril in TNI+ pts**
- **Serial LVEF measurements**

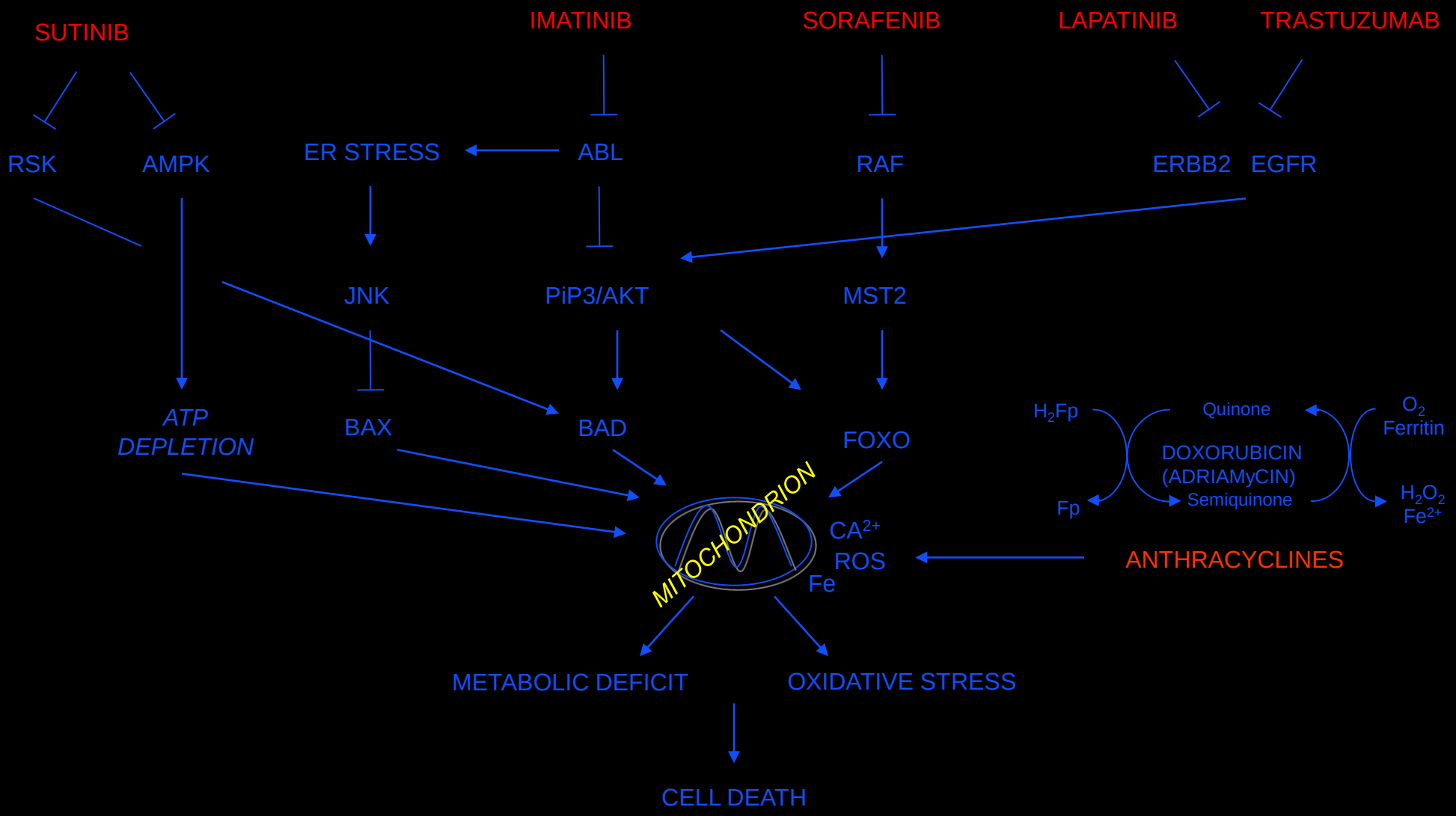


Cross targeting



Force T *et al. Nature Reviews Cancer*, 2007

MITOCHONDRIA ARE TARGET OF CARDIOTOXIC PATHWAYS

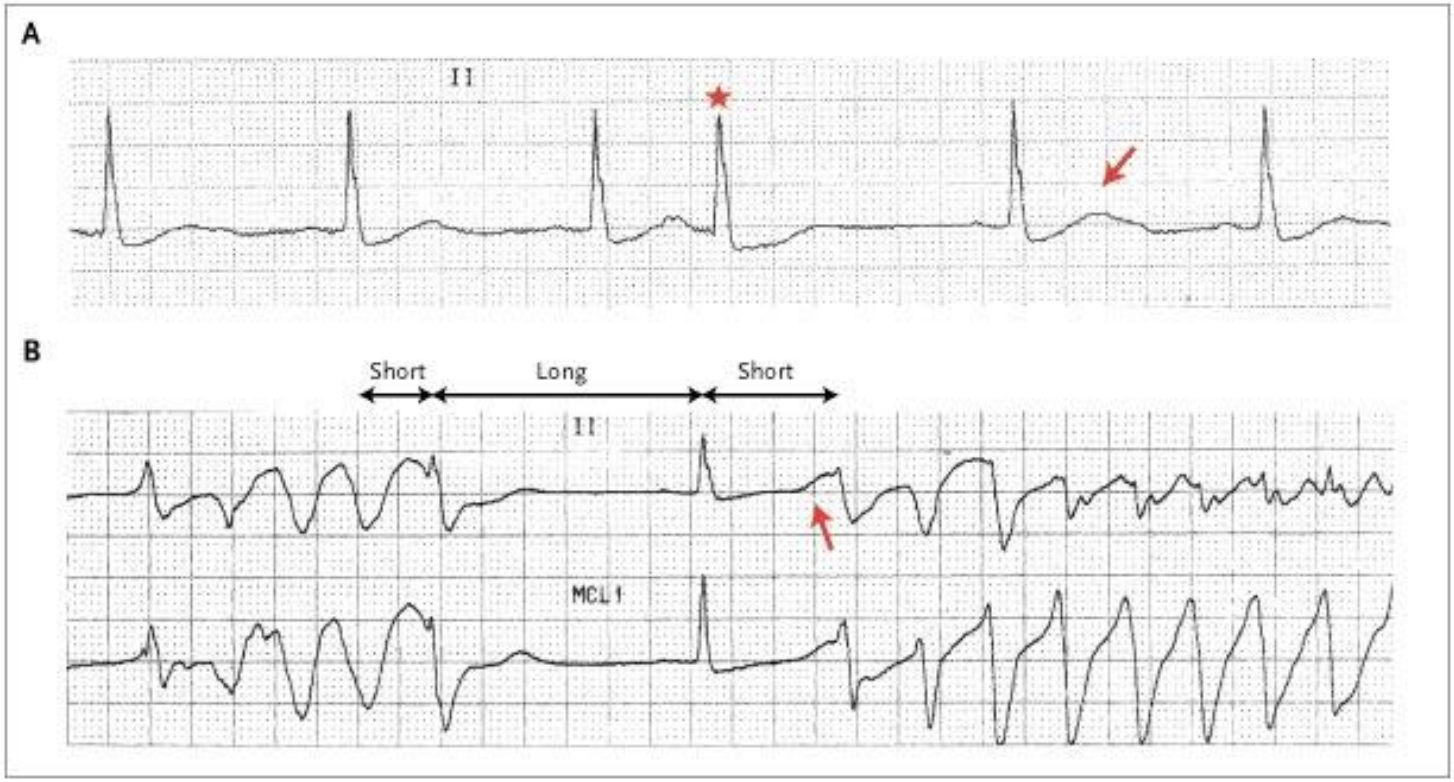


What is the role of QTc prolongation in new drugs development phase I oncology trial?

1966: French cardiologist Dessertenne first described Torsade de Pointes (TdP)

1989: First recognized case of QT prolongation and TdP associated with terfenadine was described by physicians at the National Naval Medical Center in Bethesda, Maryland.

Rhythm recording in a case of QT prolongation



QTc FDA regulatory Issues for Phase I-II

FDA and other health agencies are increasing the regulatory focus on QTc prolongation assessment for non anti-arrhythmic drugs

Issues concerning specific QT studies for oncology are not clearly addressed in ICH E14 guidance document ("The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs")

QTc FDA regulatory Issues for Phase I-II

Discontinuation Criteria:

Marked prolongation of the QT/QTc interval during treatment with the study drug.

Threshold for potential discontinuation are increases in QT/QTc to >500 ms or of >60 ms over baseline

QTc Assessment in Phase I Trials

- The decision by a physician to use a drug (or by a regulatory agency to approve one) is predicated on the assumption that the benefits of therapy outweigh the risks.

- Arsenic trioxide represents an interesting example of this balance. Although this drug is known to induce QTc prolongation and potentially a TdP, it is also uniquely effective in relapsed acute promyelocytic leukemia

QTc Assessment in Phase I Trials

- Uncertainty remains regarding the specific relationship between the degree of QT prolongation and the risk of life-threatening arrhythmias with a specific drug.

- A QT interval of at least 500 ms has been shown to correlate with an higher risk of TdP, but there is no established threshold below which prolongation of the QT interval is considered free of proarrhythmic risk.

QTc Assessment in Phase I Trials

- **"Thorough QT study" is the *in vivo* bioassay designed to evaluate the propensity of a drug to prolong the QT interval in humans**
- **Multiple ECG registrations are not sufficient to assess the risk of QT prolongation in early phase trials**
- **Timing of ECG tracings should be designed according to preclinical data concerning the kinetics of the drug**

“Classic Background 1”

- Anticancer drugs may prolong QT interval, increasing the risk of serious ventricular arrhythmias and sudden death.

- Cancer patients are considered at increased risk of life-threatening arrhythmias because of additional predisposing risk factors (electrolytes abnormalities, starvation and concomitant medications).

“Classic Background 2”

- BUT: Most of the data have been derived from clinical trials in which patients with a baseline long QT have systematically been excluded.

- AND: Information on the true incidence of a baseline long QT interval and on its possible prolongation during anticancer therapy in clinical practice are still lacking.

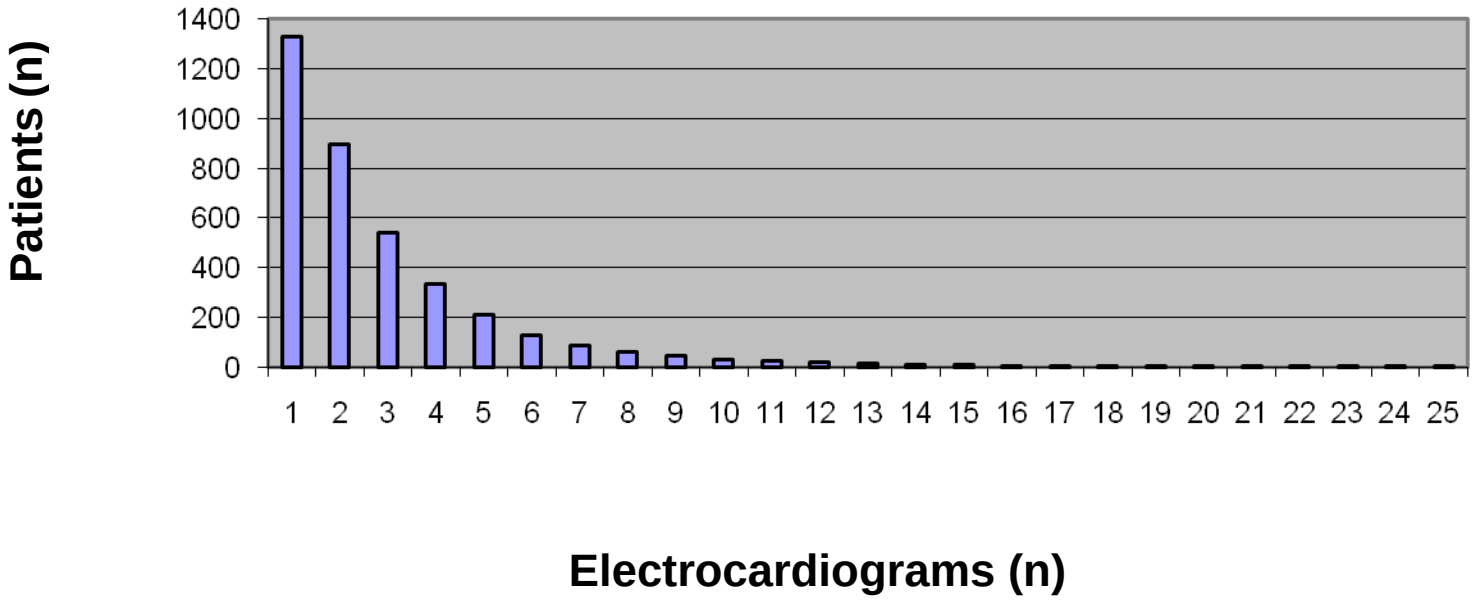
“Anti-QTc Crusade”

- 1330 records of unselected patients previously treated with CT
- EKG: QT corrected for HR by Bazett’s formula
- Prolonged QTc: >440 msec M; >460 msec F;
- Cardiac events: sudden death, NSTV, TV, torsade de point, syncope

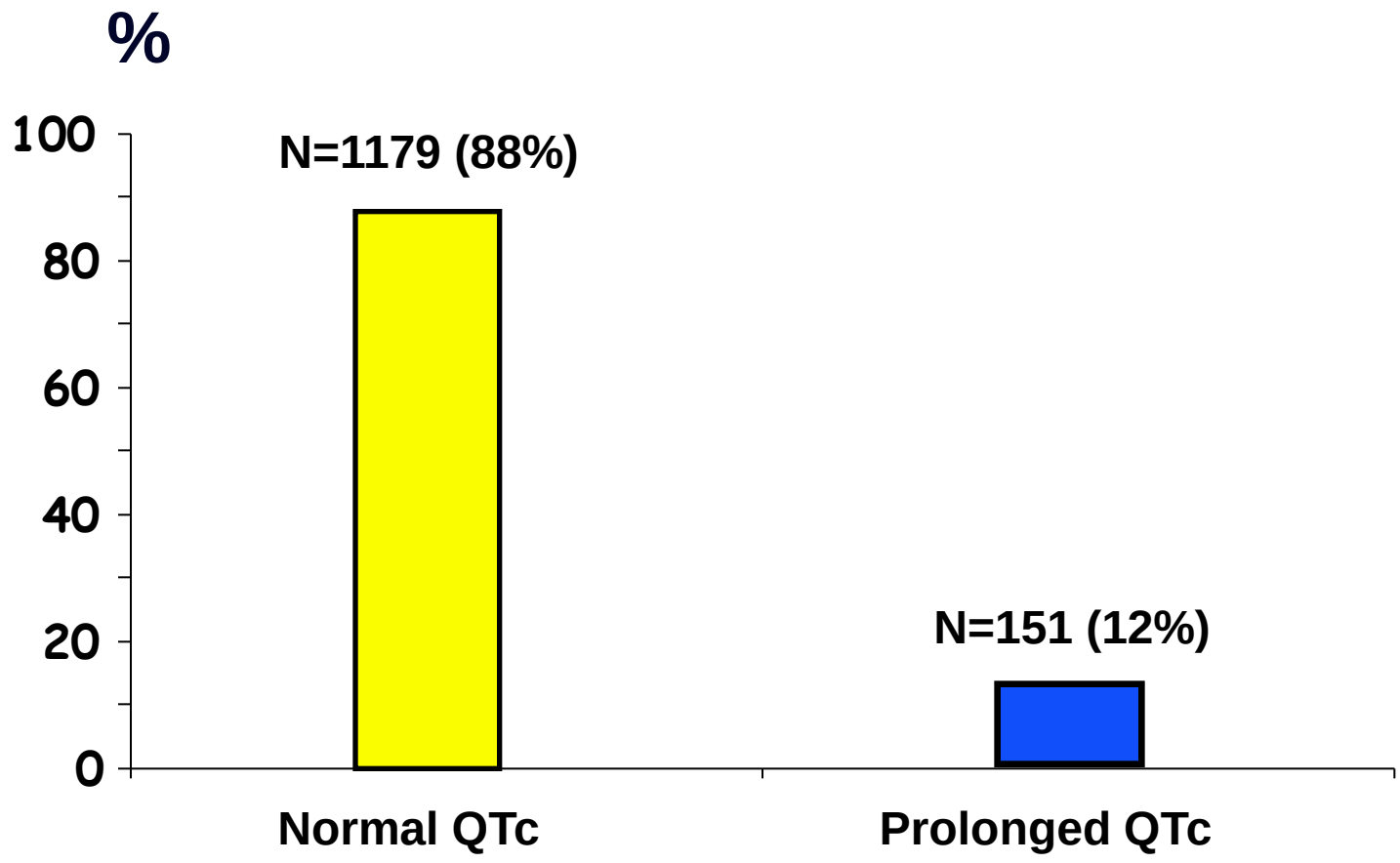
Results

- Analyzed EKG = n. 3863
- N. 1330 patients with at least 1 EKG
- Mean age 54 13 yrs
- 897 F; 433 M

EKGs/Patient



Baseline QTc – n.1330 pts



Clinical characteristics of pts with and without baseline prolonged QTc

	Normal QTc 1179 (88%)	Prolonged QTc 151 (12%)	P
Males	346 (29%)	87 (58%)	<0.001
Age (yrs)	54 13	52 15	NS
CV disease	381 (9%)	94 (20%)	<0.001
CV therapy	370 (14%)	91 (28%)	<0.001
Previous CT	475 (40%)	76 (50%)	NS
Previous AC	231 (19%)	29 (19%)	NS

Clinical characteristics of pts with and without baseline prolonged QTc

	Normal QTc	Prolonged QTc	P
Coronary Heart Dis.	34 (3%)	12 (8%)	<0.01
Hypertension	231 (19%)	41 (27%)	<0.04
Diabetes	44 (4%)	11 (7%)	NS
Hypercolesterolemia	63 (5%)	9 (7%)	NS
Ventricular arrhythmia	41 (3%)	15 (10%)	0.001
Heart Failure	8 (0.7%)	1 (0.7%)	NS
COPD	13 (1%)	3 (2%)	NS

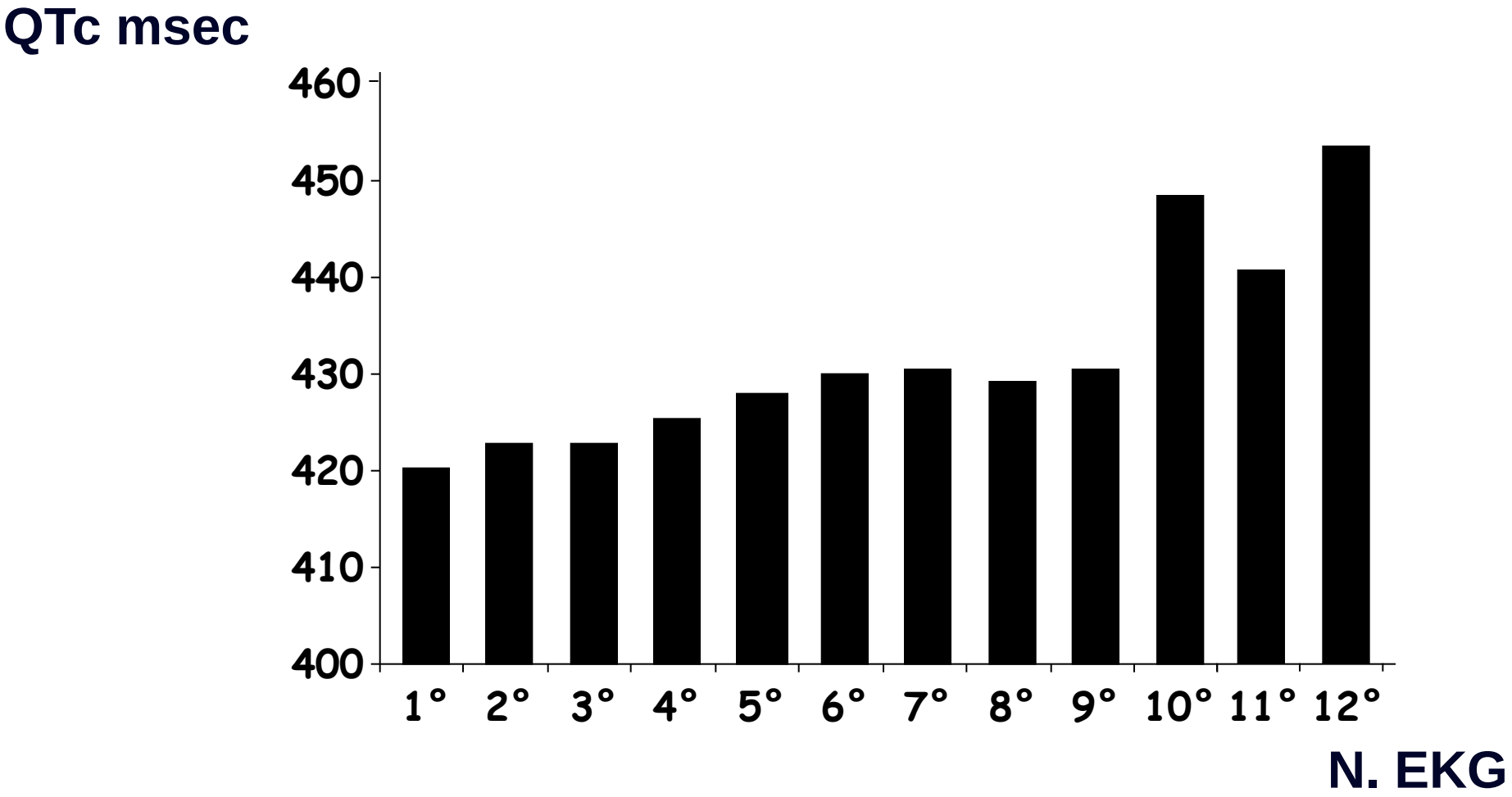
Clinical characteristics of pts with and without baseline prolonged QTc

	Normal QTc 1179 (88%)	Prolonged QTc 151 (12%)	P
Beta Blockers	89 (8%)	17 (11%)	NS
ACEI / ARB	89 (8%)	28 (12%)	<0.001
Antiarrhythmic	19 (1.6%)	6 (4%)	NS
Digitalis	6 (0.5%)	3 (2%)	NS
Diuretics	64 (5%)	17 (11%)	<0.01

QTc interval trend during CT

- 894 patients with at least 2 EKG
- Mean age 54 13 yrs
- 601 F (67%)
- anthracyclines + alkylating agents in 65% pts
- Mean follow-up = 48±39 months

QTc interval trend during CT



QTc interval trend during CT

Baseline QTc

QTc max during CT

n. 786 pts = normal QTc

n.636 pts = normal QTc

n.150 pts = prolonged QTc
(n.53 pts increase > 60 msec)

QTc interval trend during CT

Baseline QTc

QTc max during CT

n. 93 pts = prolonged QTc

n.38 pts = normalized QTc

n.55 pts = still prolonged QTc
(n.43 pts further increase
n.9 pts > 60 msec)

Cumulative cardiac events during the study follow-up: ?

	TOTAL (n=1330)	Prolonged QTc (n=1179)	Normal QTc (n=151)
Sudden death	0	0	0
Non sustained ventricular tachycardia	1	0	1
Sustained ventricular tachycardia	0	0	0
Torsade de point	0	0	0
Syncope	0	0	0
CUMULATIVE EVENTS	**1 !!!**	**0 !!!**	**1 !!!**

Conclusions

- A long QTc is almost infrequently observed in oncologic patients receiving anticancer therapy.
- Both a baseline long QTc and its weak prolongation during anticancer therapy seem associated with the occurrence of …. NOTHING (no LTAs!!).
- Cardioncologic comorbidity is 42%; we have to start thinking in a different way:
- Use biomarkers and look for

intra-cellular/mitochondrial biomarkers