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Fluoropyrimidine cardiotoxicity: time for a contemporaneous appraisal

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Abstract

IMPORTANCE: Fluoropyrimidines are a fundamental component of many chemotherapy regimens. Cardiotoxic adverse events (AEs) such as angina, ischemia, arrhythmias and cardiomyopathy associated with 5-fluorouracil (5FU) and capecitabine (cape) have been sparingly described in the literature, primarily through case reports. Data from the 1990s reveals an estimated incidence ranged from 0.5 to 19% with cardiovascular fatalities occurring in up to 28%. Current use of fluoropyrimidines (FPD) include multiple dosing regimens, oral or intravenous delivery, and administration with additional cardiotoxic therapies. As such, it is imperative to better define cardiotoxicity risk in the modern treatment era.

OBJECTIVE: To comprehensively evaluate the incidence, prevalence, and ascertainment of cardiovascular risk factors and disease within ECOG-ACRIN Cancer Research Group clinical trials incorporating 5FU and cape.

EVIDENCE REVIEW: Case report forms (CRFs) and clinical study reports (CSR) from the ECOG-ACRIN Cancer Research Group database of Phase II and III clinical trials incorporating 5FU and capecitabine were evaluated. A total of 16 trials between 2002 and 2017 were identified, using bolus 5FU (1), continuous infusion 5FU (10) or capecitabine (5).

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FINDINGS: A prior history of cardiovascular disease was variably defined and was an exclusion criterion in 81% (13/16 studies). Baseline risk factors and history of cardiac disease were specifically collected in only 19% (3/16). All studies collected cardiovascular adverse events (AE) according to the Common Terminology Criteria for Adverse Events (CTCAE) version at time of study. Less than half (7/16; 44%) of study CRFs also specifically requested information on cardiac ischemia/infarction. In the twelve completed studies with CSRs, the following AEs were reported: dyspnea up to 16%, arrhythmias up to 6%, and angina /ischemia/elevated troponin up to 5%. Some trials only recorded cardiac AEs possibly associated with the novel drug being studied and not those attributed to the standard of care 5FU/cape arm, further decreasing the numeric incidence.

CONCLUSION AND RELEVANCE: Inconsistent clinical trial reporting of cardiac events preclude accurate and precise delineation of the epidemiology of FPD-related cardiovascular AEs related. Prospective knowledge of the definition and natural history will lead to development of risk factor stratification and pre-chemotherapy interventions to reduce or prevent cardiotoxicity. We propose that prospective collection of baseline cardiac data and prespecified cardiac endpoints is necessary to fully understand the incidence and cardiac risk of 5DP.

Introduction

The fluoropyrimidines, 5-fluorouracil (5FU) and the oral pro-drug capecitabine (cape), are fundamental components of many chemotherapy regimens, beginning in 1962 with the FDA approval of 5FU. Standard of care chemotherapy regimens for colorectal carcinoma (CRC) employ either agent (5FU/cape) as neoadjuvant treatment, adjuvant therapy, and for disease stabilization with incurable cancer. An estimated 154,000 patients are potentially exposed to 5FU/cape annually. Fluoropyrimidines (FPDs) will continue to be widely prescribed, as currently there are no pharmacologic replacements on the horizon for CRC. In 2015, the combination of trifluridine and tipiracil, an oral thymidine-based nucleoside analog was approved as third or fourth line therapy (1). Serious adverse effects (AEs) associated with FDP can alter the prescribed treatment regimen (2,3). In particular, cardiovascular complications can obstruct the delivery of potentially curative or life-prolonging chemotherapy with significant morbidity as well as increased mortality for patients predicted to have long-term oncologic survival.

The mechanisms of FPD-associated cardiotoxicity are based mainly on older studies utilizing pre-clinical and cell models. These include coronary artery vasospasm potentially due to protein kinase C activation, vascular endothelial damage, increased myocardial oxygen consumption, and direct myocardial toxic effects (4–8). The described cardiovascular complications encompass a broad list including angina, arrhythmias, sudden death, hypotension/hypertension, and cardiomyopathy (8–11). Anecdotally, these conditions may occur with or without the presence of underlying cardiovascular disease. The published literature regarding cardiotoxicity is sparse despite multiple clinical reports and is mainly retrospective with a widely reported estimated incidence from systematic reviews ranging from 0.5% to 19% (8, 10).

A prospective study published in 1992 affords the best insight into the natural history of FPDs (11).. Cancer patients (N=367) scheduled to receive the first cycle of outpatient

continuous infusion (CI) 5FU were hospitalized and monitored per study parameters: 28 (7.6%) patients experienced cardiotoxicity such as angina and hypotension. Death occurred in eight of these patients (28.6%) from sudden death or hypertension followed by hypotension with cardiogenic shock (11).. The cardiovascular related mortality rate for the entire cohort was 2.2% (8/367). In the group of 28 patients with cardiotoxicity, eight patients (28.6%) had an antecedent cardiovascular condition. Whether any of these eight patients experienced fatal cardiac toxicity was not reported. For those afflicted with 5FU cardiotoxicity, prevention of disability and death is an unmet clinical problem.

To gain detailed insight into the more recent incidence of cardiotoxicity with 5FU/cape, we evaluated summary reports from national clinical trials performed through The Eastern Cooperative Group Cancer Research Group - American College of Radiology Imaging Network (ECOG-ACRIN).

Methods

The ECOG-ACRIN Cancer Research Group database of completed and ongoing Phase II and III clinical trials was searched using the indexed Cancer Chemotherapy National Service Center (NSC) number for 5FU (NSC 19893) and cape (NSC 712807) to identify all ECOG-ACRIN trials using 5FU/cape in at least one study arm. For all trials, the study protocol and case report forms (CRFs) were reviewed and the following information extracted: study population, treatment regimens, cardiovascular (CV) exclusion criteria, CV disease or CV risk factors collected at baseline, and assessment methods of CV events during the trial. For trials which had closed to accrual, the ECOG-ACRIN clinical study report (CSR) (which reports final study results including AE reporting), if available, was also reviewed and rates of CV events extracted.

Results

Sixteen trials employing 5FU and/or cape initiated from 2002–2016 were identified. (Table 1). No ECOG-ACRIN trials of trifluridine and tipiracil were conducted during this time frame.. Accrual in 13 (81%) of the trials had closed. Ten (63%) trials included 5FU, five (31%) utilized cape, and one (6%) included both. Of the 11 trials with 5FU in at least one arm, one used bolus dosing only, five contained bolus followed by continuous infusion, and four employed continuous infusion only. Capecitabine dosing ranged from 750mg/m2 twice daily to 1000mg/m2 twice daily. Ten (62%) were Phase II and six (38%) were Phase III trials. The malignancies studied were 13 gastrointestinal (81%), two breast (12%), and one head and neck (7%).

Prior CV disease was an exclusion criterion in most trials (13/16); however, the definition of CV disease varied substantially across trials. Potential participants with recent prior unstable angina (UA) or myocardial infarction (MI) were excluded in 11 studies, with exclusion intervals ranging from three to 12 months prior to enrollment. Other frequent exclusion criteria for conditions such as stroke, peripheral vascular disease, and heart failure were inconsistently defined. Only three trials specifically recorded baseline cardiovascular history or risk factors on the CRFs. Cardiac AEs were defined according to the Common

Terminology Criteria for Adverse Events (CTCAE) according to the version available during the study period (versions 2–4). In nine trials (56%) the AE CRFs specifically asked investigators to report at least one CV AE, while in other trials no CV AEs were explicitly requested and thus were reported according to the CTCAE as “other” on the AE CRF. Of the 9 trials that requested CV AEs, the specific AEs included cardiac ischemia/infarction (6/9), acute coronary syndrome (1/9), chest pain NOS (1/9), dyspnea (5/9), CNS cerebrovascular ischemia (4/9) and cardiac arrhythmias (2/9).

Of the 13 trials closed to accrual, final CSRs were available for 10 (77%) (Table 2). For many trials, only adverse events deemed possibly, probably or related to the study drug, which was rarely 5FU/cape, were included in the AE summaries. Incidence of chest pain, cardiac-troponin or cardiac-ischemia ranged from 0–5%, arrhythmias ranged from 0–6% and dyspnea as high as 16%.

Discussion

From this review of the ECOG-ACRIN Cancer Research Group database of fluoropyrimidine trials, we ascertained that cardiotoxicity has been inconsistently reported, impeding enumeration of the incidence. In these trials there were specified objectives for assessment of toxicity, but not explicitly for cardiotoxicity. As a result of this review we have identified several considerations to incorporate into trial design to increase the cardiotoxicity knowledge base.

One concern in clinical trials design is the exclusion of patients with previously diagnosed cardiovascular disease. Consequently, adverse events from clinical research will likely underestimate the incidence in the general population. In addition, we found that baseline cardiac disease or cardiac risk factors were infrequently documented on these CRFs, even though risk factors such as obesity, hypertension, hyperlipidemia, smoking and diabetes may impact the development of ensuing cardiovascular disease, including silent ischemia. To investigate the efficacy of new agents, later-phase clinical studies avoid the effects of co-morbidities and organ dysfunction on anti-cancer drug development. Whether to begin including patients with multiple medical conditions, as seen in the community setting, in clinical trials is under discussion. The current NCI director prioritizes revision of the NCI’s National Clinical Trials Network, noting “unnecessary exclusions” and “poor accrual of underrepresented populations” in trials generate results applicable only to homogenous groups of patients [12] Modifications in inclusion criteria to include common medical conditions will extend clinical trial eligibility for the broader cancer population with improved generalizability of results [13]. The assessment of FPD cardiotoxicity in real-world patients could be performed by designing pragmatic trials [14] in the community setting, including conducting studies in the National Cancer Institute’s Community Oncology Research Program [15]. The impact of comorbid conditions or their risk factors on cardiovascular health in cancer patients is critical to understand cardiotoxicity risk.

Additional data usually not reported is required to classify cardiotoxicity. Details such as procedures to diagnose the cardiovascular events, cardiovascular outcomes, and chemotherapy doses received are required to inform the natural history. Given the fluid onset

of cardiovascular AEs, the call for toxicity grading long term during therapy, as opposed to recording specific points, will broaden the definitions and incidence of all drug-related toxicity. Additionally, post-therapy surveillance is essential to characterize the ensuing morbidity from chronic cardiac disease related to FPD treatment. The CTCAE are universally accepted for AE reporting in clinical studies, albeit with known limitations. The time span of these reviewed trials evaluated clinical research across several CTCAE versions with varying terminology [16]. Specific and consistent data element terms should be captured at baseline, throughout treatment, and with surveillance. The ECOG-ACRIN Cardiotoxicity Working Group has developed a wide-ranging list of cardiovascular data elements, including the capture of risk factors, preexisting cardiovascular disease and cardiovascular outcomes (Table 3) [17]. Across FPD clinical trials, prospective collection of standardized cardiotoxicity endpoints will lead to clarification of the specific cardiac events associated with FPDs and will allow formalization of definitions.

Furthermore, the current estimates of FPD cardiotoxicity incidence will be likely influenced by the evolution of dosing and delivery of 5FU, from intravenous bolus to five-day continuous infusions to 48-hour infusions [18]. Our retrospective review encompassed a variety of fluoropyrimidine doses and schedules, some of which are no longer clinically applicable. There is suggestion that the dose and schedule may impact the risk of FPD cardiotoxicity [4, 6, 18]. The contribution of concomitantly prescribed anti-cancer treatments, such as vascular targeted agents, to FDR cardiotoxicity risk is unknown. Future combination treatments with 5FU/cape should be assessed for additive or synergistic cardiotoxic effects, which may heighten patient risk for cardiotoxicity during anti-cancer treatment. Of note, there were no ECOG-ACRIN trials of the FDA approved combination of trifluridine and tipiracil or other oral FDPs such as UFT or S1, which are not currently FDA approved, thus the reporting and cardiotoxicity of FDP agents other than 5FU and cape were not including in the current review. In the pivotal phase III trial of tifluridine and tipiracil that included800 participants with refractory metastatic colorectal cancer, < 1 % of patients were reported to have developed cardiac ischemia in both the tifluridine/tipiracil and placebo groups [19]. Potential cardiotoxicity with tifluridine and tipiracil and other oral FDPs warrants further study.

Our overall goal of defining cardiotoxicity is to ensure the safety of CRC patients receiving therapy. Currently data to inform risk-to-benefit discussions with patients, preventive strategies, and clinical practice guidelines for patients receiving fluoropyrimidines are lacking. Reporting of best clinical practices, such as the recently published single institution strategies to re-challenge patients who have incurred FPD cardiotoxicity, will aid with informing guidelines [20].

The past variable reporting of cardiac events precludes accurate and precise delineation of the epidemiology of 5FU/cape-related cardiovascular AEs. Uncertainty remains regarding the incidence and extent of FPD cardiotoxicity in the current treatment era. The influence of patient-related factors obtained from mutation analysis [21] and phenotyping, as well as the addition of concomitant cancer treatments to 5FU/cape are unknown. Given the mortality and unknown acute and chronic morbidity of cardiotoxicity there is a critical need for robust collection of CV risk factors and disease from baseline to post-chemotherapy, trial designs

with specific cardiotoxic primary or secondary objectives, and careful consideration/evaluation regarding study exclusion criteria in late phase studies. Prospective knowledge gained regarding the extent and severity of FPD cardiotoxicity will lead to the development of diagnostic criteria, risk factor stratification, and peri-chemotherapy interventions to reduce or prevent cardiotoxicity.

We propose that prospective collection of baseline cardiac data and prespecified cardiac endpoints is necessary to fully understand the incidence and cardiac risk of fluoropyrimidines.

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Table 1:

Phase II and III ECOG-ACRIN Trials of 5FU and/or Capecitabine – Description of studies, Cardiovascular (CV) exclusion criteria, and ascertainment of CV events

Study	Agent(s)	Cancer type	Phase, and Accrual	Year study activated	CV exclusion criteria	Baseline CV Data Collected	CTCAE version, grades and attribution*	CV event definitions/ ascertainment on Adverse Event (AE) Case Report Form (CRF)
E1103	**Capecitabine 1000mg/m2 twice daily** + tipifarnib	Metastatic Breast Cancer	Phase II N=71	2004	Symptomatic cardiovascular disease	None	CTC v2, all grades, treatment related**	AE CRF includes: • Cardiac ischemia/ infarction • Dyspnea
E2200	**5-FU 400mg/m2 weekly bolus** + irinotecan + leucovorin + bevacizumab	Advanced Colorectal	Phase II N=92	2000	None	None	CT v2, all grades, treatment related**	AE CRF includes: • Hypertension • Dyspnea • Thromboembolism
E2204	**Capecitabine 825mg/m2 twice daily** Arm A: + cetuximab + gemcitabine Arm B: + bevacizumab + gemcitabine	Completely resected pancreatic CA	Phase II(randomized) N=137	2006	• Cardiac arrhythmia • TIA/stroke • Arterial thromboembolic events • UA/MI within 12 months of study entry	None	CTCAE v3, all grades, treatment related**	AE CRF includes: • Cardiac ischemia/ infarction • CNS cerebrovascular ischemia • Hypertension • Dyspnea • Thrombosis/ thrombus/ embolism Grade 3+ TIA/CVA/MI/angina specifically included in the primary endpoint
E2205	**5-FU 180mg/m2 CI over 24 hours D 1–35** + oxaliplatin + cetuximab	Operable esophageal cancer	Phase II N=22	2008	• Heart failure • Stroke/TIA, UA/MI within 6 months of study entry	None	CTCAE v3,grade 3–5, treatment related**	No cardiac AEs specifically ascertained

Study	Agent(s)	Cancer type	Phase, and Accrual	Year study activated	CV exclusion criteria	Baseline CV Data Collected	CTCAE version, grades and attribution*	CV event definitions/ ascertainment on Adverse Event (AE) Case Report Form (CRF)
E2211	**Capecitabine 750mg/m2 twice daily** only or with Arm A: + temozolomide Arm B: temozolomide only no 5FU	Advanced pancreatic neuroendocrine tumors	Phase II (randomized) N=144***	2013	• Arterial thromboembolic events • PVD • UA, MI within 12 months of study entry	None	CTCAE v4***	No cardiac AEs specifically ascertained
E3200	**5FU 400mg/m2 bolus followed by 600mg/m2 CI over 22 hours** in arms A and B A: oxaliplatin + leucovorin + bevacizumab B: oxaliplatin + leucovrin C: bevacizumab alone no 5Fu	Advanced Colorectal	Phase III N=829	2001	• Heart failure • UA/MI within 3 months	None	CTC v2, grade 4–5 hematologic and grade 3–5 non-hematologic, treatment related**	No cardiac AEs specifically ascertained
E3201	**5FU bolus followed by CI 2400 mg/m2 over 46 hours adjuvant** Arms A, B, D, and E Arms C and F **5FU bolus only**	Stage II or III Rectal	Phase III N=179	2003	None	None	CTCAE v3, grade 3–5, treatment related**	No cardiac AEs specifically ascertained
E3204	**Capecitabine 825mg/m2 twice daily** + oxaliplatin + bevacizumab + radiation then surgery, then adjuvant **5FU 400mg/m2 followed by**	Locally advanced rectal cancer	Phase II N=57	2006	• Heart failure • PVD. • UA/MI within 12 months of study entry	None	CTCAE v3, all grades, treatment related**	AE CRF includes: • Chest/thorax Pain NOS • Dyspnea • Thrombosis/ thrombus/ embolism

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Study	Agent(s)	Cancer type	Phase, and Accrual	Year study activated	CV exclusion criteria	Baseline CV Data Collected	CTCAE version, grades and attribution*	CV event definitions/ ascertainment on Adverse Event (AE) Case Report Form (CRF)
	2400mg/m2 CI 46 hours + leucovorin +oxaliplatin + bevacizumab							
E3205	**5-FU 4000mg/m2 CI over 96 hours** + cetuximab + cisplatin Arm 1: two cycles Arm 2: one cycle	Anal carcinoma	Phase II N=63	2007	• Heart failure • Stroke/TIA • UA/MI within 6 months of study entry	None	CTCAE v4, grade 3–5, treatment related**	AE CRF includes: • Cardiac-ischemia/ infarction
E4203	**5-FU 400mg/m2 bolus followed by 2400mg/m2 CI over 46 hours** Arm B and C: + leucovorin + oxaliplatin + bevacizumab Arm A: irinotecan + oxaliplatin + bevacizumab **no 5FU**	Metastatic colorectal	Phase II N=211	2005	• NYHA III-IV heart failure • UA/MI within 6 months of study entry	None	CTCAE v3, all grades, treatment related**	No cardiac AEs specifically ascertained
E5202	**5FU 400 mg/m2 bolus followed by 2.4gm/m2 over 46 hours** Arm A Arm B: + bevacizumab Arm C: no chemotherapy	Stage II Colon Cancer	Phase III N=2432***	2005	• UA/MI within prior 12 months • Symptomatic PVD NYHA III/IV HF • Symptomatic arrhythmias • TIA/Stroke	Perioperative MI	CTCAE v3***	AE CRF includes: • Cardiac-ischemia/ infarction • Cardiac arrhythmia • CNS cerebrovascular ischemia • Thrombosis/ thrombus/ embolism

Study	Agent(s)	Cancer type	Phase, and Accrual	Year study activated	CV exclusion criteria	Baseline CV Data Collected	CTCAE version, grades and attribution*	CV event definitions/ ascertainment on Adverse Event (AE) Case Report Form (CRF)
E5204	**5FU 400 mg/m2 bolus followed by 2400mg/m2 CI over 46 hours** Arm A and B Arm B: + bevacizumab	Stage II or III Rectal cancer	Phase III N=355	2006	• UA/MI within prior 12 months • PVD, NYHA III/IV HF • Symptomatic arrhythmias • TIA/Stroke	History of: • Diabetes • Hypertension	CTCAE v3 grades 3–5, treatment related**	AE CRF includes: • Cardiac-ischemia/ infarction • Pain-Chest/Thorax NOS • CNS cerebrovascular ischemia • Hypertension • Dyspnea • Thrombosis/ thrombus/ embolism
E1305	**5FU 1000mg/m2 CI over 96 hours** Regimen 2: + cisplatin or carboplatin Regimen 1: docetaxel + cisplatin or carboplatin no 5FU	Recurrent or Metastatic Head and Neck Cancer	Phase III N=403***	2008	• UA/MI or Stroke within prior 6 months • PVD • NYHA II-IV HF • Serious cardiac arrhythmia requiring medication • PVD with symptoms or prior intervention • Stroke within the last 6 months	History of: • Arterial thromboembolic events • MI, stable angina, unstable angina, • HTN • Smoking status	CTCAE v4***	AE CRF includes: • Acute coronary syndrome
EA1131	**Capecitabine 1000mg/m2 twice daily** Arm C only Arm A: observation Arm B: cisplatin vs carboplatin	Triple Negative, Stage II or III Breast Cancer	Phase III Projected N=750^	2015	None	None	CTCAE v4^	No cardiac AEs specifically ascertained

Study	Agent(s)	Cancer type	Phase, and Accrual	Year study activated	CV exclusion criteria	Baseline CV Data Collected	CTCAE version, grades and attribution*	CV event definitions/ ascertainment on Adverse Event (AE) Case Report Form (CRF)
EA2133	**5FU 4000mg/m2 CI over 96 hours** Arm: A + cisplatin Arm B: carboplatin + paclitaxel no 5FU	Advanced Anal Squamous Cell Carcinoma	Phase II Projected N=80^	2016	• MI within last 6 months • Symptomatic CAD • Clinically significant cardiac failure • Uncontrolled cardiac arrhythmia	Hypertension	CTCAE v4^	AE CRF includes: • Myocardial ischemia/infarction • Arrhythmia • LV dysfunction
EA2142	**Capecitabine 750mg/m2 twice daily** Arm A: + temozolomide Arm B: platinum + etoposide no capecitabine	Advanced non-small cell GI Neuroendocrine carcinoma	Phase II (randomized) Projected N=126^	2015	• Symptomatic heart failure • Unstable angina • Cardiac arrhythmias	None	CTCAE v4^	cardiac AEs not specifically ascertained

* CTCAE version. grades, attribution as reported in the final Clinical Study Report (CSR).

** includes the following attributions: possible, probably, definitely related to protocol treatment.

*** trial is closed to accrual and final CSR not available to date.

^ accrual to trial ongoing to date.

Table 2:

Phase II and III ECOG-ACRIN Trials of 5FU and/or Capecitabine – Adverse Events reported in Trials with final Clinical Study Reports Available

Study	Agent(s)	Number of patients included in AE analyses	Cardiac-ischemia or chest pain	Arrhythmias	LV Dysfunction/ Heart Failure	Hypertension	Dyspnea	Thrombosis/ thrombus/ embolism	Other
E1103	**Capecitabine 1000mg/m2 twice daily** + tipifarnib	n=68					11 (16%)		Thrombosis/ embolism 1 (2%)
E2200	**5-FU 400mg/m2 weekly bolus irinotecan** + leucovorin + bevacizumab	n=87	Cardiac-ischemia 2 (2%)	Dysrhythmia 1 (1%) Palpitations 3 (3%) SVT 1 (1%)			14 (16%)	11(13%)	Cardiac other 1 (1%)
E2204	**Capecitabine 825mg/m2 twice daily** Arms A and B Arm A: cetuximab + gemcitabine Arm B: bevacizumab + gemcitabine	n=130	Chest pain 2 (2%)	SVT 2(2%)	LV diastolic dysfunction 1(1%)	17 (13%)	10 (8%)	8(6%)	CP arrest, nonfatal 1(<1%) Pericardial effusion 1(<1 %) Cardiac other 1(<1%),
E2205	**5-FU 180mg/m2 CI over 24 hours D 1–35** + oxaliplatin + cetuximab	Phase II n=22	Cardiac troponin 1 (5%)	Heart block/ asystole 1(5%) Atrial fibrillation 1(5%)			2 (9%)	3 (14%)	Syncope 1(5%)
E3200	**5FU 400mg/m2 bolus followed by 600mg/m2 CI over 22 hours** in arms A and B A: oxaliplatin + leucovorin + bevacizumab B: oxaliplatin + leucovrin C: bevacizumab alone no 5FU	n=808	Cardiac ischemia 2(<1%) Cardiac troponin 3(<1%) Chest pain 8(<1%)	SVT 6(<1%)	Cardiac left ventricular function 1(<1%)	40 (5%)		Thrombosis/ embolism 18(2%)	Cardiac other 2(<1 %)
E3201	**5-FU bolus followed by CI 2400 mg/m2 over 46 hours adjuvant** Arms A, B, D, and E Arms C and F **5FU bolus only**	n=177 (adjuvant portion)	Cardiac-ischemia 1(<1%)				2(1%)	2(1%)	
E3204	**Capecitabine 825mg/m2 twice daily +** oxaliplatin + bevacizumab + radiation then surgery, then adjuvant **5FU 400mg/m2 followed by 2400mg/m2 CI 46 hours** + leucovorin +oxaliplatin + bevacizumab	n=55	Chest/thoracic pain 2(4%)			2 (4%)	5(9%)	2(4%)	Cardiac-other 1(2%)
E3205	**5-FU 4000mg/m2 CI over 96 hours** + cetuximab + cisplatin Arm 1: two cycles	n=62			Left ventricular systolic dysfunction 1(2%)		1(2%)	3(5%)	

Study	Agent(s)	Number of patients included in AE analyses	Cardiac-ischemia or chest pain	Arrhythmias	LV Dysfunction/ Heart Failure	Hypertension	Dyspnea	Thrombosis/ thrombus/ embolism	Other
	Arm 2: one cycle								
E4203	**5-FU 400mg/m2 bolus followed by 2400mg/m2 CI over 46 hours** Arm B and C: leucovorin + oxaliplatin + bevacizumab Arm A: **No 5FU** irinotecan + oxaliplatin + bevacizumab	n=205	Cardiac-ischemia 1(<1%) Chest pain 3(1%)	Palpitations 3(2%)Atrial fibrillation 1(<1%) Arrhythmia other 2(1%) SVT 1 (<1%)	LV diastolic dysfunction 1(<1%)	52 (25%)		19(9%)	Sudden death 1(<1%)
E5204	**5FU 400 mg/m2 bolus followed by 2400mg/m2 CI over 46 hours** Arm: A and B Arm B: + bevacizumab.	n=347	Cardiac-ischemia 2% Cardiac/heart pain 1% Chest pain 1 %		Cardiomyopthy restrictive 1%		3%	4%	

Table 3:

Key elements to consider including in oncology clinical trials (Adapted from ECOG Baseline and Follow up Cardiovascular Form, see supplemental appendix)

History of Diagnosed CVD	**Symptoms Suggestive of CVD**	**Physical Exam Findings**	**Lab and Imaging Data**	**Cardiac Medications**
Coronary artery disease • Myocardial Infarct (date) • Revascularization history (Percutaneous coronary intervention of coronary artery bypass graft surgery) • Angina class Heart Failure/Cardiomyopathy • Heart failure with preserved Ejection Fraction • Heart Failure with Reduced Ejection Fraction • Etiology of Cardiomyopathy • Cardiac amyloidosis • Prior heart failure hospitalization • New York Heart Association Class Arrhythmias/ECG abnormalities • Atrial fibrillation • Atrial flutter • Other supraventricular tachycardia • Ventricular tachycardia • Ventricular fibrillation • Prior cardiac arrest • Long QT • Bradycardia • Sick sinus syndrome • Sinus tachycardia • Left bundle branch block	Chest pain at rest or with exertion Shortness of breath at rest or with exertion Orthopnea Paroxysmal Nocturnal Dyspnea Edema Fatigue Weight gain In patients with heart failure: New York Heart Association Class: I: no symptoms II: mild limitation during ordinary activity III: Marked limitation in activity due to symptoms, comfortable only at rest IV: symptoms at rest	• Blood Pressure • Heart rate • Height • Weight • BMI • Jugular venous distension • Carotid Bruits • S3 • S4 • Murmur • Distal pulses • Rales • Wheezing • Hepatomegaly • Ascites • Edema (grade, extent)	Lab tests: • serum creatinine • brain natriuretic peptide • N-terminal pro-brain natriuretic peptide • Troponin I • Troponin T • Total cholesterol • Triglycerides • Low Density lipoprotein • High density lipoprotein Echocardiography: • Left ventricular ejection fraction • Institutional lower limit of normal • Evidence of diastolic dysfunction (grade if present) • Evidence of moderate to severe valvular disease (list) • Left atrial dilation • Right atrial dilation • Right ventricular function • Right ventricular dilation	• Aspirin • ACE-inhibitor • Angiotensin Receptor Blocker • Beta-blocker • Alpha blocker • Calcium channel blocker • Diuretics • Nitrates • Statin • Other lipid lowering therapy • Anticoagulant therapy • Other

History of Diagnosed CVD	Symptoms Suggestive of CVD	Physical Exam Findings	Lab and Imaging Data	Cardiac Medications
• Arrhythmia - not otherwise listed • Syncope • Palpitations • Implantable Cardioverter Defibrillator • Pacemaker Valvular Disease • Aortic stenosis • Aortic Regurgitation • Aortic valve repair or replacement • Mitral stenosis • Mitral regurgitation • Mitral valve prolapse • Mitral valve repair or replacement • Tricuspid stenosis • Tricuspid regurgitation • Tricuspid valve repair or replacement • Pulmonic stenosis • Pulmonic regurgitation • Endocarditis Vascular disease • Carotid Disease • Transient Ischemic Attack • Stroke • Peripheral Vascular Disease • Thoracic Aortic Aneurysm • Abdominal Aortic Aneurysm • Deep Vein Thrombosis • Pulmonary Embolism			• Regional wall motion abnormalities	

History of Diagnosed CVD	Symptoms Suggestive of CVD	Physical Exam Findings	Lab and Imaging Data	Cardiac Medications
• Pulmonary hypertension Pericardial disease • Pericarditis • Pericardial Effusion Cardiac Risk factors • Hypertension • Diabetes • Tobacco Use (prior or current) • Metabolic Syndrome • Obesity • Hyperlipidemia • Family history of cardiomyopathy or coronary artery disease • Alcohol use (>2 drinks/day) • Prior chest radiation (dose, fractions, field, date) • Prior anthracycline chemotherapy (agent, cumulative dose, year) • Anti-HER2 agent (agent, duration, year)				