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Reporting practices of pharmacodynamic studies involving invasive research procedures in cancer trials

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Background: Tumour biopsy for pharmacodynamic (PD) study is increasingly common in early-phase cancer trials. As they are non-diagnostic, the ethical justification for such procedures rests on their knowledge value. On the premise that knowledge value is related to reporting practices and outcome diversity, we assessed in a sample of recent invasive PD studies within cancer trials.

Methods: We assessed reporting practices and outcomes for PD studies in a convenience sample of cancer trials published from 2000 to 2010 that employed invasive, non-diagnostic tissue procurement. Extracted data were used to measure outcome reporting in individual trials. Using a reporting scale we developed for exploratory purposes, we tested whether reporting varied with study characteristics, such as funding source or drug novelty.

Results: Reporting varied widely within and across studies. Some practices were sporadically reported, including results of all planned tests (78% trials reporting), use of blinded histopathological assessment (43% trials reporting), biopsy dimensions (38% trials reporting), and description of patient flow through PD analysis (62%). Pharmacodynamic analysis as a primary end point and mandatory biopsy had statistically significant positive relationships with overall quality of reporting. A preponderance of positive results (61% of the studies described positive PD results) suggests possible publication bias.

Conclusion: Our results highlight the need for PD-reporting guidelines, and suggest several avenues for improving the risk/benefit for studies involving invasive, non-diagnostic tissue procurement.

Biopsy for pharmacodynamic (PD) and biomarker analysis is increasingly common in early-phase cancer trials (Twelves, 2006; Goulart *et al*, 2007). In principle, PD end points can provide evidence of target effects for a drug, and support decision making for subsequent trials (Workman, 2003; Sarker *et al*, 2007; Sarker and Workman, 2007; Tan *et al*, 2009). However, many PD studies require invasive procedures like tumour biopsy.

Studies find that many patients are willing to undergo research biopsy (Seah *et al*, 2013) and that ethics review committees and oncologists may overestimate patient anxiety associated with biopsies (Agulnik *et al*, 2006). In one study, overall and major complication rates for tumour biopsies were 5.2% and 0.8%, respectively (Overman *et al*, 2012). However, the majority of patients describe their biopsies as being painful (Agulnik *et al*, 2006) and other studies indicate that 10% of patients receiving one common procedure – breast tumour biopsy – report moderate-to-severe pain (a more extended discussion of tumour biopsy risk and burden is available at Brown *et al* (2008); Hemmer *et al* (2008); Kimmelman *et al* (2012)). As biopsies often have no value for subjects in terms of clinical management, their ethical justification

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rests on an expectation that their performance will be redeemed by the value of the knowledge accrued (Olson *et al*, 2011).

Given that the burdens of such procedures are well understood, debates concerning their application revolve around conflicting views about the scientific utility of PD evidence. Some commentators question whether research biopsies return sufficient knowledge to justify their risks (Dowlati *et al*, 2001; Parulekar and Eisenhauer, 2004; Davis *et al*, 2005; Goulart *et al*, 2007; Ratain and Glassman, 2007). Such critics describe research biopsies as 'taking without giving in return' and an 'expensive distraction' (Helft and Daugherty, 2006; Ratain and Glassman, 2007; Olson *et al*, 2011). One critic argues, 'given that biomarker support of mechanism, or lack thereof, has not contributed to go/no-go decisions in practice, sponsors should reconsider the value of including any biomarker evaluations in phase I oncological studies' (Ratain and Glassman, 2007). Others insist that the procedures are safe and feasible, and stress the importance of gathering mechanistic evidence in drug development; defenders point to examples where enrichment trials involving biopsy enabled rapid translation of cancer strategies (Kelloff and Sigman, 2005; Agulnik *et al*, 2006; Cannistra, 2007; Brown *et al*, 2008; Peppercorn *et al*, 2010).

Such debates are hampered by a paucity of systematic evidence concerning the knowledge value of PD studies. In part, this reflects the fact that there are no widely accepted measures of knowledge value. In this report, we sought to highlight measures that could improve the risk/knowledge value of tumour biopsies and associated PD analyses. In particular, we measured two objective proxies of knowledge value: reporting practices and outcome diversity. In order for 'knowledge value' to accrue, scientific findings must be reported in sufficient detail to permit readers to form or update beliefs. They must also enable others to reproduce findings in studies addressing similar questions. We measured the extent to which publications reported on study elements that were viewed as important in similar studies – those involving tumour prognostic biomarkers. The second proxy builds on the premise that a population of studies is more informative when it reflects a diversity of outcomes for tested hypotheses. Pharmacodynamic studies generally set out to test well-formulated hypotheses about specified target effects. Finding that in a population of PD studies, hypothesised target effects are almost always confirmed suggests either publication bias, limited information gain (as outcomes were predicted in advance of the PD study), or both. Our studies highlight the potential value of reporting standards for PD studies in cancer.

MATERIALS AND METHODS

Our primary objective was to describe the reporting practices in a convenience sample of recent invasive PD studies embedded within cancer trials. Our secondary objectives were to measure diversity of study outcomes and to identify characteristics of studies that correlate with better reporting.

Sample. Our study utilised a convenience sample of studies involving tumour biopsy. To capture a sample of studies that involved PD analyses and invasive tissue procurement while excluding the very large volume of studies involving minimally invasive collection (for example, venipuncture), we devised a search strategy that was highly specific. Briefly, we used keywords like 'biopsy' and 'pharmacodynamic' to search PubMed for articles published from 2000 to 2010 (inclusive) reporting on the use of invasive, non-diagnostic tissue procurement in cancer trials. We excluded articles where (a) non-diagnostic status of tissue procurement was ambiguous; (b) biopsy was not performed; (c) trials did not involve cancer patients; or (d) tissue procurement was minimally invasive (for example, venipuncture). Our search methods are described in greater detail elsewhere (Freeman and Kimmelman, 2012). After an initial screening by title and abstract, eligibility was confirmed using the full report.

Extraction elements. We developed a data extraction form for assessing study reporting and outcomes. Our form (Appendix 1) covered three domains: (1) study characteristics (for example, the year of publication, phase of trial, drug identity); (2) PD study practices and reporting (for example, description of assays, patient flow through study, use of blinded analysis); and (3) study outcomes (for example, confirmation status of PD hypotheses, author conclusions).

Elements within the second domain were adapted from REMARK criteria and supplemented with items described in Eisenhauer *et al* (2006); McShane *et al* (2005). Extraction elements and coding conventions were initially developed by JK, and then discussed, refined, and approved by JD and JGM. After piloting extraction against 15 studies, we refined our form and coding criteria.

Extraction. All articles were extracted using paper forms by two reviewers (GF and JK) blinded to the other's extractions (but not author identities). We interpreted the absence of an affirmative practice statement as the absence of that practice (that is, studies not reporting blinded assessment were coded as not having implemented blinded outcome assessment). Studies were classified as implementing mandatory biopsy when explicitly stated in the report or when tissue samples were collected from all subjects. Data from extractions were entered into an Excel spreadsheet for analysis. Cohen's κ-inter-rater agreement was calculated; values exceeded 0.8, which we considered 'good agreement' (Fleiss, 1981; Toulmonde *et al*, 2011). Disagreements were resolved through discussion.

Reporting score. We developed a reporting score (RS) in order to explore the range of reporting quality, and to enable a series of tests concerning relationships between study characteristics and reporting. Our score was modelled after those used for prognostic tumour biomarker studies and randomized trials (Lai *et al*, 2006; Kyzas *et al*, 2007; Rios *et al*, 2008; Toulmonde *et al*, 2011) and was developed through discussions with all authors. It consisted of eight reporting domains: (1) goal and hypothesis; (2) subject eligibility; (3) specimen characteristics; (4) assay protocol; (5) statistics; (6) subject flow; (7) results; (8) discussion. Domains contained one or more evenly weighted reporting variables. Reporting on any item within a domain would result in a fractional score and each domain had a potential score of one. Scores in each domain were summed to calculate an overall RS for each study.

Outcome reporting. Studies were assessed along three outcome categories. The first was results of hypothesis tests. Results were coded as positive where a treatment caused hypothesised changes in targets (that is, an increase in apoptosis assessed by TUNEL staining with a proapoptotic drug) and negative where hypotheses failed confirmation (but were not necessarily disconfirmed). As most studies tested many markers, we coded each report according to whether some, all, or no tested hypotheses were positive. The second outcome category was discussion of results in light of hypotheses. Studies were scored as 'positive' when discussions indicated that PD results were consistent with the predicted molecular effects of the agent. Discussions were coded as ambiguous where they gave no clear indication as to whether PD supported the predicted effect of the agent, and were coded as negative where they suggested PD did not support the predicted molecular effects. The third outcome assessed was discussion of results in light of future study planning. Studies were coded as informative where PD results (whether themselves positive or negative) were said to inform planning of future studies. Discussions were coded as uninformative where they gave no clear indication of how PD results related to future investigations.

In a *post hoc* analysis, we studied the effect of industry funding on PD outcome reporting, focusing on the proportion of positive assay results and the discussion of those results in light of hypotheses and planning for future studies. Fisher's exact test of independence was used to calculate significance (McDonald, 2009).

Statistics. As this was an exploratory study, we used a convenience sample of PD studies rather than a prospectively determined sample size. We tested *a priori*-formulated hypotheses of correlation between RS and the following seven variables: (1) the year of publication, (2) public funding, (3) journal impact factor, (4) separate publication for PD results, (5) use of a non-novel test drug, (6) mandatory biopsy; and (7) author assessment of the trial outcome (negative outcome defined as studies recommending that further trials of the investigational agent should not be undertaken). Significance of relationships was tested using one-way ANOVA with SPSS software. We defined significance as $P \leqslant 0.05$. We did not correct for multiple comparisons.

RESULTS

Sample. Our PubMed search produced a sample of 68 eligible articles reporting results from early-phase cancer trials utilising non-diagnostic biopsy for PD analysis (flow of articles is described in Figure 1; see Appendix 2 for an inventory of studies). Table 1 displays the characteristics of the trials in our sample; Table 2 reports biopsy characteristics within our sample. Ten studies in our sample (15%) actively reported safety events related to biopsy; of these, one reported a single adverse event at or above grade 3.

Our sample captured a total of 2644 patients receiving invasive non-diagnostic biopsies. Although reporting of patient flow through PD studies was poor, we recorded author explanations for discrepancies between patients approached for biopsy, samples collected, and samples analysed. The most common reason for discrepancy was insufficient quality or quantity of sample for analysis (84%), followed by patient refusal (19%) and medical contraindication for biopsy (19%). Missed samples (3%) were because of patient death.

Reporting score. We calculated the RS for each article in our sample. The RS range had a score centred around 5.5 (Figure 2). Some variables, like description of causal pathway and biopsy location, were consistently reported (Table 3). However, there was broad variation within specific domains in the RS. A fifth of articles did not report results for all PD analyses performed; 57% did not report the status of blinding for pathological analysis and 62% did not provide information about the dimensions of the biopsy sample.

Reporting predictors. The use of a non-novel study drug showed positive but non-significant trend towards a higher RS (5.6 *vs* 5.2, $P = 0.219$). Pharmacodynamics as a primary end point showed a significant positive relationship with RS (5.8 *vs* 5.1, $P = 0.04$), as did the use of mandatory biopsy (5.9 *vs* 5.1, $P = 0.023$). We found no relationship between RS and the year of publication, journal impact factor, funding source, or author assessment of the trial outcome.

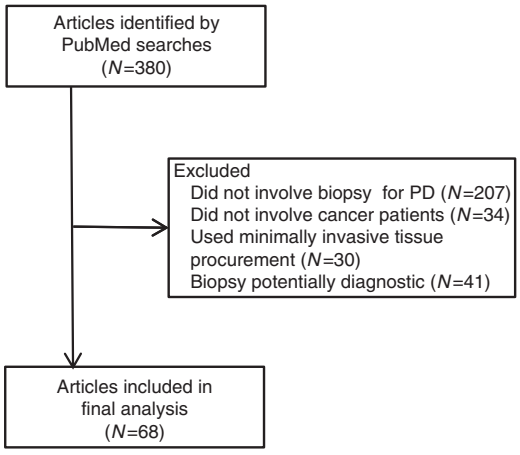

Figure 1. Diagram of flow of the published articles selection process.

Table 1. Characteristics of early-phase cancer trials included in sample ($n = 68$)

Location corresponding author	
North America	64.7%
Europe	33.8%
Australia	1.5%
Number of trials by time period	
2000–2005	36.8%
2006–2010	63.2%
Trial goals[a]	
Safety	52.9%
Dose	38.6%
Biologic effect/efficacy	42.6%
Pharmacodynamics (PD)	76.5%
Pharmacokinetics	16.2%
PD as the primary end point	41%
Trial phase	
0	3%
1	53%
1/2	6%
2	31%
Not specified	7%
Trial agent characteristics	
Single agent	66%
Novel agent[b]	53%
Patients	
Average number of patients per trial	39
Range	7–270
Total number of patients enrolled across all trials	2644
Funding source[a]	
Industry	38%
Foundation	31%
Government	51%
Trial outcome[a]	
Dose identified	38.2%
Mechanism demonstrated	29.4%
Clinical activity demonstrated	23.5%
Further trials inappropriate	35.3%
Other	26.5%

Characteristics of the parent studies.
[a]Trials reported multiple goals, outcomes, and funding sources. Percentages do not necessarily add up to 100%.
[b]Defined as not FDA approved at time of study.

Table 2. Characteristics of early-phase cancer trials included in sample ($n = 68$)

Biopsy overview	
Average number of research biopsies collected per trial	57.3
Range	1–942
Average number of biopsies per patient	2.3
Range	1–9.5
Total number of biopsies collected across all trials	3781
Mandatory biopsy[a]	
Yes	36%
No/unclear	64%
Biopsy location[a]	
Skin	46%
Breast	17%
Head and neck	17%
Liver	15%
GI tract	15%
Lung	9%
Bone marrow	5%
Ovary	5%
Other	17%
Procurement method[a]	
Core needle	41%
Punch	31%
Fine needle	16%
Surgical excision	14%
Percutaneous/trucut	14%
Endoscopic	12%
Other	12%
Purpose of pharmacodynamic (PD) investigation[a]	
Dose escalation guide	6%
Marker identification	21%
Find recommended dose	13%
Proof-of-concept	66%
Mechanism, effect on tissue or function	65%
Biodistribution	6%
Relate mechanism to response	26%
Unclear or not stated	24%
Other	13%

Characteristics of the invasive tissue procurement procedures.
[a]Refers to the percentage of studies. Trials reported multiple biopsy locations and purposes of PD investigation. Percentages will not add up to 100%.

Pharmacodynamic study outcome. The majority of articles (66%) reported some negative PD results and 10% of the articles reported all negative PD results. Fifty-six percent of studies reported at least one positive PD parameter. The majority of studies (61%) described their PD results as 'positive' in discussions (for example, PD results provided evidence of the investigational agent having intended effects on molecular targets).

A large majority of articles (78%) contained a discussion of PD results in relation to the direction of future studies. Among these, 72% discussed possible amendments to the conduct or direction of future studies based on the PD findings of the current study.

Industry funding *vs* results positivity. Industry-funded trials were more likely to report all or some positive PD results than non-industry-funded studies. No industry-funded trial reported all negative results for PD parameters tested. Trials with industry funding trended towards greater positivity in discussion both in terms of support for the predicted method of action of the drug

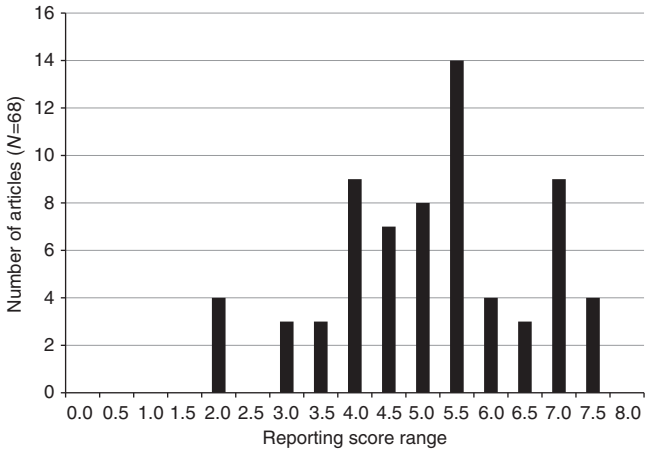

Figure 2. Distribution of RSs for sample of early-phase cancer trials utilising biopsy for PD study.

(75% *vs* 53%, $P = 0.11$) and planning for future studies (80% *vs* 67%, $P = 0.359$).

DISCUSSION

Biopsies for PD in anticancer drug trials are often burdensome and entail non-trivial costs. Justification of procedures rests on a favourable gain of scientific knowledge (Weijer and Miller, 2004). Poor PD reporting does not adequately redeem burdens and can produce biased findings that lead to unsuccessful clinical development (Tan *et al*, 2009). At present, there is little systematic evidence to inform the planning, implementation, and ethical evaluation of PD studies involving invasive tissue procurement.

Our study explored two relatively objective proxies of knowledge value in a convenience sample of PD studies using research biopsies. Encouragingly, a large fraction of studies reported tissue location, procurement method, and discussion of PD results. However, many important items were reported sporadically, including results of all planned tests, use of blinded histopathological assessment, biopsy dimensions, and description of patient flow through the PD portion of the trial. Previous studies of prognostic marker research reporting showed that over 90% of studies reported 'positive' outcomes (Kyzas *et al*, 2005; Kyzas *et al*, 2007). Disproportionate reporting of positive results was also observed in genetic association studies (Ioannidis *et al*, 2001). We entered this study expecting near-uniform positivity among PD reports. Instead, we found that two-thirds of articles contained negative outcomes, and a similar proportion described PD analysis as affirming hypotheses in discussion. This is evidence that PD is not characterised by overwhelming publication bias, and that results are not overdetermined at study inception. Nevertheless, that the fraction of studies reporting uniform positivity (34%) *vs* those reporting uniform negativity (10%) suggests, in our view, the presence of some bias. Whether this bias pertains to publication bias, or enhanced pre-test probability, we are unable to say. Analysis of positivity would be greatly aided if studies declared their primary hypothesis; the only instance where this occurred was in studies that reported only a single PD marker analysis. We further take the fact that a large fraction of PD studies were described as informing decisions for future studies as support for invasive PD evaluation. Future studies should investigate the fraction of PD findings that motivate actual new investigations.

Our study has several limitations. First, some might question the premises guiding our proxy indicators of knowledge value. Poorly reported studies can still hold value, and uniformly positive results can convert modest degrees of belief in drug effects into higher

Table 3. Reporting score (RS) outcomes ($n = 68$)

Reporting domain	Weighted reporting variable (weight)[a]	% Trials	95% confidence interval
Goal and hypothesis			
	Stated goal clearly (0.5)	76	66–87
	Description molecular causal pathway (0.5)	97	93–100
Subject eligibility			
	Patient eligibility for biopsy described (1)	62	50–73
Specimen characteristics			
	Biopsy dimensions (0.25)	38	27–50
	Method of procurement (0.25)	72	61–83
	Location (0.25)	96	91–100
	Description of specimen processing (0.25)	69	58–80
Assay protocol			
	Protocol described or reference provided (0.2)	59	47–71
	Identity of person conducting assay/analysis given (0.2)[b]	32	21–43
	Description of controls (0.2)	49	37–60
	Scoring or quantitation protocols described (0.2)	77	66–87
	Blinded outcome assessment described (0.2)	43	32–54
Statistics			
	Statistical justification sample size, significance (1)	56	44–68
Subject flow			
	Number of biopsies collected and analysed reported (0.5)	62	50–73
	Explanation for disparity or unaccounted samples (0.5)	59	46–73
Results reporting			
	Results shown for all tested hypotheses (1)	78	68–88
Discussion			
	Alternate explanations for positive or negative results (0.33)	71	60–82
	Discussion of results in light of hypotheses (0.33)	91	84–98
	Discussion of results in terms of future study planning (0.33)	78	68–88

[a]Where reporting variables were not applicable, that variable was removed from consideration and the remaining variables were reweighted to create the reporting domain score.
[b]Where qualitative assessment of tissue staining was used (e.g. immunohistochemistry).

degrees of belief. Still, uniform confirmation would seem a modest gain of information for considerable burden. Second, some items in the RS, similar to blinded outcome assessment, straddle 'good reporting' and 'good methodological practice,' and high quality reporting can mask poor methodological practice (Huwiler-Muntener *et al*, 2002; Toulmonde *et al*, 2011). Third, in line with the exploratory orientation, our study did not capture a comprehensive sample of studies involving research biopsies. A larger sample might have produced different findings and our sample may have been underpowered to detect relationships between study characteristics and reporting quality. Fourth, although our article points to ways that reporting of PD might improve, nothing in our premises, data, or analysis provides a clear basis for deciding whether current research biopsy and PD study practices meet an adequate threshold of knowledge value. Last, our RS scale should be interpreted with caution. It was not the result of a consensus building process (unlike CONSORT and REMARK) (Harris, 2005; McShane *et al*, 2005; Lai *et al*, 2006; 'How CONSORT began', 2008; Rios *et al*, 2008; Toulmonde *et al*, 2011). Furthermore, it gave uniform weighting for each criterion, which may not be appropriate, given that some items probably matter more than others with respect to valid study interpretation. Nevertheless, our scale was at least modelled on validated criteria and we believe its application is justified in the context of this exploratory exercise. Finally, although this study identifies deficiencies in current reporting practices and may aid in the development of consensus guidelines, it must be noted that delay to publication means that current study practices may not be accurately represented in our study.

Our study suggests several avenues investigators, funders, or IRBs might consider for improving the risk–benefit balance of PD studies. First, we recommend the research community develop formalized reporting guidelines similar to REMARK and CONSORT. Second, given our observation that separate PD-reporting trends towards higher quality, and that reporting quality for PD studies may be constrained by word counts at journals, we encourage investigators to consider separate PD publication, using standard methods described in a reference or reporting methods in supplementary materials (Toulmonde *et al*, 2011). Journal editors may have a role in limiting 'text limitation bias.' Third, given that PD components might not be registered in http//www.clinicaltrials.gov, IRBs might have a more active role in promoting

reporting and publication by asking investigators to provide a detailed reporting plan for PD studies. A recent article recommended the creation of an online biomarker study registry similar to http//www.clinicaltrials.gov (Andre *et al*, 2011). We support extending this initiative to PD.

Together with a previous study by our team, our results offer a complex picture of the quality of reporting for PD studies involving non-diagnostic biopsy. A preponderance of positive results, coupled with a finding that 63% of PD studies go unreported suggests biases. Low perceived quality of reports, and low reporting of basic factors like patient flow, suggests considerable room for improvement. On the other hand, some studies demonstrate careful reporting, many negative results are reported, and a large fraction of studies report that PD findings will help guide future investigations. In the end, we conclude that the evidence gathered above provides ammunition for proponents as well as opponents of research biopsies in cancer. In any event, our findings and analysis provide grounds for developing and disseminating PD-reporting standards.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX 1

Appendix 1 – PD Published Article Extraction Sheet

Coder _____ Date _____

I. GENERAL STUDY INFORMATION

A) Basic Information about overall publication

First Author _____

Location of Corresponding author

☐ N. America ☐ Europe ☐ Asia ☐ Australia ☐ Other _____

Journal _____ **Year of Publication** _____

Stated Goal ☐ Safety ☐ Dosage ☐ Efficacy ☐ PD

Financial Interest Disclosure ☐ Yes ☐ No

Sponsor ☐ Industry ☐ Foundation ☐ Government

Phase ☐ I ☐ I/II ☐ II ☐ III ☐ NA

B) Drug

1° Drug Name _____ **1°Drug Class**_____

Combination trial? ☐ Yes ☐ No

Any Drugs NOT FDA Approved at time of study? ☐ Yes ☐ No

Description of mechanism in introduction:

_____

_____

C) Patients

Number of Patients
Enrolled in trial _____

Any Pediatric Subjects? ☐ Yes ☐ No

Patient Demographics
Cancer type(s) _____ ☐ Metastatic /Advanced ☐ Refractory

Patient Eligibility for Enrollment
☐ Tumor accessible for invasive biopsy

D) Outcomes

AEs (Bx related)
G3/G4 ___ G5 ___ Actively reports no Bx AEs: ☐ Yes ☐ No

Conclusions/Recommendation in Abstract or Discussion
☐ Maximum tolerated / Optimal dose identified / recommended
☐ Mechanism identified / confirmed ☐ Clinical activity demonstrated
☐ No significant advance / further trials should not be conducted
Other _____

E) Ethics & Practice Standards

Ethics Standards for Invasive, NonDx Biopsy
Mandatory Invasvie NonDx Biopsy ☐ Yes ☐ No/NA
Consent Procedures for biopsy described? ☐ Yes ☐ No

Laboratory Practice Standards
Reference to Good Laboratory Practice or other standard ☐ Yes ☐ No

F) Comment, General Study Information

_____

II. PHARMACODYNAMIC SUBSTUDIES

INTRODUCTION

Pharmacodynamic information the primary endpoint or goal of pub? ☐ Yes ☐ No

1a. Stated Goal of Pharmacodynamic studies

☐ Dose escalation guide ☐ Marker identification ☐ Find recommended dose
☐ Proof-of-concept: ☐ Mechanism/Effect on Tissue / Function
☐ Biodistribution ☐ Relate Mechanism to Resp.
☐ Unclear and/or not stated ☐ Other, specify _____

1b. Hypothesis

Any description of molecular causal pathway?	☐ Yes	☐ No
Primary PD endpoint specified anywhere?	☐ Yes	☐ No
Hypothesis Stated in Quantitative Terms	☐ Yes	☐ No

MATERIALS AND METHODS

Patients

2. Eligibility for biopsy described ☐ Yes ☐ No
☐ Tumor accessible for biopsy ☐ Mandatory
☐ Completed Treatment ☐ NA ☐ Other, specify _____

Specimen characteristics

Describes type of biological material	☐ Tumor	☐ Healthy	☐ NA
Reason for Use of surrogate tissue explained	☐ Yes	☐ No	☐ NA

Sample Volume

4a. Dimensions clearly defined	☐ Yes	☐ No
Imaging used for procurement	☐ Yes	☐ No

4b. Method of Procurement Specified: ☐ Yes ☐ No
☐ Surgical Excision ☐ Core needle ☐ Bronchoscopy
☐ Fine needle ☐ Colonoscopy ☐ Punch Bx
☐ Other, specify _____ ☐ NA

4c. Tissue Location provided ☐ Yes ☐ No
☐ Colon ☐ Liver ☐ Lung ☐ Bone Marrow ☐ Skin ☐ NS
☐ Cervix ☐ Breast ☐ Head/neck ☐ Heart ☐ Other_____

4d. Sample Preparation Procedures provided: ☐ Yes ☐ No
Processing / Preservation / Storage (any) of tissues described ?
☐ Yes ☐ No ☐ NA
Purification/preparation before assay specified
☐ Yes ☐ No ☐ NA

Assay Procedures

Assays used
Protein ☐ Immunohistochemistry ☐ Western Blot ☐ ELISA
Nucleic Acid ☐ Northern Blot ☐ Gene Exprs arrays ☐ real-time PCR
Cell ☐ TUNEL ☐ Other, specify _____
Other _____

5a. Assay protocol described (or reference provided) ☐ All ☐ Some ☐ None

5b. Quality control procedures reported

Y	N	
☐	☐	calibration of any assay
☐	☐	identity of person doing any assay/analysis/measure
☐	☐	test of reproducibility of assay
☐	☐	- or + controls, any
☐	☐	scoring, quantitation, or reporting protocols
☐	☐	specifies what is considered a positive assay result

5c. Outcome assessment from PD

- Quantitative or semiquant assessment of marker changes		☐ Yes	☐ No	☐ NA
- Blinded/automated assessment	☐ All	☐ Some	☐ None	☐ NA
- If μscopic exam, selection of fields explained?		☐ Yes	☐ No	☐ NA

Statistics	**Y**	**N**
10a. Power Calculations/ Sample size justification for PD	☐	☐
10b. Statistical methods described in methods §	☐	☐

RESULTS

Study involves paired biopsies ☐Yes ☐No
Any use of archival tissues? ☐Yes ☐No

Data

12a. Flow of pts for PD invasive biopsies (diagnostic AND nondiagnostic)
specified in full: ☐Y ☐N ☐NA
Projected pts ____ Collected pts ____ Included pts in Analysis____
Projected bxs ____ Collected bxs____ Bxs included in analysis ____

Number of excess invasive Bx (i.e. clearly nondiagnostic)
Projected pts ____ Collected pts ____ Included pts in Analysis____
Projected bx____ Collected bx____ Included in Analysis bx____

12b. Explanation for disparity / unaccounted samples
☐Yes ☐No ☐NA

Reasons for drop-outs
☐Patient refusal ☐Medically indicated
☐Insufficient amount or quality of sample/cells ☐Death
☐Excluded b/c prespecified criteria _____
☐Other, specify _____ ☐NA

In addition, does study report PD involving minimal risk procedures (e.g. venipuncture)
☐Yes ☐No Specify _____

Analysis and Presentation

	Parameter	Hypothesis	Direction of Outcome (+ / 0 / –)	Significance (+ / – / NA)

14a. Results for relationship of marker changes(s) to all tested hypotheses shown:
☐All ☐Some ☐None

18a. If + result w/ respect to hypothesis, did the investigators perform any experiments to rule out alternative causes for the relationships observed? ☐Yes ☐No ☐NA

DISCUSSION

19a. Does the discussion section address any possible alternate explanations (eg. bias) for a + PD result? ☐ Yes ☐ No ☐ NA

19b. Are unexpected invasive PD results discussed in causal terms – is a source of error offered? ☐ Methodol. ☐ Hypothesis ☐ No ☐ NA

19c. Discussion of PD results in discussion section ☐ Yes ☐ No ☐ NA

Discussion of invasive PD Results w/respect to drug causing molecular changes
☐ Negative ☐ Neutral/Ambiguous ☐ Positive ☐ None

Discussion of invasive PD Results w/respect to PD results supporting decision-making for ph2 or for ph 3, or for preclinical development
☐ Negative ☐ Neutral/Ambiguous ☐ Positive ☐ NA

H) Comment, Pharmacodynamic Substudies

APPENDIX 2

Inventory of studies included in sample

Adjei AA, RB Cohen, WFranklin, CMorris, DWilson, JRMolina, LJHanson, L Gore, L Chow, S Leong, L Maloney, G Gordon, H Simmons, A Marlow, K Litwiler, S Brown, G Poch, K Kane, J Haney, SG Eckhardt (2008) Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor Azd6244 (Arry-142886) in patients with advanced cancers. *J Clin Oncol* **26**(13): 2139–2146.

Agulnik M, EW Cohen, RB Cohen, EX Chen, EE Vokes, SJ Hotte, EWinquist, S Laurie, DN Hayes, JE Dancey, S Brown, GR Pond, I Lorimer, M Daneshmand, J Ho, MS Tsao, LL Siu (2007) Phase Ii study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or Erbb2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol* **25**(25): 3978–3984.

Agulnik M, G da Cunha Santos, D Hedley, T Nicklee, PP Dos Reis, J Ho, GR Pond, H Chen, S Chen, Y Shyr, E Winquist, D Soulieres, EX Chen, JA Squire, P Marrano, S Kamel-Reid, J Dancey, LL Siu, MS Tsao (2007) Predictive and pharmacodynamic biomarker studies in tumor and skin tissue samples of patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with erlotinib. *J Clin Oncol* **25**(16): 2184–2190.

Albanell J, F Rojo, S Averbuch, A Feyereislova, JM Mascaro, R Herbst, P LoRusso, D Rischin, S Sauleda, J Gee, RI Nicholson, J Baselga (2002) Pharmacodynamic studies of the epidermal growth factor receptor inhibitor zd1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. *J Clin Oncol* **20**(1): 110–124.

Annunziata CM, AJ Walker, L Minasian, M Yu, H Kotz, BJ Wood, K Calvo, P Choyke, D Kimm, SM Steinberg, EC Kohn (2010) Vandetanib, designed to inhibit Vegfr2 and Egfr signaling, had no clinical activity as monotherapy for recurrent ovarian cancer and no detectable modulation of Vegfr2. *Clin Cancer Res* **16**(2): 664–672.

Badros A, AM Burger, S Philip, R Niesvizky, SS Kolla, O Goloubeva, C Harris, J Zwiebel, JJ Wright, I Espinoza-Delgado, MR Baer, JL Holleran, MJ Egorin, S Grant (2009) Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma. *Clin Cancer Res* **15**(16): 5250–5257.

Baselga J, J Albanell, A Ruiz, A Lluch, P Gascon, V Guillem, S Gonzalez, S Sauleda, I Marimon, JM Tabernero, MT Koehler, F Rojo (2005) Phase Ii and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. *J Clin Oncol* **23**(23): 5323–5333.

Baselga J, D Rischin, M Ranson, H Calvert, E Raymond, DG Kieback, SB Kaye, L Gianni, A Harris, T Bjork, SD Averbuch, A Feyereislova, H Swaisland, F Rojo, J Albanell (2002) Phase I safety, pharmacokinetic, and pharmacodynamic trial of zd1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* **20**(21): 4292–4302.

Baselga J, V Semiglazov, P van Dam, A Manikhas, M Bellet, J Mayordomo, M Campone, E Kubista, R Greil, G Bianchi, J Steinseifer, B Molloy, E Tokaji, H Gardner, P Phillips, M Stumm, HA Lane, JM Dixon, W Jonat, HS Rugo (2009) Phase Ii randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. *J Clin Oncol* **27**(16): 2630–2637.

Borghaei H, K Alpaugh, G Hedlund, G Forsberg, C Langer, A Rogatko, R Hawkins, S Dueland, U Lassen, RB Cohen (2009) Phase I dose escalation, pharmacokinetic and pharmacodynamic study of naptumomab estafenatox alone in patients with advanced cancer and with docetaxel in patients with advanced non-small-cell lung cancer. *J Clin Oncol* **27**(25): 4116–4123.

Boss DS, GK Schwartz, MR Middleton, DD Amakye, H Swaisland, RS Midgley, M Ranson, S Danson, H Calvert, R Plummer, C Morris, RD Carvajal, LR Chirieac, JH Schellens, GI Shapiro (2010) Safety, tolerability, pharmacokinetics and pharmacodynamics of the oral cyclin-dependent kinase inhibitor azd5438 when administered at intermittent and continuous dosing schedules in patients with advanced solid tumours. *Ann Oncol* **21**(4): 884–894.

Busam KJ, P Capodieci, R Motzer, T Kiehn, D Phelan, AC Halpern (2001) Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* **144**(6): 1169–1176.

Byrd JC, G Marcucci, MR Parthun, JJ Xiao, RB Klisovic, M Moran, TS Lin, S Liu, AR Sklenar, ME Davis, DM Lucas, B Fischer, R Shank, SL Tejaswi, P Binkley, J Wright, KK Chan, MR Grever (2005) A phase 1 and pharmacodynamic study of depsipeptide (Fk228) in chronic lymphocytic leukemia and acute myeloid leukemia. *Blood* **105**(3): 959–967.

Camidge DR, MN Pemberton, JW Growcott, D Johnstone, PJ Laud, JR Foster, KJ Randall, AM Hughes (2005) Assessing proliferation, cell-cycle arrest and apoptotic end points in human buccal punch biopsies for use as pharmacodynamic biomarkers in drug development. *Br J Cancer* **93**(2): 208–215.

Decensi A, R Torrisi, S Bruno, M Costantini, A Curotto, G Nicolo, B Malcangi, L Baglietto, GP Bruttini, B Gatteschi, G Rondanina, M Varaldo, M Perloff, WF Malone, P Bruzzi (2000) Randomized trial of fenretinide in superficial bladder cancer using DNA flow cytometry as an intermediate end point. *Cancer Epidemiol Biomarkers Prev* **9**(10): 1071–1078.

Dowlati A, K Robertson, T Radivoyevitch, J Waas, NP Ziats, P Hartman, FW Abdul-Karim, JK Wasman, J Jesberger, J Lewin, K McCrae, P Ivy, SC Remick (2005) Novel phase i dose de-escalation design trial to determine the biological modulatory dose of the antiangiogenic agent Su5416. *Clin Cancer Res* **11**(21): 7938–7944.

Duran I, J Kortmansky, D Singh, H Hirte, W Kocha, G Goss, L Le, A Oza, T Nicklee, J Ho, D Birle, GR Pond, D Arboine, J Dancey, S Aviel-Ronen, MS Tsao, D Hedley, LL Siu (2006) A phase Ii clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer* **95**(9): 1148–1154.

Dy GK, JP Thomas, G Wilding, L Bruzek, S Mandrekar, C Erlichman, D Alberti, K Binger, HC Pitot, SR Alberts, LJ Hanson, R Marnocha, K Tutsch, SH Kaufmann, AA Adjei (2005) A phase I and pharmacologic

trial of two schedules of the proteasome inhibitor, Ps-341 (Bortezomib, Velcade), in patients with advanced cancer. *Clin Cancer Res* **11**(9): 3410–3416.

Eder JP, GI Shapiro, LJ Appleman, AX Zhu, D Miles, H Keer, B Cancilla, F Chu, S Hitchcock-Bryan, L Sherman, S McCallum, EI Heath, SA Boerner, PM LoRusso (2010) A phase I study of foretinib, a multi-targeted inhibitor of C-Met and vascular endothelial growth factor receptor 2. *Clin Cancer Res* **16**(13): 3507–3516.

Fakih MG, L Pendyala, G Fetterly, K Toth, JA Zwiebel, I Espinoza-Delgado, A Litwin, YM Rustum, ME Ross, JL Holleran, MJ Egorin (2009) A phase I, pharmacokinetic and pharmacodynamic study on vorinostat in combination with 5-fluorouracil, leucovorin, and oxaliplatin in patients with refractory colorectal cancer. *Clin Cancer Res* **15**(9): 3189–3195.

Fakih MG, A Rajput, GY Yang, L Pendyala, K Toth, JL Smith, DD Lawrence, YM Rustum (2006) A phase I study of weekly intravenous oxaliplatin in combination with oral daily capecitabine and radiation therapy in the neoadjuvant treatment of rectal adenocarcinoma. *Int J Radiat Oncol Biol Phys* **65**(5): 1462–1470.

Felip E, F Rojo, M Reck, A Heller, B Klughammer, G Sala, S Cedres, S Peralta, H Maacke, D Foernzler, M Parera, J Mocks, C Saura, U Gatzemeier, J Baselga (2008) A phase Ii pharmacodynamic study of erlotinib in patients with advanced non-small cell lung cancer previously treated with platinum-based chemotherapy. *Clin Cancer Res* **14**(12): 3867–3874.

Fracasso PM, H Burris 3rd, MA Arquette, R Govindan, F Gao, LP Wright, SA Goodner, FA Greco, SF Jones, N Willcut, C Chodkiewicz, A Pathak, GM Springett, GR Simon, DM Sullivan, R Marcelpoil, SD Mayfield, D Mauro, CR Garrett (2007) A phase 1 escalating single-dose and weekly fixed-dose study of cetuximab: pharmacokinetic and pharmacodynamic rationale for dosing. *Clin Cancer Res* **13**(3): 986–993.

Goss G, H Hirte, WH Miller Jr, IA Lorimer, D Stewart, G Batist, DA Parolin, P Hanna, S Stafford, J Friedmann, W Walsh, S Mathews, L Douglas, LK Seymour (2005) A phase I study of oral Zd 1839 given daily in patients with solid tumors: Ind.122, a study of the investigational new drug program of the national cancer institute of canada clinical trials group.' *Invest New Drugs* **23**(2): 147–155.

Haddad RI, LJ Weinstein, TJ Wieczorek, N Bhattacharya, H Raftopoulos, MW Oster, X Zhang, VM Latham Jr, R Costello, J Faucher, C DeRosa, M Yule, LP Miller, M Loda, MR Posner, GI Shapiro (2004) A phase Ii clinical and pharmacodynamic study of E7070 in patients with metastatic, recurrent, or refractory squamous cell carcinoma of the head and neck: modulation of retinoblastoma protein phosphorylation by a novel chloroindolyl sulfonamide cell cycle inhibitor. *Clin Cancer Res* **10**(14): 4680–4687.

Herbst RS, AM Davies, RB Natale, TP Dang, JH Schiller, LL Garland, VA Miller, D Mendelson, AD Van den Abbeele, Y Melenevsky, DJ De Vries, DA Eberhard, B Lyons, SG Lutzker, BE Johnson (2007) Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non small cell lung cancer. *Clin Cancer Res* **13**(20): 6175–6181.

Jansen B, V Wacheck, E Heere-Ress, H Schlagbauer-Wadl, C Hoeller, T Lucas, M Hoermann, U Hollenstein, K Wolff, H Pehamberger (2000) Chemosensitisation of malignant melanoma by Bcl2 antisense therapy. *Lancet* **356**(9243): 1728–1733.

Jatoi A, VJ Suman, P Schaefer, M Block, C Loprinzi, P Roche, S Garneau, R Morton, PJ Stella, SR Alberts, M Pittelkow, J Sloan, R Pagano (2003) A phase Ii study of topical ceramides for cutaneous breast cancer. *Breast Cancer Res Treat* **80**(1): 99–104.

Joensuu G, T Joensuu, P Nokisalmi, C Reddy, J Isola, M Ruutu, M Kouri, PA Kupelian, J Collan, S Pesonen, A Hemminki (2010) A phase I/Ii trial of gefitinib given concurrently with radiotherapy in patients with nonmetastatic prostate cancer. *Int J Radiat Oncol Biol Phys* **78**(1): 42–49.

Koon HB, GJ Bubley, L Pantanowitz, D Masiello, B Smith, K Crosby, J Proper, W Weeden, TE Miller, P Chatis, MJ Egorin, SR Tahan, BJ Dezube (2005) Imatinib-induced regression of AIDS-related kaposi's sarcoma. *J Clin Oncol* **23**(5): 982–989.

Kummar S, R Kinders, ME Gutierrez, L Rubinstein, RE Parchment, LR Phillips, J Ji, A Monks, JA Low, A Chen, AJ Murgo, J Collins, SM Steinberg, H Eliopoulos, VL Giranda, G Gordon, L Helman, R Wiltrout, JE Tomaszewski, JH Doroshow (2009) Phase 0 clinical trial of the poly (Adp-ribose) polymerase inhibitor Abt-888 in patients with advanced malignancies. *J Clin Oncol* **27**(16): 2705–2711.

Lin J, J Gilbert, MA Rudek, JA Zwiebel, S Gore, A Jiemjit, M Zhao, SD Baker, RF Ambinder, JG Herman, RC Donehower, MA Carducci (2009) A phase I dose-finding study of 5-azacytidine in combination with sodium phenylbutyrate in patients with refractory solid tumors. *Clin Cancer Res* **15**(19): 6241–6249.

LoRusso PM, SS Krishnamurthi, JJ Rinehart, LM Nabell, L Malburg, PB Chapman, SE DePrimo, S Bentivegna, KD Wilner, W Tan, AD Ricart (2010) Phase I pharmacokinetic and pharmacodynamic study of the oral Mapk/Erk kinase inhibitor Pd-0325901 in patients with advanced cancers. *Clin Cancer Res* **16**(6): 1924–1937.

Mackay H, D Hedley, P Major, C Townsley, M Mackenzie, M Vincent, P Degendorfer, MS Tsao, T Nicklee, D Birle, J Wright, L Siu, M Moore, A Oza (2005) A phase Ii trial with pharmacodynamic endpoints of the proteasome inhibitor bortezomib in patients with metastatic colorectal cancer. *Clin Cancer Res* **11**(15): 5526–5533.

Makower D, A Rozenblit, H Kaufman, M Edelman, ME Lane, J Zwiebel, H Haynes, S Wadler (2003) 'Phase Ii clinical trial of intralesional administration of the oncolytic adenovirus onyx-015 in patients with hepatobiliary tumors with correlative P53 studies. *Clin Cancer Res* **9**(2): 693–702.

Mathew P, PF Thall, D Jones, C Perez, C Bucana, P Troncoso, SJ Kim, IJ Fidler, C Logothetis (2004) Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: a modular phase I trial in androgen-independent prostate cancer. *J Clin Oncol* **22**(16): 3323–3329.

McDaid HM, S Mani, HJ Shen, F Muggia, D Sonnichsen, SB Horwitz (2002) Validation of the pharmacodynamics of Bms-247550, an analogue of epothilone B, during a phase I clinical study. *Clin Cancer Res* **8**(7): 2035–2043.

Millward MJ, A Joshua, R Kefford, S Aamdal, D Thomson, P Hersey, G Toner, K Lynch (2005) Multi-centre phase Ii trial of the polyamine synthesis inhibitor Sam486a (Cgp48664) in patients with metastatic melanoma. *Invest New Drugs* **23**(3): 253–256.

Moschos SJ, CA Sander, W Wang, SL Reppert, LM Drogowski, DM Jukic, UN Rao, C Athanassiou, M Buzoianu, M Mandic, L Richman, L McKinney, J Leininger, DA Tice, L Hammershaimb, JM Kirkwood (2010) Pharmacodynamic (phase 0) study using etaracizumab in advanced melanoma.' *J Immunother* **33**(3): 316–325.

Moulder SL, WF Symmans, DJ Booser, TL Madden, C Lipsanen, L Yuan, AM Brewster, M Cristofanilli, KK Hunt, TA Buchholz, J Zwiebel, V Valero, GN Hortobagyi, FJ Esteva (2008) Phase I/Ii study of G3139 (Bcl-2 antisense oligonucleotide) in combination with doxorubicin and docetaxel in breast cancer. *Clin Cancer Res* **14**(23): 7909–7916.

Mullamitha SA, NC Ton, GJ Parker, A Jackson, PJ Julyan, C Roberts, GA Buonaccorsi, Y Watson, K Davies, S Cheung, L Hope, JW Valle, JA Radford, J Lawrance, MP Saunders, MC Munteanu, MT Nakada, JA Nemeth, HM Davis, Q Jiao, U Prabhakar, Z Lang, RE Corringham, RA Beckman, GC Jayson (2007) 'Phase I evaluation of a fully human anti-alphav integrin monoclonal antibody (Cnto 95) in patients with advanced solid tumors. *Clin Cancer Res* **13**(7): 2128–2135.

O'Neil BH, L Raftery, BF Calvo, AB Chakravarthy, A Ivanova, MO Myers, HJ Kim, E Chan, PE Wise, LS Caskey, SA Bernard, HK Sanoff, RM Goldberg, JE Tepper (2010) A phase I study of bortezomib in combination with standard 5-fluorouracil and external-beam radiation therapy for the treatment of locally advanced or metastatic rectal cancer. *Clin Colorectal Cancer* **9**(2): 119–125.

Ord JJ, E Streeter, A Jones, K Le Monnier, D Cranston, J Crew, SP Joel, MA Rogers, RE Banks, IS Roberts, AL Harris (2005) Phase I trial of intravesical suramin in recurrent superficial transitional cell bladder carcinoma. *Br J Cancer* **92**(12): 2140–2147.

Overmoyer B, P Fu, C Hoppel, T Radivoyevitch, R Shenk, M Persons, P Silverman, K Robertson, NP Ziats, JK Wasman, FW Abdul-Karim, JA Jesberger, J Duerk, P Hartman, S Hanks, J Lewin, A Dowlati, K McCrae, P Ivy, SC Remick (2007) Inflammatory breast cancer as a model disease to study tumor angiogenesis: results of a phase Ib trial of combination Su5416 and doxorubicin. *Clin Cancer Res* **13**(19): 5862–5868.

Perez RP, LD Lewis, AP Beelen, AJ Olszanski, N Johnston, CH Rhodes, B Beaulieu, MS Ernstoff, A Eastman (2006) Modulation of cell cycle progression in human tumors: a pharmacokinetic and tumor molecular pharmacodynamic study of cisplatin plus the Chk1 inhibitor Ucn-01 (Nsc 638850). *Clin Cancer Res* **12**(23): 7079–7085.

Perotti A, A Locatelli, C Sessa, D Hess, L Vigano, G Capri, M Maur, T Cerny, S Cresta, F Rojo, J Albanell, S Marsoni, I Corradino, L Berk, VM Rivera, F Haluska, L Gianni (2010) Phase Ib study of the Mtor inhibitor ridaforolimus with capecitabine. *J Clin Oncol* **28**(30): 4554–4561.

Posadas EM, MS Liel, V Kwitkowski, L Minasian, AK Godwin, MM Hussain, V Espina, BJ Wood, SM Steinberg, EC Kohn (2007) A phase Ii and pharmacodynamic study of gefitinib in patients with refractory or recurrent epithelial ovarian cancer. *Cancer* **109**(7): 1323–1330.

Puglisi F, GG Cardellino, D Crivellari, C Di Loreto, MD Magri, AM Minisini, M Mansutti, C Andreetta, S Russo, D Lombardi, T Perin, G Damante, A Veronesi (2008) Thymidine phosphorylase expression is associated with time to progression in patients receiving low-dose, docetaxel-modulated capecitabine for metastatic breast cancer. *Ann Oncol* **19**(9): 1541–1546.

Ramanathan RK, MJ Egorin, C Erlichman, SC Remick, SS Ramalingam, C Naret, JL Holleran, CJ TenEyck, SP Ivy, CP Belani (2010) Phase I pharmacokinetic and pharmacodynamic study of 17-dimethylaminoethylamino-17-demethoxygeldanamycin, an inhibitor of heat-shock protein 90, in patients with advanced solid tumors. *J Clin Oncol* **28**(9): 1520–1526.

Ranson M, P Hersey, D Thompson, J Beith, GA McArthur, A Haydon, ID Davis, RF Kefford, P Mortimer, PA Harris, S Baka, A Seebaran, A Sabharwal, AJ Watson, GP Margison, MR Middleton (2007) Randomized trial of the combination of lomeguatrib and temozolomide compared with temozolomide alone in chemotherapy naive patients with metastatic cutaneous melanoma. *J Clin Oncol* 25(18): 2540–2545.

Rao S, N Starling, D Cunningham, M Benson, A Wotherspoon, C Lupfert, R Kurek, J Oates, J Baselga, A Hill (2008) Phase I study of epirubicin, cisplatin and capecitabine plus matuzumab in previously untreated patients with advanced oesophagogastric cancer. *Br J Cancer* **99**(6): 868–874.

Rojo F, E Gracias, N Villena, T Cruz, JM Corominas, I Corradino, M Cedeno, C Campas, M Osorio, N Iznaga, B Bellosillo, A Rovira, S Marsoni, P Gascon, S Serrano, C Sessa, T Crombet, J Albanell (2010) Pharmacodynamic trial of nimotuzumab in unresectable squamous cell carcinoma of the head and neck: a sendo foundation study. *Clin Cancer Res* **16**(8): 2474–2482.

Rojo F, J Tabernero, J Albanell, E Van Cutsem, A Ohtsu, T Doi, W Koizumi, K Shirao, H Takiuchi, S Ramon y Cajal, J Baselga (2006) Pharmacodynamic studies of gefitinib in tumor biopsy specimens from patients with advanced gastric carcinoma. *J Clin Oncol* **24**(26): 4309–4316.

Rothenberg ML, B LaFleur, DE Levy, MK Washington, SL Morgan-Meadows, RK Ramanathan, JD Berlin, AB Benson 3rd, RJ Coffey (2005) Randomized phase Ii trial of the clinical and biological effects of two dose levels of gefitinib in patients with recurrent colorectal adenocarcinoma. *J Clin Oncol* **23**(36): 9265–9274.

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