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COMMENTS AND CONTROVERSIES

Incremental Advance or Seismic Shift? The Need to Raise the Bar of Efficacy for Drug Approval

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INTRODUCTION

Targeted agents have improved outcomes in many common solid tumors and are available for clinical practice in most countries. There are many more drugs in the developmental pipeline that have the potential to improve the treatment of some of the most deadly cancers. It is estimated that there are more than 350 antineoplastic agents in clinical development for cancer indications.[1] This number is likely to increase in the future since the most important breakthroughs will most likely come from the development of targeted agents rather than from new cytotoxic chemotherapy.[1,2]

However, there is no question that both the costs of drug development and the price of approved biologics is very high.[3]

Table 1[4-20] summarizes the key efficacy results of the pivotal phase III registration trials on biologics for the treatment of solid tumors. Unlike imatinib that plays the role of a superstar in the first-line treatment of advanced gastrointestinal stromal tumors (GISTs),[19,21] the data indicate that the benefit of approved biologics in the much more common solid tumors is much smaller. These agents appear more incremental than superstars. In fact, the median HR for PFS and OS in the pivotal phase III trials used for registration of new biologic agents approved for advanced colorectal,[11,12,20] breast,[8-10] pancreatic,[17] non–small-cell lung cancer (NSCLC),[13,14] renal cell carcinoma,[4-7] and hepatocellular carcinoma[18] are 0.57 and 0.73, respectively (Table 1). This translates into median PFS and OS gains of 2.7 and 2.0 months, respectively. The huge median benefit of cetuximab in head and neck cancer[16] refers to the locally advanced setting (Table 1), not to the metastatic condition, common to the other trials in the Table. The enthusiasm for the demonstrated proof of principle in these diseases does not match the impact on patients.

There are ambivalent positions on this problem. There is pressure for the rapid development and approval of drugs against diseases for which there are no or little effective therapies.[22,23] In contrast, many of these new agents carry a very high price tag, especially considering the relatively modest gain in overall survival offered in the palliative setting.

No matter how limited these gains are, the overall outcomes for patients have improved. One example of that improvement can be seen in colorectal cancer. Ten to 15 years ago there were only one or two active drugs, and now there are seven US Food and Drug Administration–approved drugs. Median survival has more than doubled, from 10 to 12 months in the era of fluorouracil plus leucovorin to 20 to 24 months now. This is the reason why many current studies designed to evaluate new agents in colorectal cancer (and most other solid tumors) are looking for incremental differences in efficacy, typically 0.75 to 0.80 HR for PFS.

The question is whether we should continue to look for such a small, incremental δ, if we will not be able to afford the new, more expensive agents.

This article describes the concept of the target δ for registration trials. That is, the difference that should be sought that will not only meet statistical measures of efficacy, but meet meaningful clinical criteria of efficacy. While there are many other equally important issues, such as the end point to be pursued, the relation between cost and pricing, the approval process, and the time from approval to market, consideration of those issues is beyond the scope of this report. In addition, we will focus on advanced stage solid tumors since the target δ for trials in the adjuvant setting of these diseases are based on completely different principles as a function of the treatment aims in this condition.

HOW DOES THE TARGET δ AFFECT THE SIZE AND PRECISION OF A TRIAL?

There are three variables involved in calculating sample size for a phase III clinical trial: the anticipated magnitude of the difference in outcome between the experimental and control arms (the δ); the threshold for allowing a spuriously positive result when no difference really exists (the α level); and the likelihood of detecting a given difference in outcome between the treatment arms when one really exists (the power of the study). Due to the structure of the formulas relating the so-called δ to sample size, moderate increases in the δ translate into dramatic reduction in its size (keeping power fixed). An example of this relationship is given in Table 2 where changing the target death HR from 0.9 to 0.7 (ie, looking for a larger δ) translates into an eight-fold reduction in the necessary number of patients. Most clinical trials in metastatic disease are designed to detect relative risk reductions of 20% to 30% (HR, 0.7 to 0.8) and therefore need to enroll several hundred patients, typically between 500 and 1,000.

It should also be noted that since trials are usually designed to detect a target difference with a power greater than 50%, statistical significance will be achieved also for observed differences smaller than the target one: for instance, a trial designed to detect a 20% risk

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Table 1. Phase III Registration Trials of Biologics in Advanced Solid Tumors

Condition	Indication	No. of Patients in the Study	Design	PFS: Median Improvement Over Control (months)	PFS: *P*	PFS: Hazard Ratio	OS: Median Improvement Over Control (months)	OS: *P*	OS: Hazard Ratio
Renal cell carcinoma									
Sorafenib[4]	First-line metastatic	769	Sorafenib *v* placebo	2.7	< .001	0.44	NR*	NR	
Temsirolimus[5]	First-line metastatic with high-risk features	626	Temsirolimus *v* IFN alpha	2.4	< .001	0.66	3.6*	< .001	0.73
Sunitinib[6]	First-line metastatic	750	Sunitinib *v* IFN alpha	6.0	< .000001	0.42	NR*	NR	
Bevacizumab[7]	First-line metastatic	649	IFN alpha + bevacizumab *v* IFN alpha + placebo	4.8	.0001	0.63	NR*	NR	
Breast cancer									
Trastuzumab[8]	First-line metastatic HER-2+	469	Doxorubicin + cyclophosphamide or paclitaxel plus or minus trastuzumab	2.8* (TTP, not PFS)	< .001	0.51	4.8	.046	0.80
Bevacizumab[9]	First-line metastatic	722	Paclitaxel + bevacizumab *v* paclitaxel	5.9*	< .001	0.6	1.5	.16	0.88
Lapatinib[10]	Refractory HER-2+	399	Capecitabine + lapatinib *v* capecitabine alone	1.9*	< .001	0.57	NR	NR	
Colorectal cancer									
Bevacizumab[11]	First-line metastatic	813	IFL + bevacizumab *v* IFL	4.2	< .001	0.54	4.7*	< .001	0.66
Panitumumab[12]	Refractory	463	Panitumumab *v* best supportive care	0.15*	< .0001	0.54	0.0	1	1.0
Non–small-cell lung cancer									
Erlotinib[13]	Second- and third-line metastatic	731	Erlotinib *v* placebo 2:1 randomization	0.4	< .001	0.61	2.0*	< .001	0.7
Bevacizumab[14]	First-line stage IIIB or IV	878	Paclitaxel, carboplatin, bevacizumab *v* paclitaxel and carboplatin	1.7	< .001	0.66	2.0*	.003	0.79
GIST									
Sunitinib[15]	Second line	312	Sunitinib *v* placebo	4.8 (TTP, not PFS)*	< .001	0.33	NR	NR	
Head and neck cancer									
Cetuximab[16]	Locally advanced	424	RT plus or minus cetuximab	9.5* (local control)	.005	0.68	19.7	.032	0.74
Pancreatic cancer									
Erlotinib[17]	First-line metastatic	569	Gemcitabine + erlotinib *v* gemcitabine	0.25	.03	0.76	0.46*	.025	0.81
Hepatocellular carcinoma									
Sorafenib[18]	Pretreated hepatocellular carcinoma	602	Sorafenib *v* placebo	2.7	< .001	0.58	2.8*	< .001	0.69

NOTE. The registration trial data of imatinib in GIST (first line) are not included in the table because registration was based on the results of a phase II randomized trial comparing two drug doses in terms of frequency of objective responses, as compared with historical controls treated with chemotherapy.[19] The registration of cetuximab in advanced colorectal cancer is not included in the table because registration was based upon valuable responses reported in a randomized phase II trial of cetuximab and cetuximab plus irinotecan in irinotecan refractory patients.[20] Note that the registration of cetuximab plus RT in locally advanced head and neck cancer refers to a nonmetastatic phase.

Abbreviations: PFS, progression-free survival; OS, overall survival; NR, not reported; IFN, interferon; TTP, time to progression; IFL, irinotecan, fluorouracil, and leucovorin; GIST, gastrointestinal stromal tumor; RT, radiotherapy.

*Primary end point of the study.

reduction (HR, 0.8) with 90% power, will provide a statistically significant result ($P < .05$) if the observed risk reduction is as low as 10%. This generates a paradox since a trial that is designed to detect a minimum treatment effect that deserves clinical interest may still generate a statistically positive result even when the observed effect is smaller than anticipated or deemed desirable.

DO WE NEED TO RAISE THE BAR FOR THE TARGET δ IN COMPARATIVE TRIALS ON ADVANCED SOLID TUMORS?

Two key questions drive the choice of the target δ in comparative clinical trials: what is a plausible δ in terms of a measurable clinical effect? And what is a worthwhile δ in terms of substantive clinical benefit? So far, priority has been given to the first question rather than to the second. This is due to the recognition that superstars in the treatment of common solid tumors are the exception and that progress in oncology is incremental. It is also the case that a less ambitious target δ increases the chances of a positive trial. If the current strategy continues to dominate, the likely outcome will be a succession of trials that are positive in statistical terms, but of increasingly limited clinical relevance. This is best exemplified by the registration trial for erlotinib in advanced pancreatic cancer,[17] which provided an excellent proof of principle but had marginal relevance to practice since the median improvement in OS was only 2 weeks. The question becomes whether a death HR of 0.8 for the new versus standard treatment is sufficient for drug approval in a disease, or a

Table 2. No. of Patients Needed in a Hypothetical Randomized Trial in a Metastatic Cancer (expected 1-year survival in the control group = 50%) for Different Hazard Ratios

Target Hazard Ratio	1-Year PFS		No. of Patients Needed*		95% Confidence Limits for Hazard Ratio	
	Control	Expected	Power 80%	Power 90%	Power 80%	Power 90%
0.9	0.5	0.54	2,672	3,578	0.83 to 0.97	0.84 to 0.96
0.8	0.5	0.57	858	1,148	0.68 to 0.94	0.70 to 0.92
0.7	0.5	0.61	338	454	0.54 to 0.91	0.56 to 0.88
0.6	0.5	0.66	144	206	0.41 to 0.88	0.43 to 0.83
0.5	0.5	0.71	86	116	0.30 to 0.86	0.32 to 0.79
0.4	0.5	0.76	54	72	0.20 to 0.79	0.22 to 0.73

*Assuming 2 years of accrual and 2 years of further follow-up.

disease setting with a short life expectancy when this implies a gain in PFS/OS of only few weeks.

RAISING THE BAR FOR THE TARGET δ

To address these issues, we suggest that only treatments achieving paradigm changing target δ, should in future be awarded full approval in advanced cancer. Transferring scientific concepts that are measured on a continuum scale, such as efficacy, activity, or toxicity, into categoric classifications, such as clinically worthwhile/relevant or cost effective (yes/no), implies an arbitrary judgment. Ideally this judgment should lie exclusively within the patient-doctor relationship. However, due to financial constraints, this judgment must be and is made collectively (agencies, regulatory bodies, third party payers, and other stakeholders). The consequent decisions are very complex and should be made on a case by case basis.

As an example, we suggest the following arbitrary categories, representing an oversimplification of the concept of paradigm changing drug.

For diseases where the median survival time (MST) is shorter than 1 year and the PFS is 2 to 4 months (eg, pancreatic, gastric, NSCLC), a paradigm changing agent should have at least a 50% increment in MST or 2-year survival rates and a doubling in PFS.

For diseases where the MST is in the order of 2 years or longer and the PFS is 5 to 10 months (eg, breast, colorectal, ovarian cancer), a 30% increment in MST or 2- to 3-year survival rates and a 50% increase in PFS should also be considered paradigm changing.

According to this reasoning, for aggressive neoplasms a PFS HR of 0.5 (ie, doubling the median PFS) would be paradigm changing, thus necessary and sufficient for registration, whereas this threshold could be around 0.6 to 0.7 (ie, a 50% increment in median PFS) for breast, colorectal, ovarian, and other conditions with similar prognoses.

The counterpoint to this approach would be to seek a smaller δ in more aggressive cancers, given the fact that they are so resistant to any treatment that even a small change could be noteworthy. However, such an approach would reiterate the philosophy of bias toward what is statistically demonstrable rather than clinically worthwhile.

The relationship between median OS/PFS and the increase in median OS/PFS as a function of the actual HR is shown in Table 3.

POTENTIAL BENEFITS OF RAISING THE BAR

Shifting the priority of the key questions in trial design to the second question—how worthwhile the difference is going to be?—and thus seeking a higher δ in pivotal trials may lead to four beneficial consequences in trial planning and clinical practice.

It would lead to smaller trials. The primary purpose of a large scale randomized trial is to precisely quantitate a difference in outcome when this difference is expected to be small. If it were anticipated during the planning phase that a small difference would not be of clinical interest and/or could not justify a prohibitive cost, there would no longer be a rationale for running that specific trial. Conversely, if a

Table 3. Increase in Median PFS/OS Due to Treatments Associated With a Different Hazard Ratio, As a Function of the Median PFS/OS in Control Group

Median PFS or OS With Standard Therapy	Hazard Ratio Associated With the Experimental Therapy (by increase in median PFS or OS)					
	0.9	0.8	0.7	0.6	0.5	0.4
3 months	10 days	22 days	39 days	2 months	3 months	4.5 months
6 months	20 days	45 days	9 weeks	4 months	6 months	9 months
1 year	6 weeks	13 weeks	22 weeks	8 months	1 year	1.5 years
1.5 years	9 weeks	20 weeks	33 weeks	1 year	1 year 6 months	2 years 3 months
2 years	12 weeks	26 weeks	44 weeks	16 months	2 years	3 years
3 years	17 weeks	9 months	1 year 4 months	2 years		
5 years	7 months	1 year 2 months	2 years 3 months			

Abbreviations: PFS, progression-free survival; OS, overall survival.

hazard ratio of ≤ 0.5 were anticipated, no more than 100 to 150 patients would be needed for the pivotal trial (Table 2).

It would lead to more focused patient selection. In order to enhance the chances of success, it will behoove drug companies and cooperative groups to run smaller, but definitive trials in more biologically/molecularly well-characterized and homogeneous groups. Such trials would have the double advantage of requiring fewer patients with an expectation of obtaining a larger δ.[24] Demonstration of efficacy in this well-defined group of patients would favor the selective approval for antineoplastic agents suggested by Chabner[25] and actually implemented for trastuzumab for HER2–positive breast cancer[9] and most recently applied as well (retrospectively) to panitumumab[26] and cetuximab[27] for *KRAS* wild-type colorectal cancer.

Since this approach would be possible only to the degree that biomarker-defined groups were identified and sensitive and reliable tests made available, its adoption would be likely to act as a spur to more productive biomarkers research. Commercial ventures might be reluctant to delay a drug's development until a reliable biomarker was identified, or to invest the resources necessary to develop compounds for comparatively niche indications. However, if the biomarker identified patients with other malignancies who were also likely to benefit from treatment, this might mitigate the market limitations imposed by this development model.

Raising the bar for approval would keep agents with marginal clinical efficacy off the market, leading to substantial savings to health authorities, reinforcing the credibility of the drug development community, and potentially enhancing clinical trial participation.

Finally, raising the bar would support more rapid clinical development. The evaluation of new agents through smaller trials will require a shorter time to completion, thereby clearing the way for the movement of promising new agents into pivotal clinical trials. New insights into the biology of cancer would be more rapidly translated into therapeutic strategies and improved outcomes.

DISADVANTAGES OF RAISING THE BAR

There are four major potential problems in adopting a more demanding approach to drug approval.

The first concerns increased statistical uncertainty. Smaller trials, such as those needed to detect major treatment effects, provide estimates of the treatment effect with large statistical uncertainty (ie, CIs); for instance in a trial powered to detect a HR of 0.5, the estimates of the true HR will range from 0.32 to 0.79 if the observed HR is indeed 0.5, or from 0.38 to 0.92 if the observed HR is 0.6. This problem has no solution.

The second problem is an increased likelihood of missing the cumulative effects of incremental improvements. In general, clinical research is a continuum of small advances, and besides seeking paradigm-changing advances it should also seek to capture the cumulative effect of many smaller but incremental improvements. For instance, survival in advanced colorectal cancer has doubled in the past 15 years with the approval of six new drugs, but the δ values for each of the pivotal trials ranged from 0.54 (panitumumab *v* best supportive care),[12] to 0.66 (IFL + bevacizumab *v* IFL alone),[11] to 0.74 (FOLFOX4 *v* IFL),[28] to 0.78 (IFL *v* FU + leucovorin).[29] None of these new treatments would have fallen into the category of superstars, yet taken together the incremental effect has added up to a superstar effect in the reduction of death HR to approximately 0.5. As a consequence, the MST of patients with advanced-stage disease has increased from 5 months without chemotherapy[30] to 10 months with FU alone, 12 to 14 months with FU and leucovorin,[31] 16 to 18 months with chemotherapy doublets,[12,28] 18 to 20 months when all three chemotherapeutic agents are used in first and second/third line,[32] and longer than 20 months when biologics are added. If MST with a HR for death of around 0.5 had been used as the basis for registration, only FU would currently be available to patients.

Raising the bar for regulatory approval might lead to a reduction in the number of new agents entering the market. Of the three factors impacting on the economics and performance of phase III trials, the first two—cost and developmental time—would be reduced very substantially, but the third—the risk of failure—might be prohibitively amplified. This could lead to fewer new biologic agents entering the risky and costly phase of late clinical development. Furthermore, competition among analogs with similar mechanisms of action might not develop and beneficial effects of competition on price could be lost. This latter scenario is questionable, however; for instance, the availability of several serotonin antagonist antiemetics did not lead to price reductions.

Finally, raising the bar might be expected to lead to a reduction in revenues to drug companies, and in consequence lead to less funding of investigator-initiated trials by commercial sponsors.

HOW ABOUT A LIMBO LEVEL OF DRUG APPROVAL?

To reconcile the advantages and disadvantages of raising the bar for drug approval, another level (ie, limbo level) could be considered. This might be granted to agents demonstrating proof of therapeutic principle, but translating into only a 1- to 2-month improvement in PFS/OS (eg, HR = 0.80). These treatments would not be licensed for sale, but approved for further studies along three avenues where they could reach the paradigm-changing results. First, in molecularly selected patient populations, as was the case for trastuzumab in breast cancer and could have been for panitumumab and cetuximab in advanced colorectal cancer.

Second, as a part of new drug combination with other incremental agents. For example, erlotinib plus gemcitabine affords a 25% increment in survival over gemcitabine alone in advanced pancreatic cancer. Using the proposed model, erlotinib would not receive full approval. However, if erlotinib plus bevacizumab plus gemcitabine added an additional 25% increment in survival to erlotinib plus gemcitabine (as was hoped for, but not reached, in the Roche-sponsored pancreatic trial[33]) then the three-drug combination could be regarded as paradigm changing and be fully approved. In these trials, the experimental regimens should be compared with standard regimens not including any of the tested drugs. However, the results of the original trials on the contribution of each of the components of the new combination should be incorporated in the design and analysis of trials, by means of Bayesian techniques similar to those currently used in trial monitoring,[34,35] leading to substantial reductions in trial size and duration.

The third means for approval of limbo-level compounds would be in the setting of adjuvant therapy. Because most incremental advances in the metastatic disease setting have produced positive results in the adjuvant setting, with the exception of irinotecan in colon

cancer,[36,37] drugs satisfying the limbo level could move to the adjuvant setting for definitive evaluation. This could potentially lead to registration of the agent for the adjuvant, but not palliative use and would give pharmaceutical companies an added incentive for product development when prospects for approval in advanced diseases were more limited.

CONCLUSION

The proposal discussed in this article is directed at the final stage of drug development. When the decision to develop a product for registration is taken, the phase III trial should be powered for a paradigm-changing effect (ie, a HR of 0.5 to 0.6). This would allow a preliminary analysis of efficacy to be conducted, after only 100 to 150 events had occurred. If the paradigm-changing effect is obtained, approval should be granted within a rapid timeframe. If the postulated δ is not achieved, then a decision should be made, based on analyses and projections similar to those used in futility analyses (conditional power),[38] as to whether to pursue a more conventional HR (0.8) leading only to an incremental effect, or withdraw the agent from further development. We believe that raising the bar for approval would stimulate the design of trials with stronger biologic and clinical rationales, accelerate the development of new clinically meaningful treatments for cancer ensuring that patients benefit as early as possible from very effective new therapies.

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REFERENCES

1. Rothenberg ML, Carbone DP, Johnson DH: Improving the evaluation of new cancer treatments: Challenges and opportunities. Nat Rev Cancer 3:303-309, 2003
2. Carney DN: Lung cancer–time to move on from chemotherapy. N Engl J Med 346:126-128, 2002
3. Roberts TG Jr, Lynch TJ Jr, Chabner BA: The phase III trial in the era of targeted therapy: Unraveling the "go or no go" decision. J Clin Oncol 21:3683-3695, 2003
4. Escudier B, Eisen T, Stadler WM, et al: Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125-134, 2007
5. Hudes G, Carducci M, Tomczak P, et al: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271-2281, 2007
6. Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus Interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115-124, 2007
7. Escudier B, Pluzanska A, Koralewski P, et al: Bevacizumab plus interferon alpha 2a for treatment of metastatic renal cell carcinoma: A randomised double-blind plase III trial. Lancet 370:2103-2111, 2007
8. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001
9. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-2676, 2007
10. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-2743, 2006
11. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004
12. Van Cutsem E, Peeters M, Siena S, et al: Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25:1658-1664, 2007
13. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: National Cancer Institute of Canada Clinical Trials Group: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005
14. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542-2550, 2006
15. Demetri GD, van Oosterom AT, Garrett CR: Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. Lancet 368:1329-1338, 2006
16. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567-578, 2006
17. Moore MJ, Goldstein D, Hamm J, et al: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25:1960-1966, 2007
18. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma: SHARP Investigators Study Group. N Engl J Med 359:378-390, 2008
19. Van Oosterom AT, Judson I, Verweij J, et al: Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: A phase I study. Lancet 358:1421-1423, 2001
20. Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337-345, 2004
21. Demetri GD, von Mehren M, Blanke CD, et al: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472-480, 2002
22. Johnson JR, Williams G, Pazdur R: End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 21:1404-1411, 2003
23. Schilsky RL: End points in cancer clinical trials and the drug approval process. Clin Cancer Res 8:935-938, 2002
24. Dancey JE, Freidlin B: Targeting epidermal growth factor receptor–are we missing the mark? Lancet 362:62-64, 2003
25. Roberts TG Jr, Chabner BA: Beyond fast track for drug approvals. N Engl J Med 351:501-505, 2004
26. Amado RG, Wolf M, Peeters M, et al: Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26:1626-1634, 2008
27. Karapetis CS, Khambata-Ford S, Jonker DJ, et al: K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359:1757-1765, 2008
28. Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23-30, 2004
29. Saltz LB, Cox JV, Blanke C, et al: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer: Irinotecan Study Group. N Engl J Med 343:905-914, 2000
30. Sobrero A, Kerr D, Glimelius B, et al: New directions in the treatment of colorectal cancer: A look to the future. Eur J Cancer 36:559-566, 2000
31. Sobrero AF, Aschele C, Bertino JR: Fluorouracil in colorectal cancer–a tale of two drugs: Implications for biochemical modulation. J Clin Oncol 15:368-381, 1997
32. Grothey A, Sargent D, Goldberg RM, et al: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 22:1209-1214, 2004

33. Vervenne W, Bennouna J, Humblet Y, et al: A randomized double blind placebo controlled trial to evaluate the efficacy and safety of adding bevacizumab to erlotinib and gemcitabine in patients with metastatic pancreatic cancer. J Clin Oncol 26:214s, 2008 (abstr 4507)

34. Spiegelhalter DJ, Freedman LS, Parmar MK: Applying Bayesian ideas in drug development and clinical trials. Stat Med 12:1501-1511, 1993

35. Parmar MK, Griffiths GO, Spiegelhalter DJ, et al: Monitoring of large randomised clinical trials: A new approach with Bayesian methods—CHART steering committee. Lancet 358:375-381, 2001

36. Saltz LB, Niedzwiecki D, Hollis D, et al: Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: Results of CALGB 89803. J Clin Oncol 23:3456-3461, 2007

37. Ychou M, Raoul JL, Douillard JY, et al: A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann Oncol 20:674-680, 2009

38. Lachin JM: A review of methods for futility stopping based on conditional power. Stat Med 24:2747-2764, 2005