FDA Background for Colon Cancer Endpoints Workshop

This document provides FDA background information for a November, 2003 public workshop to discuss endpoints for the approval of colon cancer drugs.

I. FDA examination of endpoints for cancer drug approval

The Food and Drug Administration is soliciting input on what endpoints are acceptable as the basis for cancer drug approval. Endpoints will be examined for the most common cancers, such as lung cancer, colon cancer, etc. For each cancer, FDA will hold public workshops to identify important issues, and these issues will be discussed in meetings of the Oncologic Drugs Advisory Committee (ODAC). Subsequently, guidance documents will be published describing FDA's current thinking on endpoints for cancer drug approval. Workshop planning is guided by a steering committee that includes representation from the FDA, the National Cancer Institute, the American Society of Clinical Oncology, and the American Association for Cancer Research. Workshop participants will include oncology experts, radiation oncologists, statisticians, industry representatives, and patient advocates. The first workshop addressed lung cancer endpoints on April 15, 2003 and will be followed by a lung cancer endpoints discussion at a December, 2003 meeting of ODAC.

II. Regulatory requirements for new drug approval

FDA must find that drugs are safe and effective before they are marketed. The legal standard for approval is "substantial evidence of efficacy from adequate and well-controlled investigations." (*Investigations* is plural, indicating that in most circumstances FDA expects evidence from more than one trial).

FDA can approve new drug applications by two different mechanisms, regular drug approval and (since 1992) by accelerated drug approval. Regular approval is granted with no restrictions and must be supported by evidence of clinical benefit or other evidence that *reliably predicts* clinical benefit (e.g., an established surrogate). Accelerated approval (AA) is approval with restrictions (to perform additional trials) and can be based on surrogate endpoints that are only *reasonably likely* to predict clinical benefit. If post-marketing trials fail to demonstrate clinical benefit, the drug may be removed from the market after special hearings. Whereas regular approval may be granted in any setting, the regulations state that AA may only be granted only in settings where the new drug provides an advantage over available therapy. (Therefore, single arm trials, which usually do not allow a reliable comparison to available therapy, generally support AA only for treatment of refractory tumors, where no effective therapy exists.)

Note the difference in endpoint requirements between regular approval and AA. The former requires evidence of clinical benefit or improvement in an established surrogate for benefit whereas the latter may rely on a *reasonably likely* surrogate. The meaning of *reasonably likely* is a matter of scientific judgement. The regulations state that this judgement can be based on "epidemiologic, therapeutic, pathophysiologic, or other evidence." Response rate has been the primary endpoint used to support AA in oncology.

III. Cancer drug endpoints, historical considerations

In the 1970's FDA approved new drugs based on tumor response rates. In the early 1980's, upon the advice of the ODAC, FDA determined that response rates would not generally be acceptable full-approval endpoints. The benefit associated with modest response rates did not necessarily outweigh use of highly toxic cancer drugs. Acceptable endpoints were determined to be survival or quality of life (specifically cited: improvements in pain or physical functioning). In addition to relying on actual measurements of these endpoints, FDA has allowed approval based on other information that were reliable surrogates for these endpoints. (There are many precedents for approval based on reliable surrogates for approval of non-oncology drugs, e.g., approval of drugs to decrease blood pressure) In the early 1990's an NCI-FDA publication outlined some non-survival endpoints that might support full approval of cancer drugs:

- complete responses of reasonable duration
- disease free survival if a large proportion of the recurrences are symptomatic
- response rates in some settings (also considering response duration, the drug toxicity, and relief of tumor-related symptoms).

Subsequently, over the next decade, cancer drug regulation mirrored the suggestions in this publication and many drugs received full approval for non-survival endpoints. Recently, the Division of Oncology Drug Products (DODP) summarized the endpoints supporting drug approval over the past 13 years. Seventy-one oncology drug marketing applications were approved. Fifty-seven applications were granted regular approval and 14 applications were granted AA. Marketing approval in 39 of the 57 applications granted regular approval was based on endpoints other than survival.

IV. Cancer drug endpoints, recent experience

FDA recently summarized the endpoints supporting 71 new cancer drug approvals over a 13-year period, from 1990 to 2002. Fourteen of these applications received accelerated approval based on response rate or another surrogate endpoint, while 54 applications were given regular approval based on evidence of effects on clinical benefit endpoints or effects on accepted surrogates for clinical benefit.

Endpoints Supporting Regular Approval of Oncology Drug Marketing Applications January 1, 1990 to November 1, 2002

Total	57
Survival	18
Response rate (RR) and/or TTP alone (predominantly hormone treatment of breast cancer or hematologic malignancies)	18
Tumor-related signs and symptoms	13
RR+ tumor-related signs and symptoms	(9)
Tumor-related signs and symptoms alone	(4)
Disease-free survival (adjuvant setting)	2
Recurrence of malignant pleural effusion	2
Decreased incidence of new breast cancer occurrence	2
Decreased impairment creatinine clearence	1
Decreased xerostomia	1

About a third (18/57) of the regular approvals were based on survival evidence. Many of the approvals were supported by response rate or TTP, in clinical settings where the endpoints were judged to be reliable surrogates for patient benefit. Considerations included the drug's toxicity, type of response (complete or partial), response duration, efficacy of available therapy, and supportive data on disease-specific symptom improvement. One setting where RR has been accepted as reliable surrogate endpoint for regular approval is in the hormonal treatment of postmenopausal women with advanced breast cancer. In this setting, multiple hormonal drugs have been approved based on randomized trials demonstrating a similar RR and TTP compared to tamoxifine, a long-accepted standard treatment. In hematologic malignancies, durable complete responses supported approval of several drugs. In this setting, CRs were judged to be surrogates for survival and for delaying morbidity (anemia, bleeding and infections). There were also numerous approvals based on patient symptom assessments and/or physical signs (thought to represent symptomatic improvement) as the primary evidence of effectiveness. These include painful bone events, cosmetic improvement in Kaposi's sarcoma and cutaneous T-cell, the consequences (decreased transfusions, etc.) of long-duration responses in leukemias and lymphomas, relief of pulmonary or esophageal obstruction, symptom benefit in pancreatic cancer (also associated with survival benefit) and pulmonary symptom benefit in lung cancer.

Disease free survival in the adjuvant setting has supported approval of drugs for breast cancer and for bone marrow transplantation for leukemia. Sponsors have sometimes proposed use of time to treatment failure, however this is not an acceptable endpoint for regulatory approval

because it does not isolate the measurement of efficacy. (FDA must assure that drugs are both safe and effective.)

V. FDA Drug Approvals in Colon Cancer

FDA approval of drugs to treat colon cancer (CC) dates back to the 1962 approval of flourouracil (5FU) for the palliative treatment of CC (an approval which also included the palliative treatment of rectal, breast, gastric, and pancreatic cancers). In the initial era of cancer drug approval, the few existing cancer drugs were approved based on modest antitumor activity. Because the patent on 5FU expired many years ago and because generic versions of 5FU are available, drug companies have not submitted data to update the 5FU drug label for additional CC indications, such as adjuvant treatment of CC. 5FU use is, however, described in the labels of other drugs for adjuvant, first-line and subsequent therapies for colorectal cancer, in combination with leucovorin, levamisole, camptosar or oxaliplatin.

As discussed in the FDA regulatory background document, starting in the 1980's FDA approval required evidence of clinical benefit such as increased survival or an improvement in patient symptoms. Modern approvals for CC treatment in the adjuvant or advanced setting are discussed in the following sections. Table 1 gives the approvals of chemotherapeutic agents for CC according to treatment setting and Tables 2-4 summarizes the designs and results of studies supporting these approvals.

VI. Adjuvant Treatment of Colon Cancer

Levamisole in combination with 5FU was approved in 1990 for adjuvant treatment of Duke's stage C colon cancer. The approval was based on two randomized, controlled trials in patients with resected colorectal cancer. The three-armed studies compared levamisole alone, levamisole in combination with bolus 5FU, and no treatment. In the larger study, which followed patients for a minimum of 2 years, treatment with the levamisole 5FU combination was associated with a 41% reduction in recurrence rate ($p < 0.0001$) and a 33% reduction in death rate ($p = 0.006$) compared to no treatment. Levamisole given alone, however, showed no benefit compared to no treatment. Even though the contribution of levamisole to the efficacy of the combination regimen was not established, levamisole (in combination with 5FU) was approved as the first adjuvant CC regimen with a proven survival benefit.

More recently, reports in the literature have described adjuvant treatment results using combinations of 5FU and leucovorin (LCV). Data supporting these results have not been submitted to the FDA. Thus, the levamisole combination remains the only adjuvant regimen approved by FDA.

VII. Advanced Colon Cancer

Irinotecan was the first drug approved in the past several decades for treatment of advanced colon cancer. The initial NDA received accelerated approval in 1996 for colorectal cancer progressing or recurring after 5FU-based chemotherapy. Accelerated approval was based on response rates ranging from 14 to 21% and response duration of 5.8 months demonstrated in

about 200 patients. A survival benefit from irinotecan in this second-line treatment setting was subsequently demonstrated in two randomized controlled trials, one comparing irinotecan to best supportive care and another comparing irinotecan to 5FU-based treatment. Thus, a survival benefit was the basis of the 1998 conversion of the irinotecan application to regular approval. Survival benefit was also the basis for irinotecan approval for first-line treatment of colorectal cancer in 2000. A significant survival benefit was seen each of two trials evaluating irinotecan added to either bolus or infusional 5FU.

In 2001, capecitabine received regular approved for initial therapy of metastatic colorectal cancer. Approval was based on a non-inferiority analysis using the combined survival data from two randomized studies of capecitabine and 5FU/LCV. This analysis, which utilized historical data to estimate the effect of 5FU/LCV on survival, demonstrated that capecitabine was non-inferior to 5FU/LCV. From this analysis one can assume that capecitabine retains at least 50% of the 5FU/LCV treatment effect on survival in a combined analysis of the 2 studies. The approved capecitabine indication is "for patients when treatment with fluoropyrimidine therapy alone is preferred."

Oxaliplatin was studied in the treatment of metastatic colorectal cancer after failure of combination therapy with irinotecan and 5FU/LV (Saltz regimen). In this 3 arm study, the combination of oxaliplatin with 5FU and leucovorin demonstrated statistically significant improvement in response rates and Time-to-Tumor Progression over 5FU/LV. Single agent oxaliplatin did not demonstrate any improvement over the control arm of 5FU/LV. On the basis of an improvement in these surrogate endpoints, accelerated approval was granted to oxaliplatin in 2002.

Two NDAs discussed before ODAC and which did not lead to drug approval merit discussion. UFT was presented to ODAC in 1999. The major issues discussed were the analysis and interpretation of non-inferiority trials and uncertainty regarding the contribution of uracil to UFT efficacy. FDA expressed reservations about the non-inferiority analyses of the two studies. In FDA's analysis of one study, the lower bound of the 95% confidence interval of the hazard ratio for survival did not appear to provide adequate demonstration of non-inferiority. In the other study, FDA questioned whether historical data allowed an adequate estimate of the control effect. ODAC, however, voted to recommend drug approval if the contribution of uracil to UFT was adequately demonstrated to the FDA. (Regulations require that the contribution to the claimed effects of each active component of a fixed-combination be shown.) ODAC was also asked whether UFT was an important therapeutic advance for patients with metastatic colorectal cancer. The majority of the committee voted that it was not. Subsequently, FDA did not issue an approval for UFT. Post ODAC discussions between the Applicant and FDA and subsequent data analyses are not public information.

Findings from two trials involving oxaliplatin were presented to ODAC in 2000 for first-line treatment of patients with metastatic colorectal cancer. One trial was designed to demonstrate an improvement in progression-free survival (PFS) and the other had response rate as the primary endpoint. The studies demonstrated an increased response rate and PFS, but neither showed a survival advantage using the protocol specified primary analysis. The Applicant presented a survival analysis adjusted for alkaline phosphatase which showed improvement in survival in

only one study. The result of this exploratory analysis was not consistent over both studies, and did not support the use of alkaline phosphatase. The committee voted no (12-0) when asked whether the analyses persuasively demonstrated a survival advantage. At the same ODAC meeting an irinotecan application was presented for the same indication, showing an improvement in survival. FDA subsequently issued an approval letter for irinotecan but not for oxaliplatin for first line treatment of colon cancer.

VIII. Conclusion, endpoints for colon cancer

In the adjuvant setting, survival benefit (along with DFS) has been the basis of approval. In the advanced setting, response rate and time to progression have supported accelerated approval in settings where there was no available effective therapy. To date, regular approval has been based on a survival benefit, either a survival improvement or a survival non-inferiority analysis (capecitabine).

Table 1: Agents approved for treatment of colon cancer in the past two decades

Adjuvant	First-line	Metastatic
Levamisole (in combination with 5FU)	Leucovorin (in combination with 5FU)	Irinotecan
	Irinotecan (in combination with 5FU/LCV)	Oxaliplatin (in combination with 5FU/LCV)
	Capecitabine	

Table 2: Adjuvant Therapy For Colorectal Cancer

Levamisole	Treatment Arms	N	Minimum follow up	Analysis	Reduction in recurrence %	P value	Reduction death %	P value
Study 1 Duke C subset	5FU + levamisole	262	5 years	Superiority	36	0.025	27	0.11
	levamisole				28	0.11	28	
Study 2	5FU + levamisole	929	2 years	Superiority	41	<0.0001	33	0.006
	levamisole				2		6	
	observation							

Table 3: First-line therapy for Metastatic Colorectal Cancer

Approval type	Trials	Treatment Arms	N	Analysis	Result			
	5FU/ Leucovorin				**RR (%)**	**TTP (months)**	**OS (months)**	**P value for OS**
Regular approval (1991)	Study 1	5-FU	70	Superiority	10	2.9	7.7	
		5-FU + LV (HD)	69		26	6.7	12.2	0.037*
		5-FU + LV (LD)	73		44	6.7	12	0.05*
		5-FU + MTX + LV rescue						
		5-FU + MTX						
		5-FU + cisplatin						
	Study 2 (Study 1 extension)	5-FU + LV (HD)	149	Superiority	31		12.7	0.04**
		5-FU + LV (LD)	153		42		12.7	0.01**
		5-FU + MTX + LV rescue	155		14		8.4	
	Irinotecan				**RR (%)**	**TTP (months)**	**OS (months)**	**P value for OS**
Regular approval (2000)	Study 1	CPT-11 Wkly x 4, q 6wks (A)	226	Superiority	18	4.2	12	
		CPT-11/ + 5-FU/LV Wkly x 4, q 6 wks (B)	231		39	7	14.8	B vs C <0.05
		5-FU/LV Daily x 5, q 6 wks (C)	226		21	4.3	12.6	
	Study 2	CPT-11 + inf 5-FU/LV	198	Superiority	35	6.7	17.4	<0.05
		5-FU/LV	187		22	4.4	14.1	
	Capecitabine				**RR (%)**	**TTP (months)[#]**	**OS (months) [#]**	**Hazard Ratio for survival**
Regular approval (2001)	Study 1	Capecitabine	302	Non-inferiority (combined studies)	21	4.3	12.7	1.00
		5-FU/LV	303		11	4.4	13.6	0.84-1.18
	Study 2	Capecitabine	301		21	4.6	13.5	0.92
		5-FU/LV	301		14	4.4	12.3	0.78 – 1.09

* p values are one-sided

** p values are probably one-sided

[#]Calculations used thirty days in each month

Table 4: Treatment for Recurrent Metastatic Colorectal Cancer

Approval type	Trials	Treatment Arms	N	Analysis	Result			
	Irinotecan				**RR (%)**	**Response duration (months)**	**Survival (months)**	
Accelerated approval (1996)	Study 1	Weekly camptosar q 6 weeks @125 mg/m2	48	Single arm study	21	6.4	10.4	Combined studies: Median R duration: 5.8 m (2.6-15.2)
	Study 2	Weekly camptosar q 6 weeks@125 mg/m2	90	Single arm study	13	5.9	8.1	
	Study 3	Weekly camptosar q 6 weeks@125 mg/m2 @100 mg/m2	64	Single arm study	14	5.6	10.7	
			102		9	6.4	9.3	
Regular approval (1998)	Study 4	Camptosar q 3 weeks	189	Superiority			9.2	p: 0.0001
		Best supportive care	90				6.5	
	Study 5	Camptosar q 3 weeks	127	Superiority			10.8	p: 0.035
		5FU based regimens	129				8.5	
	Oxaliplatin				**RR (%)**	**TTP (months with 95% C.I.)**		**P value for RR**
Accelerated approval (2002)	Study 1	Oxaliplatin + 5FU/LV (FOLFOX4)	152	Superiority	9	4.6 (4.2-6.1)		0.0002
		5FU/LV	151		0	2.7 (1.8-3.0)		
		Oxaliplatin	156		1	1.6 (1.4-2.7)		