have an advantage over the endpoint of overall survival, in the situation where deaths result from health factors other than the cancer. The Park (39) study demonstrates the fact-pattern where TTP may have an advantage over the endpoint of overall survival, in the situation where subjects receive second-line treatment.

XII. THYMIDINE PHOSPHORYLASE AS A BIOMARKER FOR SURVIVAL—THE MEROPOL STUDY

In a study of colorectal cancer, Meropol et al. (40) administered the same chemotherapy to all patients. The treatment was irinotecan plus cepecitabine. Cepecitabine is distinguished in that it is converted in the cell to 5-fluorouracil. This conversion is catalyzed by *thymidine phosphorylase*. This enzyme is preferentially expressed by colorectal cancer cells, thus lending specificity of cepecitabine's toxic effects to the cancer cells, rather than to normal tissues. The efficacy of capecitabine is similar to that of 5-fluorouracil. The toxicity of capecitabine is less than the toxicity of bolus 5-fluorouracil, but similar to that with infusional 5-fluorouracil (41).

The goal of the study was to assess the possible correlation of *thymidine phosphorylase* expression with outcome. Thus, this was a study of a predictive biomarker. The difference between a "predictive biomarker" and a "prognostic biomarker" is detailed in Chapter 19.

TABLE 14.5 The Meropol Study

	Biopsy Positive (+) for Thymidine Phosphorylase	Biopsy Negative (−) for Thymidine Phosphorylase
TTP		
Primary tumor	8.7 months	6.0 months
Metastatic tumor	8.7 months	5.4 months
OVERALL SURVIVAL		
Primary tumor	28.2 months	14.9 months
Metastatic tumor	26.2 months	9.8 months

The data demonstrated that increased expression of *thymidine phosphorylase* is an excellent predictor of increased TTP (Table 14.5). Also, the data demonstrated that increased expression was an excellent predictor of increased overall survival.

The data on overall survival were especially dramatic.

All 52 patients provided biopsies of primary tumors. But at the time of diagnosis, only 30 of these patients had metastatic tumors. Most of the metastatic colorectal cancer tumors were located in the liver, lung, and lymph nodes. Hence, data from only 30 patients are available for correlating the biomarker expressing on metastatic tumors with the endpoints.

Regarding the predictive value of *thymidine phosphorylase* found in the Meropol study, it has been suggested that the medical community

[39]Park JO, Kim SW, Ahn JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. J. Clin. Oncol. 2007;25:5233−9.

[40]Meropol NJ, Gold PJ, Diasio RB, et al. Thymidine phosphorylase expression is associated with response to capecitabine plus irinotecan in patients with metastatic colorectal cancer. J. Clin. Oncol. 2006;24:4069−77.

[41]O'Neil BH, McLeod HL. Thymidine phosphorylase and capecitabine: a predictive marker for therapy selection? J Clin. Oncol. 2006;24:4051−3.