Sleeping with the Enemy: Inter-firm Product Combinations in the Pharmaceutical Indsutry

Claudio Lucarelli
Cornell University

Sean Nicholson
Cornell University and NBER

Minjae Song *
University of Rochester

October, 2008

PRELIMINARY: PLEASE DO NOT CITE

Abstract

There is a substantial literature in economics that focuses on explaining the reasons for intra-firm product combinations, such as bundling. Little is known, however, about the implications of inter-firm product combinations that are frequent in pharmaceutical markets. We propose and estimate a model to study the pricing strategies and the welfare effects of this practice. We find that firms increase their profits by participating in inter-firm combinations as they achieve further product differentiation, and consumers in general benefit from the extra variety. In addition, we find that if a firm introduces a second regimen, profits decrease as a less cooperative equilibrium arises, and consumers experience larger welfare gains. The last result suggests that inter-firm combinations may inhibit further innovation.

*Please send comments to minjae.song@simon.rochester.edu

1 Introduction

There is a substantial literature in economics focusing on product combinations such as bundling or tying. This literature offers explanations of why a firm would want to bundle two or more of its products into one package. Bundling may allow a firm to engage in price discrimination (e.g.McAfee and Whinston (1989)), to leverage monopoly power in one market by foreclosing sales and discouraging entry (Whinston (1990); Chen (1997); Carlton and Waldman (2002); Nalebuff (2004)), or alter the pricing game among oligopolists even when entry is not deterred or no firms exit (Carlton et al. (2007)). A common theme in this literature is the idea that the bundled products are produced by the same firm.

However, there are markets in which the firms produce one final product, and this product is sold to the consumer combined with another firm's product. In particular, in certain pharmaceutical markets it is common for patients to be treated with a regimen of two or more drugs approved for the same condition, and produced by different firms. Most HIV/AIDS patients receive a cocktail, such as efavirenz, lamivudine, and zidovudine (better known as AZT). In 2006, seventy-nine percent of U.S. colon cancer patients receiving chemotherapy treatment were administered a regimen of multiple drugs, such as a combination of oxaliplatin, bevacizumab, fluorouracil, and leucovorin. Six of the nine breast cancer regimens with the largest market share in 2007 were cocktails containing two or more distinct component drugs. Despite its importance, to our knowledge this is the first paper that studies the pricing and welfare effects of markets with inter-firm combinations.

Although the market for pharmaceutical inter-firm combinations share some characteristics of existing economic models, there are some important differences. First, most models of tying involve a firm requiring customers to purchase two of its existing products in combination rather than either product separately. In the pharmaceutical market, most drugs that are components of a regimen are also available as standalone products. Second, most of the component drugs in a regimen are produced by separate

firms (e.g., Sanofi, Genentech, and many generic firms in the colon cancer example above) rather than a single firm (e.g., Microsoft with Windows and Internet Explorer). Third, in pharmaceutical markets it is usually the firm entering a market that bundles its new product with an existing product through the design of a clinical trial, rather than an incumbent firm that initiates bundling or tying. This is possible because the entering firm can buy the other firm's product in the market to perform its clinical trials, however, the two drugs are sold separately. Fourth, bundled products in pharmaceutical markets are differentiated from their constituent components. In fact, the Food and Drug Administration will not approve a drug unless it demonstrates superior efficacy and/or fewer side effects relative to existing drugs on the market. Finally, firms are usually constrained to set a single price (e.g., per milligram of active ingredient) for a drug rather than setting a different price for the drug in each regimen. This constraint exists because physicians usually (e.g., in the case of oncology) purchase the component drugs and then infuse the regimen into a patient.

In this paper we focus on the market for colon cancer chemotherapy drugs to study the pricing decisions of firms in markets with inter-firm combinations, and the welfare impact of this practice. Our demand system comes from the aggregation of individual preferences at the regimen level since the attributes are reported at the regimen level, and we observe each regimen's market share. This demand system is then combined with a Nash-Bertrand equilibrium assumption to generate equilibrium prices and quantities. We explicitly model the game firms play and allow the price that each firm sets to affect all the regimens the firm participates in.

We use our model to perform counterfactuals to better understand the implications of inter-firm combinations. We find that firms benefit from participating in cocktails as they achieve further product differentiation without investing in additional R&D, and consumers in general benefit from the extra variety. We also find that when a firm offers a second product, a less cooperative equilibrium arises, and consumer welfare improves significantly from this "true" innovation.

The paper is organized as follows: Section 2 presents an overview of Colorectal

Cancer, section 3 describes our data, section 4 presents our model, section 6 presents the results from our estimation and the counterfactual exercises, and section 7 concludes.

2 Overview of Colorectal Cancer

According to the National Cancer Institute, approximately 112,000 patients will be diagnosed with colorectal cancer in the United States in 2007, and 52,000 will die from the disease. This places colorectal cancer as the fourth most common cancer based on number of new patients, after breast, prostate, and lung. It is estimated that people born today will have a 5.4 percent chance of being diagnosed with colorectal cancer over their lifetime. The disease is treatable, however; between 1996 and 2003, colorectal cancer patients had a 64 percent chance of surviving for five years. The probability a patient will survive for five years ranges from 93 percent for those diagnosed with Stage I cancer to eight percent for those diagnosed with Stage IV cancer (NCCN).

Almost all colorectal cancer patients who are treated with pharmaceuticals receive multiple drugs in the form of a regimen rather than a single drug, similar to anti-retroviral "cocktail" treatments for AIDS patients. For example, the regimen with the greatest market share in 2005 contained four separate drugs: bevacizumab, oxaliplatin, fluorororicil, and leucovorin. The 12 regimens in our sample are reported in Table 1. The most interesting feature is that the regimens are composed by drugs produced by different firms. In Table 1, the fourth regimen is a combination if Irinotecan, produced by Pfizer, and Capecitabine, produced by Roche.[1] The sixth regimen combines Oxaliplatin, produced by Sanofi, with Capecitabine. Bevacizumab is produced by Genentech, and it is combined with Oxaliplatin and Irinotecan and with Oxaliplaitin and Capecitabine in one case. Finally, Cetuximab is produced by ImClone, and it is combined with Irinotecan. In addition, each drug could be used by itself as a solo regimen. This creates an interesting economic problem to the firm when choosing the price for its drug. This is due to the fact that each drug is sold separately, and the

[1]The regimen 5FU/LV is a generic.

physicians may combine them into cocktails in their office. Therefore, the only variable that a firm control is its own price, but this will have an impact on the demand for all the cocktails the firm's drug participates in. We propose a model to study this complex decision, which is described in section 4.

Most oncology drugs are infused into a patient intravenously in a physician's office or an outpatient hospital clinic by a nurse under a physician's supervision.[2] Unlike drugs that are distributed through pharmacies, physicians (and some hospitals on behalf of their physicians) purchase oncology drugs from wholesalers or distributors (who have previously purchased the drugs from the manufacturers), store the drugs, and administer them as needed to their patients. Physicians then bill the patient's insurance company for an administration fee and the cost of the drug. In our model we assume physicians are imperfect agentsfor their patients, and the details of the imperfect agency will be explained in the model section.

3 Data

We use a number of different data sources to collect four types of information: drug prices, regimen market shares, typical drug dosage amounts for each regimen, and regimen attributes. IMS Health collects information on the sales in dollars and the quantity of drugs purchased by 10 different types of customers (e.g., hospitals, physician offices, retail pharmacies) from wholesalers in each quarter from 1993 through the third quarter of 2005. Prices and quantities are reported separately by National Drug Classification (NDC) code, which are unique for each firm-product-strength/dosage-package size. We calculate the average price paid per milligram of active ingredient of a drug by averaging across the different NDC codes for that drug. IMS Health reports the invoice price a customer actually pays to a wholesaler, not the average wholesale

[2]Based on data from IMS Health, 59% of colorectal cancer drugs in the third quarter of 2005 were purchased by physician offices/clinics and 28% by hospitals. The remainder was purchased by retail and mail order pharmacies, health maintenance organizations, and long-term care facilities.

price (AWP) that is set by a manufacturer and often differs substantially from the true transaction price.

The price we calculate does not include any discounts or rebates a customer may receive from a manufacturer after purchasing the product from the wholesaler. Based on interviews with a few oncologists, we do not believe that manufacturers offered substantial rebates during this period. Although we have information on 10 different types of customers, we focus on the prices paid by the two largest customers - hospitals and physician offices. Because most oncology drugs are infused in a physician's office or hospital clinic, nursing homes and retail pharmacies purchase relatively little.

Most colon cancer patients are treated with regimens that combine two or more drugs. The IMS Health data contain information on market share by drug, but not market share for the combinations of drugs (regimens) actually used on patients. We rely, therefore, on two different sources for regimen-specific market shares. IntrinsiQ is a company that provides information systems to oncologists to help them determine the proper chemotherapy dosing for their cancer patients. As a result, IntrinsiQ collects monthly data from its oncology clients on the types of chemotherapy drugs used for patients. IntrinsiQ provided data on the proportion of colorectal cancer patients (of all ages) treated with chemotherapy who are treated with each regimen for each month between January 2002 and September 2005.[3]

We derive market shares for the 1993 to 2001 period from the Surveillance Epidemiology and End Results (SEER) data set, which tracks the health and treatment of cancer patients over the age of 64 in states and cities covering 26 percent of the

[3]Because we observe the market shares of regimens among patients with colorectal cancer, we do not need to worry about off-label use. Off-label use occurs when a physician treats a colorectal cancer patient with a drug that has not been approved by the FDA to treat colorectal cancer, or when a physician uses a drug approved for colorectal cancer on a patient with a different type of cancer. In October 2005, seventy-six percent of patients being treated with the four drugs approved solely for the treatment of colorectal cancer (irinotecan, oxaliplatin, cetuximab, and bevacizumab) actually had colorectal cancer. That is, off-label use accounted for approximately 24 percent of the quantities of these drugs.

United States population.[4] We calculate the proportion of colorectal cancer patients who are treated with each drug regimen in each quarter based on Medicare claims data available in SEER. In October 2003, approximately 48 percent of all colorectal cancer patients treated with chemotherapy were 65 years or older.[5]

In our analysis, we include as inside goods all regimens that contain drugs that were explicitly approved by the Food and Drug Administration (FDA) for colorectal cancer and had a market share greater than two percent. The outside option includes off-label drugs [6], regimens with less than one percent market share in the third quarter of 2005 (the end of the sample period), and regimens with missing attribute data.

Market shares for the 12 regimens in our sample and the outside option are plotted in Figure 1. The regimens are also described more fully in Table 1, arranged in order of entry. Between 1993 and 1996, about 95 percent of colorectal cancer patients were treated with 5-FU/leucovorin, which at that time was generic, with the remainder treated with off-label drugs or regimens with very small market share.[7] Irinotecan (brand name Camptosar) was approved by the FDA for treating colorectal cancer in 1996, and over the next several years the market share of irinotecan (approved as a second-line treatment for patients who had already been treated with a different chemotherapy regimen) and irinotecan combined with 5-FU/LV grew at the expense of 5-FU/LV.[8] Capecitabine (Xeloda), a tablet that produces the same chemical response as 5-FU/LV, was approved for treatment of colorectal cancer in April of 2001 and was administered as a standalone therapy or combined with irinotecan. All other drugs for treating colorectal cancer in our sample are delivered intravenously (IV) under the supervision of a physician or nurse.

[4]SEER contains data on the incidence rate of cancer among the non-elderly, but only has medical claims available for Medicare patients.

[5]Data from IntrinsiQ.

[6]Off-label use is more likely to occur if a patient's initial treatment has been unsuccessful.

[7]5-FU contains the drug fluorororacil.

[8]Because it takes Medicare a while to code new drugs into their proper NDC code, for several quarters a new drug will appear in the outside option.

Oxaliplatin (Eloxatin) was introduced in August of 2002, followed by cetuximab (Erbitux) and bevacizumab (Avastin) in February of 2004. By the third quarter of 2005, two of the regimens created by these three new drugs (oxaliplatin + 5-FU/LV; and bevacizumab + oxaliplatin + 5-FU/LV) surpassed the market share of 5-FU/LV, whose share had fallen to about 14 percent.

The market shares of several regimens change sharply in the first quarter of 2002 when we use market share data from IntrinsiQ rather than SEER. One explanation for these changes is that Medicare patients may be treated with different regimens than non-Medicare patients. Another possible explanation is that the samples used by IntrinsiQ and/or SEER may not be consistent.[9] In order to homologate market shares between the pre- and post-2002 periods, we take advantage of the fact that the two data sets overlap for the 4 quarters of 2002. We apply a regimen-specific factor to adjust the pre-2002 market shares based on the ratio of total (from IntrinsiQ) to Medicare-only (from SEER) market shares for the four quarters of 2002, when the two data sets overlap.

We price the regimens for a representative patient who has 1.7 meters squared of surface area (Jacobson et al., 2006) weighs 80 kilograms, and is treated for 24 weeks. Regimen prices are derived by multiplying the average price a customer paid per milligram of active ingredient in a quarter by the recommended dosage amounts for each drug in the regimen over a 24-week period.[10] Thus, calculating the regimen price requires information on dosage of each drug in a regimen. The National Comprehensive Cancer Network (NCCN) reports the typical amount of active ingredient used by physicians for the major regimens. We supplement this where necessary with dosage information from drug package inserts, conference abstracts, and journal articles. Dosage information is reported in Appendix 1. For example, the standard dosage schedule for oxaliplatin+5-FU/LV, the regimen with the second largest market share in 2005, is 85milligrams (mg) of oxaliplatin per meter squared of a patient's surface area infused

[9]The SEER sample is drawn from locations representing 26 percent of the U.S. population.

[10]The regimens are priced using price data for the contemporaneous quarter only.

by IV on the first day of treatment, followed by a 1,000 mg infusion of 5-FU per meter squared of surface area on the first and second treatment days, and a 200 mg infusion of leucovorin per meter squared on the first and second treatment days. This process is repeated every two weeks.

We obtain most of the attribute information for each regimen from the FDA-approved package inserts that accompany each drug. These inserts describe the phase 3 clinical trials that were conducted, including the number and types of patients enrolled in the trials, the health outcomes for patients in the treatment and control groups, and the side effects experienced by those patients. Often there are multiple observations for a regimen, either because a manufacturer conducted separate trials of the same regimen, or because a regimen may have been the treatment group in one clinical trial and the control group in a subsequent trial. In these cases we calculate the mean attributes across the separate observations. Where necessary, we supplement the package insert information with abstracts presented at oncology conferences and journal articles.

The attribute information is summarized in Table 1, organized according to the year when each regimen was introduced. We record three measures of a regimen's efficacy: the median number of months patients survive after initiating therapy; the percentage of patients who experience a complete or partial reduction in the size of their tumor (i.e., the response rate); and the mean number of months (across patients in the trial) before their cancer advanced to a more serious state.[11] For all three of these measures, higher values are associated with superior health outcomes. We also record whether a regimen contains the capecitabine tablet, which should make the administration of the regimen more convenient for a patient, and whether the regimen is approved (and was tested) as a second-line treatment. Efficacy measures for second-line regimens will generally be worse than those for first-line regimens because the patients' cancer is likely to be more advanced at the beginning of the clinical trial and the first treatment was not completely successful.

[11] Cancers are classified into four stages, with higher numbers indicating that the cancer has metastasized beyond its initial location.

We also collected data on the percentage of patients in phase 3 trials who experienced either a grade 3 or a grade 4 side effect for six separate conditions: abdominal pain, diarrhea, nausea, vomiting, neutropenia, and dehydration. Although many more side effects are recorded for most regimens, these six were consistently recorded across the 12 regimens in the sample. Side effects are classified on a standard one to four scale, with four being the most severe. Higher values for the side effect attributes should be associated with worse health outcomes although, as we will show later, regimens that are more toxic are likely to be both more effective and have more severe side effects.

New colorectal cancer regimens tend to be more efficacious than the existing regimens, with side effect profiles that are sometimes more and sometimes less severe than earlier regimens. Consider the new entrant in 1996, irinotecan + 5-FU/LV (second row of Table 1). Relative to patients who received 5-FU/LV in a clinical trial (first row of Table 1), patients in clinical trials who received irinotecan + 5-FU/LV lived 3.1 months longer, on average, had a 14.6 percentage point higher probability of experiencing a reduction in the size of their tumor, and experienced a two month delay in the time it took for the cancer to advance to a more severe state. However, patients taking the new regimen were more likely to experience five of the six side effects listed in Table 1.

Oxaliplatin + 5-FU/LV, which was launched in 2002 (fifth row of Table 1), is more efficacious and has fewer severe side effects than irinotecan + 5-FU/LV. Patients in clinical trials of the former regimen lived an average of 3.8 months longer, had a 10.7 percentage point higher probability of experiencing a reduction in the size of their tumor, and experienced a 2.4 month delay in the time it took for the cancer to advance to a more severe stage relative to the latter regimen. Oxaliplatin + 5-FU/LV patients are also less likely to experience a grade 3 or 4 side effect for five of the six measures relative to irinotecan + 5-FU/LV. Finally, the arrival of bevacizumab + oxaliplatin + 5-FU in 2004 increased the median survival time by about four months relative to oxaliplatin + 5-FU/LV, with substantial improvements on three side effect measures and worse performance on the other three side effect measures.

Two new second-line regimens entered the market in 2004 to compete against the

first second-line regimen (irinotecan) that was launched in 1996.[12] Cetuximab + irinotecan has a substantially better response rate than irinotecan administered by itself. The new regimen also is superior than irinotecan on five of the six side effect measures.

4 Model

4.1 Supply

We assume the firms play a static Nash-Bertrand game with differentiated products, however, a distinctive feature of our model is the fact that additional product differentiation is achieved by combining drugs of multiple firms into regimens. Therefore, the equilibrium conditions are different than what we would observe if products were consumed separately, and also, they are different than the conditions we would observe if firms were producing multiple products.

To describe our model, we introduce the following notation. Let p_f be the price the firm f charges for its product. Consistent with our data, we assume that each firm produces only one product, and therefore, p_f is the only endogenous variable in the firm's optimization problem. We denote mc_f the marginal cost for firm f, and $q_f(p)$ the quantity produced by firm f. In this way we define the profits for firm f as

$$\pi_f = (p_f - mc_f)q_f(p)$$

, where $q_f(p)$ is obtained from the aggregation of quantities across the regimens that the firm participates in. Formally, if firm f participates in R_f regimens, and $r = 1, \ldots, R_f$, then $q_f(p)$ can be written as

$$q_f(p) = \left(\sum_{r=1}^{R_f} s_r(p) q_{rf} \right) M$$

[12] Regimens that include the tablet, capecitabine, are chemically equivalent to regimens that include 5-FU/LV.

, where $s_r(p)$ is the share of patients that are prescribed regimen r, q_{rf} is the quantity of drug produced by firm f that is used in regimen r, and M is the market size.[13] The equilibrium conditions can then be written as:

$$\frac{\partial \pi_f}{\partial p_f} = \sum_{r=1}^{R_f} s_r(p) q_{rf} + (p_f - mc_f) \sum_{k=1}^{R_f} \sum_{r=1}^{R_f} \frac{\partial s_r(p)}{\partial p_k} \frac{\partial p_k}{\partial p_f} q_{rf} = 0 \tag{1}$$

From the equilibrium conditions, it is clear that in setting the price for its drug, the firm takes into account its effect on the overall price of each regimen ($\partial p_k / \partial p_f$), and how the regimen price changes will impact market shares for all the regimens the drug participates in ($\partial s_r(p) / \partial p_k$). The former effect is determined by drug dosage in regimens and is fixed by the regimen "recipes." The latter effect is determined by the price elasticity of regimen demand and is estimated from the regimen level data. It can also be seen that we can recover the marginal costs for each drug by re-writing this equation for them.

4.2 Demand

We obtain our demand system by aggregating over a discrete choice model of physician behavior, in which, following the Lancasterian tradition, products are assumed to be bundles of attributes, and preferences are represented as the utility derived from those attributes. The indirect utility of the physician i over regimens $j \in \{0, \ldots, J_t\}$ at time (market) t are represented by:

$$u_{ijt} = -\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_j + \varepsilon_{ijt}$$

where p_{jt} is the price of regimen j at time t, x_{jt} are the observable attributes of the regimen, ξ_j is the mean of the unobserved characteristics, and $\Delta\xi_{jt}$ is a time-specific deviation from this mean. ε_{ijt}, which is an idiosyncratic shock to preferences for regimen j, is assumed to follow a Type I Extreme Value distribution. This specification implies that the physician's utility has 2 components: patient utility (including patient

[13] The quantities used of each drug used for each regimen q_{rf} are reported in the appendix.

payments, observed and unobserved attributes of the treatment), and an unobserved taste shock ε_{ijt}, which represents any unobserved effect that changes the physician choice from purely patients' utility (e.g. rebates).

The outside option ($j = 0$) in this paper includes off-label colon cancer treatments and regimens with very small market shares for which a complete set of attributes is not observed. In this way, we can write the physician's utility as:

$$u_{ijt} \geq u_{ikt} \qquad \forall k \neq j$$

This implicitly defines a region of the unobserved term for which alternative j yields a higher utility than any other alternative k

$$A_{jt} = \{\varepsilon_{it} | u_{ijt} \geq u_{ikt} \forall k \neq j\}$$

The market shares for each regimen j can be obtained by aggregating the individual preferences over the region A_{jt}

$$s_{jt} = \int_{A_{jt}} dP(\varepsilon)$$

If ε is assumed to be drawn from the extreme value distribution, the integral can be computed analytically:

$$s_{jt} = \frac{\exp(-\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_j)}{1 + \sum_{k=1}^{J_t} \exp(-\alpha p_{kt} + \beta x_{kt} + \xi_k + \Delta\xi_k)}$$

The market shares predicted by the model as above, are matched with the observed market shares in the estimation.Berry (1994) shows that the mean utility can be uniquely identified by inverting the market share function . For the logit model, the inversion yields

$$\ln s_{jt} - \ln s_{0t} = -\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_j$$

,

which is the expression we take to the data.

The usual price endogeneity problem may be present in our application. That is, it is likely that the more expensive regimens present higher levels of unobserved quality. We correct for this endogeneity problem by using two sets of instruments. The first set is derived from product differentiation, and we use counts and sums of attributes of other regimens in the market Bresnahan et al. (1997). A more or less crowded product space will shift prices via markups, however, this would not be correlated with the regimen's unobserved quality as long as product attributes are exogenous, as the literature usually assumes. The second set of instruments are the lagged prices of other regimens, which are valid under the assumption that prices are autocorrelated, but the demand shock is not.

5 Numerical Examples

Before we apply the model to data, we numerically examine the inter-firm product combination between two firms in a pharmaceutical market. Without the inter-firm combination firm 1 and 2 sell one solo regimen each, competing a la Bertrand. This is our benchmark case. Given the price coefficient, say -1, price firms set is a function of product quality, which we denote δ_j for $j = 1$ and 2, and is a linear function of both observed and unobserved product attributes. The product quality is one of the variables we change to study its impact on economic outcomes.

Given δ_1 and δ_2, suppose these two firms combine their drugs to make the third regimen. We assume that the third regimen's product quality, say δ_3, is the maximum of δ_1 and δ_2. This cocktail regimen can be made in multiple ways depending on how the two drugs are combined. Let r_{13} and r_{23} be proportions of drugs 1 and 2 used in regimen 3 where $r_{13} + r_{23} = 1$ and $0 < r_{13} < 1$ and $0 < r_{23} < 1$. Then the price of regimen 3, p_3, will be determined by

$$p_3 = r_{13}p_1 + r_{23}p_2$$

where p_1 and p_2 are prices of drug 1 and 2 respectively. This proportion is another

variable we change to study its impact on economic outcomes.

In our first numerical example we fix $r_{13} = 0.5$ and $\delta_1 = 1$, and let δ_2 change from 1 to 5. For each δ_2 a new equilibrium is computed. This simple exercise allows us to understand the incentives of firms when they participate in a regimen, and how these incentives vary as the difference in quality between components gets larger. The results from this simulation are presented in Figure 2. The *baseline low quality* and the *baseline high quality* lines represent profits of the low quality firm and the high quality firm without the cocktail regimen respectively. The *sim low quality* and the *sim high quality* lines represent profits of the low and the high quality firms with the cocktail. The figure shows that the low quality firm always gets better off with the cocktail (represented by the sim low quality line being higher than the baseline low quality line.) However, the high quality firm is only better off with the cocktail when quality difference is not large (less than 0.8.) In fact, as the quality difference becomes larger, the high quality firm is increasingly worse off than when it offers only the solo regimen.

The low quality firm is always better off with the cocktail because it can "free-ride" high quality provided by the cocktail regimen. The low quality firm's pricing strategy is interesting. It increases its price dramatically such that the market share for its solo regime gets negligible but it gets considerable profits from the cocktail. The high quality firm, on the other hand, set a lower price than without the cocktail to sell both its solo regimen and the cocktail regimen but its profit is lower than without the cocktail.

In our second numerical example we fix $\delta_1 = 1$ and $\delta_2 = 1$, and let r_{13} change from 0.5 to 0.9. This exercise allows to understand how the incentives to participate in a cocktail change as the firm increases its participation in the mixture. The *baseline* line in Figure 3 shows profits in the benchmark case (the case without the cocktail.) Since the two firms' qualities are equal, there is no difference in profit. The *sim high ratio* line represents firm 1's profit as r_{13} changes from 0.5 to 0.9 and the *sim low ratio* line represents firm 2's profit as r_{23} changes from 0.5 to 0.1. We find, not surprisingly, that

firm 1 is getting better off as its mixture ratio increases and firm 2 is getting worse off as its mixture ratio decreases. Compared to the benchmark case, firm 1's profit is always higher and firm 2's profit is higher up to r_{23}=0.35 and then becomes lower as r_{23} gets lower.

In our last numerical example we let one of the two firms set two separate prices, one for the solo regimen and the other for the cocktail regimen and study how this more flexible pricing changes economic outcomes. [Results are to be reported here.]

6 Results

The estimates for the preference parameters are presented in Table 2. The first column shows the results of the OLS logit model. The second column labeled IV Logit I, corresponds to the regressions with product attribute instruments, and the third column labeled IV Logit II, corresponds to the lagged price instruments. In all specifications we use the log of price and include time dummy variables.

The price coefficients across the columns show that there is positive correlation between price and the unobserved characteristics, and the instrumental variables mitigate this problem. However, the attribute instruments do not seem to correct the price endogeneity as much as the lagged price instruments. We suspect this is mainly because the regimen attributes do not change over time. The price coefficient change from -0.733 without instruments to -0.841 with the attribute instruments. The lagged price instruments, on the other hand, change the price coefficient from -0.733 to -2.176. We check if this change is due to weak correlation between the current price and the lagged price with the first stage F-test. The F-statistic is over 60 and we reject the weak instrument hypothesis.

The efficacy attribute coefficients such as *the response rate* and *survival* show the expected positive signs and are statistically significant in OLS logit and IV logit I. The response rate coefficient becomes much larger in IV logit II, but the sign of the survival variable becomes negative, although it is not statistically significant. Time

to progression has an unexpected and statistically significant negative sign in all three specifications.

Among the side effect variables, only two of them are statistically significant and only one of these two shows an expected negative sign. And two out of the three insignificant ones have positive signs. This may be due to the fact that cancer patients often take drugs that ameliorate the impact of certain side effects, such as pain, nausea, and diarrhea. If a physician prescribes anti-pain and antiemetic drugs in conjunction with the anti-cancer drugs, she may downgrade the importance of these side effects when choosing a regimen.[14]

6.1 Counterfactual I

Given the demand estimates, we can solve for the marginal costs from equation (1) , and compute hypothetical equilibrium prices under counterfactual scenarios in order to better understand the effects of inter-firm combinations on pricing, profits and welfare.

We focus on the last 6 quarters of the sample period, i.e., from the second quarter of 2004 to the third quarter of 2005. That is a period after all 12 major regimens were introduced in the market. All results are averaged over these six quarters.

We take a regimen out of the market one at a time and find new Nash equilibrium prices for all branded drugs and compute profits for all major firms. We also compute consumer surplus for each case. Because there are 6 regimens that include inter-firm combinations, we evaluate 6 hypothetical cases. The results of this exercise are reported in Tables 3 to 5. The baseline in the first row is what we observe in the market and is normalized to 100. Therefore, the tables shows percentage changes compared to the market we observe. The numbers in bold typeface are the changes for the firms that

[14] A second possible explanation for the positive coefficients on three of the side effect attributes is that physicians may believe that the efficacy of the newer drugs are better than the measures reported in phase 3 clinical trials. This could occur, for example, if physicians use the drugs differently in practice than as they were used in the trials due to learning about patient-drug matching. Because the more effective drugs are more toxic and generally have greater side effects, the physician beliefs would be captured as positive coefficients on the side effect measures.

participate in the removed regimen.

Table 3 shows the price changes for each firm (in the columns) when the regimen in the rows is absent. For example, the second row corresponds to the case in which the regimen by Pfizer and Roche is removed. Without this regimen Pfizer's drug price is higher by 14.9 percent while Roche's is lower by 8.2 percent. Other firms' drug prices also change, although the magnitude of changes is relatively small. Sanofi's drug price is lower by 1.3 percent while those of Imclone and Genentech are higher by 2.5 and 2.3 percents respectively. Removing a regimen triggers complex best responses in terms of the prices of the remaining regimens, given the fact that firms control only one price and their choice of price will impact many other regimens, which may also involve competitors.

In Table 4 we present the profit changes for firms due to the removal of a regimen. The table shows that no participating firm is better off without a regimen. Sometimes the profit losses can be substantial as shown in the case where the regimen by Sanofi and Genentech is removed (the 7th row). In this case, Genentech's profits are only 25 percent of the baseline profits. This regimen is one of the market leaders and Genentech's best selling regimen. This regimen is also very profitable for Sanofi, whose profits are decreased by almost 30 percent when this regimen is removed. This regimen does not cannibalize Sanofi's solo regimen (its share did not change much after the introduction of Bevacizumab by Genentech).

The case where the regimen by Imclone and Pfizer is removed is another example of a huge loss. Imclone's profit is only 21.3 percent of the baseline profits and this loss is explained by the fact that this regimen's market share is larger than Imclone's solo regimen. Pfizer also suffers a significant loss without this regimen. Its profit decreases by almost 25%.

This result shows that firms mutually benefit from the inter-firm product combination by populating the product space without investing in additional and expensive R&D. The fact that all participating firms benefit suggests that quality difference among drugs used in the cocktail regimens is not substantially large. Note that our

numerical example shows that a high quality firm can get hurt by the presence of the cocktail with substantially large quality difference.

The table also shows that firms that do not participate are affected either way by the removal, although the magnitude of profit changes is marginal. For example, when the regimen by Roche and Sanofi is removed (the 3rd row), profits of Pfizer and Imclone become higher by 3.1 percent and 6.2 percent respectively, but Genentech's profit goes down by 2.7 percent. An interesting case is when the regimen by Roche, Sanofi and Genentech is removed. All firms' profit goes down without it.

Finally, Table 5 shows the impact of removing a regimen on consumers' surplus. Consumers in the logit demand model are usually worse off with fewer products as they love more variety. However, consumer surplus can go up if product prices are lower with fewer products. This rarely happens in the oligopolistic market as firms usually set higher prices with fewer products.

Nevertheless, Table 5 shows that there are two cases where consumers are better off with one less regimen. They are cases where the loss in variety is outweighed by price decreases. When the regimen by Genentech, Roche and Sanofi is removed, Roche responds with an 8% decrease in price which propagates to its other regimens, while the other firms' prices remain fairly constant. Note that all firms' profits are lower without this regimen. So this regimen benefits all firms at the expense of consumers. A similar case is observed when the regimen by Imclone and Pfizer is removed, which generates a substantial price decrease by both firms. Again, all firms other than Genentech are worse off without this regimen and Genentech's profit is only 0.9 percent higher without it.

6.2 Counterfactual II

In this counterfactual, we try to mimic a case where firms have two separate drugs, one for the solo regimen and another for the cocktail regimens. In particular, we are interested in understanding firms' pricing behavior in this situation. Instead of adding a new drug, we allow one of the firms to set two separate prices for the same drug, one

for its solo drug and another for the drug used in cocktail regimens. By doing so we suppress pricing effects that may arise from regimen attributes.

Allowing firms to set two separate prices introduces a strategic incentive that we observe in other parts of the pharmaceutical market. A prominent example is the AIDS drug market. In this market, a firm offered two drugs, one of them used in cocktails to boost its competitors' performance and the other one was a new launch. The firm's chosen strategy was to increase the price of the drug used in cocktails by 5 times while pricing its new drug more competitively.

Table 6 shows the resulting prices from this counterfactual. As before we normalize the baseline to 100. The column called Solo reports price for the solo regimen and the numbers in bold typeface are prices for a drug used in all cocktail regimens. For example, the second row represents a case where Pfizer sets different prices for Irinotecan used in its solo regimen and Irinotecan used in three cocktail regimens. In this case Pfizer lowers price for the solo regimen by more than 50 percent and increases price for cocktail regimens by almost 30 percent.

The table shows that the drug price for cocktail regimens can go up dramatically as shown in the 4th and 5th rows. Roche increases its drug price for cocktail regimens by a factor of 5.5 and Sanofi does so by more than twice. The drug price for the solo regimens goes down significantly without exceptions. It varies from a 25 percent decrease for Roche to a 56.7 percent decrease for Pfizer.

Table 7 shows the profits associated to the new pricing scheme. The table shows that the new pricing scheme decreases profits except for two cases. It is interesting to see profit decreases with a more flexible pricing strategy. In principle firms can duplicate the single pricing by setting the two prices equal to each other. However, it seems that our numerical solver, i.e., Newton-Raphson method, does not automatically consider the constrained pricing. This result implies that firms may need the single pricing constraint as the commitment device to stay in a more cooperative equilibrium.

The two cases where firms' profit becomes higher with the two separate pricing are when Roche sets two prices for Capecitabine and when Imclone sets two prices for

Cetuximab. In the former case Roche's profit goes up by 52.2 percent and in the latter case Imclone's profit goes up by 1.4 percent.

Table 8 shows consumer surplus for each case. Since the regimen qualities do not change in this counterfactual, the only variable affecting consumer surplus is pricing. The only case where consumer surplus is lower is when Roche sets two separate prices. This is driven by Roche increasing its drug price for cocktails by a factor of 5.5 and two other firms, Pfizer and Sanofi, reacts to this by increasing their drug prices by more than 10 percent. In all other cases consumer surplus is higher thanks to lower prices of major drugs.

7 Conclusions

This paper is a first attempt to understand the complicated economic decisions that firms need to make when their products are combined by consumers (or their agents) into "cocktails" or regimens. The firms control only the price of its own product, and therefore, they need to take into account the effect of their pricing strategy on all the regimens the firm participates in, in addition to the usual strategic interactions with competitors.

We applied our framework to the pharmaceutical industry, in particular to colon cancer drugs. We perform two counterfactuals in order to study the effect of inter-firm product combinations on prices, profits and consumer welfare. We find that inter-firm combinations are profit enhancing, as they serve as a vehicle for further product differentiation without additional and expensive investment in R&D, and that consumers for the most part like the extra variety.

In addition, we find that if any of the firms launched a new drug as a solo regimen, it would trigger pricing strategies that would lead to a less cooperative equilibrium, and in most cases consumer welfare would increase, therefore, true product differentiation would be more beneficial to consumers.

References

Bresnahan, T. F., Stern, S., and Trajtenberg, M. (1997). Market segmentation and the sources of rents from innovation: personal computers in the late 1980s. *RAND Journal of Economics*, 28(0):S17–S44.

Carlton, D. W., Gans, J. S., and Waldman, M. (2007). Why tie a product consumers do not use? NBER Working Paper 13339.

Carlton, D. W. and Waldman, M. (2002). The strategic use of tying to preserve and create market power in evolving industries. *Rand Journal of Economics*, 33(2):194–220.

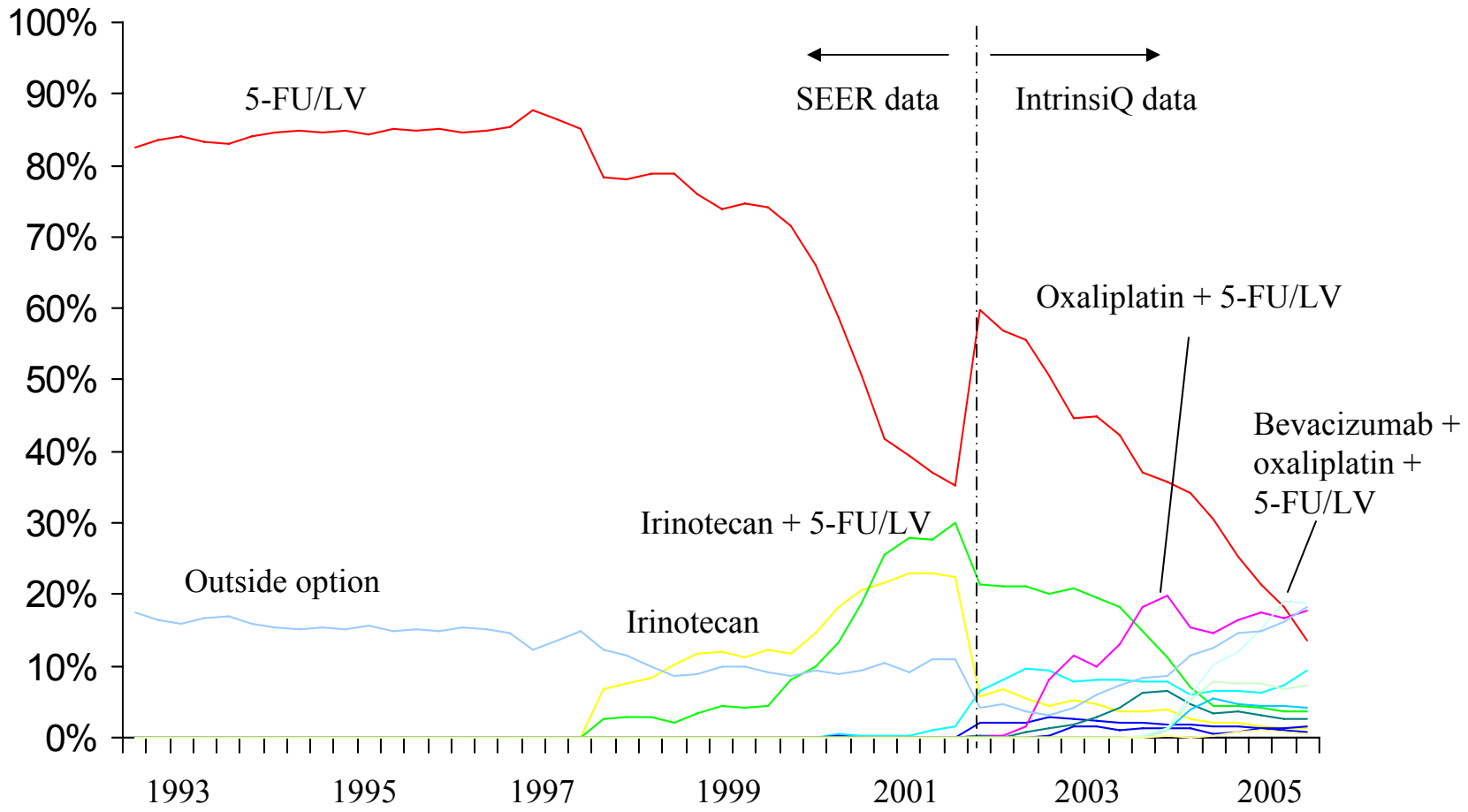
Chen, Y. (1997). Equilibrium product bundling. *Journal of Business*, 70(1):85–103.

McAfee, R. Preston, J. M. and Whinston, M. D. (1989). Multiproduct monopoly, commodity bundling, and correlation of values. *The Quarterly Journal of Economics*, 104:371–383.

Nalebuff, B. (2004). Bundling as an entry barrier. *The Quarterly Journal of Economics*, 119:159–187.

Whinston, M. D. (1990). Tying, foreclosure, and exclusion. *American Economic Review*, 80(4):837–859.

Figure 1: Regimen Market Shares, 1993-2005



Source: IntrinsiQ and SEER.
Note: Market share is measured as the percentage of colon cancer patients who are treated with drugs that are treated with a specific regimen.

Figure 2
Numerical Exercise 1: Change in Quality

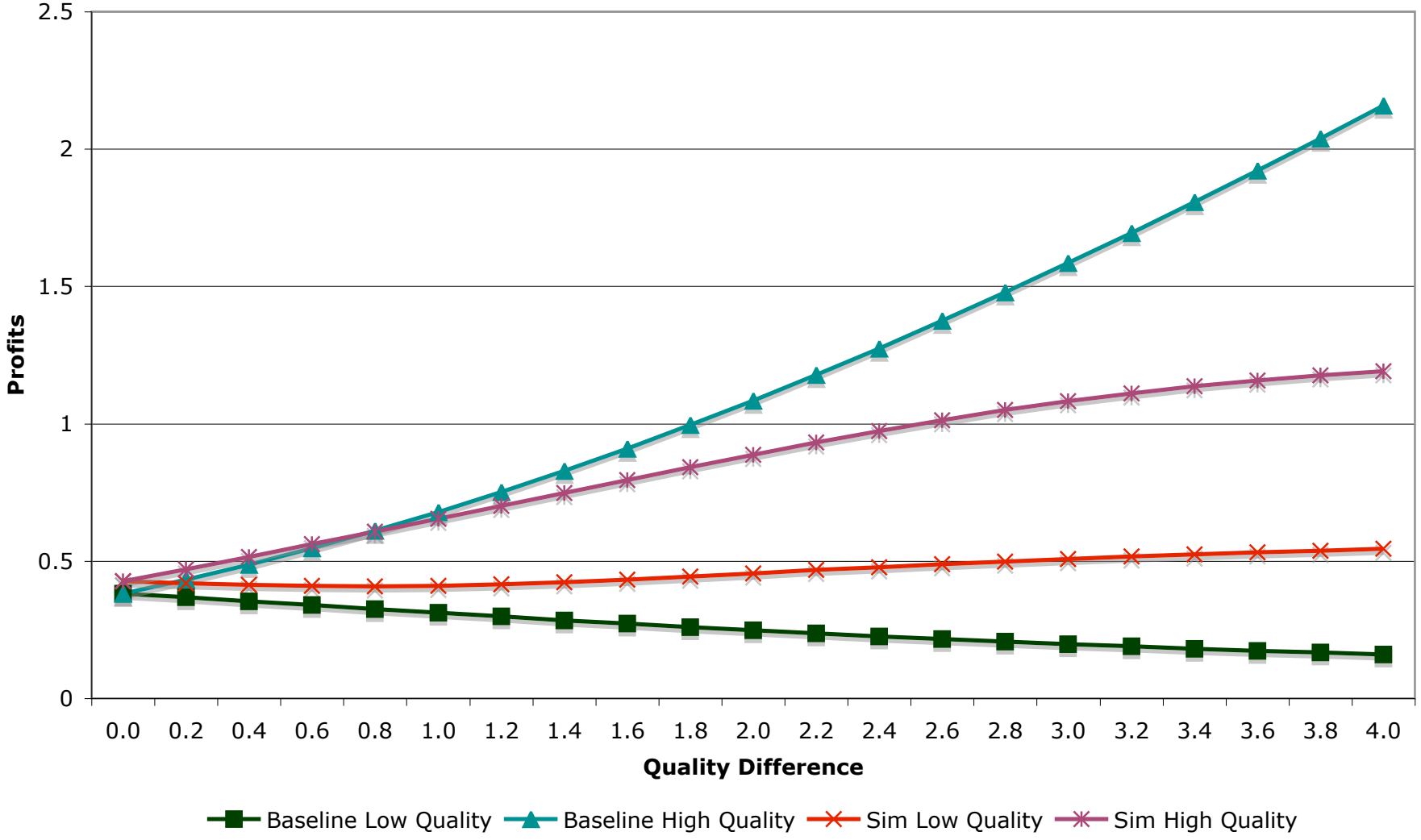


Figure 3
Numerical Example 2: Change Ratio

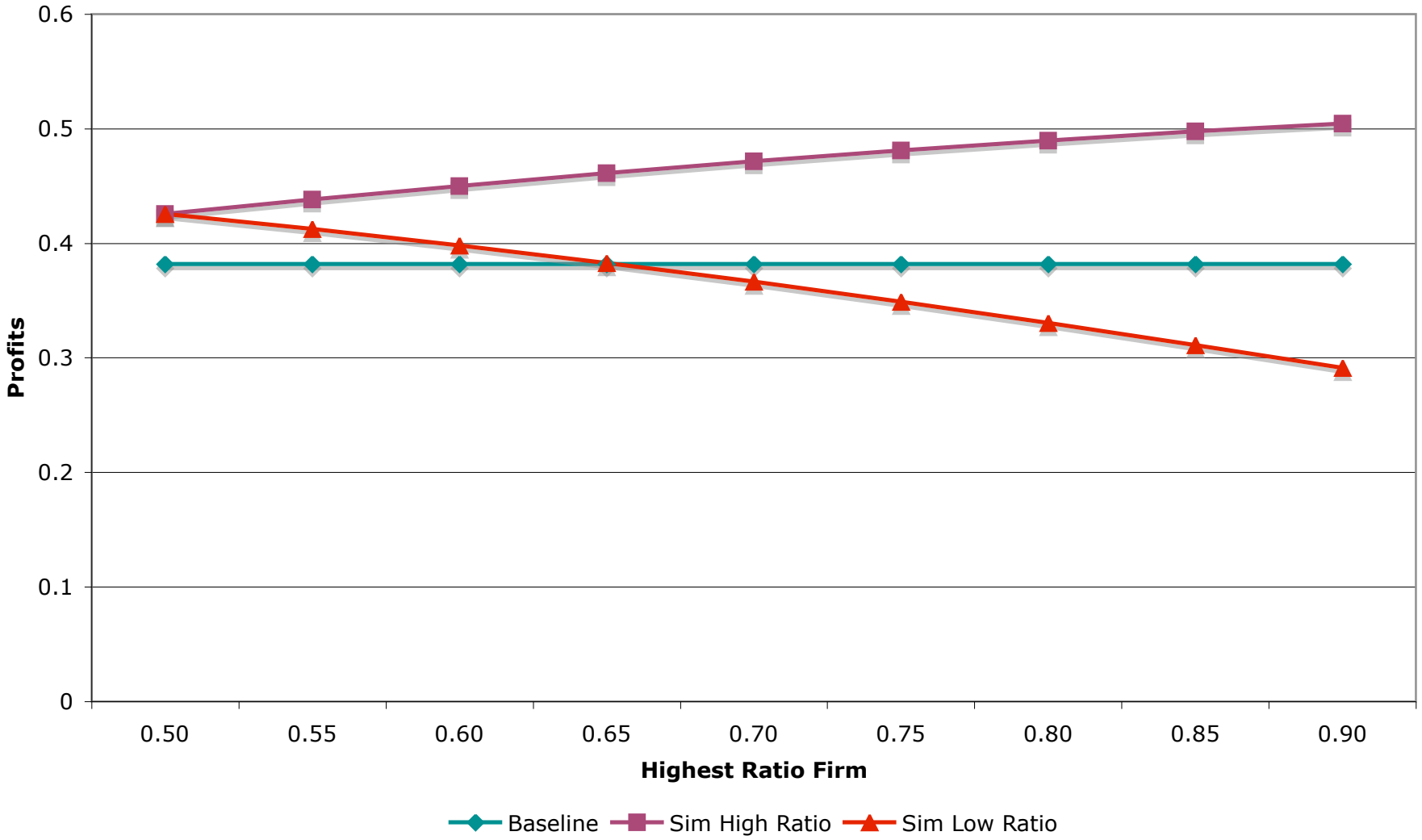


Table 1: Attributes of the Drug Regimens

		Efficacy Measures			Grade 3 or Grade 4 Side Effects (%)					
Regimen	Launch Year	Survival Months	Response Rate	Time to Progression	Abdominal Pain	Diarrhea	Nausea	Vomiting	Neutropenia	Dehydration
First-line therapies										
5-FU + Leucovorin	1991	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7	4.0
Irinotecan (Camptosar) + 5-FU/LV	1996	15.6	35.4	6.7	5.3	24.0	11.9	8.0	39.5	11.0
Capecitabine (Xeloda)	2001	13.1	21.0	4.4	9.5	15.0	4.0	4.5	3.0	2.5
Irinotecan + capecitabine	2001	15.6	35.4	6.7	5.3	24.0	11.9	8.0	39.5	11.0
Oxaliplatin (Eloxatin) + 5-FU/LV	2002	19.4	46.1	9.1	6.0	15.4	4.4	5.5	38.8	4.4
Oxaliplatin + capecitabine	2002	18.0	36.5	8.1	6.0	21.9	15.6	11.3	3.7	8.0
Bevacizumab (Avastin) + oxaliplatin + 5-FU/LV	2004	23.2	41.0	9.9	8.0	23.1	7.9	8.6	12.2	10.5
Bevacizumab + oxaliplatin + capecitabine	2004	23.2	41.0	9.9	8.0	23.1	7.9	19.0	12.0	21.0
Bevacizumab + irinotecan + 5-FU/LV	2004	20.3	45.0	10.6	8.0	34.0	1.0	1.0	21.0	1.0
Second-line therapies										
Irinotecan	1996	9.5	15.0	4.2	16.0	31.0	17.0	12.0	26.0	4.0
Cetuximab (Erbitux)	2004	N/A	10.8	1.5	9.0	2.0	2.0	3.0	5.0	3.0
Cetuximab + irinotecan	2004	N/A	22.9	4.1	8.0	22.0	6.0	7.0	5.0	6.0

Notes: the brand name of a drug appears in parentheses in the first column. All attribute information is based on the experiences of patients in Phase clinical 3 trials. The median survival is measured in months. Cetuximab was approved without demonstrating a longer survival, and therefore survival is coded as not available (N/A). Response rate is the percentage of patients whose tumor shrunk. Time to progression is the mean number of months for a tumor to advance to a more severe stage. Second-line therapies are approved by the FDA to be used on patients who have been treated previously with a different therapy. The final six columns measure the percentage of patients who experienced a grade 3 or grade 4 (on a 1-4 scale, where 4 is the most severe) side effect of a particular type.

Table 2: Estimation Results

Variable	OLS Logit	IV Logit I	IV Logit II
$\log(price)$	-0.733**	-0.841**	-2.176**
	(0.098)	(0.117)	(0.448)
Survival (months)	0.179**	0.155**	-0.138
	(0.052)	(0.058)	(0.120)
Response Rate (%)	0.285**	0.341**	1.030**
	(0.058)	(0.069)	(0.232)
Time to Progression	-1.265**	-1.398**	-3.051**
(months)	(0.215)	(0.224)	(0.599)
Diarrhea	0.011	0.015	0.057
	(0.018)	(0.014)	(0.034)
Nausea	0.081	0.088	0.167
	(0.065)	(0.067)	(0.098)
Abdom_pain	0.186**	0.236**	0.851**
	(0.061)	(0.071)	(0.208)
Vomiting	-0.111	-0.107	-0.053
	(0.097)	(0.096)	(0.143)
Neutropenia	-0.058**	-0.066**	-0.161**
	(0.010)	(0.011)	(0.032)

Table 3: Counterfactual I: Price Changes (per mg)

	Pfizer	Roche	Sanofi	Imclone	Genentech
Baseline	100.0	100.0	100.0	100.0	100.0
Pf + Ro out (r19)	**114.9**	**91.8**	98.7	102.5	102.3
Ro + Sa out (r11)	98.0	**79.4**	**114.7**	99.8	104.1
Pf + Ge out (r5)	**74.8**	106.3	99.8	95.7	**107.1**
Ro + Sa + Ge out	100.8	**92.6**	**99.9**	100.1	**100.6**
Pf + Im out (r6)	**78.2**	106.2	101.4	**76.2**	95.5
Sa + Ge out (r2)	100.9	113.1	**88.8**	100.4	**127.0**

Table 4: Counterfactual I: Profit Changes

	Pfizer	Roche	Sanofi	Imclone	Genentech
Current	100.0	100.0	100.0	100.0	100.0
Pf + Ro out	**96.5**	**98.7**	102.0	96.3	101.0
Ro + Sa out	103.1	**87.9**	**93.7**	106.2	97.3
Pf + Ge out	**64.8**	105.0	96.9	115.9	**80.2**
Ro + Sa + Ge out	99.1	**96.3**	**97.7**	99.3	**97.6**
Pf + Im out	**76.6**	99.4	99.7	**21.3**	100.9
Sa + Ge out	101.7	118.3	**70.4**	112.9	**25.2**

Table 5: Counterfactual I: Consumer Welfare

	CW
Current	100.0
Pf + Ro out	98.4
Ro + Sa out	97.3
Pf + Ge out	99.0
Ro + Sa + Ge out	100.2
Pf + Im out	101.6
Sa + Ge out	93.3

Table 6: Counterfactual II: Price Changes (per mg)

	Solo	Pfizer	Roche	Sanofi	Imclone	Genentech
Current		100.0	100.0	100.0	100.0	100.0
Pfizer 1 (r8)	43.3	**129.4**	95.8	99.7	104.7	103.7
Pfizer 2 (r17)	43.3	**129.4**	95.8	99.7	104.7	103.7
Roche (r3)	67.5	115.6	**550.1**	114.6	102.7	107.9
Sanofi (r1)	73.8	104.7	80.3	**214.0**	100.6	132.3
Imclone (r14)	71.2	98.9	100.0	100.1	**109.4**	99.9

Table 7: Counterfactual II: Profit changes

	Pfizer	Roche	Sanofi	Imclone	Genentech
Current	100.0	100.0	100.0	100.0	100.0
Pfizer 1 (r8)	**85.1**	82.8	82.1	74.0	79.1
Pfizer 2 (r17)	**95.5**	94.0	93.7	84.0	90.6
Roche (r3)	98.0	**152.2**	93.7	98.1	93.4
Sanofi (r1)	83.9	80.7	**96.2**	92.2	54.7
Imclone (r14)	95.8	99.3	99.3	**101.4**	99.2

Table 8: Counterfactual II: Consumer Welfare

	CW
Current	100.0
Pfizer 1 (r8)	109.1
Pfizer 2 (r17)	102.3
Roche (r3)	97.2
Sanofi (r1)	103.2
Imclone (r14)	100.4

Appendix: Composition and Dosages of the Chemotherapy Regimen

Regimen	1st Drug	2nd Drug	3rd Drug	4th Drug
5-FU + Leucovorin[20]	425 mg of 5-FU/m^2/day for days 1-5, every 4 weeks	20 mg of Leucovorin/m^2/day for days 1-5, every 4 weeks		
Irinotecan	125 mg of irinotecan per week/m^2 for 4 weeks, every 6 weeks			
Irinotecan + 5-FU/LV[21]	180 mg of irinotecan/m^2 on day 1, every 2 weeks	1,000 mg of 5-FU/m^2 on day 1 and 2, every 2 weeks	200 mg of Leucovorin/m^2 on day 1 and day 2, every 2 weeks	
Capecitabine	2,500 mg of capecitabine per m^2/day for days 1-14, every 3 weeks			
Capecitabine + irinotecan	70 mg of irinotecan/m^2/week, every 6 weeks	2,000 mg of capecitabine per m^2/day for days 1-14, every 3 weeks		
Oxaliplatin + 5-FU/LV[22]	85 mg of oxaliplatin per m^2 on day 1, every 2 weeks	1,000 mg of 5-FU/m^2 on day 1 and day 2, every 2 weeks	200 mg of Leucovorin/m^2 on day 1 and day 2, every 2 weeks	
Oxaliplatin + capecitabine	130 mg of oxaliplatin per m^2 on day 1, every 3 weeks	1,700 mg of capecitabine per m^2/day for days 1-14, every 3 weeks		
Cetuximab	400 mg of cetuximab per m^2 on day 1; then 250 mg/m^2 once a week, every 6 weeks			

[20] Mayo treatment method.
[21] FOLFIRI treatment method.
[22] FOLFOX treatment method.

Cetuximab + irinotecan	400 mg of cetuximab per m^2 on day 1; then 250 mg/m^2 once a week, every 6 weeks	125 mg of irinotecan per week/m^2 for 4 weeks, every 6 weeks		
Bevacizumab + oxaliplatin + 5-FU/LV	5 mg of bevacizumab per kg, every 2 weeks	85 mg of oxaliplatin per m^2 on day 1, every 2 weeks	1,000 mg of 5-FU/m^2 on day 1 and day 2, every 2 weeks	200 mg of Leucovorin/m^2 on day 1 and day 2, every 2 weeks
Bevacizumab + irinotecan + 5-FU/LV	5 mg of bevacizumab per kg, every 2 weeks	180 mg of irinotecan/m^2 on day 1, every 2 weeks	1,000 mg of 5-FU/m^2 on day 1 and 2, every 2 weeks	200 mg of Leucovorin/m^2 on day 1 and day 2, every 2 weeks
Bevacizumab + oxaliplatin + capecitabine[23]	7.5 mg of bevacizumab per kg, every 3 weeks	130 mg of irinotecan/m^2 on day 1, every 3 weeks	1,700 mg of capecitabine per m^2/day for days 1-14, every 3 weeks	

Notes: each regimen is assumed to last for 24 weeks. The four-week 5-FU + Leucovorin regimen, for example, is assumed to be repeated six times during a patient's treatment cycle. mg = milligram of active ingredient; m^2 = meter squared of a patient's surface area; kg = kilogram of a patient's weight. We price the regimens for a patient who has a surface area of 1.7 m^2 and weighs 80 kilograms.

Source: National Comprehensive Cancer Network, Colon Cancer, Version 2.2006; package inserts.

[23] CAPOX treatment method.