1 Introduction

There is a substantial literature in economics focusing on product combinations such as bundling or tying. This literature o□ers 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 en

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

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,

price (AWP) that is set by a manufacturer and often di□ers 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 o□ered substantial rebates during this period. Although we have information on 10 di□erent types of customers, we focus on the prices paid by the two largest customers - hospitals and physician o□

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

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

by IV on the first day of treatment, followed by a 1,000 mg infus

, 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:

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

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 ($\partial p / \partial p_f$), and how the regimen price changes will impact market shares for all the regimens the drug participates in ($\partial s_r(p) / \partial p$). 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

payments, observed and unobserved attributes of the treatm

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 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 δ_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

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

participate in the removed regimen.

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

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 a□ecting 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 e□ect 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 e□ect 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.

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.

Nalebu□, 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.

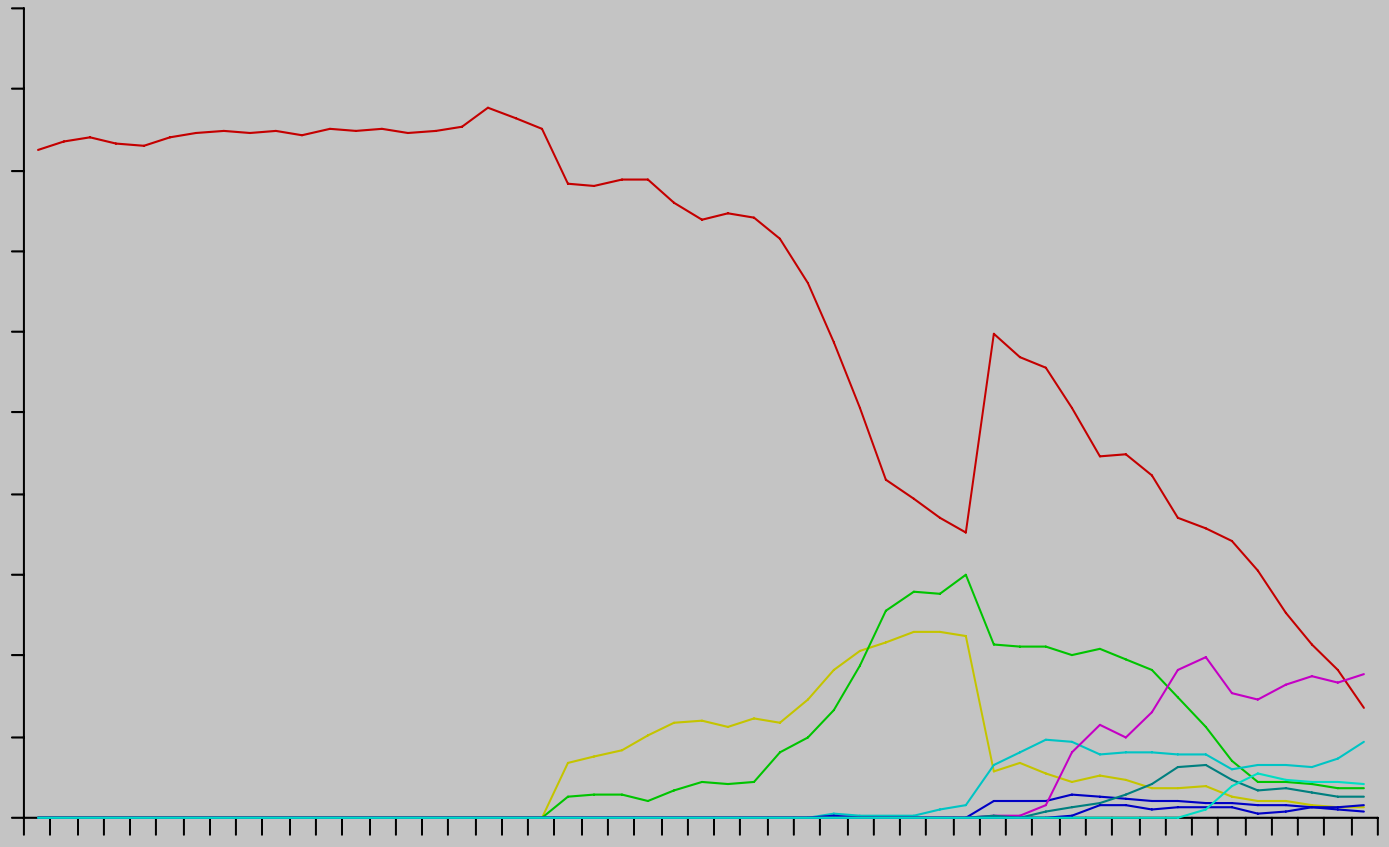

Figure 3
Numerical Example 2: Change Ratio

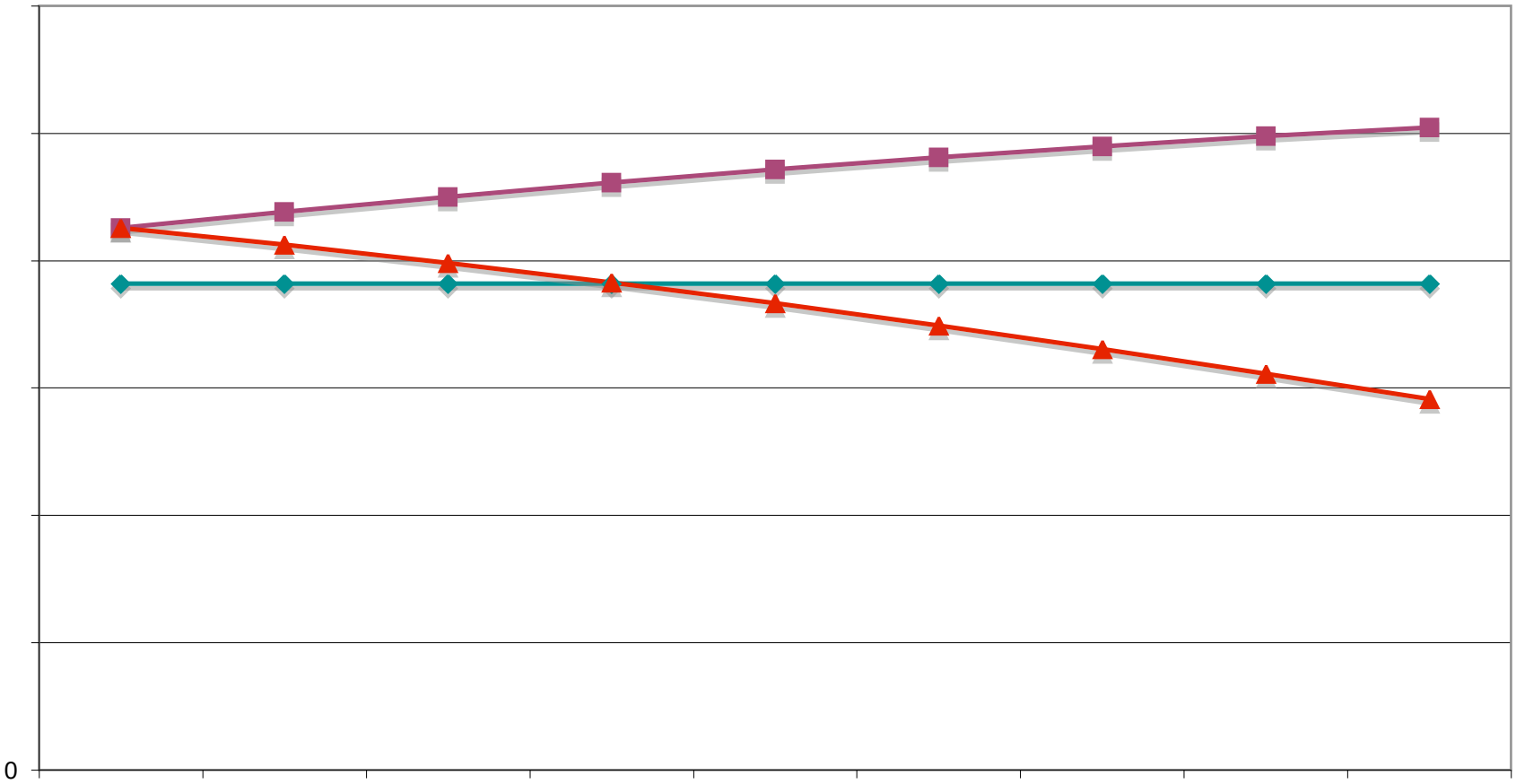

Table 1: Attributes of the Drug Regimens

		Efficacy Measures			Grade 3 or Grade 4 Side Effects (%)					
Regimen	Launch Year	Survival Months	Response Rate	Time to Progression	Abdominal Pain	Diarrhea	Nausea	Vomi-ting	Neutro-penia	Dehy-dration
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					

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**

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 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				