Mergers with Inter-Firm Bundling: A Case of Pharmaceutical Cocktails

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June 2016

Abstract

Pharmaceutical combination therapies, or cocktails, are examples of inter-firm bundling where a bundle consists of drugs produced by competing firms and the components of the bundle are also sold as stand-alone products. We empirically analyze the welfare effects of a merger between two pharmaceutical firms that sell complements for the treatment of colorectal cancer. We show that the merging firms would internalize the effect of selling complements and reduce the price of the cocktail product, but would also raise the prices of their stand-alone products to exploit enhanced market power. As a result, mergers are less harmful and can even be beneficial in the presence of inter-firm bundles.

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‡Universidad de los Andes, Chile. E-mail: claudio.lucarelli@uandes.cl. We have benefited from discussions with Yongmin Chen, Joshua Lustig, Jae Nahm, Michael Raith, Michael Riordan, Michael Waldman, and comments by seminar participants at Columbia University, University of Southern California, the Cowles Foundation, the Federal Trade Commission, the 2009 IIOC, Korea University, SKK University, the University of Rochester and the University of Wisconsin-Madison. James Elwell provided excellent research assistance. All errors are ours.

1 Introduction

Patients often take a combination of two or more prescription drugs in order to improve the efficacy of treating a disease or to alleviate side effects. Most HIV/AIDS patients, for example, receive a "cocktail" regimen, such as a combination of efavirenz, lamivudine, and zidovudine. Harvoni, a combination of the drugs ledipasvir and sofosbuvir, has a 95 percent cure rate for hepatitis C and generated $13.9 billion in sales in 2015. In 2008, thirty-one percent of U.S. colorectal cancer patients receiving drug treatment were administered a combination therapy, or cocktail regimen. Many of these combination therapies are quite expensive. Harvoni, for example, has a list price of $94,500 for a 12-week treatment.

Some pharmaceutical combination therapies are examples of inter-firm bundling where a bundle consists of products (drugs) produced by competing firms, and the components to the bundle are also sold as stand-alone products. A firm's pricing problem involving an inter-firm cocktail regimen is effectively the same as a situation where two firms unilaterally set prices of complements. When one firm raises the price of its component drug, demand is reduced both for its own drug and the rival firm's drug. Such a pricing problem was first analyzed by Cournot (1838) who shows that the price of complements is higher when set unilaterally by competing firms than when set by a monopolist. In such a setting, a merger can increase both producer surplus and consumer welfare by eliminating double marginalization. Although the pricing of complements has been studied theoretically in various settings, there are few empirical analyses in the economic literature.[1]

The pharmaceutical industry has been consolidating over the past several decades. The market value of mergers and acquisitions in this industry exceeded $200 billion in the first six months of 2015 alone. When a drug is used in multiple regimens, including as a stand-alone product and as a component of a cocktail regimen, it is not clear whether a merger between the two firms sharing a cocktail regimen would increase welfare. While the firms would want to lower price of the cocktail product post merger to internalize the effect of selling complements, which we refer to as the complementarity effect, they would also want to exploit enhanced market power by raising prices for their stand-alone products, which we refer to as the market power effect.

[1] Examples of theoretical treatments include Economides and Salop (1992), Economides (1998), Davis and Murphy (2000), Choi (2008), Dari-Mattiacci and Parisi (2006), and Yan and Bandyopadhyay (2011).

This trade-off created by an inter-firm bundle is present in other industries. The merger between AT&T and DIRECTV, approved by the Federal Communications Commission (FCC) in July 2015, provides such an example (FCC, 2015). Prior to the merger, DIRECTV offered customers video programming services only while AT&T offered video only, broadband internet access only, and a bundle of those two products for customers seeking a more interactive viewing experience. Although DIRECTV did not offer broadband services before the merger, consumers could create a synthetic bundle consisting of video and broadband components offered by two separate firms, including AT&T with DIRECTV, and firms other than AT&T with DIRECTV. The merging firms were therefore producing complements that could be consumed together as a "cocktail" as well as stand-alone products. Furthermore, the stand-alone products and inter-firm bundle competed with one another at the product level, which is also the situation in our context.

In this paper we empirically analyze the welfare effects of a merger between two firms selling complements, focusing on pharmaceutical treatment of colorectal cancer patients. In the colorectal cancer treatment market, most drugs used in cocktails are also available as a stand-alone product, and physicians choose a single regimen (at a point in time) for their patients. In the early 2000s, for example, five patent-protected drugs were used in 12 major regimens. Six of these were stand-alone regimens while six cocktail regimens were created by combining the five drugs in various ways. Therefore, the welfare effects of a merger between any two firms producing components of a cocktail will be ambiguous because the two firms have products that are both complements and substitutes.

A cocktail regimen must be approved by the Food and Drug Administration (FDA) by demonstrating superior efficacy, fewer side effects, or greater convenience relative to existing drugs, even if the cocktail combines already-approved drugs.[2] Thus, we treat a cocktail regimen as a new product with distinctive characteristics rather than as a bundle with the same characteristics as its component drugs. The implication is that we need to estimate the utility of a cocktail regimen separately from the utility of the stand-alone regimens that use the same component drugs. This approach differs from a typical bundling situation where the utility of a bundle is equal to the sum of the utilities of the products included in the bundle, modified by an additional utility component

[2] Firms entering the oncology market often test their experimental drug in combination with a drug that is already approved. The entering firm can purchase the approved drug without the permission of the incumbent firm and administer the two drugs together in a clinical trial.

due to substitutability or complementarity among these products.

One unique feature of the market we study is that oncologists purchase the component drugs from different manufacturers and then infuse them into a patient in an office or hospital clinic. This means that firms are constrained to set linear prices, i.e., a price per milligram, regardless of how their drugs are used.[3] Due to this linear pricing constraint, the merging firms cannot offer a discount just for the cocktail regimen they have in common post merger. Instead, the merging pharmaceutical firms will either lower or raise their drug prices post merger for all of their products, depending on whether the complementarity or market power effect is stronger. In the AT&T-DIRECTV merger and in most other markets, by contrast, firms have greater flexibility to discount the price of an inter-firm bundle while raising prices of the stand-alone products following a merger.

In addition to the merger effects, we also analyze the welfare effects of introducing a new inter-firm cocktail regimen. It is not clear a priori if patients (as consumers) always benefit from a new cocktail regimen. By revealed preference, patients treated with a new cocktail regimen benefit. The welfare effect for those treated with existing regimens, however, depends on how the new cocktail regimen affects existing drug prices. If the new cocktail regimen raises the price of other existing regimens substantially, the overall welfare effects can be ambiguous.

We estimate a structural model that allows us to analyze hypothetical merger effects as well as the welfare effects of each regimen. We begin by estimating a demand system at the regimen level using data on regimen prices, market shares, and attributes. Regimens, which can be single drugs or cocktails of two or more drugs, are well defined and standardized. The National Comprehensive Cancer Network (NCCN) recommends the amount of each drug an oncologist should use in each regimen. Market share is defined as the proportion of colorectal cancer patients treated with a particular regimen. Data from randomized clinical trials provide information on attributes such as regimen efficacy (e.g., the median number of months patients survived in the clinical trial) and side effects (e.g., the percent of patients in the clinical trial who experienced abdominal pain).

We use the demand estimates and profit maximization conditions to recover the marginal cost of each drug. We then fix the marginal costs and demand parameters and conduct a series of

[3] Most HIV/AIDS patients, on the other hand, take a single pill that contains two or more separate drugs, which allows a single firm to set a bundle price.

counterfactual scenarios. In the merger analysis we separately measure the market power and the complementarity effects. To capture the former effect, we remove the cocktail regimen that two given firms have in common and compare the pre- and the post-merger equilibrium prices. We show that merging firms in the colorectal cancer treatment market would raise drug prices substantially, more than twice in some cases, if they merged with no cocktail regimen in common. To measure the latter effect, we allow two firms to sell only a cocktail regimen pre- and post-merger. The price of a cocktail regimen falls by more than 50 percent following a merger in all five cases we consider. The full merger effect, which combines the two opposing forces, demonstrates that the merging firms would usually raise their drug prices moderately compared to the case without the cocktail regimen, and would even lower prices in two of the five cases. As a result, mergers are less harmful and can even be beneficial in the presence of inter-firm bundles.

In order to evaluate whether the merger results are due to the linear pricing constraint unique to the oncology drug treatment market, we simulate a scenario where merging firms have greater pricing flexibility. Specifically, a firm is able to set a separate drug price for its drug when used as a cocktail component and its drug when used in other regimens (stand-alone regimens or cocktails with non-merging firms). We find that merging firms always offer a bundle discount for the cocktail regimen post merger while raising prices of other regimens. Nevertheless, changes in prices and consumer welfare are similar to those in the linear pricing case.

This bundle discount setting is directly applicable to the AT&T-DIRECTV merger described above. Our results are consistent with the post-merger predictions of the FCC; they concluded that the merging firms would lower prices for the bundled product (broadband and video services combined) post merger while raising prices for the stand-alone video service (FCC, 2015). However, our results regarding consumer welfare are more nuanced. While the FCC concluded that there would be a net welfare gain for consumers in this particular merger, our results suggest that this is less likely in the colorectal cancer treatment market and, more importantly, that the welfare effects depend on merger-specific market conditions.

We evaluate the welfare effects of introducing a new cocktail regimen by removing cocktail regimens one at a time and computing new equilibrium prices. We find that firms usually lower drug prices when a cocktail is removed and consumers gain more from the lower prices than they lose from having less product variety.

In addition to the literature on the pricing of complements, our paper is also related to the bundling literature.[4] Firms have two main motivations for offering a bundle. One is to extract more consumer surplus when consumers have heterogeneous valuations for two individual products produced by the same multiproduct firm (Adams and Yellen, 1976; Long, 1984; McAfee, McMillan, and Winston, 1989, among many others). The other motivation is to leverage monopoly power in the primary market by foreclosing sales and discouraging entry in the secondary market (Whinston, 1990; Chen, 1997; Carlton and Waldman, 2002; Nalebuff, 2004; Carlton, Gans, and Waldman, 2007). The second motivation typically involves a bundle of complements such as Microsoft's Internet Explorer bundled with its operating system, but they are usually in two different markets.

More recently, Armstrong (2013) relaxes two key assumptions in the literature by allowing products in a bundle to be (1) produced by separate sellers and (2) substitutes. He shows that an integrated firm typically has a greater incentive to offer a bundle discount when products are substitutes (than when products are unrelated) and that separate sellers also wish to offer a joint-purchase discount when there is a constant disutility of consuming the two products together. Gans and King (2006) analyze inter-firm bundling of unrelated products such as discounts for joint purchase of gasoline at gas stations and groceries at supermarkets. They show that unrelated products can be complements if the discount (or premium) rate of a bundle is fixed ex ante.

In Section 2 we present an overview of colorectal cancer treatment and describe the data in Section 3. We present the model in Section 4, followed by results from the demand estimation in Section 5. The merger and welfare analyses are reported in Section 6 and we conclude in Section 7.

2 Overview of Colorectal Cancer

Colorectal cancer is the fourth most common cancer based on the number of newly-diagnosed patients, after breast, prostate, and lung cancers. About one in 20 people born today is expected to be diagnosed with colorectal cancer over their lifetime. The disease is treatable if it is detected before it metastasizes, or spreads, to other areas of the body. According to the National Cancer Institute, colorectal cancer patients had a 65 percent chance of surviving for five years and a 58

[4] This paper is also related to the literature on the determinants of pharmaceutical prices, including Saha et. al. (2006), Frank and Salkever (1997), Grabowski and Vernon (1992), Duggan and Scott Morton (2006), Duggan and Scott Morton (2010), Lichtenbeg and Sun (2007), Ketcham and Simon (2008), Yin et. al. (2008), and Lakdawalla and Yin (2010).

percent chance of surviving for 10 years between 1999 and 2006. The probability that a patient will survive for five years ranges from 90 percent for those diagnosed with Stage I cancer to 12 percent for those diagnosed with Stage IV (or metastatic) cancer.[5]

The way a colorectal cancer patient is treated depends on the stage of the tumor at diagnosis. Most patients with a Stage I, II, or III tumor will have the tumor removed surgically, i.e., resected. The NCCN recommends that patients with Stage III disease receive six months of chemotherapy following the resection; they do not recommend chemotherapy for Stage I patients and they encourage Stage II patients to discuss the benefits and costs of chemotherapy with their oncologist before deciding. The majority of patients diagnosed with Stage IV disease have an unresectable tumor. Some of these patients receive chemotherapy to shrink the tumor such that it can be resected, and many receive chemotherapy without prior surgical treatment. Our demand model describes patients' chemotherapy treatment choices once they have decided to receive chemotherapy; we assume patients have already decided whether or not to receive surgery prior to chemotherapy treatment.

There were 12 major treatment regimens during our sample period and we estimate demand parameters for a system of all 12 regimens. Although many of these regimens consist of multiple drugs, we make a distinction between regimens that consist of two or three branded (or patent-protected) drugs produced by separate firms (often combined with generic drugs), versus regimens that consist of either a single branded drug or a single branded drug combined with generic drugs. We refer to the former regimens as "cocktail" regimens because the regimen price is determined by the separate decisions of two or three firms that each has market power, and the latter regimens as "stand-alone regimens," whose price is essentially determined by a single firm. We restrict our attention in the counterfactual exercises to the six cocktail regimens in order to focus on inter-firm bundling. Many of the regimens include generic drugs such as fluorouracil (5-FU) and leucovorin (LV). Because the patents on these drugs have expired, many firms produce them, the prices for these regimen components should be close to marginal cost, and we do not expect generic drug prices to respond to changes in market conditions such as mergers and new product introduction. We take the generic drug prices as given and assume they are priced at marginal cost, not the result

[5] Cancers are classified into four stages, with higher numbers indicating that the cancer has spread to the lymph nodes (Stage III) or beyond its initial location (Stage IV).

of firms' strategic pricing.

Five pharmaceutical firms produced a patent-protected (or branded) colorectal cancer drug during our study period: Pfizer (which produced irinotecan), Roche (capecitabine), Sanofi (oxaliplatin), ImClone (cetuximab), and Genentech (bevacizumab).[6] In one cocktail regimen, Roche's capecitabine is combined with Pfizer's irinotecan. In another capecitabine is combined with Sanofi's oxaliplatin. Genentech's bevacizumab is combined separately with oxaliplatin and capecitabine; oxaliplatin; and irinotecan to create three distinct cocktail regimens. Finally, ImClone's cetuximab is combined with Pfizer's irinotecan.

Three of the six non-cocktail regimens are individual drugs used in the cocktail regimens mentioned above, but in different dosages. The other non-cocktail regimens are fluourouracil combined with leucovorin (5-FU/LV), both of which are generic drugs, Pfizer's irinotecan combined with 5-FU/LV, and Sanofi's oxaliplatin combined with 5-FU/LV. We consider all six of these regimens above as being stand-alone regimens. Appendix I provides a complete description of the recommended dosage for the 12 regimens for which we have complete data.

The National Comprehensive Cancer Network (NCCN) divides colorectal cancer chemotherapy regimens into two groups. For early-stage patients who cannot tolerate intensive therapy, it recommends 5-FU/LV (the generic regimen), Roche's stand-alone regimen (capecitabine), or the Pfizer-Roche cocktail regimen (irinotecan plus capecitabine). The other regimens are recommended for those who can tolerate the possible side effects of intensive therapy.[7] The NCCN also provides chemotherapy guidelines for patients whose cancer progresses in spite of the first chemotherapy treatment. For example, if the Roche-Sanofi cocktail regimen (capecitabine plus oxaliplatin) was selected for initial therapy, the NCCN recommends the Pfizer-ImClone cocktail (irinotecan plus cetuximab) for second-line chemotherapy treatment. In Section 4.2 we use these guidelines to define the nests for a nested logit demand model.

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. Unlike drugs that are distrib-

[6] Drugs have brand names in addition to the generic names that we provide in the text. The brand names of the five patent-protected drugs are as follows: Camptosar (irinotecan), Xeloda (capecitabine), Eloxatin (oxaliplatin), Avastin (bevacizumab), and Erbitux (cetuximab). ImClone has since been acquired by Bristol Myers; Genentech has since been acquired by Roche; and Pharmacia, which developed irinotecan, has since been acquired by Pfizer.

[7] Although there is a genetic test approved by the Food and Drug Administration (FDA) associated with cetuximab, in practice oncologists do not generally rely on this test to determine the appropriate regimen for a patient. Decisions regarding an appropriate therapy are not affected substantially by a patient's genetic profile.

uted 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. Patients usually pay a percentage of the price. Medicare patients, for example, pay 20 percent of the price if they have Part B coverage and no Medigap supplemental insurance.

Although physicians are eventually reimbursed by health insurers, they do take temporary ownership of oncology drugs. As such, physicians face the possible risk of not being reimbursed by health insurers and may incur substantial carrying costs. For example, a physician who pays $50,000 for the drugs in a patient's regimen and experiences a three-month delay between when he acquires the drugs and when he is reimbursed by a health insurer would incur an inventory carrying cost of $1,333 at an interest rate of eight percent. Because we observe the full price that physicians pay for colorectal cancer drugs, we can estimate physicians' demand for those drugs. In our model we assume physicians act as agents for their patients, in which case we indirectly observe patients' willingness to pay for these drugs. We explain details of physician agency in Section 4.2.

Because each drug is sold separately to physicians who then combine them (when relevant) into a cocktail regimen, the only variable a firm controls is the price of its own drug. This price, in turn, affects the demand of all regimens in which the drug is used. We explicitly account for this impact in our supply-side (pricing) model in Section 4.1.

3 Data

We use several data sources to collect four types of information: drug prices, regimen market shares, the quantity/dose of each drug typically used in a regimen, and regimen attributes from clinical trials. IMS Health records transactions between wholesalers, who previously purchased the drugs from manufacturers, and the end customer, such as a physician practice. IMS Health reports 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) codes, which are unique for each firm-product-strength/dosage-package

size. We calculate the average price paid by physician offices per milligram of active ingredient of a drug across the different NDC codes for a particular drug. IMS Health reports the invoice price a customer actually pays to a wholesaler, not the average wholesale price (AWP) that is set by a manufacturer and often differs substantially from the true transaction price or the wholesale acquisition cost (WAC).

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 oncologists and an analysis reported in Lucarelli, Nicholson, and Town (2010), we do not believe that manufacturers offered substantial rebates during this period.[8] Although we have information on 10 different types of customers, we use the prices paid by the largest customer - physician offices - because almost 60 percent of colon cancer chemotherapy drugs are infused in a physician's office and our market share data for 2002 to 2005 are for physician offices.[9]

We compute the price of each regimen for a representative patient who has a surface area of 1.7 meters squared, weighs 80 kilograms, and is treated for 12 weeks (Jacobson and Newhouse, 2006). Regimen prices are derived by multiplying the average price per milligram of active ingredient in a quarter by the recommended dosage of each drug in the regimen over a 12-week period. The 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 I. For example, the standard dosage schedule for oxaliplatin+5-FU/LV, the regimen with the second largest market share in 2005, is 85 milligrams (mg) of oxaliplatin per meter squared of a patient's surface area infused 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 LV per meter squared on the first and second treatment days. This process is repeated every two weeks.[10]

[8] For the five patent-protected colorectal cancer drugs in our study, Lucarelli, Nicholson, and Town (2010) compared prices that include discounts and rebates to the IMS prices that we use in this paper. They found that prices from the two data sources were within two to four percent of one another, which is consistent with no or small rebates/discounts. Although pharmacy benefit managers, or PBMs, are able to negotiate price discounts for health insurers for many self-administered oral drugs, PBMs are less effective at negotiating discounts on the physician-administered drugs that we study in this paper

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

[10] Our data show that the dosage of drugs in cocktail regimens are usually no larger than their dosages in stand-alone regimens. In fact, the only exception is Sanofi's drug, whose dosage in its cocktail with the Roche and Genentech

The IMS Health data contain information on market share by drug, but not market share for combinations of drugs (i.e., regimens). Rather than using IMS for market share data, therefore, we rely on two different sources for regimen-specific market shares, where market share is defined as the proportion of colorectal cancer chemotherapy patients treated with a particular regimen. IntrinsiQ, a company that sells information systems to help oncologists dose chemotherapy regiments, collects monthly data from its oncologist clients on the types of chemotherapy drugs administered to patients who are treated in physician practices. Based on these data, we derive monthly market shares for each regimen between January 2002 and September 2005.

Since IntrinsiQ's data only go back to 2002, we rely on the Surveillance Epidemiology and End Results (SEER) data set for market shares for the 1993 to 2001 period. SEER tracks the health and treatment of cancer patients over the age of 64 in states and cities covering 26 percent of the U.S. population.[11] Based on Medicare claims data available in SEER, we calculate each colorectal cancer regimen's market share in each quarter based on patients treated in all settings.[12]

In order to standardize market shares between the pre- and post-2002 periods, we take advantage of the fact that the two data sets overlap for the four 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. The underlying assumption in this adjustment is that the proportion of total patients represented by Medicare is time invariant for each regimen.

All regimens we include in the sample contain drugs that were approved by the FDA for colorectal cancer and had a market share greater than one percent at the end of the sample period. The outside option includes off-label drugs, regimens with less than one percent market share at the end of the sample period, and regimens with missing attribute data.[13]

We plot market shares for the 12 regimens in the sample and the outside option in Figure 1. Between 1993 and 1996, about 95 percent of colorectal cancer patients were treated with 5-FU/LV, a generic regimen, with the remainder treated with off-label drugs or regimens with small market

drugs is 2 percent larger than in its stand-alone regimen.

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

[12] According to IntrinsiQ's data, approximately 48 percent of all colorectal cancer chemotherapy patients were 65 years or older in October 2003.

[13] Off-label use occurs when a physician treats a colorectal cancer patient with a drug that has not been approved by the FDA explicitly for colorectal cancer.

share. In 1996 irinotecan was approved by the FDA for treating colorectal cancer, and over the next several years the market share of irinotecan and irinotecan combined with 5-FU/LV grew at the expense of 5-FU/LV.[14] Capecitabine, a tablet that produces the same chemical response as 5-FU/LV, was approved for treatment of colorectal cancer in April 2001 and was administered as a stand-alone therapy or combined with irinotecan. Besides capecitabine, all other drugs for treating colorectal cancer in our sample are delivered intravenously (i.e., by IV) under the supervision of a physician or nurse.

Oxaliplatin was introduced in August 2002, followed by cetuximab and bevacizumab in February 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.

We obtain most of the attribute information from the FDA-approved package inserts that accompany each drug. These inserts describe the performance of the drug/regimen in phase 3 clinical trials, 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 these patients. Because patients are randomized to the treatment or control regimens in phase 3 trials, the attributes are not subject to selection bias, such as the possibility that healthier patients might choose more toxic regimens. 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 used for 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 conferences and journal articles.

We summarize the attribute information in Table 1, taking a weighted (by market share) average across regimens in each quarter, and then averaging across quarters for each year. The efficacy and side effect attributes are time invariant while price can change each quarter. We record three measures of a regimen's efficacy: the median number of months patients survive after initiating therapy (*Survival Months*); the percentage of patients who experience a complete or partial

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

reduction in the size of their tumor (*Response Rate*); and the median number of months (across patients in the trial) before the cancer advanced to a more serious state (*Time to Progression*).

We also record the percentage of patients in phase 3 trials who experienced either a grade 3 or a grade 4 side effect for five separate conditions: abdominal pain, diarrhea, nausea, vomiting, and neutropenia. Although many more side effects are recorded for most regimens, these five were consistently recorded across the 12 regimens in the sample. Side effects are classified on a 1 to 4 scale, with grade 4 being the most severe. Higher values for the side effect attributes should be associated with worse health outcomes, although regimens that are relatively toxic are likely to be both more effective and have more severe side effects.

This table demonstrates that the average regimen price rose over time as new drugs were introduced and their market shares increased. The average price for a 12-week treatment cycle increased from $47 to $344 in 1998 when Pfizer's irinotecan was introduced. The average price jumped to over $1,300 in 2000 and then to $3,346 in 2001 as the market share of irinotecan+5-FU/LV continued to increase and Roche introduced capecitabine in the market. Oxaliplatin (Sanofi) was introduced in the third quarter of 2002, and we see the average price go up to $6,276 in 2003. Cetuximab (ImClone) and bevacizumab (Genentech) were introduced in the first quarter of 2004 and the average price jumped to $11,942 in 2004 and to $17,590 in 2005. New 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 (Lucarelli and Nicholson, 2008).

4 Model

4.1 Supply

We assume that firms play a static Bertrand Nash game with differentiated products. Although the firms have considerable market power due to patent protection, they are in an oligopolistic competitive environment as physicians and patients have multiple treatment options.[15]

Nevertheless, Bertrand-Nash price setting may not fully describe pharmaceutical firms' strategic behavior. Marketing to physicians (i.e., detailing) is the most important non-price action.

[15] The prices of individual drugs do not show any common time trend consistent with dynamic pricing, such as a below-marginal-cost pricing or intertemporal price discrimination.

We do not observe detailing activity and do not attempt to include it in the model. We also do not explicitly model decisions by some pharmaceutical firms to provide rebates to certain physician practices if their purchased volume exceeds a certain threshold. We are not aware of any study that examines how physicians react to rebates, presumably because firms do not disclose rebates. Moreover, as mentioned above, discounts/rebates in the colorectal chemotherapy market appear to be small. Although these features are not considered in the supply side model, we introduce a random shock in the demand model to capture physicians' choices that are influenced by characteristics other than price and measured efficacy and side effects.

Another potential concern is if the five branded drugs approved for colorectal cancer were used for other diseases, their prices may depend on the competitive environment of markets other than just the colorectal cancer market. Three of the five patent-protected drugs in our sample (irinotecan, oxaliplatin, and cetuximab) are approved only for colorectal cancer. Although physicians are allowed to use drugs off-label, in practice none of these drugs captured more than a three percent share of the breast or lung cancer chemotherapy treatment markets, which are two of the most common types of cancer, between 2002 and 2005. Bevacizumab was eventually approved for lung cancer (2006) and breast cancer (2008). In 2005 at the end of our sample period, however, it only had a five percent and 0.2 percent share of these two markets, respectively. Capecitabine was approved for breast cancer in 1998 and colorectal cancer in 2001. It never captured more than a 0.2 percent market share in lung cancer, whereas in breast cancer it had a market share between six and nine percent during the 2002 to 2005 time period. We believe, therefore, that the prices for these five drugs will be determined primarily in the colorectal cancer market.

Let p_f be the price firm f charges for its drug/product. Consistent with our data, we assume that each firm produces only one drug, and therefore p_f is the only strategic variable for firm f. We denote mc_f as the marginal cost for firm f, and $q_f(\mathbf{p})$ the drug quantity produced by firm f given all drug prices. This drug quantity is obtained by adding up the quantity of firm f's drug used in all regimens. Formally, if firm f's drug is used in R_f regimens, $q_f(\mathbf{p})$ can be written as

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

where $s_r(\mathbf{p}^R(\mathbf{p}))$ is the share of patients treated with regimen r, q_{rf} is the dosage of the drug

(produced by firm f) used in regimen r, and M is the market size. The price of regimen k denoted by p_k^R is determined by p_f and q_{rf}. For example, if regimen 1 is firm 1's stand-alone regimen, $p_1^R = q_{11}p_1$; if regimen 3 is a cocktail regimen, comprised of drugs from firm 1 and firm 2, $p_3^R = q_{31}p_1 + q_{32}p_2$.

The profit maximization conditions can then be written as

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

Equation (1) shows that a firm will take into account the effect of its drug price on the overall price of each regimen ($\partial p_k^R / \partial p_f$), and how changes in regimen prices affect the market shares of all regimens in which its drug is used ($\partial s_r(p) / \partial p_k^R$). The former effect is determined by the quantity of a drug used in a regimen, which is fixed by a recommended "recipe", and the latter effect is determined by the regimen's price elasticity of demand, which we estimate using regimen-level data. Note that the recommended recipe is generally chosen years earlier when structuring the clinical trial so we treat it as an exogenous factor. This profit-maximization condition also allows us to recover the marginal costs of each drug.

We can use a simple example to gain some insights regarding the firms' pricing strategies with the cocktail regimen. Consider a case where firm 1 and firm 2 each sell a stand-alone regimen (regimens 1 and 2 respectively) and one cocktail regimen (regimen 3) that combines these two firms' drugs. Suppose the two firms' stand-alone regimens use one unit of their own drugs and the cocktail regimen combines one unit of each drug. This implies that the stand-alone regimen prices are the same as the drug prices $\left(p^R = p\right)$ and the cocktail regimen price is the sum of the stand-alone regimen prices ($p_3 = p_1 + p_2$). Given these assumptions, the first-order condition for firm 1 is simplified to

$$\frac{\partial \pi_1}{\partial p_1} = (s_1(p_1, p_2) + s_3(p_1, p_2)) + (p_1 - mc_1) \left(\frac{\partial s_1}{\partial p_1} + \frac{\partial s_3}{\partial p_1} \right) = 0 \tag{2}$$

Equation (2) shows that the firms are constrained to charge a single price for both the cocktail regimen and the stand-alone regimen. Without the cocktail regimen this equation becomes

the profit maximization condition for the Bertrand Nash competition. Without the stand-alone regimen, on the other hand, the firms' pricing becomes effectively the same as setting prices of complements unilaterally. In such a situation, the firms would set higher prices than a monopolist would if it owned both drugs.[16]

Consider next what would happen if these two firms merge. Without the cocktail regimen, the merged firm would raise prices in order to exploit its enhanced market power. The presence of the cocktail regimen, however, mitigates this effect and could lead the merged firm to reduce prices if the effect of internalizing the complementarity is sufficiently strong. These two offsetting price effects can be seen in the markup equation. The merged firm's markup for drug 1 can be written as

$$\frac{p_1 - mc_1}{p_1} = \frac{1}{\varepsilon_{13,1}} + (p_2 - mc_2)\frac{\varepsilon_{23,1}}{\varepsilon_{13,1}}\frac{(s_2 + s_3)}{p_1 (s_1 + s_3)} \tag{3}$$

where $\varepsilon_{13,1} = -\left(\partial (s_1 + s_3)/\partial p_1\right)\left(p_1/(s_1 + s_3)\right)$ and $\varepsilon_{23,1} = \left(\partial (s_2 + s_3)/\partial p_1\right)\left(p_1/(s_2 + s_3)\right)$. Whether prices rise after a merger depends on the sign of $\varepsilon_{23,1}$. In an oligopolistic market with substitutes, this cross-price elasticity term is positive so the post-merger price is always higher than the pre-merger price. However, because $\partial s_2/\partial p_1 > 0$ and $\partial s_3/\partial p_1 < 0$, the sign of $\varepsilon_{23,1}$ can be positive or negative. Even when this term is positive, the price increase will not be as large as in a merger without cocktails.

4.2 Demand

We obtain our demand system by aggregating over a discrete choice model of physician behavior. Following the characteristics approach in Lancaster (1966) and Gorman (1980), we assume that regimens are a set of attributes and physicians choose a regimen based on these attributes. However, physicians may observe regimen-specific attributes beyond those we observe in the clinical trials data so we allow for unobserved attributes in the utility function. We also include price as an attribute. It is not obvious whether physicians pay attention to price because of health insurance. However, most Medicare patients pay about 20 percent of the treatment cost out of their pocket, most private insurance plans require patient cost sharing, and private plans often have a lifetime maximum coverage limit. Therefore, as long as physicians place some weight on their patients'

[16] An interesting question is how equilibrium outcomes would change if firms could set different prices for their component drugs used in the cocktail regimen. This is analyzed in 6.1.

out-of-pocket costs, physicians will take price into consideration when recommending or selecting a regimen. Furthermore, as mentioned above, because physicians take ownership of the drugs, they incur carrying costs and face reimbursement risk.

Regimen attributes are not adequate to describe physicians' choices fully, regardless of how many we include. Factors such as patient health conditions, detailing activities, and rebates affect regimen choices as well. Because of data limitations, we summarize all these factors with an idiosyncratic shock. We assume a physician draws an *i.i.d.* shock from the Type I Extreme Value distribution every time she makes a choice. Thus, a physician choice is a probabilistic event with regimen attributes determining the probability.

We partition the whole set of regimen choices into multiple disjoint subsets according to recommendations by the NCCN and estimate a nested logit demand model. As mentioned in Section 2, the NCCN recommends 5-FU/LV (the generic regimen),Roche's stand-alone regimen (capecitabine), and the Pfizer-Roche cocktail regimen (irinotecan plus capecitabine) for patients who cannot tolerate intensive therapy and other regimens for less frail patients. Following this recommendation, we categorize the former three regimens as non-intensive treatment regimens and the other nine as intensive treatment regimens, and form three subsets: a non-intensive treatment regimen group, an intensive treatment regimen group, and the outside option. Alternatively, we also form four subgroups by dividing the intensive treatment regimens further into two groups, one including the Sanofi-Genentech cocktail, the Pfizer-Genentech cocktail, and the Roche-Sanofi-Genentech cocktail regimens and the other including the rest of the intensive treatment regimens.[17] These nested logit models allow physicians' preferences to be more highly correlated across regimens within groups and thus allows for more reasonable substitution patterns as compared to the simple logit model.

The indirect utility of physician i for regimen j in group g in period (market) t is

$$u_{ijt} = \delta_{jt} + \zeta_{ig} + (1-\sigma)\,\varepsilon_{ij}$$

where $\delta_{jt} = -\alpha p_{jt} + \mathbf{x}_j\boldsymbol{\beta} + \xi_t + \Delta\xi_{jt}$ and ε_{ijt} represents the idiosyncratic shock from Type I Extreme Value distribution. ζ_{ig} is physician $i's$ utility that is common to all regimens in group g. Cardell

[17] The former group is known as the first line treatment and the latter as the second line treatment.

(1997) shows that if ε_{ij} is an extreme value random variable, $\zeta_{ig} + (1-\sigma)\,\varepsilon_{ij}$ is also an extreme value random variable and that σ determines the degree of the within-group correlation of utility. p_{jt} is the price of regimen j at time t, $\mathbf{x}_j$ a set of observable regimen attributes such as efficacy and side effects, ξ_t the mean of unobserved attributes for each period, and $\Delta\xi_{jt}$ the regimen specific deviation from ξ_t and represents demand shocks or regimen attributes that physicians observe but we do not. The outside option ($j = 0$) includes off-label colon cancer treatments, regimens with small market shares, or regimens without a complete set of attributes. The utility of the outside option is set to zero.

Two aspects of our demand model merit further discussion. One concern is that if profits influence physicians' prescribing decisions, our demand estimates may be biased. This could occur if profits are correlated with the observed price and/or the attributes, and we do not control for this correlation in the demand estimation. Oncologists were able to earn profits on most cancer drugs through 2004. This occurred because Medicare reimbursed oncologists 95 percent of a drug's listed average wholesale price (AWP), whereas physicians could usually acquire drugs from wholesalers for less than the AWP. For example, physicians were acquiring irinotecan in 2001 for 23 percent less than AWP, on average, which allowed them to earn an approximate 18 percent profit (General Accounting Office, 2001). Most private health insurance companies reimburse physicians using a formula similar to Medicare's, so these profits occurred for all patient types.[18] Most of these profits were eliminated in 2005 when Medicare started reimbursing oncologists based on the actual average selling price (ASP) of a drug rather than the list price (MedPAC, 2006). In the first quarter of 2005, for example, oncologists were acquiring three branded colorectal cancer drugs (bevacizumab, irinotecan, and oxaliplatin) for two or three percent less than the new Medicare reimbursement amount, on average.

However, several studies find that the profits that oncologists earned on cancer drugs prior to 2004 did not have a pronounced effect on patient treatment. Jacobson and Newhouse (2006) estimate the influence of physician profits on treatment decisions and find that the magnitude of the effect is small.[19] Shea et al. (2008) find that the 2004 reduction in reimbursement had little

[18] In the IntrinsiQ data set that we use in this paper, Medicare patients account for just over one-half of all colorectal cancer patients who receive cancer drugs.

[19] They estimate that a one-standard deviation increase in reimbursement generosity is associated with an increase of about five percent in the cost of chemotherapy prescribed to colorectal cancer patients.

impact on how long patients had to wait to initiate treatment or how far they had to travel to receive chemotherapy. Jacobson et. al. (2010) find that the new reimbursement method shifted the mix slightly, away from drugs that formerly had high profit levels, but that it did not decrease the likelihood that lung cancer patients received chemotherapy.

The second aspect is that because we treat a pharmaceutical cocktail as a new product whose characteristics differ from those of its component drugs, we assume that demand is not correlated across cocktail regimens that share a component drug. This is usually not a valid assumption in a typical bundling situation where the utility of a bundle can be modeled as the sum of the utilities of the products included in a bundle plus the degree of substitutability or complementarity among these products.[20] In such a situation, demand for two bundles that include the same product should be correlated because a demand shock for the common product affects demand for both bundles.

Our approach is consistent with how new drugs are approved. A cocktail is tested in a randomized controlled trial against an existing treatment; the Food and Drug Administration (FDA) examines the effect of the cocktail on patients' health; and the FDA approves the cocktail if the benefits of the new product exceed the safety risks. If the FDA knew that the utility of a cocktail is equal to the sum of the utilities of the stand-alone drugs in the cocktail, presumably it would approve cocktails without requiring lengthy and expensive clinical trials.

We believe our approach is also consistent with how physicians choose regimens for their patients. Take the Roche-Sanofi-Genentech cocktail regimen as an example. This regimen is recommended as a first-line treatment option for metastatic patients who are able to tolerate intensive therapy. However, Roche's stand-alone regimen (capecitabine) is recommended as a first-line treatment option for metastatic patients who cannot tolerate intensive treatment. Thus, even if physicians use Roche's stand-alone regimen more often, say, after new research finds that it is more effective in treating colon cancer than previously believed, the demand for the Roche-Sanofi-Genentech cocktail is unlikely to be affected.

This difference from the "typical" bundling situation arises partly because the dosage of a drug when it is used as a stand-alone treatment generally differs from its dosage in a cocktail.

[20] Gentzkow (2007), for example, uses such a model to estimate the degree of complementarity between the paper and online versions of newspapers.

In the example above, the Roche-Sanofi-Genentech cocktail regimen uses 1,700 mg of capecitabine per meter (of a patient's surface area) squared per day, whereas Roche's stand-alone regimen uses 2,500 mg of capecitabine per meter squared per day. It is worth emphasizing that complementarity still arises between the component drugs used in the same cocktail regimen because a price increase in one component drug reduces demand for the other component drug through a lower demand for the cocktail regimen. Our modeling assumption is vulnerable, however, if there is a demand shock associated with a component drug regardless of dosage. For example, if clinicians find that capecitabine is more effective than previously believed no matter how it is used, this would increase demand for all regimens that use capecitabine.

As shown in Berry (1994) , we can derive and estimate the following demand equation:

$$\ln s_{jt} - \ln s_{0t} = \mathbf{x}_j\beta + \alpha p_{jt} + \sigma \ln s_{j/g} + \xi_t + \Delta\xi_{jt} \tag{4}$$

where $s_{j/g}$ is a regimen's within-group market share. $\Delta\xi_{jt}$ is likely to be correlated with prices and within-group market shares. All terms other than ε_{ijt} represent patient utility (e.g., patient co-payments, observed and unobserved attributes of the treatment) and ε_{ijt} captures any unobserved shocks that affect a physician's choice.

One might consider the random coefficient logit model of Berry, Levinsohn, and Pakes (1995), referred to hereafter as "BLP", as an alternative demand model. BLP allows for more flexible substitution patterns by allowing random coefficients for price and product attributes. The nested logit model is a particular random coefficient model with a special kind of random coefficients on the group indicator variables. Although adding random coefficients for product attributes renders our model more flexible, estimating such a model is computationally challenging. Moreover, whether patients can tolerate intensive treatments may not necessarily be correlated with observed consumer characteristics such as income, age, gender, etc. Thus, we use the nested logit model and rely on the nesting structure based on the NCCN recommendations to capture key aspects of substitution patterns. The NCCN recommendations allow us to capitalize on experts' knowledge regarding the similarity between regimens that is difficult to obtain from typical product- and consumer-level data. Nevertheless, we still estimate the BLP model where we allow a random coefficient on the price variable. This model implies that regimens with similar prices are closer

substitutes than those with distinct prices.

5 Estimation Results

We estimate equation (4) using regimen-level market share, price, and attribute data. The price variable is likely correlated with unobserved attributes or the contemporaneous demand shock because firms observe these before setting prices. The within-group market share variable is also an endogenous variable because any unobserved attribute or contemporaneous demand shock that increases a regimen's market share also increases its within-group market share. This endogeneity problem requires using instruments to estimate the demand equation consistently.

We construct instruments using lagged prices.[21] An identifying assumption is that unobserved attributes or demand shocks are not correlated over time. This assumption implies that any correlation between the endogenous variables and past-period prices are due to time-persistent cost-side factors. Under this assumption we can use any function of past-period prices, and we construct two instruments using the lagged prices of other regimens. In particular, for the price of regimen j in period t, one instrument is the average price in period $t-1$ of all regimens other than regimen j. The other instrument is the average price in period $t-1$ of regimens produced by firms whose drugs are not used in regimen j. For the Pfizer-Roche cocktail regimen (irinotecan plus capecitabine) in the third quarter of 2005, for example, the second instrument is the average price in the second quarter of 2005 of eight regimens that use drugs produced by Sanofi, ImClone, and Genentech.

We use the generalized method of moments with $(\mathbf{Z}'\mathbf{Z})^{-1}$ as the weighting matrix, where $\mathbf{Z}$ includes the instrumental variables, all the observed regimen attributes other than price, and the time indicator variables.[22] We report the demand estimates in Table 2. The first column reports the results of the OLS logit model; the second column, labeled *IV Logit*, reports results using the instruments; and the third column, labeled *Nested I*, reports results of the nested logit with two regimen groups and the outside option. The fourth column, labeled *Nested II*, corresponds to

[21] We do not use other products' attributes as instruments because they do not vary much over time due to infrequent product entry and exit. The first stage F-statistics on joint significance when using these instruments is less than five, and the estimation results are not substantially different from the OLS logit results that we present. Although we considered using the prices that hospitals pay for drugs to instrument for the prices that physician practices pay, the two price variables are too highly correlated for this method to work.

[22] Our sample size is not large enough to use the optimal weighting matrix.

the nested logit where regimens for patients who can tolerate intensive therapy are again divided into two groups (three regimen groups and the outside option) and the last column, labeled *BLP*, corresponds to the BLP model where we allow a random coefficient on the price variable. Because we have two excluded instruments, the two nested logit models and BLP are exactly identified. In all specifications we use the logarithm of price as a regressor, and standard errors are reported in parentheses. Although quarter indicator variables are included in all specifications, their estimates are not reported.

Comparing the price coefficient from the first column with the others reveals that there is a positive correlation between price and the demand shock and that the instrumental variables mitigate this problem. The price coefficient increases in absolute value from -0.690 without instruments (*OLS*) to -2.150 in *IV Logit*, to -1.557 and -1.794 in the two nested logit models, and to -2.698 in the BLP model. The price coefficient is significantly different from zero at the one-percent level in all models. The F-statistic from the first stage F-test for the joint significance of the excluded instruments is 12.0 for the price variable and 27.2 and 21.0 for the within-group share variable in the two nested logit models, respectively. In the IV logit model we test whether the two instruments are exogenous using the over-identification test and do not reject the null hypothesis that they are.[23]

The coefficients for the within-group share variable are 0.403 and 0.421 for the *Nested I* and *Nested II* models respectively, and are statistically significant. This indicates that regimens are closer substitutes within a group than between groups. Allowing for more nesting in the *Nested II* model does not substantially affect the results. The standard deviation for the random coefficient in the BLP model is 0.407 and is statistically significant, indicating that regimens of similar prices are closer substitutes than those with different prices. This substitution pattern is not necessarily consistent with that implied by the nested logit model. For example, in BLP the Pfizer-ImClone cocktail regimen (irinotecan plus cetuximab), the second most expensive regimen, is the closest substitute for the Sanofi-Genentech cocktail regimen (oxaliplatin plus bevacizumab), the most expensive regimen, but they belong to different groups in the *Nested II* model. As explained in Section 4.2, we rely on the nesting structure based on the NCCN recommendation because it reflects the scientific underpinning of oncologists' decisions. Despite this difference, however, the

[23] The over-identification test statistic is 3.48 while the 5% critical value is 3.84.

simulations results of the BLP model are not qualitatively different from those of the nested logit model.[24]

The efficacy attribute coefficients are statistically significant in all models except the OLS logit model, but only the response rate coefficient is positive as expected. Because these three variables are correlated with one another, we use a linear combination of these three variables to evaluate preferences for efficacy. In the IV logit model, the average willingness to pay for obtaining the mean efficacy from a 12-week treatment (relative to the outside option) is about $70,000 in 2005. The average cost for that treatment in the same year is about $18,000. The average willingness to pay for the mean efficacy is slightly smaller (by about $3,000) in the nested logit models.

Among the side effect variables, only the neutropenia coefficient is both statistically significant and negative as expected. Its estimate implies that the average willingness to pay to reduce a chance of having neutropenia by one percent is about $900. The other side effect variables are either positive or insignificant. This may occur because cancer patients often take drugs that ameliorate the impact of certain side effects, such as pain, nausea, and diarrhea, while neutropenia is fatal and harder to prevent with other drugs. If a physician prescribes anti-pain and antiemetic drugs in conjunction with the chemotherapy drugs, she may downgrade the importance of these side effects when choosing a regimen. Another possible explanation is that the toxic drugs are more likely to cause side effects but have other favorable unmeasured attributes. Thus, it is important to include these side-effect variables because, if left in the unobserved attribute term, they are likely to be correlated with the efficacy variables.

The demand estimates imply that the firms benefit from substantial markups. The median (drug-level) percentage markup is 84.5 percent for Genentech's bevacizumab, 82.3 percent for Pfizer's irinotecan, and 70.3 percent for Sanofi's oxaliplatin. These markup estimates imply that the marginal cost is a dollar or less per milligram for the Genentech and the Pfizer drugs and about four dollars per milligram for Sanofi's oxaliplatin. The unit price of oxaliplatin is over 14 dollars, so a 70-percent markup still implies quite a high unit cost. The percentage markups for the Roche and ImClone drugs are relatively low, but still over 50 percent. However, because the unit price of Roche's capecitabine is less than two cents per milligram, its implied marginal cost is less than one

[24] The simulation results of the BLP model are available upon request.

cent.[25] The implied unit cost for ImClone's cetuximab is about two dollars per milligram.

The sometimes non-intuitive coefficient estimates on the attributes raises the possibility that the model might be mis-specified or our identifying assumption is not realistic. To address the mis-specification concern, we estimate a number of alternative models and report the results in Tables A-1 and A-2 in Appendix II. Specifically, we report estimates of alternative versions of the OLS, IV logit, nested logit, and BLP models that include fewer attributes, both with and without firm fixed effects. For the most part, the results from these alternative models are similar to our main models presented in Table 2. With these sparser models, however, the willingness to pay for the mean regimen efficacy is substantially lower and some of the marginal cost estimates are negative. We believe this occurs because the omitted attributes capture some of the value of the regimens, and their omission results in a upward bias of the price coefficient because these omitted variables are correlated with the price variable.

We also check the robustness of our identifying assumption by allowing the unobserved demand component to follow an AR(1) in the main specification. Recall that lagged prices are valid instruments only if the unobserved demand component is not serially correlated. The AR(1) specification allows us to control for serial correlation that is not captured by the attribute variables. Demand estimates in the AR(1) model do not change substantially and are actually similar to those from one of the alternative specifications where we include fewer attributes and firm fixed effects. We provide more details in Appendix III.

6 Counterfactual Exercises

Given the estimates for the demand parameters and the marginal cost of each regimen, we compute hypothetical equilibrium prices under various counterfactual merger scenarios. We also investigate the welfare effects of introducing a new cocktail regimen. We focus on the last six quarters of the sample period, *i.e.*, from the second quarter of 2004 through the third quarter of 2005 because that is a period when all 12 major regimens are present in the market. We average the results over these six quarters and use the estimates reported in the third column of Table 2 (*Nested I*).[26]

[25] The differences between drugs in their marginal costs are larger when reported on a per milligram basis than a per treatment-cycle basis because the drugs are often administered in very different dosages.

[26] Results are qualitatively the same when the estimates of other specifications are used.

6.1 Merger Analysis

In this section we consider five hypothetical mergers between two firms whose drugs are used in the same cocktail regimen.[27] It is not clear a priori how a merger would affect prices. When firms that sell complements merge, they have an incentive to reduce prices to internalize the effects of having complements. However, because the merging parties also sell other products that are substitutes with one another, either stand-alone regimens or cocktail regimens shared with non-merging firms, a merger also creates incentives to increase prices to exploit enhanced market power.

To demonstrate the magnitude of these two offsetting effects and the combined effect of a merger on prices, we first remove the cocktail product in question and simulate the effect of a merger on the pre- and the post-merger equilibrium prices. This allows us to calculate the prices of the two firms' drugs that maximize profits pre- and post-merger without taking into consideration how those prices affect the profits of the cocktail, or bundled, product that the two firms share. Because the merging parties do not have an incentive to internalize the complements, this simulation highlights the market power effect.

We report results in the first two columns of Table 3 (the columns labeled *Market power effect*). We predict that firms would increase prices significantly once gaining additional market power. In the Pfizer and Genentech merger case, for example, Pfizer would increase its drug price by a factor of four while Genentech would increase its price by 92 percent. The two merger cases that involve Roche also show a big price increase where Roche more than doubles its price. In the Pfizer and ImClone merger case where the price effect is the smallest, Pfizer increases its price by 8 percent while ImClone increases it by 13 percent.

The substantial price increases are driven, in part, by the presence and importance of six cocktail regimens that the merging parties share with non-merging firms. In the Pfizer-Genentech merger case, for example, the two firms produce drugs used in four cocktails other than the one they share. That is, an increase in Pfizer's drug price also drives up the prices of the cocktail regimens Pfizer shares with Roche and ImClone, and an increase in Genentech's drug price drives up prices of cocktail regimens Genentech shares with Roche and Sanofi. Because the merging pharmaceutical firms benefit by diverting sales from cocktail regimens where they share profits to

[27] We consider five instead of six cases because we exclude a three-firm merger case that involves the Roche-Sanofi-Genentech cocktail regimen (capecitabine plus oxaliplatin plus bevacizumab).

their other regimens where they often capture all the profits, merging firms in this unique setting are likely to raise prices more than in a situation where firms have direct control over fewer product prices.

In the next set of simulations, we isolate the effect of internalizing complementarities by comparing the pre- and the post-merger equilibrium prices for a situation where the only regimen that the merging parties sell (before and after merger) is the cocktail regimen they share in common. In this simulation we separate the merging firms' cocktail regimen from their other regimens in the profit function and calculate the profit maximizing prices for each component drug of this cocktail regimen pre- and post-merger.[28]

We report results of the complementarity effects in the third and fourth columns of Table 3 (the columns labeled *Complementarity effect*). We find that mergers would result in substantially lower cocktail regimen prices. In all five cases, at least one of the merging firms lowers its drug price by more than 50 percent, which causes the overall cocktail regimen price to go down by more than 50 percent in all five cases, and by more than 60 percent in four cases.

Because of the linear pricing constraint, the sign of the overall merger effect depends on whether the complementarity effect is stronger than the market power effect.[29] We report the overall merger results in the last two columns of Table 3 (the columns labeled *Full merger effect*). In the Pfizer-ImClone merger, both firms reduce their prices, Pfizer by 3.4 percent and ImClone by 21.9 percent. In the Sanofi-Genentech merger, Sanofi raises its price by about four percent whereas Genentech reduces its price by 28 percent. In the other three merger scenarios, both merging parties raise prices but much more modestly than if they did not share a cocktail regimen.

We predict that two of the mergers would increase consumer welfare.[30] Consumer surplus is predicted to increase by two percent in the Pfizer-ImClone merger and by 3.7 percent in the Sanofi-Genentech merger, the two cases where a merger leads to lower prices. Mergers reduce

[28] This is effectively the same as adding two new independent firms to the market that produce component drugs for this cocktail regimen, and allowing them to merge.

[29] As demonstrated in equation (3) in Section 4.1, the direction of a price change following a merger depends on the sign of $\varepsilon_{23,1} = \left(\partial\left(s_2 + s_3\right)/\partial p_1\right)\left(p_1/\left(s_2 + s_3\right)\right)$, which can be positive or negative because $\partial s_2/\partial p_1 > 0$ and $\partial s_3/\partial p_1 < 0$.

[30] We use consumers, patients, and physicians interchangeably in our welfare analysis. We acknowledge that a price decrease may affect physicians in two opposite ways: it increases their utility because physicians care about their patients' out-of-pocket costs, and it decreases their utility because physicians' profits are a percentage of the drug price. Currently we emphasize the former, in part because our review of the literature indicates that physician decisions are not greatly affected by changes in profit.

consumer welfare by less than 10 percent in the three cases where the merger leads to higher drug prices.

The linear pricing constraint is a unique feature of the oncology pharmaceutical sector because physicians purchase component drugs and then administer them separately or as a bundle. Firms in most other industries have greater ability to price discriminate by setting different prices for products purchased separately versus in a bundle. Firms usually offer a bundle discount when feasible, as AT&T did with its broadband and video service bundle. In such a setting, the merging firms would lower the price of the bundle they have in common while raising prices of their stand-alone products. The overall price effects would be ambiguous.

In our next set of merger simulations we examine whether the overall merger price results presented above are due to the linear pricing constraints that are unique to the pharmaceutical industry. In this simulation we allow a firm the flexibility to set one price for its component drug in the common (with the merging firm) cocktail regimen and a separate price for its other regimens, both before and after a merger. In the Pfizer-Genentech merger, for example, Pfizer can set one price for its component drug (irinotecan) used in the cocktail regimen it shares with Genentech, and a different price for irinotecan when used in its stand-alone regimen and in the two cocktail regimens it shares with Roche and ImClone.

In Table 4 we report the predicted price changes resulting from mergers separately for the component drugs used in the cocktail regimen the merging firms have in common in the columns labeled *Cocktail Regimen*, and for their drugs used in the non-cocktail regimens in the *Other Regimens* columns. Interestingly, the price changes for the common cocktail regimens are similar to the price changes associated with the complementarity effects in Table 3, while the price changes for the other regimens are similar to those resulting from the market power effects reported in the same table.

These bundle discount results are consistent with the post-merger predictions in the recent analysis of the AT&T-DIRECTV merger, but the magnitude of the price effect is substantially different. The predicted price increases due to enhanced market power are much smaller in the AT&T-DIRECTV merger analysis where the FCC predicted that DIRECTV and AT&T would increase their stand-alone video product prices by less than one percent and two percent, respectively, following a merger (FCC, 2015). As explained above, the larger price increase in our pharmaceutical

setting is in part due to the presence of the cocktail regimens that the merging parties share with non-merging firms. The price reductions due to the complementarity effect are also much smaller in the AT&T-DIRECTV merger analysis where the firms were predicted to reduce their bundle product price by only two percent (FCC, 2015). This difference is likely due to high margins in the pharmaceutical market that lead to a particularly acute double marginalization problem.

It is not clear whether consumers are better off with this more flexible pricing scheme. Consumers benefit from the large bundle discount the merging parties offer post merger, but at the same time they face substantially higher prices for other regimens. With linear pricing, on the other hand, the two opposing effects result in either a higher price for a component drug across all products that involve that drug, or a lower price across all products. If the market power effect is stronger for both merging parties, for example, consumers face higher prices for all regimens that they sell.

In Table 5 we report changes in consumer welfare separately for the linear pricing and bundle discount situations. Welfare changes are small in both situations. Although consumer welfare falls with flexible pricing in four out of the five merger scenarios, it never falls by more than eight percent. Consumers are worse off with linear pricing versus a bundle discount in two of the merger scenarios. The Pfizer-ImClone merger is predicted to increase consumer welfare by two percent under linear pricing versus a one percent reduction when a bundle discount is available. In the Roche-Sanofi merger scenario, consumer surplus is predicted to fall by 4.7 percent under linear pricing versus a seven percent reduction with more flexible pricing. Nevertheless, these results indicate that mergers are less harmful and can even be beneficial in the presence of inter-firm bundles, and this is true whether firms can offer a bundle discount or must set linear prices.

6.2 Introduction of New Cocktail Regimen

In this section we investigate whether consumers benefit from the introduction of a new cocktail regimen. Consumers benefit from the addition of a new product. On the other hand, a new cocktail regimen can lead to a higher price of a component drug, which may be used in multiple regimens. The impact of higher prices may exceed the benefit of a new treatment option.

To investigate this question we remove the cocktail regimens from the market one at a time and calculate the new equilibrium prices for all branded drugs. We evaluate six hypothetical

cases for each of the six cocktail regimens. We report the results in Table 6. The numbers in bold typeface are changes for the firms participating in the removed cocktail regimen.

The first five columns of Table 6 report price changes when the regimen in a row is absent. For example, the final row corresponds to a scenario where the Sanofi-Genentech cocktail regimen, which had the highest market share of all regimens in 2005, is removed. Without this regimen, Sanofi and Genentech are predicted to decrease their drug prices by 46.9 percent and 24.8 percent, respectively.

In five out of six cases the prices of participating firms' drugs fall when a regimen is removed, indicating that new cocktail regimens usually lead to higher prices. A new product introduction usually lowers prices by intensifying competition, especially when the new product is not substantially different from the existing products. The cocktail regimens considered here, however, make competing firms' drugs complements. Because firms do not internalize the effect of selling the complements, drug prices can rise with a new cocktail regimen. The only instance where prices fall is with the introduction of the Pfizer-Roche cocktail regimen, which is likely due to the competition effect dominating the complementarity effect. This suggests that the Pfizer-Roche cocktail is a close substitute for Pfizer's other regimens and less differentiated from other cocktail regimens. This is not surprising considering that this was the first cocktail regimen introduced for colorectal cancer drug treatment.

We report changes in consumer welfare in the last column of Table 6. In five of the six cases, consumers are worse off when a specific cocktail regimen is introduced. Consumers are usually harmed more by the higher prices than they are helped by increased product variety. In all five of the cases where consumers are worse off with a cocktail, the prices of most drugs increase. In the one case where consumers are better off with the cocktail, most drug prices fall.

To highlight the importance of the price effects in the welfare results, we run the same counterfactual simulation with drug prices fixed. We find that consumer welfare always falls when a cocktail regimen is removed and the welfare loss is proportional to the market share of the removed cocktail regimen. Consumer welfare falls the least (by less than one percent) when the Roche-Sanofi-Genentech cocktail regimen, whose market share is 0.6 percent, is removed; welfare falls the most (by about five percent) when the Sanofi-Genentech cocktail regimen, which has a 19-percent market share, is removed.

The results presented in Table 6 indicate that this inter-firm bundling in this setting creates a less competitive market that benefits firms and harms consumers. This is disappointing because designing a cocktail regimen is a cost-effective way of providing more treatment options for cancer patients. Recall that the 12 major regimens only use five drugs that currently have patent protection. Empirical studies such as Petrin (2002) show that new products usually increase consumer welfare, especially when they are of higher quality than existing products, by providing more and better choices for consumers. Although a firm that introduces a new product may raise its prices, other firms usually reduce prices in response. However, most of the cocktail regimens in the colorectal cancer treatment market harm consumers by increasing the prices of all regimens that use the same drugs.

7 Conclusions

In this paper we empirically analyze firms' pricing behavior when their products are consumed in conjunction with their competitors' products. We focus on the pharmaceutical industry, and on colorectal cancer drug treatment in particular. We show that a merger between firms that have a cocktail regimen in common does not have as strong an anticompetitive effect as mergers involving substitutes only. While the merging firms have an incentive to raise prices to exploit enhanced market power, they also have an incentive to lower prices in order to internalize the effect of selling complements. Because the firms in this market set linear prices, these opposing price effects lead the merged firms to increase drug prices much less substantially, or even decrease them, versus a case without a bundled product in common. As a result, consumers are better off than in a merger involving substitutes only, and can even be better off if the complementarity effect dominates the market power effect.

We also show that introducing a new cocktail regimen that mixes drugs used in other regimens is likely to render the market less competitive and harm consumers. Firms that share the new cocktail regimen do not internalize the effect of selling complements, so they usually increase the prices of all regimens that use the same drug. Because of this price effect, consumers benefit less from having a new treatment option and can become worse off even with greater product choice.

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Table 1: Regimen Attributes: The Sample Average

		Efficacy			Grade 3 or Grade 4 Side Effects (%)				
Time	Regimen Price (12 week treatment)	Survival Months	Response Rate	Time to Progression	Abdominal Pain	Diarrhea	Nausea	Vomiting	Neutro-penia
1993	60	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
1994	60	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
1995	58	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
1996	63	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
1997	47	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
1998	344	12.5	20.9	4.8	5.7	11.0	5.1	4.6	33.6
1999	533	12.5	21.0	4.8	5.8	11.3	5.3	4.7	33.6
2000	1,319	12.6	21.9	4.9	5.9	12.5	6.0	5.1	33.9
2001	3,346	13.0	23.8	5.1	6.4	15.3	7.3	5.8	33.0
2002	4,163	13.3	24.7	5.3	6.4	15.5	7.2	5.8	32.0
2003	6,276	14.3	28.1	5.9	6.4	16.0	7.3	6.0	31.5
2004	11,942	15.3	30.8	6.6	6.7	17.2	6.3	5.8	26.9
2005	17,590	16.8	33.9	7.4	7.1	18.7	6.0	6.0	23.3

This table presents a weighted (by market share) average of drug attributes across regimens for each quarter, and then averages across quarters for each year. *Regimen Price* is the drug transaction price between wholesalers and the end customer such as a physician practice, assuming that a patient receives the dose per drug as recommended by the NCCN. The efficacy and side effects of regimens are taken from the randomized controlled trials that manufacturers submit to the FDA when seeking approval.

Table 2: Demand Estimation Results

Variable	OLS	IV Logit	Nested I	Nested II	BLP
$\log(price)$	-0.690*	-2.150*	-1.557*	-1.794*	-2.698*
	(0.125)	(0.483)	(0.411)	(0.412)	(0.668)
Survival (months)	-0.087	-0.421*	-0.323*	-0.356*	-0.503*
	(0.056)	(0.116)	(0.093)	(0.097)	(0.148)
Response Rate (%)	0.166*	0.913*	0.644*	0.784*	1.150*
	(0.072)	(0.254)	(0.214)	(0.215)	(0.332)
Time to Progression	-0.335	-2.070*	-1.395*	-1.830*	-2.664*
(months)	(0.244)	(0.644)	(0.538)	(0.545)	(0.834)
Diarrhea	0.024	0.072*	0.051*	0.052	0.080
	(0.023)	(0.034)	(0.026)	(0.030)	(0.044)
Nausea	-0.137	-0.065	-0.059	-0.017	-0.031
	(0.078)	(0.116)	(0.082)	(0.090)	(0.137)
Abdom_pain	0.135	0.806*	0.561*	0.681*	1.021*
	(0.077)	(0.229)	(0.196)	(0.193)	(0.297)
Vomiting	0.166	0.245	0.196	0.176	0.235
	(0.118)	(0.166)	(0.116)	(0.134)	(0.199)
Neutropenia	-0.008	-0.109*	-0.082*	-0.098*	-0.143*
	(0.011)	(0.034)	(0.027)	(0.028)	(0.045)
$\log(s_{j/g})$			0.403*	0.421*	
			(0.154)	(0.166)	
Std. Dev.					0.407*
$(\sigma_{\log(price)})$					(0.155)
R-square	0.836				
1st Stage		11.983			
F-statistics			27.235	20.960	

The first column reports the results of the OLS logit model; the second column reports results using the instruments; and the third column reports results of the nested logit with two regimen groups. The fourth column corresponds to the nested logit where regimens for patients who can tolerate intensive therapy are again divided into two groups (three regimen groups and the outside option) and the last column corresponds to the BLP model where we allow a random coefficient on the price variable. The F-statistic for the IV logit model is for the price variable and the F-statistics for the nested logit models are for the within-group share variable. The quarter dummy variables are included in all specifications but their estimates are not reported. * = significant at the 5 percent level.

Table 3: Post-merger Price Changes

	Market power effect		Complementarity effect		Full merger effect	
Merging firms	Firm 1	Firm 2	Firm 1	Firm 2	Firm 1	Firm 2
Pfizer + Roche	23.3%	329.0%	-98.9%	-12.9%	22.7%	179.8%
Roche + Sanofi	155.6%	16.1%	-19.6%	-99.6%	63.3%	6.1%
Pfizer + Genentech	383.4%	91.9%	-68.3%	-58.5%	60.5%	14.1%
Pfizer + ImClone	8.1%	13.2%	-78.3%	-49.2%	-3.4%	-21.9%
Sanofi + Genentech	34.6%	79.1%	-88.1%	-41.8%	4.2%	-28.0%

The table reports price changes for each merging firm when a pair of firms (the rows) merge. The columns labeled *Market power effect* report price changes resulting from merger when the merging firms do not have the cocktail regimen in common; the columns labeled *Complementarity effect* report price changes when the only product that the merging firms sell pre and post merger is the cocktail regimen; and the columns labeled *Full merger effect* report price changes when the merging firms maintain all of their products pre and post merger. The demand estimates are from the *Nested I* specification, the third column of Table 2.

Table 4: Post-merger Price Changes with Bundle Discount

	Cocktail regimen		Other regimens	
Merging firms	Firm 1	Firm 2	Firm 1	Firm 2
Pfizer + Roche	-98.9%	-13.7%	24.1%	374.1%
Roche + Sanofi	-1.9%	-99.6%	166.2%	21.8%
Pfizer + Genentech	-57.3%	-49.8%	257.6%	33.8%
Pfizer + ImClone	-78.8%	-46.2%	32.8%	20.3%
Sanofi + Genentech	-87.0%	-27.8%	45.5%	57.5%

The table reports price changes resulting from merger when allowing each merging firm to set one price for its drug used in the cocktail regimen, and a separate price for its drug used in the other regimens. The columns labeled *Cocktail regimen* show price changes for the merging firms' drugs used in the cocktail regimen. The colums labeled *Other regimens* show price changes for the merging firms' drugs used in the rest of the regimens. The demand estimates are from the *Nested I* specification, the third column of Table 2.

Table 5: Comparison of consumer welfare

Merging firms	Merger with linear pricing	Merger with a bundle discount
Pfizer + Roche	-8.7%	-7.2%
Roche + Sanofi	-4.7%	-7.0%
Pfizer + Genentech	-9.1%	-6.0%
Pfizer + ImClone	2.0%	-0.9%
Sanofi + Genentech	3.7%	13.9%

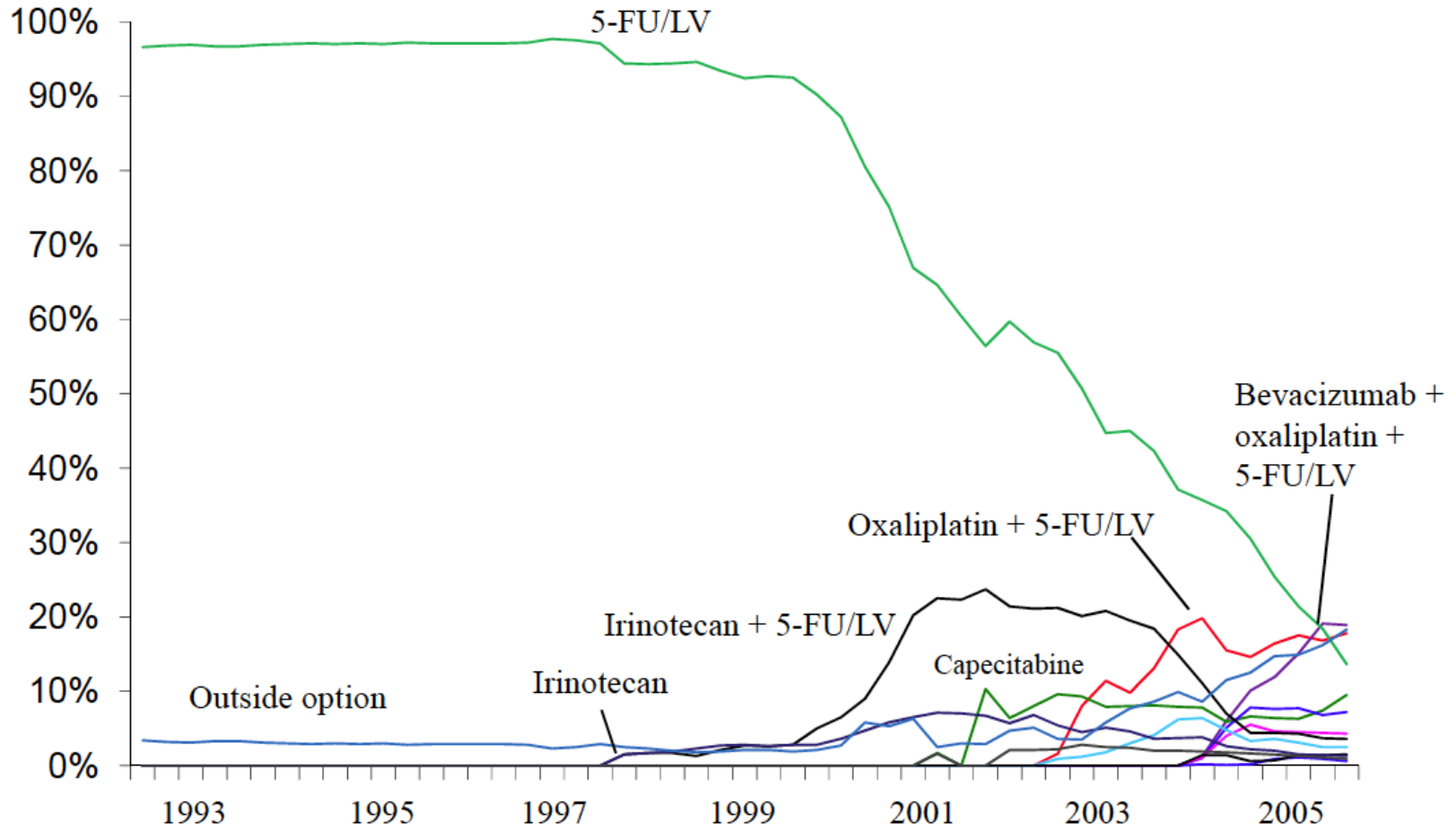
The table compares changes in consumer welfare post merger between the linear pricing case and the bundle discount case. The column labeled *Merger with linear pricing* shows changes in consumer welfare when the merging firms set linear prices. The colum labeled *Merger with bundle discount* shows changes in consumer welfare when the merging firms set nonlinear prices so that they can offer a bundle discount for the cocktail regimen they have in common. The demand estimates are from the *Nested I* specification, the third column of Table 2.

Table 6: Effects of removing cocktail regimens

	Drug price					Consumer
Removed cocktail regimen	Pfizer	Roche	Sanofi	ImClone	Genentech	welfare
Pfizer + Roche	**8.7%**	**-9.4%**	5.1%	1.6%	3.2%	-1.7%
Roche + Sanofi	-2.0%	**-19.8%**	**-6.8%**	-0.5%	-1.9%	2.5%
Pfizer + Genentech	**-41.0%**	51.2%	-6.2%	-6.5%	**-2.7%**	6.9%
Roche + Sanofi + Genentech	-0.6%	**-5.6%**	**-1.8%**	-0.2%	**-2.4%**	1.1%
Pfizer + ImClone	**-32.1%**	51.5%	-16.3%	**-22.6%**	-9.8%	7.5%
Sanofi + Genentech	-22.6%	61.3%	**-46.9%**	-6.3%	**-24.8%**	20.5%

The table reports changes in drug prices and consumer welfare when a particular regimen (a row) is removed from the market. We remove each cocktail regimen from the market one at a time and calculate price changes for all branded drugs. The numbers in bold typeface are changes for the firms participating in the removed cocktail regimen. The demand parameters from column 3 of Table 2 are used in the simulation.

Figure 1: Regimen Market Shares, 1993-2005



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

Appendix I: Composition and Dosages of the Chemotherapy Regimen

Regimen	1^{st} Drug	2^{nd} Drug	3^{rd} Drug	4^{th} Drug
5-FU + LV	425 mg of 5-Fu/m^2/day for days 1-5, every 4 weeks	20 mg of LV/m^2/day for days 1-5, every 4 weeks		
Irinotecan (Pfizer)	125 mg of irinotecan per week/m^2 for 4 weeks, every 6 weeks			
Irinotecan + 5-FU/LV	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 LV/m^2 on day 1 and 2, every 2 weeks	
Capecitabine (Roche)	2,500 mg of capecitabine per m2/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 (Sanofi) + 5-FU/LV	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 LV/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 (ImClone)	400 mg of cetuximab per m^2 on day 1; then 250 mg/m^2 once a week, every 6 weeks			
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 (Genentech) + Oxaliplatin + 5-FU/LV	5 mg of bevacizumab per kg, every 2 weeks	85 mg of oxaliplatin per m2 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 LV/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 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 LV/m^2 on day 1 and day 2, every 2 weeks
Bevacizumab + Oxaliplatin + Capecitabine	7.5 mg of bevacizumab per kg, every 3 weeks	130 mg of oxaliplatin per m^2 on day 1, every 3 weeks	1,700 mg of capecitabine/m^2/day for days 1-14, every 3 weeks	

mg=milligram of active ingredient; m^2=meter squared of a patient's surface area; kg=kilogram of a patient's weight.
Source: National Comprehensive Cancer Network, Colon Cancer, Version 2.2006; package inserts.

Appendix II: Alternative specifications for the demand model

Tables A-1 and A-2 report estimates of alternative versions of the OLS, IV logit, nested logit, and BLP models, including versions where we include selected efficacy and side effect variables and versions where we include manufacturer fixed effects. In each specification the first column, labeled *OLS*, reports the results of the OLS logit model; the second column, labeled *IV Logit*, reports results using the instruments; and the third column, labeled *Nested I*, reports results of the nested logit model with two regimen groups and the outside option. The last column, labeled *BLP*, corresponds to the BLP model where we allow a random coefficient on the price variable. We use the same instruments as in Table 2. In the last two rows of the tables we report the F-statistics from the first stage F-test for the joint significance of the excluded instruments. The F-statistic for the IV logit model is for the price variable and the F-statistic for the nested logit model is for the within-group share variable.

When we estimate the nested logit model with a single efficacy variable (survival months) and a single side effect variable (neutropenia), the attribute coefficients have their expected signs (see Specification 1 in Table A-1). The survival months coefficient is positive and significant and the side effect coefficient is negative but not significant. The 1st stage F-statistic on the IVs is 53 for the price variable and 43 for the within-share variable. However, the drug-level markup implied by the estimates is too high, over two for four out of five drugs. This is mainly due to the price coefficient being "too low". The low price coefficient suggests that some important attributes that are correlated with the price variable are missing. Because the survival months variable is not adequate to capture the complete regimen value, the willingness to pay for the mean efficacy is much lower than in the baseline model and only $2,000 higher than the average treatment cost.

When the firm indicator variables are added (see Specification 2 in Table A-1), the results become more sensible but are not superior to the results from our main specification. This is because some of the firm indicator variables are highly correlated with the regimen efficacy and side-effect attributes. For example, all three regimens that use Genentech's drug (bevacizumab) have high survival months, so the Genentech indicator variable absorbs some of the efficacy-related demand factors. In particular, when the Pfizer and ImClone indicator variables are added (Specification 3 of Table A-2), the drug-level markup is still higher than one for three drugs.[31] When the full firm indicator variables are added (Specification 4 of Table A-2), the drug-level markup falls below one, but the within-group correlation parameter is not statistically significant and the 1st stage F-statistic for the price variable falls to 5.76. In addition, the average willingness to pay for the average survival month is only slightly higher than the average treatment cost, and this is mainly due to the firm indicator variables absorbing some of the efficacy effects.

Appendix III: Demand estimation with serial correlation in the unobserved demand component

The identifying assumption in our demand estimation is that the unobserved demand component, i.e., the error term in the demand equation, is not serially correlated. One concern is that this assumption is too strong, especially because we do not include regimen fixed effects. Although the fixed effect estimator or minimum distance estimator would allows us to estimate attribute coefficients with regimen fixed effects, this model is not appropriate when one uses lagged prices as instruments. The first-differencing estimator would be a feasible alternative when using lagged prices as instruments, but we would not be able to estimate the attribute coefficients using this approach.

In this section we explore another way to control for serial correlation in the error term. In particular, we allow the error term to follow an AR(1) and use lagged prices as IVs after taking

[31] The Pfizer drug is used in five regimens and the ImClone drug is most weakly correlated with the efficacy variable.

a quasi first difference.[32] In this approach, the error term in equation (4) becomes

$$\Delta\xi_{jt} = \lambda\Delta\xi_{jt-1} + u_{jt}$$

and the identifying assumptions are $Cov\left(p_{jt-s}, u_{jt}\right) = 0$, for $s \geq 1$, while $Cov\left(p_{jt}, u_{jt}\right) \neq 0$. Note that the identifying assumption used in the main specification, i.e., $Cov\left(p_{jt-s}, \Delta\xi_{jt}\right) = 0$, is no longer valid because p_{jt-1} is correlated with $\Delta\xi_{jt}$ through $\Delta\xi_{jt-1}$.

The demand system is estimated as follows. (1) Estimate the demand system as in the main specification and obtain an estimated residual, i.e., $\Delta\widehat{\xi}_{jt}$. (2) Regress $\Delta\widehat{\xi}_{jt}$ on $\Delta\widehat{\xi}_{jt-1}$ to estimate λ. (3) Take a quasi first difference and estimate the following equation using lagged prices as IVs:

$$y_{jt} - \widehat{\lambda}y_{jt-1} = \left(1 - \widehat{\lambda}\right)\mathbf{x}_j\beta + \alpha\left(p_{jt} - \widehat{\lambda}p_{jt-1}\right) + \sigma\left(\ln s_{j/g,t} - \ln s_{j/g,t-1}\right) + \xi_t + \left(\xi_{jt} - \widehat{\lambda}\xi_{jt-1}\right)$$

where $y_{jt} = \ln s_{jt} - \ln s_{0t}$. (4) Obtain an estimated residual using estimates from step (3). (5) Repeat steps (2)-(4) until the change in $\widehat{\lambda}$ goes to zero. We use the same instruments as in the main specification but use two and three lagged prices to construct these IVs and take a quasi first difference of them.

We use the generalized method of moments with the inverse of $\left(Z_j'\Omega Z_j\right)$ as the weighting matrix, where Z_j includes the instrumental variables and all exogenous variables, and Ω denotes the variance of the error term. This weighting matrix provides the efficient estimator under the homoscedasticity assumption that the variance is the same for all moment conditions.

Estimation results, reported in Table A-3, show that $\widehat{\lambda} = 0.98$, indicating that the unobserved demand term is highly correlated over time. The efficacy and side effect coefficients imply a much higher willingness to pay for drug treatment relative to our main specification. However, the coefficients for the price and the within-share variables are not very different from those in the main specification, and the price coefficient is very similar to that of Specification 4 reported in Table A-2 (-1.278) in Appendix II. In that specification we include five firm indicator variables in addition to one efficacy variable (survival months) and one side effect variable (neutropenia). This means that the price elasticity and the implied margin are also similar in these two models.

It is not clear whether the AR(1) specification is superior to the main specification. The F-test on the joint significance of the instrumental variables in the first-stage regression indicates that the instrumental variables are weak for the price variable. The F-statistic for the price variable is 1.3, while it is over 11 for the within-share variable. These values are also similar to those for Specification 4, where the first-stage F-statistic is 5.8 for the price variable and 13.1 for the within-share variable.

The similarity with the AR(1) model and Specification 4 is noteworthy and suggests that the serial correlation in the unobserved demand term controls for part of the time persistent demand that is not captured by the attribute variables. Furthermore, the firm indicator variables may control for the time persistent component as well as the AR(1) model does. And, more importantly, the demand estimates are not meaningfully affected by whether one controls for this unobserved component of demand using attribute variables, the AR(1) model, or the firm indicator variables.

[32] We thank the Editor for suggesting this estimator.

Table A-1: Demand Estimation with Various Specifications in the Logit Demand Model

	Specification 1				Specification 2			
Variable	OLS	IV	Nested I	BLP	OLS	IV	Nested I	BLP
$\log(price)$	-0.436*	-0.603*	-0.461*	-0.721*	-0.281*	-1.210*	-1.055*	-1.754*
	(0.036)	(0.053)	(0.073)	(0.111)	(0.060)	(0.302)	(0.282)	(0.856)
Survival	0.031*	0.044*	0.034*	0.050*				
(months)	(0.015)	(0.017)	(0.012)	(0.018)				
Neutropenia	0.007	0.001	-0.003	-0.003				
	(0.006)	(0.005)	(0.004)	(0.006)				
Pfizer					-0.695*	2.730*	2.560*	4.221
					(0.266)	(1.213)	(1.053)	(2.631)
Roche					-1.315*	-0.063	0.415	0.658
					(0.174)	(0.485)	(0.550)	(1.167)
ImClone					-0.988*	2.029*	2.951*	4.769
					(0.333)	(1.095)	(1.088)	(2.699)
Sanofi					-0.125	3.244*	2.349*	3.486
					(0.298)	(1.236)	(0.973)	(2.529)
Genentech					-0.332	0.553	0.779	0.989
					(0.241)	(0.504)	(0.447)	(0.943)
$\log(s_{j/g})$			0.341*				0.415	
			(0.170)				(0.330)	
Std. Dev.				0.329*				0.410
$(\sigma_{\log(price)})$				(0.143)				(0.346)
R-square	0.813				0.862			
1st Stage		53.027				8.231		
F-statistics			43.189				9.096	

Table A-2: Demand Estimation with Various Specifications in the Logit Demand Model

	Specification 3				Specification 4			
Variable	OLS	IV	Nested I	BLP	OLS	IV	Nested I	BLP
$\log(price)$	-0.426*	-0.991*	-0.699*	-1.492*	-0.299*	-1.475*	-1.278*	-2.291
	(0.058)	(0.181)	(0.143)	(0.332)	(0.057)	(0.420)	(0.361)	(1.294)
Survival	0.054*	0.201*	0.153*	0.297*	0.248*	0.255*	0.146*	0.273*
(months)	(0.026)	(0.049)	(0.040)	(0.079)	(0.030)	(0.051)	(0.089)	(0.081)
Neutropenia	0.014	-0.031	-0.028*	-0.060*	-0.035*	-0.098*	-0.073*	-0.134*
	(0.008)	(0.017)	(0.012)	(0.024)	(0.008)	(0.027)	(0.028)	(0.065)
Pfizer	-0.197	1.622*	1.149*	2.563*	-0.679*	4.149*	3.813*	6.825
	(0.246)	(0.647)	(0.475)	(0.930)	(0.267)	(1.831)	(1.586)	(4.696)
Roche					-2.036*	-1.398*	-0.431	-0.871
					(0.178)	(0.328)	(0.743)	(0.837)
ImClone	0.831	2.653*	2.173*	3.863*	-1.442*	2.825	3.011*	4.102
	(0.457)	(0.644)	(0.514)	(1.086)	(0.315)	(1.626)	(1.434)	(2.571)
Sanofi					0.539	2.644*	2.545*	5.187
					(0.351)	(1.054)	(0.947)	(4.194)
Genentech					-2.094*	-1.775*	-0.650	-1.630
					(0.297)	(0.562)	(0.917)	(0.877)
$\log(s_{j/g})$			0.526*				0.458	
			(0.126)				(0.314)	
Std. Dev.				0.540*				0.456
$(\sigma_{\log(price)})$				(0.179)				(0.345)
R-square	0.819				0.905			
1st Stage		13.563				5.764		
F-statistics			25.672				13.149	

Table A-3: Quasi First Difference Estimator in the Nested Logit Demand Model

Variable	AR(1)	Nested I
$\log(price)$	-1.366*	-1.557*
	(0.486)	(0.411)
Survival (months)	-1.337*	-0.323*
	(0.091)	(0.093)
Response Rate (%)	1.190*	0.644*
	(0.326)	(0.214)
Time to Progression	-0.183	-1.395*
(months)	(0.906)	(0.538)
Diarrhea	0.201*	0.051*
	(0.094)	(0.026)
Nausea	-1.208*	-0.059
	(0.338)	(0.082)
Abdom_pain	1.068*	0.561*
	(0.246)	(0.196)
Vomiting	1.743*	0.196
	(0.377)	(0.116)
Neutropenia	-0.256*	-0.082*
	(0.069)	(0.027)
$\log(s_{j/g})$	0.634*	0.403*
	(0.106)	(0.154)
Lagged variable (λ)	0.982*	
	(0.001)	
1st stage F-statistics	1.302	11.983

The first column reports the results of the AR(1) model where we let the error term to follow an AR(1) and use lagged prices as IVs after taking a quasi first difference and the second column reports results of the main specification, the *Nested I* specification in Table 2, for comparison. The first stage F-statistic is for the price variable. The quarter dummy variables are included in all specifications but their estimates are not reported. * = significant at the 5 percent level.