From business development and marketing within biopharmaceutical companies to corporate finance and equity research houses in the City and on Wall Street, forecasting is a critical but deceptively abstract art. No matter the role one plays, the consequences of missing the mark on a forecast can range from embarrassment to catastrophe – people lose jobs, and investors can lose money. Today, accuracy in forecasting has more than ever to do with understanding how stakeholders (physicians, patients, payers etc.) will react to the product, than the intrinsic attributes of the product. But how do we know what is real, what is wrong, and what may just work out in the end? Through three informative case studies, forecasting drivers are evaluated for their predictability and ultimate impact on the commercial success of a launch and the preceding forecasting efforts. Ultimately, price and access represent the highest impact, but least predictable factors dictating commercial performance – and learning from these hallmark forecasts and launches, can help to inform more accurate estimates today and in the future.
FORECASTING TODAY: WHAT HAS CHANGED?

There was a time when it was acceptable to simply have a well thought through understanding of potential patient population, competitive entrants, and physician preferences in order to formulate the year-on-year revenue estimates which supported product valuations. However, even with these “traditional approaches”, there are a number of considerations which have been overlooked, and if a critical eye is applied, one recognises that revenue forecasting is never really that simple.

Today’s market realities mean that getting a revenue forecast right often takes more than just handy EXCEL skills and guessing physician preference / market share. It requires an appreciation and opinion on the sub-context and environment of decision-making. For example, predicting physician choice of therapy is not only about selecting the right analogue, understanding the competitive landscape or testing the right product profile, but about appropriately weighting dimensions such as physician experience, pricing expectations, and reimbursement uncertainty. In this age of information, partial data-sharing and subsequent speculation can wrongly shift attention from the forecast drivers that have the highest impact and greatest level of predictability. For less predictable drivers, such as how a manufacturer will price a new product, or whether the increasingly spirited payer and provider environment will take a stand on access or utilisation, experience-based insights are critical. Even when these drivers are considered, how does the astute forecaster ensure that the pricing and access aspects are not ‘double-counted’ when also taken into account uptake and discounting assumptions and dynamics? Getting these variables wrong is not just a matter of a few prescriptions, but can lead to missing the mark by 10s, if not 100s of millions of dollars.

FIGURE 1.

<table>
<thead>
<tr>
<th>FORECAST DRIVERS</th>
<th>IMPACT VS. PREDICTABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW IMPACT / HIGH PREDICTABILITY</td>
<td>Typically involve ‘HYPE’ drivers, such as speculation about discretionary use, low-significance clinical data</td>
</tr>
<tr>
<td>HIGH IMPACT / HIGH PREDICTABILITY</td>
<td>Typically involve the ‘ADDRESSABLE MARKET’ drivers, based on clinical evidence and competitive landscape</td>
</tr>
<tr>
<td>LOW IMPACT / LOW PREDICTABILITY</td>
<td>Typically ignored in most forecasting efforts</td>
</tr>
<tr>
<td>HIGH IMPACT / LOW PREDICTABILITY</td>
<td>Typically affect ‘PRICING’, as well as ‘ACCESS’-based uptake</td>
</tr>
</tbody>
</table>

SOURCE: CBPartners Analysis

Before anticipating the magnitude of the impact of each forecast driver, one must understand which assumptions should even be considered. To ensure a comprehensive view of a product’s future performance, today’s forecaster must have an organised understanding of the significance and likely impact of each commercial driver.
To assist with this process, CBPartners has developed a subjective, though systematic method of evaluating the impact and predictability of drivers that affect the commercial performance of a product still under development (FIGURE 1). This categorisation allows the forecasting team to review and isolate those drivers most likely to affect the most sensitive aspects of a projection. In addition, this framework enables us to see the important shift in forecast driver predictability based on the timing of forecast development.

Generally, pre-launch forecasting efforts are conducted during two stages: during PHASE II, when many companies are assessing long-term commercial potential for potential deal-making, and at LAUNCH as the realities of the product’s highest impact variables come into focus as companies get serious about planning details and meeting great expectations set through earlier forecasts.

**FORECASTING FOR M&A: PHASE 2 PREDICTIONS**

Predicting the addressable market is fairly possible if unsubstantiated excitement is distinguished from the realities of evidence generated and planned through further PHASE III studies. The most challenging factors are around go-to-market decisions involving pricing, access, and market authorisation. All three of these forecast drivers, in particular, require seasoned expertise to assess not just which assumptions to make, but to understand which scenarios are realistic to explore as part of the forecasting process.

**FORECASTING FOR LAUNCH: REALITY SETS IN**

Assessing forecast drivers becomes a very different exercise at launch. As assumptions become reality, their direct impact becomes more critical. Importantly, however, incorporating changes in these values, once known, is not as simple as substituting price points and patient populations based on regulatory labels and access. Rather, a comprehensive view of the effect of price and the label on access must be developed – and the forecast should be adjusted accordingly. An expert view on these issues can raise the forecasting level of accuracy, by incorporating dynamics around the impact of price on major and emerging access influencers. In the USA, this may include high-profile KOLs, CMS, and now major health insurers who are beginning to show greater willingness to incorporate value frameworks within their steadily increasing grip on oncology and specialty expenditure. Globally, emerging stakeholders also play a role, but it is a keen understanding of how both these emerging and existing stakeholders are exacting their power over patient access and price based on the available evidence that should inspire forecasts.

By combining this awareness of the time sensitive shifts in driver predictability with expertise in commercial, competitive, pricing, and access issues, the accuracy of the revenue forecast, particularly earlier iterations at PHASE II can be significantly improved.

In an effort to illustrate a consistent approach to isolating these drivers and demonstrating impact and shifts in predictability, the CBPartners’ Portfolio Optimisation and Commercial Planning teams conducted a retrospective evaluation of product launches in oncology and other specialty therapeutic areas.

For this analysis, the team assessed three high profile oncology launches with several of the most sensitive drivers from the past five years (FIGURE 2): PROVENGETM (sipuleucel-T, DENDREON), ZALTRAP™ (aflibercept, SANOFI / REGENERON), and YERVOY™ (ipilimumab, BMS). Each one tells a different story – not just about how far forecasting can be from reality, but of how product attributes, the competitive environment, and hypothetical launch dynamics specifically can affect uptake, pricing, and net revenue.
FIGURE 2.

SOURCE: CBPartners Analysis, FDA, and EMA.

For each case study, the main revenue forecasting drivers are explored. Each driver is assessed for its impact on forecasting assumptions, as well as the resulting market realities.

1. CASE STUDY: PROVENGE – THE ESSENTIAL CAUTIONARY TALE

There are few examples of a company that went as sharply from ‘darling’ to ‘dreg’ in investors’ eyes than DENDREON’s PROVENGE™ for hormone refractory prostate cancer (HRPC). The period leading to FDA approval was one of the most dramatically eventful run-ups to a product launch over the past decade, only to disappoint market estimates once the product was approved and available for use.

1.1 FORECAST DRIVER ONE: ADDRESSABLE MARKET

Prostate cancer is the most frequently diagnosed tumour type in the USA, the market which spelled PROVENGE™’s fate. In 2010, when the product received FDA approval, CMS (Centers for Medicare and Medicaid Services) estimated approximately 192,000 new prostate cancer diagnoses, and over 27,000 deaths from the disease.

1.1.1 FORECAST DRIVER TRANSLATION: LARGE ADDRESSABLE MARKET

The obvious conclusion to draw from the high incidence rate of prostate cancer is that the PROVENGE™ addressable market was going to be substantial, and capturing it would mean it had the potential to eclipse some of the most successful oncology launches to date.

Forecasters sized the USA market alone as a peak of 35,000 new HRPC patients in 2015 who would receive PROVENGE™—which, at the eventual price of USD 93,000 per course of treatment would lead to a market of USD 3.3b (estimated market was based on incidence alone and did not consider penetration of prevalent population). With a clean safety profile, initiation on PROVENGE™ could be expected to occur ahead of any chemotherapeutics. If PROVENGE™ sales in the USA alone achieved a third of expectations, it would be a blockbuster—and many analysts suggested two-thirds market share would be possible (FIGURE 3).
FIGURE 3.

**REVENUE MODEL: PROVENGE™ ELIGIBLE, PROSTATE CANCER**

<table>
<thead>
<tr>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEW CASES</td>
<td>229,000</td>
<td>232,500</td>
<td>236,000</td>
<td>239,500</td>
<td>243,000</td>
</tr>
<tr>
<td>% ANDROGEN INDEPENDENT</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td># ANDROGEN INDEPENDENT</td>
<td>80,150</td>
<td>81,375</td>
<td>82,600</td>
<td>83,925</td>
<td>85,050</td>
</tr>
<tr>
<td>% CHOOSING PROVENGE™</td>
<td>65%</td>
<td>65%</td>
<td>65%</td>
<td>65%</td>
<td>65%</td>
</tr>
<tr>
<td># CHOOSING PROVENGE™</td>
<td>52,097</td>
<td>52,863</td>
<td>53,690</td>
<td>54,486</td>
<td>55,282</td>
</tr>
<tr>
<td>PROVENGE™ PENETRATION</td>
<td>5%</td>
<td>10%</td>
<td>20%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>PROVENGE™ PATIENTS</td>
<td>2,604</td>
<td>5,289</td>
<td>10,738</td>
<td>21,794</td>
<td>27,041</td>
</tr>
<tr>
<td>COST OF TREATMENT</td>
<td>USD 48,000</td>
<td>USD 45,000</td>
<td>USD 45,001</td>
<td>USD 45,002</td>
<td>USD 45,003</td>
</tr>
<tr>
<td>PROVENGE™ REVENUE</td>
<td>USD 117M</td>
<td>USD 238M</td>
<td>USD 483M</td>
<td>USD 981M</td>
<td>USD 1,244M</td>
</tr>
</tbody>
</table>

**SOURCE:** Seeking Alpha

### 1.1.2 MARKET REALITY: ZYTIGA™ SPOILED THE PROVENGE™ PARTY

As is widely known today, several issues came into play that eventually collapsed the PROVENGE™ launch, some of which became more obvious at the time of PROVENGE™'s launch – these will be explored in the following sections. While these issues have varying levels of predictability, one was particularly easily anticipated: JnJ was expected to launch ZYTIGA™ (abiraterone) in the pre-chemotherapy metastatic castration-resistant prostate cancer setting within which PROVENGE™ was expected to flourish, and also initially in the post-chemotherapy setting.

ZYTIGA™’s success was a question of when, not if – combining the high unmet need already noted in metastatic castration-resistant prostate cancer setting, with strong clinical data, JnJ’s product was likely to be used instead of, or at least in advance of, PROVENGE™. Around the time of PROVENGE™’s launch, only ZYTIGA™’s post chemotherapy indication efficacy was known. ZYTIGA™’s post chemotherapy OS improvement was 3.9 months (14.8 vs. 10.9), while PROVENGE™’s demonstrated efficacy in pre-chemotherapy patients was 4.1 months (25.8 vs. 21.7) – but the absolute number of months always matters, and particularly so in this case. ZYTIGA™’s absolute values were lower because these patients were chemotherapy-failure patients – a more difficult treatment setting than PROVENGE™ used. Hence, the magnitude of improvement was similar, but the degree of difficulty was clearly higher for ZYTIGA™ to achieve the incremental OS.

One often overlooked point is that PROVENGE™ did not give clear diagnostic visibility into tumour or disease activity – the therapy did not consistently shrink tumour size observed via CT scans, and typically did not yield a change in PSA (prostate-specific antigen) levels. On the other hand, ZYTIGA™ demonstrated an ability to shrink tumours, and lower PSA levels – both factors that are critical to the culture of prostate cancer patients and their oncologists as treatment options are considered.

In summary, ZYTIGA™ was poised to dominate PROVENGE™ – this should have been obvious to forecasters from JnJ’s initial clinical investigations and strong results in the post-chemotherapy setting.

### 1.2 FORECAST DRIVER TWO: HYPE – TREATMENT PARADIGM SHIFT

Although other oncology products prior to PROVENGE™ may qualify as immunotherapies, DENDREON’s product was one of the first to leverage the immune response, and was touted as the first ‘cancer vaccine’. Not only was immunotherapy viewed at the time as a major paradigm shift in treatment for any cancer type, it was also a leap ahead of existing metastatic castrate resistant (hormone refractory) prostate cancer chemotherapeutic standard of care, docetaxel. There was no immediate competition to PROVENGE™ in the pre-chemotherapy metastatic castrate resistant (hormone refractory) prostate cancer arena.
1.2.1 FORECAST DRIVER TRANSLATION: NOVELTY ECLIPSED LEGITIMATE CONCERNS

The perception of major progress in treatment approach led observers to believe that PROVENGETM would be readily embraced by oncologists, leading to steep uptake. It was one of the few therapies for which stakeholders, particularly patient advocates and oncologists, were willing to look past poor clinical trial design, questionable manufacturing capabilities, and a general lack of information about how to initiate therapy at the point of launch. The combination of an innovative treatment approach, high unmet need, and a vocal patient advocacy led many forecasters to downplay these concerns about the product, and instead suggest generous potential revenues.

1.2.2 MARKET REALITY: NOVELTY BEGETS UNCERTAINTY

Like the realities of PROVENGETM’s peak patient volume, uptake was also faltering during the first (and subsequent) year of launch. There were two main issues at play: limited manufacturing capacity and reimbursement uncertainty. Both are explored in later sections, and both are direct results of the novelty of the treatment paradigm used by PROVENGETM.

1.3 FORECAST DRIVER THREE: PRICING

As a partial byproduct of the bloated expectations built around PROVENGETM, anticipation of a premium price relative to other innovative oncology therapies, such as monoclonal antibodies, ran high.

1.3.1 FORECAST DRIVER TRANSLATION: ‘BREAKTHROUGH’ PRICING

At the time, ARZERRATM (ofatumumab, NVS) was one of the most expensive therapies at USD 117k, but was only approved for use in chronic lymphocytic leukaemia (CLL), an orphan disease. Analysts’ assumptions for PROVENGETM’s cost-of-therapy were approximately USD 61,700 (FIGURE 4) – a value that was counterintuitively in the same range as REVLIMIDTM (lenalidomide, CELG), for multiple myeloma, a far less prevalent condition compared to metastatic castrate resistant prostate cancer. Hence, analysts were expecting an unrealistic price ‘premium’ for PROVENGETM. Given the large size of the metastatic castrate resistant prostate cancer’s addressable market, many would have expected DENDREON to price PROVENGETM in the USD 40-50k range. However, as noted later in this piece, such a price point would still have been commercially unsustainable – though no one would have known it at the time.

FIGURE 4.

| PRICING: PRE-LAUNCH, PROVENGETM ANALYST ASSUMPTIONS |
|-----------------|-----------------|----------------|
| **ANALYST**     | **AFFILIATION** | **EST. PRICE** |
| REN BENJAMIN    | RODMAN & RENSHAW| $40,000  Nov 12 note to clients |
| CORY KASIMOV    | JP MORGAN       | $65,000  Feb 22 note to clients |
| HOWARD LIANG    | LEERINK SWANN   | $60,000  Apr 13 email |
| DAVID MILLER    | BIOTECH STOCK RESEARCH | $72,000  Feb 27 note to clients |
| MARK MONANE     | NEEDHAM & CO.   | $50,000  Apr 13 email |
| CHRISTOPHER RAYMOND | ROBERT W. BAIRD & CO. | $70,000  March 12 note to clients |
| ERIC SCHMIDT    | COWEN & CO.     | $75,000  Feb 1 note to clients |
| **AVERAGE**     |                 | **$61,700** |

SOURCE: RODMAN & RENSHAW, JP MORGAN, LEERINK SWANN, BIOTECH STOCK RESEARCH, NEEDHAM, ROBERT W. BAIRD, COWEN
1.3.2 MARKET REALITY: USD 93,000 EXCEEDS EVEN THE MOST AGGRESSIVE EXPECTATIONS

While DENDREON clearly felt that the combination of metastatic castrate resistant prostate cancer’s unmet need and PROVENGETM’s clinical trial data would justify a significant premium to the analyst average, few expected they would go as far as where they landed: USD 93,000 (USD 31,000 per infusion of a three-course cycle). In retrospect, what is known of the manufacturing process and presently understood of PROVENGETM’s cost of goods, this launch pricing should not have surprised the marketplace.

Although the world has since changed, at the time aggressively high pricing (USD 93,000 was over 50% higher than average analyst estimates) may have been positively rewarded by investors and forecasters. Such a price can build brand equity, and certainly helps the financial status of the company. However, wise forecasters would understand that the world was progressing to an era where such a surprisingly high price set off alarm bells, rather than a parade of support. These points are explored in the following section.

1.4 FORECAST DRIVER FOUR: ACCESS – NO PRECEDENCE FOR SERIOUS RESISTANCE

Although ‘open access’ could be confidently applied to most oncology therapeutics launched through the 2000s, access for PROVENGETM was generally predicted to be without question- given the unmet need and definition around metastatic castrate resistant prostate cancer patients. Patient advocacy was particularly vocal about regulatory approval, although these same stakeholders did not have an appreciation of the underlying dynamics which would arise from PROVENGETM’s eventual price point – a decision by DENDREON which would limit both payer coverage policy and oncologist willingness to prescribe.

1.4.1 FORECAST DRIVER TRANSLATION: SILENCE

From a forecasting perspective, access at the time of PROVENGETM’s approval was broadly unaddressed. Naïve silence on the topic of oncology access restrictions prevailed for most novel therapeutics at the time. There was some justification for this in the USA, given that oncology therapeutics that arrived to market ahead of PROVENGETM were generally reimbursed with minimal restrictions beyond the FDA approved label and even extending into NCCN guidelines. There was a universal feeling that oncology was ‘untouchable’ with regard to payer restrictions beyond the FDA approved label. This sense of unencumbered pricing and access freedom was likewise expected to be the case for PROVENGETM, and ultimately its downfall.

1.4.2 MARKET REALITY: CMS NCD AND RESULTING UNCERTAINTY

Given that PROVENGETM’s target population was prostate cancer, a tumour type that typically affects elder men (average age is 66), MEDICARE played a particularly important role in the payer mix – the prediction at the time was that they would be responsible for 75% of patients going on therapy. At the time, MEDICARE local carriers generally covered oncology therapeutics upon FDA approval, and CMS tended to turn a blind eye towards the need for any formal assessment of clinical value for money.

Perhaps it was due to the ‘sticker shock’ of USD 93,000 per course of therapy. Or maybe it was PROVENGETM’s pricing combined with the high prevalence of metastatic castrate resistant prostate cancer. Some even speculated that it was a vengeful CMS that was unhappy that DENDREON did not engage with them during the development process to provide reassurance around expected patient population, duration of therapy, and trial design. During an investor call in April 2010, DENDREON admitted that they were not concerned with CMS, and were only focussed on the FDA. Regardless of the reasons, within two months of FDA approval, CMS announced that it would initiate the process for a national
coverage analysis (NCA), and that a national coverage decision (NCD) would be issued within a year. Such a decision by CMS was unprecedented at the time, and even today continues to stand as an example of the power CMS can wield, if it chooses.

Although CMS eventually gave the green light for PROVENGE™ to be reimbursed nationally, the overall effect of the unusual decision to conduct an NCA suffocated the launch. The impending NCD meant that CMS was dubious on the clinical and economic dynamics of PROVENGE™ – causing many, and most importantly oncologists, to think twice about initiating patients on the new therapy. The environmental uncertainty caused by CMS led to many practices refusing to float the cost of PROVENGE™ with the possibility that local MEDICARE carriers and private insurers may resist or simply deny reimbursement.

The USD 93,000 needed to be floated by oncologists, many of whom worked within small to mid-sized practices – and this upfront investment was concentrated within only a four-to-six-week treatment period. This high-cost density meant that any delays or uncertainty around reimbursement fueled reluctance to prescribe. Although CMS eventually issued a PROVENGE™-specific Q-code, the prior year of uncertainty meant that prolonged use of the miscellaneous code inspired stakeholder insecurity and a time-intensive manual review.

1.5 FORECAST DRIVER FIVE: ADDRESSABLE MARKET – DISCRETIONARY USE

When the FDA approved PROVENGE™, the label it issued was for asymptomatic or minimally symptomatic prostate cancer that has spread to other parts of the body, and is resistant to standard hormone treatment. However, data around patients without symptom specification, as well as non-metastatic prostate cancer (hormone resistant or sensitive) did exist, though was inconclusive.

Nevertheless, given the immediate lack of treatment options in this pre-chemotherapeutic space, some observers speculated that use could spread to these populations at oncologists’ discretion.

1.5.1 FORECAST DRIVER TRANSLATION: PROVENGE™ USE BEYOND THE LABEL

Nobody likes to admit it, but discretionary use of a new oncology therapy does happen – especially when supported by a vague FDA label. However, to factor this into a forecast is indeed a bold step.

Many analysts consumed the excitement around PROVENGE™ to the extent that use of the product beyond the FDA approved label would be common, accepted, and reimbursed. Such an assumption opens the gate to a significant revenue increase – all without acknowledging the validity of supporting data, or whether payers were willing to fund these more experimental uses of PROVENGE™.

1.5.2 MARKET REALITY: CMS CALLS AN ‘INAUDIBLE’

As PROVENGE™ became commercially available, payers immediately received reimbursement requests for use beyond the FDA approved label. CMS eventually decided not to make a uniform NCD on whether reimbursement would be limited to only the FDA approved label. Rather, they stated that reimbursement of such discretionary use would be relegated to local carriers – which is essentially a signal to its regional system of contractors to not provide funding for patients outside the FDA approved label (at the time, half of CMS local carriers already limited coverage to PROVENGE™’s label, and this statement within the NCD seemed to encourage the rest to follow suit). All of these insinuations were implied with the backdrop of its perspective that evidence in support of unlabelled use of PROVENGE™ was ‘virtually nil’. The message was encoded, but clear nonetheless.
By the time the dust of CMS’ NCD had settled, a year of oncologists’ hesitation had elapsed, leading to poor uptake. This subpar performance engulfed investors, and the stench of reality overpowered most analysts’ forecasts. Investors slashed USD 3.6 billion off of DENDREON’s market cap, resulting in 62% of stock value being erased in a single day following CMS’ announcement.

1.6 FORECAST DRIVER SIX: ADDRESSABLE MARKET – MANUFACTURING CAPACITY

It was a well-known fact that the PROVENGE™ manufacturing process was complicated and costly. Once the patient was identified as a candidate for therapy, white blood cells needed to be drawn and sent to one of two sites in the country to identify specific immune cells for use and processing. The process took three days, and was viewed as a barrier to PROVENGE™ initiation, particularly as ZYTIGA™ (an oral therapy) loomed on the horizon.

1.6.1 FORECAST TRANSLATION: PATIENT WAITING LISTS

DENDREON announced that they expected only 2,000 patients to go on PROVENGE™ therapy during the first year of availability. This belief, although viewed as ‘honest’, was a far cry from the 35,000 metastatic castrate resistant prostate cancer patient incidence upon which many forecasters had fixated. Many forecasters took DENDREON at their word on this 2,000 patient constraint, and forecast expectations were tempered as a result – though many expected a ‘hockey-stick’ reaction the following year due to patient waiting lists.

1.6.2 MARKET REALITY: SLUGGISH START

Analysts who did their homework discovered that most oncology practices did not have these mythical PROVENGE™ waiting lists. Generally, oncologists were not only hesitating to use the product due to the CMS assessment, but they were also under-informed. DENDREON was not actively promoting PROVENGE™ through its first year on the market – there was no oncology detailing, and no known direct-to-consumer advertising. DENDREON’s behaviour could be explained by the possibility that the company knew the reality of their supply constraints, and did not wish to stoke patient demands without sufficient capacity for addressing them. On the other hand, this lack of stakeholder training could just as well be the result of a low ability-to-spend on physician and patient education. The two issues are related – after all, the complex manufacturing process led PROVENGE™ cost of goods to peak at 77% of sales, a fact that also likely led to ultimate bankruptcy filing in 2014.
The PROVENGE™ launch is a cautionary tale for so many reasons. DENDREON exacerbated many of its obstacles by pushing the price-point of a product with known supply issues and questionable evidence derived from its pivotal studies. The company was simply not prepared to launch an oncology product that challenged the modern care paradigm. The fact that a superior treatment option in the form of ZYTIGA™ was around the corner should alone have reduced forecasts. Less predictable was the CMS response to the lack of engagement in the run-up to FDA approval, which was only exacerbated by the disruptive price point.

Several high impact forecast drivers around the addressable market and realities of the clinical trial evidence were as clear in PHASE II, as at launch – however only a seasoned eye could have predicted the magnitude of the impact of price on access and uptake, even at the point of launch (FIGURE 5).

In the end, no amount of patient advocacy could save DENDREON from itself with an approximately -80% discrepancy in USA forecast for peak sales (USD 150m, 2015) versus actual peak sales (USD 30m, 2012). The company was sold to VALEANT for less than USD 500m in 2015.

**2. CASE STUDY: ZALTRAP™ – MISCALCULATING SUCCESS**

When looking at the USA market alone, the ZALTRAP™ case is a remarkable one, and arguably the most confirmatory of the detriment of price-setting in a vacuum. Beyond pricing, however, the launch was challenged for a variety of other reasons that would affect the product’s forecast projections globally, even if price was not the centerpiece of discussion.

Some ZALTRAP™ observers held great expectations that it could be ‘the next AVASTIN™ (bevacizumab, ROCHE), and possibly even a superior form of AVASTIN™ – however, the pivotal trial data did not support this romanticism. When the clinical value profile of ZALTRAP™ became clear and pricing was set based on what is likely a misjudged dosing assumption, the product’s immediate post-launch fate was decided.
2.1 FORECAST DRIVER ONE: HYPE – AVASTIN™ PIE

Colorectal cancer is the third most common non-skin cancer in both men and women globally. This overall patient volume and the unrelenting unmet need for this devastating tumour type is further complicated by the fact that the mCRC arena had several innovative brands already in play, including ERBITUX™ (cetuximab, BMS / MERCK) and VECTIBIX™ (panitumumab, AMGEN). However, the opportunity for ZALTRAP™ was touted given the success of the world’s largest oncology brand in mCRC, AVASTIN™. In other words, if ZALTRAP™ could disrupt the marketplace and acquire share, the clinical evidence would need to be convincing enough for oncologists to want to use it instead or ahead of the existing options, including fellow VEGF-targeting (vascular endothelial growth factor) AVASTIN™. If ZALTRAP™ could accomplish this, though, the opportunity was substantial.

2.1.1 FORECAST DRIVER TRANSLATION: ADDRESSABLE MARKET UPSIDE

Given the number of competitors already present within this tumour type, SANOFI / REGENERON needed to carve out a role for ZALTRAP™ in the treatment paradigm. Early on, this role was defined as a second-line treatment option for mCRC patients.

The challenge presented was that many were calculating ZALTRAP™‘s opportunity in this setting as one that would need to ‘steal’ share from a powerful AVASTIN™ brand from oncology giant ROCHE – an opinion based primarily on the VEGF pathway common to both products, and early conjecture that ZALTRAP™‘s superior binding ability would make it a preferred option over AVASTIN™.

2.1.2 MARKET REALITY: AVASTIN™‘S EDGE ON EXPERIENCE

The idea that ZALTRAP™ could eat into the powerful AVASTIN™ brand in this setting was, on first-pass, a charming proposition. During the run-up to ZALTRAP™ approval in 2011, AVASTIN™ was the world’s largest oncology brand, with USD 2.6b in the USA and USD 6.2b globally. While most forecasters understood that over half of AVASTIN™‘s revenue was derived from use in other solid tumours (including the recently withdrawn metastatic breast cancer indication), less clear was that under 10% of AVASTIN™‘s use was in the second-line mCRC setting – the actual addressable market for ZALTRAP™.

Nevertheless, there was indeed a race for second-line patients – at the time of ZALTRAP™‘s FDA review, ROCHE was also barreling AVASTIN™ towards a second-line label expansion in mCRC. That eventual approval for ROCHE meant that they would leverage the advantage of physician experience and confidence through years of use in the first-line mCRC use to expand within the second-line population.

2.2 FORECAST DRIVER TWO: ADDRESSABLE MARKET – AVASTIN™‘S EDGE

ZALTRAP™ targets the VEGF pathway by inhibiting the activity of subtypes VEGF-A and VEGF-B, as well as of PGF (placental growth factor). This causes the prevention of new blood vessel growth in the tumour. At the time that the initial deal was completed between REGENERON and AVENTIS (prior to the SANOFI merger), AVASTIN™ was making regular headlines for the breakthrough approach of ‘tumour starvation’ based on its VEGF mechanism of action. The alignment of ZALTRAP™‘s MOA with the buzz surrounding AVASTIN™ caused many observers to declare it as likely to achieve similar levels of efficacy.

Some went further, believing that ZALTRAP™ could be superior to AVASTIN™ before the former was studied in human models. Indeed, at the time of the deal, this is the evidence on which AVENTIS based their valuation. This perception was built based on the fact that ZALTRAP™ had greater binding affinity to multiple VEGF isoforms than AVASTIN™.
2.2.1 FORECAST DRIVER TRANSACTION: THE PEAK OF WISHFUL THINKING

Following the top-line results from ZALTRAP™’s VELOUR study, some analysts expected that ZALTRAP™ could win substantial share from existing mCRC biologics, including ERBITUX™, VECTIBIX™, and most notably AVASTIN™. DEUTSCHE went so far as to note that ZALTRAP™ would take 50% of the 34,000 patients in treatment within the second- and third-line settings, which yielded USD 200m peak year revenue projections – an opinion that was further supported by the assertion that ZALTRAP™’s superior mechanism of action would be favoured over AVASTIN™ in this setting. Analysts at BERENBERG likewise projected peak sales of USD 404m by 2019 (FIGURE 6), however sales appear to have peaked at 77m in 2015.

FIGURE 6.

SOURCE: BERENBERG; SANOFI / REGENERON Annual Reports

2.2.2 MARKET REALITY: GOOD, NOT GOOD ENOUGH

Although ZALTRAP™ had compelling pharmacological profile relative to AVASTIN™, the clinical data arising from the VELOUR study with a FOLFIRI backbone regimen was not as convincing. Median OS was 13.5 months for the ZALTRAP™ arm, while the placebo arm was 12.1 months – an improvement of 1.4 months. When OS improvement was compared to AVASTIN™’s 1.4 month improvement, it became easy to fixate on ZALTRAP™’s inferior side effect profile and understand how oncologist comfort with AVASTIN™ leads to the inability for ZALTRAP™ to fulfil hefty expectations of clinical superiority to AVASTIN™ upon launch.

2.3 FORECAST DRIVER THREE: PRICING

SANOFI / REGENERON approached the pricing of ZALTRAP™ surprisingly aggressively, with a WAC price of USD 11,063 per month – a position that was more than twice the monthly cost of AVASTIN™ in the same line of therapy. While premiums are expected for comparable products launching almost a decade later, this price position defied logic for many observers. Some pointed to the premium as a remnant of the ‘hope for superiority’ to AVASTIN™. Others incorrectly rationalised the price by citing the much smaller patient population in play for ZALTRAP™ relative to AVASTIN™ – and that the total budget impact was a fraction relative to ROCHE’s blockbuster. The more cynical believed SANOFI / REGENERON priced this high simply ‘because they could’. After the dust settled, it became clear that the reasoning was more unfortunate – ZALTRAP™’s pricing may have been pegged to a higher dose (10mg/kg) of AVASTIN™ compared to what is routinely used and recommended in NCCN guidelines (5mg/kg) – thus leading to an inflated price point for ZALTRAP™.
2.3.1 FORECAST DRIVER TRANSLATION: THE PRICING YO-YO

Once ZALTRAP™’s initial pricing was announced, many forecasters adjusted their projections upward. If forecasters were assuming a parity to AVASTIN™ price at the lower dosing, then revenue would be expected to double assuming that oncologists’ use of the product would be unaffected by price – a dangerous assumption in hindsight. The now infamous reaction from the oncologist community led to an eventual price reduction. As a result, forecasters yo-yoed back to lower projections due to the price-based reduction – for instance, BERENBERG lowered their 2017 projection from USD 404m to USD 251m. However, this 38% reduction is still less than the simple math of halving the price point. Hence, it is clear that forecasters did not expect the launch price effect to have long-term effects on utilisation.

2.3.2 MARKET REALITY: GOOD, NOT GOOD ENOUGH

Although ZALTRAP™ had compelling pharmacological profile relative to AVASTIN™, the clinical data arising from the VELOUR study with a FOLFIRI backbone regimen was not as convincing. Median OS was 13.5 months for the ZALTRAP™ arm, while the placebo arm was 12.1 months – an improvement of 1.4 months. When OS improvement was compared to AVASTIN™’s 1.4 month improvement, it became easy to fixate on ZALTRAP™’s inferior side effect profile and understand how oncologist comfort with AVASTIN™ leads to the inability for ZALTRAP™ to fulfil hefty expectations of clinical superiority to AVASTIN™ upon launch.

2.3.3 MARKET REALITY: ONCOLOGISTS TAKE A STAND

Although a surprisingly high price would be most likely to cause payers to act through restrictions to access, this time it was the KOL community who led the charge against pricing. In a well-documented letter published in The New York Times, renowned oncologists from Memorial Sloan Kettering Cancer Center (MSKCC) pledged they would not use ZALTRAP™ given that it was providing the same clinical effectiveness as to have negotiated up to a 50% discount for providers, thus lowering their price by half to meet AVASTIN™’s cost of therapy at more than twice the cost. In this instance, payers did not need to limit access – influential oncologists refused to use the product due to their perception of a poor cost-benefit argument.

Two months later, SANOFI / REGENERON appeared to have negotiated up to a 50% discount for providers, thus lowering their price by half to meet AVASTIN™’s cost of therapy at 5mg/kg, but the damage was done.
When assessing the ZALTRAP™ case comprehensively, the product could have carved a reasonable share of mCRC patients in the second-line setting from AVASTIN™. ZALTRAP™ was a new option, and oncologists sometimes need to push the boundaries of conventional regimens, which some would argue includes reliance on AVASTIN™. However, the simple math involved with ‘double the price of AVASTIN™ with the same clinical benefit’ caused the media to latch onto the striking story of the world-renowned MSKCC standing up to a pharmaceutical company. The argument was a simple one, and placed a heavy burden on a product that could have otherwise captured its estimates. Predicting the price-miscalculation at launch is nearly impossible for stakeholders interested in the commercial performance of ZALTRAP™. However, at the point that the price point was announced, shrewd forecasters would have realised the likely implications of the MSKCC outcry – not on payers, but on other oncologists who ultimately still determine the fate of oncology products (FIGURE 7).

3. CASE STUDY: YERVOY™ – DEFYING GRAVITY

In 2009, BMS acquired MEDAREX for USD 2.4B, assigning approximately USD 1.0B of this valuation to YERVOY™ (ipilimumab, BMS). Perhaps more than other therapies launching during the same time period, predicting YERVOY™’s success at launch and BMS’ ability to counter new competitor launches over the subsequent years proved extraordinarily challenging.

3.1 FORECAST DRIVER I: UNMET NEED AND HYPE

At the time of YERVOY™’s impending launch following the MEDAREX acquisition, standard of care for advanced melanoma patients had remained primitive and unswerving for decades. Dacarbazine and interferon therapy were the go-to options, both of which
required high dosing that led to serious patient tolerability issues. At the time, there were no approved therapies for these patients that demonstrated OS improvement through clinical study.

In addition to the obvious clinical need for an innovative approach to treating advanced melanoma, there were some red herrings in the mix that complicated a clear view of YERVOY™’s potential.

### 3.1.1 FORECAST DRIVER TRANSLATION: PROSTATE CANCER SMOKE SCREEN

YERVOY™ was expected to change the treatment paradigm in advanced melanoma – if it could reach the market. However, the conversation leading up to BMS’ acquisition of MEDAREX instead was distracted to prostate cancer as the MAYO CLINIC inexplicably released anecdotal evidence about three patients in which they observed that YERVOY™ exceeded their expectations – in prostate cancer. These three patients on YERVOY™ shrunk their tumours to the extent that they were then surgery candidates – a critical stage in treating prostate cancer.

YERVOY™ forecasts ballooned, share prices surged as much as 22%, and BMS’ asking price to acquire MEDAREX presumably needed to be raised – but not for the value of the therapy in its ‘go-to-market’ indication of advanced melanoma. By the time the deal closed, BMS’ USD 2.4B acquisition of MEDAREX went at a 90% premium to the company’s closing share price that day.

The YERVOY™ opportunity in metastatic melanoma was already substantial. Most forecasts pointed at approximately 40,000 new patients each year in the USA and around 60,000 ex-USA. Given that half of these patients are under 60 and could likely tolerate immunotherapy, and that the disease progresses quickly (many would die in under a year from diagnosis), and there was no available treatment that demonstrated OS, most patients would likely have a shot at trying YERVOY™.

As a result, many pushed forecasts well over the USD 1b mark at peak year (FIGURE 8) – even without a first-line approval at launch.

### FIGURE 8.

<table>
<thead>
<tr>
<th>AFFILIATION</th>
<th>ESTIMATED REVENUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein</td>
<td>USD 1.7B (2015)</td>
</tr>
<tr>
<td>BMO Capital Markets</td>
<td>&gt;USD 1B</td>
</tr>
<tr>
<td>Thomson Reuters</td>
<td>USD 820M (2015)</td>
</tr>
<tr>
<td>UBS</td>
<td>USD 1.2B (2015)</td>
</tr>
<tr>
<td>Leerink Swann</td>
<td>USD 1.23B (2016)</td>
</tr>
<tr>
<td>Evaluate Pharma</td>
<td>USD 879M (2016)</td>
</tr>
</tbody>
</table>

SOURCE: BERNSTEIN, BMO, THOMSON REUTERS, UBS, LEERING SWANN, EVALUATE PHARMA

### 3.1.2 MARKET REALITY: MELANOMA BACK IN FOCUS

The reality was that data coming from YERVOY™’s pivotal trial, presumably designed by MEDAREX, was questionable. Beneath the headline that YERVOY™ led to a median OS increase of 3.7 months in an area where OS was not previously demonstrated, there lay confounding trial design issues.
The first is that fewer than half (46%) of these patients were still alive after one year of YERVOY™ treatment – it was still better than the placebo arm, but dampened expectations of the product being a miracle cure – at least for melanoma. Additionally, the distribution of study arm patient allocation was unclear and led to some analytical challenges – the YERVOY™ + gp100 arm had over 400 patients, while the YERVOY™ monotherapy had 137 and gp100 monotherapy had 136. Perhaps most damaging was that the comparison was indeed to gp100, an experimental vaccine which had questionable efficacy, according to clinical experts. Adding further to this disputable comparator, clinicians suggested that this vaccine caused some toxicity, which could have led to an exaggerated perception of clinical tolerability in the YERVOY™ arm.

Still, even if a longer-term approval in prostate cancer was being taken into account within the value of MEDAREX and its YERVOY™ opportunity, a more clearheaded assessment would have recognised that the company announced this three-patient anecdotal evidence, but neglected to develop a press release on results from MSKCC’s PHASE II study of YERVOY™ in aggressive prostate cancer published at ASCO just months before.

3.2 FORECAST DRIVER TWO: REGULATORY – FDA UNCERTAINTY

Given the clinical trial design challenges already noted, some speculated that the FDA may drag its heels in the lead up to the PDUFA date. Most analysts expected a second-line melanoma approval given that the pivotal trial screened enrollees have had some prior treatment experience with aldesleukin (IL-2), dacarbazine, temozolomide, fotemustine, or carboplatin.

3.2.1 FORECAST DRIVER TRANSLATION: COMPLETE RESPONSE LETTER – NOT APPROVAL

YERVOY™’s FDA PDUFA date was on March 25, 2011, and given the questions around YERVOY™’s trial design, many expected a ‘complete response letter’ – that approval may ultimately be possible in the second-line setting, but that there would be the need to either generate new data or conduct additional analysis.

The skepticism of an FDA approval on the PDUFA date was further compounded by the fact that BMS released additional first-line data just days in advance of this date – meaning more time would be needed to make a disciplined decision.

3.2.2. MARKET REALITY: FDA’S BROAD APPROVAL

The FDA surprised the world of oncology when they approved YERVOY™ on its PDUFA date (a more traditional event would have been either a delay or a complete response letter given the data being reviewed). While the market authorisation alone was notable, the fact that the FDA granted approval for all patients across first and second lines of treatment was jarring.

Just days before YERVOY™’s PDUFA, BMS announced PHASE III data on YERVOY™ in the first-line setting – and they were relatively positive: among the first-line YERVOY™ + dacarbazine patients, there was an OS improvement of 2.1 over those patients using dacarbazine alone. The results couldn’t be ignored, and a rapid assessment of the data led to the FDA’s inclusion of first-line patients within their approved label for the product. First-line includes approximately 10,000 new patients, which meant that forecasters needed to scramble to adjust forecasts on at least this point.

Beyond the new patients, forecasters would need to take into account that these first-line patients were studied using 10mg/kg dosing, which was more than three times the 3mg/kg dosing used in the second-line pivotal trial data upon which approval was generally believed to be based. Another dosing issue is that maintenance therapy, which was interpreted to be part of the FDA approved label, also required 10mg/kg – again tripling the cost and revenue implications for these patients.
3.3 FORECAST DRIVER THREE: PRICING

Whether BMS liked the comparisons or not, many viewed the pricing opportunity for YERVOY™ to resemble that for PROVENGETM. It was an immunotherapy, highly innovative, and addressing a major unmet need with few treatment options. In the immediate aftermath of PROVENGETM's USD 93,000 price-point and disappointing launch, forecasters expected that BMS would be far more cautious in their pricing approach – did BMS know something the rest of the world did not?

3.3.1 FORECAST DRIVER TRANSLATION: PROVENGETM AS BENCHMARK?

Forecasters generally fell into two categories: PROVENGETM level pricing of USD 93,000, or substantially lower at USD 50-60,000. Those who estimated PROVENGETM as a reasonable pricing comparator latched onto the similar characteristics among the two products and that PROVENGETM had ‘shattered’ the pricing ceiling and ushered in a new comfort with pricing of innovative oncology therapies in that range.

On the other hand, those gravitating towards the USD 50-60,000 range felt that BMS would be wise to retreat to lower pricing given the backlash against DENDREON's PROVENGETM. An additional consideration was that BMS could not afford to price at the same level as PROVENGETM due to the impending REMS programme and additional supportive therapy costs associated with using YERVOY™ – something that PROVENGETM generally avoided.

3.3.2 MARKET REALITY: WHEN THEY GO LOW, YOU GO HIGH

BMS went in the third-direction and priced at a significant premium to PROVENGETM: USD 120,000 for a course of therapy – which assumed about USD 30,000 per infusion at 3mg/kg. Simple math allows that the same infusion in the first-line setting or maintenance setting would be over USD 100,000, with total cost of therapy being multiples of that. The FDA’s last minute decision to include first-line patients meant that forecasts were in a tailspin – but the net effect was a substantial rise in estimates. Given the extraordinary pricing, one would wonder why the marketplace reacted so differently to YERVOY™ relative to the very recent history of PROVENGETM. With a surprisingly higher price set than the forecasters were expecting, a ZALTRAP™-like (provider-inspired) or PROVENGETM-like (payer-inspired) market reaction could have been triggered, which meant that forecasters who opted to simply increase the pricing multiplier in forecasts may have missed the harder to detect market undercurrents that could have been in play.

There is an abundance of rationale for why BMS was successful where DENDREON and SANOFI / REGENERON were not. BMS avoided the payer and provider backlash by investing resources and leveraging experience to establish a more willing environment for its impending oncology launch. There is more to it, including that BMS had communicated publically that it evolved its launch strategy for oncology, perhaps in part due to PROVENGETM learnings. YERVOY™ did not just ship to oncology practices with melanoma patients – it was supported by an integrated model involving a reimbursement specialist, a medical science liaison (MSL), with a 24-hour support centre. Once a potential patient is identified, a process triggers that leads with the MSL explaining basic details around YERVOY™ use to the oncologist, as well as a webinar and support team contact details. The MSL follows up on this interaction with a visit to the oncology practice, while the rest of the team actively supports reimbursement and product use processes. Today, this model may be the expectation, but at the time it was clearly a departure from recent launches by other companies within the oncology space.
The lead-in to YERVOY™'s launch was rife with uncertainty and distractions. Confidence in the melanoma data was shaken, and the FDA was not expected to decide on time, nor with the expanded label that was eventually defined. The markets were dazed by oscillating news around MAYO’s HRPC success and the questionable timing of the news during BMS’ acquisition negotiations. To top it off, the whimper of PROVENGE™'s launch drew concern when the price point and higher first-line dosing became clear.

In the end, performance fairly closely matched expectations with forecast USA peak sales of USD 1.7b by 2015, and actual sales of USD 1.3b in 2014. However, just as with the other two cases, the YERVOY™ forecasting effort was challenged by the predictability of the impact of price on the launch (FIGURE 9).
IN CLOSING

As is demonstrated through these three case studies, defining the nature of the impact of forecast drivers is just as important as understanding their likelihood.

FIGURE 10.

Importantly, predictability varies, with stark changes from forecasting at PHASE II (FIGURE 10) to forecasting at launch (FIGURE 11).

FIGURE 11.
The subsequent step of applying experience-based judgement to each driver’s likelihood and magnitude of impact is vital to the forecasting process.

CBPartners’ experience of routinely addressing commercial, competitive, pricing, and access issues in support of product launch and M&A decision support allows the team to raise the degree of accuracy. While anyone’s hindsight is 20/20, accuracy can be sharper if the same expertise of developing the commercial, value, pricing, and market access strategy is applied to predicting another company’s plan for a given asset, and how it will be received by the market.
ABOUT CBPARTNERS:

CBPartners is a global consultancy committed to providing unparalleled strategic support to pharmaceutical companies, biopharmaceutical companies, medical device companies, and government health authorities. The firm has four practice areas:

- Value, Access & Pricing
- Commercial Planning
- Portfolio Optimisation
- Government Policy Advisory

The firm has four offices; our US operations run out of New York City and San Francisco. London, UK is our European regional hub, and our Asian engagements are anchored in Shanghai, China.

Cyrus A. Chowdhury  
CEO & Managing Director  
CBPartners  
e. cyrus.chowdhury@cbpartners.com  
m. +1 347 221 9536  
o. +1 646 604 0607

Bami Oshinowo  
Senior Associate, Portfolio Optimisation and Commercial Planning  
CBPartners  
e. bami.oshinowo@cbpartners.com  
m. +44 (0) 7495 136 383  
o. +44 (0) 020 3794 1761