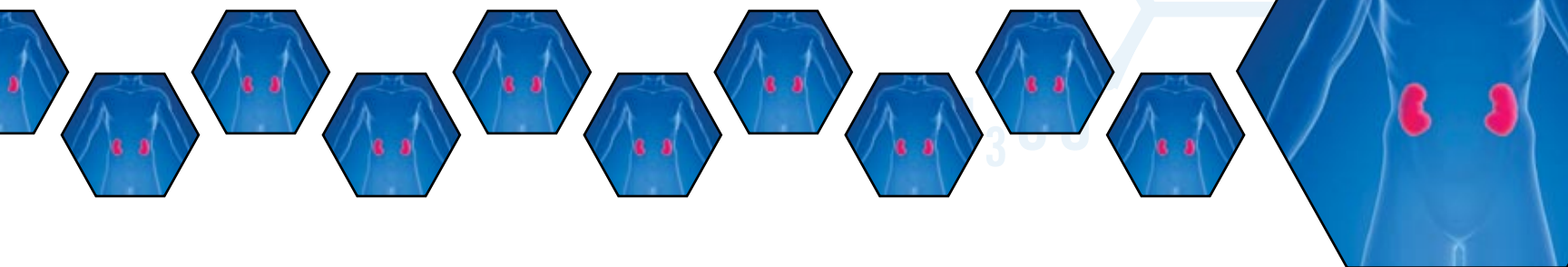


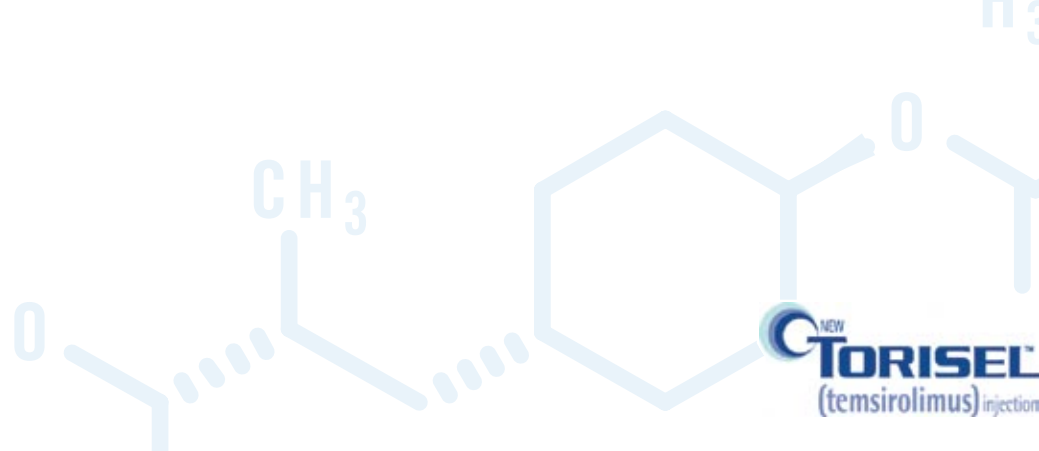
# Torisel:

## The New Kid on the Block for Advanced Renal Cell Carcinoma

Wyeth Pharmaceuticals recently launched Torisel™ (temsirolimus), a targeted, first-in-class mTOR inhibitor. This new treatment for metastatic renal cell carcinoma is the third targeted therapy for RCC launched in as many years; however, Torisel is the first such targeted agent proven to extend survival.

By Michelle Nolin Flewell, Erinn Goldman





Wyeth Pharmaceuticals' recent launch of the targeted, first-in-class mTOR inhibitor Torisel™ (temsirolimus) ushered in a third new therapeutic option for the treatment of advanced renal cell carcinoma (RCC)—a difficult-to-treat cancer that accounts for 85% of all renal carcinomas with an estimated 5-year survival rate of less than 10%.

Coming on the heels of two new product launches for RCC in the last 2 years, Nexavar [sorafenib; Bayer] and Sutent [sunitinib; Pfizer], Wyeth reports that Torisel is the first such targeted agent proven to extend median overall survival in this disease category.

The FDA approved Torisel on May 30 of this year after a second quarter delay in approval stemming from the agency's request for additional data regarding tumor evaluation (the original action date was April 5). Torisel became commercially available as of July 2, and is currently available throughout the wholesale and GPO distribution networks. Wyeth chalked up the delay to "working out the details."

After completing promising Phase 2 studies, Wyeth faced the decision of which tumor types and indications to pursue. "After much internal deliberation, we decided on a Phase 3 program that investigated Torisel for the treatment of breast cancer, RCC, and mantle cell lymphoma. We also sought additional input and agreement from the various regulatory bodies around the world and clinical investigators to design an optimal Phase 3 clinical trial program that included the appropriate endpoints. Once we had this input and agreement, the Phase 3 clinical program for Torisel moved quickly," Wyeth reported.

### Scientific Discoveries Yield New Targets in RCC and a Rapid Evolution in Therapy

According to the National Cancer Institute, approximately 39,000 Americans will be diagnosed with RCC each year, and approximately 12,800 will die annually. If the cancer has not yet metastasized to other organs at the time of initial diagnosis, RCC may be cured by surgery (nephrectomy) to remove all or part of the diseased kidney along with surrounding tissues. Unfortunately, in 25%-30% of cases, the initial diagnosis is of advanced or metastatic RCC (mRCC), which historically has been very difficult to treat.

Cytotoxic chemotherapy agents and hormonal agents are not effective in treating mRCC. Because RCC evokes an immune response, which occasionally results in a spontaneous and dramatic remission, various immunotherapeutic strategies have been explored in an attempt to accentuate or reproduce this response. One such biologic strategy is the use of cytokines, which are natural proteins produced by the body's immune system. Until recently, this strategy has been the only option for treatment, and the only effective cytokine therapy choices were either with interferon-alpha or interleukin-2 [IL-2; Proleukin, Chiron Corporation]. IL-2 is the only FDA-approved cytokine therapy and is only effective at very high doses. It is associated with severe toxicity and requires inpatient administration with intensive support care. Furthermore, IL-2 treatment only induces complete remission in about 10% of patients. Until recently, no agent has shown any evidence of clinical benefit for patients with progressive mRCC after [cont. on pg 40 >>](#)

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cytokine therapy. Consequently, the median survival with cytokine therapy is approximately 12 months.

However, several important scientific discoveries have been made that positively impact the clinical management of this aggressive cancer. Researchers identified a defect in a tumor suppressor gene known as the von Hippel-Lindau (VHL) gene. The VHL gene produces a protein, which suppresses several other proteins involved in angiogenesis. A malfunctioning VHL gene tips the scale in favor of tumor growth. When inactivated, the VHL gene causes up to 80% of all non-hereditary RCC cases. The VHL discovery provided researchers with several potential targets for developing novel therapies for treating mRCC, and the hunt for new compounds began.

Nexavar and Sutent also target pathways involved in tumor angiogenesis. Approved in December 2005, the small molecule tyrosine kinase inhibitor Nexavar blocks a variety of angiogenic pathways. In Phase 3 studies comparing Nexavar with placebo in previously-treated patients, the time-to-disease progression averaged 24 weeks compared with 6 weeks among those on placebo. A trend toward improved survival has also been reported in patients taking Nexavar. Adverse effects associated with Nexavar are classified as mild or moderate.

In January 2006, the FDA approved Sutent to treat mRCC. Sutent targets pathways involved in angiogenesis by inhibiting proteins in the body's cells which promote the growth of tumor blood vessels. Preliminary studies suggested that Sutent could shrink tumors and delay disease recurrence in patients previously treated with biologic therapy. In a

Phase 3 clinical trial comparing Sutent with interferon-alpha, the median time-to-disease progression more than doubled among patients receiving Sutent (11 mos vs. 5 mos, respectively). Likewise, response rates were increased among those receiving Sutent (31%) versus interferon-alpha (6%). Like Nexavar, Sutent can be administered orally on an outpatient basis and is generally well tolerated. Based on the demonstrated improvement in progression-free survival and objective response rate in patients, Sutent became the standard therapy for first-line treatment of mRCC after launch.

Torisel's chief strength among these recently launched therapeutic options lies in the survival data. At ASCO in June, S. Parasuraman and colleagues reported results from their pivotal trial comparing quality-adjusted survival without symptoms or toxicity among 626 advanced RCC patients receiving first-line therapy with Torisel, interferon-alpha, or a combination of the two [*Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5049].

Patients who received Torisel alone experienced 38% greater time without symptoms and toxicity than those who received interferon-alpha alone (6.5 mos vs. 4.7 mos respectively;  $P=.00048$ ). In addition, when results of a quality-of-life questionnaire were factored in, patients receiving Torisel alone had 23% greater quality-adjusted time without symptoms and toxicity than those who received interferon-alpha alone (7.0 mos vs. 5.7 mos, respectively;  $P=.0015$ ). There were no statistical differences in either parameter between the group of patients who received



*Until recently, no agent has shown any evidence of clinical benefit for patients with progressive mRCC after cytokine therapy.*

the combination of Torisel plus interferon-alpha and interferon-alpha alone.

In a second analysis reported at ASCO, researchers reported the correlation of survival with tumor histology, age, and prognostic risk group for treatment-naïve patients with advanced RCC receiving Torisel or interferon-alpha [*Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5033]. The authors reported that compared with interferon-alpha, Torisel increased both overall survival and progression-free survival, regardless of tumor cell type.

#### Where Torisel Falls in the Current Treatment Paradigm

Sutent and Nexavar are pretty close in terms of cost of therapy at roughly \$4600 per treatment/month, and Wyeth reports that the price for Torisel is in the range of the existing targeted agents. With all three targeted agents pricing similarly, Wyeth expects that science will guide oncologists' treatment decisions related to which is the best treatment option for a particular patient. Of the three agents, Torisel is the first and only targeted therapy that demonstrates a survival advantage in a Phase 3 randomized clinical trial. These data may make Torisel more attractive as a first-line agent.

Wyeth reports that there are a number of proposed clinical trials currently being considered to learn more about the sequencing and combination of treatment for advanced RCC, with the intent of more durable responses and potentially, even complete responses, which they note is clearly a long-term treatment goal.

The clinical trials for both Torisel and Sutent involved active comparators, while Nexavar included a placebo arm in its pivotal clinical trial. Sutent and Nexavar were each approved on the basis of significant improvement in progression-free survival, while Torisel was approved on the basis of a significant improvement (49%) in overall survival versus interferon-alpha. In addition, Torisel demonstrated a 100% improvement in progression-free survival versus interferon-alpha in poor risk advanced RCC patients.

Wyeth expects that Torisel will be used in accordance with the recently published Oncology Practice Guidelines, i.e., first-line for poor-prognosis patients (category 1) and as subsequent therapy after cytokine therapy (2A) and category 2B following tyrosine kinase inhibitors. The recently updated NCCN Guidelines for RCC also addressed the issue of first-line and subsequent therapy for advanced RCC. The latest version of the NCCN guidelines released this spring added Torisel as a first-line therapy option for both "predominant clear cell histology" and "non clear cell histology" and as a subsequent therapy option for "predominant clear cell histology."

Wyeth reports that the ideal candidate for Torisel therapy exhibits three of six of the following prognostic risk factors:

- >1 metastatic organ site
- Karnofsky performance status of 60 or 70
- Hemoglobin less than the lower limit of normal
- Corrected calcium >10 mg/dL
- Lactate dehydrogenase >1.5 times the upper limit of normal

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- <1 year from time of initial RCC diagnosis to randomization

Dr. Wayne Harris, Assistant Professor of Hematology & Oncology at Emory University Medical School, stated, “This new therapy [Torisel] is desperately needed for [advanced kidney cancer] patients and will be prescribed immediately for the many patients with no alternatives.” Community oncologist, Dr. Al Brady of Washington Hematology Oncology, Yakima, Washington, concurred with this sentiment further stating that Torisel would “compete with the oral agents [Sutent and Nexavar].”

### The Future for Torisel

Wyeth is currently conducting additional clinical trials with Torisel. Still in the development stages, the upcoming BeST trial will compare combination targeted therapy with Avastin® [bevacizumab; Genentech], Nexavar, and Torisel in advanced RCC. Progression-free survival is the primary endpoint for the study along with safety and overall survival.

In addition to ongoing studies in advanced/mRCC, researchers are evaluating the efficacy of Torisel in patients with relapsed, refractory mantle cell lymphoma in a Phase 3 trial. According to Wyeth, oncology trials “looking at IV Torisel for the treatment of brain, breast, endometrial, ovarian, skin, head and neck, and prostate cancers, as well as hematological cancers” are being conducted through a cooperative research and development agreement with the National Cancer Institute.

Wyeth continues to invest in its oncology pipeline. The company could initiate registration trials this year for three other oncology candidates in development for non-Hodgkin’s

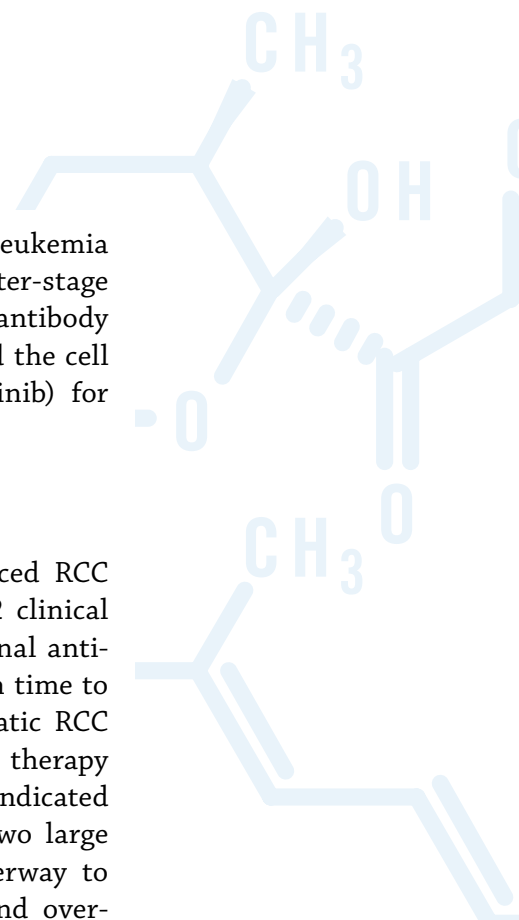
lymphoma (NHL), chronic myeloid leukemia (CML), and breast cancer. Those later-stage candidates include targeted cytotoxic antibody CMC-544 (inotuzumab) for NHL, and the cell signaling inhibitors SKI-606 (bosutinib) for CML, and HKI-272 for breast cancer.

### Future Directions for Advanced Kidney Cancer Treatment

Several other therapies for advanced RCC are in late stage trials. In a Phase 2 clinical trial, Avastin, a humanized monoclonal antibody, showed a significant increase in time to progression in patients with metastatic RCC who had either received biologic IL-2 therapy previously or for whom it was contraindicated to receive IL-2 therapy. Currently, two large randomized Phase 3 trials are underway to compare progression-free survival and overall survival in untreated patients receiving the combination of Avastin plus interferon-alpha or interferon-alpha alone. Avastin is already FDA-approved for treating colorectal and lung cancer.

In addition to Nexavar and Sutent, several new small molecule tyrosine kinase inhibitors are also being evaluated in advanced RCC, and the pipeline includes the following: AG013736 [Pfizer], pazopanib [GlaxoSmithKline], PTK787 [Novartis], imatinib [Gleevec, Novartis], gefitinib [Iressa, AstraZeneca], and erlotinib [Tarceva®, Genentech].

Combination therapy is another approach also being assessed in patients with advanced RCC. Studies are being formulated and are underway to evaluate combining therapies that target different pathways in tumor angiogenesis. One such efficacy and safety study combines Avastin with Tarceva which is cur-



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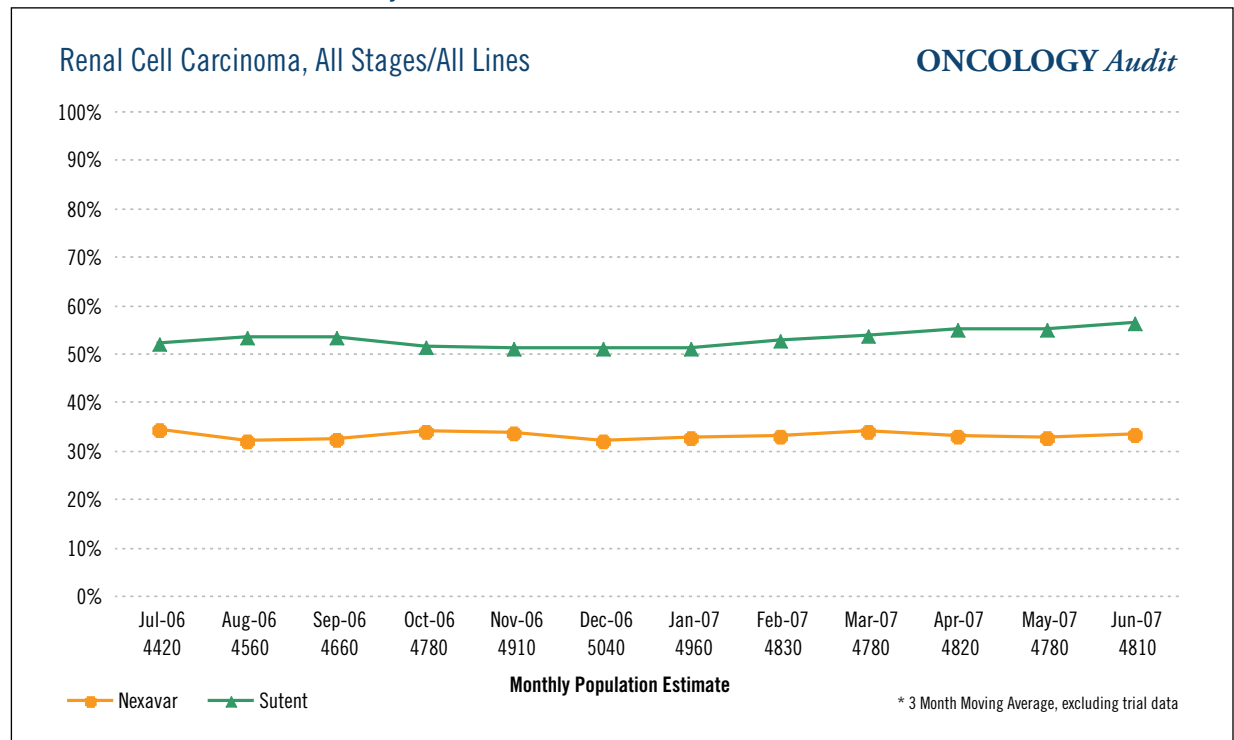
rently approved for the treatment of lung and pancreatic cancers. Previous studies in combination therapy have pointed to the importance of patient selection factors, and these studies are expected to indicate ideal patient types for that clinical strategy.

### The Targeted Therapy Marketplace

The standards of care in many cancer types are expanding to include molecular-targeted therapies. According to Datamonitor, the molecular-targeted therapy industry was worth \$7.5 billion in 2005 with the forecasted sales of already marketed therapies expected to grow to \$25.2 billion by 2015. Additional therapies introduced to the market will only increase the 2015 estimates. Datamonitor forecasts Nexavar revenues to reach \$122 million and Sutent to reach \$179 million by 2010.

As noted earlier, all three agents (Torisel, Nexavar, and Sutent) cost about the same per treatment/month. Industry analysts have estimated that Torisel could generate sales of \$50 million in 2007 and increase to up to \$400 million by 2010. Dr. Harris stressed the importance of exercising caution when predicting the success of a new cancer treatment stating, "This is a crucial time in the development of a new drug. New toxicities or unforeseen problems may arise [after the new drug comes to market]." Dr. Harris further explained, "Clinical trials test relatively small populations of carefully selected patients. Once on the market, every local oncologist will prescribe the drug to whomever they choose. That patient population is typically different than the study population." **MNF EG**

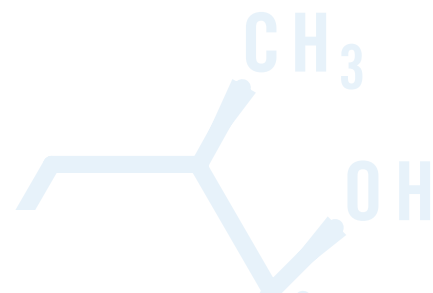
### Renal Cell Carcinoma Marketshare by Product



Source: Oncology Inc.

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### Torisel's Mechanism of Action, Packaging, and Administration

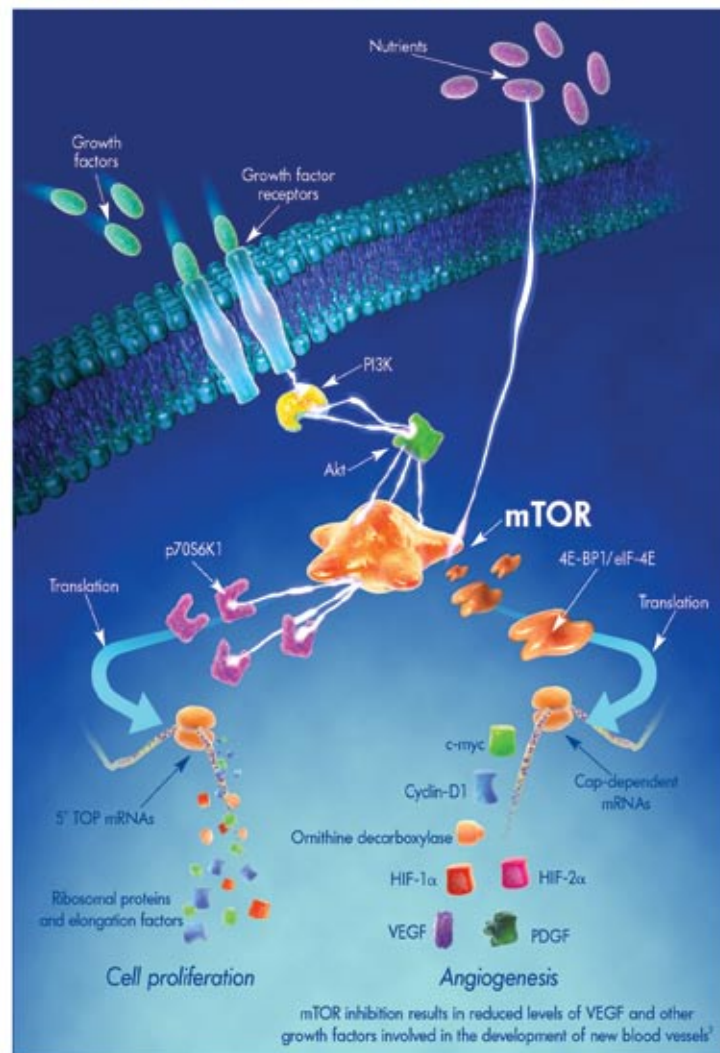
The mTOR (mammalian target of rapamycin) kinase is a protein that regulates cell proliferation, cell growth, and cell survival. Torisel is a derivative of rapamycin, which has shown pre-clinical anti-tumor effects not only in renal cancer, but in other cancer models as well. This unique MOA is exerted via a drug-protein complex when mTOR binds to the protein FKBP-12, as shown in the figure that follows.

Although the other two currently available targeted therapies are available in an oral dosage form that can be taken at home, Torisel is administered intravenously (IV) once weekly. When asked why Wyeth chose this delivery format for Torisel, Candace Steele, a spokesperson for Wyeth, explained, "We investigated an oral formulation for Torisel; however, we are developing an IV formulation of Torisel because it supports a more predictable bioavailability of the therapy in patients."

Dr. Brady indicated that the IV formulation was not necessarily negative stating, "There is a certain patient population that prefers the injection over taking pills, particularly when you are dealing with agents that are not easy to take and you have compliance problems." Dr. Harris considers "Sutent and Nexavar to be [like] chemotherapy with side effects that must be managed properly and carefully." Having already prescribed the drug through Wyeth's Expanded Access Program, Dr. Brady reports, "Our experience with it thus far is very good. [Torisel] has been well-tolerated with only mild depression of blood counts."

Torisel is packaged as a kit that contains 1 vial of Torisel for injection 25 mg/ml together with 1 vial of diluent. The administration of Torisel involves a two-step process.

A Simplified Depiction of the mTOR Pathway



Source: Wyeth. Reprinted with permission.