



Bob Oliver

VP & Global Business Manager of the Oncology Franchise at Wyeth Pharmaceuticals



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On May 30th Torisel (Temsirolimus) was approved by the FDA for patients with advanced renal cell carcinoma (RCC). Torisel is the first targeted renal cell carcinoma renal cancer therapy proven to extend median overall survival versus interferon-alpha, an active comparator, in RCC. Torisel is also entering a suddenly crowded RCC market with two targeted therapies already approved, Sutent and Nexavar, and a relatively low incidence. We spoke to the VP and Global Business Manager, Bob Oliver, in the oncology franchise at Wyeth Pharmaceuticals to better understand the launch of this new product.

OBR: *What can you tell us about the road to FDA approval for Torisel™ (temsirolimus) Injection in advanced renal cell carcinoma (RCC)?*

BO: After we completed Phase 2 studies, which were quite promising, we needed to decide which tumor types and indications to pursue, and the answer wasn't immediately obvious. After much internal deliberation, we decided on a Phase 3 program that investigated Torisel for the treatment of three tumor types: 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, we believe the Phase 3 clinical program for Torisel moved quickly.

OBR: *Torisel™ is now commercially available to hem/oncs treating RCC, right? Through which distribution channels is Torisel made available? Are you bundling it with any other oncology products, such as Neumega® (oprelvekin) or Mylotarg® (gemtuzumab ozogamicin for Injection)?*

BO: Torisel became available commercially as of July 2, 2007. The product is essentially available throughout the wholesale and GPO distribution network. There is no intent to bundle Torisel with any other products.

OBR: *How much does Torisel cost per month and how does it compare with Sutent and Nexavar?*

BO: Torisel's price is in the range of the existing targeted agents. Regarding oncologists' treatment decisions, we expect the science to guide decisions related to which is the best treatment option for a particular patient. Torisel is the first and only targeted therapy to demonstrate a "proven" survival advantage in a Phase 3 randomized clinical trial. In my view, that is the basis for selection, in addition to other considerations, i.e., patient prognostic features.

OBR: *Can you describe the FDA's requirement for how Torisel will be packaged with diluent, and how the drug is prepared for IV administration?*

BO: Torisel™ will be packaged as a "Kit" with 1 vial TORISEL™ (temsirolimus) injection 25 mg/ml together with 1 vial **cont. on pg 52** >>

DILUENT for TORISEL™. Administration of Torisel™ is a two step process:

Step 1:

Inject 1.8 mL of DILUENT for TORISEL™ into the vial of TORISEL™ (temsirolimus) injection (25mg/ml). The TORISEL™ (temsirolimus) vial contains the overfill of 0.2 mL (30 mg/1.2 mL). Due to the intentional overfill in the TORISEL™ injection vial, the drug concentration of the resulting solution will be 10 mg/mL. A total volume of 3 ML will be obtained including the overfill. Mix well by inversion of the vial. Allow sufficient time for air bubbles to subside. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in step 2 below.

The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates. The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature.

Step 2:

Withdraw the required amount of temsirolimus from the 10 mg/mL drug solution/diluent mixture prepared in step 1. Inject rapidly into a 250 mL container (glass, polyolefin, or polyethylene) of 0.9% sodium chloride injection. Mix the admixture by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.

OBR: *There was a brief delay in the FDA approval for Torisel earlier this spring, reportedly due to their request for more information regarding tumor evaluation. Can you explain?*

BO: Essentially, the FDA had additional questions about tumor evaluation, so Wyeth responded and ultimately received approval on the May 30th date instead of the original action date of April 5th.

OBR: *Can you discuss how Torisel might be used in relation to the other two new agents we previously mentioned, Sutent and/or Nexavar, to increase survival in RCC? How were the pivotal clinical trial results for Torisel different from the registration trials for Sutent and Nexavar?*

BO: There are a number of proposed clinical trials being considered to learn more about sequencing and combination treatments, with the intent of more durable responses and potentially, even complete responses—which is clearly the goal in the long run.

Torisel and Sutent both had active comparators while Nexavar had a placebo arm in its pivotal trial. Sutent and Nexavar were each approved on the basis of significant improvement in progression-free survival (PFS), while Torisel was approved on the basis of a significant improvement (49%) in overall survival versus Interferon. Although Torisel demonstrated a 100% improvement in PFS versus Interferon in poor risk advanced RCC patients.

We expect Torisel to 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.

OBR: *Can you describe Torisel's unique mechanism of action (MOA) as an mTOR inhibitor?*

BO: mTOR functions as a key controller of cell proliferation, cell growth, and cell survival. This unique MOA is exerted via a drug-protein complex when mTOR binds to the protein FKBP-12.

OBR: *Were you surprised by the registration trial findings that showed that the combination of Torisel and interferon did not result in a significant increase in overall survival when compared with interferon alone?*



BO: Yes, we were surprised with this outcome. However, the studies confirm the efficacy of Torisel as a stand-alone product in treating RCC. We are pleased with this outcome as Torisel is now an approved option for the 51,000 patients who suffer annually with renal cell carcinoma.

OBR: *Can you comment on the post-marketing commitment you've made to submit two completed study reports and data sets regarding the QT prolongation study and the ongoing hepatic impairment study?*

BO: We are on track to fulfill our commitment on both studies.

OBR: *What type of advanced RCC patient is the ideal candidate for the product?*

BO: The ideal Torisel patient 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
- < 1 year from time of initial RCC diagnosis to randomization

OBR: *What about other tumor types in which Torisel is currently being tested? Can you give us a preview of any other Wyeth oncology drug candidates that you may have in the pipeline?*

BO: There is an ongoing Phase 3 clinical trial with Torisel in mantle cell lymphoma. In addition, there are multiple ongoing trials at Cancer Treatment Evaluation Program in an array of tumor types. Wyeth could initiate registration trials this year for three oncology candidates in development for non-Hodgkin's lymphoma (NHL), chronic myeloid leukemia (CML) and breast cancer.

These 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.

As you can see, Wyeth Oncology is quite active with the vision of delivering innovative medicines that give hope to cancer patients.

OBR: *Thank you, Bob, for talking with us.*