

# Tension Rises as Three Products For Hard-to-Treat Tumors Reach a Pivotal Point

By Don Sharpe

There are certain tumor types for which it seems the incremental gains in defeating that cancer hasn't netted much upside for patients, providers, or manufacturers. For metastatic prostate cancer patients, Taxotere has made a positive impact, but over the years it seems as if the prostate cancer scales have been heavily weighed down with disappointment rather than lifted up by excitement. Another tumor type that comes to mind when discussing futility is malignant melanoma, and for small cell lung cancer (SCLC) there is only one product approved that hasn't already gone generic. However, all of that may be about to change—if all goes well in the next few months—as pivotal Phase 3 data for these three hard-to-treat tumor types will be revealed

and determine the fates of three products and three companies. Taken as a whole, this data reflects on the hope and pessimism surrounding the cancer drug development industry, and squeezes into several months a time of great risk and potential reward in the industry.

## FDA Approved Treatments in Three Tumor Types

Tumor Type	First-line Treatment	Second-line Treatment
Metastatic androgen independent prostate cancer	Taxotere (docetaxel); Novantrone (mitoxantrone)	Palliation - Emcyt (estramustine)
Malignant melanoma	Proleukin (IL-2); Adjuvant - Intron A (interferon alpha-2b)	N/A
Small cell lung cancer	Generics such as etoposide, doxorubicin, methotrexate	Hycamtin (topotecan)

## 1 ➤ Metastatic Prostate Cancer

Dendreon's Provenge could be considered the poster child for biotech promise and pitfalls. In March '07, an FDA advisory committee reviewed two completed Phase 3 studies with Provenge and recommended that the FDA approve the product, which sent Dendreon shares skyrocketing. A short while later, the FDA requested more data to support the trials' efficacy claim and Dendreon watched its shares plummet. Refusing to be defeated, the company is using a third metastatic prostate cancer study, IMPACT, to reinforce the efficacy claim and that pivotal data is scheduled to be released sometime in April.

Provenge is an active cellular immunotherapy where cells are extracted via a standard blood collection procedure, and loaded into an *Antigen Delivery Cassette* with a recombinant form of prostatic acid phosphatase (PAP), an antigen found in about 95% of prostate cancers. The Cassette is combined with the patient's own dendritic cells to generate an immune response against the antigen. Thus Provenge belongs in a completely novel class of cancer immunotherapy, and although there is a challenging track record to date, there is also a tremendous upside for stakeholders should the pivotal data be positive.

In October '08, Dendreon reported interim results of the IMPACT trial. According to the company, interim survival rates are consistent with what they observed in their two previous studies. Positive survival data from IMPACT will reinforce the previous studies' data and undoubtedly lead to a New Drug Application and a Fast Track Review from the FDA. On the other hand, a negative survival analysis for this patient population—men with metastatic, androgen independent prostate cancer—will likely put the final fork in the development of this immunotherapy and likely the entire class of immunotherapies in development for cancer treatment. **cont. on pg 12 >>**



○ — NDA

○ — PHASE 3

○ — PHASE 2

○ — PHASE 1

## 2» Metastatic Melanoma

Next up on the calendar is elesclomol, an investigative drug candidate from Synta Pharmaceuticals being studied in metastatic (stage IV) melanoma. Elesclomol is first in a class of drugs that act by increasing the level of oxidative stress in cancer cells beyond sustainability, thus inducing apoptosis. Cancer cells operate at a higher level of reactive oxygen species (ROS) than normal cells, making them more vulnerable to an agent (like elesclomol) that elevates oxidative stress. This approach represents a new way of selectively targeting and killing cancer cells.

Synta's pivotal study, SYMMETRY, is a large Phase 3 trial (N=630) comparing elesclomol in combination with paclitaxel versus paclitaxel alone. Prior to SYMMETRY, in a double-blind, randomized, controlled Phase 2 study in patients with metastatic melanoma (N=81), elesclomol plus paclitaxel hit the primary endpoint: progression-free survival ( $P = .035$ ), and doubled the median time patients survived without disease progression compared with the paclitaxel-alone arm. The response rate and overall survival also trended positively in the Phase 2 trial. SYMMETRY is the same design as the Phase 2 except it has a much larger patient enrollment.

The study has finished accrual and final results are pending and we hope to see this data in the May/June '09 timeline. The drug has received Fast Track and Orphan Drug designation from the FDA for metastatic melanoma.

## 3» Small Cell Lung Cancer

Last on the calendar, and certainly not least, is Poniard Pharmaceuticals' investigational product called picoplatin. This new generation platinum was designed to overcome platinum resistance while at the same time has lower rates of toxicities compared to other platinum—specifically, neurotoxicity and renal toxicity. Picoplatin has

demonstrated signals of efficacy in multiple cancers and treatment combinations

in more than 750 patients. It is currently under evaluation in four clinical trials for treatment of small cell lung, prostate and colorectal cancers as well as an oral formulation of picoplatin. Poniard caused a bit of a stir mid-year '08 when Phase 2 data revealed that picoplatin had a survival benefit of 27 weeks when compared with best supportive care in patients with SCLC refractory to or relapsing within 6 months of first-line platinum-based chemotherapy. Best supportive care in refractory SCLC has a median survival of 14 weeks.

The pivotal Phase 3 trial, Study of Picoplatin Efficacy After Relapse (SPEAR), is similar to the Phase 2 study—SCLC patients refractory to first-line platinum compared against best supportive care—except that the number of patients entering the trial has vastly increased from 77 in the Phase 2 to 400 in SPEAR. The Phase 3 study has completed enrollment in India and Europe, and the primary endpoint is overall survival.

## Putting it all in Perspective

Provenge has already taken us on a wild roller coaster ride, and since the FDA asked for more data in May '07 prostate cancer patient advocates have not backed down from letting everyone know they disagree with that decision. One question to ponder is: Should the FDA approve treatments for hard-to-treat tumor types while waiting for more robust data? The advocates say “give patients options”, but the opposition notes that statistics can be misleading, and that patients need to enroll in clinical trials, not opt-out for an approved alternative. Since May '07, other immunotherapy companies have seen their pivotal data fail—Cell Genesys for prostate cancer, and both Favrilite and Genitope for NHL. Dendreon is the last, hopeful, immunotherapy company still in business and they credit their clinical successes to date to their proprietary *Antigen Delivery Cassette*.

Of the three companies advancing products in this story, Synta is the only one that has a partner. In October '07, Synta and GSK signed an agreement where both will share development and commercialization in the US with elesclomol, but GSK has rights to devel-

opment and commercialization outside of the US. Is this a message that there is more credence in elescolmol's mechanism of action, or maybe more strength in the clinical development to date? It certainly means that if the pivotal data is positive, a large company with big resources can help to support and conduct a successful commercial launch.

SCLC hasn't had a new therapy approved in the first-line setting for a long time, and it has been more than 10 years since Hycamtin first received an indication in the second-line setting. Against that backdrop, Poniard Pharmaceuticals is almost ready to unveil pivotal Phase 3 data with their platinum chemotherapeutic, picoplatin. The survival benefit of 27 weeks shown in their Phase 2 study is likely to decrease in the Phase 3, but SPEAR is a big enough study that any positive results aren't likely to be tainted by statistics. SPEAR is being conducted under a Special Protocol Assessment from the FDA. Poniard says that given a positive outcome, they plan to commercialize in 2010. Results are expected late summer.

### Other Notable Mentions

Another trial to look forward to is the much-hyped C-08 study which is examining the effect of adding Avastin to Folfox in adjuvant colorectal cancer. It seems the hype has more to do with the purchase price that Roche would have to pay for Genentech if the study is positive, but reverting back to the clinical story, this has the potential to be a big win for patients and providers if there is a significant improvement in progression free or overall survival. A little further down the road is the data evaluating Nexavar plus carbo/taxol in unresectable melanoma. And lastly, as of the time we went to press, the approval of Afinitor, a novel m-TOR inhibitor, for advanced renal cell cancer is expected very soon.

In retrospect '08 seemed a little lean with exciting clinical gains, FDA outcomes, and high-risk pivotal trials, but we're making up for it early in '09. Could we go 3 for 3? Even 5 for 5? Let's hope biotech, and in particular the cancer industry, can provide some hope, excitement, and progress in the next several months.

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