Enzalutamide Improves Outcomes in Metastatic Prostate Cancer

BACKGROUND: Prostate cancer is the sixth most common cause of cancer-related death among men worldwide. Androgen receptor overexpression is common in patients with advanced prostate cancer. Suppressing androgen receptor signaling has been shown to be a successful strategy for the treatment of prostate cancer. The recently published PREVAIL trial investigated the benefit of enzalutamide, an oral androgen receptor inhibitor, in patients with metastatic castration-resistant prostate cancer (mCRPC) who had not received chemotherapy.

METHODS: PREVAIL was a multinational, double-blind, placebo-controlled, phase 3 clinical trial. Between September 2010 and September 2012, PREVAIL included 1717 chemotherapy-naïve patients with asymptomatic or with mildly symptomatic mCRPC that progressed with androgen deprivation therapy. The patients were randomly assigned to receive 160 mg daily of enzalutamide (N = 872) or placebo (N = 845); 1715 patients received at least 1 dose of a study drug. The coprimary end points were radiographic progression-free survival (PFS) and overall survival (OS). The secondary end points included the time until initiation of cytotoxic chemotherapy, the time until first skeletal-related event, the best overall soft-tissue response, the time until prostate-specific antigen (PSA) progression, and a decline in PSA of ≥50% from baseline.

RESULTS: Enzalutamide significantly reduced the risks for radiographic progression of disease and improved OS. The study was stopped after a planned interim analysis—which was conducted when 540 deaths had been reported—showed a benefit of the active treatment. The findings showed an 81% reduction in the risk for radiographic progression in the enzalutamide group (hazard ratio [HR], 0.19; P < .001). At the planned interim analysis of OS, the median follow-up time was approximately 22 months. Treatment with enzalutamide compared with placebo resulted in a 29% decrease in the risk of death (HR, 0.71; P < .001). The median OS was an estimated 32.4 months in the enzalutamide group and 30.2 months in the placebo group.

The benefit of enzalutamide was shown with respect to all of the secondary end points. For example, in patients with measurable soft-tissue disease, 59% of the patients receiving enzalutamide (20% of whom achieved complete response and 39% of whom achieved partial response) versus only 5% of patients in the placebo group had an objective response (P < .001). The researchers found that enzalutamide delayed the median time to chemotherapy initiation by 17 months; patients receiving enzalutamide did not need to initiate chemotherapy until a median of 28 months versus 10.8 months in the placebo arm (HR, 0.35; P < .001).

Enzalutamide also exhibited a favorable safety profile. The grade ≥3 adverse event rates were similar between the enzalutamide and the placebo arms (43% vs 37%, respectively), although the safety observation period was 3 times longer with enzalutamide than with placebo (17.1 months vs 5.4 months, respectively). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide.

In this phase 3 clinical trial, enzalutamide provided a clinically meaningful benefit for men with mCRPC when factoring in its reduced risk of radiographic progression of disease, improved OS, delayed initiation of chemotherapy, and excellent side-effect profile.


Commentary by Robert J. Ignoffo

Enzalutamide was approved August 31, 2012, for the treatment of metastatic prostate cancer in patients who had previously received docetaxel. Beer and colleagues report their results in patients with metastatic disease who have not been previously treated with chemotherapy. The results were very impressive in that not only did survival improve, but the objective responses improved as well. For example, complete tumor shrinkage and partial tumor shrinkage were significantly better with enzalutamide than with placebo. This is a major advance in the treatment of metastatic prostate cancer, with enzalutamide delaying the use of systemic chemotherapy while increasing the duration of a patient’s...
quality of life. This orally administered drug appears to be comparable, if not preferable, to the use of abiraterone, which necessitates the use of the systemic corticosteroid prednisone and its attendant adverse effects. Enzalutamide was very well tolerated and did not produce any extraordinary side effects.

The package insert for enzalutamide warns of significant drug interactions and recommends that the concomitant administration of enzalutamide with strong cytochrome (CY)P3A4 and CYP2CB inducers be avoided if possible.

Ibrutinib Outperforms Ofatumumab, Extends Survival in Patients with CLL

BACKGROUND: A head-to-head randomized study compared 2 recently approved therapies, ibrutinib and ofatumumab, for the second-line treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or with small lymphocytic lymphoma (SLL). Ibrutinib is a first-in-class, oral covalent inhibitor of Bruton’s tyrosine kinase, whereas ofatumumab is a monoclonal antibody that binds to the CD20 antigen on the CLL or SLL cells.

METHODS: In RESONATE, a multicenter, open-label, phase 3 clinical trial, 391 patients with relapsed or refractory CLL or SLL in whom ≥1 therapies had failed were randomized in a 1:1 ratio to receive ibrutinib (N = 195) 420 mg once daily or ofatumumab (N = 196) 300 mg intravenously at week 1, followed by 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks. The primary end point was progression-free survival (PFS), with secondary end points evaluating overall survival (OS) and response rate. The median follow-up time was 9.4 months.

RESULTS: Ibrutinib significantly improved PFS time, OS, as well as response rate. Ibrutinib significantly extended PFS, with the median not reached (88% at 6 months) at the follow-up compared with a median PFS of 8.1 months in the ofatumumab group (hazard ratio [HR], 0.22; 95% confidence interval [CI], 0.15-0.32; P <.001).

Furthermore, ibrutinib significantly improved the duration of OS (HR for death, 0.43; 95% CI, 0.24-0.79; P = 0.05), with the risk of death reduced by 57%. The OS rate was 90% at 12 months in the ibrutinib group versus 81% in the ofatumumab group.

Overall, 57 patients in the ofatumumab group whose disease had progressed had crossed over and began receiving treatment with ibrutinib at the time this analysis was conducted. The partial response rate was much higher for patients in the ibrutinib group (43%) than for patients in the ofatumumab group (4%). In the ibrutinib group, 20% of the patients showed a partial response with lymphocytosis; if these patients are included, the resulting response rate is 63%. Similar effects were observed in patients with chromosome 17p13.1 deletion or those with resistance to purine analogs.

More patients in the ibrutinib group than in the ofatumumab group had at least 1 adverse event of grade ≥3 (57% vs 47%, respectively). Adverse events (grade ≥3) that occurred more often in the ibrutinib group than in the ofatumumab group included diarrhea (4% vs 2%, respectively) and atrial fibrillation (3% vs 0%, respectively). Bleeding-related adverse events of any grade were also more common in the ibrutinib group (44%) than in the ofatumumab group (12%).

These results support ibrutinib as an effective single-agent therapy for difficult-to-treat patients with CLL or SLL given its positive effect on PFS, OS, and response rate. The improvement in survival was observed across all subgroups that were examined. Phase 3 trials examining the effect of ibrutinib in patients with previously untreated CLL or SLL are ongoing.


COMMENTARY BY ROBERT J. IGNOFFO

This study reports a major advance for ibrutinib, an oral covalent inhibitor of Bruton’s tyrosine kinase, over ofatumumab, an inhibitor of an essential enzyme in the B-cell receptor pathway. The response parameters of PFS and overall response rate are improved over the comparator. However, adverse effects were more common with ibrutinib than with ofatumumab, especially petechiae, rash, and blurred vision. This study confirms that ibrutinib is superior to ofatumumab in patients with relapsed or refractory CLL or SLL without chromosome 11q or 17p deletions. The National Comprehensive Cancer Network guidelines recommend ibrutinib as the preferred agent for relapsed or refractory CLL or SLL without chromosome 11q or 17p deletions.

Caution must be exercised with the concomitant use of ibrutinib and strong cytochrome P3A4 inhibitors. The use of ibrutinib with ketoconazole,itraconazole, voriconazole, or posaconazole should be avoided.

Panitumumab and Cetuximab Show Comparable Survival Benefit in Patients with Metastatic Colorectal Cancer

BACKGROUND: Panitumumab proved noninferior to cetuximab in overall survival (OS) in patients with chemotherapy-refractory wild-type KRAS exon 2 meta-
static colorectal cancer (mCRC), according to the results of ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab). ASPECCT is the first head-to-head, open-label, randomized, multicenter, international, phase 3 clinical study designed to determine if the 2 epidermal growth factor receptor (EGFR)-targeted monoclonal antibodies provide a comparable survival benefit in patients with mCRC.

**METHODS:** From February 2010 to July 2012, researchers enrolled patients aged ≥18 years with chemotherapy-refractory mCRC, an Eastern Cooperative Oncology Group performance status of ≤2, and wild-type KRAS exon 2 status. Of the 1010 patients enrolled, 999 began receiving the study treatment. Patients were randomized in a 1:1 ratio to receive panitumumab (N = 499) 6 mg/kg intravenously once every 2 weeks or cetuximab (N = 500) 400 mg/m² intravenously followed by 250 mg/m² weekly. The primary end point was OS. Noninferiority was determined if panitumumab preserved ≥50% of cetuximab’s OS effect compared with best supportive care. The median durations of treatment were 14.3 weeks for panitumumab and 14.1 weeks for cetuximab.

**RESULTS:** At a median follow-up of ≥9 months, the findings showed that panitumumab was noninferior to cetuximab. The median OS times were 10.4 months with panitumumab and 10 months with cetuximab (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.84-1.11; P = .007). The Z score was −3.19, meeting the criteria of noninferiority of less than −1.96. The median progression-free survival (PFS) times were also similar between panitumumab and cetuximab (4.1 months and 4.4 months, respectively; HR, 1; 95% CI, 0.88-1.14).

The incidence of adverse events of any grade was consistent across the treatment groups. Serious adverse events were reported in 30% of patients in the panitumumab group and in 34% of patients in the cetuximab group, with 35% and 36% of patients, respectively, needing dose reductions as a result of adverse events. Grade 3 or 4 skin toxicity was more common with panitumumab than with cetuximab (13% vs 10%, respectively), as was hypomagnesemia (7% vs 3%, respectively). However, infusion reactions were more common with cetuximab than with panitumumab (2% vs <0.5%, respectively). Considering the consistencies of efficacy and toxicity that were observed, small but meaningful differences in the rate of grade 3 or 4 infusion reactions and the differences in dose scheduling can guide clinician choice of anti-EGFR therapy for this patient population, concluded the researchers.


**COMMENTARY BY ROBERT J. IGNOFFO**

This is the first comparative trial of 2 first-line targeted agents, panitumumab and cetuximab, in patients with chemotherapy-refractory wild-type KRAS exon 2 mCRC. The response rates, OS, PFS, and toxicities are almost identical between these 2 agents. So, which drug is preferable? Factors that may affect drug selection include the drug cost, insurance coverage, time spent in the clinic receiving therapy, and convenience.

With regard to drug cost, the average wholesale price of panitumumab is $38,900 for 420 mg (average weight, 70 kg), administered every 2 weeks; the average wholesale price of cetuximab is $26,531 for 680 mg, followed by 425 mg (average body surface area, 1.7 m²), administered weekly for 14 weeks. Cetuximab would require twice as many clinic visits as well as twice the cost for supplies and nursing care, thus making it more inconvenient for the patient. Medicare and private insurance beneficiaries are likely to have access to either drug, whereas patients with limited insurance may opt for a less expensive treatment.

The discussion by the study’s authors and the accompanying editorial in the same issue by Waddell bring up the topic of known resistance to EGFR inhibitors in patients with KRAS exon 2, 3, and 4 mutations. This study evaluated patient tumors for only exon 2 mutations, but not exon 3 and 4 mutations. Therefore, the results of this study are somewhat blurred by the lack of important biomarker data. At this time, the selection of 1 of these EGFR inhibitors may be made on the basis of the factors mentioned above, as well as on physician and patient preferences.

Positive Outcomes for Diffuse Large B-Cell Lymphoma with Lenalidomide plus R-CHOP

BACKGROUND: Intensive high-dose chemotherapy can be used as salvage therapy for some patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The majority of patients will die from this cancer; therefore, the development of a more effective initial therapy is crucial to improving outcomes. A recent study investigated the potential benefits of adding lenalidomide to the R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) regimen (ie, R2CHOP) in patients with newly diagnosed DLBCL and the nongerminal center B-cell (GCB) phenotype. Lenalidomide has previously shown activity in patients with relapsed or refractory DLBCL with the non-GCB subtype.

METHODS: Researchers from the Mayo Clinic conducted a phase 2, open-label, single-arm study of 64 patients with newly diagnosed, untreated, stage II to stage IV CD20-positive DLBCL. For comparison, 87 patients with DLBCL who had received treatment with conventional R-CHOP were selected from the Mayo Clinic lymphoma database. This control group was treated during a similar time frame and met the same inclusion criteria as the patients in the active study group. The DLBCL molecular subtypes were determined by tumor immunohistochemistry and were classified as GCB or non-GCB. Of the 64 patients enrolled, 60 patients were eligible for response evaluation. The treatment consisted of 25-mg lenalidomide daily on day 1 to day 10 with standard R-CHOP every 3 weeks for 6 cycles. All patients received a subcutaneous injection of pegfilgrastim 6 mg on day 2 of each cycle and aspirin prophylaxis throughout the treatment period. The primary end point was event-free survival (EFS), and the secondary end points were progression-free survival (PFS) and overall survival (OS).

RESULTS: Among the 60 evaluable patients, the overall response rate was 98%, with 80% of the patients achieving a complete response. At a median follow-up of 23.5 months, the median duration of response had not yet been reached. In patients receiving the R2CHOP treatment regimen, the 24-month EFS rate was 59%. Because no patients received subsequent treatment for lymphoma before disease progression, the results for EFS and PFS were identical. The 24-month OS rate was 78%. In the patients receiving the R-CHOP regimen, the 24-month PFS and OS rates were 64% and 28%, respectively, in patients with non-GCB DLBCL versus 46% and 78%, respectively, in patients with GCB DLBCL. Conversely, no significant differences were observed in the 24-month PFS or OS rates in patients receiving the R2CHOP regimen between the non-GCB and GCB subtypes.

The R2CHOP treatment regimen was well tolerated. The most common grade ≥3 adverse events were neutropenia (88%), leukopenia (80%), and thrombocytopenia (44%). One patient had grade 5 sepsis after the first cycle of therapy.

Overall, the addition of lenalidomide to the conventional R-CHOP regimen resulted in similar PFS rates and OS rates between the non-GCB and GCB subtypes. Typically, patients with the non-GCB phenotype have poorer outcomes.


COMMENTARY BY ROBERT J. IGNOFFO

This study investigated the addition of lenalidomide to R-CHOP in patients with DLBCL. The comparator group was based on a data set of patients from the Mayo Clinic who had received the R-CHOP treatment regimen in previous trials. Improvements in the PFS and OS rates were observed primarily in patients with non-GCB DLBCL when lenalidomide was added to R-CHOP, suggesting that lenalidomide prevents resistance to R-CHOP therapy. Lenalidomide is not approved for use in patients with DLBCL, and a randomized, phase 2 trial is ongoing to confirm these results.

It is important to note that neurologic toxicity was not worse with lenalidomide plus R-CHOP than with R-CHOP alone. Furthermore, the risk for thrombosis (approximately 6% in patients with non-Hodgkin’s lymphoma) was minimal (1.6%) with the addition of low-dose aspirin.

Only a few drug interactions with lenalidomide are well documented. Lenalidomide should not be administered concurrently with itraconazole or other cytochrome P3A4 inhibitors.