Adding Antiandrogen to Radiation Therapy Extends Survival in Relapsed Prostate Cancer

BACKGROUND: Patients with prostate cancer who undergo radical prostatectomy and have disease relapse often require salvage radiation therapy, which leads to disease progression in 50% of patients. Combining radiation therapy with antiandrogen therapy has prolonged survival in certain men with intact prostates. A new study evaluated whether adding antiandrogen therapy (bicalutamide) to radiation therapy could extend overall survival after radical prostatectomy.

METHODS: This double-blind, placebo-controlled clinical trial randomized 760 patients with prostate cancer that relapsed after radical prostatectomy with lymphadenectomy to receive radiation therapy combined with 24 months of antiandrogen therapy (bicalutamide tablets, 150 mg daily) or placebo. Patients were given salvage radiation therapy within 12 weeks of randomization, with a total dose of 64.8 Gy administered in 36 daily fractions of 1.8 Gy. Placebo or bicalutamide 150 mg was administered daily since the start of radiation therapy for 24 months. The primary end point was overall survival. Secondary end points included disease-specific death, distant metastases (ie, metastatic prostate cancer), local disease progression, non–disease-specific death, any prostate cancer progression, including a second biochemical recurrence, and adverse events.

RESULTS: The median follow-up was 13 years. Adding antiandrogen therapy to radiation therapy resulted in a higher overall survival rate (76.3%) at 12 years in patients with persistent or recurrent postoperative disease compared with those who received placebo plus radiation therapy (71.3%). At 12 years, the cumulative incidence of distant metastatic prostate cancer was 14.5% in the bicalutamide group versus 23% in the placebo group; the cumulative incidence of a second biochemical recurrence was 44% compared with 67.9%, respectively. The rate of local disease progression and disease progression of any type (ie, a second biochemical recurrence) were lower in the patients who received bicalutamide than in patients who received placebo.

Multivariate analyses demonstrated that negative prognostic factors that significantly affected overall survival included receiving placebo, having a prostate-specific antigen level >1.5 ng/mL at study entry, a prostate cancer Gleason score of 8 to 10, a Karnofsky performance status of 80 or 90, and age ≥ 65 years. Adverse events were similar between the 2 groups; however, grade 1 to 3 gynecomastia occurred in 69.7% of patients who received bicalutamide versus 10.9% of those who received placebo.

The addition of antiandrogen therapy to radiation therapy resulted in increased overall survival, as well as disease-specific, and metastasis-free survival, with the higher rate of overall survival becoming more apparent in the second decade after therapy.


COMMENTARY BY ROBERT J. IGNOFFO

This placebo-controlled, randomized study showed that the addition of antiandrogen therapy to radiation can have a significant effect on the survival of patients with recurrent prostate cancer. Furthermore, the effect is long-lasting, with an increased percentage of patients who remained disease-free 12 years after therapy. To put this in perspective, we can extrapolate these results to real-life numbers of the annual mortality rate and the incidence of prostate cancer recurrence, which is approximately 26,730 deaths, and 100 cases per 100,000 people, or approximately 31,000 cases annually. Thus, there would be 11,539 fewer deaths (43% reduction) and 19,543 cases remaining progression-free compared with 31,000 cases or a 63% reduction in the number of prostate cancer recurrences annually. In addition, the incidence of a second recurrence is decreased by 35% ([68.7% – 44%]/69.7%) = 0.352.

This study is vigorous and appears to be well-designed, demonstrating that the addition of an antiandrogen treatment to radiation is an effective and safe therapy.

Venetoclax plus Rituximab an Attractive Treatment Option for Relapsed or Refractory CLL

BACKGROUND: Monotherapy with venetoclax has demonstrated robust responses and complete remission in patients with relapsed or refractory BCL-2–positive chronic lymphocytic leukemia (CLL). Encouraging synergy results from preclinical models combining venetoclax with rituximab led to this new study.

METHODS: This phase 1b-dose-escalation clinical trial included 49 patients with relapsed or refractory CLL or small lymphocytic lymphoma, all of whom received oral venetoclax in a daily, stepwise increase to target doses ranging from 200 mg to 600 mg, plus monthly infusions of rituximab (375 mg/m² in month 1, and 500 mg/m² in months 2–6). The primary end points included an assessment of the safety profile, defining a maximum tolerated dose, and determining the recommended phase 2 venetoclax dose when used in combination with rituximab. The secondary end points were an evaluation of the pharmacokinetic profile, and an analysis of efficacy (ie, overall response, duration of response, and time to tumor progression).

RESULTS: The overall response rate with venetoclax plus rituximab was 86% (42 patients); 51% of patients had a complete response (CR), and 57% of patients achieved negative marrow minimal residual disease in their bone marrow, with acceptable safety. The 2-year estimates for ongoing response and progression-free survival (PFS) were 89% and 82%, respectively. Overall, 11 patients had disease progression during therapy; 6 of these patients achieved a partial response before their CLL progressed.

The adverse event profile and pharmacokinetics of venetoclax were not significantly altered by the addition of rituximab. Grade 3 or 4 adverse events occurred at similar rates as reported in previous studies of venetoclax monotherapy, with no significant increase in the incidence or severity of neutropenia, and without an increase in the percentage of patients who had a severe infection.

The most serious adverse events included pyrexia, febrile neutropenia, lower respiratory tract infection, and pneumonia. The most common grade 3 or 4 peripheral blood cytopenias included neutropenia, thrombocytopenia, anemia, febrile neutropenia, and leukopenia.

Overall, the combination of venetoclax and rituximab was found safe and effective in this patient population and does not compromise the venetoclax dose. These results suggest that rituximab can be safely administered with venetoclax at a dose of 400 mg daily. The maximum tolerated dose of venetoclax was not defined.


According to the National Comprehensive Cancer Network (NCCN) guidelines, the current standards of care for relapsed B-cell CLL with high-risk features, such as 17p deletion (del17p), are ibrutinib monotherapy or idelalisib plus rituximab. In a phase 1b/2 clinical trial, ibrutinib monotherapy produced an estimated 75% PFS and 83% overall survival (OS) at 26 months, and an objective response rate of 68%. In a follow-up phase 3 clinical trial, ibrutinib significantly prolonged PFS and reduced mortality risk by 57%, with a partial response of 43%.

After the first planned interim analysis of a phase 3 placebo-controlled clinical trial of idelalisib plus rituximab, the study was stopped early as a result of a significant difference in the efficacy of the active combination versus rituximab plus placebo. At 12 months, the PFS and OS were significantly improved in the idelalisib arm compared with the placebo arm—81% versus 13%, and 92% versus 80%, respectively.

Venetoclax has been studied as a single drug, showing impressive activity in patients with relapsed B-cell CLL with del17p, leading to the US Food and Drug Administration (FDA) approval of venetoclax (Venclexta) in April 2016. Venetoclax is indicated for patients with CLL with del17p as detected by an FDA-approved test who received previous therapy. Venetoclax received accelerated approval for this indication based on overall response rate, and continued approval is dependent on confirmatory results of the drug’s clinical benefit. Major precautions listed in the prescribing information include tumor lysis syndrome, neutropenia, immunosuppression, and embryo-fetal toxicity.

The purpose of the current study by Seymour and colleagues was to determine whether venetoclax in combination with rituximab could improve the results of venetoclax given as monotherapy. This phase 1b study of venetoclax plus rituximab showed a comparable response rate and PFS to the standard regimens above. CRs were seen in an impressive 51% of patients. The median duration of treatment was approximately 10 months for those achieving a CR. OS was not evaluated because of additional therapies that were allowed after disease relapse associated with venetoclax. These results support the outcomes of earlier studies. Currently, the NCCN guidelines recommend venetoclax as a first-line treatment for patients with refractory CLL.

Finally, because of the risk for tumor lysis syn-
In patients with oligometastatic non–small-cell lung cancer (NSCLC), local consolidative therapy was practical, tolerable, and significantly prolonged PFS in patients with ≤3 metastases compared with maintenance therapy or observation. Overall, 13 patients had disease progression or died in the consolidative therapy group compared with 17 patients in the maintenance therapy group. The median PFS was significantly longer with consolidative therapy than with maintenance treatment (11.9 months vs 3.9 months, respectively), and at 1 year, PFS was 48% in the consolidative therapy group versus 20% in the maintenance treatment group.

No grade 4 adverse events or treatment-related deaths occurred in either treatment groups, and adverse events were similar between the 2 groups. Grade 3 adverse events in the consolidative therapy group were esophagitis, anemia, pneumothorax, and abdominal pain. Grade 3 adverse events in the maintenance therapy group included fatigue and anemia.

Commentary by Robert J. Ignoffo

Other studies have demonstrated variable results because of errors in study design, notably a selection bias involving patients who could tolerate surgery in the local consolidative group. Furthermore, previous studies were limited in their analysis by the lack of a comparison group. Therefore, more rigorous study design is needed. This study was a phase 2 randomized clinical trial with PFS as the primary end point. The Data Safety Monitoring Committee stopped this study early, because of the large difference in PFS, concluding that the probability of a significant benefit from local consolidative therapy would be 99.5% if the current trend continued.

Gómez and colleagues noted that it was not possible to perform subset analysis in patients with different molecular profiles. Local consolidative therapy was tolerated very well, and did not increase serious adverse events. Because this was a phase 2 study, crossover to other therapies was allowed; therefore, overall survival was not an end point. The results of this study strongly support a prospective phase 3 clinical trial comparing local consolidative therapy in patients with ≤3 metastases versus a standard-of-care maintenance regimen that could include a new immunotherapeutic drug.
Lutetium-177-Dotatate Extends Progression-Free Survival in Patients with Midgut Neuroendocrine Tumors

**BACKGROUND:** Limited treatment options exist for patients with advanced midgut neuroendocrine tumors that progressed during therapy with a first-line somatostatin analog. Since 1992, radiolabeled somatostatin analog treatment has demonstrated considerable therapy potential in patients with advanced, well-differentiated neuroendocrine tumors. Investigators in the multicenter NETTER-1 clinical trial sought to compare the safety and efficacy of lutetium-177 (\(^{177}\)Lu) with that of high-dose octreotide long-acting repeatable (LAR) in patients with advanced, progressive, somatostatin-receptor–positive neuroendocrine tumors of the midgut.

**METHODS:** NETTER-1 was an open-label, randomized, international, phase 3 clinical trial that randomized 229 patients with inoperable, metastasized, or locally advanced midgut neuroendocrine tumors that progressed during treatment with octreotide LAR to receive \(^{177}\)Lu-Dotatate 7.4 GBq every 8 weeks plus best supportive care or high-dose octreotide LAR 60 mg monotherapy every 4 weeks in a 1:1 ratio. The best supportive care for the \(^{177}\)Lu-Dotatate group comprised octreotide LAR 30 mg every 4 weeks for symptom control. Progression-free survival (PFS) was the primary end point. The secondary end points included the objective response rate, safety, side-effect profile, and overall survival.

**RESULTS:** \(^{177}\)Lu-Dotatate demonstrated longer PFS and was associated with fewer adverse events than octreotide LAR monotherapy. A primary analysis revealed that PFS at 20 months was an estimated 65.2% in the \(^{177}\)Lu-Dotatate group versus 10.8% in the octreotide LAR monotherapy group. Response rates were 18% in the \(^{177}\)Lu-Dotatate group compared with 3% in the octreotide LAR group, and regardless of stratification and prognostic factors (eg, tumor grade, age, tumor marker levels), \(^{177}\)Lu-Dotatate was associated with consistent treatment benefits. Overall survival was assessed in a planned interim analysis; 14 deaths occurred in patients who received \(^{177}\)Lu-Dotatate, whereas 26 deaths occurred in patients who received octreotide LAR, representing an estimated risk for death that was 60% lower in the \(^{177}\)Lu-Dotatate group than in the octreotide LAR group.

Overall, 129 patients had ≥1 adverse event associated with the trial therapy (86% of patients in the \(^{177}\)Lu-Dotatate group vs 31% of patients in the octreotide LAR group). Fatigue, asthenia, abdominal pain, and diarrhea were among the most common adverse events reported in the \(^{177}\)Lu-Dotatate group, and ≥97% were grade 1 or 2. Grade 3 or 4 adverse event rates were similar between the treatment groups, but 1%, 2%, and 9% of patients in the \(^{177}\)Lu-Dotatate group had grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia, respectively, compared with no patients in the octreotide LAR group. No renal toxic effects were reported during the observation period.


**COMMENTARY BY ROBERT J. IGNOFFO**

Most neuroendocrine tumors of the gut that have progressed after initial somatostatin therapy are incurable. There are very few options for patients whose disease relapses after initial treatment. These options include regional surgery or chemembolization; long-acting octreotide or lanreotide; everolimus; or cytotoxic chemotherapy. Patients whose disease relapsed with a somatostatin analog drug are candidates for treatment with everolimus. Everolimus was evaluated in a placebo-controlled, randomized, phase 3 clinical trial that showed a 3-fold prolongation of PFS compared with placebo, indicating a significant 52% risk reduction in favor of everolimus. The benefit of everolimus was maintained across most of the prespecified subgroups. The adverse event findings were consistent with the known safety profile of everolimus.\(^1\)

The current study by Strosberg and colleagues demonstrated that at 20 months, the radionuclide \(^{177}\)Lu-Dotatate improves PFS compared with an escalated dose of somatostatin-LAR (65% vs 11%, respectively) as well as responses (18% vs 3%). The drug also appears to have a good safety profile. These results suggest that the new drug may be considered in addition to everolimus for patients whose disease relapses with octreotide or lanreotide therapy. \(^{177}\)Lu-Dotatate is currently not included in the National Comprehensive Cancer Network guidelines, because the latest version (published September 28, 2016) predates the results of this study. These data appear to be solid enough to recommend this drug as another treatment option for patients in this setting.