Survivin, the smallest member of the inhibitors of apoptosis (IAP) gene family, functions as an essential regulator of mitosis and apoptosis as well as a promoter of tumor-associated angiogenesis.1-3 Survivin is rarely expressed in most normal adult tissues, but it is preferentially and highly expressed in a broad spectrum of human cancers.4-6 Survivin overexpression in human cancers correlates with an increased risk of metastasis, depth of invasion, and locoregional recurrence.7-11 Down-regulation of survivin may have broad therapeutic applications.

The survivin mRNA antagonist, designated EZN-3042, is a potent locked nucleic acid (LNA) antisense oligomer that specifically down-regulates survivin mRNA and protein.8-10 The oligosticker EZN-3042 is composed of 16 monomeric units, a 16-mer, of which 7 DNA nucleotides are replaced with LN nucleotides. The sequence of EZN-3042 is 5′-CAGCAGCAAGCAGCAAGCA-3′. Like LNA monomers, and lowerclass letter dots denote LNA monomers.

When transfected into tumor cells, the survivin antagonist was a highly potent inhibitor of survivin expression and function.12-13 Preferentially, EZN-3042 enhanced apoptotic and antitumor effects of taxanes.12,13 When EZN-3042 was tested in combination with subtherapeutic doses of paclitaxel in ascitic models of human lung cancer, EZN-3042 significantly enhanced apoptotic and antitumor effects of taxanes.12,13 EZN-3042 antagonized the effect of chemotherapy and resulted in a decreased tumor progression in mouse primary xenograft models of relapsed acute lymphoblastic leukemia, and in combination with chemotherapy sensitized drug-resistant cells to chemotherapeutic regimens preferentially.12,13

Single-agent EZN-3042 Results

Single-agent results were previously reported.14 EZN-3042 was generally well tolerated in 24 previously treated patients with advanced malignancies.

Dose-limiting toxicity (DLT), was observed in 2 patients who received EZN-3042 at a dose of 8 mg/kg: reversible Grade 3 increased aspartate or alanine transaminase (ALT) activity (range = 5.00 hours), the mean volume of distribution of the drug was 1.85 hours (range = 1.20-2.00 hours), the mean volume of distribution of the central compartment was 12.95 L (range = 8.35-18.59 L), and the mean clearance was 5.1 L/h (1.64-9.3 L/h).

Patient and Treatment Information

Sixteen patients received the combination regimen (Table 1). The median age was 65 years (range = 19-82 years). Of the 16 patients, 9 (56%) were men and 7 (44%) were women: 15 patients (94%) were white. Fourteen patients (88%) had an ECOG/PS performance status of 0 or 1.

Tumor types included prostate cancer (6 patients); breast cancer (3 patients); pancreatic cancer (2 patients); and NSCLC, leukemia, gastric, esophagus, colon, and skin cancer (1 patient each). The 16 patients who completed the study received between 1 and 9 cycles (median = 2). Two patients each received single-agent EZN-3042 + docetaxel after progressing on single-agent EZN-3042. Six patients were treated directly with the combination regimen.

Safety and Tolerability

EZN-3042 + Docetaxel

Adverse events

Fifteen of 16 patients (94%) had at least one treatment-emergent AE. Most AEs were Grade 1 or 2. The most commonly reported AEs (≥2 patients), regardless of relationship to study treatment, were fatigue (9 patients); neutropenia (5 patients); peripheral sensory neuropathy, allopnea (6 patients each); constipation; anorexia, and tumor pain (3 patients each); and leukopenia, diarrhea, mucosal inflammation, cough, and dyspnea (3 patients each).

Thirty-three patients (11%) who received combination treatment had Grade 3/4 AEs regardless of relationship to study treatment, the most common (1+ patients) of which were neutropenia (8 patients), leukopenia (3 patients), and peripheral sensory neuropathy (2 patients). Two patients in the 6.5 mg/kg EZN-3042 + docetaxel cohort experienced Grade 4 AEs not related to study treatment. One patient had Grade 4 neutropenia and another patient had Grade 4 obstructive airway disorder. Both of these events resolved. One patient (5 mg/kg EZN-3042 + docetaxel) died due to PD within 35 days of last dose.

Treatment-related adverse events

Thirteen patients (81%) who received combination treatment had Grade 3/4 AEs which were neutropenia (8 patients), leukopenia (3 patients), and peripheral sensory neuropathy (6 patients). Eight patients (50%) had treatment-related Grade 3/4 AEs: neutropenia (5 patients), leukopenia (4 patients), peripheral sensory neuropathy (4 patients each), and leukopenia (3 patients) (Table 2).

Eight patients (50%) had Grade 3/4 adverse events in both EZN-3042 and docetaxel. The most frequently reported treatment-related AEs (≥2 patients) were fatigue (9 patients), anorexia (5 patients), nausea (5 patients), and peripheral sensory neuropathy (4 patients each), and leukopenia (3 patients) (Table 2).

Methods

Grade 3 neutropenic fever was observed in 1 patient who received EZN-3042 (2.5 mg/kg). Grade 3/4 nausea, anorexia, and peripheral sensory neuropathy (4 patients each), and leukopenia (3 patients) (Table 2).

Patient and Treatment Information

Patient and Treatment Information

Secondary Objectives

Detect preliminary evidence of antitumor activity

EZN-3042 + Docetaxel

Objective tumor response assessed every 6 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST).

Objective tumor response assessed every 6 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST).

Results of a Phase 1, open-label, dose-escalation study evaluating the safety and tolerability of EZN-3042, a survivin messenger RNA (mRNA) antagonist, administered with or without docetaxel in adult patients with advanced solid tumors or lymphoma.

Conclusions

EZN-3042 + docetaxel was well tolerated in previously treated patients with advanced malignancies. Thirteen of 16 patients (81%) who received combination treatment had Grade 3/4 AEs which appeared to increase in a dose proportional manner. There was one partial response in a patient with prostate cancer after treatment with 2.5 mg/kg EZN-3042 + docetaxel. A window-of-opportunity study of EZN-3042 in combination with chemotherapy is ongoing in pediatric patients with relapsed acute lymphoblastic leukemia.

Pharmacokinetics

EZN-3042 + Docetaxel

Patient and Treatment Information

Table 2. EZN-3042 + Docetaxel: Treatment-Related Adverse Events Reported in ≥1 Patient

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Results (continued)

Table 3. Best Overall Response to EZN-3042 + docetaxel

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Results (continued)