

Phase 2 Study of 2-Methoxyestradiol (2ME2 or Panzem®) Administered in Combination with Bevacizumab in Patients (Pts) with Advanced Carcinoid Tumors

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ABSTRACT

Background: Recent studies suggest that carcinoid tumors are sensitive to antiangiogenic therapies. 2-Methoxyestradiol (2ME2, Panzem®) is a nonestrogenic metabolite of estradiol that has been shown in preclinical studies to have antiangiogenic activity and cause down regulation of HIF-1 α . Treatment with bevacizumab (Avastin®), a VEGF inhibitor, was associated with tumor responses and improved time to tumor progression in a randomized phase 2 study of carcinoid tumor pts. To build on these observations, we performed a phase 2 study evaluating the safety and antitumor efficacy of 2ME2 administered in combination with bevacizumab in pts with advanced carcinoid tumors.

Methods: Thirty-one pts with advanced carcinoid tumors self-administered 2ME2 (Panzem® NanoCrystal® Dispersion [NCD]) at a dose of 1000 mg by mouth four times daily. Bevacizumab 5 mg/kg was administered intravenously every other week. Pts receiving octreotide at the time of study entry continued octreotide at a stable dose level during study treatment. Restaging was performed at 8-week intervals. Pts were followed for evidence of toxicity, radiologic response (RECIST), time to tumor progression, and survival.

Results: Pt characteristics were as follows: median age 57 (range 36-76), M:F=18:13; ECOG PS 0:1=14:17. Primary tumor sites were small bowel (14), lung (5), rectum (2), duodenum (1), stomach (1), other/unknown (8). Twenty-six pts received concurrent octreotide. Pts have received a median of four 4-week treatment cycles (range 0-15). Grade 3/4 adverse events included hypertension (4:1), elevated liver function (4:0), gastrointestinal bleeding (3:0) and deep venous thrombosis (1:0). Median follow up time is 8.9 mos. No pts have achieved a partial response; 27 (87%) had stable disease, and 2 (7%) had progressive disease as their best response to therapy. Median progression-free or overall survival has not been reached.

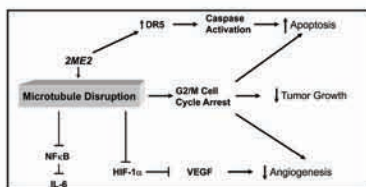
Conclusion: The combination of 2ME2 and bevacizumab is well tolerated in pts with advanced carcinoid tumors. A high rate of observed stable disease and lack of progression events at the time of this analysis suggest that 2ME2 and bevacizumab may slow tumor growth in this patient population.

BACKGROUND

- Carcinoid tumors are highly vascular
- Recent phase 2 studies with the angiogenesis inhibitors bevacizumab, sunitinib, and sorafenib have shown activity in carcinoid tumors
- 2-methoxyestradiol (2ME2, Panzem®) is an endogenous product of estradiol metabolism
- 2ME2 is an angiogenesis inhibitor
- 2ME2 causes apoptosis and G2M cell cycle arrest and can overcome drug resistance in myeloma cells
- 2ME2's activities are related to its ability to downregulate hypoxia inducible factor-1 α (HIF-1 α), its effects on cellular tubulin, upregulation of DR5 and the generation of reactive oxygen species

Figure 1: MECHANISM OF ACTION FOR 2ME2

2ME2 binds to the colchicine binding site of tubulin causing microtubule destabilization, cell cycle arrest and induction of apoptosis. Through the disruption of microtubules, 2ME2 inhibits both the activation of NF- κ B and its downstream target, IL-6 (EntreMed, unpublished data), and decreases the protein levels of HIF-1 α and its downstream target, VEGF (Mabjeesh, 2003). Inhibition of these transcription factors contribute to the antitumor and antiangiogenic properties of 2ME2.



OBJECTIVE

- To assess the safety of Panzem® NCD administered orally in combination with bevacizumab
- To evaluate the objective tumor response rate (RECIST) of Panzem® NCD + bevacizumab in advanced carcinoid tumors
- To determine the progression-free and overall survival times of patients with advanced carcinoid tumors treated with Panzem® NCD + bevacizumab

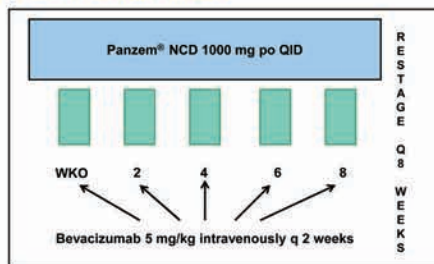
ELIGIBILITY

- Histologically documented, measurable, unresectable or metastatic carcinoid, ECOG < 2
- Adequate hepatic, renal, and hematologic function
- No history of MI or angina in last 12 months
- No major surgery within 4 weeks of study treatment
- No concurrent treatment with anticoagulants (except prophylactic warfarin)
- Prior treatment with chemotherapy (> 4 weeks prior to study treatment), chemoembolization or radioembolization is allowed.
- Patients receiving concurrent octreotide must continue at current dose level during study treatment

TREATMENT

- Panzem® NCD administered orally at 1000 mg four times daily
- Bevacizumab administered intravenously at 5 mg/kg
- Patients restaged with CT scan every 8 weeks
- Patients without evidence of progression or unacceptable toxicity were allowed to continue protocol therapy

Figure 2: TREATMENT SCHEMA



PATIENT CHARACTERISTICS (N=31)

| | |
|---------------------------|----------------|
| Median Age | 57 yrs (36-76) |
| Gender | N (%) |
| M | 18 (58%) |
| F | 13 (42%) |
| ECOG PS | |
| 0 | 14 (45%) |
| 1 | 17 (55%) |
| Tumor primary site | |
| Small bowel | 14 (45%) |
| Lung | 5 (16%) |
| Rectum | 2 (7%) |
| Duodenum | 1 (3%) |
| Stomach | 1 (3%) |
| Unknown primary | 8 (26%) |

GRADE 3 or 4 ADVERSE EVENTS

| Event | Grade 3 (%) | Grade 4 (%) |
|-------------------------------|-------------|-------------|
| Hypertension | 4 (13%) | 1 (3%) |
| Elevated Liver Function Tests | 4 (13%) | 0 |
| GI Bleeding | 3 (10%) | 0 |
| Deep Venous Thrombosis | 1 (3%) | 0 |

BEST RADIOLOGIC RESPONSE TO THERAPY

| | N=31 (%)* |
|---------------------|-----------|
| Partial Response | 0 |
| Stable Disease | 27 (87%) |
| Progressive Disease | 2 (7%) |

* 2 patients did not complete the first cycle.

Figure 3: PROGRESSION-FREE SURVIVAL

Progression-Free Survival (PFS) was measured using the Kaplan-Meier Method and was calculated from time of treatment initiation to time of progression or death. Median PFS has not been reached.

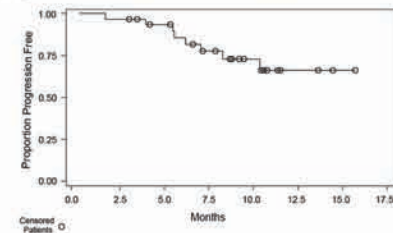
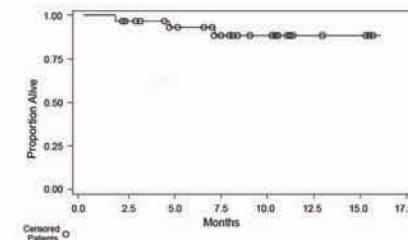


Figure 4: OVERALL SURVIVAL

Overall Survival (OS) was measured using the Kaplan-Meier Method and was calculated from time of treatment initiation to time of death. Median OS has not been reached.



CONCLUSION

- The combination of Panzem® NCD and bevacizumab is well tolerated in patients with advanced carcinoid tumors
- This combination is associated with a high rate of stable disease
- The high rate of stable disease and lack of progression events at >8 months of follow up in this patient population suggest that Panzem® NCD and bevacizumab may slow tumor growth