Clinical Evaluation of Tavocept to Decrease Diuresis Time and Volume in Dogs with Bladder Cancer Receiving Cisplatin

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Background: Transitional cell carcinoma is the most common bladder cancer of dogs. Cisplatin combined with piroxicam provides superior response rates, but unacceptable rates of nephrotoxicity. Tavocept is a chemoprotectant that has mitigated cisplatin toxicity and decreased the required infusion/diuresis volume in clinical trials in humans.

Hypothesis/Objectives: We hypothesized that Tavocept would decrease diuresis volume and time and facilitate safe administration of a cisplatin/piroxicam protocol to dogs with bladder cancer. Secondary objectives were to compare response rate and survival times to an historical comparator group treated without Tavocept.

Animals: Fourteen client-owned dogs were prospectively enrolled.

Methods: Tumor volume was measured by computed tomography at days 0, 42, and 84. Dogs received combination Tavocept/cisplatin with a shortened diuresis protocol. A total of 4 doses was planned, with concurrent administration of piroxicam. Serial biochemical analyses were evaluated for azotemia.

Results: A 90-minute infusion/diuresis time was used for all dogs. Three dogs (21%) had concurrent increases in serum creatinine (>2.0 mg/dL) and BUN (>42 mg/dL) concentrations; 2 of these dogs were isosthenuric. This frequency of nephrotoxicity is significantly less (P = 0.0406) than that of an historical control group treated without Tavocept. Overall response rate was 27%. Median survival time was comparable to historical controls (253 vs. 246 days).

Conclusions and Clinical Importance: Tavocept decreased the required diuresis time with cisplatin from > 6 hours to 90 minutes, while also decreasing occurrence of azotemia. Survival time was comparable, but the response rate was inferior to an historical comparator group. Further evaluation in other tumors susceptible to platinum agents is warranted.

Key words: Chemoprotectant; Neoplasia; Nephrotoxicity; Urogenital.

Transitional cell carcinoma (TCC) is the most common malignancy of the canine bladder, often diagnosed in a late stage of disease.1 Because of location in the trigone, localized invasion, and high metastatic rates, localized treatment options are often ineffective.1-9 Single-agent chemotherapy agents, including cisplatin, carboplatin, and vinblastine, have provided poor to modest remission rates (16, 0, and 36%, respectively), and median survival times are <6 months.4,7,10 The most effective chemotherapy protocol to date utilizes cisplatin and piroxicam, resulting in an overall response rate of 71%.11,12 In 1 study, however, 12/14 dogs experienced renal toxicity, and therefore, this combination is not used in practice.12 Other chemotherapy protocols have reported response rates of 0–58%.2-6,8,10,13-17 Although the use of a cyclooxygenase-2 selective nonsteroidal anti-inflammatory drug (NSAID) may decrease overall nephrotoxicity associated with combination therapy, cisplatin’s nephrotoxicity is not diminished and reported response rates are similar.15 Novel therapies that decrease cisplatin nephrotoxicity and allow combination therapy are necessary to more effectively treat dogs with TCC. Cisplatin chemotherapy is technically more difficult to administer in veterinary practice than an alternative platinum agent, carboplatin, because of the requirement for a prolonged saline diuresis protocol to prevent cisplatin-induced nephrotoxicity. Carboplatin does not require lengthy diuresis and, as such, is routinely substituted for cisplatin as a treatment for osteosarcoma and other solid malignancies in dogs, but the comparative efficacy of carboplatin has been questioned.15 Carboplatin has not been proven to be a superior drug for treatment of TCC in dogs,5,10,19 and...
meta-analyses suggest it is inferior to cisplatin against many malignancies in humans including non-small-cell lung cancer.20,21 Tavocept (BNP7787; disodium 2,2′-dithio-bis-ethane sulfonate) is a water-soluble disulfide form of mesna under investigation as a chemoprotectant.22–24 Tavocept is converted to mesna in the kidneys, which then locally inactivates the toxic platinum species.25 In preclinical studies, Tavocept protected against cisplatin nephrotoxicity in both rats and dogs, and the use of Tavocept before cisplatin in people allows a 75% decrease in fluid diuresis.26–28 A similar decrease in fluid diuresis volume requirements would be ideal for dogs at risk of volume overload using the standard cisplatin administration protocol. Tavocept does not contain the free thiol group that could diminish the antitumor effects of cisplatin. Furthermore, Tavocept was found to potentiate the activity of cisplatin in studies in animals and in clinical trials in humans.29–32 Therefore, the objective of our study was to determine the safety and tolerability of combination Tavocept, cisplatin, and piroxicam therapy in dogs diagnosed with TCC of the bladder using a shortened diuresis protocol.

### Materials and Methods

Client-owned dogs that were diagnosed with TCC of the urinary bladder by cytology or histopathology and were presented to the University of Missouri Veterinary Medical Teaching Hospital of any age, sex, or breed and >10 kg by body weight were eligible for enrollment with informed owner consent (University of Missouri ACUC protocol #6757). Dogs not eligible were those treated previously with chemotherapy, radiation therapy, or surgery (mass excision) or dogs with evidence of renal dysfunction (azotemia). Dogs not eligible were those treated for enrollment with informed owner consent (University of Missouri Veterinary Medical Teaching Hospital). Before treatment, all dogs were staged using thoracic radiographs and abdominal computed tomography (CT). Before abdominal imaging, the urinary bladder was catheterized, emptied of urine, and then infused with 1.5 mL/kg of sterile saline to allow for consistency in repeated tumor measurement methodology. Tumor volume was calculated by means of 3-dimensional measurements using programmed imaging system software. i Staging was repeated at days 42 and 84. Complete remission (CR) was defined as resolution of all clinical and imaging evidence of disease, partial remission (PR) was defined as >50% decrease in tumor volume with no new lesions, stable disease (SD) was defined as <50% change in tumor volume in new lesions, and progressive disease (PD) was defined as >50% increase in tumor volume or development of new lesions. Overall response rate (ORR) was defined as CR + PR.

Table 1. Infusion protocol: Tavocept is administered for 30 minutes, then in conjunction with saline for 15 minutes. A short 5-minute diuresis is then followed by cisplatin administration. A final 20-minute diuresis is performed. The entire protocol takes 90 minutes.

| Drug                  | Dosage | Time (min) |
|-----------------------|--------|------------|
| Tavocept              | 18.4 g/m² | 30         |
| Tavocept and NaCl     | 18.4 g/m², 18 mL/kg | 15         |
| 0.9% NaCl             | 18 mL/kg | 5          |
| Cisplatin and NaCl    | 60 mg/m², 18 mL/kg | 20         |
| 0.9% NaCl             | 18 mL/kg | 20         |
| Total Infusion Time   |         | 90         |

Prompted a piroxicam holiday and institution of omeprazole (0.5–1.0 mg/kg PO q48h). If BUN returned to normal, piroxicam was reinstituted and omeprazole continued. If the BUN did not return to within reference range, the piroxicam holiday and institution of omeprazole was used as a second-line NSAID and deracoxib (1–2 mg/kg PO q24h) as third-line NSAID. Complete blood counts were performed before cisplatin therapy and 1 week post-treatment. Neutrophil counts >2,500 cells/µL, platelet counts >100,000/µL, and hematoctit ≥25% were required for cisplatin treatment. Drug toxicity was graded according to standard Veterinary Cooperative Oncology Group criteria.13

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Study dogs were compared to a group of historical control dogs treated with the same dosages of cisplatin and piroxicam, but by standard diuresis protocol and without Tavocept.11 The grade of renal toxicity (none, mild, moderate, severe), objective response rate (ORR), and median survival time (MST) were compared among the studies. Renal toxicity scores were compared between historical controls and study dogs using Fischer's exact test. A $P$ value of <0.05 was considered statistically significant.

### Results

Fourteen dogs with treatment-naïve TCC were enrolled; 4 dogs were diagnosed histologically, whereas the remaining 10 dogs were diagnosed on the basis of cytology. Eight dogs completed the 12-week protocol, whereas 6 required protocol alteration or did not finish the 12-week protocol because of complications (2 dogs died from necropsy-confirmed acute renal failure or hepatic fibrosis), loss of follow-up (1 dog), withdrawn from study (2 dogs), or disease progression or no resolution of clinical signs (1 dog). The mean number of
cisplatin/Tavocept doses administered was 3.3, with a median of 4 (range 1–4). The study’s primary end point was incidence of peak serum creatinine concentration >2.0 mg/dL (Table 2). Three of 14 dogs had an increase in serum creatinine concentration >2.0 mg/dL during the course of treatment, compared to 9/14 in the historical control group. Dogs receiving Tavocept/cisplatin and piroxicam had significantly lower nephrotoxicity grade than dogs receiving cisplatin and piroxicam without Tavocept (P = 0.04). Mean baseline serum creatinine concentration and peak serum creatinine concentration were 0.74 and 1.6, mg/dL, respectively; median concentrations were 0.7 and 1.4 mg/dL, respectively. The BUN concentration increased from baseline in all 14 dogs (peak BUN range, 42–84 mg/dL), with 3/14 dogs having concurrent increase in serum creatinine concentration ≥2.0 mg/dL. Of those 3 dogs, 2 also were isoethenuric. For the increase in all dogs’ BUN, gastrointestinal bleeding was suspected as the primary cause and fecal occult blood tests were performed when feasible. Only 2 dogs had negative fecal occult blood tests or absence of gastrointestinal upset while receiving NSAIDs; the remaining dogs (12/14) had mild gastrointestinal signs (vomiting, decrease in appetite, hematochezia), melena, or a positive fecal occult blood test. All received an antacid (famotidine, omeprazole), a gastrophroptectant (sucralfate), or a combination thereof, as needed outside of the VHC. Increases in BUN were almost always attributable to NSAID therapy, as gastrointestinal clinical signs resolved after discontinuation of the NSAID; 2 dogs did have gastrointestinal upset after dietary indiscretion.

The shortened saline diuresis protocol was clinically well tolerated. All dogs were treated in 90 minutes (Fig 1), with decreased total diuretic infusion volumes compared to historically administered cisplatin (Fig 2). Without pretreatment anti-emetics, the first 2 dogs enrolled vomited after cisplatin was administered. However, after the protocol change and addition of maropitant before chemotherapy administration, no further emesis was noted during administration. Five dogs had evidence of myelosuppression, with all except 1 being mild grade I–II neutropenia or a 1-week dose delay as a consequence of insufficient neutrophil count for subsequent treatments. One dog had grade IV neutropenia and thrombocytopenia after its fourth dose of cisplatin. The dog subsequently died and necropsy disclosed fulminant pancreatitis and liver failure.

Secondary end points included ORR and MST compared to historical control dogs receiving cisplatin and piroxicam by standard protocol.11 The ORR was 27%, with no CR, 3 PR, and 8 SD; 1 patient’s imaging changes with a partial response are evaluable in Figure 3A and B. Three dogs were unevaluable because of lack of second measurement at day 42. The MST in the Tavocept group of dogs was 253 days (range, 20–983 days; Fig 4) in comparison with the MST of 246 days (range, 46–810 days) in the historical control group. Dogs in our study were only censored if they were lost to follow-up. Three early deaths were noted (dogs died or were euthanized before second measurements of their tumors could be completed; 2 of these dogs underwent necropsy). Two of these 3 dogs had serum creatinine concentration >2 mg/dL at the time of death. One dog died 20 days after starting the protocol from acute renal failure, cystic tubular degeneration, and liver fibrosis. A second died 32 days after study initiation because of interstitial nephritis, pancreatic

Table 2. Grades of nephrotoxicity were compared with historical data from Knapp et al.,11 where cisplatin was administered without Tavocept. Tavocept significantly reduced nephrotoxicity grades (P = 0.0406) in dogs receiving cisplatin and piroxicam compared to dogs not receiving the disulfide compound. Only 3/14 dogs had an increase in creatinine greater than 2.0 mg/dL in this protocol, compared to 9/14 in the historical control group.

| Grade of Nephrotoxicity | Serum Creatinine Concentration (mg/dL) | Cisplatin/Piroxicam | Tav-Cis/Piroxicam |
|-------------------------|----------------------------------------|---------------------|-------------------|
| None                    | 0.5–1.5                                | 2                   | 8                 |
| Mild                    | 1.6–2.0                                | 3                   | 3                 |
| Moderate                | 2.1–3.5                                | 8                   | 2                 |
| Severe                  | >3.5                                   | 1                   | 1                 |

Fig 1. Diuresis infusion time reduces from over 6 hours, historically, to 1.5 hours with the addition of Tavocept.

Fig 2. Tavocept reduces total diuresis volume compared to historically administered cisplatin, especially in dogs with increased body surface area.
fibrosis, and hepatic fibrosis, and a third dog died 69 days after starting the protocol as a result of progressive disease and hydroureter. Rescue or continued chemotherapy after cessation of the study was variable, as it was not part of the initial study design and often occurred outside of the VHC under treatment by other specialists or primary veterinarians. For dogs that continued treatment at the VHC, 7 dogs had continued chemotherapy. The most commonly administered single agent was mitoxantrone, followed by vinblastine. The

Fig 3. A and B Pretreatment (A) and post-treatment (B) computed tomography images in a patient treated with Tavocept and cisplatin. This specific patient had a partial response, with a 54% reduction in tumor volume; tumor is outlined with white arrows. In B, the urinary catheter is visible adjacent to the mass.

Kaplan Meier Survival Analysis

Fig 4. Kaplan-Meier curve of overall survival time in these patients as a function of time. Y-axis is survival (percentage of patients still alive). X-axis is time (days). Censoring is noted as a dot on the curve. Dogs were only censored if they were lost to follow-up.
majority of dogs continued to receive various NSAIDs intermittently until their deaths; 1 dog also received 6 fractions of palliative radiation therapy.

Discussion

Our study shows that Tavocept allows a shortened diuresis protocol for cisplatin. This approach could be transformative for private practice, because the current standard of care for administering cisplatin to dogs requires all-day hospital admission or even overnight hospitalization. Tavocept facilitated outpatient treatment and markedly decreased the infusion fluid volume requirements for cisplatin administration. This is especially clinically relevant when treating small dogs or those at risk for volume overload. Shortening diuresis from over 6 hours to 90 minutes would dramatically increase the number of patients treatable in a day, free-up staff time, and decrease the volume of cisplatin-containing urine to which personnel and clients are potentially exposed.

Because the aforementioned comparator study did not disclose all patients with azotemia, direct comparison with our study was not possible. Serum creatinine concentrations of dogs in our study appear to compare favorably to those of dogs in another study that did not receive Tavocept (Table 2). This observation is consistent with the decrease in moderate-to-severe nephrotoxicity reported here, as compared to the prior study (21% vs. 75%). Although dogs had increased serum creatinine concentrations from baseline, only 2 dogs had concurrent isosthenuria in the face of azotemia (based on serum creatinine concentrations >1.6 mg/dL). One of these patients died within 20 days of initiation of the study. On necropsy, this dog had acute renal failure, cystic tubular degeneration, and hepatic fibrosis. The other isosthenuric and azotemic patient had stable disease after cisplatin and NSAIDs still raises concerns for risk of azotemia in dogs with bladder cancer. The severity of increases in serum creatinine concentration was mitigated by Tavocept, but alleviation of increases in BUN was not achieved. A longer infusion time, along with the administration of Tavocept, may be a more appropriate protocol for use in dogs at higher risk for renal impairment.

Based on our results, we plan to incorporate Tavocept into cisplatin protocols for other tumors, especially those that do not involve simultaneous administration of an NSAID. It also would be interesting to monitor for renal toxicity in dogs with tumor types not associated with the urinary system, because it would be expected that dogs with urinary cancers may have decreased renal function secondary to the impact of their cancer on the urinary system. Our group has treated 3 dogs with osteosarcoma with this Tavocept/cisplatin combination on a compassionate-use basis and obtained encouraging preliminary data in those dogs. Interestingly, 1 dog developed azotemia after long-term carprofen administration for arthritis several months after finishing its Tavocept/cisplatin regimen. Disease-free intervals in the 3 dogs were 352 days, 350 days, and 980 days; and corresponding survival times were 483, 362, and 1031 days. We believe that Tavocept evaluation which, on ultrasound examination would likely have been considered a CR. Overall, this biologic response rate (CR, PR, and SD) was 90.9% (10/11), with only 1 evaluable dog having progressive disease. As previously stated, 3 dogs were unevaluable because of concurrent disease or not reaching repeat imaging at day 42.

After NSAID holidays, BUN often returned to within the reference range. Despite altering the NSAID used (piroxicam to deracoxib or firocoxib), most dogs continued to have increases in BUN, but without concurrent increases in serum creatinine concentration >2 mg/dL or isosthenuria. Although we did not determine that all dogs with increases in BUN but normal serum creatinine concentrations had verifiable gastrointestinal bleeding (because fecal occult blood tests were not performed on all dogs), 12/14 dogs had vomiting, diarrhea, hematemesis, hematochezia, melena, a positive fecal occult blood test result, or some combination of these. These signs repeatedly resolved with cessation of the NSAIDs.

Another study limitation is that 3 dogs were not evaluable by repeat tumor measurement using CT. Given the advanced stage of disease in many dogs before they are diagnosed and presented for treatment of bladder cancer, improvement in quality of life needs to be dramatic before clients will consent to continued therapy and anesthesia for repeated imaging. In the 2 early deaths (before day 42), it is not clear whether the concern if life-threatening renal disease was related to effects of the cancer, therapy, or both. Overall, the 21% occurrence rate of serum creatinine concentration >2.0 mg/dL is an improvement upon that historically reported with cisplatin/piroxicam (86%) or with single-agent cisplatin (50%). In both cases, cisplatin and NSAIDs still raises concerns for risk of azotemia in dogs with bladder cancer. The severity of increases in serum creatinine concentration was mitigated by Tavocept, but alleviation of increases in BUN was not achieved. A longer infusion time, along with the administration of Tavocept, may be a more appropriate protocol for use in dogs at higher risk for renal impairment.

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could have an important role in the treatment of malignancies in dogs, with decreased severity of renal toxicity and also improvement in the feasibility of administration of cisplatin.

Conclusion

We conclude that Tavocept markedly decreases the time required for saline diuresis in dogs receiving cisplatin and decreases the severity of renal toxicity, based upon serum creatinine concentrations. A 5-hour decrease in required cisplatin infusion time is clinically relevant and can facilitate the reassessment and more routine use of cisplatin chemotherapy for a variety of cancers in dogs.

Footnotes

a Tavocept, BioNumerik Pharmaceuticals Inc., San Antonio, TX; now TriviumVet, Waterford, Ireland
b Cerenia, Zoetis, Florham Park, NJ
c Cisplatin, Teva Pharmaceuticals, Mexico, MO
d Piroxicam, active principal ingredient Letco Medical, Decatur, AL; compounded at University of Missouri, Columbia, MO
e Omeprazole, Kremers Urban Pharmaceuticals, Seymour, IN
f Sucrafate, Teva Pharmaceuticals, Mexico, MO
g Piroxicam, active principal ingredient Letco Medical, Decatur, AL; compounded at University of Missouri, Columbia, MO
h Darapoxax, Novartis, East Hanover, NJ
i XiO, Elekta AB, Stockholm, Sweden
j Flesner BK, Tate DJ, Bechtel SM, et al. Tavocept/Cisplatin in Dogs 375

Acknowledgments

Conflict of Interest Declaration: Tavocept was provided by BioNumerik Pharmaceuticals, Inc., for use in this clinical trial. BioNumerik Pharmaceuticals, Inc., and its licensees hold proprietary rights with respect to Tavocept. Rights to animal health treatment indications for Tavocept have been licensed to Lantern Pharma, Inc.; L. Grubb is an employee of TriviumVet DAC.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Henry CJ. Management of transitional cell carcinoma. Vet Clin North Am Small Anim Pract 2003;33:597–613.
2. Schrempf DR, Childress MO, Stewart JC, et al. Metronomic administration of chlorambucil for treatment of dogs with urinary bladder transitional cell carcinoma. J Am Vet Med Assoc 2013;242:1534–1538.
3. Boria PA, Glickman NW, Schmidt BR, et al. Carboplatin and piroxicam therapy in 31 dogs with transitional cell carcinoma of the urinary bladder. Vet Comp Oncol 2005;3:73–80.
4. Arnold EJ, Childress MO, Fourez LM, et al. Clinical trial of vinblastine in dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 2011;25:1385–1390.
5. Knapp DW, Richardson RC, Chan TC, et al. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1994;8:273–278.
6. McMillan SK, Boria P, Moore GE, et al. Antitumor effects of deracoxib treatment in 26 dogs with transitional cell carcinoma of the urinary bladder. J Am Vet Med Assoc 2011;239:1084–1089.
7. Moore AS, Cardona A, Shapiro W, Madewell BR. Cisplatin (cis-diamminedichloroplatinum) for treatment of transitional cell carcinoma of the urinary bladder or urethra. A retrospective study of 15 dogs. J Vet Intern Med 1990;4:148–152.
8. Poirier VJ, Forrest LJ, Adams WM, Vail DM. Piroxicam, mitoxantrone, and coarse fraction radiotherapy for the treatment of transitional cell carcinoma of the bladder in 10 dogs: A pilot study. J Anim Hosp Assoc 2004;40:131–136.
9. McMillan SK, Knapp DW, Ramos-Vara JA, et al. Outcome of urethral stent placement for management of urethral obstruction secondary to transitional cell carcinoma in dogs: 19 cases (2007–2010). J Am Vet Med Assoc 2012;241:1627–1632.
10. Chun R, Knapp DW, Widmer WR, et al. Phase II clinical trial of carboplatin in canine transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1997;11:279–283.
11. Knapp DW, Glickman NW, Widmer WR, et al. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. Cancer Chemother Pharmacol 2000;46:221–226.
12. Greene SN, Lucroy MD, Greenberg CB, et al. Evaluation of cisplatin administered with piroxicam in dogs with transitional cell carcinoma of the urinary bladder. J Am Vet Med Assoc 2007;231:1056–1060.
13. Chun R, Knapp DW, Widmer WR, et al. Cisplatin treatment of transitional cell carcinoma of the urinary bladder in dogs: 18 cases (1983–1993). J Am Vet Med Assoc 1996;209:1588–1591.
14. Henry CJ, McCaw DL, Turnquist SE, et al. Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive urinary bladder carcinoma. Clin Cancer Res 2003;9:906–911.
15. Knapp DW, Henry CJ, Widmer WR, et al. Randomized trial of cisplatin versus firocoxib versus cisplatin/firocoxib in dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 2013;27:126–133.
16. Robat C, Burton J, Thamm D, Vail D. Retrospective evaluation of doxorubicin-piroxicam combination for the treatment of transitional cell carcinoma in dogs. J Small Anim Pract 2013;54:67–74.
17. Marconato L, Zini E, Lindner D, et al. Toxic effects and antitumor response of gemcitabine in combination with piroxicam in dogs with transitional cell carcinoma of the urinary bladder. J Am Vet Med Assoc 2011;238:1004–1010.
18. Moncharront C, Auberdac P, Melis A, et al. Cisplatin or carboplatin, that is the question. Bull Cancer 2011;98:164–175.
19. Alistadt SD, Rodriguez CO Jr, Boostrom B, et al. Randomized phase III trial of piroxicam in combination with mitoxantrone or carboplatin for first-line treatment of urogenital tract transitional cell carcinoma in dogs. J Vet Intern Med 2015;29:261–267.
20. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: An analysis of the literature. Ann Oncol 1998;9:13–21.
21. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: An individual patient data meta-analysis. J Natl Cancer Inst 2007;99:847–857.
22. Haasheer FH, Kochat H, Parker AR, et al. New approaches to drug discovery and development: A mechanism-based approach to pharmaceutical research and its application to
BNP7787, a novel chemoprotective agent. Cancer Chemother Pharmacol 2003;52(Suppl 1):S3–S15.

23. Hausheer FH, Parker AR, Petluru PN, et al. Mechanistic study of BNP7787-mediated cisplatin nephroprotection: Modulation of human aminopeptidase N. Cancer Chemother Pharmacol 2011;67:381–391.

24. Verschraagen M, Boven E, Ruijter R, et al. Pharmacokinetics and preliminary clinical data of the novel chemoprotectant BNP7787 and cisplatin and their metabolites. Clin Pharmacol Ther 2003;74:157–169.

25. Hausheer FH, Ding D, Fau-Shanmugarajah D, et al. Accumulation of BNP7787 in human renal proximal tubule cells. (1520–6017 (Electronic)).

26. Hausheer FH, Shanmugarajah D, Leverett BD, et al. Mechanistic study of BNP7787-mediated cisplatin nephroprotection: Modulation of gamma-glutamyl transpeptidase. Cancer Chemother Pharmacol 2010;65:941–951.

27. Masuda N, Negoro S, Hausheer F, et al. Phase I and pharmacologic study of BNP7787, a novel chemoprotector in patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol 2011;67:533–542.

28. Boven E, Westerman M, van Groeningen CJ, et al. Phase I and pharmacokinetic study of the novel chemoprotector BNP7787 in combination with cisplatin and attempt to eliminate the hydration schedule. Br J Cancer 2005;92:1636–1643.

29. Boven E, Verschraagen M, Hulscher TM, et al. BNP7787, a novel protector against platinum-related toxicities, does not affect the efficacy of cisplatin or carboplatin in human tumour xenografts. Eur J Cancer 2002;38:1148–1156.

30. Hausheer F, Bain S, Perry M, et al. Comprehensive meta-analysis of survival outcomes from two randomized multicenter trials in first-line advanced non-small cell lung cancer in patients treated with the novel investigational antitumor-enhancing and chemoprotective agent Tavocept. Asia-Pacific J Oncol Hematol 2010;2:1–13.

31. Parker AR, Petluru PN, Nienaber VL, et al. Novel covalent modification of human anaplastic lymphoma kinase (ALK) and potentiation of crizotinib-mediated inhibition of ALK activity by BNP7787. (1178–6930 (Electronic)).

32. Verschraagen M, Boven E, Torun E, et al. Pharmacokinetic behaviour of the chemoprotectants BNP7787 and mesna after an i.v. bolus injection in rats. Br J Cancer 2004;90:1654–1659.

33. Veterinary cooperative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. Vet Comp Oncol 2016;14:417–446.

34. Purysko AS, Leao Filho HM, Herts BR. Radiologic imaging of patients with bladder cancer. Semin Oncol 2012;39:543–558.