While the majority of cutaneous canine mast cell tumors (MCTs) can be treated successfully with surgery, locally recurrent, large or infiltrative tumors and those in locations not amenable to wide surgical excision can present a therapeutic challenge. Part I of this two-part article covered prognostic factors, diagnostics, and criteria for selection of canine MCT patients for treatment with toceranib phosphate (Palladia®). Treatment protocols in combination with other modalities, adverse events and quality of life issues, and the roles of the oncologist and referring veterinarian in monitoring patients treated with Palladia are covered here in Part 2.

**Treatment Protocols**

A complete review of the treatment of MCTs is beyond the scope of this discussion, which focuses on the use of Palladia in treatment protocols for dogs with Grade III MCTs and any Grade II MCTs with negative prognostic indicators. In these cases, Palladia preferably is not used as a single agent but rather as part of a protocol that can include surgery, radiation therapy, chemotherapy, and ancillary medications (see sidebar for summary of treatment options).

**IMPORTANT SAFETY INFORMATION:** During clinical studies, the most common adverse events associated with PALLADIA included: diarrhea, anorexia (including decreased appetite), lethargy, neutropenia, emesis, lameness, weight loss, musculoskeletal disorder, and blood in stool/GI bleed/hemorrhagic diarrhea. PALLADIA may cause vascular dysfunction, which can lead to edema and thromboembolism, including pulmonary thromboembolism. Serious and sometime fatal GI complications, including GI perforation, have occurred rarely in dogs treated with PALLADIA. If GI ulceration is suspected stop drug administration and treat appropriately. Children should not come in contact with PALLADIA. In addition, all individuals, including children and pregnant women, should avoid direct contact with broken or partially dissolved PALLADIA tablets or biological waste from dogs treated with PALLADIA. To report a suspected adverse reaction call Zoetis at 1-888-963-8471. See full Prescribing Information.
Dr. Gloyd: How have your treatment protocols changed since Palladia came on the market?

Dr. Garrett: Participating in the clinical trials allowed us to use Palladia and get the experience with the drug, and it allowed us to treat dogs that we could not have otherwise treated in any other way.

Dr. Thamm: Some of the adverse effects, mainly gastrointestinal (GI), that we observed during that early experience with Palladia — and communication among oncologists about what we were seeing — led to a shift towards eventual dose reductions as allowed by the label which indicates a starting dose of 3.25 mg/kg.

Dr. Gloyd: How do you determine where to set the dose?

Dr. London: We went back to the data from the original phase I study when we were dose escalating and had expanded two cohorts, one in a lower dose and one at MTD (the maximum tolerated dose) (London et al, 2003). In the pivotal study, there were also dose reductions and there was still biologic activity (London et al, 2009). As oncologists, we are typically driven to using a MTD and at the time there wasn’t as clear an understanding about a biologically relevant dose versus a MTD. We recently published a paper that evaluated the adverse event profile and pharmacokinetics of Palladia at 2.4 to 2.9 mg/kg that showed that we get a good drug exposure and a lower adverse event profile (Bernabe et al, 2013).

Dr. Klein: What is the biologically relevant dose you now recommend?

Dr. London: Based in part on the pharmacokinetic (PK) data we have, for the majority of dogs a dose of 2.5 to 2.75 mg/kg should get into the appropriate therapeutic range. I may start an old dog with comorbidities at a little lower dose.

Dr. Vail: We start at 2.75 mg/kg, and I think most of us are in the 2.5 to 2.75 mg/kg range.

Dr. Johannes: The label provides for dose modification based on toxicity observed, to a minimum of 2.2 mg/kg every other day, so the

Discussion

Surgical excision is the treatment of choice for early-stage and low- and intermediate-grade cutaneous canine MCTs. Systemic adjuvant therapy should be offered in cases of poorly differentiated and metastatic MCTs.

Adjuvant therapy refers to administration of radiation or chemotherapy, including Palladia, after surgery to remove or debulk the tumor, preferably to microscopic size. For dogs with gross (macroscopic) disease, every attempt is made to downstage the cancer to microscopic disease prior to initiation of Palladia therapy.

- If surgery is not possible, dogs can receive chemotherapy, radiation therapy, or a combination of chemotherapy and radiation therapy prior to Palladia therapy.

Chemotherapy with the combination of vinblastine and prednisone is a commonly used regimen for canine MCTs.

- Single-agent chemotherapy with lomustine is another option.

Supportive care with antihistamines, such as Benadryl (diphenhydramine); antiemetics, such as Cerenia (maropitant citrate); and antacids, such as Prilosec (omeprazole) or Pepcid (famotidine), can be helpful to address signs caused by mast cell degranulation.

Multi-agent protocols, including targeted therapy with Palladia, are now used to achieve higher response rates. Palladia is rarely used as a single agent but is incorporated into treatment protocols that can include surgery, radiation therapy, and chemotherapy.
dose we are recommending is still within the label range.

Dr. Henry: We are all used to “more is better,” but we have learned over the last 7 years that that’s not necessarily true with these targeted drugs. I’m not sure that’s something that the general group of practitioners out there knows.

Dr. Jones: I have had a couple of cases that I started at a low dose and they responded for a while and then there was recurrence of gross disease. One client actually asked me if we could just go to a higher dose. The dog was tolerating the drug well so we went up to 3.1 mg/kg, and that tumor started responding again. Has anybody else ever done this or do you just abandon Palladia if it fails at 2.4 or 2.5 mg/kg?

Dr. Vail: I have increased the dose on occasion, up to 3.25 if the dog is tolerating it.

Dr. Gloyd: Do you administer Palladia every other day (EOD) or Monday-Wednesday-Friday (MWF)?

Dr. London: I usually do MWF for three reasons: 1) I think it is easier for clients to remember, 2) easier to sequence other drugs with Palladia, and 3) less expensive.

Dr. Gloyd: I see Dr. Mitchener, Dr. Henry, and Dr. Jones agree with you, while Dr. Hohenhaus, Dr. Johannes, Dr. Vail, and Dr. Clifford generally do EOD dosing.

Dr. Thamm: It’s variable for me – I do some of both depending on the patient and owner.

Dr. Vail: We will switch to MWF dosing if adverse events occur on the EOD dosing protocol.

Dr. London: I believe that either protocol is correct, and depending on the dog and the type of cancer and therapeutic situation, I may start the dog on EOD then transition to MWF.

**CONSENSUS POINT**

Veterinary oncologists are now using a lower Palladia dose ranging from 2.5 to 2.75 mg/kg rather than the label dose of 3.25 mg/kg. The dose reduction was driven by adverse events and efficacy at the lower doses is supported by the Phase I, pivotal, and subsequent pharmacokinetic studies.

**LACK OF CONSENSUS**

Some veterinary oncologists administer Palladia on a Monday-Wednesday-Friday schedule while others use an every other day (EOD) protocol.
**Dr. Vail:** Dr. London, you mentioned giving other drugs on the days you are not giving Palladia. What drugs are you sequencing with Palladia?

**Dr. London:** Often it is prednisone, which we will administer on the days when we are not giving Palladia; or chlorambucil (Leukeran) or cyclophosphamide (Cytoxan) as part of a metronomic treatment protocol, and it’s easier for them to be given Tuesday, Thursday, and Saturday.

**Dr. Thamm:** In the Mitchell study of Palladia and metronomic cyclophosphamide, the cyclophosphamide was given every day and tolerability was fine (Mitchell, 2012). That’s generally what we do.

**Dr. Clifford:** It has been challenging learning what drugs we can add to Palladia; that’s when we often reach out to Dr. London. Dr. Vail has published a study with Palladia and piroxicam (Chon et al, 2011), but personally, I have had a hard time adding NSAIDs because of the added gastrointestinal effects and often administer them on the “off” Palladia days.

**Dr. London:** There are now several studies published looking at Palladia in combination with vinblastine (Robat et al, 2012), CCNU (Pan et al, 2014; Burton et al, 2015), and doxorubicin (Burton et al, 2015) and a study with carboplatin is underway.

To help manage the systemic effects of mast cell mediators, I put all of my MCT patients on omeprazole (Prilosec; a proton pump inhibitor) from the beginning.

**Dr. Klein:** It seems like the consensus is to use omeprazole instead of famotidine (an H2 blocker), although that has gone back and forth. But sometimes omeprazole will upset a dog’s stomach, too. I will go with famotidine if a dog can’t tolerate the omeprazole.

**Dr. Thamm:** Omeprazole is given once a day and it’s over the counter, so it’s very easy for clients. I also recommend the use of antiemetics such as Cerenia as needed for management of GI signs.

**Dr. Thamm:** All of my patients with gross disease get prednisone at 1 mg/kg EOD on the days they don’t get the Palladia. They also get an antihistamine (Benadryl) and an antacid (omeprazole).

**Dr. Garrett:** Depending on the pet — if they are in good condition and have bulky disease — sometimes I will just start Palladia along with omeprazole to see what sort of response I am going to have without prednisone. I may then add it in.

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**Ancillary therapy with antiemetics such as Cerenia and protectants such as omeprazole can be given as needed to manage disease effects and treatment side effects.**
Dr. Hohenhaus: I tend to do the opposite. I might put the pet on prednisone and see if I can get the tumors a little smaller before I add the Palladia.

Dr. Thamm: Yes, ideally I like to pretreat with prednisone for about 72 hours and then start Palladia.

Dr. Jones: In that situation, if I start them on prednisone first and if I really think it is necessary I will even give them a dose of vinblastine if I am waiting a week or two to start Palladia. I don’t hesitate to get aggressive with cytoreduction.

Dr. London: A multicenter trial evaluated Palladia plus radiation therapy and prednisone for non-resectable MCTs; this is probably what most are doing now (Carlsten et al, 2012).

Dr. Clifford: We are currently conducting a study evaluating patients that are Kit mutation positive that have the tumor removed surgically. Within 14 days after surgery patients receive 4 weeks of vinblastine and then based upon mutation status receive either four more doses of vinblastine (on an every other week basis) or move to a Palladia maintenance (4 to 6 months). We currently have >30 patients along with a contemporaneous control group of vinblastine-only patients from cases at CSU.

Dr. Thamm: Dr. Christine Mullin will be presenting the data at the next VCS meeting in 2017.

Dr. Gloyd: Do you routinely use vinblastine to treat MCTs? Most of you say yes.

Dr. Thamm: In our practice, most of our gross MCT cases end up on a study. If they don’t, I will give the owner two choices. We can try prednisone and vinblastine or we can try Palladia. With no other information, I will usually start them on chemotherapy instead of Palladia because chemotherapy is less expensive and better tolerated in our practice. In my opinion, based on the published literature, it seems that the efficacy is roughly equivalent. We conducted a trial with combined Palladia and lomustine (CeeNu) so all of our dogs receiving combination therapy were on that (Burton et al, 2015). I haven’t had any experience with Palladia and vinblastine in combination.

Dr. Vail: Is anybody using vinblastine with Palladia?

Dr. Klein: Yes, but sequentially, not concurrently.

Dr. Vail: We have published on this combination and will use this combination in some cases (Robat et al, 2012)
Dr. London: Typically what I will do in those gross disease cases is present options to the client and then we will aspirate to get a c-kit mutation status. While we are waiting for that we will start prednisone and vinblastine. If the dog is doing well, we continue with that until we max out the response and then we may flip them over to Palladia. But if they haven’t maxed out at a complete response (CR) and they are c-kit mutation positive and disease is stable, I may flip them over to Palladia to see if we can convert it to a CR. We just don’t have enough owners who are committed to doing that, and of those who are, many are in clinical trials.

Dr. Thamm: I am not using the results of c-kit mutation testing to guide therapy yet because I don’t know what the results of the ongoing study are going to be.

Dr. Gloyd: For others of you in private specialty practice, does your experience differ?

Dr. Hohenhaus: My clients would do the opposite. If I told a client that their dog has a MCT and we can’t do surgery but we can do Palladia or we could do vinblastine, they would choose the oral medication 99 times out of 100 even with potential side effects and cost of the monitoring, which is definitely more for Palladia than vinblastine. People like giving pills at home and they don’t like their pets getting injections. If the tumor shrinks and goes away, I keep giving it, and when the tumor comes back, I do something different. In the referral center setting, people who come to see me are very highly selected and are prepared for the financial commitment.

Dr. Johannes: My experience is similar. My clients are generally well informed and in many cases they have asked me about Palladia before I mentioned it. They come to me wanting Palladia for their dog. I present both options and they usually opt for Palladia.

Dr. Henry: I think a lot depends on the signalment of your patient — what comorbidities they have and how chemotherapy is going to affect that versus the effects of a TKI. The other huge factors in our practice are cost and what the owner is able to do. If the owner is going to have to travel 2 hours every time the dog is treated, it may be easier to give the owner something that they can treat with at home.
Dr. Clifford: I only see a small number of cases that are truly unresectable MCTs. Most of my cases are high grade tumors that have been excised and referred for follow up. I see cases more in the adjuvant setting. I tend to use the c-kit mutation status to make treatment decisions. If the tumor is positive for the mutation then the dog is going to receive Palladia. It takes about 10 to 14 days to get the test results back, so I will start them on vinblastine and prednisone and then I will switch them over to Palladia after four cycles. If they are c-kit negative, I just continue them on vinblastine, using Dr. Thamm’s paper as my guideline (Thamm et al, 2006).

Dr. Thamm: We are still not doing any adjuvant Palladia at all and partly it’s because we are waiting for the results of your study, Dr. Clifford. We are also waiting for the results of the AKC study, too, to see if we can make an educated guess translating what we see in gross disease to what we see in the microscopic setting.

Dr. Vail: I do use Palladia in the adjuvant setting. If a case has negative prognostic indices and I have finished off the vinblastine, I always offer Palladia as a possibility to get aggressive with the caveat that we don’t have data yet to show that it works in this setting, and about 20% of these clients opt to start Palladia in this setting. We use a slightly different protocol. We do six weekly vinblastine doses. If we are dealing with initially unresectable MCTs, we will start the vinblastine protocol and then perform cytoreductive surgery if the chemotherapy downstages the tumor enough for surgery. I tell these clients that we’ll generally give Palladia in the adjuvant setting for a minimum of a year, although that may vary.

Dr. Garrett: For my high-risk patients that have had excision, we’ll usually do the course of eight doses of vinblastine (four weekly, four every other week) with prednisone, and then after that (again, if there’s still no evidence of disease), talk about doing Palladia. I haven’t had that many cases because financially most of my clients will say no.

Dr. Jones: For high grade tumors or those with demonstrated or documented metastasis, I will recommend the c-kit PCR testing. While waiting for results I usually start vinblastine and prednisone. My schedule is like Dr. Garrett’s — eight doses total. I then recommend following with Palladia,

LACK OF CONSENSUS

While some veterinary oncologists are using Palladia in the adjuvant setting (after surgery and/or cytotoxic chemotherapy), there is no consensus on the role of c-kit mutation status in making the decision to do so.
Dr. Gloyd: How do you treat the patient with multiple MCTs?

Dr. Clifford: Dogs with multiple MCTs are a challenge, especially in cases in which the tumors have been removed surgically and keep appearing up every couple of months. In those cases, I will send the dog to a dermatologist to see if the dog is atopic, which could be a factor. I would also look at history of NSAID use. There is some unpublished and published data to suggest NSAIDs may have preventative role.

Dr. Vail: If a MCT recurs, and if it’s in an easily cut-able area in an otherwise healthy dog — not a breed at risk like a shar pei — then I tell the owner that 80% of these are curable with surgery alone but we will have a look at the mitotic index plus or minus the grade afterwards and we may be recommending some additional treatments.

Dr. Klein: Pugs get multifocal low grade mast cell disease and they live forever.

Dr. Vail: It depends whether there are two tumors or forty, and how quickly they are cropping up. It’s all anecdotal. I see the following scenarios constantly in my clinic. An owner will report that their veterinarian has cut six tumors off over the last six months or more; now, the tumors are still recurring, the owner is frustrated, or out of money, or just doesn’t want to turn their dog into a pin cushion. In these cases, based on anecdotal experience, I give a complete cycle of vinblastine and prednisone and see what happens.

Dr. Gloyd: Do you test those dogs for c-kit mutations?

Dr. London: I do, and I’ve been surprised that some of these dogs have been positive. Earlier tumors may have been read as low grade or grade II, and then the sixth tumor is positive for the mutation.

Dr. Gloyd: Do these dogs respond to Palladia?

Dr. Mitchener: I have one case that is responding, but I haven’t tested for c-kit.

Dr. London: All of my patients are also on prednisone, so sometimes it’s not clear whether the effect is due to prednisone, Palladia, or both.

Dr. Gloyd: Do you see any difference in outcomes with MCTs in general since the introduction of Palladia?

Dr. London: With aggressive multimodality therapy I think we’re doing far better. It used to be a death sentence to have an aggressive, grade III MCT. We can now increase survival in some of these dogs out to a year or longer, which is a definite improvement from the past. We can provide a better quality of life and a happier dog for a year or two, which frankly is better than we do
with many of other diseases. In the gross disease setting, the radiation/Palladia/prednisone combination has made a huge difference for some of our patients.

**Dr. Thamm:** It certainly has made a difference in my study cases (Carlsten et al, 2012) with survival out to 310 days. Radiation/Palladia/prednisone is now my go-to protocol with localized gross disease. It has changed my standard of care in that population where it’s possible to do radiation and the owner is willing to do both.

**Adverse Events**

**Dr. Gloyd:** What have you learned about adverse events associated with Palladia and how do you manage them?

**Dr. Klein:** Adverse events are much more manageable at the lower doses of Palladia than with the label starting dose.

**Dr. Vail:** Hypertension associated with Palladia use in dogs is seen in a significant percentage of cases (Tjostheim et al, 2016). Every dog that we treat with Palladia gets a baseline blood pressure and is followed. We have plenty of dogs that have developed hypertension while on Palladia but we have been able to control it medically so they can continue Palladia treatment.

**Dr. Clifford:** Are the patients clinical for hypertension? If you weren’t testing them, could you tell? I generally haven’t been testing all of my dogs for blood pressure when they come in.

**Dr. Vail:** We do it as a routine; they get a baseline blood pressure and then we follow them and we’re finding elevations that are significant enough that they require treatment.

**Dr. Klein:** In my experience, the hypertension has been high but not life threatening.

**Dr. Jones:** Most are managed on low dose enalapril once a day. I have not had problems getting these dogs controlled, and I haven’t had to put them on a drug holiday.

**Dr. London:** I don’t do a drug holiday either. If the dog has gross disease that is being managed or responding to Palladia, I don’t do a drug holiday because the dog is likely going to die of gross disease before it is going to die of hypertension of sequela like protein-losing nephropathy (PLN), so I just try to manage the PLN. In the microscopic disease setting, you have more time to address it.

**Dr. Gloyd:** Is there a time frame when you expect to see hypertension start?

**Dr. Vail:** Most of the time it happens quite regularly, and there is a data set already on this (Tjostheim et al, 2016). Furthermore, dogs with cancer already have a higher incidence of hypertension than the
normal population. We start the dog on Palladia and treat hypertension concurrently, whether it was present at diagnosis or whether it developed during Palladia therapy.

**Dr. Thamm:** Are they’re spilling protein in their urine at that same time?

**Dr. Vail:** Not necessarily, but we always look for it. In most cases, it is modest.

**Dr. Gloyd:** Is the PLN associated with the TKI drug class?

**Dr. London:** I think Palladia-induced PLN is really common; it has a very gradual onset and is easy to pick up and relatively easy to manage. While the exact mechanism of hypertension associated with Palladia is not clear, it may be directly related to inhibition of VEGF signaling pathways (Zhu et al, 2009).

**Dr. Henry:** What are you following in lab work and how often?

**Dr. Klein:** In many cases it depends on the owner’s budget. I will always get at least a total protein because that’s included with their CBC. If I see changes there then I will do a urinalysis (UA). In a perfect world, I test every 2 or 3 months.

**Dr. Jones:** I get the lab work every 6 to 8 weeks: full chemistry, urine protein:creatinine (UPC) ratio, and urinalysis, and blood pressure depending on the case.

**Dr. Hohenhaus:** My highest UPC in a dog that’s been on Palladia for nearly a year is 3.7, and it gradually crept up from 0.8, to 1.7, to 3, and so on.

**Dr. Jones:** How often do you see lameness as a side effect?

**Dr. Mitchener:** I have had two cases of muscle spasm, and they were very dramatic. The dogs become acutely painful. It resolved when the drug was stopped, and the owners did not want to put their dogs back on Palladia. I found it interesting that owners will tolerate diarrhea but they won’t tolerate the muscle spasm.

**Dr. Gloyd:** Have you have seen hepatopathy in your patients on Palladia?

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**CONSENSUS POINT**

Hypertension associated with Palladia treatment is common in dogs but may be subclinical. A baseline blood pressure should be obtained and ideally followed throughout treatment. The hypertension responds well to treatment with an ACE inhibitor.

1. Palladia-induced PLN is common. It has a gradual onset and is easy to detect and relatively easy to manage.
**Dr. Thamm:** It’s uncommon.

**Dr. London:** I don’t think I’ve seen a clinically relevant hepatopathy. We have seen elevations in liver function tests with Palladia, but they’ve been manageable by stopping the drug. We have been able to get many of these dogs back on drug and they have never been clinically affected by it, so I don’t know what it means.

**Dr. Gloyd:** Do side effects ever become so severe that you decide that the side effects are worse than the disease?

**Dr. Thamm:** It’s incredibly rare for us to be faced with that situation. I specifically tell my clients that there is a pretty high likelihood that we’re going to see some side effects, but in the vast majority of cases we can manage them either with additional medications, a drug holiday, and/or dosage adjustments.

**Dr. Clifford:** As long as the owners have that in the back of their mind, then we can adjust the doses or add in concomitant medications.

**Dr. Jones:** A lot of it comes down to client education. The client needs to understand that we’re not going to just put their dog on the drug and then see them in 6 months. They need to let us know if something comes up so we can adjust doses or add other medications. I don’t think I’ve ever had a case where I threw up my arms and said we just can’t do this anymore.

**Dr. London:** We have a Palladia handout that the clients are required to sign—and we put it in the pet’s medical record—that states what the side effects are, what their expectations should be, and what we expect them to do. We have gotten better about patient selection, too, and making sure we’re not putting dogs on Palladia that are doomed to failure because they’re already really sick to begin with. We try to intervene very early on, because sometimes owners will give up because they’ve been dealing with a chronic toxicity like diarrhea, which can ruin their quality of life. They will burn out before you have a chance to adjust the dose or the medication. That was a learning curve as well—people tolerate far more in the way of side effects in themselves than they will in their pets.

**Dr. Gloyd:** Are these clients so committed to having their pet live just a little bit longer by the time they reach you that they aren’t as concerned about cost at that point?

**Dr. Clifford:** We select for a very specific clientele, the majority of which have some idea what they’re getting into when they come to us.

**Dr. Mitchener:** I very rarely start that quality of life conversation; most of the time the client initiates
it. Most of my clients would rather get one month of quality life for their dog than 6 months of poor quality life. It’s almost a uniform verbalization.

**Dr. Hohenhaus:** People really care about their pet’s quality of life. Some of the owners that have decided to stop Palladia have been cases that I didn’t think were that bad. When we put one of these dogs on a drug holiday, the owner said the dog was back to himself, wagging his tail, way more energetic, and so on, and declined to continue with the drug. In many of these cases there was no diarrhea or vomiting, but the pet “wasn’t right,” and the owner perceived that that was a poor quality of life for their pet. In my experience, it’s not severe side effects that lead people to stop the drug, it’s the vague “not doing right” complaints.

**Dr. Klein:** I always tell owners that we’re looking for every good day there is to be had, but quality of life is the first objective. But you also have to remember that a year is a really long time if you’re a dog or a cat. Everybody’s emotional attachments are different, too. It’s different for the widow whose husband gave her the dog 15 years ago and he’s gone and her kids are gone, and she’s not going to get another dog. She wants every single good day she can have with this dog. It’s different for each case, and part of our challenge is to figure out exactly what owners want because they don’t always tell us.

**Dr. Garrett:** This fits in with the discussion with the owner about adverse events. We can tell them even though it’s very likely there will be side effects with Palladia — although it is certainly much less likely with the lower doses we are using now — we can manage them so that the quality of life is good. We’re not just trying to extend time; we absolutely want quality of life, too; and Palladia can provide that.

**Dr. Vail:** The other thing we’ve learned is to not get frustrated in that first month. When Palladia first came out we didn’t know how to manage the side effects and some owners became frustrated. I tell people it may take us a few weeks to find the right dose for their dog. It’s really important to point that out to clients — give us a month and don’t get frustrated up front.

**CONSENSUS POINT**

When considering treatment options for their dog’s MCT, the pet’s quality of life is paramount to owners.

1. Setting client expectations is an important part of Palladia therapy. Owners must be told that while side effects are likely, these issues can be managed with dose reductions, a drug holiday, and ancillary medications to provide a good quality of life for the pet, but there may be an adjustment period.

2. So many patients in the gross disease setting also have comorbidities. For a while everything that we saw in those patients was blamed on Palladia while it was...
clearly the disease progression that was causing it. In the field study, all the dogs had major side effects on placebo (London et al, 2009). That was a really important learning experience, but one that we obviously didn’t take home because everything was blamed on Palladia. The bias that some people come in with when they’ve read about terrible side effects has been a huge challenge to overcome.

Monitoring

**Dr. Gloyd:** What is your protocol for monitoring dogs during Palladia treatment for MCTs?

**Dr. Hohenhaus:** When we first started with Palladia we were checking patients after the first week. I didn’t find that to be useful because they’re usually not having problems at that point. Now I see them in 2 weeks and if they’re doing really well then I might not see them for a month. If anything is not okay then I am going to bring them back 2 weeks after that. I usually see them monthly after that because if we’re managing bulky mast cell disease you need to keep tabs on what the tumor is doing and how the pet is doing.

**Dr. Henry:** I only write the prescription for the first 2 weeks of treatment so if they come back and they’re having problems and we need to alter the dose we can do that.

**Dr. Gloyd:** What are you doing in terms of lab work?

**Dr. Klein:** If you’re seeing them monthly, usually a complete blood count (CBC) every time and a biochemical profile and urinalysis every other month.

**Dr. Thamm:** For us the cost difference between checking four things and checking twenty is minimal so we check the entire chemistry.

**Dr. Gloyd:** Is it any different in private practice?

**Dr. Mitchener:** I see them day one, 2 weeks, 4 weeks, and then 6 weeks. At the 4-week and 6-week rechecks, I like to get a CBC, chemistry panel, and UA with reflex urine protein:creatinine ratio (UPC).

**Dr. Jones:** I think everybody has gone to a 2-week first recheck. I also do the same thing as far as blood work, on rechecks every 6 weeks: full chemistry, UA, UPC, and blood pressure.

**Dr. Thamm:** If the owner doesn’t think that they can commit to the recheck schedule I lay down, or doesn’t want to pay for monitoring, I don’t recommend that they put their dog on the drug. It’s a commitment of time and money.

CONSENSUS POINT

Owners should bring their dogs back for the first recheck appointment 2 weeks after starting the drug, with subsequent rechecks at 4 and 6 weeks. Lab work at each of these visits, and then every 6 weeks after that, should include CBC, chemistry profile, and urinalysis.

**Dr. Gloyd:** What is the role of the referring veterinarian (rDVM)?

**Dr. Jones:** In my experience, almost all follow-up care is provided by the veterinary oncologist. If an owner has a problem when I’m not
available, however, I have instructed them to go right to their veterinarian.

Dr. Hohenhaus: Our patients see us for the rechecks, not the rDVM, which causes some friction because the appointment with the rDVM is usually less expensive. What some owners really want is to go to their regular veterinarian, get the blood work and then fax the blood work to me to interpret and call the rDVM, who then writes the prescription for Palladia. If the owner won’t come back to us for rechecks, we don’t put their dog on Palladia. I don’t want to be managing a pet without ever seeing it.

Dr. Henry: That’s what we do, or else we won’t write the prescription. I usually like to see them back at 2 weeks because you get a chance to hear what they’ve been seeing at home and you’re not getting it third person from the rDVM. I think if you’re going to have problems there will be an indication within that first 2 weeks.

Dr. Thamm: We may have the rDVM do the 2- and 4-week rechecks but we want them to see us for that 6-week recheck. Then we usually see them every 6 weeks after that.

Dr. Johannes: I do once a month for the first 3 months and then every 6 weeks.

Dr. Klein: I usually do, too, but every 6 weeks would be fine. I like to weigh them on the same scale, too, because weight is truly indicative of how they’re doing.

Dr. Thamm: We draw our clients from a 300-mile radius so I do a lot of tag teaming with the rDVMs. I tell clients to go see their regular veterinarian in 2 weeks for a body weight and a CBC. If anything happens before then, the owner should call us. In order to make it at all feasible for the owners, we do work closely with the rDVMs.

Dr. London: We also draw from a large demographic, so if the client has to drive 3 or 4 hours to get here, we will alternate rechecks every month with the rDVM. Most of them work well with us and I think it’s a good learning experience for them as well. It’s a happy medium: you maintain contact with clients; you get to see the pet and get to keep them on drug; and the rDVMs are learning as well.

Dr. Gloyd: In these cases where clients may be several hours away, how are you helping the rDVMs manage adverse events?

Dr. Thamm: We instruct owners to call us first, and not the rDVM, if there are adverse events. I would not leave it up to the rDVM to manage; I feel it’s my respon-

CONSENSUS POINT

The veterinary oncologist is primarily responsible for monitoring and follow-up care during Palladia treatment. The rDVM’s role is to work closely with the veterinary oncologist to monitor for and report adverse events.

Dr. Klein: How often do your patients need a drug holiday or dose reduction?

Dr. Hohenhaus: Dr. London made it very clear at the beginning of
the Palladia clinical trials that if the dog is not acting right, stop the drug. That is a complete paradigm shift for oncologists. It’s hard for people to stop giving a drug that they think is going to save their pet’s life, so convincing them to take a drug holiday has sometimes been a challenge.

Dr. Clifford: We generally add information to the label of the prescription to state “If there are abnormal gastrointestinal signs — usually the most common side effect — just stop the medication and contact the Oncology service.”

Dr. Henry: Yes, that’s what I tell clients. The problem is that some of these dogs have other reasons that they could be feeling sick, too.

Dr. Thamm: For me, slightly less than half of cases will need a drug holiday or a dose reduction.

Dr. Hohenhaus: The dogs that I’ve treated with vinblastine followed by Palladia that had bad prognostic indicators tend to do well initially. After a couple of months on Palladia, that’s when I see those dogs have GI upset or weight loss, or vomiting; it’s not always right up front in the microscopic disease adjuvant setting. With bulky disease, it’s difficult to know whether it’s the tumor or the drug. In the cases with microscopic disease, I have to think it is the drug.

Dr. London: I tell owners that their dog will likely have a side effect; it may be very mild, maybe just an episode of diarrhea, but expect a side effect. We do tell them that you may need to stop the drug for a period of time. About 50% to 75% of our MCT patients skip a dose or have a week off so we can get things adjusted. I think sometimes they need to wash out of the drug so they can reset themselves and then restart.

Dr. Gloyd: After the drug holiday, can you usually continue on, or does it tend to be an on-again, off-again phenomenon with these cases from that point on?

Dr. London: It depends on the patient, the burden of disease, and the comorbidities. Some dogs have intermittent diarrhea that we’re treating and then when it comes back, I stop the Palladia and wash them out and then put them on an antidiarrheal drug for the duration of their treatment.

Dr. Gloyd: Do you tend to reduce the Palladia dose after a drug holiday?

Dr. London: I usually don’t. If the Palladia dose is between 2.5 and 2.75 mg/kg and the tumor is responding, and the problem is just some mild diarrhea or vomiting, I usually add something else in such as metronidazole, metoclopramide, or Cerenia. I have some dogs that get Cerenia the day they get Palladia. Every dog is a little bit different.

CONSENSUS POINT

Adverse events, mostly mild to moderate gastrointestinal, necessitating a drug holiday occur in about 50% of canine MCT patients on Palladia.

Dr. Gloyd: After the drug holiday, can you usually continue on, or does it tend to be an on-again, off-again phenomenon with these cases from that point on?

Dr. London: It depends on the patient, the burden of disease, and the comorbidities. Some dogs have intermittent diarrhea that we’re treating and then when it comes back, I stop the Palladia and wash them out and then put them on an antidiarrheal drug for the duration of their treatment.

Dr. Gloyd: Do you tend to reduce the Palladia dose after a drug holiday?

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Final Thoughts

Dr. Clifford: We all have had cases where the response is just phenomenal, much more than you would have seen with any other drug. I have had cases where the dog had extensive disease and I’ve
been able to watch the disease essentially, or at least palpably, disappear over a very short time.

**Dr. Hohenhaus:** In a gross disease setting, sometimes we see a response right away and everyone is happy. Other times it may take 4 weeks to see a response. If the pet is not having adverse events and the tumor is not getting worse, I try to get the owners to hang on and not declare failure on the first recheck. It’s common that it may take longer than the owners had anticipated.

**Dr. Henry:** With Palladia, I see MCTs as a potentially long-term treatable disease. It used to be you gave patients vinblastine for a set amount of weeks or you had a certain protocol that you ran to its end, and then you didn’t know where to go from there. We have had dogs on Palladia for a long, long time and it becomes more of a chronic disease treatment situation, which is not how we have traditionally thought of mast cell disease.

**Dr. Klein:** For me, the huge relief came when efficacy was retained at the lower doses and the adverse events became so much more manageable.

**Dr. Clifford:** For me, it’s the ability to provide personalized medicine. In the past, we mainly had chemotherapy. Now, with TKIs, we can potentially tailor a protocol towards a specific patient, on a basic level at least, if we find out the patient has a mutation and we have a drug that we know likely has a higher response rate with that mutation. Whether it’s truly better, we don’t know yet; we’ll have to see long term.

**Dr. Mitchener:** It’s just nice to have choices and options to offer to clients. Now, if you have a treatment fail, you have another option, a backup plan.

**Dr. Jones:** Palladia has added another valuable tool for oncologists. This is especially true in the setting of high grade MCT where the best outcomes are seen with aggressive multi-modality therapy. It also provides a treatment option for those owners that may be aversive to traditional injectable “chemotherapy” because of personal experience or misnomers that translate from the human oncology experience to veterinary patients. The lower and manageable side-effect profile on the lower effective dose helps make it attractive to these clients as well.

**Dr. Thamm:** Our toolbox of choices is definitely a lot deeper than it was seven years ago and Palladia is certainly a big part of that.

IMPORTANT SAFETY INFORMATION: During clinical studies, the most common adverse events associated with PALLADIA included: diarrhea, anorexia (including decreased appetite), lethargy, neutropenia, emesis, lameness, weight loss, musculoskeletal disorder, and blood in stool/GI bleed/hemorrhagic diarrhea. PALLADIA may cause vascular dysfunction, which can lead to edema and thromboembolism, including pulmonary thromboembolism. Serious and sometime fatal GI complications, including GI perforation, have occurred rarely in dogs treated with PALLADIA. If GI ulceration is suspected stop drug administration and treat appropriately. Children should not come in contact with PALLADIA. In addition, all individuals, including children and pregnant women, should avoid direct contact with broken or partially dissolved PALLADIA tablets or biological waste from dogs treated with PALLADIA. To report a suspected adverse reaction call Zoetis at 1-888-963-8471. See full Prescribing Information.
References


PALLADIA tablets are indicated for the treatment of Patnaik grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement in dogs.

Dosage and Administration:
Administer an initial dosage of 3.25 mg/kg (1.48 mg/lb) body weight, orally every other day for the first 6 weeks and approximately every 6 weeks, thereafter. PALLADIA may be administered with or without food. Do not split tablets.

Table 1. 3.25 mg/kg Dose Chart

<table>
<thead>
<tr>
<th>Dog Body Weight</th>
<th>Number of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pounds</td>
<td>Kilograms</td>
</tr>
<tr>
<td>11.0 – 11.8</td>
<td>5.0 – 5.3</td>
</tr>
<tr>
<td>11.9 – 15.2</td>
<td>5.4 – 6.9</td>
</tr>
<tr>
<td>15.3 – 18.5</td>
<td>7.0 – 8.4</td>
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<tr>
<td>18.6 – 22.0</td>
<td>8.5 – 10.0</td>
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<tr>
<td>22.1 – 25.4</td>
<td>10.1 – 11.5</td>
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<td>25.5 – 28.7</td>
<td>11.6 – 13.0</td>
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<tr>
<td>28.8 – 32.2</td>
<td>13.1 – 14.6</td>
</tr>
<tr>
<td>32.3 – 35.5</td>
<td>14.7 – 16.1</td>
</tr>
<tr>
<td>35.6 – 38.8</td>
<td>16.2 – 17.6</td>
</tr>
<tr>
<td>38.9 – 42.3</td>
<td>17.7 – 19.2</td>
</tr>
<tr>
<td>42.4 – 45.6</td>
<td>19.3 – 20.7</td>
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<tr>
<td>45.7 – 50.7</td>
<td>20.8 – 23.0</td>
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<td>50.8 – 59.3</td>
<td>23.1 – 26.9</td>
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<td>59.4 – 65.9</td>
<td>27.0 – 29.9</td>
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<td>66.0 – 71.2</td>
<td>30.0 – 32.3</td>
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<td>71.3 – 76.3</td>
<td>32.4 – 34.6</td>
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<td>76.4 – 79.6</td>
<td>34.7 – 36.1</td>
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<td>79.7 – 84.7</td>
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<td>84.8 – 94.8</td>
<td>38.5 – 43.0</td>
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<td>94.9 – 105.0</td>
<td>43.1 – 47.6</td>
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<td>105.1 – 110.0</td>
<td>47.7 – 49.9</td>
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<td>110.1 – 113.5</td>
<td>50.0 – 51.5</td>
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<td>113.6 – 118.6</td>
<td>51.6 – 53.8</td>
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<td>118.7 – 128.8</td>
<td>53.9 – 58.4</td>
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<td>128.9 – 138.9</td>
<td>58.5 – 63.0</td>
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<td>139.0 – 144.0</td>
<td>63.1 – 65.3</td>
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<tr>
<td>144.1 – 157.6</td>
<td>65.4 – 71.5</td>
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<tr>
<td>157.7 – 173.1</td>
<td>71.6 – 78.5</td>
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<td>173.2 – 177.9</td>
<td>78.6 – 80.7</td>
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<tr>
<td>178.0 – 191.6</td>
<td>80.8 – 86.9</td>
</tr>
<tr>
<td>191.7 – 220.5</td>
<td>87.0 – 100.0</td>
</tr>
</tbody>
</table>

Contraindications:
Do not use in dogs used for breeding, or for pregnant or lactating bitches (see Clinical Pharmacology).

Warnings:
PALLADIA may cause vascular dysfunction which can lead to edema and thromboembolism, including pulmonary thromboembolism. Discontinue drug until clinical signs and clinical pathology have normalized. To assure vasculature homeostasis, wait at least 3 days after stopping drug before performing surgery (see Adverse Reactions).

Serious and sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred rarely in dogs treated with PALLADIA (see Adverse Reactions). If gastrointestinal ulceration is suspected, stop drug administration and treat appropriately.

Human Warnings:
NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Children should not come in contact with PALLADIA. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering PALLADIA and wear protective gloves to prevent direct contact with feces, urine, vomit, and broken or moistened PALLADIA tablets. Place all waste materials in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician. Gastrointestinal discomfort such as vomiting or diarrhea may occur if this drug is accidentally ingested.

Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions. (See handling instructions above.) PALLADIA, like other drugs in its class, prevents the formation of new blood vessels in tumors. In a similar manner, PALLADIA may affect blood vessel formation in the developing fetus and may harm an unborn baby (cause birth defects). For pregnant women, accidental ingestion of PALLADIA may have adverse effects on pregnancy.

Precautions:
Temporarily discontinue the use of PALLADIA if anemia, azotemia, hypoalbuminemia, and hyperphosphatemia occur simultaneously. Resume treatment at a dose reduction of 0.5 mg/kg after 1 to 2 weeks when values have improved and albumin is >2.5 g/dL. Temporary treatment interruptions may be needed if any one of these occurs alone: hematocrit <26%, creatinine >2.0 mg/dL or albumin <1.5 g/dL. Then resume treatment at a dose reduction of 0.5 mg/kg once the hematocrit is >30%, the creatinine is <2.0 mg/dL, and the albumin is >2.5 g/dL.

Temporarily discontinue the use of PALLADIA if neutrophil count is <1000/μL. Resume treatment after 1 to 2 weeks at a dose reduction of 0.5 mg/kg, when neutrophil count has returned to >1000/μL. Further dose reductions may be needed if severe neutropenia recours.
The presence of systemic mast cell tumor prior to treatment may predispose a dog to clinically significant mast cell degranulation with possible severe systemic adverse reactions when treated with PALLADIA. Attempts should be made to rule out systemic mastocytosis prior to initiation of treatment with PALLADIA.

PALLADIA has been associated with severe diarrhea or GI bleeding that requires prompt treatment. Dose interruptions and dose reductions may be needed depending upon the severity of clinical signs. (See Table 2 in Dosage and Administration.)

Use non-steroidal anti-inflammatory drugs with caution in conjunction with PALLADIA due to an increased risk of gastrointestinal ulceration or perforation.

PALLADIA is metabolized in the liver. Co-administration of PALLADIA with strong inhibitors of the CYP3A4 family may increase PALLADIA concentrations. The effect of concomitant medications that may inhibit the metabolism of PALLADIA has not been evaluated. Drug compatibility should be monitored in patients requiring concomitant medications.

The safe use of PALLADIA has not been evaluated in dogs less than 24 months of age or weighing less than 5 kg.

Adverse Reactions:

A US clinical field study comprised of a 6-week masked phase, followed by an open-label phase, evaluated the safety and effectiveness of PALLADIA in 151 client-owned dogs that had Patnaik grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement. The most common adverse reactions reported during the masked phase are summarized in Table 3; those reported during the entire study (masked phase combined with the open-label phase) are summarized in Table 4.

Table 3. Summary of the most common adverse reactions during the masked phasea

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n = 64)</th>
<th>PALLADIA (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>26.6% 3.1%</td>
<td>46.0% 6.9%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>31.3% 6.3%</td>
<td>39.1% 6.9%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>29.7% 3.1%</td>
<td>35.6% 4.6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32.8% 6.3%</td>
<td>32.2% 9.2%</td>
</tr>
<tr>
<td>Lameness</td>
<td>9.4% 0.0%</td>
<td>17.2% 0.0%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3.1% 0.0%</td>
<td>14.9% 1.1%</td>
</tr>
<tr>
<td>Blood in stool/GI bleed/</td>
<td>3.1% 0.0%</td>
<td>12.6% 2.3%</td>
</tr>
<tr>
<td>hemorrhagic diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal disorder</td>
<td>6.3% 0.0%</td>
<td>11.5% 1.1%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4.7% 0.0%</td>
<td>9.2% 2.3%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>9.4% 1.6%</td>
<td>9.2% 0.0%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4.7% 0.0%</td>
<td>9.2% 0.0%</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>4.7% 0.0%</td>
<td>8.0% 1.1%</td>
</tr>
<tr>
<td>Localized pain</td>
<td>4.7% 0.0%</td>
<td>8.0% 0.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1% 0.0%</td>
<td>8.0% 1.1%</td>
</tr>
<tr>
<td>General pain</td>
<td>4.7% 1.6%</td>
<td>6.9% 0.0%</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>7.8% 0.0%</td>
<td>6.9% 0.0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3.1% 0.0%</td>
<td>5.7% 2.3%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3.1% 0.0%</td>
<td>5.7% 0.0%</td>
</tr>
<tr>
<td>Pigmentation disorder</td>
<td>1.6% 0.0%</td>
<td>5.7% 0.0%</td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6.3% 0.0%</td>
<td>46.0% 0.0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20.3% 0.0%</td>
<td>24.1% 0.0%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21.9% 4.7%</td>
<td>24.1% 1.1%</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>7.8% 0.0%</td>
<td>12.6% 0.0%</td>
</tr>
<tr>
<td>Decreased hematocrit</td>
<td>7.8% 0.0%</td>
<td>5.7% 3.4%</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1.6% 1.6%</td>
<td>5.7% 0.0%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>4.7% 0.0%</td>
<td>5.7% 0.0%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.6% 0.0%</td>
<td>5.7% 0.0%</td>
</tr>
</tbody>
</table>

Table 4. Summary of the most common adverse reactions during the study (masked phase combined with the open-label phase)b

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Any Gradeb</th>
<th>Grade 3 or 4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>58.6%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>49.7%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47.6%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>39.3%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Lameness</td>
<td>22.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>21.4%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Blood in stool/GI bleed/hemorrhagic</td>
<td>18.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>15.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pigmentation disorder</td>
<td>11.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>11.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Musculoskeletal disorder</td>
<td>11.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>General pain</td>
<td>8.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Otis externa</td>
<td>8.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>8.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.6%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>7.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>6.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Localized edema</td>
<td>6.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bacterial skin infection</td>
<td>5.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>5.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
<td>Any Gradeb</td>
<td>Grade 3 or 4b</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>44.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>28.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28.3%</td>
<td>2.1%</td>
</tr>
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<td>6.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7.6%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

a The mean time on study during the masked phase was 37.0 days for PALLADIA-treated dogs (median, 42.0 days) and 27.6 days for placebo-treated dogs (median, 21.0 days); no adjustments were made in the statistical comparisons for this disparity.

b Investigators assigned severity grade of 1, 2, 3 or 4 (1 – least severe; 4 – most severe).

c Grading of laboratory abnormalities was based on the National Cancer Institute’s Common Toxicity Criteria guideline adapted for canines (1 – least severe; 4 – most severe).

There were 5 deaths during this study that were possibly drug related. Pathology findings generally revealed evidence of vascular dysfunction including pulmonary thromboembolism (post-operative); multi-organ failure associated with vasculitis and thrombosis; vascular thrombosis with disseminated intravascular coagulopathy (DIC) and pancreatitis; and vasculitis with DIC. One dog died secondary to gastric perforation; the duration of treatment with PALLADIA was 221 days and there was no evidence of mast cell tumor at necropsy. These deaths occurred in the presence or absence of gross-disease; treatment durations ranged from 18 to 221 days.

The relationship of the following deaths to drug are unknown. One dog, first treated for 3 weeks with a placebo, died of unknown cause 7 days after initiation of PALLADIA therapy. Another dog died of unknown cause 92 days after initiation of PALLADIA therapy. No necropsy was conducted in either dog.

Twenty seven dogs developed some form of gastrointestinal bleeding with 2.8% of dogs having severe bleeding. One dog developed gastric ulceration which was possibly drug related. Three dogs died from gastric (1 dog) or duodenal (2 dogs) perforations during the study. One dog with a duodenal perforation received only 1 dose of study drug and, therefore, it was not considered drug related.

Seven dogs developed nasal depigmentation within the first few weeks of treatment. Eleven dogs developed coat color or skin changes during the study. Two of these dogs had complete coat color changes from fawn to white and from deep red to blonde. Seven dogs experienced alopecia.

There is a drug related effect on body weight: 20.0% of dogs had >13% weight loss in the masked plus open-label phase attributable to drug. Of these, 5 dogs had >25% weight loss. Three dogs had seizure-like activity while on study drug. It can not be determined if these were drug related.

Two dogs developed epistaxis that was not associated with thrombocytopenia. Another dog developed epistaxis with concurrent disseminated intravascular coagulopathy.

For a copy of the Safety Data Sheet (SDS) or to report adverse events call Zoetis at 1-888-963-8471.
PALLADIA treatment was compared to placebo treatment using response rates at the end of PALLADIA in the treatment of mast cell tumors in dogs that had recurrent measurable clinical field study. The purpose of this study was to evaluate the effectiveness and safety of PALLADIA oral tablets for the treatment of mast cell tumors. To date, no clinical pharmacology studies of toceranib have not been investigated.

In vitro difference was observed in the N-oxide derivative of toceranib in dogs, humans, cats, and rats. Although a small gender-related clinical pharmacology study demonstrated the highest incidence, stiffness and weakness were not observed in all treatment groups. One dog in the 4 mg/kg group had oral ulcerations and one dog in the 6 mg/kg group had skin ulcerations, both with bacterial infections present. Diarrhea or soft stool were seen in all four groups.

Pharmacokinetics

Following intravenous administration, the pharmacokinetics of toceranib is characterized by a very large volume of distribution (>20 L/kg, indicating partitioning into tissues), a terminal elimination half-life of about 16 h, and a clearance of ~1 L/hr/kg. With a regimen of 3.25 mg free base equivalent (tbe/kg) doses of toceranib administered by tablet orally every other day for 2 weeks (7 doses), the pharmacokinetic parameters of toceranib in plasma in healthy Beagle dogs (between 7.2 – 12.5 kg) are shown in the table below.

Table 5. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=11; 5M, 6F)</td>
<td></td>
</tr>
<tr>
<td>Total (n=10; 5M, 5F)</td>
<td></td>
</tr>
<tr>
<td>Elimination half-life, t 1/2 (h)</td>
<td>16.4 ± 3.6</td>
</tr>
<tr>
<td>Time to maximum plasma concentration, T max (h)</td>
<td>5.3 ± 1.6</td>
</tr>
<tr>
<td>Maximum plasma concentration, C max (ng/mL)</td>
<td>86 ± 22</td>
</tr>
<tr>
<td>AUC 0-24 (ng*h/mL)</td>
<td>12.7 ± 6.0</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters for dogs treated with toceranib are shown in the table above. Oral bioavailability of toceranib is 77%. PALLADIA is highly protein bound at 91% to 93%.

Effectiveness

The effectiveness and safety of PALLADIA oral tablets for the treatment of mast cell tumors was evaluated in a randomized, placebo-controlled, double-masked, multicenter clinical field study. The primary objective of this study was to evaluate the effectiveness and safety of PALLADIA in the treatment of mast cell tumors in dogs that had recurrent measurable disease after surgery and to evaluate objective response (complete or partial response). PALLADIA treatment was compared to placebo treatment using response rates at the end of the 6-week masked phase. Response rates were determined using the National Cancer Institute’s Response Evaluation Criteria in Solid Tumors (RECIST) which was modified specifically for the evaluation of canine mast cell tumors.

One-hundred-fifty-three dogs were randomly assigned to treatment with either 3.25 mg/kg PALLADIA (n = 88) or placebo (n = 65) orally, every other day for 6 weeks, or until disease progression or withdrawal from the study for another cause. Treatment was unmasked at the time of disease progression: dogs receiving placebo were then offered crossover to open-label PALLADIA; dogs receiving PALLADIA were discontinued from the study. Dogs were required to have Patnaik grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement. At least 1 tumor had to be at least 20 mm in diameter. Dogs had a limit of 1 completed radiation protocol and a limit of 1 prior systemic chemotherapy regimen. Dogs with evidence of systemic mast cell tumor exclusion. Treatment with systemic corticosteroids during the study or within 14 days prior to study initiation was not permitted. If needed to manage adverse reactions, dose interruptions were allowed. The effectiveness analysis showed a statistically significant advantage for PALLADIA over placebo in the primary effectiveness endpoint of objective response at the end of the six-week masked phase. Objective response is complete + partial response. Partial response is ≥ 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum, non-progression of non-target lesions and appearance of no new lesions.

Mast Cell Tumor – Primary Effectiveness Endpoint Results

<table>
<thead>
<tr>
<th>Effectiveness Parameter</th>
<th>Placebo (n = 63)</th>
<th>PALLADIA (n = 86)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate *</td>
<td>7.9%</td>
<td>37.2%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* The difference in objective response rate between groups was not significantly associated with tumor burden (presence vs. absence of regional lymph node involvement) or tumor grade (P > 0.05).

During the study, PALLADIA was administered concomitantly with other medications such as antimicrobials, H-2 receptor blockers, antihistamines, anti-emics, non-steroidal anti-inflammatory drugs, locally-acting anti-ulcer medications, opiate gastrointestinal motility modifiers, opioids, vaccines, antihelmintics, antiparasitics, and topical/opthalmic/otic corticosteroid preparations. During the open-label phase only, 5 dogs received a brief course of short-acting corticosteroids.

Animal Safety:

In the target animal safety study presented below, PALLADIA was demonstrated to have a narrow margin of safety; dogs being treated with PALLADIA should be monitored for adverse reactions which may indicate a dose adjustment is required. Two dogs in the 6 mg/kg group were euthanized for clinical toxicities on Days 23 and 27 of the study, respectively.

Toferanib was administered orally to 20 male and 20 female adult Beagle dogs (approximately 2 years of age) at doses of 0 mg/kg (placebo, 12 dogs), 2 mg/kg (0.5X, 8 dogs), 4 mg/kg (1X, 10 dogs), or 6 mg/kg (1.5X, 8 dogs) once daily for 13 consecutive weeks without dose interruption. Toceranib caused weight loss, decreased feed consumption, pancreatic, gonadal, adrenal, muscle, and hematopoietic changes.

Feed consumption was decreased in the 6 mg/kg group compared to placebo, with the largest difference in means occurring at Day 35. Decrease in body weights in the 4 mg/kg group were seen at Day 31 and in the 6 mg/kg group at Day 15 compared with placebo and continued through the study. Dose related lameness, observed almost exclusively in the hind limbs, and limb pain was greater in all treatment groups as compared to placebo, with the 6 mg/kg group demonstrating the highest incidence. Stiffness and weakness were not observed in all treatment groups. One dog in the 4 mg/kg group had oral ulceration and one dog in the 6 mg/kg group had skin ulcerations, both with bacterial infections present. Diarrhea or soft stool were seen in all four groups.

Hematology analyses showed decreases in hematocrit, hemoglobin, and erythrocyte count and a decrease in reticulocyte count in the 4 and 6 mg/kg groups that tended to recover sufficiently to limit further toceranib exposure in dogs. White blood cell counts were significantly lower across the study in all treated groups compared to placebo, primarily due to a decrease in neutrophils. Lymphocytes decreased to a lesser degree, especially at the low dose. Eosinophils and basophils showed marked, persistent decreases. Monocytes were not affected.

Platelet counts increased slightly in 4 and 6 mg/kg groups. Increases were observed in fibrinogen in the 4 and 6 mg/kg group.

Increases were observed in aspartate aminotransferase, creatine kinase, and serum phosphorus concentrations in the 4 and 6 mg/kg groups. Increases in alkaline phosphatase were seen in the 6 mg/kg group. An increase in amylase was seen in one dog in each of the treatment groups. An increase in serum potassium was seen in one dog in the 6 mg/kg group. Increases in lactate dehydrogenase and globulins were observed in the 6 mg/kg group.

Treatment-related microscopic changes included slight to marked reduction in cellularity of sternal and femoral bone marrow. There was a corresponding mild extramedullary hematopoiesis, mainly erythropoiesis, in the spleen. In the pancreas, dose-related slant to moderate acinar degranulation, characterized by diffuse loss of zymogen granules, occurred. In the adrenal glands, minimal cortical congestion/hemorrhage occurred at all doses, with suggestive dose-relationship. Adrenal cortical vacuolation was noted with low frequency in all groups. Dose related changes were noted in reproductive organs of both sexes. Males showed a dose-related germ cell depletion, tubular vacuolation, and reductions in numbers of mature spermatozoa. In females, ovaries showed a reduced incidence of mature/regressing corpora lutea and an increased incidence of small follicles.

Two dogs (one male, one female) in the 6 mg/kg group were euthanized for treatment-related clinical toxicities on Days 28 and 27 of the study, respectively. Onset of the terminal syndrome was seen as markedly reduced feed intake and melena. Over the following 9 days, the decreased feed intake progressed to near-complete anorexia and hematochezia appeared. Weight loss, lethargy, hindlimb lameness and weakness were observed. The following clinical pathology results are consistent with changes seen in the other dogs in the 6 mg/kg group as well as changes due to the dogs’ debilitated conditions just prior to euthanasia. Both dogs had increases in total protein, globulins, phosphorus, cholesterol, triglycerides, fibrinogen, and PT in the 4 and 6 mg/kg groups. One dog in the 6 mg/kg group had pancytopenia, decreased hematocrit, hemoglobin, platelets, reticulocytes, albumin, and PT and increased bands. Hematrua was also present. The other dog also had decreased lymphocytes, eosinophils, chloride, and sodium and increases in RBC, hematocrit, hemoglobin, platelets, ALT, amylase, creatinine, BUN, magnesium, potassium, and total bilirubin. Clotting profile showed a decreased PT and increased in PTT in both dogs. These dogs showed lymphoid depletion in lymph nodes, thymus, and gut-associated lymphatic tissues and mild to marked gastrointestinal lesions consistent with the microscopic findings described in animals surviving to the end of the study. These two dogs also had lesions in the gastrointestinal tract, kidneys, pancreas, pituitary gland and adrenal glands.

Storage Conditions: Store at controlled room temperature 20° to 25° C (68° to 77° F).

How Supplied: PALLADIA tablets contain 10, 15, or 50 mg of toceranib as toceranib phosphate per tablet. The tablets are packaged in 30 count bottles.
What is PALLADIA?

- PALLADIA, a tyrosine kinase inhibitor, is a drug used to treat mast cell tumors, a common form of cancer that affects dogs.
- PALLADIA works in two ways:
  - By killing tumor cells.
  - By cutting off the blood supply to the tumor.
- Your veterinarian has decided to include PALLADIA as a part of your dog's treatment plan for mast cell tumor. Other types of treatment, such as surgery, drug treatment and/or radiation may be included in the plan. Be sure to speak with your veterinarian about all parts of your dog's treatment plan.

What do I need to tell my veterinarian about my dog before administering PALLADIA?

- Tell your veterinarian about all other medications your pet is taking, including: prescription drugs; over the counter drugs; heartworm, flea & tick medications; vitamins and supplements, including herbal medications.
- Tell your veterinarian if your dog is pregnant, nursing puppies, or is intended for breeding purposes.

How do I give PALLADIA to my dog?

- PALLADIA should be given to your dog by mouth (orally).
- PALLADIA may be hidden inside a treat; be certain your dog swallows the entire tablet(s).
- Follow your veterinarian's instructions for how much and how often to give PALLADIA.
- See the Handling Instructions section below in order to administer PALLADIA safely to your dog.

How will PALLADIA affect my dog?

- PALLADIA may help shrink your dog's tumor. Like other cancer treatments, it can be difficult to predict whether your dog's tumor will respond to PALLADIA, and if it does respond, how long it will remain responsive to PALLADIA. Regular check ups by your veterinarian are necessary to determine whether your dog is responding as expected, and to decide whether your dog should continue to receive PALLADIA.

What are some possible side effects of PALLADIA?

- Like all drugs, PALLADIA may cause side effects, even at the prescribed dose. Serious side effects can occur, with or without warning, and may in some situations result in death.
- The most common side effects which may occur with PALLADIA include diarrhea, decreased/loss of appetite, lameness, weight loss and blood in the stool.

Stop PALLADIA immediately and contact your veterinarian if you notice any of the following changes in your dog:

- Refusal to eat
- Vomiting or watery stools (diarrhea), especially if more frequent than twice in 24 hours
- Black tarry stools
- Bright red blood in vomit or stools
- Unexplained bruising or bleeding
- Or if your dog experiences other changes that concern you

There are other side effects which may occur. For a more complete list, ask your veterinarian.

Handling Instructions

What do I need to know to handle PALLADIA safely?

Because PALLADIA is an anti-cancer drug, extra care must be taken when handling the tablets, giving the drug to your dog, and cleaning up after your dog.

- PALLADIA is not for use in humans.
- You should keep PALLADIA in a secure storage area out of the reach of children.
- Children should not come in contact with PALLADIA. Keep children away from feces, urine, or vomit of treated dogs.
- If you are pregnant, a nursing mother, or may become pregnant and you choose to administer PALLADIA to your dog, you should be particularly careful and follow the handling procedures described below.
- PALLADIA prevents the formation of new blood vessels in tumors. In a similar manner, PALLADIA may affect blood vessel formation in the developing fetus and may harm an unborn baby (cause birth defects). For pregnant women, accidental ingestion of PALLADIA may have adverse effects on pregnancy.
- If PALLADIA is accidentally ingested by you or a family member, seek medical advice immediately. It is important to show the treating physician a copy of the package insert or label. In cases of accidental human ingestion of PALLADIA, you may experience gastrointestinal discomfort, including vomiting or diarrhea.

The following handling procedures will help to minimize exposure to the active ingredient in PALLADIA for you and other members of your household:

- Anyone who administers PALLADIA to your dog should wash their hands after handling tablets.
- When you or others are handling the tablets:
  - Do not split or break the tablets to avoid disrupting the protective film coating.
  - PALLADIA tablets should be administered to your dog immediately after they are removed from the bottle.
  - Protective gloves should be worn if handling broken or moistened tablets.
- If the PALLADIA tablet is "hidden" in food, make sure that your dog has eaten the entire dose. This will minimize the potential for exposure to children or other household members to PALLADIA.

Cleaning up after your dog:

- Because PALLADIA is present in the stool, urine and vomit of dogs under treatment, you must wear protective gloves to clean up after your treated dog.
- While your dog receives/PALLADIA, place the stool, feces or vomit, and any disposable towels used to clean up in a plastic bag which should be sealed for general household disposal. This will minimize the potential for exposure to people in contact with the trash.
- You should not wash any items soiled with stool, urine or vomit from your dog with other laundry.

This client information sheet gives the most important information about PALLADIA. For more information about PALLADIA, talk with your veterinarian.

To report a suspected adverse reaction call Zoetis at 1-888-963-8471.

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