Toceranib: Summary of the current literature and treatment recommendations

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Toceranib phosphate kinome

Potential targets at biologically relevant drug levels:

**1-10 nM:**
Kit, PDGFRα and β, VEGFR1 and 2, FLT3, CSF1R

**100 nM:**
VEGFR 3, RET, ALK, AXL

London et al., unpublished data
The initial phase 1 study demonstrated activity against MCTs, metastatic sarcomas, metastatic carcinomas, melanoma and multiple myeloma.

PD study demonstrated KIT target inhibition 8 hrs after the first dose of drug in dogs with MCT.

Subsequent clinical field study showed 43% CR/PR rate in dogs with MCTs; over 70% of dogs with KIT mutation responded to treatment.
Sunitinib (Sutent®)

- Sunitinib is a multi-targeted kinase inhibitor closely related to toceranib (Palladia®)
- Standard of care for primary and metastatic renal cell carcinomas: VEGFR2 inhibition
- Thyroid neoplasia: 80% clinical benefit rate
  7% CR, 25% PR, 48% SD, target thought to be mutant RET
- Imatinib-refractory GIST: Kit inhibition
- Advanced pancreatic neuroendocrine tumors
- Experimental data supports use as angiogenesis inhibitor
Toceranib use Beyond MCTs
Preliminary evidence for biologic activity of toceranib phosphate in solid tumors

- Retrospective analysis of dogs treated with solid tumors treated with toceranib

- Clinical benefit (CB: SD + PR + CR) was observed in 63/85 (74%)

- AGASACA: 28/32 (8 PR, 20 SD)

- Metastatic OSA: 11/23 (1 PR and 10 SD)

- Thyroid Carcinoma: 12/15 (4 PR and 8 SD)

- Head and Neck Carcinoma: 7/8 (1 CR, 5 PR and 1 SD)

- Nasal carcinoma: 5/7 (1 CR and 4 SD)
Solid Tumors Treated with Toceranib

SCC

Nasal Carcinoma

Pre

Post

April 2010

July 2010

Sept 2010
Role of Toceranib Targets in Thyroid CA and AGASACA

**RTK expression in primary AGASACA samples by IHC**

<table>
<thead>
<tr>
<th>RTK</th>
<th>Negative</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>Predominant localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR2</td>
<td>4 (17)</td>
<td>6 (25)</td>
<td>2 (8)</td>
<td>11 (46)</td>
<td>C</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>24 (100)</td>
<td>N, C</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>20 (83)</td>
<td>3 (13)</td>
<td>1 (4)</td>
<td>0</td>
<td>M</td>
</tr>
<tr>
<td>Kit</td>
<td>16 (67)</td>
<td>3 (13)</td>
<td>2 (8)</td>
<td>3 (13)</td>
<td>C</td>
</tr>
</tbody>
</table>

C: cytoplasmic; M: membranous; N: nuclear.

**RTK expression in TC samples by IHC**

<table>
<thead>
<tr>
<th>RTK</th>
<th>Negative</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>Predominant localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR2</td>
<td>13 (87)</td>
<td>1 (7)</td>
<td>0</td>
<td>1 (7)</td>
<td>C</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15 (100)</td>
<td>C</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>11 (73)</td>
<td>1 (7)</td>
<td>2 (13)</td>
<td>1 (7)</td>
<td>C</td>
</tr>
<tr>
<td>Kit</td>
<td>6 (40)</td>
<td>1 (7)</td>
<td>4 (27)</td>
<td>4 (27)</td>
<td>C</td>
</tr>
</tbody>
</table>

Phosphorylation Status of Toceranib Targets

Phosphoprotein screening results from AGASACA and TC tumor samples

<table>
<thead>
<tr>
<th>RTK</th>
<th>Primary AGASACA n (%)</th>
<th>Metastatic AGASACA n (%)</th>
<th>Thyroid carcinoma n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>16 (67)</td>
<td>7 (64)</td>
<td>14 (100)*</td>
</tr>
<tr>
<td>Dtk/TYRO3</td>
<td>21 (87)</td>
<td>3 (27)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Insulin-R</td>
<td>12 (50)</td>
<td>1 (9)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>ROR-1</td>
<td>22 (92)</td>
<td>11 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>ROR-2</td>
<td>15 (62)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ret</td>
<td>13 (54)</td>
<td>1 (9)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Tie-1</td>
<td>5 (21)</td>
<td>11 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Tie-2</td>
<td>6 (25)</td>
<td>1 (9)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Ron</td>
<td>13 (54)</td>
<td>1 (9)</td>
<td>5 (30)</td>
</tr>
<tr>
<td>FGFR3</td>
<td>9 (38)</td>
<td>1 (9)</td>
<td>-</td>
</tr>
</tbody>
</table>

None of the recognized targets of toceranib were noted to be phosphorylated

Role of Toceranib Targets in Thyroid CA and AGASACA

• Both ASACA and thyroid CA express mRNA and protein for known targets of toceranib.
  - Intracellular expression PDGFR-α in both
  - Stromal expression of PDGFR-β in both
  - Intracellular expression of VEGFR2 in both

• RET is not expressed in the majority of ASACA and thyroid CA samples evaluated and may not be a target in these tumors

• Proteome Profiler™ Human Phospho-RTK Arrays identified other RTKs that may play a role in the molecular biology of both ASACA and thyroid CA, although these are not targets of toceranib.
Toceranib Dosing
Guidelines for Toceranib Dosing

- In the Phase I study, of 16 dogs treated with Palladia at 2.5 mg/kg EOD, 6/16 (37.5%) had responses (4 CR, 2 PR) while an additional 5 dogs had SD.
  - biologic activity of 68% at 2.5 mg/kg

- This compares favorably with 20 dogs treated with 3.25 mg/kg EOD in which 8 (40%) had responses (2 CR, 6 PR) and an additional 4 dogs had SD.
  - biologic activity of 60% at 3.25 mg/kg

- In field study of dogs with MCTs, dose reductions to 2.2 mg/kg occurred in some dogs.

- These data suggested that doses below the MTD were associated with biologic activity of toceranib
Dosing: Summary of Retrospective Study in 85 dogs with Solid Tumors

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>CR/PR</th>
<th>SD</th>
<th>CR/PR/SD</th>
<th>PD</th>
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<tbody>
<tr>
<td>Number of Dogs</td>
<td>85</td>
<td>20 (24%)</td>
<td>44 (52%)</td>
<td>64 (75%)</td>
<td>21 (25%)</td>
</tr>
<tr>
<td>Age</td>
<td>10 (3-18)</td>
<td>10 (7.5-13)</td>
<td>10 (3-18)</td>
<td>10 (3-18)</td>
<td>10 (4-13)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FS</td>
<td>40</td>
<td>8</td>
<td>25</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>M</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MC</td>
<td>41</td>
<td>9</td>
<td>19</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>2.8 (2.2-3.25)</td>
<td>2.8 (2.48-3.25)</td>
<td>2.8 (2.2-3.25)</td>
<td>2.8 (2.2-3.25)</td>
<td>2.7 (2.2-3.25)</td>
</tr>
<tr>
<td>≥3 mg/kg</td>
<td>25 (29%)</td>
<td>6 (30%)</td>
<td>11 (25%)</td>
<td>17 (27%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>&lt;3 mg/kg</td>
<td>60 (71%)</td>
<td>14 (70%)</td>
<td>33 (75%)</td>
<td>47 (73%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>MWF Schedule</td>
<td>50 (59%)</td>
<td>7 (35%)</td>
<td>30 (68%)</td>
<td>37 (57%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Duration of Tx (wks)</td>
<td>N/A</td>
<td>22 (4-48)</td>
<td>24.5 (3-50)</td>
<td>22.5 (3-50)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- The data indicated that Palladia has activity at doses below the MTD of 3.25 mg/kg and at altered dosing regimens (MWF)
- The lower dose and MWF schedule appeared to be associated with less toxicity: average 6 months of therapy

London et al, VCO, 2011
The main clinical toxicities observed were GI, hematologic (neutropenia) and musculoskeletal in nature and the majority (86%) were either grade 1 or grade 2 in severity (74% and 12%, respectively).

No grade 3 or 4 GI adverse events were noted

Pharmacokinetics and pharmacodynamics of toceranib at lower doses

- While tumor response was not one of the main objectives of this study, clinical benefit was observed in 36/40 (90%) of the patients, with 12.5% experiencing PR and 77.5% experiencing SD.

- Furthermore, 35 of the 40 dogs remained on toceranib for an average of 16.7 weeks after day 30.

- During this time, one dog with a thyroid carcinoma transitioned from SD to a PR and 3 dogs transitioned to CR (two SCC and one salivary gland adenocarcinoma).

- These data support the notion that administration of toceranib at doses ranging from 2.4-2.9 mg/kg is associated with meaningful clinical benefit in dogs with cancer.

Toceranib in Combination
Hypofractionated Radiation Therapy Plus Palladia for Unresectable Canine MCTs

Dogs were treated with prednisone 1 mg/kg daily, Palladia MWF 2.75 mg/kg, and omeprazole while receiving RT given once per week (coarse fractionation) for 4 treatments.

The protocol was tolerated well and no enhancement of toxicity from RT was noted from the addition of Palladia.

Biologic activity of the treatment combination was high:

- response rate: 76%,
- 58.8% CR, 17.6% PR

Median PFI = 316 days
MST not reached

Karlsten et al, JVIM, 2011
Toceranib for Nasal Carcinoma +/- RT

Ehling et al, VCS, 2014
Toceranib for Nasal Carcinoma +/- RT

Tumor-specific Overall Survival Probability

- Historical Controls (n = 39)
  Median = 371 days; 95% CI (249 - 570)

- Plus Toceranib (n = 51)
  Median = 615 days; 95% CI (433 - 942)

\[ p = 0.0502 \]
\[ \text{Hazard Ratio} = 1.708 \]
\[ 95\% \ CI = 0.9995 - 2.918 \]
Toceranib for Nasal Carcinoma +/- RT

Post Hoc power calculation based on numbers of dogs in each group with a type one (α) error probability of 0.05 using a Log Rank Test

Sample Size grp 1 = 39
Survival Rate Observed in grp 1 = 0.5
Sample Size grp 2 = 51
Survival Rate Observed in grp 2 = 0.64
Power = 0.2744

Study was underpowered at 27% which makes the results strongly suggestive of activity

Ehling et al, VCS, 2014
Phase I study performed to determine optimal dose for combining vinblastine/Palladia

Primary toxicity was neutropenia resulting in dose reduction of vinblastine to 1.6 mg/m², lower than standard 2-2.3 mg/m²

Palladia could be used up to the label dose (3.25 mg/kg) of drug

Biologic activity of combination was high indicating possible synergy:

71% (2 CR, 8 PR)

This compares to single agent response rates of Vinblastine (12%) and Palladia (43%)
Phase 1 evaluation of combination CCNU and continuous toceranib in tumor-bearing dogs

- Standard toceranib dosage [2.75 mg kg\(^{-1}\), PO EOD], three dose-escalating CCNU cohorts up to and including 60 mg m\(^{-2}\) PO q3wk were completed.

- The DLT for the combination were neutropenia and the MTD for CCNU when given with toceranib was determined to be 50 mg/m\(^{-2}\) q3wk.

- While activity was not a primary objective, 1 CR (lymphoma) and 4 PR (lymphoma, sarcoma, undifferentiated carcinoma and prostatic carcinoma) were documented; 2 dogs experienced SD for >6 weeks (gastric ADC and metastatic MLO).

- Objective RR of 38.4% and a biological RR of 53.8%.

- Toceranib (2.75 mg kg\(^{-1}\), EOD) and pulse dose CCNU (50 mg m\(^{-2}\), q3wk) was well tolerated.

*Pan et al, VCO, 2014*
Pulse-Administered Toceranib Plus CCNU for Treatment of Unresectable Mast Cell Tumors

- Toceranib phosphate was given PO on days 1, 3 and 5 of a 21-day cycle at a target dosage of 2.75 mg/kg. CCNU was given PO on day 3 of each cycle at a starting dosage of 50 mg/m². All dogs were concurrently treated with diphenhydramine, omeprazole, and prednisone.

- The MTD of CCNU was established at 50 mg/m² when combined with pulse-administered toceranib; the DLT was neutropenia.

- The ORR was 46% (4 CR, 15 PR) and the overall median PFS was 53 days (1 to >752 days).

- On multivariate analysis, variables significantly associated with improved PFS included response to treatment, absence of metastasis, and no previous chemotherapy.

Burton et al, JVIM, 2015
Doxorubicin and Toceranib

- Toceranib phosphate was given PO at a target dosage of 2.75 mg/kg EOD. Doxorubicin initiated at 20 mg/m² q 21 days, with dose increases of 5 mg/m² per cohort.

- The MTD of doxorubicin was established at 25 mg/m² when combined with toceranib; the DLT was neutropenia.

- Anti-tumor activity observed in several cases.

Burton et al, JVIM, 2015
A phase I trial was performed in tumour-bearing (non-mast cell) dogs to establish the safety of the combination.

The combination of standard dosages of both drugs (toceranib, 3.25 mg kg\(^{-1}\), every other day; piroxicam, 0.3 mg kg\(^{-1}\) daily) is generally safe.

Several antitumor responses were observed:
- PR: 2 SCC, 1 AGASACA, 1 STS
- SD: 5 carcinomas (nasal, salivary, pulmonary, prostatic), 1 oral melanoma, 1 STS, 1 oral FSA

As with single-agent toceranib, label-indicated treatment holidays and dose reductions (e.g. 2.5-2.75 mg kg\(^{-1}\)) may occasionally be required owing to gastrointestinal events.

Piroxicam is now typically given on an every other day basis at 0.3 mg/kg alternating with toceranib.
Toceranib in Microscopic Disease
Toceranib/Piroxicam/Cyclophosphamide Maintenance Therapy in Dogs with Appendicular Osteosarcoma Following Amputation and Carboplatin Chemotherapy

### Disease Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Palladia</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFI (Intent to Treat) (days)</td>
<td>233</td>
<td>215</td>
<td>0.274</td>
</tr>
<tr>
<td>DFI (Adherence) (days)</td>
<td>223</td>
<td>198</td>
<td>0.300</td>
</tr>
</tbody>
</table>
Toceranib/Piroxicam/Cyclophosphamide Maintenance Therapy in Dogs with Appendicular Osteosarcoma Following Amputation and Carboplatin Chemotherapy

Short-term Mortality Risk:
Time dependent
\( p = 0.06 \) at 100 days
Converged at 400 days

Proximal Humerus:
\( \text{DFI 182 days (} p = 0.281) \)
\( \text{OS 243 days (} p = 0.280) \)

<table>
<thead>
<tr>
<th></th>
<th>Palladia</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (days)</td>
<td>318</td>
<td>242</td>
<td>0.080</td>
</tr>
</tbody>
</table>
Maintenance therapy with toceranib following doxorubicin-based chemotherapy for splenic HSA

A

Toceranib Treated

Median PFS = 161 days
95% CI = 140 - 215 days

B

Intent to Treat

Median PFS = 138 days
95% CI = 122 - 174 days
Maintenance therapy with toceranib following doxorubicin-based chemotherapy for splenic HSA
Toceranib in Microscopic Metastatic Disease Setting for Solid Tumors

- No significant improvement in outcome
  - Treatment of microscopic metastatic disease using toceranib alone or in combination does not appear to improve outcome

- No increased rate of disease progression
  - Several preclinical studies suggest anti-VEGF therapy can accelerate metastasis
    - Ebos et al; Cancer Cell 2009
    - Paez-Ribes et al; Cancer Cell 2009
  - May not occur outside of certain limited preclinical scenarios
Toceranib and Immunomodulation
In mice, treatment with sunitinib decreased MDSC accumulation, prevented Treg development, and improved the efficacy of tumor immunotherapy.

In humans with renal cell carcinoma, sunitinib reversed peripheral immune dysfunction through restoration of a Th1 T-cell-mediated immune response.

Tregs isolated from these patients demonstrated diminished suppressive function against autologous effector T cells.

Sunitinib appears to modulate Treg indirectly through suppressive effects on MDSCs and TAMs.
Immunomodulatory effects of toceranib combined with low dose cyclophosphamide in dogs with cancer

The mean percentage and the mean absolute number of Tregs decreased in dogs with cancer 14 days after initiation of toceranib therapy at 2.75 mg/kg every other day.

Mitchell et al, JVIM, 2012
Immunomodulatory effects of toceranib combined with low dose cyclophosphamide in dogs with cancer

Dogs were started toceranib at day 0 and then CYC was added at 15 mg/m²/day at day 14. Blood samples were collected for Treg analysis at days 0, 14, 28, 42, and 56. The mean percentage and absolute number of Tregs remained decreased from baseline at 8 weeks post treatment.
Immunomodulatory effects of toceranib combined with low dose cyclophosphamide in dogs with cancer

Toceranib did not inhibit the expansion of Tregs generated in vitro from healthy dog PBMCs, suggesting that the in vivo effects of toceranib may occur through indirect immunomodulatory mechanisms.

Mitchell et al, JVIM, 2012
Immunomodulatory effects of toceranib combined with low dose cyclophosphamide in dogs with cancer

Serum levels of interferon gamma (IFN-g) increased initially following toceranib administration and continued to increase with the addition of CYC during treatment. This increase directly correlated with the decrease in percent of circulating Tregs.

Mitchell et al, JVIM, 2012
Toceranib and Metronomic Therapy

- Based on immunomodulatory effects, toceranib may have enhanced activity in the metronomic setting.

- While both cytotoxic agents and anti-angiogenic agents appear to be critical for effective metronomic therapy, there is little data regarding the class of cytotoxic that is most appropriate (cyclophosphamide vs chlorambucil), particularly in combination with toceranib.

- However, recent clinical trial data demonstrates little efficacy of toceranib alone or in combination with a metronomic cytotoxic in the setting of minimal residual disease.

- There are currently no established biomarkers to monitor the potential efficacy of metronomic protocols that incorporate VEGF/VEGFR inhibition.
Guidelines for Use
Guidelines for Palladia Use and Monitoring

- **Starting dose:** label dose is 3.25 mg/kg
  2.5-2.75 mg/kg EOD, may use MWF dosing if patient needs dictate

- **Baseline body weight, CBC, chemistry panel, UA, UPC, BP**

- **Recheck 2 weeks after starting drug**
  - body weight
  - CBC (chemistry panel, UA on week 4)

- **Rechecks q 4-6 wks thereafter including body weights, CBC, chemistry panel, UA +/- UPC, BP**

- **Owners are instructed to report ANY side effects immediately, including loss of appetite, loose stool, etc. and to STOP DRUG**
Managing/Preventing Side Effects

Always administer with food/meal

Anorexia/nausea
- Ondansetron, maropitant can be used and some dogs are on these daily
- Prednisone at 0.5 mg/kg can significantly improve appetite
- Give in the evening, MWF, and/or at a lower dose

GI ulceration
- Drug holiday followed by omeprazole, sucralfate if GI ulceration has occurred; reinstitute at lower dose/MWF
- Sucralfate should be given after toceranib so as not to impede absorption
Managing/Preventing Side Effects

Diarrhea
- Aggressive management of diarrhea EARLY is imperative
- Metronidazole and probiotics
- Some dogs respond to loperamide and/or tylosin if metronidazole doesn’t work
- Some dogs need to be on continual anti-diarrhea treatments to maintain a normal stool; metronidazole SID M-F, probiotics

Lethargy
- In many cases, this responds to the addition of 0.5 mg/kg of prednisone can make a huge difference in QOL
- If non-responsive to this, then drug holiday and dose reduction and/or schedule modification would be indicated
Managing/Preventing Side Effects

**Neutropenia**
- If counts are maintained above 1500, then no changes in therapy are indicated
- If counts are below 1500, a drug holiday is indicated followed by dose reduction and/or schedule modification

**Hepatotoxicity**
- Elevation in ALT/ALP has now been noted in some dogs
- Immediate drug holiday is indicated followed by administration of Denamarin
- Can re-institute toceranib at a lower dose, consider continuing administration of Denamarin
The development of PLN in dogs treated with toceranib has not been well-described in clinical trials, but based on anecdotal reports, it appears to occur relatively frequently (25% of cases).

In human patients that receive sunitinib the incidence of PLN has been reported to be approximately 2.5%.

Proposed causes of PLN when VEGF/VEGFR inhibitors are used include loss of healthy, fenestrated glomerular capillaries which seems to be a direct consequence of blocking VEGFR signaling and possibly disruption of podocyte integrity.
In human patients with renal cell carcinoma (RCC) receiving sunitinib, 24% developed hypertension and 8% of these were classified as grade 3 in nature.

The incidence of hypertension in dogs treated with tocetranib is largely unknown, although efforts are underway to assess how frequently it occurs.

Hypertension may be directly related to inhibition of VEGF signaling pathways. Additionally, anti-angiogenic drugs used in human patients have been shown to induce increased concentrations of endothelin-1, and this may contribute to hypertension.
Recommendations

- Always get baseline UPC and BP if possible; dogs with cancer may have underlying PLN and hypertension.

- If UPC increases during treatment (mild to moderate), add ACE inhibitor to therapy and repeat UPC after 2-4 weeks. Discontinue toceranib if UPC continues to increase.

- For hypertension, amlodipine is often very effective; enalapril alone typically does not work well.
Guidelines on treatment for MCT patients based on the OSU experience

- Typically incorporated into treatment protocols for Grade III MCT, any Grade II MCT with negative prognostic indicators or any dog with KIT mutation.

- In general, it is part of a treatment protocol that includes surgery +/- RT and chemotherapy.

- For dogs with gross disease, every attempt is made to downstage disease prior to initiation of therapy.

- Combined hypofractionated RT/toceranib/prednisone for dogs with non-resectable tumors
GIST Experience

Recurrence-free Survival

- Intention-To-Treat Population

- 3 years of imatinib: 71.1%
- 1 year of imatinib: 52.3%

HR 0.60, 95% CI 0.44-0.81

P < .001
<table>
<thead>
<tr>
<th></th>
<th>No. of patients/group</th>
<th>No. of events/group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mo (n)</td>
<td>36 mo (n)</td>
</tr>
<tr>
<td>Tumor size: &lt;=10 cm</td>
<td>0.51 (0.33, 0.80)</td>
<td>120</td>
</tr>
<tr>
<td>Tumor size: &gt;10 cm</td>
<td>0.63 (0.42, 0.96)</td>
<td>78</td>
</tr>
<tr>
<td>Location: Stomach</td>
<td>0.64 (0.39, 1.06)</td>
<td>97</td>
</tr>
<tr>
<td>Location: Other</td>
<td>0.58 (0.40, 0.85)</td>
<td>101</td>
</tr>
<tr>
<td>Local Mitotic count: &lt;=10</td>
<td>0.97 (0.60, 1.55)</td>
<td>100</td>
</tr>
<tr>
<td>Local Mitotic count: &gt;10</td>
<td>0.36 (0.23, 0.57)</td>
<td>85</td>
</tr>
<tr>
<td>Central Mitotic count: &lt;=10</td>
<td>0.77 (0.49, 1.20)</td>
<td>121</td>
</tr>
<tr>
<td>Central Mitotic count: &gt;10</td>
<td>0.46 (0.30, 0.71)</td>
<td>77</td>
</tr>
<tr>
<td>Tumor mutation: KIT exon 11</td>
<td>0.51 (0.35, 0.74)</td>
<td>129</td>
</tr>
<tr>
<td>Tumor mutation: KIT exon 9</td>
<td>0.71 (0.29, 1.79)</td>
<td>12</td>
</tr>
<tr>
<td>Tumor mutation: PDGFRA D842</td>
<td>0.82 (0.22, 3.06)</td>
<td>22</td>
</tr>
<tr>
<td>Tumor mutation: Other</td>
<td>0.59 (0.20, 1.68)</td>
<td>25</td>
</tr>
<tr>
<td>Age group: &lt;=65 years</td>
<td>0.67 (0.46, 0.99)</td>
<td>121</td>
</tr>
<tr>
<td>Age group: &gt;65 years</td>
<td>0.52 (0.31, 0.85)</td>
<td>78</td>
</tr>
<tr>
<td>Tumor spillage prior to/at surgery: No</td>
<td>0.51 (0.35, 0.75)</td>
<td>164</td>
</tr>
<tr>
<td>Tumor spillage prior to/at surgery: Yes</td>
<td>0.72 (0.42, 1.24)</td>
<td>35</td>
</tr>
</tbody>
</table>
Remaining Questions

- Should treatment be based on the presence of Kit mutation?
- How should toceranib be combined with standard therapies?
- What should be the duration of treatment?
- Macroscopic vs microscopic disease setting?
QUESTIONS?