Radiographic Predictors of Response to 177Lu-DOTATATE
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Background
• Can we identify early the gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients most likely to benefit from 177Lu-DOTATATE, the newly approved peptide receptor radionuclide therapy (PRRT)?
• Hypothesis: pre-treatment maximum standardized uptake value (SUVmax) on DOTATATE scans and mid-treatment radiographic response predict overall response to 177Lu-DOTATATE.

Material & Methods
• We identified patients at University of California, San Francisco (UCSF) who received 177Lu-DOTATATE through the expanded access protocol (Table 1. N=18, median age 63 years, 44% male, 78% midgut).
• Open-label trial for patients with inoperable, well-differentiated NETs progressing despite somatostatin analog therapy (NCT02705313).
• Patients received up to 4 cycles of 177Lu-DOTATATE and underwent restaging CT or MRI scans mid-treatment after 2 cycles, immediately following completion of therapy ("post treatment"), and then per routine clinical follow-up ("last follow up").
• We determined SUVmax for the 16 patients with baseline 68-Ga-DOTATATE/TOC PET scans.
• Objective response rate (ORR) determined via RECIST 1.1.
• Spearman non-parametric correlations were used to determine associations between continuous variables.

Table 1: Study Population Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>63 (52-66)</td>
</tr>
<tr>
<td>Females, % (N)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Primary Site, % (N)</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>78% (14)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6% (1)</td>
</tr>
<tr>
<td>Bronchial</td>
<td>6% (1)</td>
</tr>
<tr>
<td>Renal</td>
<td>6% (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6% (1)</td>
</tr>
<tr>
<td>Grade, % (N)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44% (8)</td>
</tr>
<tr>
<td>2</td>
<td>56% (10)</td>
</tr>
<tr>
<td>Median Ki-67%</td>
<td>2.9%</td>
</tr>
<tr>
<td>SUVmax, median (IQR)</td>
<td>28 (23-39)</td>
</tr>
</tbody>
</table>

Results
• We observed high baseline 68-Ga-DOTATATE/TOC uptake in this population, with a median SUVmax of 28 (interquartile range (IQR): 23-39).
• ORR immediately after therapy completion was low (6%), but most patients achieved stable disease (77%). A minority of patients progressed (17%; Figure 1).
• We found a strong association between the % change in tumor size on the mid-treatment scan after 2 cycles and the post treatment scan (Spearman rho 0.83, p <0.001).
• There was also a strong association between the % change in tumor size on the mid-treatment scan and last follow up scan (rho 0.92, p<0.001).
• Patients with higher baseline SUVmax tended to have more disease shrinkage on the post treatment scan, although this was not statistically significant (rho - 0.41, p=0.13; Figure 2).

Conclusions
• Both disease progression and response to PRRT tended to occur early, by mid treatment scan after first 2 cycles.
• Further investigation in larger, prospective studies is merited to confirm whether baseline SUVmax predicts treatment response to PRRT.
• Importance of defining rate of disease progression pre-treatment.
• Study limitations: heterogeneity of imaging modalities, small sample size, limited follow up.
• Hypothesis generating regarding patient selection and when to stop PRRT.
Results, Continued

Figure 1. % Change in Target Lesion Size with Treatment for Patients with Progressive Disease Compared to Those with Stable Disease or Partial Response

- Individual patient-level response data are shown for the patients (N=3) with progressive disease (Subjects 9, 8, and 15), along with the patients (N=2) who achieved an objective response by last follow up (Subject 1, 14).
- Subject 9 died from rapidly progressive disease shortly after completing 2 cycles of therapy. Subjects 8 and 15 progressed on their mid-treatment scans, but subsequently had a period of disease stability in the absence of additional therapies.
- In contrast, the other (N=12) patients on this study had generally stable disease; mean % change in tumor size at each timepoint is depicted in the figure above.
- Click here to see radiology images for example patients

Figure 2. Scatterplot of Baseline SUVmax and % Change in Tumor Size following PRRT

- Patients with higher baseline pre-treatment SUVmax tended to have more disease shrinkage on their post-treatment scans, although this was not statistically significantly (rho -0.41, p=0.13).
- This association is even stronger if the one SUV outlier is excluded (rho -0.50, p=0.066).
- We found a similar association between SUVmax and % change in tumor size on last follow up scan (rho -0.51, p=0.090).
- Further investigation in larger, prospective studies is warranted to confirm whether baseline SUVmax predicts treatment response.
Figure 3. Scans for Subject with Partial Response
A. Pre-Treatment OctreoScan MIP 2.9.2017
B. Pre-Treatment MRI Liver (2.17.2017)
C. Post-Treatment MRI Liver (5.4.2018)
Last Follow Up

Figure 4. Scans for Subject with Stable Disease
A. Pre-Treatment Ga-68 DOTATOC PET/MRI (8.2.2017)
B. Post-Treatment MRI Liver (5.16.2018)
Last Follow Up