CLINICAL TRIALS OF MEDICAL THERAPIES COMBINED WITH PRRT

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DISCLOSURES
Chris Verslype

Research funding – consultancy

BAYER
IPSEN
LILLY
NOVARTIS
SIRTEX
NETTER-1: METASTATIC MIDGUT NET

• RECIST progression on fixed dose SSA
• Ki67 <20% (Gr 1/2)
• SRS + all lesions
• Adequate GFR, blood, liver
• No prior PRRT

Stratification:
• Fixed dose SSA: <6 months vs >6 months
• SRS uptake score

PRRT $^{177}$Lu-DOTATATE
4 x 7.4 GBq; interval 8±1w + 30 mg Octreotide LAR/4w

1st endpoint: PFS
2nd endpoint: ORR, TTP, OS, DoR, PFS$_2$

NETTER-1: METASTATIC MIDGUT NET

NETTER-1: METASTATIC MIDGUT NET

<table>
<thead>
<tr>
<th></th>
<th>(^{177}\text{Lu-Dotatate (n=101)})</th>
<th>(\text{Octreotide LAR 60mg (n=100)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (n)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (n)</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Objective Response Rate (CI 95%)</td>
<td>19 (11-26) %</td>
<td>3 (0-6) % *</td>
</tr>
<tr>
<td>Progressive Disease (n, %)</td>
<td>5 (4%)</td>
<td>27 (24%)</td>
</tr>
<tr>
<td>Stable Disease (n, %)</td>
<td>77 (66%)</td>
<td>70 (62%)</td>
</tr>
</tbody>
</table>

*\(P<0.0004\)

THE CONCEPT OF CHEMO-PRRT

The introduction of radiosensitizing chemotherapy in combination with PRRT to enhance efficacy without concomitant toxicity
CHEMORADIONUCLIDE THERAPY (PRRT + 5FU)

Retrospective study

Inclusion:
- 52 patients GEP-NET, FDG-avid and SRS + (Krenning 3), majority grade 2 NET
- Progressive; 67% prior chemotherapy

Methods:
- 6 – 10 GBq of LuTate, 3-5 cycles every 6 – 8 weeks
- Continuous infusion 5FU at a dose of 200 mg/m2/day from the 2nd cycle of PRRT starting 4 days prior to radionuclide administration and continuing for up to 3 weeks

Safety:
- Lymphopenia (grade 2), thrombocytopenia in 38 % (grade 3/4 in 6 %) and anaemia in 38 % (no grade 3/4)

Fig. 1  Kaplan-Meier curves for (a) OS and (b) PFS (with 95 % confidence bands)

Table 2  Imaging responses at 3 months after completion of PRCRT

<table>
<thead>
<tr>
<th>Response Type</th>
<th>RECIST 1.1 (n=40)</th>
<th>FDG PET (n=31)</th>
<th>SSTR imaging (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>11</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>Stable disease</td>
<td>27</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1</td>
<td>4</td>
<td>17^a</td>
</tr>
</tbody>
</table>

^a A proportion of these patients had a mixed response with response in dominant preexisting lesions but progression of existing small-volume disease defining progression.

PRRT and CAPECITABINE, phase 2

Inclusion criteria
- Progressive NET, grade 1/low 2 (n=33)
- Majority of patients no prior chemotherapy (87%)

Therapy schedule: CAP + PRRT
- Day of PRRT: CAP 1,650 mg/m² for 14 days;
- TEM 200 mg/m² daily during last 5 days of each 14-day capecitabine period
- 4 x 7.9 GBq $^{177}$Lu-octreotate every 8 weeks

Endpoints:
- RR (RECIST), PFS, OS, Toxicity

PRRT and CAPECITABINE, results

Table 2  Adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>33 (100%)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Angina</td>
<td>0</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0</td>
</tr>
</tbody>
</table>

PR: 24%  -  SD: 70%  -  PD: 6%

PRRT + CAP – NCT02736448 – PHASE 2 (ONGOING)

G1 - G2 and G3 GEP-NET
SSR positive
FDG positive
N = 176

1:1

Lu-PRRT

Lu-PRRT + CAP

1 endpoint: PFS
2 endpoint: DCR, safety, OS

Lu-PRRT: 3.7 Gbq per cycle x 7 cycles

Lu-PRRT+ CAP: 3.7 Gbq per cycle x 7 cycles + CAP low dose (?)
PRRT and CAPTEM, phase 2

Inclusion criteria
- Progressive pNET, grade 1/2 (Ki67 < 20%) (n=30)
- Majority of patients no prior chemotherapy (87%)

Therapy schedule: CAPTEM + PRRT
- 5 days before PRRT: CAP 1,500 mg/m² for 14 days;
- TEM 200 mg/m² daily during last 5 days of each 14-day capecitabine period.
- 4 x 7.9 GBq $^{177}$Lu-octreotate every 8 week

Endpoints:
- RR (RECIST), PFS, OS, Toxicity

Claringbold et al. Neuroendocrinology 2016
PRRT and CAPTEM, results

Fig. 1. Waterfall plot of ORR (RECIST version 1.1) 4–8 months after $^{177}$Lu-octreotide-capcitabine-temozolomide PRRT in the 30 participants of the study. The 30% reduction in tumor size constituting PR is shown as a dashed line.

RR: 80%

Claringbold et al. Neuroendocrinology 2016
PRRT and CAPTEM, toxicity

Dose intensity:
- CAP 90%, TEM 83%
- PRRT (29/30 4 cycles, 1 patient 3 cycles)

Toxicity:
- Transient nausea of grade 2 (33%) or 3 (7%)
- Hematological toxicity was limited to grade 3 thrombocytopenia (10%) and anemia (10%)
- no grade 4 adverse events, no renal functional impairment
- 1 late myelodysplastic syndrome (4 years after treatment)

Claringbold et al. Neuroendocrinology 2016
CONTROL NETS TRIAL – NCT02358356 – PHASE 2

G1/G2 pancreatic NET (n=90)

CAPTEM: Oral capecitabine 750mg/m² b.i.d. days 1-14 and temozolomide 75mg/m² b.i.d. days 10-14 every 28 day cycle, up to 8 cycles

PRRT + CAPTEM: 7.8GBq 177Lu Octreotate (Lutate) IV on day 10 every 8 weeks for 4 cycles, with concurrent oral capecitabine 750mg/m² b.i.d. days 1-14 and temozolomide 75mg/m² b.i.d. days 10-14 up to 4 cycles

1 endpoint: PFS 12 mo; 2 endpoint: RR, OS, safety, QoL
CONTROL NETS TRIAL – NCT02358356 – PHASE 2

PRRT: 7.8GBq 177Lu Octreotate (Lutate) IV on day 1 every 8 weeks for 4 cycles

PRRT + CAPTEM: 7.8GBq 177Lu Octreotate (Lutate) IV on day 10 every 8 weeks for 4 cycles, with concurrent oral capecitabine 750mg/m2 b.i.d. days 1-14 and temozolomide 75mg/m2 b.i.d. days 10-14 up to 4 cycles

G1/G2 midgut NET (n=75)

1 endpoint: PFS 24 mo;
2 endpoint: RR, OS, safety, QoL
Inclusion criteria
- Progressive GEP-NET, (n=16)

Therapy schedule: PRRT+ EVEROLIMUS
- 4 x 7.9 GBq $^{177}$Lu-octreotate every 8 weeks
- Successive cohorts of 3 patients received escalating doses of everolimus comprising 5, 7.5, and 10 mg daily for 24 weeks

Endpoints:
- Optimal safe dose of Everolimus
- Dose-limiting toxicity

Claringbold et al. Cancer Biother Radiopharm. 2015
PRRT AND EVEROLIMUS, PHASE 1B, NETTLE

Toxicity:

- Hematological toxicity with both neutropenia and thrombocytopenia
- DLT: renal impairment with everolimus doses above 7.5 mg and was dose limiting.
- Conclusion: MTD of everolimus was 7.5 mg daily in combination with 7.8 GBq $^{177}$Lu-octreotate in a four-cycle course over 24 weeks.

Responses:

<table>
<thead>
<tr>
<th>ORR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNETS ($n=5$)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI-NETS ($n=11$)</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
CONCLUSIONS - CHEMO-PRRT

- The combination of PRRT with chemotherapy (5FU, Capecitabine or even CAPTEM) is safe and well tolerated.

- The combination of PRRT and everolimus was tested in phase I (MDT Everolimus 7.5 mg/day).

- It remains difficult to determine whether there is a true benefit to combination therapy versus sequential therapy.

- Prospective, randomized, controlled trials are required to definitively state whether or not there is an advantage to combination therapies (e.g. CONTROL NETS TRIAL: CAPTEM + PRRT).