MEETING SUMMARY
ESMO 2020, VIRTUAL MEETING
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HIGHLIGHTS FROM NET CONNECT
SEPTEMBER 2020
Please note: The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author’s academic institutions or the rest of the NET CONNECT group.

This content is supported by an independent educational grant from Ipsen.

Dr. Rachel van Leeuwaarde has no relevant financial relationships to disclose.
A MULTI-COHORT PHASE 2 STUDY OF DURVALUMAB PLUS TREMELIMUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED NENs OF GEP OR LUNG ORIGIN: THE DUNE TRIAL (GETNE 1601)

Capdevila J, et al.
ESMO 2020. Abstract #1157O. Oral presentation

GEP, gastroenteropancreatic; NENs, neuroendocrine neoplasm
Immune checkpoint blockade (ICB) has shown limited activity in advanced NENs to date, mainly due to the background biology of these neoplasms, with usually low tumour mutational burden, low expression of PD-L1 and low lymphocyte filtration.

Targeting both PD-L1 and CTLA-4 may increase the efficacy of ICB in NENs and revert the intrinsic resistance:

- The PD-1 inhibitors, pembrolizumab and spartalizumab, have shown limited activity in well differentiated NETs.
- The combination of anti-PD-L1 (nivolumab) and anti-CTLA-4 (ipilimumab) has shown promising activity in high-grade NENs.

The DUNE study investigated the activity of durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4).

**BACKGROUND**

- **Cohorts 1-3:** 9-month CBR
- **Cohort 4:** 9-month OS rate

**Secondary endpoints:**
- Safety, PFS, OS, ORR, DOR and biomarker analysis
123 patients were included (C1=27, C2=31, C3=32, C4=33)

Median age 62 years, 59% males, 43% ECOG PS 0

91% of C4 (grade 3 GEP-NEN) had poorly differentiated tumours

RESULTS

With a median follow-up of 10.8 m:

CBR at 9 months (by RECIST v1.1) was:

- Cohort 1, Typical/atypical lung carcinoids: 7.4%
- Cohort 2, Grade 1/2 gastrointestinal: 32.3%
- Cohort 3, Grade 1/2 pancreatic: 25%

OS rate at 9 months for cohort 4 was:

- Cohort 4, Grade 3 GEP: 36.1% (95% CI: 22.9-57) (N=33)

Cohort 4 - Well differentiated

SAFETY

- Most common TRAEs: fatigue (43.0%), diarrhoea (31.7%), pruritus (23.6%), nausea (13.8%), hypothyroidism (9.8%)
- Most frequent grade ≥3 TRAEs: liver toxicity (9.7%), diarrhoea (6.5%), fatigue (2.4%) and vomiting (2.4%)

irORR, %

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PD-L1+</th>
<th>PD-L1 -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1: Typical/atypical lung carcinoids</td>
<td>7.4</td>
<td>16.6*</td>
<td>0</td>
</tr>
<tr>
<td>Cohort 2: Grade 1/2 gastrointestinal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cohort 3: Grade 1/2 pancreatic</td>
<td>6.3</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Cohort 4: Grade 3 GEP</td>
<td>9.1</td>
<td>0</td>
<td>7.7</td>
</tr>
</tbody>
</table>

* PD-L1 expression only enriched irORR in cohort 1 (p=0.033)
SUMMARY

- Durvalumab and tremelimumab combination showed modest activity in this heavily pre-treated population
- In WHO grade 3 NENs (cohort 4), the combination therapy met the predefined threshold for OS at 9 months and deserves further evaluation
- Objective radiological responses were infrequent
- No new safety concerns were identified in this large population of advanced NENs
EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG EVERY 14 DAYS IN PROGRESSIVE PANCREATIC OR MIDGUT NETs: CLARINET FORTE STUDY RESULTS

Pavel M, et al.
ESMO 2020. Abstract #1162MO. Mini oral presentation
Currently, patients with progressive disease after treatment with lanreotide (120 mg every 28 days) have limited treatment options and receive less well-tolerated systemic chemotherapy or molecular targeted therapies.

**CLARINET FORTE** is a prospective, open label, exploratory, European phase 2 study that investigated the efficacy and safety of an increased dosing frequency of lanreotide in patients with progressive pancreatic neuroendocrine tumours (panNETs) and midgut NETs.

**BACKGROUND**

DCR, disease control rate; LAN, lanreotide; NET, neuroendocrine tumour; PFS, progression free survival; RECIST, Response Evaluation Criteria In Solid Tumours; SSTR2, somatostatin receptor type 2; wks, weeks

RESULTS

PFS (PRIMARY ENDPOINT)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>PanNET N=48</th>
<th>Midgut NET N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAEs, %</td>
<td>37.5</td>
<td>51.0</td>
</tr>
<tr>
<td>TRAEs grade ≥3, n (%)</td>
<td>1 (2.1)*</td>
<td>-</td>
</tr>
<tr>
<td>Most common (≥10%) TRAEs, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>25.0</td>
<td>37.3</td>
</tr>
<tr>
<td>General disorders/administration site conditions</td>
<td>13.7</td>
<td>-</td>
</tr>
</tbody>
</table>

* Grade 3 TRAE of fatigue

- TRAEs of note:
  - hyperglycaemia (n=2), bile stones (n=1), steatorrhea (n=1)

SECONDARY ENDPOINTS

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>PanNET N=48</th>
<th>Midgut NET N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCR at week 24, % (95% CI)</td>
<td>43.8 (29.5-58.8)</td>
<td>58.8 (44.2-72.4)</td>
</tr>
<tr>
<td>DCR at week 48, % (95% CI)</td>
<td>22.9 (12.0-37.3)</td>
<td>33.3 (20.8-47.9)</td>
</tr>
</tbody>
</table>

POST-HOC SUBGROUP ANALYSIS

<table>
<thead>
<tr>
<th>mPFS by Ki-67</th>
<th>PanNET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67 ≤10% (n=43)</td>
<td>8.0 months (95% CI: 5.6-8.3)</td>
</tr>
<tr>
<td>Ki-67 &gt;10% (n=5)</td>
<td>2.8 months (95% CI: 2.8-2.9)</td>
</tr>
</tbody>
</table>

CI, confidence interval; DCR, disease control rate; mPFS, median progression free survival; NET, neuroendocrine tumour; panNET, pancreatic NET; TRAE, treatment-related adverse event

SUMMARY

- **Lanreotide (LAN) 120 mg every 14 days** in patients with progressive panNETs or midgut NETs (progressive on standard LAN dose) **provided encouraging PFS and disease control rate data**
  - In the panNET cohort, the outcome was more favourable in patients with Ki-67 ≤10%

- No new safety concerns were identified with the increased dose frequency of LAN
  - The **safety was consistent with the known safety profile of LAN**

- Escalating LAN dosing frequency in patients with progressive NETs **may be an alternative treatment option before switching to more toxic agents** such as PRRT/targeted therapies/chemotherapy

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NET, neuroendocrine tumour; panNET, pancreatic NET; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy
SURVIVAL AND PROGNOSTIC ANALYSIS OF 535 GRADE 3 GEP-NEN: DATA FROM THE SPANISH TASKFORCE OF NEUROENDOCRINE TUMOURS REGISTRY (R-GETNE)

Jimenez Fonseca P, et al.
ESMO 2020. Abstract #1159MO. Mini oral presentation
Grade 3 neuroendocrine carcinomas (NECs) represent the most aggressive spectrum of neuroendocrine neoplasms (NENS) and have limited treatment options.

A previous analysis from the GETNE (Spanish) registry confirmed the worse prognosis associated with grade and Ki-67 index in patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs).\(^1\)

The R-GETNE database includes 4807 GEP-NENs patients diagnosed between 2004-2019.

The study cohort for this analysis included 535 patients with grade 3 NECs with a Ki-67 index >20\(^%\).\(^2\)

### Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Grade 3 NEC Ki-67 &gt;20% N=535</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70 years</td>
<td>29% (median age 64) 80% 85%</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 0-1</td>
<td></td>
</tr>
<tr>
<td>Most common primary sites</td>
<td></td>
</tr>
<tr>
<td>Colorectum</td>
<td>30% 24% 16% 13% 4%</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3% 9% 20% 68%</td>
</tr>
<tr>
<td>II</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
</tr>
<tr>
<td>IV</td>
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</tr>
</tbody>
</table>

- 87% stage I-III NECs were resected
  - 54% of these received adjuvant chemotherapy

- 73% of patients with advanced NECs received platinum and etoposide
  - Response rate: 64%
  - Median progression-free survival (mPFS): 6.1 months

ECOG PS, Eastern Cooperative Oncology Group performance status; R-GETNE, Registry of Grupo Español de Tumores Neuroendocrinos
Median overall survival (OS) was 14 months; 353 patients died (67%)

Median follow up of 4 years

Prognostic factors: stage, primary site, ECOG PS and gender were identified as independent prognostic factors for OS (p<0.05)

### RESULTS

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>14</td>
</tr>
<tr>
<td>Median OS by stage (95% CI), years</td>
<td></td>
</tr>
<tr>
<td>- I</td>
<td>6.1 (1.8-NA)</td>
</tr>
<tr>
<td>- II</td>
<td>5.8 (1.9-NA)</td>
</tr>
<tr>
<td>- III</td>
<td>2.1 (1.5-6.7)</td>
</tr>
<tr>
<td>- IV (months)</td>
<td>9.7 (6.7-12.9)</td>
</tr>
<tr>
<td>Median OS by site in stage IV (95% CI), months</td>
<td></td>
</tr>
<tr>
<td>- Small Intestine</td>
<td>14.0 (12.6-15.8)</td>
</tr>
<tr>
<td>- Pancreas</td>
<td>10.1 (9.5-11.8)</td>
</tr>
<tr>
<td>- Rectum</td>
<td>9.9 (8.2-11.2)</td>
</tr>
<tr>
<td>- Stomach</td>
<td>7.3 (5.2-9.3)</td>
</tr>
<tr>
<td>- Colon</td>
<td>4.7 (2.8-7.0)</td>
</tr>
<tr>
<td>- Unknown primary</td>
<td>2.7 (1.9-3.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- I-III</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>- Primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Small intestine, pancreas, rectum</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>- ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2</td>
<td></td>
<td></td>
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<tr>
<td>- 0-1</td>
<td>Reference</td>
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</tr>
<tr>
<td>- Gender</td>
<td></td>
<td></td>
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<tr>
<td>- Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>Reference</td>
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</tbody>
</table>
SUMMARY

• One of the largest reported series of grade 3 GEP-NECs to date, providing important information to help stratify patients for clinical decisions

• Performance status, stage and primary tumour location are known prognostic factors for NETs but this is the first cohort study to identify gender as a potential new variable
  – Requires validation in clinical trials

GEP-NECs, gastroenteropancreatic neuroendocrine carcinomas; NET, neuroendocrine tumour
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