Systemic antitumor therapies: Do we have real algorithms in advanced NENs?

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Personal conflicts of interest: Scientific consultancy role (speaker and advisory roles) from Novartis, Pfizer, Ipsen, Exelixis, Bayer, Eisai, Advanced Accelerator Applications, Amgen, Sanofi and Merck Serono.

Research support: Research grants from Novartis, Pfizer, Astrazeneca, Advanced Accelerator Applications, Eisai and Bayer.
## TREATMENT OPTIONS = TREATMENT ALGORITHM?

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<tr>
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TREATMENT SEQUENCE BASED ON GUIDELINES?

- **Resection of primary**
  - (a) Simple pattern of LMs G1/G2 (unilobar or limited)
    - Resection (minor or anatomical)
  - (b) Complex pattern of LMs G1/G2 (bilobar)
    - Surgery contraindicated
    - One-step surgery
      - Major liver resection ± RFA
  - (c) Diffuse LMs G1/G2
    - Or surgery contraindicated
      - Two-step surgery
        - (1) Minor resection ± RFA, RPVE, RPVL
        - (2) Sequential major liver resection
      - Small intestinal
        - SSA (IFN)
        - PRRT
        - Everolimus
      - Pancreatic
        - SSA (IFN)
        - Chemotherapy
        - Everolimus
        - Sunitinib
        - PRRT
  - Selected cases (<1%)
  - Liver transplantation

SEQUENTIAL THERAPIES: COUNTRY-BASED...

panNETs

SSAs → CHT → EVEROLIMUS → SUNITINIB

SSAs → EVEROLIMUS → PRRT → SUNITINIB

SSAs → SUNITINIB → CHT → SSAs

EVEROLIMUS → SUNITINIB → CHT

SUNITINIB → CHT
## ADVANCED NENs: THERAPEUTIC ALGORITHM

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Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Lanreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Adler, Hans-Joachim Blum, German Schmidt-Bohme, Klaus-Jürgen Kliner, Peter Smith, Matthias Wind, Christine Mayer, Sebastian Armengaud, Ulrike Fend-Pop, Michael Hahner, Joa Flesch, Christian Arnold, Thomas Coss, and Roland Arnold

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jaroslav B. Čwikla, M.D., Ph.D., Alexandra T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators

PFS in midgut vs pancreatic NET
# RADIANT PROGRAM: EVEROLIMUS IN NETs

| RADIANT-1 | Phase II | Pancreatic NETs | Everolimus w/wo Octreotide LAR | E | ORR 9.6%  
PFS 9.7m  
E+O | ORR 4.4%  
PFS 16.7m |
|-----------|----------|----------------|-------------------------------|---|----------------------|----------------------|
| RADIANT-2 | Phase III | Non-Pancreatic NETs | Octreotide LAR + Everolimus vs Octreotide LAR + placebo | 16.4 vs 11.3m  
HR 0.77 P=0.026 (one sided) |
| RADIANT-3 | Phase III | Pancreatic NETs | Everolimus vs Placebo | 11 vs 4.6m  
HR 0.35 P<0.001 |
| RADIANT-4 | Phase III | GI & Lung NETs | Everolimus vs Placebo | 11 vs 3.9m  
HR 0.48 P<0.00001 |
RADIANT-4 STUDY DESIGN

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)
- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Radiologic disease progression in ≤ 6 months

Endpoints:
- **Primary**: PFS (central)
- **Key Secondary**: OS
- **Secondary**: ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:
- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

Everolimus 10 mg/day
N=205
Treated until PD, intolerable AE, or consent withdrawal

Placebo
N=97

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worst prognosis)** – lung, stomach, rectum, and colon except caecum.

Crossover to open-label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

PRIMARY ENDPOINT: PFS BY CENTRAL REVIEW

52% reduction in the relative risk of progression or death with everolimus vs placebo
HR = 0.48 (95% CI, 0.35-0.67); P < 0.00001

Kaplan–Meier medians
Everolimus: 11.0 months (95% CI, 9.23-13.31)
Placebo: 3.9 months (95% CI, 3.58-7.43)

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model. CI, confidence interval; HR, hazard ratio.

## PFS HR by Primary Origin

**Retrospective Centrally Reviewed**


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*One patient with thymus as primary tumor origin was not included.

†Stomach, colon, rectum, appendix, cecum, ileum, duodenum, and jejunum are grouped under GI.

Hazard ratio obtained from unstratified Cox model.

GI, gastrointestinal; NET, neuroendocrine tumors.

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study

NETTER-1 STUDY DESIGN

Aim
Evaluate the efficacy and safety of $^{177}$Lu-Dotatate (Lutathera®) plus Octreotide30 mg compared to Novartis Octreotide LAR 60mg (off-label use) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use).

Design
International, multicenter, randomized, comparator-controlled, parallel-group

Baseline and Randomization
n = 115

Treatment and Assessments
Progression free survival (Recist criteria) every 12 weeks

- Dose 1
- Dose 2
- Dose 3
- Dose 4

4 administrations of 7.4 GBq of LUTATHERA every 8 weeks + Octreotide30 mg

n = 115

Octreotide LAR 60mg every 4 weeks

5 Years follow up

# PATIENTS’ CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>(^{177}\text{Lu-Dotatate (n=116)})</th>
<th>(\text{Octreotide LAR 60mg (n=113)})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>63 (±9)</td>
<td>64 (±10)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (46%)</td>
<td>60 (53%)</td>
</tr>
<tr>
<td>Female</td>
<td>63 (54%)</td>
<td>53 (47%)</td>
</tr>
<tr>
<td><strong>Primary tumor site, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>6 (5%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Ileum</td>
<td>86 (74%)</td>
<td>82 (73%)</td>
</tr>
<tr>
<td>Appendix</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Right colon</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (17%)</td>
<td>19 (17%)</td>
</tr>
<tr>
<td><strong>Site of metastasis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>97 (84%)</td>
<td>94 (83%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>77 (66%)</td>
<td>65 (58%)</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>13 (11%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Lungs</td>
<td>11 (10%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>40 (35%)</td>
<td>37 (33%)</td>
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PRIMARY ENDPOINT: PFS

Strosberg J, et al. ENETS 2018

HR 0.212 (0.137 to 0.327)  
$P<.0001$
TREND ON OVERALL SURVIVAL BENEFIT

HR 0.536 (0.333 to 0.864)
\[ P = .0094 \]

mOS
Oct LAR 60 mg: 27.4 months
\[^{177}\text{Lu-DOTATATE}: \text{NR}\]

Strosberg J, et al. ENETS 2018
**SWOG S0518: STUDY DESIGN**

**Study population**
Advanced G1/2 NET with poor prognosis
- Progressive disease
- Refractory syndrome
- G2 with 6+ lesion
- Colorectal or gastric primary

**Randomize**

1:1

**Bevacizumab 15 mg/kg q21 d**
**Octreotide LAR 20 mg q21 d**

**Treatment until disease progression**

**Interferon α-2b 5 μg 3 d/wk**
**Octreotide LAR 20 mg q21 d**

**Multiphasic CT or MRI performed every 9 wk**

**Primary endpoint:**
- PFS (Central radiology review)

**Stratification factors:**
- Primary site: Midgut vs others
- PD since diagnosis
- Histologic grade: G1 vs G2
- Octreotide 2 months prior to registration

MY TENTATIVE ALGORITHM FOR siNETs

1st Treatment option
- SOMATOSTATIN ANALOGUES:
  - Functioning & non-functioning
  - SSRT scintigraphy +ive & -ive (?)
  - Ki67 up to 10% (and over…)

2nd Treatment option

3rd Treatment option
- EVEROLIMUS (EVEROLIMUS + SSAs)
  - Non-functioning (functioning)
  - SSRT scintigraphy +ive & -ive
  - High & low tumor burden

4th Treatment option
- 177Lu-DOTATATE
  - Functioning & non-functioning
  - SSRT scintigraphy +ive

- Interferon… ¿?
  - Indication based on a negative trial & old trials…

- CHT?
# ADVANCED NENs: THERAPEUTIC ALGORITHM

## Unresectable NENs

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- Everolimus RADIANT-3 & RADIANT-4
- PRRT NETTER-1
- Interferon
- Sunitinib
- Chemotherapy
- Everolimus RADIANT-4
- Chemotherapy
- Somatostatin Analogues?
- Targeted agents?
CLARINET: PFS IN panNETs

PFS in midgut vs pancreatic NET

Midgut NETs (n = 73)
Lanreotide Autogel vs placebo
$P = .0091$ HR = 0.35 [95% CI: 0.16, 0.80]

pNETs (n = 91)
Lanreotide Autogel vs placebo
$P = .0637$ HR = 0.58 [95% CI: 0.32, 1.04]

RADIANT-3: STUDY DESIGN

Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pNET (N = 410)
- Advanced well or moderately differentiated
- Radiologic progression ≤12 months
- Prior antitumour therapy allowed
- WHO PS ≤2

Stratified by:
- WHO PS
- Prior chemotherapy

Randomise

1:1

Everolimus 10 mg/d + best supportive care¹
n = 207

Placebo + best supportive care¹
n = 203

Crossover at disease progression

Multiphasic CT or MRI performed every 12 weeks

Primary Endpoint: Progression-free survival By investigator review
Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

¹Concurrent somatostatin analogues allowed

PRIMARY ENDPOINT: PFS BY CENTRAL REVIEW

Kaplan-Meier median PFS
- Everolimus: 11.0 months
- Placebo: 4.6 months

Hazard ratio = 0.35; 95% CI 0.27-0.45

P value: <.0001

In the everolimus arm, median PFS did not significantly differ in patients who did and did not receive prior chemotherapy.

In the placebo arm, a trend toward shorter median PFS was observed in patients who had received prior chemotherapy compared with chemo-naive patients.

\( p \) value is obtained from the unstratified one-sided log-rank test. Hazard ratio is obtained from unstratified unadjusted Cox model.


**Phase III randomised, placebo-controlled, double-blind trial**

**Trial terminated after unplanned early analysis**

Well differentiated advanced pNET patients (N = 171 enrolled / 340 planned)
- Disease progression in past 12 mos
- Not amenable to curative treatment

**Primary Endpoint:**
- PFS

**Secondary Endpoints:**
- OS
- ORR
- TTR
- Duration of response
- Safety
- Patient-reported outcomes

*S with best supportive care
Somatostatin analogues were permitted

Sunitinib 37.5 mg/day orally
Continuous daily dosing*

n = 86

Placebo*

n = 85

**PRIMARY ENDPOINT: PFS BY CENTRAL REVIEW**

Kaplan-Meier median PFS
- Sunitinib: 11.4 months
- Placebo: 5.5 months

HR = 0.42; 95% CI [0.26-0.66]

P value <.001; nominal critical z value = 3.8506

DEGREE OF TUMOR SHRINKAGE

Maximum change from baseline of target lesions in patients from the sunitinib phase III study

The RECIST-defined ORR in patients receiving sunitinib was 9.3%; however, the majority of patients had some degree of tumour shrinkage (Clinical Benefit Rate 72%)†

OVERALL SURVIVAL


![Graph showing overall survival with Sunitinib and Placebo](image)

- **Sunitinib**
  - Events: 55 (64%)
  - mOS, mo: 38.6

- **Placebo**
  - Events: 58 (68%)
  - mOS, mo: 29.1

HR 0.73 (95% CI: 0.50–1.06)

*P* = 0.094

<table>
<thead>
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<tr>
<td>Sunitinib</td>
<td>86 77 69 57 49 46 41 37 35 32 26 19 8 3</td>
</tr>
<tr>
<td>Placebo</td>
<td>85 68 56 45 42 37 29 25 22 16 16 11 4 3</td>
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STZ-BASED CHEMOTHERAPY

TEMOZOLOMIDE-BASED CHEMOTHERAPY

**Progression Free Survival**

<table>
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<tr>
<th>Group</th>
<th>Median (mo)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tr>
<td>A: Tem</td>
<td>14.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Tem+ Cape</td>
<td>22.7</td>
<td>0.58 (0.36, 0.93)</td>
<td>0.023</td>
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RR: 28% vs 33% (p=0.47)
G3-4 AEs: 22% vs 44% (p=0.007)

Kunz PL, et al. ASCO 2018
MY TENTATIVE ALGORITHM FOR panNETs

1st Treatment option
- SOMATOSTATIN ANALOGUES:
  - Functioning & non-functioning
  - SSRT scintigraphy +ive
  - Ki up to 10%
  - Not too much liver involvement

2nd Treatment option
- EVEROLIMUS / SUNITINIB / CHT

1st Treatment option
- EVEROLIMUS / SUNITINIB / CHT
  - Progressive disease
  - Higher tumor burden
  - Symptoms related with tumor burden

Sequential therapies

Refractory setting
- PRRT ¿?
- Alternative CHT regimens ¿?
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- **Somatostatin Analogues?**
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- **Sunitinib**
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EVEROLIMUS THE ONLY APPROVED DRUG FOR LUNG NETS

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†Stomach, colon, rectum, appendix, cecum, ileum, duodenum, and jejunum are grouped under GI.

Hazard ratio obtained from unstratified Cox model.
GI, gastrointestinal; NET, neuroendocrine tumors.

LIMITED EFFICACY OF CHT IN LUNG NETs

Table 7. Results of the treatment with streptozotocin and 5-FU.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of courses</th>
<th>Biochemical result</th>
<th>Time to progression</th>
<th>Objective result</th>
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<tr>
<td>1</td>
<td>11</td>
<td>Progression</td>
<td>9</td>
<td>Progression</td>
<td>6</td>
</tr>
<tr>
<td>8 (a)</td>
<td>6</td>
<td>Progression</td>
<td>4</td>
<td>Progression</td>
<td>2</td>
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<tr>
<td>11 (a)</td>
<td>14</td>
<td>Progression</td>
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<td>Progression</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
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<tr>
<td>13</td>
<td>15</td>
<td>Progression</td>
<td>11(^a)</td>
<td>Progression</td>
<td>12(^a)</td>
</tr>
<tr>
<td>27</td>
<td>6</td>
<td>Stable</td>
<td>5(^b)</td>
<td>Progression</td>
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<td>31</td>
<td>5</td>
<td>Progression</td>
<td>1</td>
<td>Progression</td>
<td>4</td>
</tr>
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</table>

Table 6. Results of the treatment with cisplatinum and etoposide.

<table>
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<th>Patient</th>
<th>Number of courses</th>
<th>Biochemical result</th>
<th>Response duration/ time to progression(^a)</th>
<th>Objective result</th>
<th>Response duration/ time to progression(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>Progression</td>
<td>2</td>
<td>Progression</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>Stable</td>
<td>6</td>
<td>Regress</td>
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<td>4</td>
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<td>8</td>
<td>Progression</td>
<td>4</td>
</tr>
<tr>
<td>14 (a)</td>
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<td>Regress</td>
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<td>Progression</td>
<td>4</td>
</tr>
<tr>
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<td>6</td>
<td>Stable</td>
<td>6</td>
<td>Stable</td>
<td>7</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>Progression</td>
<td>3</td>
<td>Progression</td>
<td>3</td>
</tr>
<tr>
<td>25</td>
<td>8</td>
<td>Stable</td>
<td>8</td>
<td>Regress</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) In the patients displaying stable disease or regression the figures denote response duration and in those patients who progressed the figures show time to progression. Time is expressed in months.

SSAs IN LUNG NETs: ONLY RETROSPECTIVE DATA

- 61 patients with advanced lung NET (1986 – 2014) with SSA monotherapy
- 55.7% male
- 95% with PS ≤1
- 80% had liver metastases

Tumor evaluation by CT scan and/or MRI q 3-6 months; reassessed according to RECIST v1.0 and v1.1
Octreotide LAR 20/30 mg
Lanreotide AG 90/120 mg
Median SSA Tx: 13.7 months (3-155)

First-line SSA: 75% (70% PD, 30% CS)
Best response: SD in 43 patients (70.5%)
    PD in 14 patients (23%)
Median PFS: 17.4 months [95% CI = 8.7–26.0]
Median OS: 58.4 months [44.2–102.7]

**MY TENTATIVE ALGORITHM FOR LUNG NETs**

1st **Treatment option**
- SOMATOSTATIN ANALOGUES...
  - Functioning & non-functioning
  - SSRT scintigraphy +ive
  - Typical (atypical)

2nd **Treatment option**
- EVEROLIMUS

3rd **Treatment option**
- CHT (TMZ?) / PRRT?
## ADVANCED NENs: THERAPEUTIC ALGORITHM

<table>
<thead>
<tr>
<th>Unresectable NENs</th>
<th>G1</th>
<th>G2</th>
<th>G1</th>
<th>G2</th>
<th>G1</th>
<th>G2</th>
<th>NETG3</th>
<th>NECG3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-NET</td>
<td>Octreotide (PROMID)</td>
<td>Everolimus RADIANT-4</td>
<td>Chemotherapy</td>
<td>Lanreotide (CLARINET)</td>
<td>Somatostatin Analogues?</td>
<td>Somatostatin Analogues?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>panNET</td>
<td>Everolimus RADIANT-3 &amp; RADIANT-4</td>
<td>Chemotherapy</td>
<td>Targeted agents?</td>
<td>PRRT NETTER-1</td>
<td>Sunitinib</td>
<td></td>
<td></td>
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<tr>
<td>LUNG NET</td>
<td>Interferon</td>
<td>Chemotherapy</td>
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<tr>
<td>NEN G3</td>
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<td></td>
<td></td>
<td>NETG3</td>
<td>NECG3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PLATINUM-BASED CHT IN G3 NENs

Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study

TREATMENT SUGGESTIONS...

Advanced NEN G3 Treatment Algorithm

**NET G3** (Ki67<60%)

- NET-like presentation

**Uncertain G3** (Ki67<50%-60%)

- NET-like presentation

**NEC Ki67<50%-60%**

- Rapid growth

1-line:

- NET G2 options
  - TemCap
  - Everolimus
  - Sunitinib if pancreas
  - PRRT if SRI positive
  - EP if rapid PD.
  - Metastatic surgery.

2-line: FOLFIRI, TemCap or FOLFOX.

**NEC Ki67>50%-60%**

- **1-line:** EP
- **2-line:** FOLFIRI, TemCap or FOLFOX.

MSI high = immunotherapy?

CRC primary: FOLFIRINOX/
FOLFOX/FOLFIRI 1-line?

INITIAL DATA TO TREAT NET G3 AS NET G2...

<table>
<thead>
<tr>
<th>Table 2. Response Evaluation by RECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of evaluable patients</td>
</tr>
<tr>
<td>Non evaluable</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Tumor stabilization</td>
</tr>
<tr>
<td>Tumor control</td>
</tr>
<tr>
<td>Tumor progression</td>
</tr>
</tbody>
</table>

SUNITINIB

RECIST ORR: 34% (Ki67<55%) vs 17% (Ki67>55%)

RR: 43/31/57%

PRRT

TMZ-BASED CHT
Thank you 😊