Clinical Scenario #1

Advanced, Grade 2, Neuroendocrine Tumor in the Midgut: Watch and Wait or Initiate Treatment?

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Clinical Scenario #1

- 40-year-old white Caucasian male
- No relevant family history
- Previously fit
- July 2004: Underwent an abdominal CT scan following trauma experienced in a car accident
  - No traumatic organ damage
  - However, 2.0 cm mass in terminal ileum plus three liver lesions suspicious for metastases
- Endoscopic biopsy of ileum mass
  - Grade 2 neuroendocrine tumor
  - Ki-67 4%; 3 mitoses per 10 high power fields

Clinical Scenario #1

Additional investigations:

- Somatostatin receptor scintigraphy (Octreoscan®)
  - Uptake in liver lesions noted
- 5-HIAA levels and neuron-specific enolase (NSE) within normal range

Clinical Scenario #1

- Patient underwent radical resection
  - Full recovery and in complete remission
  - Lost to follow-up in 2009
- In 2014, he presented a renal colic and abdominal ultrasound was performed, showing multiple liver metastases
  - Body CT scan identified bilobar liver metastases and mesenteric lymph nodes
  - Octreoscan: Uptake in liver and lymph nodes (Krenning scale 4)
  - No carcinoid syndrome, asymptomatic
  - Lab tests within normal range, including liver function, except for CgA 1450 U/L (N<100 U/L)

Parameters With an Impact on Therapeutic Decision Making

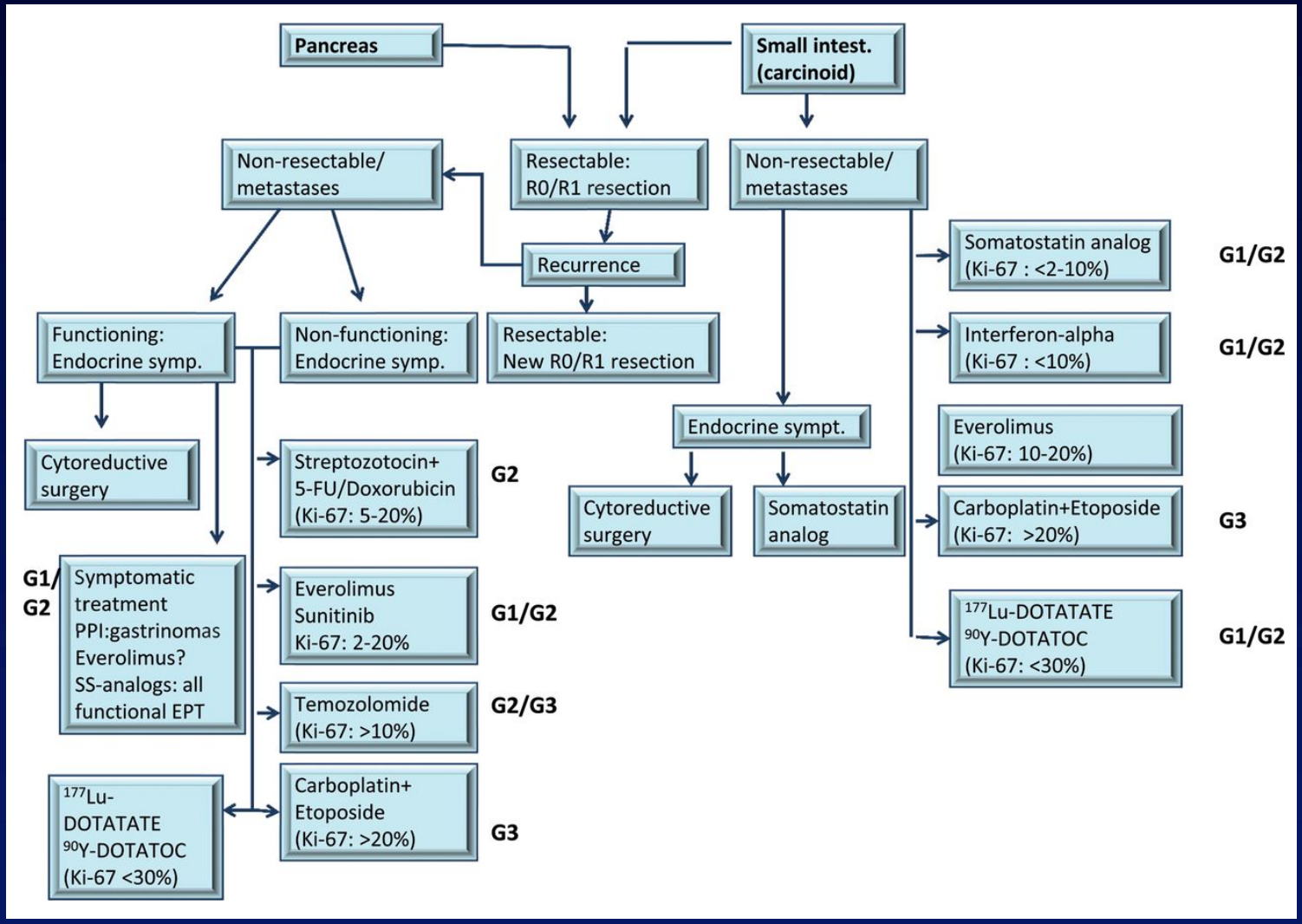
- Histology
  - Grading grade 1 / grade 2 (NET) vs grade 3 (NEC) (WHO 2010)
  - Well / moderately or poorly differentiated NET / NEC (US)
- Hormonal release
  - Carcinoid syndrome, insulinoma, gastrinoma, VIPoma
- Primary tumor site
  - Pancreatic vs intestinal
- Somatostatin receptor imaging
- Tumor burden / extrahepatic disease

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; WHO, World Health Organization

Locoregional Treatments in Metastatic Setting

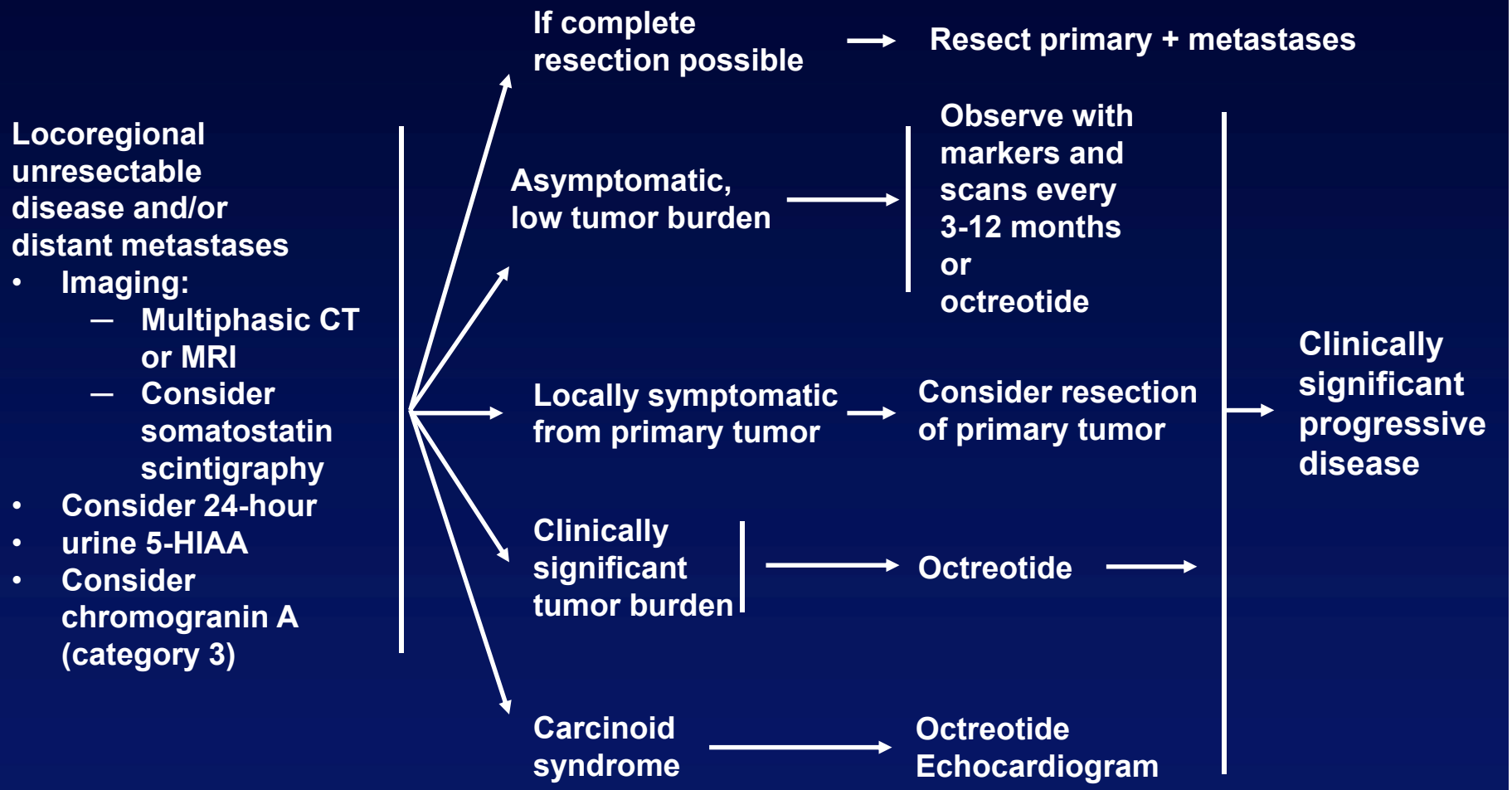
- Radical surgery of primary tumor and metastases is recommended when R0 can be achieved
- No data of adjuvant therapy are available in this setting
- Locoregional liver therapies (radiofrequency ablation, hepatic artery (chemo)embolization) could be a treatment option based on tumor size, anatomical location, number of metastases and presence of extrahepatic disease

Systemic Therapy: How Guidelines Could Help Us



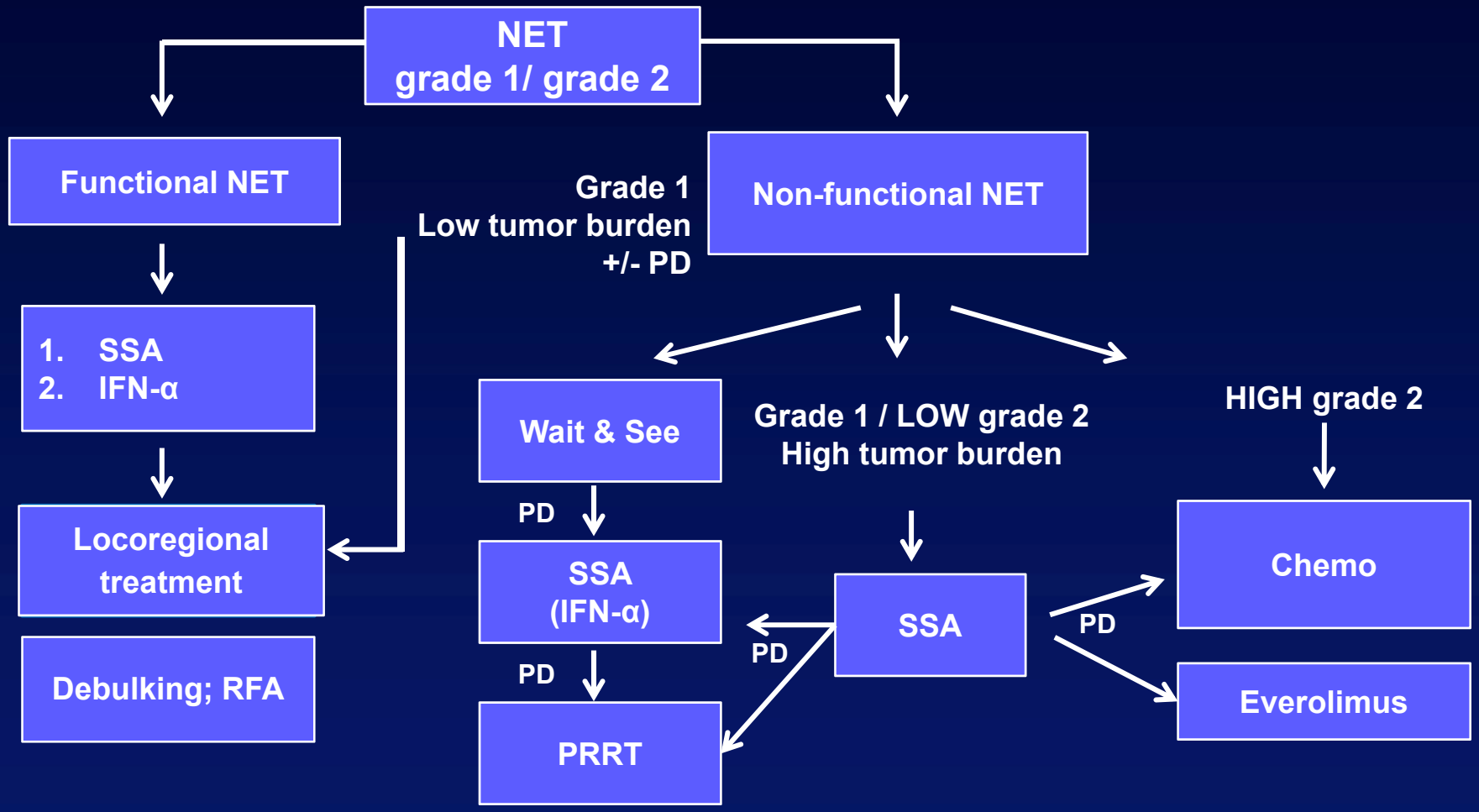
Öberg K, et al. *Ann Oncol.* 2012;23 Suppl 7:vii124-130

Systemic Therapy: How Guidelines Could Help Us



National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed: September 22, 2014.

Systemic Therapy: How Guidelines Could Help Us



PD, progressive disease; SSA, somatostatin analog; IFN, interferon; RFA, radiofrequency ablation

Adapted from Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157-176.

Chemotherapy: Limited Role in Enteric NETs

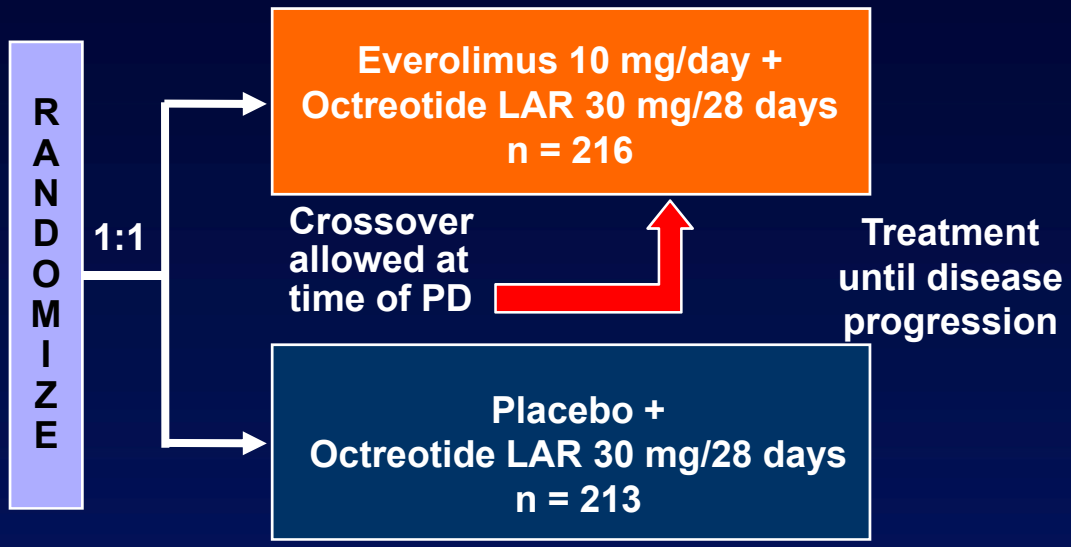
Treatment	Author	Histology	No.	ORR, %	Median survival
Doxorubicin	Engstrom [53]	Carcinoid	81	21	12
DTIC	Bukowski [54]	Carcinoid	63	16	20
Paclitaxel	Ansell [55]	Carcinoid	24	8	18
Docetaxel	Kulke [56]	Carcinoid	21	0	24
Gemcitabine	Kulke [57]	Carcinoid	18	0	11.5
Topotecan	Ansell [58]	Carcinoid	22	0	22
Temozolomide	Ekeblad [59]	Pancreatic NET	12	8	7
Pemetrexed	Chan [60]	Pancreatic and carcinoid	17	6	12.1

Grande E, et al. *Clin Transl Oncol.* 2010;12(7):481-492.

Molecular Targeted Therapies in Extrapancreatic NETs

Patients with advanced NET and a history of secretory symptoms (N = 429)

- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- History of secretory symptoms (flushing, diarrhea)
- Prior antitumour therapy allowed
- WHO PS ≤2



Primary Endpoint:

- PFS

Statistical boundary = .0246

Secondary Endpoints:

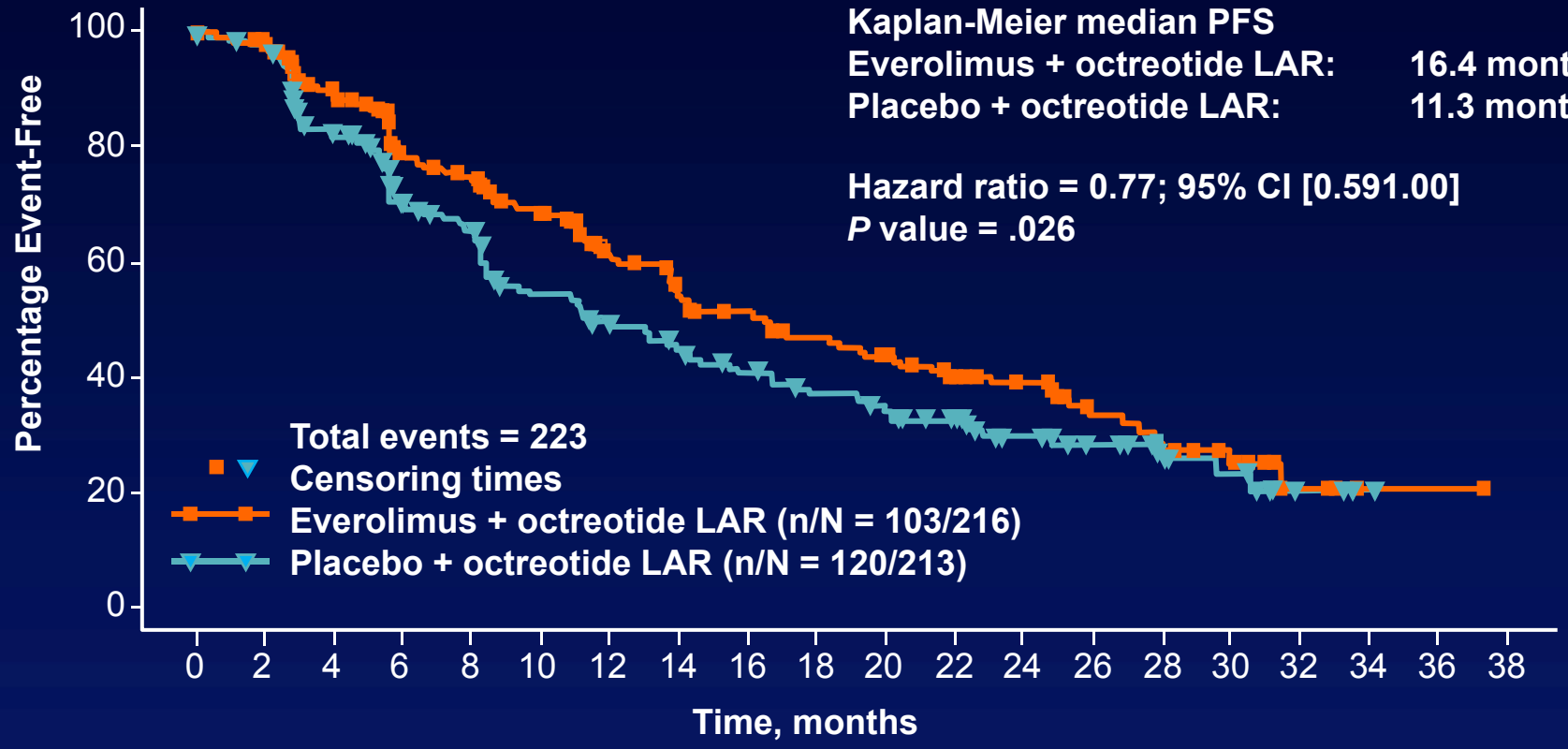
- OS
- ORR
- Biomarkers
- Safety
- PK

Enrollment January 2007-March 2008

PD, progressive disease; ORR, overall response rate; PK, pharmacokinetics

Pavel M, et al. *Lancet.* 2011;378(9808):2005-2012.

RADIANT-2: Border-Line Negative Trial



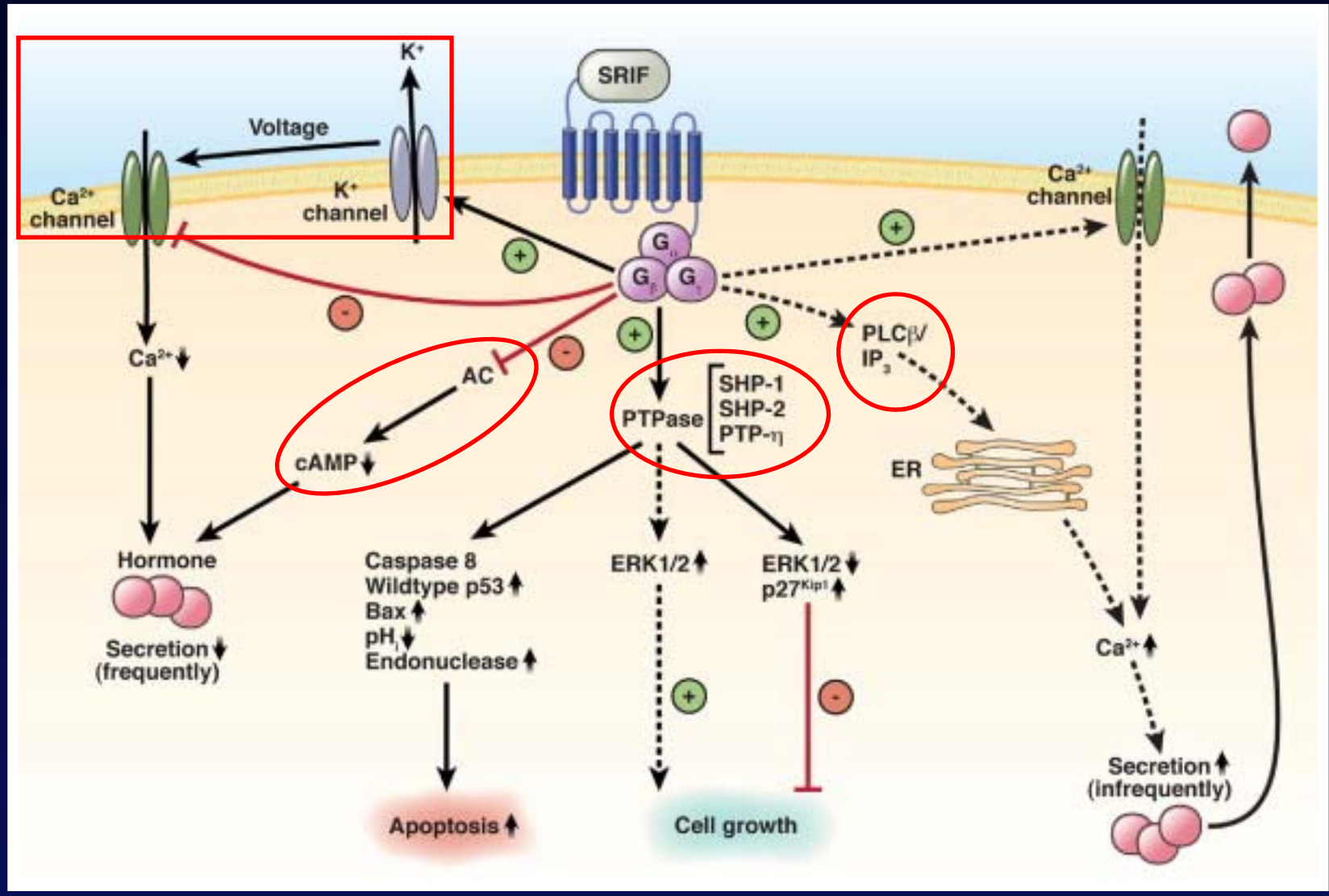
123 placebo + octreotide LAR patients crossed over at the time of progression

Pavel M, et al. *Lancet.* 2011;378(9808):2005-2012.

Ongoing Phase III Clinical Trials in Extrapancreatic NETs

- RADIANT-4
  - Nonfunctioning gastrointestinal and lung grade 1 / grade 2 NETs
  - Documented disease progression
  - Everolimus vs placebo
- SWOG0518
  - Octreotide + bevacizumab vs octreotide + IFNα
  - Grade 2 small intestine NETs in prior disease progression
- NETTER-1
  - Lutetium + octreotide vs octreotide
  - Grade 1 / grade 2 small intestine in progression after somatostatin analog (SSA)

Antiproliferative Effect of SSA in NETs



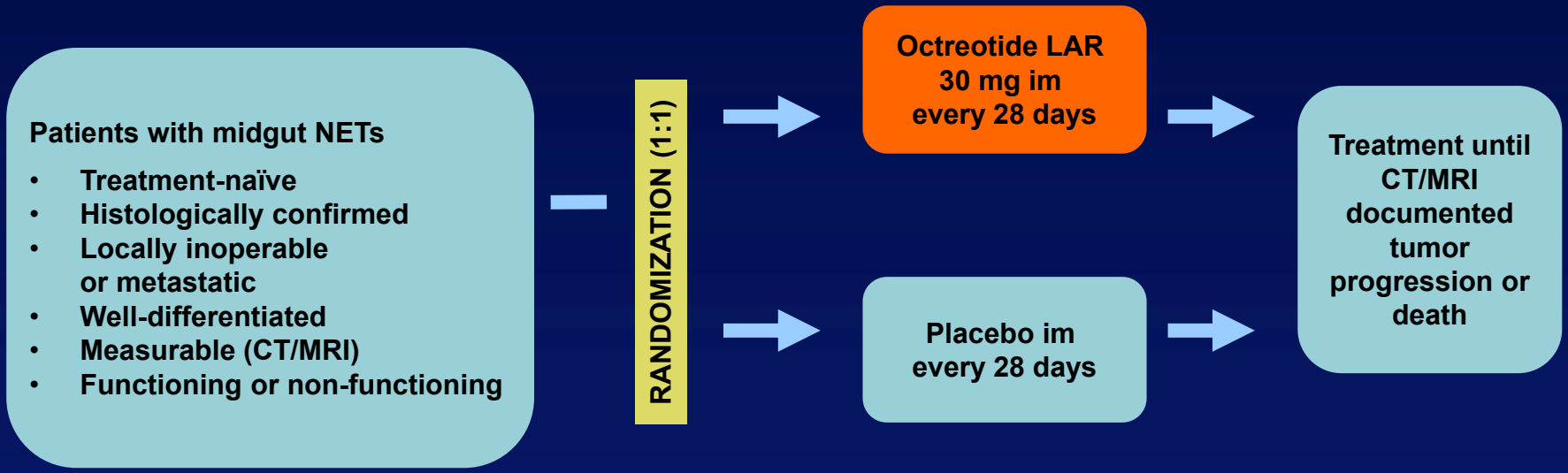
Öberg KE, et al. *Gastroenterology.* 2010;139(3):742-753.

Prospective Trials of SSA in Small Intestine NETs

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

Phase III, randomized, double-blind, placebo-controlled

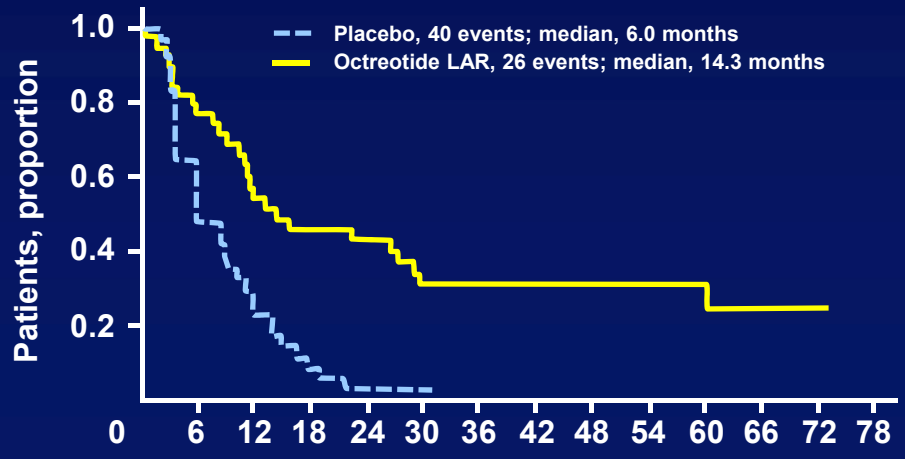
18 centers in Germany (2001–2008)



Rinke A, et al. *J Clin Oncol.* 2009;27(28):4656-4663.

PROMID Study: Grade 1 and Low Liver Involvement Small Intestine NETs

	Octreotide LAR n = 42	Placebo n = 43
Median age, years (range)	63.5 (38-79)	61.0 (39-82)
Carcinoid syndrome (%)	40.5	37.2
Hepatic tumor load		
0%	16.7	11.6
0% - 10%	59.5	62.8
10% - 25%	7.1	4.7
25% - 50%	11.9	9.3
>50%	4.8	11.6
Octreoscan positive (%)	76.2	72.1
Ki-67 up to 2% (%)	97.6	93.0



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

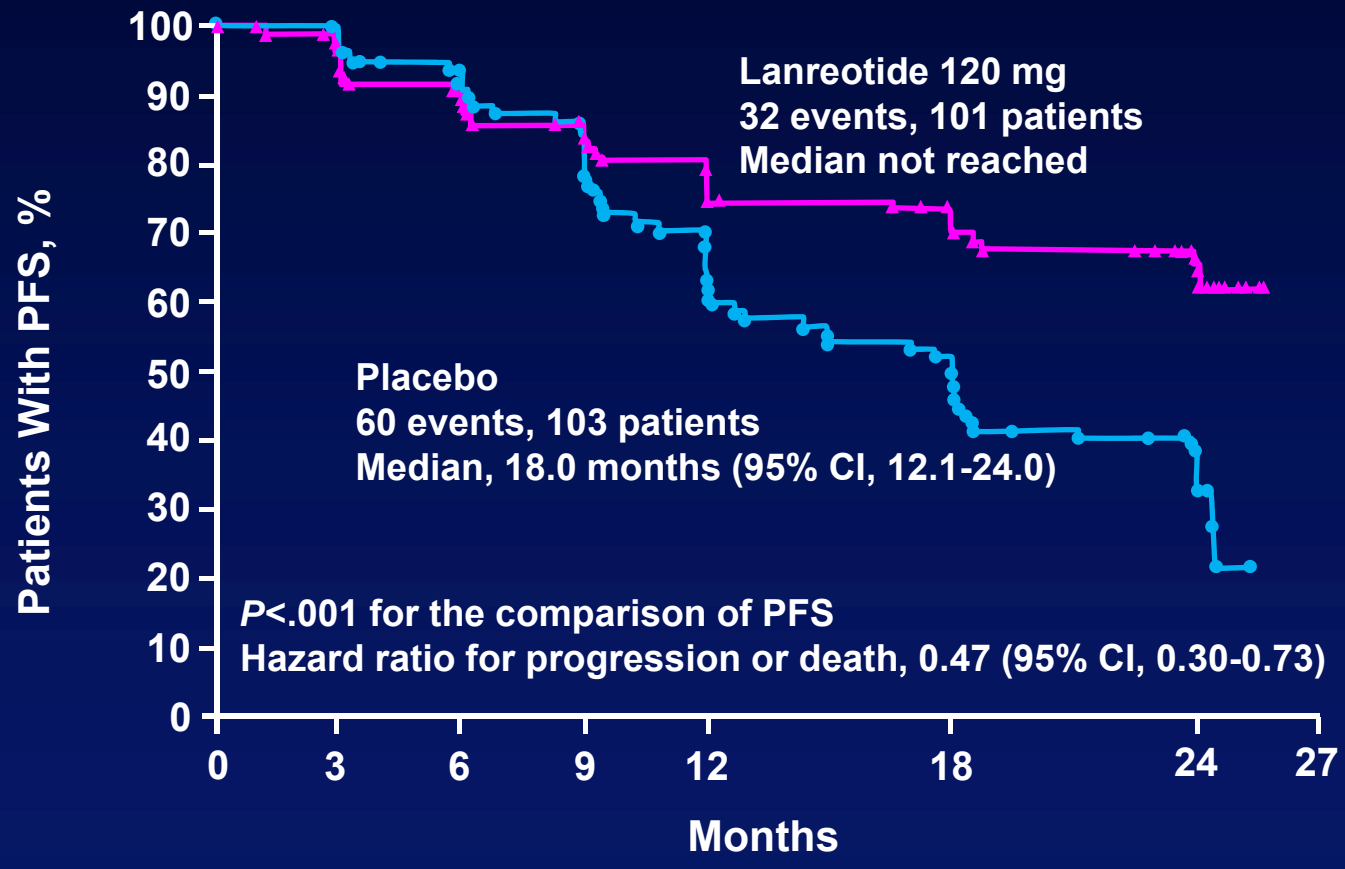
Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, 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*

- **Nonfunctional**
- **Nonprogressive**
- **Enteropancreatic**
- **G1/G2 (Ki67<10%)**

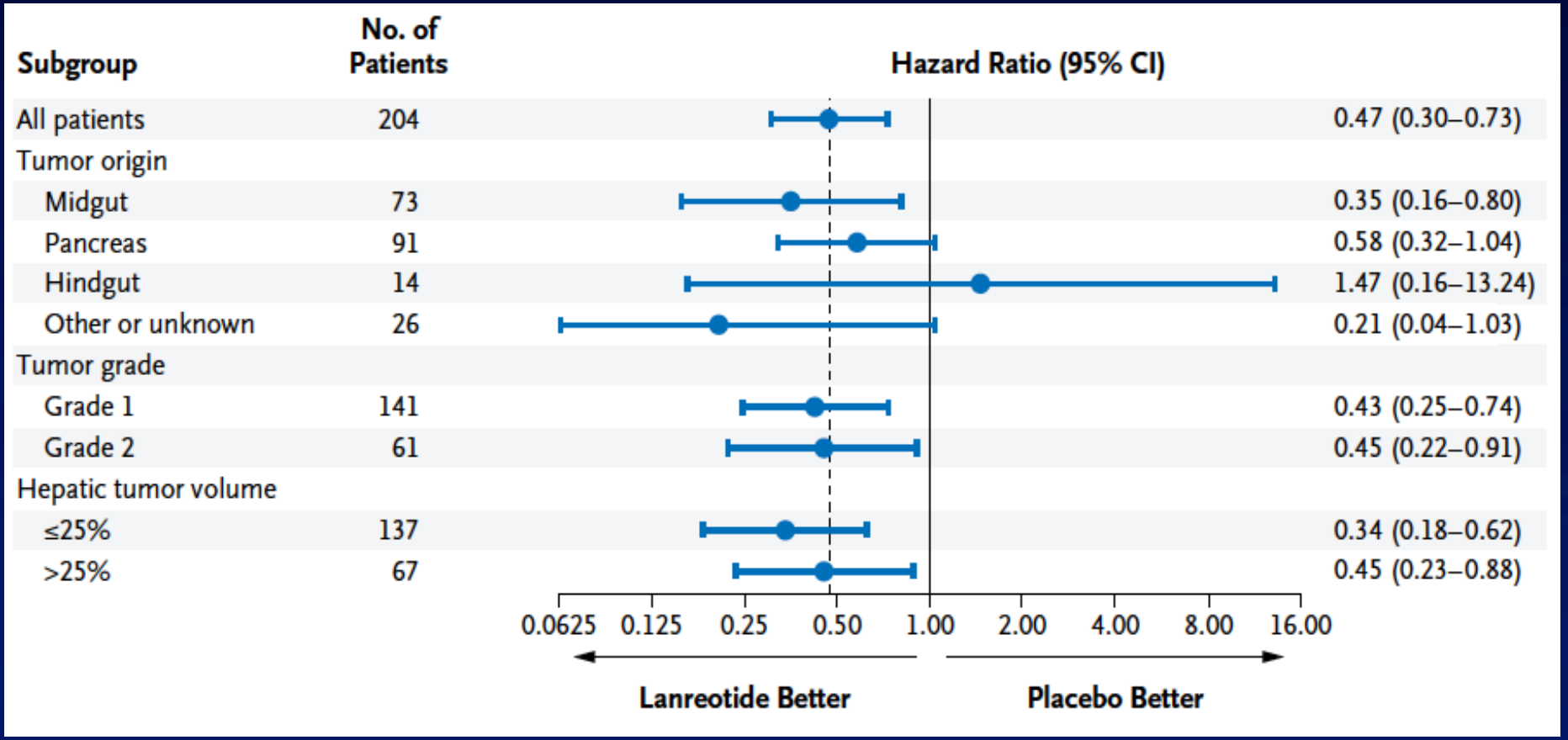
Caplin ME, et al. *N Engl J Med.* 2014;371(3):224-233.

CLARINET Study - Progression-Free Survival (PFS)



Caplin ME, et al. *N Engl J Med.* 2014;371(3):224-233.

CLARINET: Increase PFS in Grade 1 / Grade 2, High Liver Involvement, Enteropancreatic NETs



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Evidence-Based Treatment Decisions

- Radical surgery for the primary and all metastatic sites suggests increases survival
- Disease progression status is not always easy or feasible to assess
- Phase III clinical trials with targeted agents include populations with documented disease progression
- The CLARINET study results challenge the traditional wait & see policy

THANK YOU FOR YOUR ATTENTION

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