Neuroendokrinní tumory novinky z ASCO GI 2021

MUDr. Jiří Tomášek, Ph.D.

Masarykův onkologický ústav, Brno

PragueONCO 2021

Přehled:

- Připomenutí: klasifikace GEP-NET 2017
- Stručný přehled systémové léčby GEP-NET
- Studie AXINET (Octreotid LAR + axitinib vs octreotid LAR +placebo u pokročilého nepankreatického NET)
- PRRT - elementární informace

WHO klasifikace NEN 2017

Table 1. The 2017 World Health Organization classification of neuroendocrine neoplasms [2]

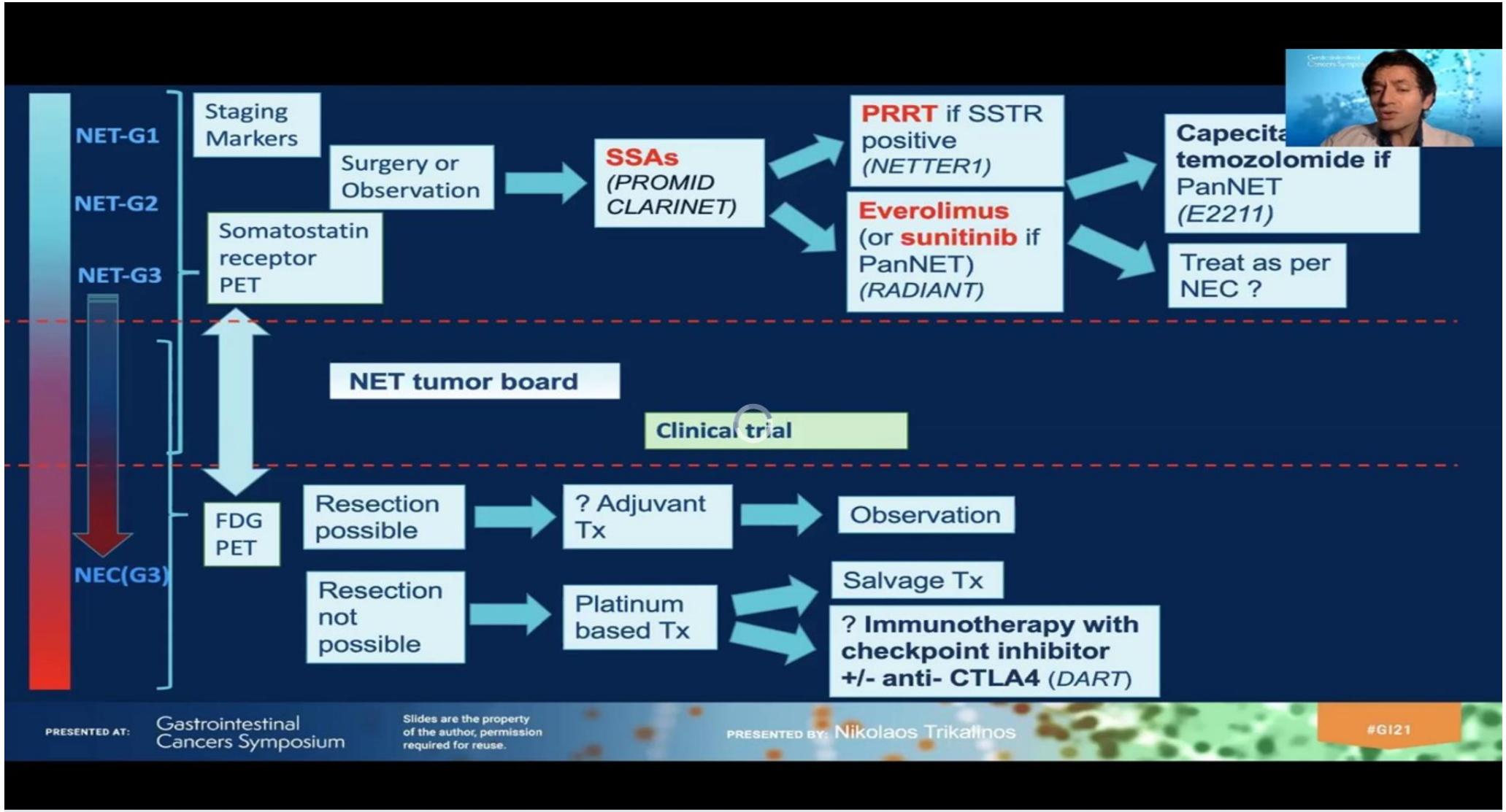
	Ki67, %	Mitotic index, mitoses per 10 high-power fields
Grade 1	<3	<2
Grade 2	3–20	2–20
Grade 3	>20	>20
	Grade	**Differentiation**
G1 neuroendocrine tumour	Grade 1	Well differentiated
G2 neuroendocrine tumour	Grade 2	Well differentiated
G3 neuroendocrine tumour	Grade 3	Well differentiated
G3 neuroendocrine carcinoma	Grade 3	Poorly differentiated
MiNEN	All grades	Association of a neuroendocrine and a non-neuroendocrine component

Recent Advances in NETs

1980 | 1985 | 1990 | 1995 | 2000 | 2005 | 2010 | 2015 | 2020

- Streptozocin (1982)
- Octreotide (1988)
- Everolimus, Sunitinib in pNET (2011)
- Lanreotide in GEP-NET (2014)
- Everolimus in GI/Lung NET (2016)
- Telotristat in Carcinoid Syndrome (2017)
- ^{177}Lu Dotatate (2018)
- *CapeTem (2018)
- *Surufatinib (2020)

*Not FDA-Approved


NET-G1
NET-G2
NET-G3
NEC(G3)
Staging Markers
Somatostatin receptor PET
FDG PET
Surgery or Observation
SSAs (PROMID CLARINET)
PRRT if SSTR positive (NETTER1)
Everolimus (or sunitinib if PanNET) (RADIANT)
Capecita
temozolomide if PanNET (E2211)
Treat as per NEC ?
NET tumor board
Clinical trial
Resection possible
? Adjuvant Tx
Observation
Resection not possible
Platinum based Tx
Salvage Tx
? Immunotherapy with checkpoint inhibitor +/- anti- CTLA4 (DART)
PRESENTED AT: Gastrointestinal Cancers Symposium
Slides are the property of the author, permission required for reuse.
PRESENTED BY: Nikolaos Trikalinos
#GI21

Abstract ID (Temp. ID): 360 (322043)

AXINET trial (GETNE-1107)
Phase II/III randomized double-blind study of Axitinib and octeotride LAR versus Placebo and octeotride LAR in patients with advanced G1-G2 NETs of extra-pancreatic origin

Rocio Garcia-Carbonero*, Marta Benavent, Paula Jiménez Fonseca, Daniel Castellano, Teresa Alonso, Alex Teule, Ana Custodio, Salvatore Tafuto, Adelaida La Casta Munoa, Francesca Spada, Carlos López-López, Toni Ibrahim, Maria Jose Villanueva Silva, Vega Iranzo, Pilar Garcia-Alfonso, Encarnación González, Enrique Grande, Guillermo Crespo, Jaume Capdevila.

** Hospital Universitario 12 de Octubre, Universidad Complutense, Madrid, Spain*

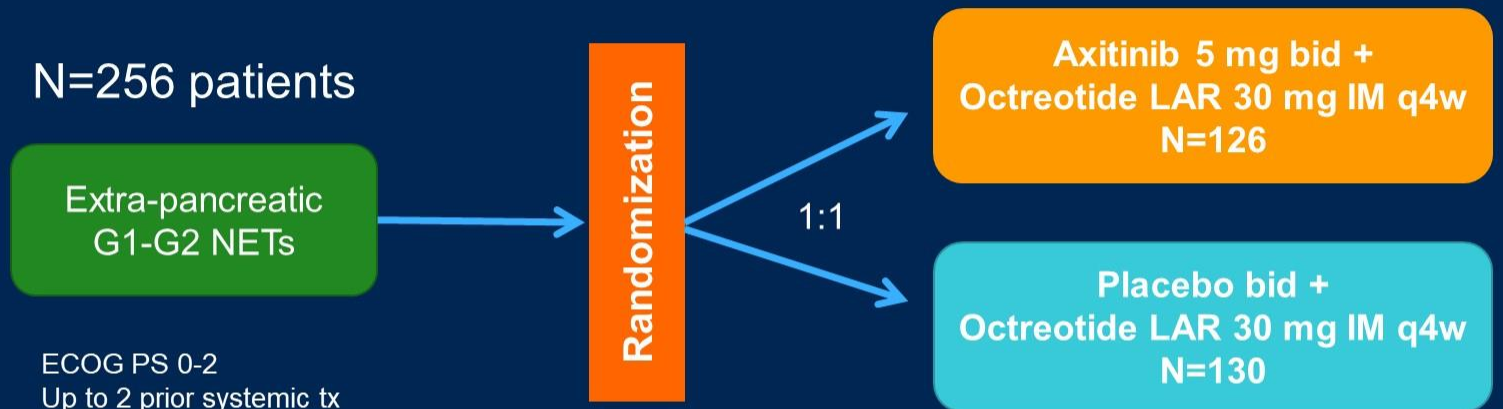
PRESENTED AT: Gastrointestinal Cancers Symposium

#GI21

Rationale

- Angiogenesis plays an important role in NET development and progression
- Axitinib is a potent and selective VEGFR-1,2,3 inhibitor, with proven activity against other vascular-dependent solid tumors
- Effective therapeutic options for patients with advanced, progressive, extra-pancreatic NETs are limited
- The aim of this randomized, double-blind phase II/III trial was to assess the efficacy of axitinib in patients with advanced G1-G2 extra-pancreatic NETs

Study Design



Study Endpoints:

- **Primary:** PFS
- **Secondary:** ORR, DoR, OS, safety, biochemical response, biomarkers

Stratification factors:

- Time from diagnosis to study entry (> or ≤ 12m)
- Primary tumor site (GI tract vs non-GI)
- Ki-67 index (≤ 5% vs > 5%)

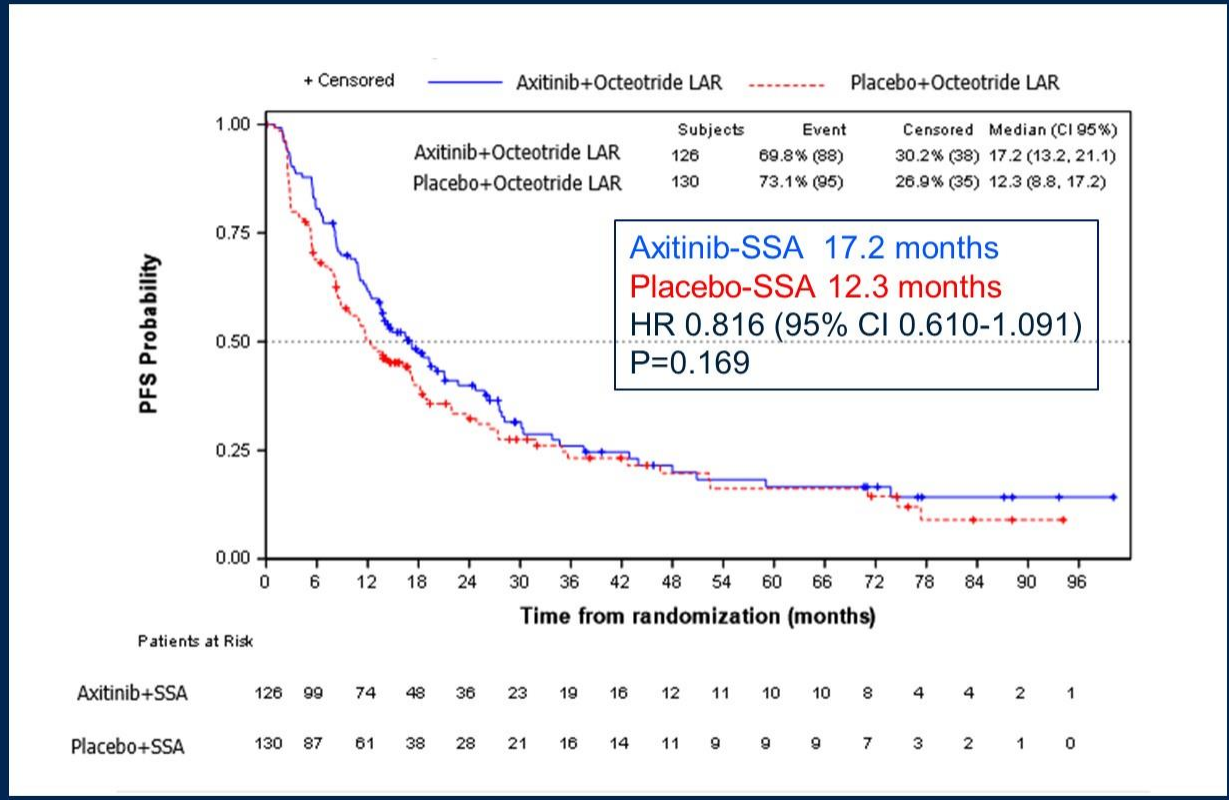
Patient and disease characteristics

	AXITINIB-SSA (N=126)	PLACEBO-SSA (N=130)
Age, median (range)	62 (21, 85)	60 (26, 83)
Gender, female/male	55/70	63/67
Grade		
G1	28 (22.2%)	44 (33.8%)
G2	**98 (77.8%)**	**86 (66.2%)**
Primary tumor site		
- Gastrointestinal	**77 (61.1%)**	**74 (56.9%)**
Gastric	3(2.4%)	4 (4.3%)
Duodenum	2 (1.6%)	2 (1.5%)
Jejunum-ileon	59 (46.8%)	58 (44.6%)
Appendix	1 (0.8%)	1 (0.8%)
Colon	2 (1.6%)	3 (2.3%)
Rectum	10 (7.9%)	6 (4.6%)
- Lung	**37 (29.4%)**	**34 (26.2%)**
- Unknown primary	**8 (6.3%)**	**13 (10.0%)**
- Other	**4 (3.2%)**	**9 (6.9%)**

	AXITINIB-SSA (N=126)	PLACEBO-SSA (N=130)
Carcinoid syndrome	35 (27.8%)	29 (22.3%)
Time from dx to randomization		
Median, range	16.5 (0.3, 184.3)	19.1 (0.7, 341.6)
≤ 12 months	57 (45.6%)	52 (40.0%)
> 12 months	68 (54.4%)	78 (60.0%)
Prior therapy		
Surgery	57 (45.2%)	65 (50.0%)
SSA	61 (48.4%)	61 (46.9%)
PRRT	5 (4.0%)	3 (2.3%)
Everolimus	17 (13.5%)	15 (11.5%)
Chemotherapy	18 (14.3%)	14 (10.8%)
Locoregional/ablative tx	7 (5.6%)	11 (8.5%)
Other	8 (6.3%)	3 (2.3%)
Prior systemic therapy		
No prior systemic tx	**55 (43.7%)**	**60 (46.2%)**
1 line of prior tx	53 (42.1%)	46 (35.4%)
≥ 2 lines of prior tx	18 (14.3%)	24 (18.5%)

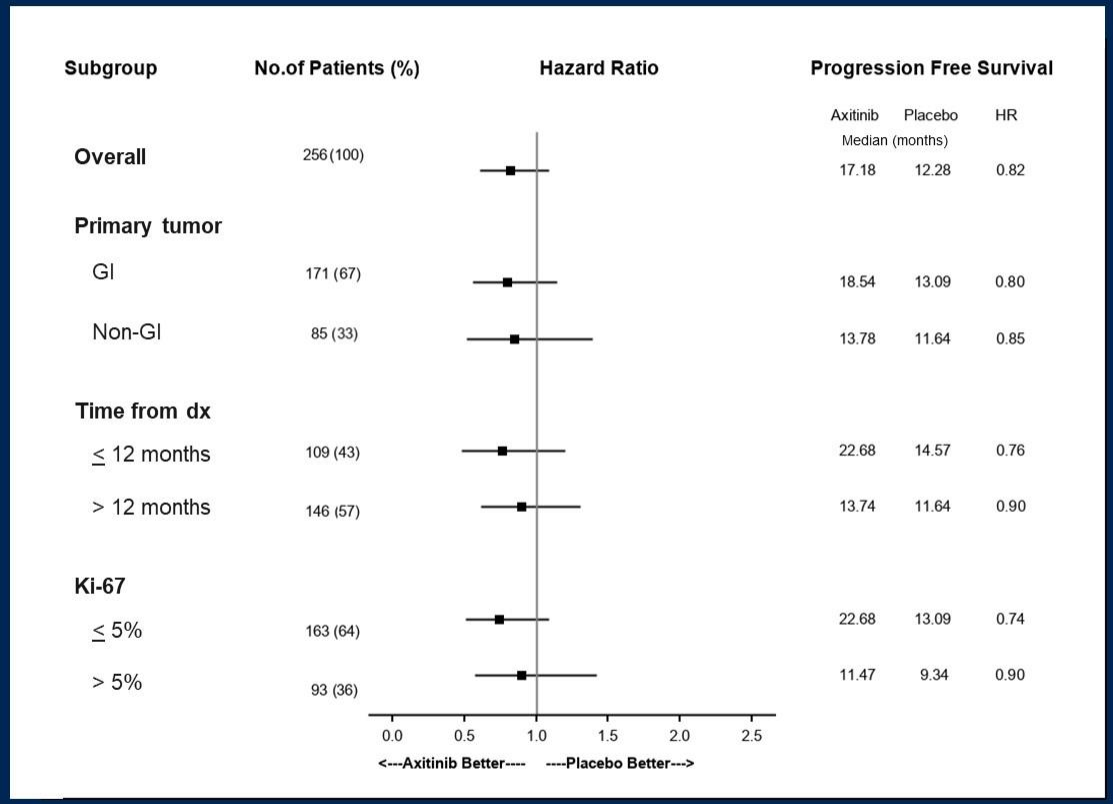
* One patient in the axitinib arm withdrew consent after randomization and no further data was reported for this patient

Progression Free Survival (Investigator-Assessment)



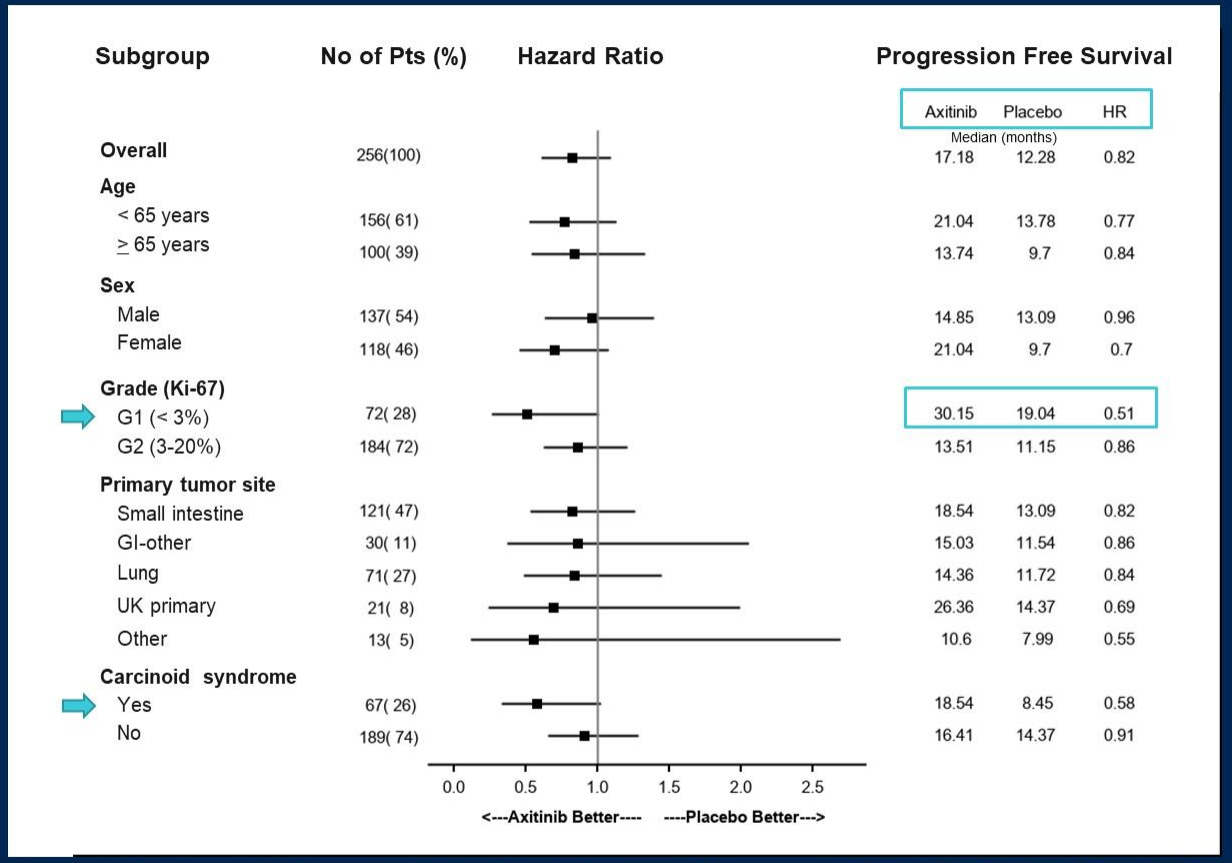
Presented By Rocio Garcia-Carbonero at 2021 Gastrointestinal Cancers Symposium

PFS HR by Stratification Factors



Presented By Rocio Garcia-Carbonero at 2021 Gastrointestinal Cancers Symposium

PFS HR by Patient and Tumor Features

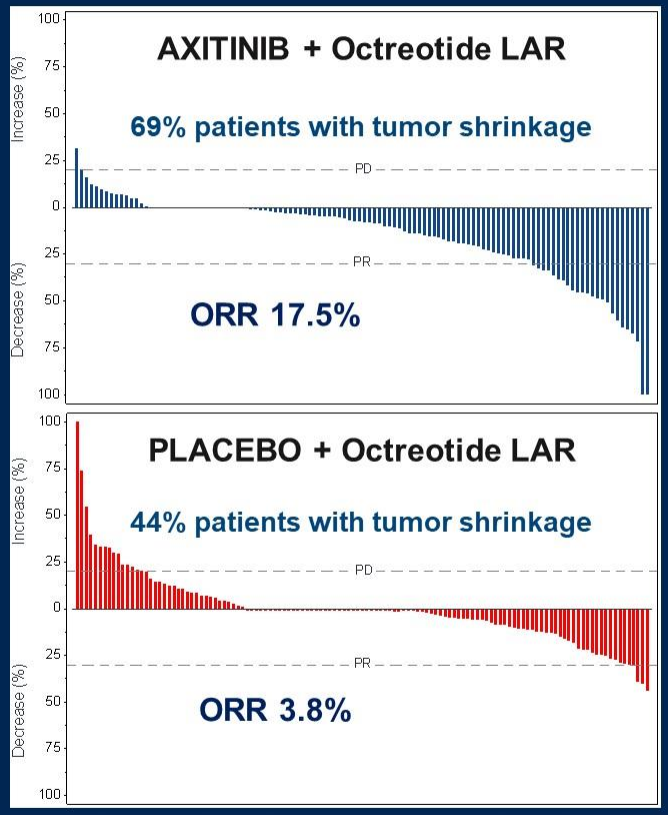


Presented By Rocio Garcia-Carbonero at 2021 Gastrointestinal Cancers Symposium

Best Overall Response and Tumor Shrinkage

Best Overall Response	AXITINIB-SSA N=126, n (%)	PLACEBO-SSA N=130, n (%)	p-value
CR	2 (1.6)	0 (0.0)	Fisher: 0.0001
PR	20 (15.9)	5 (3.8)	
SD	87 (69.0)	98 (75.4)	
PD	8 (6.3)	23 (17.7)	
Not Evaluable	9 (7.1)	4 (3.1)	

Best Overall Response	AXITINIB-SSA N=126, n (%)	PLACEBO-SSA N=130, n (%)	p-value
CR or PR	22 (17.5)	5 (3.8)	Chi-Square: 0.0004
SD or PD	95 (75.4)	121 (93.1)	
Not Evaluable	9 (7.1)	4 (3.1)	



Conclusions

- AXINET failed to demonstrate a significant improvement in PFS per investigator assessment for the combination of Axitinib and Octeotride LAR as compared to Placebo and Octeotride LAR in patients with advanced G1-2 extra-pancreatic NETs
  - Median PFS: 17.2 months (Axitinib-SSA) vs 13.2 months (Placebo-SSA), HR 0.816, p=0.169
- Axitinib in combination with Octreotide LAR significantly improved the ORR as compared to Placebo and Octreotide LAR in patients with advanced G1-2 extra-pancreatic NETs
  - ORR: 17.5% (Axitinib-SSA) vs 3.8% (Placebo-SSA), p=0.0004
- Safety profile is consistent with known safety profile for axitinib and octreotide
- Independent blinded radiological assessment of PFS is currently ongoing

PRRT - Peptide Receptor Radionuclide Therapy

- Léčba izotopovým zářičem vázaným na nosič.
- LUTATHERA : ^{177}LU - oxodotreotid ….. Vysoká afinita k somatostatinovým receptorům SST2
- Registrační studie III. fáze NETTER-1 (LUTATHERA vs Octreotid LAR
  - PFS: 28,4 měsíce vs 8,5, HR: 0,21 (95% CI: 0,14 – 0,33)

SPC: Lutathera se indikuje k léčbě neresekovatelných nebo metastázujících, progresivních a dobře diferencovaných (G1 a G2) gastroenteropankreatických neuroendokrinních nádorů (GEP-NET), pozitivních na somatostatinový receptor, u dospělých.

- Plicní karcinoid (typický, atypický) a NET jiné než gastroenteropankreatické etiol …§16

Discordance between central versus local response assessments in neuroendocrine tumor (NET) patients (pts) enrolled in A021202.

- Studie A021202: II. fáze pokroč. NET mimo pankreas pazo vs placebo
- n=151 (pacienti) , celkový počet CT vyšetření: 724

- Celkově 20% CT vyšetření mělo diskordantní hodnocení :
  - Nejčastěji lokálně SD vs centrálně PD : 82/143 …57%
  - Lokálně PD vs centrálně SD : 32/143 … 22%

  - Na úrovni pacientů… 78/151 pacinetů rozdílné hodnocení
    - 45 (30%) centrálně PD vs lokálně SD nebo lepší …. To vede k delšímu podávání neúčinné léčby …
    - Odchylky v obou směrech : 30% pacientů léčeno příliš dlouho a u 20% léčba vysazena předčasně …
- Nutnost hledat jednoznačnější metody hodnocení účinnosti léčby!

Geyer SM et al. Abstrakt 361, ASCO GI 2021