Differences and Similarities among NEN Patients from Different Continents - Lessons from Chinese Patients

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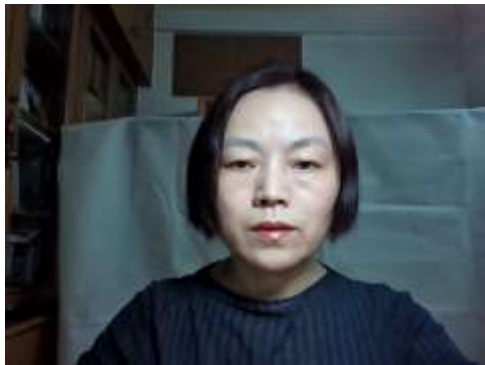
DISCLOSURE INFORMATION

Honoraria for advisory boards; speaker bureau; research grants

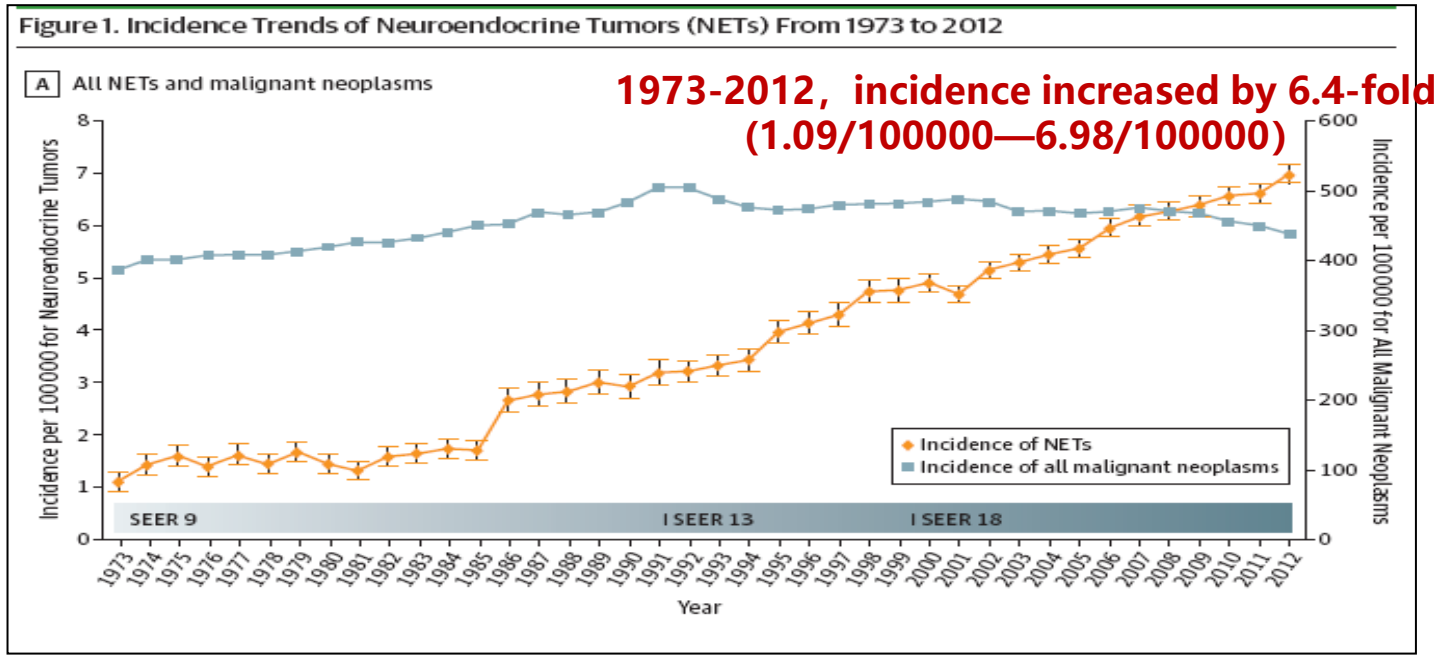
- **Ipsen**
- **Novartis**
- **Pfizer**
- **Hutchison Medipharma Limited**

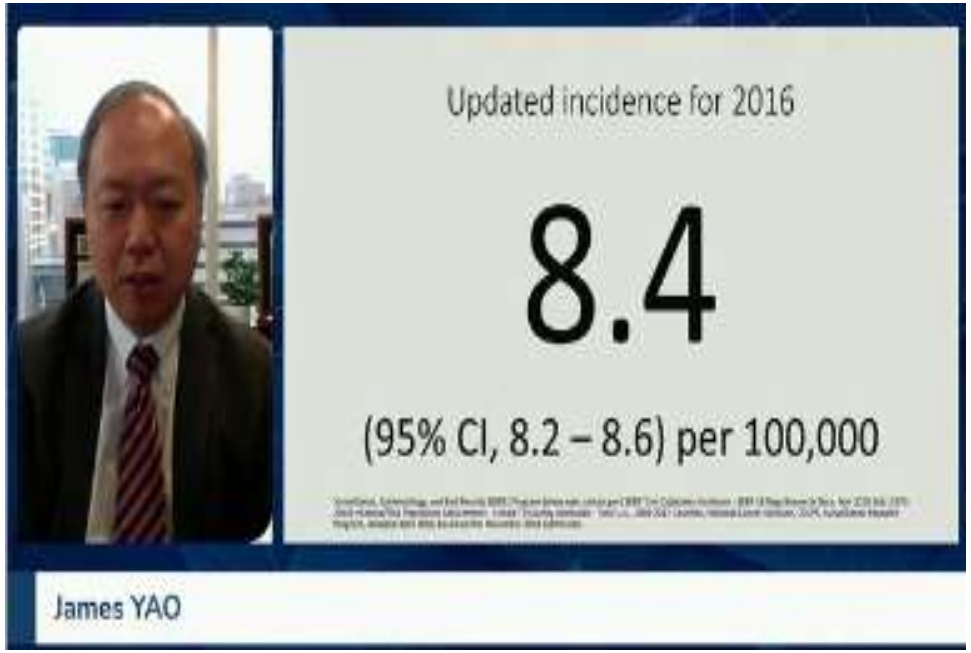


Outlines

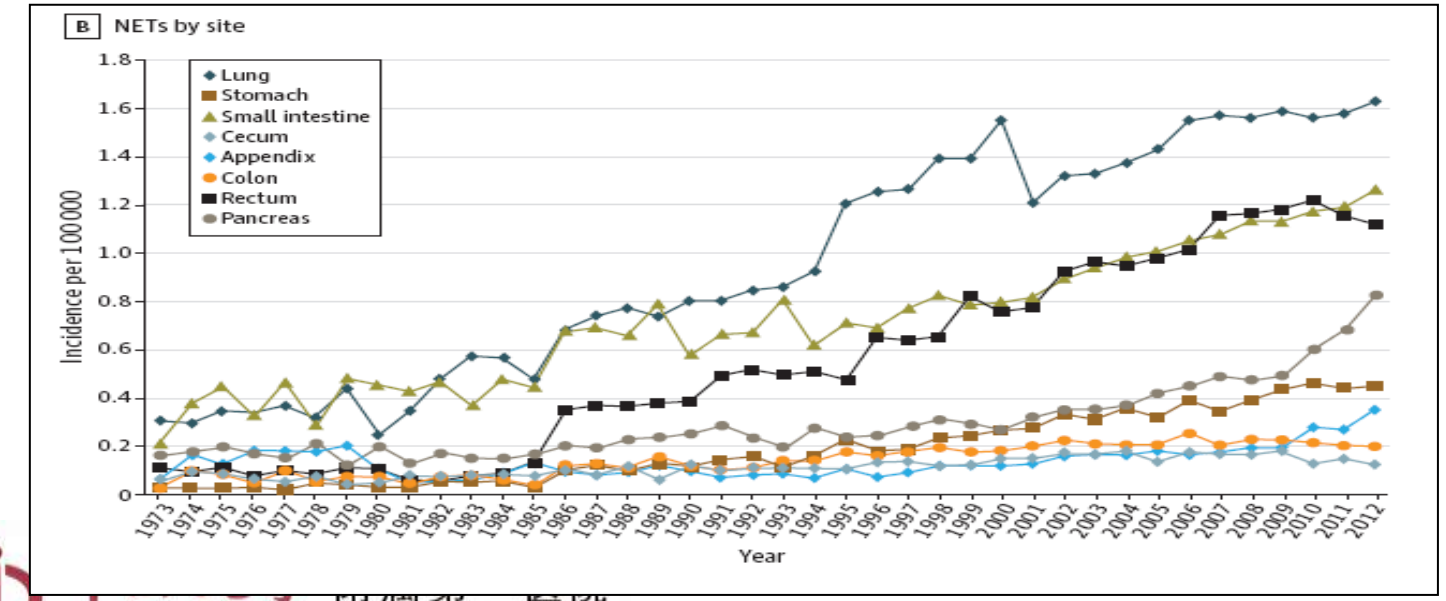
- Epidemiology
- Overall Situations of NET treatment in China
- Current Systemic Treatment strategy in China
- Chinese Clinical trail in NET treatment
- Summary

NET epidemiology—Data from USA SEER





ENETS 2020



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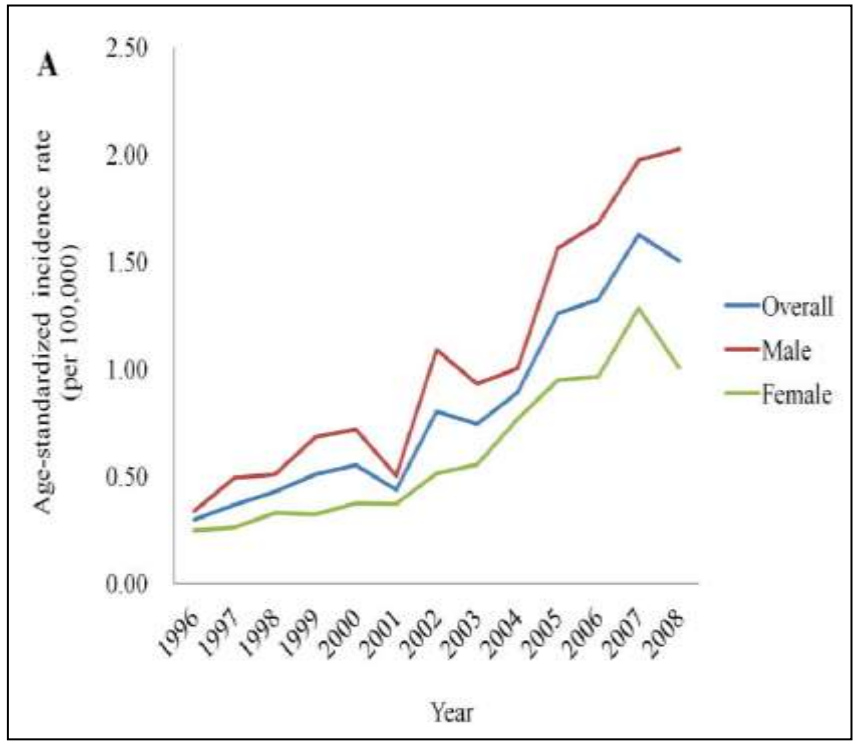
Yao J, et al. JAMA Oncol. doi:10.1001/jamaoncol.2017.0589

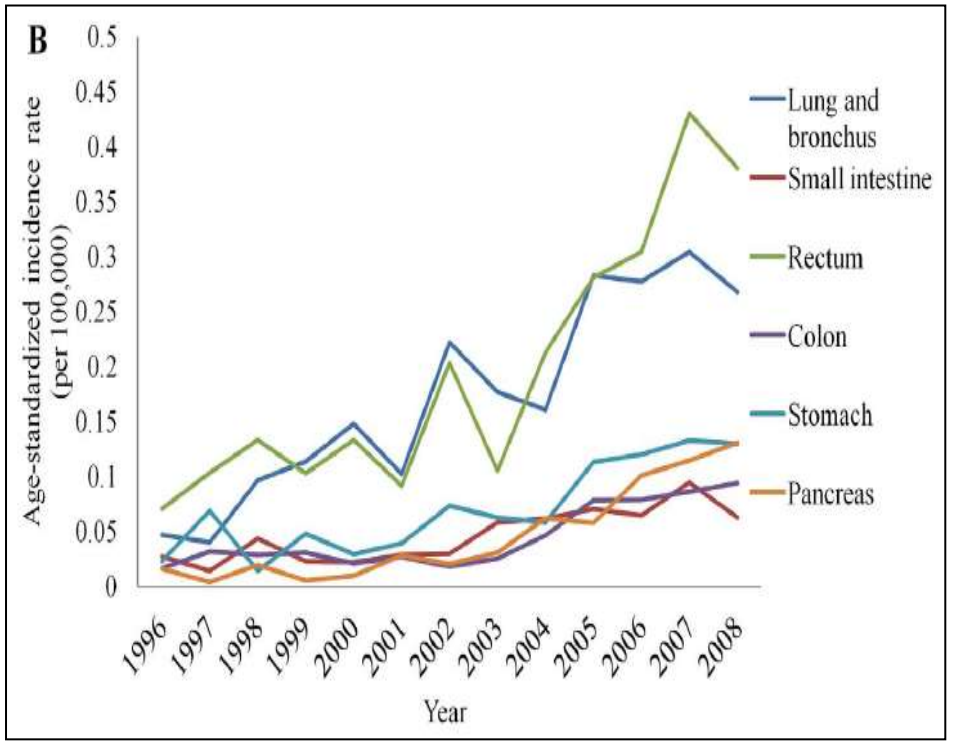
Incidence of NET in Taiwan：

1996: 0.3 per 100000 population

2008: 1.5 per 100000 population

Increased by 5-folds





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2013，PLOS ONE

Incidence rate of neuroendocrine tumors in China, 2014

56091 new NETs cases were diagnosed in 2014, including 38430 male cases and 17661 female cases. Then crude incidence rate was **4.10 per 100,000 (5.48 per 100,000 for males, 2.64 per 100,000 for females).**

(Data source: Chinise national cancer center ,574 cancer registration sites, covering population 438 million)

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Unpublished data

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

A nation-wide retrospective epidemiological study of gastroenteropancreatic neuroendocrine neoplasms in china

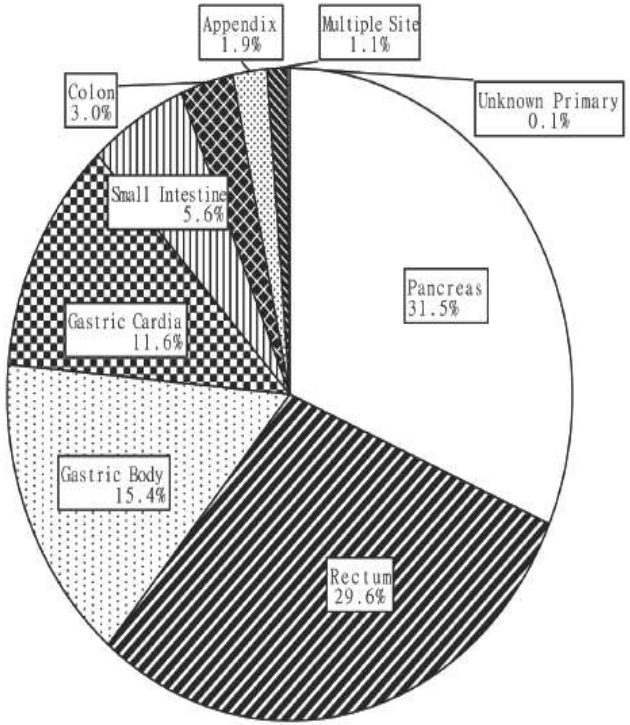

Figure 1: The proportion of primary tumor site in all cases.

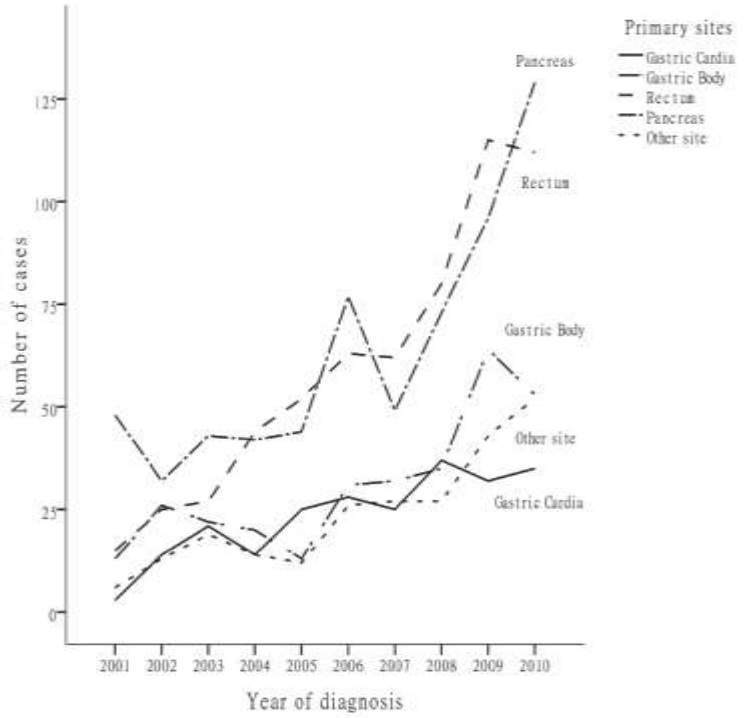

Figure 2: Number of patients diagnosed in each year.

- A multi-center retrospective study of 23 general and oncology hospitals in mainland China， with 2010 GEP-NEN cases since 2001 to 2010, indicated an increase in number of patients diagnosed each year , The most common primary sites of NET in Chinese patients were pancreas, rectum and stomach

Fang et al. Chin J Cancer (2017) 36:51
DOI 10.1186/s40880-017-0218-3

Chinese Journal of Cancer

ORIGINAL ARTICLE Open Access

Clinicopathologic characteristics and prognosis of gastroenteropancreatic neuroendocrine neoplasms: a multicenter study in South China

Cheng Fang[1†], Wei Wang[1†], Yu Zhang[2†], Xingyu Feng[3†], Jian Sun[4†], Yujie Zeng[5†], Ye Chen[6*†], Yong Li[3*†], Minhu Chen[2], Zhiwei Zhou[1*†] and Jie Chen[2*†]

1183 cases diagnosed as GEP-NENs with complete clinicopathological and follow-up data from 5 high volume medical centers in south China

Results: The most common tumor location was the rectum (37.4%), followed by the pancreas (28.1%), stomach (20.7%), small intestine (7.2%), appendix (3.4%), and colon (3.3%). After initial definitive diagnosis, 1016 (85.9%) patients underwent surgery. The 1-, 3-, and 5-year overall survival (OS) rates for the entire cohort were 87.9%, 78.5%, and 72.8%, respectively. The 3-year OS rates of patients with G1, G2, and G3 tumors were 93.1%, 82.7%, and 43.1%, respectively ($P < 0.001$). The 3-year OS rates of patients with stage I, II, III, and IV tumors were 96.0%, 87.3%, 64.0%, and 46.8%, respectively ($P < 0.001$). Patients with distant metastasis who underwent palliative surgery had a longer survival than those who did not ($P = 0.003$). Similar survival benefits of palliative surgery were observed in patients

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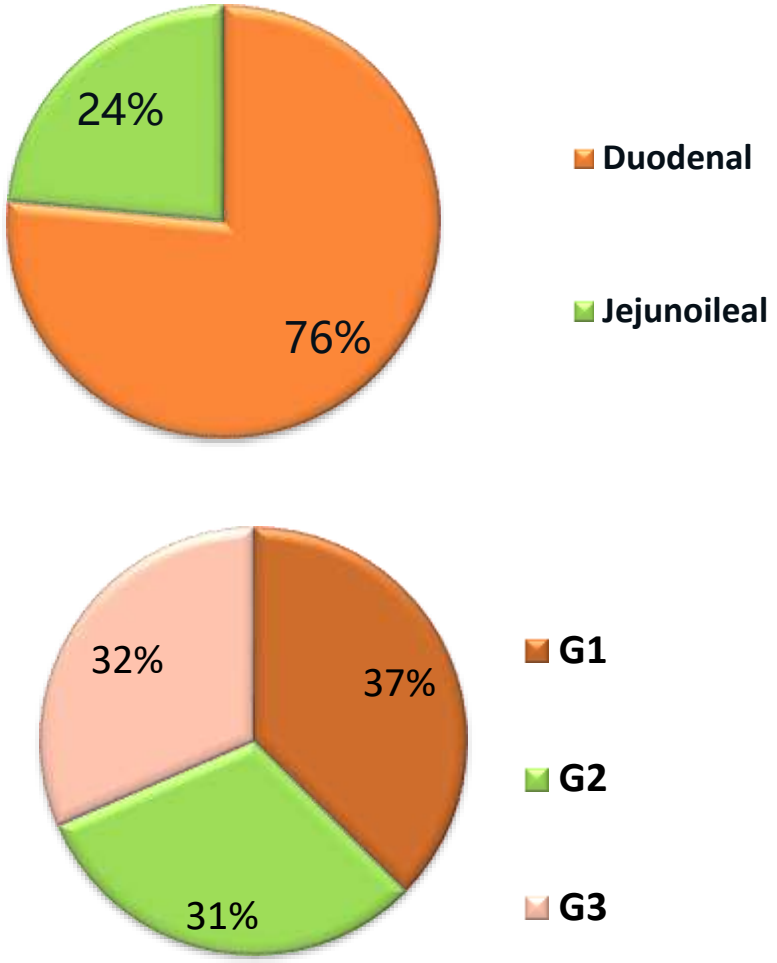
Small intestinal neuroendocrine neoplasms (from 11 Chinese centers，N=277)



Compared with western populations:

- **Younger age at diagnosis**
- **More male patients**
- **Jejunoileal NET is much rarer**
- **Abdominal pain is the most frequent symptom, while carcinoid syndrome is rare**
- **Larger tumor size**
- **More grade 3 disease**
- **24.9% of patients had advanced disease when diagnosed. Among them, 86.7% of patients had liver metastases**

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Jie Chen， Leping Li， et al. Clinicopathological Features and Prognostic Validity of WHO Grading Classification of SI-NENs. *BMC Cancer* 2017; 17：521

Situations in China

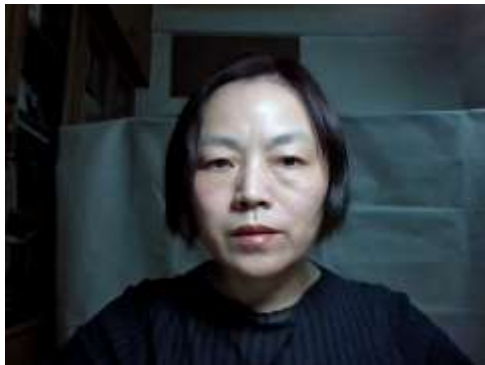
- NEN patients were handled respectively by each specialized department before 2010
- Nomenclature and classification of Neuroendocrine tumors of digestive system were updated by WHO in 2010
- New targeted drugs were approved to be used in NEN treatment in 2011
- Chinese doctors started to pay attention to this rare tumors after 2010
- NET-MDT teams started to successively set up in large medical centers
- Various professional society/study groups have released related guidelines/consensus for NEN treatment
- Some NEN study teams gradually focused on certain research field of NET

NET Center in
The First Affiliated Hospital , Sun Yat-sen University（2011）

The first NET MRC and first MDT group in China

- Department of Gastroenterology
- Department of Endocrinology
- Surgical Department of Gastrointestinal Diseases
- Surgical Department of Hepatobiliary Disease
- Department of Pathology
- Department of Radiology
- Department of Nuclear Medicine
- Department of Interventional oncology

Multidisciplinary referral Center (MRC)



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Establishment of an integrated system for diagnosis and treatment of NENs

- Serologic detection of CgA
- Quantitative detection of gastrin and other hormones
- Localization diagnosis by ultrasound, endoscope, CT， MRI, 68Ga- DOTANOC-PET-CT， 18F-DOPA-PET-CT and 18F-FDG-PET-CT
- Standardized pathological diagnosis
- Endoscopic surgery, surgical operation, interventional therapy, drug therapy for NET treatment, PRRT is pending…
- NET MDT members ,outpatient clinic, NET inpatient ward

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- Routine weekly NET-MDT discussion
- Telemedicine for NET patients from all across the country
- More than 700 new diagnosed NET patients per year
- The largest NET treatment center in China

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NEN diagnosis and treatment workshop

The NEN diagnosis and treatment workshop has been held every year since 2012 in our center, training more than 400 qualified specialists for NEN field from all over the country.

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Other NEN-MRCs in China

- NEN-MDT in Sun Yat-sen University Cancer Center ,Guangzhou
- NEN-MDT in Shanghai Cancer Center, Fudan University, Shanghai
- NEN-MDT in Zhongshan Hospital, Fudan University, Shanghai
- NEN-MDT in Shanghai Changzheng Hospital, Navy Medical University, Shanghai
- NEN-MDT in Peking University Cancer Hospital, Beijing
- NEN-MDT in China-Japan Friendship Hospital, Beijing
- NEN-MDT in Cancer Hospital, Chinese Academy of Medical Sciences, Beijing
- NEN-MDT in Peking Union Medical College Hospital, Beijing
- NEN-MDT in PLA 307 Hospital, Affilated Hospital of Military Medical Sciences, Beijing

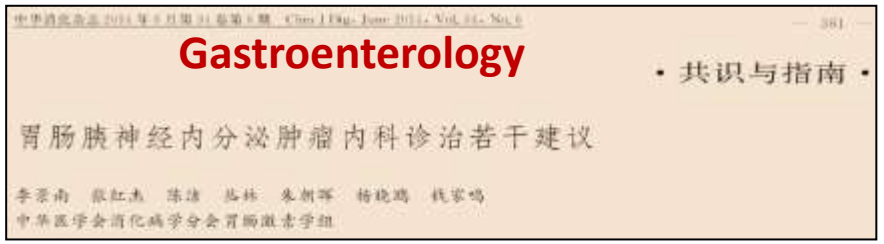
Distribution of Leading NEN-MRCs in China

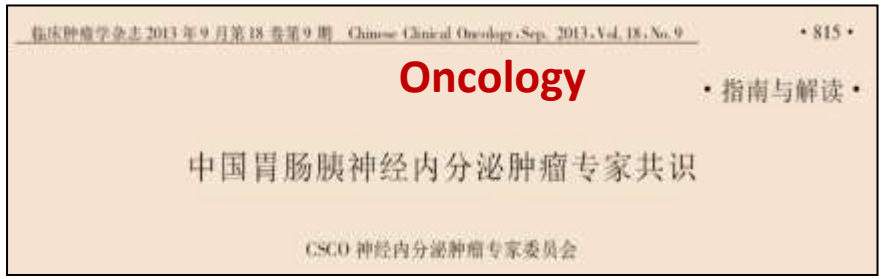
- All MRCs are in university hospitals
- Most of them Located in Beijing, Shanghai, and Guanzghou, three first tier cities in China

NEN academical associations

- Expert Commitee of Neuroendocrine Carcinoma in Chinese Society of Clinical Oncology (CSCO) (2011)（Oncologist)
- Chinese Study Group for Neuroendocrine Tumors (CSNET) in Chinese Anti-Cancer Association (CACA)(2015) (Multidisciplinary)
- Chinese Neuroendocrine Tumor Society (CNETS) in China International Exchange and Promotive Association for Medical and Health Care (CPAM)（2015) (Multidisciplinary)
- Expert Commitee of Pancreatic Neuroendocrine Tumors in Chinese Medical Doctor Association (CMDA) (2017) (Pancreatic surgeon)
- Study Group for Gut Hormone and Neuroendocrine Tumors in Chinese Medical Association（CMA)（2018)（Gastroenterologist)
- Study Group for Neuroendocrine Tumors in Chinese Research Hospital Association（CRHA)（2018) (Gastroenterologist and digestive surgeon)

Chinese Guidelines and Consensus





Various medical associations (including the disciplines of pathology, gastroenterology, oncology, and pancreatic surgery) have released several related guidelines/consensuses for NENs diagnosis and treatment respectively since 2011

INTERNATIONAL JOURNAL OF ONCOLOGY 49: 1991-2000, 2016

Surgical management for non-functional pancreatic neuroendocrine neoplasms with synchronous liver metastasis: A consensus from the Chinese Study Group for Neuroendocrine Tumors (CSNET)

KAIZHOU JIN[1*], JIN XU[1*], JIE CHEN[2], MINHU CHEN[2], RUFU CHEN[3], YE CHEN[4], ZHIYU CHEN[5], BIN CHENG[6], YIHEBALI CHI[7], SHI-TING FENG[8], DELIANG FU[9], BAOHUA HOU[10], DAN HUANG[11], HEGUANG HUANG[12], QIANG HUANG[13], JIE LI[14], YING LI[15], HOUJIE LIANG[16], RONG LIN[17], AN'AN LIU[18], JIXI LIU[19], XUBAO LIU[20], MING LU[14], JIE LUO[21], GANG MAI[22], QUANXING NI[1], MENG QIU[23], CHENGHAO SHAO[18], BAIYONG SHEN[24], WEIQI SHENG[11], JIAN SUN[3], CHUNLU TAN[20], HUANGYING TAN[25], QIYUN TANG[26], YINGMEI TANG[27], XIAODONG TIAN[28], DANIAN TONG[29], XIAOHONG WANG[30], JIAN WANG[31], JIE WANG[32], WEI WANG[33], WEI WANG[34], YU WANG[35], ZHENG WU[36], LING XUE[37], QIANG YAN[38], NING YANG[39], YINMO YANG[28], ZHIYING YANG[40], XIAOYI YIN[41], CHUNHUI YUAN[42], SHAN ZENG[43], RENCHAO ZHANG[44] and XIANJUN YU[1]

INTERNATIONAL JOURNAL OF ONCOLOGY

Surgery management for sporadic small (≤2 cm), non-functioning pancreatic neuroendocrine tumors: A consensus statement by the Chinese Study Group for Neuroendocrine Tumors (CSNET)

GUANG YANG[1*], MENG JI[1*], JIE CHEN[2], RUFU CHEN[3], YE CHEN[4], DELIANG FU[5], BAOHUA HOU[6], HEGUANG HUANG[7], LIMING JIANG[8], KAIZHOU JIN[9], NENGWEN KE[10], YING LI[11], YONG LI[6], HOUJIE LIANG[12], AN'AN LIU[1], JIE LUO[13], QUANXING NI[9], CHENGWEI SHAO[14], BOYONG SHEN[15], WEIQI SHENG[16], BIN SONG[17], JIAN SUN[3], CHUNLU TAN[10], HUANGYING TAN[18], QIYUN TANG[19], YINGMEI TANG[20], XIAODONG TIAN[21], JIAN WANG[22], JIE WANG[23], WEI WANG[24], WEI WANG[25], ZHENG WU[26], JIN XU[9], QIANG YAN[27], NING YANG[28], YINMO YANG[21], XIAOYU YIN[29], XIANJUN YU[9], CHUNHUI YUAN[30], SHAN ZENG[31], GUOCHAO ZHANG[32], RENCHAO ZHANG[33], ZHIWEI ZHOU[25], ZHAOHUI ZHU[34] and CHENGHAO SHAO[1]

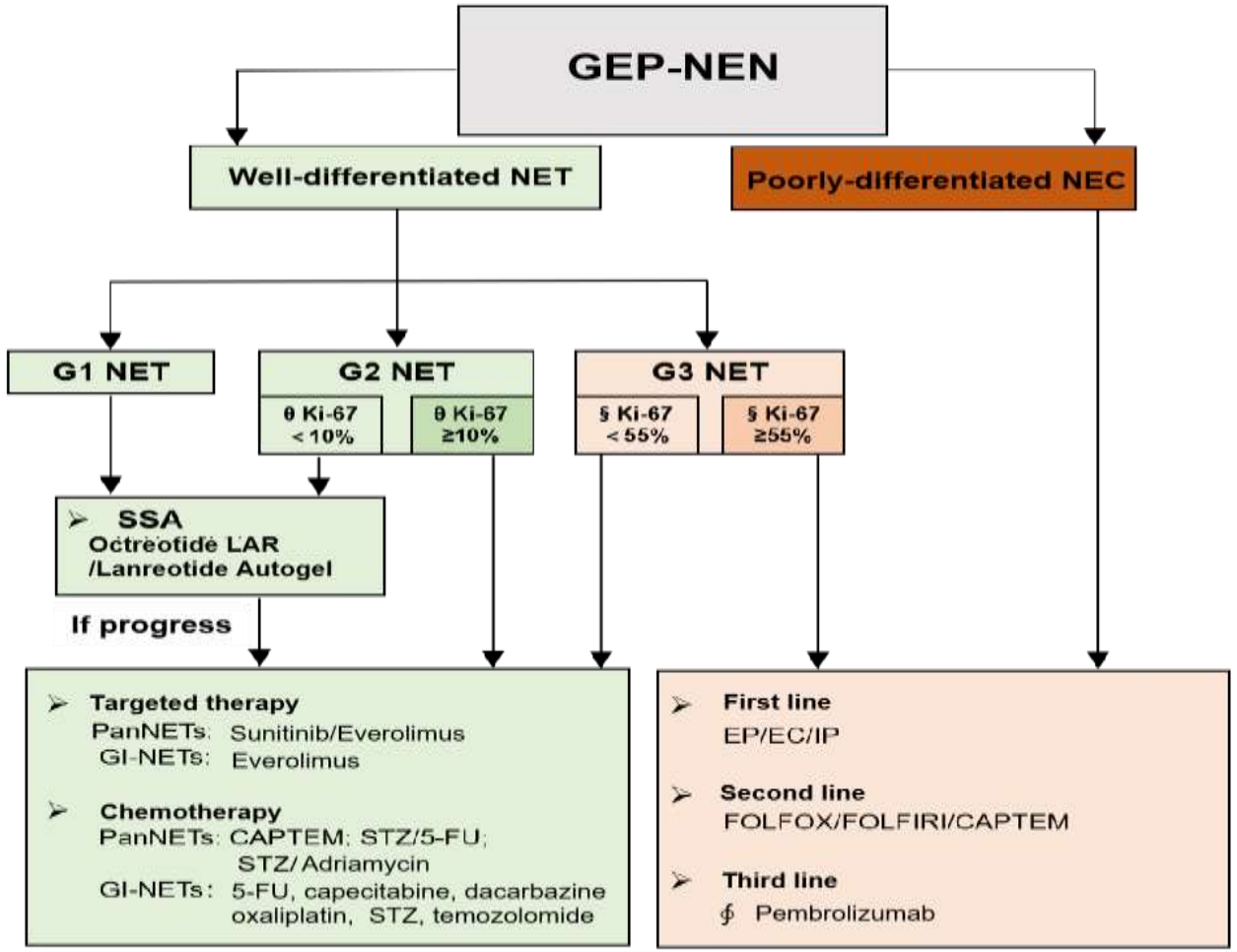
Wechat groups of NET patients

Wechat groups of NET doctors

Management of my NET patients via online clinic

Besides formal NET academic associations, Chinese doctors and patients also communicate with each other via Wechat groups and other online social media. Doctors also use online clinic for NET patients management.

The treatment selection strategy for controlling tumor growth in progressing GEP-NENs



θ: The Ki-67 cutoff is based on CLARINET NET study
§: The Ki-67 cutoff is based on NORDIC NEC study
ϕ: 2019 NCCN recomments that patients with dMMR and high MSI can consider immunotherapy if progress after systemic treatment

- Streptomycin is not available in China
- PRRT are not approved in China
- Surufatinib, a novel antiangiogenesis TKIs, will soon be applied in Chinese patients with both pancreatic NETs and non-pancreatic NETs

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Jie Chen，Chinese digestive journal，2019, 39 (8)：508-512

ONCOLOGY LETTERS 13: 1165-1174, 2017

Somatostatin receptor expression indicates improved prognosis in gastroenteropancreatic neuroendocrine neoplasm, and octreotide long-acting release is effective and safe in Chinese patients with advanced gastroenteropancreatic neuroendocrine tumors

YUHONG WANG[1*], WEI WANG[2*], KAIZHOU JIN[3], CHENG FANG[2], YUAN LIN[4], LING XUE[4], SHITING FENG[5], ZHIWEI ZHOU[2], CHENGHAO SHAO[6], MINHU CHEN[1], XIANJUN YU[3] and JIE CHEN[1]

Table IV. Time to progression and its association with the sub-groups (n=54).

Characteristics	n	Median (months)	95% CI	χ^2 value	P-value
Patients with octreotide LAR treatment	54	20.2	13.9-26.5		
Functional status				2.474	0.116
Non-functional	41	17.5	11.0-23.9		
Functional	13	67.9	NC		
Tumor site				0.188	0.665
Gastrointestinal tract	13	17.5	0.0-43.7		
Pancreas	41	20.2	12.0-28.4		
Ki-67 index (%)				1.340	0.512
≤2	11	67.9	NC		
3-10	33	20.6	15.0-26.2		
>10	10	10.9	3.3-18.5		
Previous treatment				1.288	0.256
No	16	NR	NC		
Yes	38	16.0	5.6-26.5		
Combined therapy				0.053	0.817
No	31	17.5	4.5-30.5		
Yes	23	20.2	10.9-29.5		
SSTR2 expression[a]				0.867	0.352
Positive	19	20.6	10.5-30.7		
Negative	3	9.4	NC		
SSTR5 expression[a]				0.314	0.575
Positive	18	16.0	6.4-25.7		
Negative	4	NR	NC		

[a]In total, 22 cases for both SSTR2 and SSTR5 expression were observed. CI, confidence interval; NR, not reached; NC, not computable; LAR, long-acting release; SSTR, somatostatin receptor.

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Cancer Chemother Pharmacol
DOI 10.1007/s00280-017-3367-9

ORIGINAL ARTICLE

Sunitinib is effective and tolerable in Chinese patients with advanced pancreatic neuroendocrine tumors: a multicenter retrospective study in China

Yuhong Wang[1] · Kaizhou Jin[2] · Huangying Tan[3] · Pan Zhang[3] · Qiuchen Yang[1] · Wei Wang[4] · Jie Li[5] · Chenghao Shao[6] · Ling Xue[7] · Shiting Feng[8] · Minhu Chen[1] · Xianjun Yu[2] · Jie Chen[1]

- Data from 6 Chinese NET centers
- Investigating the efficacy and safety of Sunitinib in 60 patients with advanced pancreatic NET
- Median OS, 47.5 months; Median TTP, 15.3 months; ORR, 5.0%; DCR, 81.7%
- 35.2% of patients required dose decreasing from 37.5mg/d to 25mg/d
- Median blood concentration of Sunitinib are comparable in patients treated with 37.5mg and 25mg Sunitinib; But it’s higher in patients had partial remission disease when compared with patients having stable disease or progression disease
- Sunitinib-related hypertension may be an indicator of better efficacy of sunitinib

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Neuro endocrinology

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Published(online): 7/15/2020

A Ki-67 Index to Predict Treatment Response to the Capecitabine Temozolomide (CAPTEM) Regimen in Neuroendocrine Neoplasms: A Retrospective Multicenter Study

Wang W. Zhang Y. Peng Y. Jin K.Z. Li Y.L. Liang Y. Tan H.Y. Yu X.J. Zhou Z.W. Chen J.

ISSN: 0028-3835 (Print), eISSN: 1423-0194 (Online)
https://www.karger.com/NEN
Neuroendocrinology

Results and Conclusions The overall response rate (ORR) and disease control rate (DCR) of the entire cohort (N = 151) were 26.5% and 76.2%, respectively, with a median progression-free survival (PFS) of 12.0 months. CART analysis showed that patients with the Ki-67 range group 10-40% demonstrated a significantly higher ORR than those with Ki-67 > 40% and < 10% groups ($P < 0.001$ in the training cohort and $P = 0.036$ in the validation cohort). Response to the CAPTEM regimen was not influenced by the expression of MGMT or primary tumor location. Multivariate analysis identified the Ki-67 index as the only independent prognostic factor for overall survival ($P = 0.031$) and PFS ($P = 0.006$).

The proposed Ki-67 index was externally validated and could be used to clinically identify suitable metastatic NENs patients who could achieve an optimal cytoreduction using the CAPTEM regimen.

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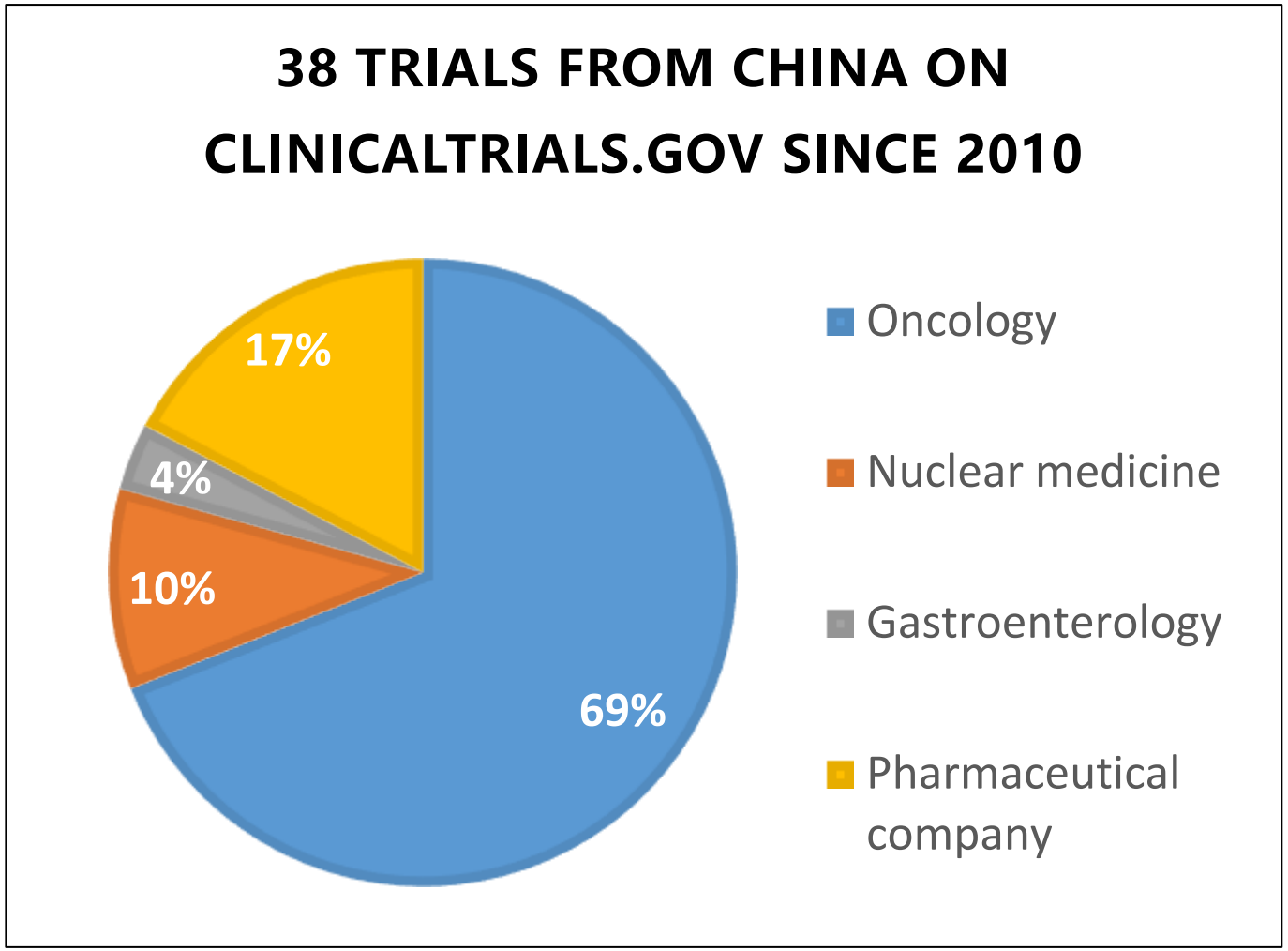
Clinical trials from China



Data from clinicaltrial.com

Phase III Trial of Surufatinib in Advanced Extrapancreatic NETs(SANET-ep) and pancreatic NETs(SANET-p)

Extrapancreatic NET; n = 273 pts

- **G1 or G2** advanced **extrapancreatic NETs** with origins i**ncluding**, but not limited to, the **lung, thymus**, **the gastrointestinal tract and unknown origin**
- No more than two prior systemic treatments
- Radiological documentation of disease progression within 12 mo. prior to randomization

R (2 : 1)
- Surufatinib 300 mg/day
- Placebo

Pancreatic NET; n = 195 pts

- **G1 or G2** advanced **pancreatic NETs**
- No more than two prior systemic treatments incl. SSA, IFN, PRRT, CTx, mTORi
- Radiological documentation of progression of disease within 12 mo. prior to randomization

R (2 : 1)
- Surufatinib 300 mg/day
- Placebo

Primary Endpoint:
- Investigator-assessed PFS

Secondary Endpoints:
- ORR, DCR, DoR, TTR, OS
- Safety and tolerability

Hutchison China MediTech Limited . NCT02588170, NCT02589821

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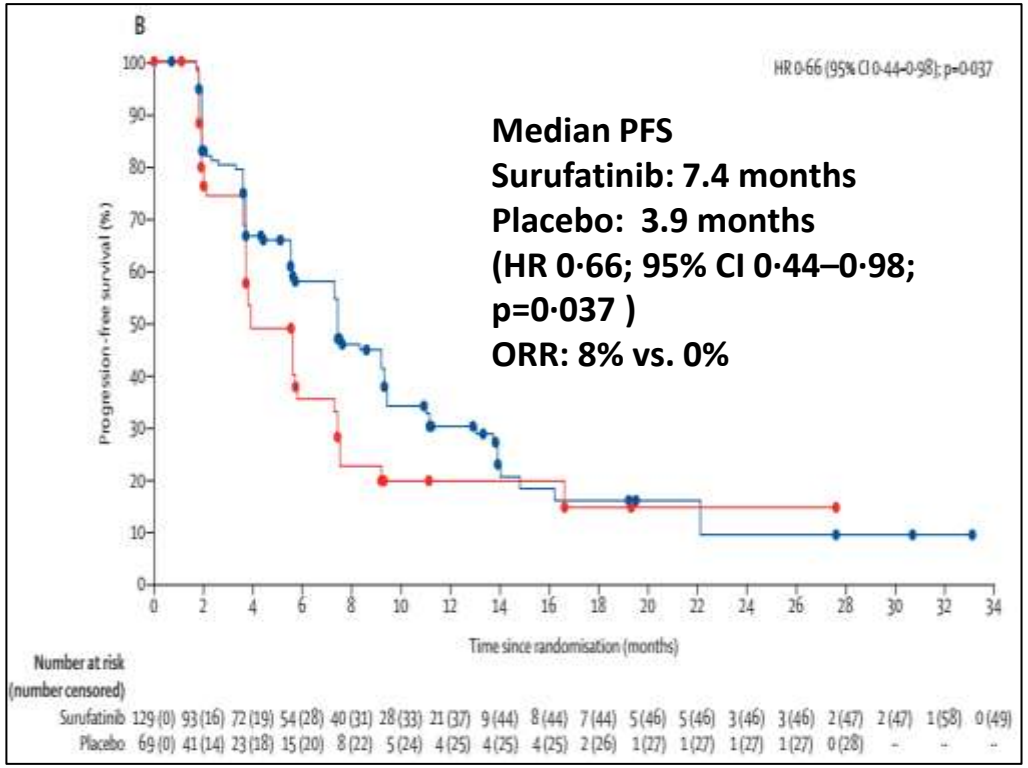
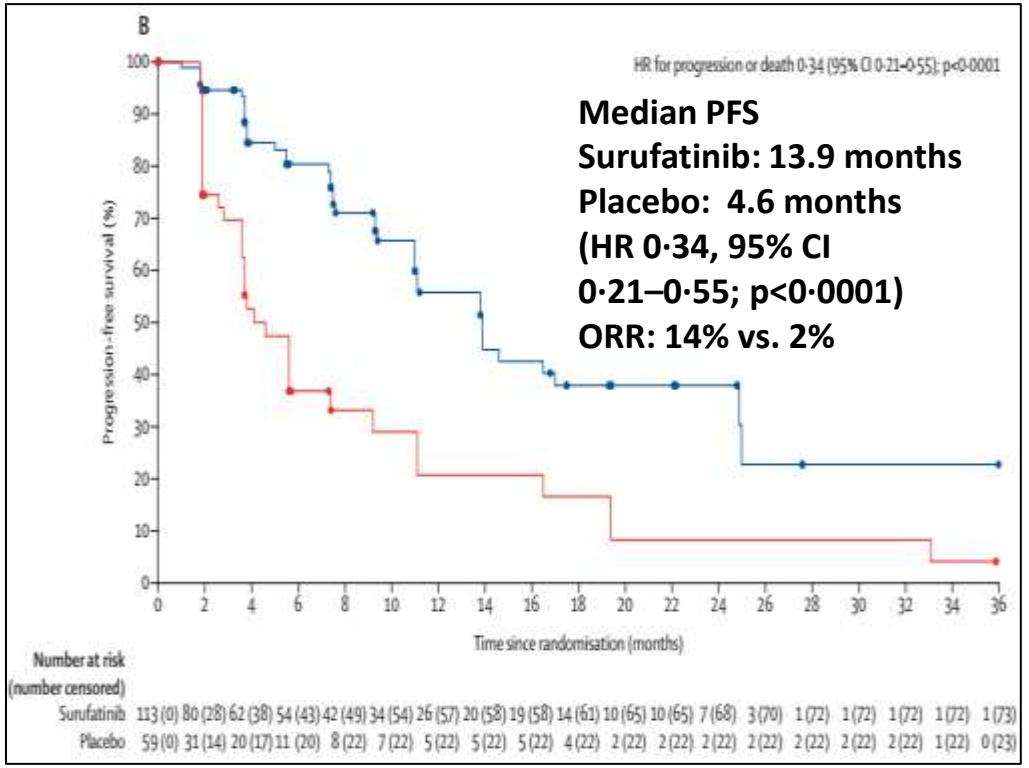
Results from SANET-ep and SANET-p



Median PFS
Surufatinib: 7.4 months
Placebo: 3.9 months
(HR 0·66; 95% CI 0·44–0·98; p=0·037)
ORR: 8% vs. 0%



Median PFS
Surufatinib: 13.9 months
Placebo: 4.6 months
(HR 0·34, 95% CI 0·21–0·55; p<0·0001)
ORR: 14% vs. 2%

PFS and ORR assessed by blinded independent image review committee

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Summary

- During the past ten years, Chinese doctors have shown increased interest in the NET field
- An increase in research and clinical trials in the NET field have been shown during the past 10 years
- However, more NET centers need to be established to fulfill the increasing medical demand from increasing NET patients
- Alliance established by patients, similar to INCA, may also needed in China in the future

THANK YOU FOR YOUR ATTENTION