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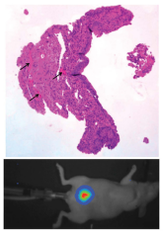

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Review

Role of targeted agents in neuroendocrine tumours: results from a meta-analysis

Running title: Target therapies in NETs

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Keywords

NET; sunitinb; everolimus, bevacizumab.

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Abstract

Background: Several randomized phase III trials in neuroendocrine tumors (NETs) showed the clinical role of new targeted agents and their impact on tumor response and outcome of whose patients affected by advanced NET. In this study, we summarize the

available clinical data related to clinical efficacy of targeted therapies in the treatment of advanced NETs.

Methods: A meta-analysis of randomized studies in accordance with the PRISMA guidelines was performed after searching the databases of PubMed, the Cochrane Library, and the ASCO University Meeting for relevant publications.

Results: One thousand nine hundred and eight cases were included in the meta-analysis; among these, 1012 were in the experimental arm and 896 were in the control arm. The pooled analysis of the use of target agents in NETs revealed significantly increased of progression free survival compared to control group (hazard ratio=0.59, 95% CI:0.42-0.84; P=0.003). Subgroup analysis of patients according to tumour site showed a difference in favour of pancreatic neuroendocrine tumors. Moreover, targeted therapies improved the overall survival (hazard ratio=0.79, 95%CI: 0.63-0.98; P=0.03), and response rate (hazard ratio=3.33, 95% CI 2.02-5.49; P<0.00001) in all types of NETs.

Conclusion: Our analysis supports the routine use of targeted agents for treatment of neuroendocrine tumors with particular regards to the pancreatic neuroendocrine tumors.

Introduction

Neuroendocrine tumors (NET) arise from cells of the endocrine (hormonal) and nervous systems. NETs are considered a rare disease even their incidence appear to be increasing **[1,2]**. The prognosis of NETs may vary widely, depending on stage, grade or primary tumor site **[3]**. Surgical resection of the primary tumors usually offer the only change of a long curative treatment; however, only a low percentage of patients are candidate to surgery as more than 50% of patients with NET have regional or distant metastatic disease at diagnosis **[3]**. In advanced diseases, the therapeutic options may include: a close surveillance for slowly progressive tumours; a liver-directed treatments such as transarterial embolization; systemic treatment with cytotoxic chemotherapy or radionuclide. However, none of these approaches has been directly compared in randomised clinical trials **[4]**.

In the armamentarium of systemic treatment, somatostatin analogues, such as octrotide and lanreotide, are currently indicated for the relief of symptoms in patients with functionally active NETs **[5,6]**. In addition, octreotide long-acting repeatable (LAR) has significantly prolonged time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs **[7],** supporting their use as a primary approach in the NET treatment. More recently, due to a better understanding of the biological mechanisms driving the growth of tumor cells with neuroendocrine phenotype has led to the development of targeted anti-cancer agents **[8,9].** To date, two agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with progressive, well-differentiated pancreatic NET: sunitinib (a vascular endothelial growth factor receptor-tyrosine kinase inhibitor) and everolimus (a mammalian target of rapamycin (mTOR)**.** Three phase III trials demonstrated an improved

in progression-free survival (PFS) of both sunitinb and everolimus compared with placebo **[10-12],** supporting their role in clinical practice.

The aim of this study is to analyse the available clinical data from randomized controlled trials (RCTs) looking for efficacy of target agents in patients with advanced NETs.

Materials and methods

Data retrieval strategies

We conducted the meta-analysis of randomized studies in accordance with the PRISMA guidelines **[13].** The databases of PubMed/MEDLINE, the Cochrane Library, and the American society of clinical oncology (ASCO) Meeting were searched for relevant publications using the following terms: ‘‘Neuroendocrine tumour’’ or ‘‘NET’’ or ‘‘Carcinoid tumours’’ and “target therapy” or “sunitinib” or “everolimus” or “bevacizumab”. The publications that were available in these databases up to December 31, 2015, were analysed. The search was restricted to human studies, and the search criteria were limited to phase II or phase III trials. The computer search was supplemented with manual searches of the references listed in all of the retrieved review articles, including primary studies. When the results of a study were reported in subsequent interim analysis, only the most recent or complete and updated version was included in the analysis.

Inclusion criteria

The studies were identified according to the following inclusion criteria: 1) human participants with a NET; 2) a targeted agent therapy alone or in combination for experimental arm; 3) the presence of a control for comparison (placebo or not); 4) a primary outcome of response expressed as the hazard ratio (HR) for either PFS or overall survival (OS), as well as the response rate expressed as relative risk (RR). The following

exclusion criteria were used: 1) insufficient data were available to estimate the outcomes; 2) animal studies; 3) the size of each arm was fewer than 10 participants; and 4) the presence of a single-arm study.

Data extraction

LZ and SV independently extracted the relevant data of each trials, including the name of the first author, country, publication year, characteristics of the enrolled patients, median follow-up and information about the study design (i.e., the type of blinding, type of control, and methods for randomization allocation), survival outcomes expressed as HRs for OS and PFS, and the number of patients who experienced a response rate with a grade 3-4 adverse event. The arm with the targeted agent has been considered as the experimental. For the time-to-event variables (OS or PFS), HRs with the 95% confidence intervals (95%CIs) were calculated for each study. For the dichotomous variables (partial or complete response rate and toxicity) RRs with the 95% CIs were calculated for each study.

Quality assessment and statistical analysis

The methodological quality of each included study was assessed by two independent researchers (GA and PC). The study quality was assessed using the Jadad 5-item scale. The final score ranged from 0 to 5 **[14]**. Disagreements were evaluated by the kappa test, and consensus was achieved in discussion with the corresponding author (GR).

Statistical analysis

Statistical analyses were performed using Revman 5.3. The summary estimates were generated using a fixed-effects model (Mantel–Haenszel method) or a random-effects model (DerSimonian–Laird method) **[15,16]** depending on the absence or presence of heterogeneity. Statistical heterogeneity was assessed using the Q-test and the I^2 statistic. I^2 values of 25%, 50% and 75% were considered to indicate low, moderate and high

heterogeneity, respectively **[17].** When P>0.1 in the Q-test and I^2<50%, the fixed-effects model was used; otherwise, the random-effects model was used. Due to the small number of trials that were included, no publication bias was assessed. A sub-group analysis was performed to highlight any difference between studies with different tumour sites (pancreatic NETs versus other location). For all of the statistical analyses, a value of P<0.05 was regarded as statistically significant, and all of the tests were two-sided.

Results

Literature review, characteristics and quality of the included studies

The search yielded 8454 potentially relevant articles. Of these, 7744 studies were excluded as duplicates. After viewing the titles and abstracts of the 710 remaining studies, the full texts of 21 studies were retrieved and seven studies **[10-12,18-21]** with 1012 cases in experimental arm and 896 cases in the control group were included in the meta-analysis according to the inclusion and exclusion criteria described in the materials and methods section **(Fig. 1).** One study was excluded because retracted by the authors **[22]**. Among these studies, 3 studies **[10,12,18]** investigated everolimus single agent as experimental arm, 3 studies sunitinib and bevacizumab respectively **[11,19,20]** and one study the combination of everolimus and bevacizumab **[21]**. Three studies enrolled patients with pancreatic NET **[10,11,21,22]** only**.** The patients' characteristics were obtained for all studies. The characteristics of the studies included in the meta-analysis are summarized in **Table 1.** There were 2 phase II studies **[20,21]** and 5 phase III studies **[10-12,18,19]**. All studies had a comparator: in 3 **[10-12]** the comparator was placebo, while in 1 was placebo plus octreotide LAR **[18];** in 2 studies the comparator was pegylated (PEG)-interferon alfa-2b and interferon respectively **[19,20]** and everolimus in on trial **[21].** The median Jadad score was 5, showing a good quality of the included studies **(Table 1)**.

Efficacy data

Data about OS and PFS were reported in **Table 2.** With regard to OS, data were obtained from 4 studies **[10-12,21].** The pooled analysis revealed that the new target therapies definitely improved the OS compared with control arm (0.79, 95%CI: 0.63-0.98; P=0.03, **Figure 2**). The analysis was performed using a fixed-effects model (I^2=46%). In the experimental arm, a higher PFS has been observed respect control arm for all the included studies. All the studies reported HR for PFS, the pooled analysis revealed an improvement with new target therapies (HR=0.59, 95% CI:0.42-0.84; P=0.003 **Figure 3**). The random-effects model was used for the analysis of the PFSs due to the presence of high heterogeneity (I^2=87%) between the trials. In the subgroups analysis of the targeted agents in pancreatic and non-pancreatic NET, the results revealed the targeted therapies significantly improved the PFS to a greater extent in the pancreatic NET (HR=0.49 95%CI: 0.29-0.83) than in non-pancreatic NET setting (HR=0.71 95%CI: 0.49-1.02) **(Figure 3)**.

Five studies reported the RR of the target agents in NET **[11,19-21].** RR has been obtained in a total of 59/384 (15.3%) patients for the experimental group and in a total of 17/383 (4.4%) patients in the control group. Using the Mantel–Haenszel method for combining trials, the pooled RR for achieving an objective response with targeted agents versus placebo or other therapies was 3.33 (95% CI 2.02–5.49; P<0.00001; I^2=0%) **(Figure 4)**. Regarding the toxicity, the data of the adverse events unfortunately were not homogeneously reported in the studies; therefore, an associated meta-analysis could not be performed.

Discussion

Although the molecular background of sporadic NETs is unknown, several studies suggested that the abnormal PI3K-AKT-mTOR pathway signalling is implicated in their pathogenesis **[23]**. The mTOR protein is a serine-threonine kinase regulating cell growth, proliferation, metabolism, and angiogenesis and its autocrine activation, mediated mainly by the Insulin-like Growth Factor 1, has been associated with neuroendocrine tumour cell proliferation **[24].** The crucial role of mTOR pathway in NETs is also supported by the fact that NETs pathogenesis is frequently linked with familial cancer syndromes, such as neurofibromin 1 (NF-1) or tuberin (TSC). In particular, the chromosome arm 16p, which contains TSC-2, has been found to be lost in 37% of pancreatic NETs **[25].** The phosphatase and tensin homologue (PTEN) has been also detected mutated or deleted in the 10% up to 29% of patients with pancreatic NETs **[25].** All these tumor suppressor genes, if inactivated, led to an over-expression of the mTOR pathway **[26].** Moreover, mTOR pathway is linked to a progression of disease, in this context, Missiaglia et al showed that the down-regulation of the tumor suppressor of the Akt/mTOR pathway TSC-2 and PTEN which leads to deregulation of the mTOR pathway are linked to progression of pancreatic NETs to an increased rate of proliferation, and shortened PFS and OS **[25]**. Although the crucial role of mTOR seems to be mainly confined in the subgroup of pancreatic NETs (in fact about the 14% of these last present mutations in genes in the mTOR pathway) **[26,27]**. The positive recent data from the RADIANT-4 trial **[12]** based on the use of mTOR targeting agent (everolimus) supported the leading role of mTOR axis in NETs not only in is pancreatic but also in lung or gastrointestinal tumors.

The angiogenesis process along with one of its “driver” such as the vascular endothelial growth factor (VEGF) play also an important role in NETs progression. Over expression of VEGF has been demonstrated in pancreatic or not pancreatic NETs and it has been

associated to a worse outcome **[26,28].** Moreover the VEGF receptor-2 (VEGFR-2) is also generally over-expressed also in gastro-intestinal carcinoid tumors and carcinoid cancers **[26,29].** Thus, targeting these markers potentially arrest the NETs related-angiogenesis inducing, as a consequence, a tumor downstage and an improvement in PFS/OS **[12,20,21].**

The present study is a systematic review and a meta-analysis of trials to assess the efficacy of targeted agents in patients with advanced NET. NETs are a heterogeneous disease arising from various primary sites such as the small intestine or other sites of the gastrointestinal tract, and the lung **[30,31]**, therefore their management is complicated by a different clinical presentations, clinical disease course, symptoms and degree of aggressiveness **[3]**. In our analysis, target agents improved the PFS and OS of advanced NETs patients compared with control group. Therefore, we may confirm the important role of targeted agents in treating the advanced NETs and in this setting, the completion of several randomized phase III studies has brought to the approval of two new sunitinib, and everolimus **[32]**. Because of the observed long survival after progression of many patients, PFS is recommended as a feasible and relevant primary end point for both phase III studies and phase II studies **[33]**, however we have been able to show a statistically significant improvement also in OS for patients with NETs treated with targeted therapies. In the subgroup analysis, we have reported a better PFS in patients with pancreatic NETs versus other site of NETs (HR=0.49 and 0.71 respectively). However, it is well known for chemotherapy and targeted treatment than better response is observed for pancreatic NETs than non-pancreatic NETs. Therefore our study empowered this issue.

The identification of the patients who will benefit or will be resistant to targeted agents is mandatory in a clinical setting. Unfortunately, there are less established biomarkers able to predict the response of advanced NETs to targeted agents. In the near future, studies

based on identification of biomarkers predicting response and clinical benefit to novel targeted agents in advanced NETs patients are needed.

It is worth of notes our meta-analysis presents several important limitations: 1) not all considered studies reported data on HRs of OS, PFS and RR, 2) different drugs with different mechanism of action have been analysed with different impact on outcome-related variables, 3) only one study directly compared the combination of two targeted therapies, however an increase in toxicity in the combination arm was observed **[21],** 4) this is not a meta-analysis performed from individual data from randomized studies, but from data available in literature, which is known to be much less robust, 5) data on toxicities were very heterogeneous and did not allow a reasonable pooling of the results, 6) although, we found a good global quality of examined studies (median Jadad score of 5), the quality and the design of clinical studies for advanced NETs are poor **[34]** due to several factors: the heterogeneity of the disease (different primary sites), very low incidence leading to a relative paucity of comparative and strategy studies. NET treatment strategy may include several options such as surgery, through liver-targeted therapies and several lines of systemic therapy.

Conclusions

NETs are a heterogeneous disease leading to a very difficult trial design and algorithm of therapy. Therefore, the optimal management of advanced NETs is still a challenge for medical oncologist. The recent success of phase III trials demonstrate that the novel agents such as sunitinib, and everolimus are an effective therapeutic options for patients with advanced NETs with particular regards to the pancreatic tumors. While, the combination of everolimus plus octreotide LAR improves PFS in patients with advanced NETs, no data are available on the antitumor activity of the combination of sunitinib and everolimus or sunitinb octreotide and LAR. Nowadays, new pathways with new targeted

therapies are under investigation in advanced NETs, but it is still mandatory to design and conduct trials properly to solve the issue of the optimal management in any subgroups of advanced NETs, maybe thankful also the identification of “driver” biomarker for selected treatment.

Conflict of interest

The authors declare that there are no conflicts of interest. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Table 1. Characteristics of the analysed trials.

Study	Design	Primary endpoint	Number of Patients Experimental Arm	Number of Patients Control Arm	Experimental drug	Control	Tumor location	Jaded score
Yao 2011 **[10]**	III	PFS	207	203	Everolimus	Placebo	Pancreatic	5
Raymond **[11]**	III	PFS	86	85	Sunitinib	Placebo	Pancreatic	5
Yao 2015 **[12]**	III	PFS	205	97	Everolimus	Placebo	Non-pancreatic NETS	5
Pavel **[18]**	III	PFS	216	213	Everolimus+ Octreotide LAR	Placebo + octreotide LAR	Non-pancreatic NETS	5
Yao 2015 ASCO **[19]**	III	PFS	201	201	Bevacizumab+ Octereotide	Interferon α-2B+ Octereotide	Non-pancreatic NETS	4
Yao 2008 **[20]**	II	PFS	22	22	Bevacizumab	PEG interferon α-2B	Non-pancreatic NETS	3
Kulke 2015 **[21]**	II	75	75	75	Everolimus+ Bevacizumab	Everolimus	Pancreatic	3

Table 2. Data on overall survival, progression free survival, median treatment duration and median follow-up of the included studies.

Study	OS (months)		P value	PFS (months)		P value	Median treatment Duration (months)		Median Follow-up (months)
	Experimental drug	Control		Experimental drug	Control		Exp	Control	
Yao 2011 **[10]**	NR	NR	0.59	11.4*	5.4*	< 0.001	8.79	3.74	17
Raymond **[11]**	NR	NR	0.02	11.4	5.5	<0.001	4.6	3.7	NR
Yao 2015 **[12]**	NR	NR	0.04	11	3.9	< 0.0001	40.4**	19.6**	21
Pavel **[18]**	NR	NR	NR	16.4	11.3	0.026	9.25	9.15	28
Yao 2015 ASCO **[19]**	NR	NR	NR	16.6*	15.4*	0.55	NR	NR	NR
Yao 2008 **[20]**	NR	NR	NR	16.5	14	0.34	4.5	4.5	4.5
Kulke 2015 **[21]**	36.7	35	0.16	16.7	14	0.12	13***	12***	25.9

OS: overall survival; PFS: progression free survival; NR: not reported.

*according to central assessment; ** Weeks; *** Cycles

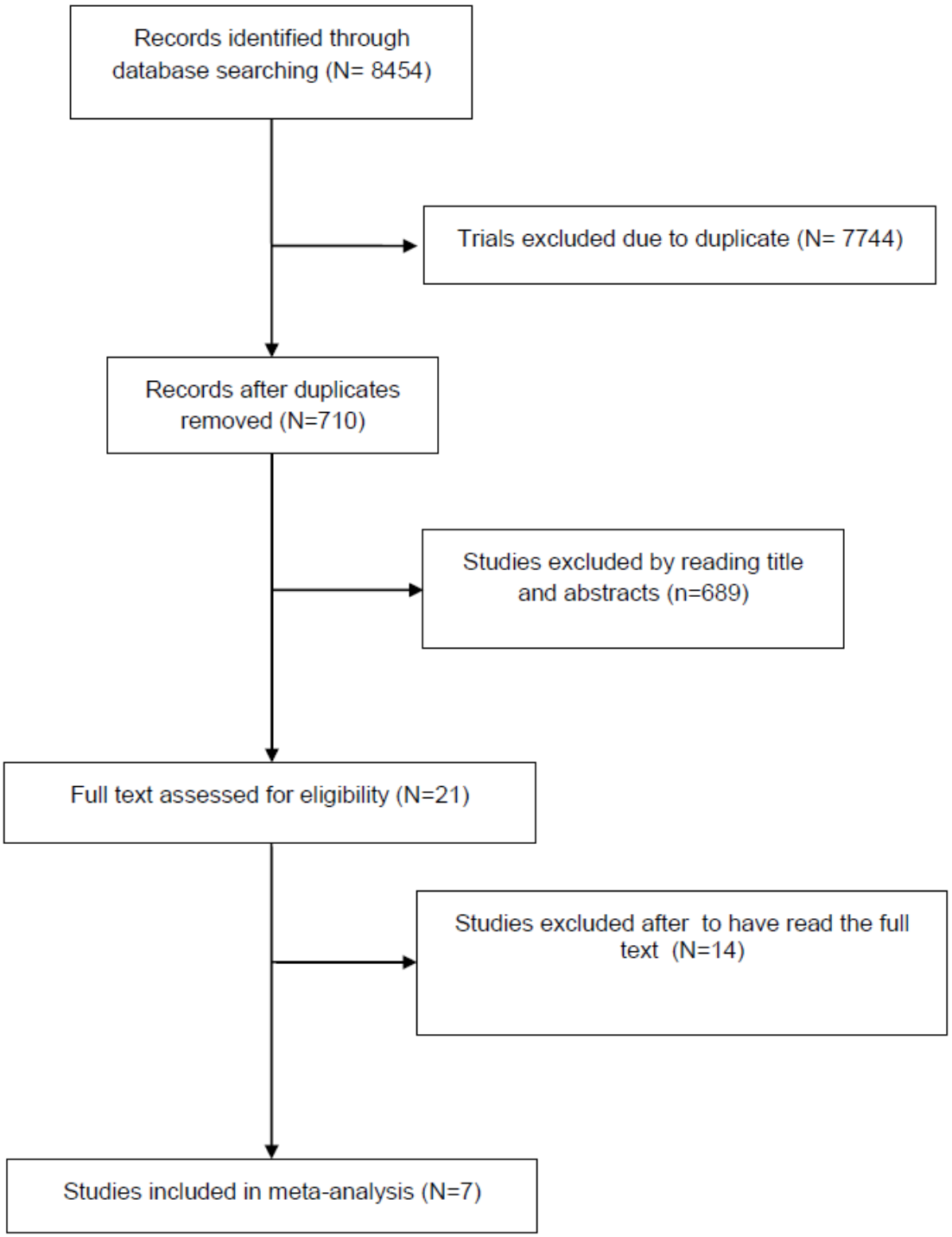

Figure 1. Trial selection flow chart.

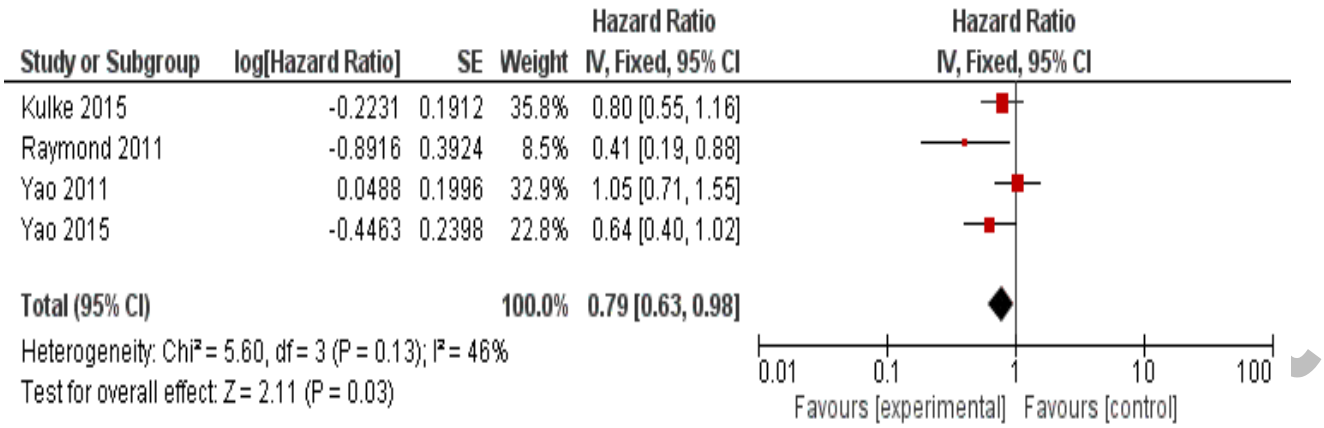

Figure 2. Forest plots of hazard ratios (HRs) for overall survival (OS) comparing new target agents to control group. The Chi-squared test showed low heterogeneity between the trials. The fixed effects model was used.

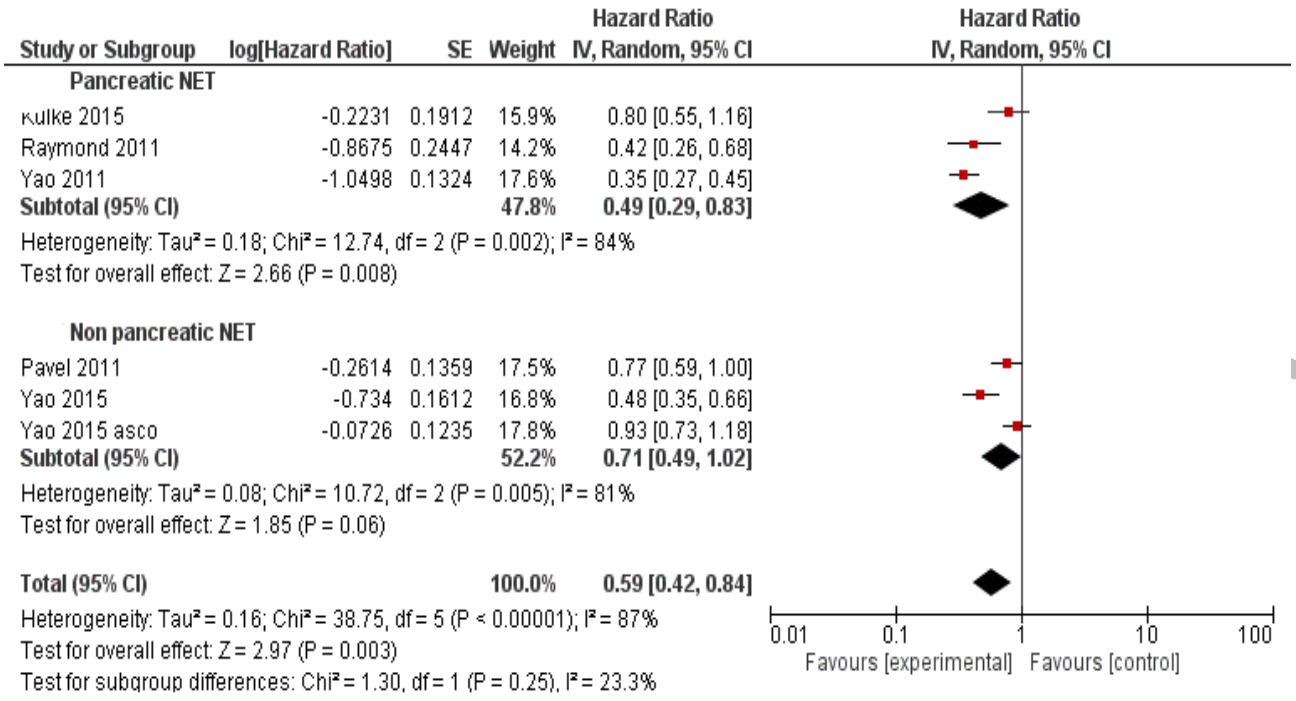

Figure 3. Forest plots of hazard ratios (HRs) for progression-free survival (PFS) comparing new target agents to control group. The Chi-squared test showed high heterogeneity between the trials. The random effects model was used

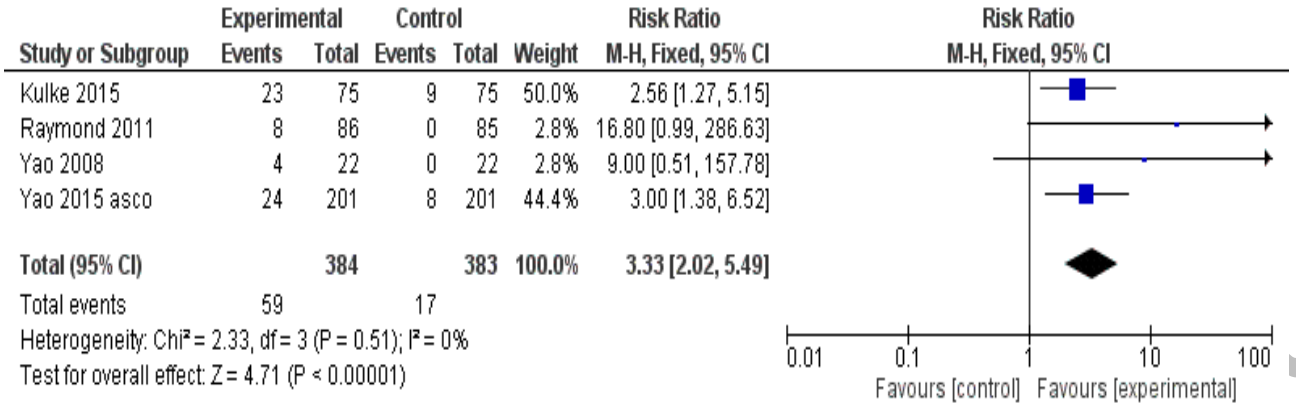

Figure 4. Forest plots of hazard ratios (HRs) for progression-free survival (PFS) comparing new target agents to control group in the subgroup of pancreatic NETs versus non pancreatic NETs. The Chi-squared test showed high heterogeneity between the trials. The random effects model was used