

2015 EUROPEAN CANCER CONGRESS

25-29 September 2015

Vienna, Austria

SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European CanCer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

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NEUROENDOCRINE TUMOURS

Progression-free survival prolonged with everolimus in patients with advanced lung/gastrointestinal neuroendocrine tumours

Findings from the pivotal RADIANT-4 study presented by lead investigator James Yao, University of Texas MD Anderson Cancer Centre, Houston, USA, showed that everolimus provided a significant 52% risk reduction in patients with advanced, progressive lung/gastrointestinal (GI) neuroendocrine tumours (NET) who also achieved progression-free survival (PFS) that was 7.1 months longer than PFS in similar patients receiving placebo. Everolimus is a mTOR inhibitor that has been approved in advanced pancreatic NET; however, advanced, non-functional NET of lung/GI origin remains an area of significant unmet medical need wherein the efficacy and safety of everolimus had not yet been determined.

RADIANT-4 was a randomised, placebo-controlled, double-blind, multicentre, phase III trial of everolimus versus placebo that was conducted in 302 patients with advanced, progressive, well-differentiated, non-functional lung/GI NETs. Patients were stratified by tumour origin, WHO performance status (PS), and prior somatostatin analogue treatment, and then randomised 2:1 to receive best supportive care (BSC) plus either everolimus at 10 mg per day (n=205) or placebo (n=97). Patient median age was 63 years, 53% of patients were female, and 76% were Caucasian. Disease status was grade 1/grade 2 in 64% and 35% of patients, respectively, and WHO PS was 0 in 74% or 1 in 26% of patients. The most commonly reported tumour sites were the lung in 30%, and the ileum in 24% of patients; 53% versus 56% of patients in the everolimus and placebo groups respectively had received prior somatostatin analogue therapy, 26% versus 24% had received chemotherapy and 22% versus 20% had undergone previous loco-regional radiotherapy.

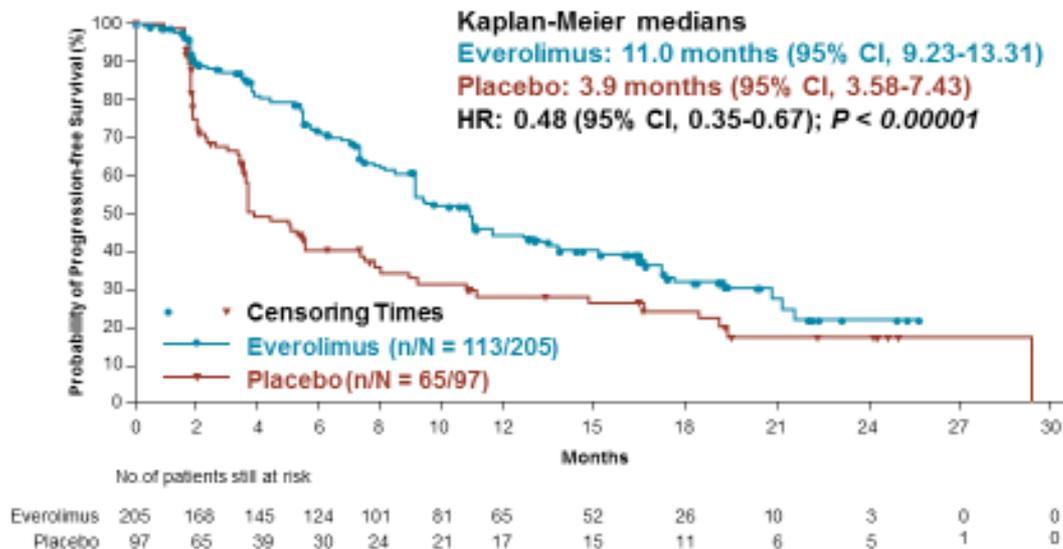
Progression-free survival (PFS) assessed by central radiology review (modified RECIST 1.0), the primary endpoint, was median 11.0 (95% CI 9.2, 13.3) months with everolimus compared to 3.9 months (95% CI 3.6, 7.4) months with placebo, HR 0.48; 95% CI 0.35, 0.67 ($p < 0.001$).

Investigator-assessed PFS was consistent with the central review; PFS with everolimus was 14.0 (95% CI 11.2, 17.7) months compared to 5.5 (95% CI 3.7, 7.4) months with placebo, HR 0.39; 95% CI 0.28, 0.54 ($p < 0.001$). Subgroup PFS analyses by stratification factors also were consistent with these assessments.

Primary Endpoint: PFS by Central Review

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52% reduction in the relative risk of progression or death with everolimus vs placebo



P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

Caption: Treatment of patients with advanced lung and gastrointestinal neuroendocrine tumours was associated with a 2.8 fold improvement in median progression-free survival from 3.9 months to 11 months.

Credit: James Yao

Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. ORR by central review, showed no complete response (CR) but 4 (2%) everolimus patients and one (1%) placebo patient showed partial response (PR). DCR was 82% with everolimus versus 65% with placebo. Progressive disease was reported for 9% of everolimus patients compared to 27% of patients receiving placebo. Tumour response was unknown in the remaining patients. A pre-planned interim OS analysis showed a trend toward improved OS favouring everolimus that did not reach statistical significance, HR 0.64, 95% CI 0.40, 1.05 ($p = 0.037$).

The most commonly reported adverse events (AEs) grades 1/2 included stomatitis, diarrhoea, peripheral oedema, fatigue, and rash. Grades 3/4 AEs of diarrhoea and anaemia were reported by 9% versus 2% and 5% versus 2% of patients receiving everolimus and placebo, respectively. Grades 3/4 abdominal pain was reported for 5% of each treatment arm and stomatitis was reported by 7% of patients receiving everolimus.

Results from all 4 RADIANT studies support the use of everolimus in grade 1 and 2 disseminated and progressive NET, regardless of primary tumour origin, and the authors noted that findings from the RADIANT-4 study may guide treatment of patients with advanced, non-functional NETs of the lung or GI tract. Yao *et al.* Abstract 5LBA.

Practice point and future research opportunities

RADIANT-4 is the first large, placebo-controlled, prospective phase III trial to unequivocally demonstrate clinical benefit with everolimus versus placebo. These findings may represent practice-changing data that support the efficacy and safety of everolimus across the broad spectrum of neuroendocrine tumours.

NETTER-1: Novel peptide receptor radionuclide therapy shows clinical benefit in patients with midgut neuroendocrine tumours

According to lead investigator Philippe Ruszniewski, Beaujon Hospital, Clichy, and Paris Diderot University in Paris, France, Lutathera® has shown promising results in thousands of patients with advanced midgut neuroendocrine tumours (NETs). Lutathera is a ¹⁷⁷Lu-Dotatate peptide receptor radionuclide therapy (PRRT) that targets somatostatin receptors, which are overexpressed in about 80% of NETs, to deliver cytotoxic radiation directly to the tumour. The NETTER-1 trial was

the first phase III multicentre, stratified, randomised, controlled trial to compare Lutathera to octreotide LAR, the current standard of care, in patients with inoperable, progressive, somatostatin receptor positive midgut NETs. The primary endpoint was progression-free survival (PFS) by RECIST 1.1 criteria and secondary objectives included objective response rate (ORR), overall survival (OS), time to progression (TTP), safety, tolerability and health-related quality of life.

NETTER-1 enrolled 230 patients with grade 1–2 metastatic midgut NETs that were randomised in a 1:1 ratio to receive Lutathera in 4 intravenous doses at 7.4 GBq administered every 8 weeks together with renal protection consisting of an amino acid solution infusion or octreotide LAR at 60 mg by deep intragluteal injection every 4 weeks.

After a median 30 months of follow-up, analysis of data from 229 patients in the intent to treat (ITT) population revealed the median PFS with Lutathera was not reached compared with 8.4 months with octreotide LAR, HR 0.209; 95% CI 0.129, 0.338 ($p < 0.0001$); Professor Ruzniewski remarked that the estimated PFS derived from the immature data placed the median PFS at approximately 40 months with Lutathera. ORR was 19% in the Lutathera arm; 95% CI 11%, 26% versus 3% with octreotide LAR; 95% CI 11%, 26 ($p < 0.0004$). One patient receiving Lutathera achieved complete response (CR) and 18 patients showed partial response (PR) compared to no CR and 3 PR with octreotide LAR. Stable disease was achieved by 77 (66%) patients and by 70 (62%) patients in the respective cohorts, while progressive disease was experienced by 5 (4%) Lutathera patients and by 27 (24%) octreotide LAR patients. The interim OS analysis of the ITT population revealed a trend toward improved OS ($p < 0.0186$) that did not reach statistical significance. This ongoing trial will continue to follow survival parameters until the data mature.

At the time of the interim analysis, 13 patients receiving Lutathera and 22 octreotide LAR patients had died. The number of centrally confirmed disease progressions or deaths was 23 in the Lutathera group compared to 67 with octreotide LAR. The safety profile in NETTER was consistent with the safety information generated in the phase I and II clinical trials. Serious adverse events (SAEs) with Lutathera included lymphocytopenia, reported in 3 patients, and thrombocytopenia, neutropenia, pancytopenia and bicytopenia, which each occurred in one patient. There were 2 SAEs of acute kidney injury and one case of renal failure. The authors suggest that Lutathera may also have clinical benefit in other types of NETs, for example, pancreatic and bronchial.

Ruzniewski *et al.* Abstract 6LBA.

Practice point and future research opportunities

These findings confirmed data from phase I and II trials and provide reasonable evidence that Lutathera represents a major advance in treatment of patients with advanced midgut NETs, wherein treatment options are limited for patients who progress following first-line somatostatin analogues. Midgut NETs comprise 20 to 45% of overall NETs, which has an estimated incidence of 47,300 in Europe; moreover incidence has been seen to increase steadily over the past years, most probably due to improved diagnosis. These results showed that Lutathera was superior to octreotide LAR for the treatment of advanced midgut NETS and may be practice changing for the treatment of these patients.

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AFFILIATION AND DISCLOSURE

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

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