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Towards personalized medicine in lung and thymus neuroendocrine tumours

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Running head: Personalised medicine in neuroendocrine tumours

Keywords: neuroendocrine, tumours, lung, thymus, everolimus, pasreotide

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Editorial

A personalized treatment approach is increasingly the aim of oncology care, with focus on effective efficacy on the one hand, low grade and frequency of adverse effects on the other; more recently we are beginning to take into account characteristics of individual tumours and the dynamic evolution of a patient's disease. This can be conceptualised in the axiom "the right drug, to the right patient, at the right time", and needs to be implemented also when dealing with neuroendocrine tumours (NETs). Although these tumours have long been considered as monolithic entities under a unifying umbrella of NE differentiation, they differ significantly in clinical outcomes. In particular the organ of origin is likely to account for profound differences in disease development and response to treatment [1]. Accordingly, it is highly relevant to define predictive and prognostic pre-treatment criteria to allow stratification of NET patients [2]. In gastrointestinal tract NETs an effective grading system has been devised to guide therapy strategies [3,4], but in lung and thymus NETs there remains a lack of reliable information, especially in metastatic tumours, where diagnostic material is limited and for cases with similar histology [2].

Somatostatin receptor analogues (SSA) and m-TOR inhibitors have been assessed in the therapy of NETs at several anatomical sites [5-11] (**Table 1**), but trials devoted to TC and AC in the lung and thymus have been lacking. Ferolla et al. address this gap with the LUNA trial presented in this issue of the Journal. The LUNA study was a prospective, randomized, 3-arm phase 2 trial of everolimus, pasireotide, and everolimus plus pasireotide. The m-TOR pathway inhibitor everolimus had previously been used for metastatic lung carcinoids jn the RADIANT-4 trial [10]. Here the SSA pasireotide was additionally tested. Well-differentiated lung and thymus NETs are likely to express somatostatin receptors or have an activated m-TOR pathway [12,13]. In clinical practice, many patients with lung and thymus NETs will receive everolimus and a SSA in series; combination treatment had remained unexplored. LUNA addresses this as preclinical data suggest benefit from simultaneous inhibition of the IGF1-, PI3K- and mTOR pathways and clinical evidence shows that everolimus is effective in combination with octreotide, an octapeptide mimicking somatostatin pharmacologically [7].

The primary study aim was to determine the proportion of patients who were progression-free at 9 months to allow rejection of the null hypothesis that any treatment arm was ineffective but the trial was not powered to compare efficacy between the three arms. The trial met its primary endpoint, and also provides useful data on the combination of everolimus and pasireotide. The combination was well tolerated with no evidence that addition of pasireotide compromised the dosing of everolimus. The authors are to be commended on rapidly completing a randomized trial in these uncommon tumours: 124 patients were recruited over 12 months in a collaboration across 36 centres. It is hoped that this excellent starting point will enable future studies on lung and thymus NETs. The SPINET study, a phase

III study of lanreotide plus best supportive care vs. best supportive care in pulmonary carcinoid, is currently recruiting and will answer the important question of whether SSA are effective in delaying progression in TC and AC of the lung (see https://clinicaltrials.gov/ct2/show/NCT02683941).

The LUNA trial leaves us with open questions. Should the combination of everolimus plus a SSA be tested further, and is the evidence thus far sufficiently promising? Could we select patients rationally for combination treatment on the basis of molecular traits or with the Ki-67 labelling index by adopting specifically devised cut-off thresholds for lung or thymus NETs [14]? Two studies now show promise for combination over single agent treatment. In LUNA with lung/thymus NETs, the proportion of patients with disease control at 9 months was 58% in the combination arm vs. 33% in the two single agent arms. In the COOPERATE-2 study of pancreatic NETs, 20.3% of patients treated with everolimus plus pasireotide achieved a partial response vs. 6.2% treated with everolimus alone, but without improvement in PFS in the combination arm [6]. Neither study, however, has compared parallel to serial treatment. Treatment with one agent at a time is clinically attractive because toxicity can be minimized and comparison of everolimus plus SSA vs. everolimus then SSA would be of interest because the timing could have biological relevance. Such a study would need to be powered for long term survival and quality of life, would be long and expensive and may therefore not be done.

In a disease setting where large trials are difficult to carry out, clinicopathologic data become critically important and this also applies to NETs with divergent clinical behaviour. SSA receptor status was not assessed in the LUNA study, nor m-TOR activity as a surrogate marker, so it is not possible to assess whether selecting patients according to SSA or m-TOR pathway status would have increased the benefit of a combination treatment. However, 48% of patients in the study had received a prior SSA. This was well balanced between the arms but may well have reduced the overall efficacy of the combination treatment. It would be appealing to evaluate somatostatin receptor status and the activation status of the m-TOR in this patient cohort.

Currently, the evidence in the LUNA trial is not sufficient to change clinical practice in pulmonary carcinoids. The novel information on thymus NETs is worth expanding in near future and the NET community should be encouraged to carry out more studies in this cohort of patients. The LUNA trialists have demonstrated admirably that recruitment in a timely fashion is feasible. It is now critical to achieve biological stratification of NETs, including markers that describing the inherent biologic aggressiveness of NETs, such as Ki-67 labelling index [2]. Only then will we be able to select treatments, most likely to offer clinical benefit to the individual patient.

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Table 1: Randomised trials evaluating disease control with mTOR inhibitors and/or somatostatin analogues in NETS

Study name	Authors	Reference number	Primary site and number of patients	Functional status	Intervention arm	Control arm	Primary outcome	Survival data
PROMID	Rinke et al, JCO 2009	9	Midgut N=85	Functioning and nonfunctioning	Octreotide LAR	Placebo	TTP 14.3 vs. 6 months HR 0.34 (95% CI 0.2 – 0.59)	HR 0.81 (95% CI 0.3-2.18)
RADIANT -2	Pavel et al, Lancet 2011 & Ann Oncol 2017	7,8	Mixed N=429	Functioning	Everolimus + Octreotide LAR	Placebo + Octreotide LAR	PFS 16.4 vs. 11.3 HR 0.77 (95% CI 0.59-1)	No OS difference between Everolimus + Octreotide and Placebo + Octreotide
RADIANT-3	Yao et al, NEJM 2011	11	Pamcreas N=410	Functioning and nonfunctioning	Everolimus	Placebo	PFS 11.0 vs. 4.6 HR 0.35 (95% CI 0.27-0.45)	44 vs. 37 months HR 0.94 (95% CI 0.73-1.20)
CLARINET	Caplin et al, NEJM 2014	5	Pancreas, midgut or hindgut N=204	Nonfunctioning	Lanreotide	Placebo	PFS not reached vs. 18 monts ($p<0.001$)	Not reported
RADIANT-4	Yao et al, Lancet 2016	10	Lung and thymus N=302	Nonfunctioning	Everolimus	Placebo	PFS 11.0 vs. 3.9 months HR 0.48 (95% CI 0.35 – 0.67)	HR 0.64 (95% CI 0.4-1.05)
CO-OPERATE 2	Kulke et al, Ann Onc 2017	6	Pamcreas N=160	Functioning and nonfunctioning	Everolimus + pasireotide	Everolimus	PFS 16.8 vs. 16.6 months HR 0.99(95% CI 0.64 – 1.54)	No improvement

NETs: neuroendocrine tumours; TTP: time to progression; PFS: progression-free survival; HR: hazard ratio; CI: confidence intervals; OS: overall survival