Editorial

No room for statins in the quest for survival benefits in small cell lung cancer

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Targeted agents and immunotherapy are revolutionizing the continuum of care for patients suffering from non-small cell lung cancer (NSCLC) (1). On the other hand, SCLC management remains a critical and disappointing issue. The definition of a "fast, hungry and unstable" disease provided by Christine Hann and Charles Rudin more than 10 years ago (2) is unfortunately still applicable. Given this premise, the encouraging activity signals observed for immune checkpoint blockers (3,4) and the antibody-drug conjugate rovalpituzumab tesirine (5) in their early clinical development justify the hope for their transposition in the daily clinical practice.

Recently, Seckl and collaborators reported the final results of the phase III LUNGSTAR study run in United Kingdom between 2007 and 2013, envisaging the potential role of pravastatin added to first-line standard chemotherapy in prolonging the overall survival (OS) of SCLC patients (6). Eight hundred and forty-six patients were randomized to receive either pravastatin 40 mg daily or placebo in association to platin/etoposide regimens, the large majority (n=750) receiving carboplatin. Globally, LUNGSTAR was methodologically well designed and conducted. Patients' characteristics mirrored a real-life scenario, with more than 25% of the patients presenting with an ECOG PS of 2 or 3; a potential slightly high proportion of limited diseases (43%) was observed. Although safe and not engendering additional toxicities, pravastatin did not provide any survival improvement. Median OS was 10.7 and 10.6 months in the placebo and control arm, respectively, with a hazard ratio (HR) adjusted for the stratification factors of 1.02 [95% confidence interval (CI): 0.89 to 1.18; P=0.76]. Median progression-free survival (PFS) was 7.7 and 7.3 months in the two respective arms (adjusted HR of 1.01; 95% CI: 0.88 to 1.17; P=0.86). This translated in 2-year OS rates of 14% and 13% and in 1-year PFS rate of 25% and 24%, respectively. In patients diagnosed with limited disease (LD), median OS was 14.6 months in both arms, whereas 9.1 and 8.8 months in the extensive disease (ED) population receiving pravastatin or placebo, respectively (interaction P=0.53). The results observed in the ED group are overlapping with more or less recent studies (7,8). Authors attribute the relative shorter survival obtained in LD patients, when compared to the 25–30 months in the global CONVERT trial (9), to the lower amount of radiotherapy administered in United Kingdom in previous years. Post-progression therapies were well balanced, thus reducing potential biases potentially affecting survival data, and no differential effect was observed for any subgroup, frustrating any potential further investigation in a precise subset of SCLC patients.

Given these considerations, at the first glance LUNGSTAR trial appears quite disappointing, taking into account the significant enrollment of almost 850 patients. In SCLC, pravastatin 40 mg daily failed to engender any benefit when added to first-line standard chemotherapy

and nullified the promising role depicted for statins in both cancer prevention and mortality reduction, as emerged by observational studies (10-12). We refer to Table 3 of the manuscript of Seckl and colleagues (6) for a comprehensive approach to randomized trials involving statins in oncology. Nevertheless, putting the data in the context, as authors soberly and properly do in their discussion, it does emerge that the way the trial have been led was the only one to provide definitive results. Unfortunately it was so, but not in the direction envisaged. It is noteworthy that the study had been developed in 2005 and recruitment was active from 2007 to 2013. Considering the lack of relevant improvements in SCLC treatment in the last decade, we do not think that in the mentioned timeframe, patients could be allocated into different and potentially more promising trials. Given the affordability and the nature of the experimental arm, we moreover find such policy acceptable, favoring a definitive large trial instead of obtaining more robust preclinical hints and/or clinical solidity emerging from phase II studies.

As stated by authors, we agree that the experimental data "from the bench" supporting the usefulness of statins in SCLC were not *per se* impressive (13). Authors cite that statins could act as anticancer agents, synergizing with cytotoxic agents, by impairing geranylation and farnesylation of RAS superfamily. Albeit different strategies (i.e., tacking the downstream effector MEK) have been envisaged in NSCLC, researchers and clinicians dedicated to lung cancer know how challenging and frustrating is to deal with RAS members (14). Moreover, specifically developed anti-geranylation and/or -farnesylation agents have still not found their definite place in clinical oncology (15,16). Nevertheless, in the oncology field it is not so uncommon to see strategies, presented as wonderful in the preclinical setting, collapse at the first clinical test, as well as the opposite scenario is possible. In the affordable setting of a potential repurposing of an "old" drug, the choice of such a big phase III trial appears not only justifiable, but even correct.

Evidence sustaining the potential higher antitumor effect of lipophilic statins, such as simvastatin, compared to hydrophilic agents, such as pravastatin, dates after the trial design, as well as the putative significance of a higher dose of pravastatin (i.e., 80 mg daily, compared to the 40 mg used in the study) (10,12,17). Given the lack of any signal of activity (response rates overlapped in the two arms) and efficacy in such a large population of patients, the type and the dose of statin does not seem to be dramatically in charge.

In conclusion, LUNGSTAR study provides the first and definitive answer to the putative usefulness of statins associated with chemotherapy for the treatment of SCLC patients. Although unfortunately disappointing, such an answer has been achieved in the most complete and correct way. We do not agree with the authors on one point only. They assume that the poor prognosis of SCLC "made it a good candidate for an inexpensive therapy even with a modest effect". We are indeed tented to face the issue in the opposite way, as the dismal prognosis of SCLC calls for therapeutic solutions that are deeply and significantly impacting into patients' outcomes. Form this point of view, we have stated above that LUNGSTAR found its sense when collocated in the timeframe it was run. We do believe that in the present and upcoming times, scientific, financial and clinical efforts should be dedicated to really promising strategies, either inherited from other tumor types (3,4) or sustained by biological insights (5).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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