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**CONFIRM trial: what is the real efficacy of second-line immunotherapy in mesothelioma?** Authors' reply

We thank Pierpaolo Correale and colleagues for their interest in our CONFIRM trial published in The Lancet Oncology.

Treatment advances in the setting of relapsed mesothelioma have been lacking over the past two decades. Despite the numerous single arm studies published, until recently no positive randomised trials have been reported. The recent reporting of NVALT19[1], RAMES[2] and VIM[3] have generated promising evidence of incremental benefit, otherwise unobtainable in single arm studies. In the treatment of non-small cell lung cancer, docetaxel demonstrated superiority compared with active symptom control[4]. This was in 2000, yet docetaxel remains a treatment standard today for patients with relapsed squamous lung cancer. This demonstrates the robust inferences resulting from appropriately controlled studies, measuring efficacy in an unbiased and well-powered study design. With further randomised studies in the future, we should hope to see accelerated advances, building on solid evidence.

The DETERMINE trial[5] randomised Tremelimumab against placebo in a double blind treatment setting, and was robustly negative. This important result rightly drew a line under future development of anti-CTLA4 monotherapy in the relapsed setting, highlighting of the power of the randomised study to inform drug development. CONFIRM used a very similar 2:1 double blind placebo controlled design to evaluate single agent anti-PD1. In response to Correale et al, some important clarifications about this study must be made.

Firstly, we would like to clarify that CONFIRM was not restricted to second-line mesothelioma patients but included patients who had received at least one prior line of standard platinum based chemotherapy and had then progressed: 100 patients (30%) were second-line, 190 (57%) third-line and 42 (13%) patients later than third-line.

Secondly, as with the DETERMINE study, we designed CONFIRM to include patients who had received multi-lines of chemotherapy to a point where they were considered to have failed chemotherapy as a treatment strategy, therefore here placebo was not substituting an alternative standard of care chemotherapy as implied. The use of a placebo also has advantages with respect to reducing bias with the assessment of progression in a trial with a highly heterogeneous population and this design is therefore consistent with contemporary studies in other settings.

The randomised data from CONFIRM objectively document the evidence of benefit of using nivolumab in the relapsed setting and whilst the absolute gains (differences in median PFS/OS) are arguably modest, we believe that they are clinically meaningful for the patients: the relative gains (hazard ratios) equate to a 33% reduction in risk of progression/death and 31% reduction in the risk of death). CONFIRM is the first reported phase 3 trial to have demonstrated a statistically significant improvement in survival in a setting of unmet need. To date licenced therapy in this setting has been generally lacking. The exception is, interestingly for nivolumab, which was licenced in Japan based on the MERIT[6] single arm study. Based on CONFIRM the UK's National Health Service is offering nivolumab for relapsed mesothelioma free at the point of care during the COVID pandemic.

Thirdly, as experienced trialists, we recognise that clinical research commonly generates data that raises further questions, but are puzzled why the authors raises concern that CONFIRM may confuse patients. Patients were involved in CONFIRM from its conception following their prioritisation of this research question at a mesothelioma James Lind Alliance Priority Setting Partnership[7], patient representative involvement on the Trial Management Group while conducting the trial, authorship on

the paper and dissemination of the results on the Cancer Research UK website[8]. As to our knowledge, randomised data remain the gold standard of drug evaluation, thus it was our aim to add to the body of evidence (which we will discuss with patients) in this difficult-to-treat cancer and we conclude that CONFIRM does that.

The decision to use nivolumab off label in the relapsed setting is however impacted by Checkmate 743[9], which has now been approved internationally as a first line standard of care. The future licenced space is likely to dictate the use of anti-PD1 monotherapy in the relapsed setting, and which is arguably destined to move to the front line as for non-small cell lung cancer, based on CheckMate 743 and ongoing promising chemoimmunotherapy studies such as IND227, BEAT-meso and DREAM3R.

However, we agree with Correale and colleagues that real steps forward in the treatment of mesothelioma could be achieved from translation of new biological discoveries. But this can be notoriously slow, especially for rare cancers. By contrast, patients need effective therapy now. Randomised trials such as CONFIRM, RAMES and VIM have provided in a short period, important evidence upon which physicians and patients can base treatment decisions in the knowledge that the interventions have measurable benefit, and are not futile. Understanding why immunotherapy works in some patients is a major question in oncology today. The samples collected within CONFIRM are currently being analysed within our CONFIRM-IT/MEDUSA projects to contribute to this knowledge. Precision therapy for mesothelioma is still very much in its infancy, however umbrella studies such as MIST[10] is showing that this is indeed feasible. Randomisation is however, likely to underpin most of the future advances for patients. Positive increments in benefit can only help to push this field forward, hopefully with an accelerating pace.

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