Discussion to: Salvage lung resection after immunotherapy is feasible and safe

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I also would like to thank them for forwarding the manuscript in advance of this meeting. In a National Cancer Database (NCDB) study, they demonstrate that what they deem to be salvage resections are not associated with the worst perioperative metrics, such as readmissions and 30- and 90-day mortality rates, when compared with salvage resections following chemoradiation therapy. I think the additional pearls in the study come in the form of lobectomies being the predominant operation, indicating the absence of the routine need for extended resections such as pneumonectomy. Of further interest is that when pneumonectomies were required, the mortality burden sometimes observed with more traditional therapies were not observed in this study. Cumulatively, I think this information is important because it informs many thoracic surgeons that the salvage resection paradigm is worth pursuing. With that said, I believe the authors should offer some additional commentary to provide some sage advice in this domain to better equip practicing thoracic surgeons to work in this paradigm wisely.

So for my first question, according to the NCDB data dictionary, and as you note in the manuscript, an update to the Participant User File to recategorize certain chemotherapeutic medications to immunotherapy was made in 2013. That said, the 6 drugs they included were—forgive the mispronunciations—alemtuzumab, bevacizumab, rituximab, trastuzumab, pertuzumab, and cetuximab. None of these medications have been the ones included in the now-landmark clinical trials showing benefits and disease-free survival. I am sure since 2013, the NCDB incorporated many of the more recent immunotherapies included in these trials. That said, the larger Phase 2 and Phase 3 trials, such as the Lung Cancer Mutation Consortium 3 (LCMC), Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM), Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small-cell lung cancer (NEOSTAR), Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer (CheckMate 816), Neoadjuvant atezolizumab for resectable non-small-cell lung cancer (IMpower030), and Perioperative Durvalumab for resectable non-small-cell lung cancer (AEGEAN) trials, evaluating the different combinations of therapy, all began their enrollment in 2016 or after. So, do you think the results would change had you exclusively evaluated these more recent agents? And along these lines, do you think there would be any benefit to starting the analysis after 2016?

Dr Attila Nemeth (Tübingen, Germany). Thank you very much for the comments. I think this is a big limitation of the study because we don’t know exactly which drugs were used. We don’t know the time points. Was the therapy started, for example, with direct immunotherapy? It would be interesting to have, firstly, a larger number of patients to have the possibility to analyze it, and it’s definitely something as a future perspective.

Dr Kim. Great, thank you. I appreciate your comments in the manuscript regarding how the 5-month mark was determined as the cutoff for salvage therapy, and although the 5-month window is reasonably late enough to constitute an appropriate time frame, salvage often denotes a longer interval. And so, your better survival, albeit not statistically
significant, was at >9 months. This point speaks to perhaps a different disease process than those that require a salvage resection, say, at 5 months. So, with this in mind, and understanding that the NCDB cannot provide insight as to the reason for pursuing the salvage resections, can you posit some of your practical theories as to what the differences in the indications and disease processes possibly could be? And I can’t put my finger on it, but I wonder if some of it has to do with the fact that you included some stage I patients as well? I may be wrong.

**Dr Nemeth.** Yeah. That’s another limitation. First, we considered 5 months as a time point to exclude the patients who were undergoing neoadjuvant therapy. That was because most of them are around 90 days, so 3, 4 months, or 5 months was considered to be reasonable to take into the study as a time point. Secondly, I didn’t include these results about more than 9 months having a slightly better survival. But probably it’s due to longer survivals or time periods where the patient did not get any metastases are probably a better factor for survival. And regarding the stages, I showed a slide at the beginning where we had a couple of patients who were in stages I and II. We cannot opt out if these were patients in trial. We don’t know if these were patients who were initially not treated or not operative patients. We don’t have any data about lung function, if that’s mainly a reason.

**Dr Kim.** Okay, thank you again. Last question. You have included wide resections in your studies. How can you assure us that this type of resection truly represented a curative intent procedure? I raise this issue because of all the recent attention garnered by sublobar resections, although well deserved, may not be translatable to the salvage setting. Furthermore, I shudder to think that the art of the anatomic resection may be falling by the wayside, and in circumstances such as clinical stage of diseases that warrant immunotherapy, there is a need to be the best oncologic surgeon. Some clinical trials had excluded wide resections. Therefore, could you opine as to whether you truly believe that wide resections truly are in the best interest of patients in this exact setting?

**Dr Nemeth.** Thank you. I think that, firstly, we need to look up the data of the pneumonectomies. We considered, or our initial thought was, that the rate of pneumonectomies would be much, much higher. And there are a couple of sublobar resections with wedge resections being the lowest ones. Again, I think these could be patients who didn’t have enough lung function and were treated as salvage resections. We also know that we're getting more and more data that resecting lung tissue without cancer maybe does not have additional benefits. But I don’t consider wedge resection as a perfect solution in these kinds of patients. Most of them are lobectomies or anatomical resections and have feasible results.

**Dr Kim.** Right. Thank you again, and congratulations on your important contribution.

**Dr Nemeth.** Thank you very much.

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