Discussion of 2021-1758

TREAT NOW OR TREAT LATER: COMPARATIVE EFFECTIVENESS OF ADJUVANT
THERAPY IN RESECTED STAGE IIIA MELANOMA

**DR DOUGLAS S TYLER** (Galveston, TX): As healthcare costs continue to rise in the field of oncology, and novel effective but expensive new drugs come on the market, studies like this decision analysis modelling one presented by Dr Hu and colleagues will become increasingly important. Melanomas have rapidly become the poster child for how these novel therapies can drastically change treatment paradigms, remembering it is just 10 years ago, melanoma systemic therapy was DTIC, IL-2, and interferon, and metastatic melanoma had measured survivals of months. Today almost 50% of patients with metastatic melanoma can enjoy long‑term survival, if not cure, with various combinations of immunotherapy and targeted agents. And just last week, apropos to this paper, the FDA approved expanded indications for adjuvant immunotherapy to the Stage IIB and IIC individuals, both of whom have a worse prognosis than the IIIA patients presented and are focused on in this paper.

 In exploring the ethical and financial questions about how much we are willing to spend to save a life, as was done in this paper by Dr Hu with targeted agents, they did focus on the correct subset of melanoma patients to IIIAs to start asking how truly beneficial is adjuvant therapy. I wonder if their analysis could be made more powerful if they really went beyond using just age as a breakdown of other statistics. Why not use a stronger predictor of recurrence like burden of disease and sentinel node versus age or in addition to age as part of the analysis?

 Second, with this kind of modeling, how do you factor in the possibility that adjuvant therapy at an earlier point in time might actually cure people, or a higher percent of patients than if you wait until recurrence occurs?

 Third, how might you think about this analysis or how would you factor in the patient preference component of things frequently that's done in this type of modelling? So, for example, how much they want to be in truly a disease‑free state or what is their preference for being in an adjuvant state or adjuvant treatment state with its intendant complications.

 And then, finally, how would the analysis change as patients have to pay an increasing component of their health care costs as is probably likely in the future?

 Again, I appreciate the opportunity and privilege of the floor. I commend the authors on a very well-presented paper and thinking about health care and value in the management of oncology patients.

**DR CRAIG L SLINGLUFF, JR** (Charlottesville, VA): This paper builds on a body of work by Dr Hu using Markov modeling to understand the impact of treatments on patient outcomes and on cost. The survival of patients faced with melanoma has been dramatically extended by treatments over the past decade, as Dr Tyler points out, including immune checkpoint antibody therapy and targeted blockade of mutated BRAF. However, these have also added very high costs, thus the question you have addressed is timely and important. This will be a growing concern since the FDA, as was also mentioned, recently expanded indications for adjuvant PD‑1 blockade.

 This paper is timely also in addressing needs of patients across the age continuum, which is particularly important for elderly patients. This is a new priority for the NIH and for national cooperative groups, so the impact of this work is likely to be large. You have done an excellent job of selecting Markov model estimates based on solid data from pivotal clinical trials and you have appropriately acknowledged limitations of this sort of approach. The findings that the number needed to treat and the cost per mortality avoided are both much higher for patients over age 75, especially for those 85 and older. These are compelling findings that should be considered in future clinical trial designs and in clinical practice.

 You focused your analysis on patients with Stage IIIA melanoma where it's reasonable to question the role for adjuvant therapy. However, I am interested in how you translated the data from the landmark trials, since the definition for Stage IIIA patients changed over that interval. Both the COMBI‑AD and KEYNOTE‑054 trials were performed using AJCC version 7, where the definition included primary melanomas of all thicknesses, plus one to three positive sentinel nodes, whereas the current definition of Stage III in version 8 is limited to patients, as you point out, with thinner primary lesions T1 to 2a with one to 3 positive nodes. Are your results inclusive of patients with thicker primaries and one to three positive nodes which had been considered IIIA in prior trials, but we would now consider Stage IIIB or IIIC?

 Second, for patients with BRAF‑mutant melanomas, you modeled the impact of BRAF/MEK inhibition therapy. However, PD‑1 blockade is also approved for those patients and is commonly favored over BRAF/MEK inhibition for adjuvant therapy. Did you consider modeling use of pembrolizumab in the BRAF‑mutant population also?

 Third, the hazard ratios used in your modeling have a defined confidence interval. Can those be incorporated into your analyses to provide confidence intervals on your endpoints?

 And finally, the model includes systemic treatment strategies for salvage after development of Stage IV disease. Can you also develop models that incorporate surgical treatment of resectable metastases?

**DR KELLY McMASTERS** (Louisville, KY): I think the points have been raised that the 10‑year survival rate for Stage IIIA melanoma is 88% and probably better if you include those with micrometastases. Many centers do not treat those patients and observe them closely, which is reasonable because they have a very good survival rate. I think it is worthwhile to try to identify patients who are at high risk and would benefit from adjuvant therapy, as well as those at low risk who will not benefit. But I really want to try to put what we do in melanoma adjuvant therapy in perspective compared to adjuvant therapy for other kinds of cancer.

 So my question is, can you compare this to other types of cancer, like breast cancer, where we give multi‑agent cytotoxic chemotherapy and biologic therapy that is expensive, toxic, that has hazard ratios that are usually not as favorable as what we see for adjuvant therapy in melanoma? A number needed to treat (NNT) of 25 would look pretty good in breast cancer or pancreatic cancer adjuvant therapy; why do you think it is not appropriate for melanoma? How does this cost and NNT for melanoma adjuvant therapy compare to other cancers where we are accustomed to giving adjuvant therapy with lower benefit and higher toxicity?

**DR YININ HU** (Baltimore, MD): The impact of tumor burden is certainly prognostic. The NCCN recommendations acknowledge that the prognosis of patients with submillimeter sentinel node burden is superior to patients with greater disease burden. Previous work has shown that patients with greater than 4-millimeter nodal burden have worse prognosis than patients with 1 to 4 millimeter nodal disease.

 We selected a 1-millimeter threshold to reflect the inclusion criteria for previous adjuvant trials, such as KEYNOTE‑054 and COMBI‑AD, in order to make our model assumptions valid based on those trials. However, I agree that incorporating additional risk stratifiers in the future would be important.

 The question about whether adjuvant therapy can result in an increased long‑term cure rate in the early setting was integrated into our model through the use of hazard ratios from KEYNOTE‑054 and COMBI‑AD. If we look specifically at the Stage IIIA population in KEYNOTE‑054, the absolute risk reduction in long‑term disease‑free survival is less than 10%. And ultimately the conclusion of this model is that this effect is eclipsed in older populations by the contributing risk of non‑cancer mortality.

 I think stated preference research is going to be a large component of future clinical trials. That is a focus of my own research. Thus far, stated preference work in melanoma, particularly in the adjuvant setting, is not well reported. Therefore, we did not include quality adjustment for life years in our model.

 Finally, out‑of‑pocket cost is going to be a contributing factor to patient decision making. This is the core concept of moral hazard and health economics where third‑party payers shouldering the burden of costs can cause product demand to be inefficient from a societal perspective. Based on this concept, we may expect that adjuvant utilization would decrease as patient cost burden increases.

 The definition of Stage IIIA has indeed changed over time. As noted, KEYNOTE‑054 and COMBI‑AD had a Stage IIIA definition that in some ways favored adjuvant treatment due to its more expansive definition. By using the hazard ratios from COMBI‑AD and KEYNOTE‑054, our model carries an inherent bias in favor of adjuvant therapy. Using the more recent definition of only T1 to T2a tumors would likely cause the NNT to be even higher than what we presented here.

 The use of pembro in the adjuvant setting for BRAF‑mutant patients is approved and considered by many medical oncologists. If we look at the hazard ratios for Stage IIIA in COMBI‑AD and KEYNOTE‑054, they are .61 for COMBI‑AD and .64 for KEYNOTE‑054. So, by using BRAF/MEK inhibition as first‑line adjuvant in BRAF‑mutants, we are mathematically maximizing the upfront recurrence‑reduction in favor of adjuvant therapy.

 I would like to address the question of whether we should analyze a Markov model of surgical treatment of metastatic disease. When deciding on transition probabilities, it is important to try to derive these variables from robust data. Unlike for adjuvant therapy, there has been no randomized trial on metastasectomy. If we look at surgical cohort studies, there is too much selection bias to generate a valid transition probability for modeling. Even though it would be an interesting project, it would be hard to justify the validity of the results.

 In general, the number needed to treat is small when adjuvant therapy has a large effect on recurrence reduction and when the natural history of a given cancer is aggressive. Breast cancer has much more data than melanoma, and consensus guidelines do set age limits for patients that are suitable for chemotherapy. I am not as familiar with the number needed to treat literature in breast cancer. I do believe that breast cancer is often overtreated in the early stage adjuvant setting, but that discussion is beyond the scope of this study.