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ASO AUTHOR REFLECTIONS

ASO Author Reflections: Survival for Stage III Melanoma—Where Do We Stand in the Current Landscape of Melanoma Therapies?

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PAST

Stage III melanoma comprises a heterogeneous group of patients with varying survival outcomes, which can be associated with several patient and tumor factors, including number of nodes involved and the presence of microscopic versus macroscopic metastases.[1] Historically, clinical stage III melanoma, defined by the presence of clinically evident lymph node or intralymphatic metastases, was associated with a 5-year overall survival (OS) rate of less than 50%.[1] During the past decade, the introduction of immune checkpoint and BRAF/MEK pathway inhibitors have transformed the treatment options for advanced melanoma, starting with the FDA approval of ipilimumab and vemurafenib in 2011.[2,3] In randomized, clinical trials, these agents have significantly impacted OS in treated patients in the metastatic setting. Therefore, we sought to better characterize the population-level survival outcomes in patients diagnosed with clinical stage III melanoma in the current landscape of melanoma therapies as historic data would be inadequate for accurate prognostication.

PRESENT

Using the National Cancer Database, we found that patients diagnosed with clinical stage III melanoma in the novel therapeutic era (2012–2013) experienced a significantly longer OS time compared with the historic cohorts (2004–2005, 2008–2009).[4] Specifically, diagnosis in 2012–2013 was associated with an 8-month longer median OS time (log-rank $P < 0.001$) and 24% hazard reduction in all-cause deaths ($P < 0.001$) compared with diagnosis in 2004–2005. Because study patients were diagnosed before the first adjuvant approval for ipilimumab in 2015, these results do not reflect the impact of novel therapies in the adjuvant setting. Nevertheless, patients in the more contemporary cohort may have benefited from participation in clinical trials or treatment in the recurrent setting. Interestingly, the results from our study are concordant with the OS benefit observed in the phase III trial of adjuvant ipilimumab versus placebo in patients with resected stage III melanoma (hazard ratio 0.72, 95% confidence interval 0.58–0.88).[5]

FUTURE

Survival outcomes of patients with advanced melanoma continue to evolve in the current treatment landscape. The results from our study provide an early glimpse into the population-level effect that novel systemic treatments have had on OS in patients diagnosed with clinical stage III melanoma. As utilization of immune checkpoint and BRAF/MEK pathway inhibitors increase in the adjuvant setting, survival outcomes at a population level will likely continue to evolve and will require further investigation as these data mature. A discussion of prognosis with newly diagnosed patients should take into consideration the survival benefits afforded by these novel therapies rather than

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simply relying on outdated historic survival data. Furthermore, neoadjuvant approaches are increasingly being investigated, and these may help to direct early treatment approaches in the perioperative period based on pathologic response.

DISCLOSURES Yun Song and Giorgos C. Karakousis report no conflict of interest.

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