Association of programmed cell death 1 (PD-1) inhibitor therapy with overall survival (OS) in stage IV melanoma treated with targeted therapies

A.Z. Torres1, R. Mathur1, K. Maignan1, M. Tucker1, K.J. Ciofalo1, S. Khizin2, K.R. Carson3

1Real-World Evidence, Flatiron Health Inc., New York, NY, USA, 2Oncology Center of Excellence, FDA, New York, NY, USA

Background: The impact of oncology drug regulatory approvals on population-level patient (pt) outcomes is often unknown. Before targeted therapies, chemotherapy treatment of stage IV melanoma resulted in minimal OS improvement. To understand how PD-1 inhibitor approval influenced OS in treatment eligible stage IV melanoma pts, we assessed OS before and after the US Food and Drug Administration approval date of pembrolizumab (P), a second generation (2nd gen) immune checkpoint inhibitor (ICI), in a cohort treated with targeted therapies.

Methods: US-based pts diagnosed with stage IV melanoma from 1/1/2011 to 3/31/2019 and receiving BRAF/MEK inhibitors or ICI in first-line (1L) in the deidentified nationwide Flatiron Health electronic health record–derived database were eligible. We used a multivariable Cox model indexed to 1L start and adjusted for age. Follow-up time relative to approval of P (9/4/2014) was a time-varying covariate.

Results: Of 882 pts, 692 (78.5%) started 1L after P approval. Of those, 40.6% (n=281) received 2nd gen ICI and 27.3% (n=189) received combination ICI therapy in 1L. During pre-approval, 56.3% (n=107) received 1L first gen ICI (CTLA-4 inhibitor). Pre-approval pts were younger than post-approval pts (median 64.0 [IQR: 57.0, 72.8] vs 68.0 yrs [IQR: 58.8, 77.0]; p < 0.001) but similar in other clinical and demographic characteristics. In unadjusted analyses, median OS was twice as long for post-approval pts compared to pre-approval pts (14.0 mos [95% CI: 11.6, 17.5] vs 6.7 [95% CI: 5.5, 9.2]; log rank = 0.001). In the multivariable time–varying model, mortality risk decreased by 22% (HR = 0.78 [95% CI: 0.62, 0.98]; p < 0.035) following P approval. When comparing treatments during post-approval, unadjusted median OS was 8 mos longer in pts receiving combination ICI relative to those treated with 2nd gen ICI monotherapy in 1L (20.6 mos [95% CI: 14.0, not reached] vs 12.7 mos [95% CI: 9.7, 17.5]; log rank = 0.069).

Conclusions: Introduction of 2nd gen ICI therapy was associated with longer OS in stage IV melanoma pts treated with targeted therapies. Future analyses could assess outcomes relative to regulatory approvals for specific subpopulations, such as those who would have been excluded from trials.

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