Association of First-in-Class Immune Checkpoint Inhibition and Targeted Therapy With Survival in Patients With Stage IV Melanoma

The management of advanced melanoma has witnessed dramatic changes in recent years with the rational development of novel systemic therapies. The efficacies of immune checkpoint inhibitors and targeted BRAF/MEK pathway inhibitors have been demonstrated in well-designed randomized clinical trials. These drugs subsequently gained approval from the US Food and Drug Administration, first becoming available to patients with stage IV melanoma in the United States in 2011 with the approval of ipilimumab (March 2011) and vemurafenib (August 2011). The efficacies of these drugs have been demonstrated in the context of randomized clinical trials, but their association with patient outcomes on a population level is less well defined. We present here early findings of the initial national outcomes resulting from these therapies.

Methods | Patients with a new diagnosis of clinical stage IV melanoma were identified using the National Cancer Database, an oncology outcomes database representing patients from more than 1500 hospitals nationwide. The primary outcome of interest was overall survival (OS), which was estimated using the Kaplan-Meier method after categorizing patients by year of diagnosis. The OS among a contemporary cohort (diagnosed from 2011 to 2012) was compared with the OS of those in historical cohorts (diagnosed from 2004 to 2008 and from 2009 to 2010). Statistical analysis was performed in Stata, version 14 (StataCorp LLC). Two-sided P < .05 was considered statistically significant. This study was reviewed and approved by the institutional review board of the University of Pennsylvania. Patient informed consent was waived as the national data set used in this study contained deidentified data, which make contacting individual patients impossible.

Results | In total, there were 11,807 study patients: 4869 (41.2%) diagnosed from 2004 to 2008, 3352 (28.4%) diagnosed from 2009 to 2010, and 3586 (30.4%) diagnosed from 2011 to 2012. The median (interquartile range) age was 64 (53-75) years, and 7976 (67.6%) were male. Compared with those diagnosed from 2004 to 2008, patients diagnosed from 2011 to 2012 were more commonly treated with immunotherapy (15.8% vs 9.1%; P < .001) and less commonly treated with systemic chemotherapy (29.8% vs 34.9%; P < .001).

Overall survival was significantly longer for the 2011-2012 cohort compared with either the 2009-2010 or 2004-2008 cohorts (2011-2012 vs 2009-2010: hazard ratio [HR], 0.89; 95% CI, 0.84-0.94; P < .001; 2011-2012 vs 2004-2008: HR, 0.85; 95% CI, 0.81-0.89; P < .001), and no difference in OS was observed between the 2004-2008 and the 2009-2010 cohorts in the era before novel therapies were used (HR, 0.97; 95% CI, 0.92-1.02; P = .19). Three-year OS rates were 15.1% for the 2011-2012 cohort and 14.3% for the 2004-2008 cohort. Improvement in OS appeared to be driven primarily by an improvement in OS for patients with stage M1c disease (HR, 0.84; 95% CI, 0.77-0.91; P < .001) because there was no significant difference in OS for patients with stage M1a disease (HR, 1.12; 95% CI, 0.93-1.35; P = .24) or stage M1b disease (HR, 0.93; 95% CI, 0.80-1.08; P = .33) (Figure). Three-year OS rates for stage M1c disease were 14.5% for the 2011-2012 cohort and 10.1% for the 2004-2008 cohort. Diagnosis in 2011 to 2012 remained significantly associated with improved survival after a multivariable Cox regression analysis adjusted for age, sex, and comorbidity score overall (HR, 0.83; 95% CI, 0.79-0.88; P < .001) and among patients with stage M1c disease (HR, 0.82; 95% CI, 0.75-0.89; P < .001).

Discussion | With the rational development of targeted agents and novel immunotherapies, the management of advanced melanoma has rapidly transformed and continues to evolve. The efficacy of these modern therapies has been well established, but our analysis provides perspective on how these modern therapies have begun to be instituted and what their clinical impact is on a national scale. National 3-year OS rates improved by approximately 5% with the approval of the first-in-class drugs among these novel therapies. Furthermore, choice of immunotherapy as part of first-course therapy nearly doubled for patients diagnosed from 2011 to 2012 compared with those in a cohort before novel therapies were used.

The observation that OS was not significantly improved for patients with stage M1a or stage M1b disease in the 2011-2012 cohort is consistent with published trial data. In the BRIM 3 trial, improved progression-free survival was seen with vemurafenib use vs dacarbazine use for stage M1a and stage M1b disease, but significant improvement in OS in these subgroups was not observed. In the CA184-024 trial, treatment with a combination of ipilimumab and dacarbazine did not demonstrate significantly improved OS compared with a com-
The prognosis of patients with stage IV melanoma will no doubt continue to change with the approval of PD-1 (programmed cell death 1) therapy, combination checkpoint inhibition, and combined targeted therapies. This study provides valuable perspective of the magnitude of the initial change in outcomes that first-generation novel therapies have had on a population level.

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Trends in Breast, Colorectal, and Cervical Cancer Incidence Following the Affordable Care Act: Implications for Cancer Screening

The 2010 Patient Protection and Affordable Care Act (ACA) emphasizes preventive care. In addition to expanding insurance coverage, the ACA eliminates cost sharing for services graded “A” or “B” by the US Preventive Services Task Force (USPSTF). Although these policies have improved preventive care generally, their impact on cancer screening specifically is uncertain. Whereas a recent study showed more screening in Accountable Care Organizations, a health care model pioneered by the ACA,1 an earlier study found increases in use of medical preventive services such as blood pressure and cholesterol checks but not in cancer screening.2

Although it may take years for screening to affect mortality, higher screening rates should quickly affect incidence. We hypothesized that the implementation of major ACA policies on January 1, 2014, would be followed by an increased incidence in early-stage breast, colorectal, and cervical cancer—3 malignant neoplasms with “A” or “B” screening grades from the USPSTF.

Methods | We compared age-adjusted incidence rates of early-stage breast, colorectal, and cervical cancer in the first 9 months of 2013 (pre-ACA) and the last 9 months of 2014 (post-ACA) with an intervening 6-month “wash-in” period. Incidence rates were per 100 000 person-years and age-adjusted to the 2000 US Standard Population. To assess for change between pre- and post-ACA, we computed the incidence rate ratios (IRRs) and associated 95% confidence intervals. Then, using weighted least squares (weighting by the inverse of the variance) with a log link, we ascertained whether the relative difference in IRRs (ie, ratio of IRRs) for early-stage disease varied in a statistically significant fashion compared with locally advanced/metastatic disease. The relative difference in IRRs was estimated by exponentiating the difference-in-differences (DID) of the log IRRs. To generate the incidence rates and IRRs, we used SEER®Stat Version 8.3.4. All other analyses were performed using SAS, version 9.4. The study received an institutional review board waiver from the Brigham and Women’s Hospital.

Results | From pre- to post-ACA, the incidence of early-stage breast cancer increased from 55.5 (95% CI, 54.6-56.3) to 56.9 (95% CI, 56.0-57.7) cases per 100 000 person-years, with an IRR of 1.025 (95% CI, 1.006-1.048). Furthermore, the difference in IRRs was significantly greater in early vs locally advanced/metastatic stages (DID, 1.050; 95% CI, 1.006-1.098; P = .03) (Table).

The incidence of early-stage colorectal cancer increased from 13.5 (95% CI, 13.0-14.1) to 15.3 (95% CI, 14.7-15.9) cases per 100 000 person-years, with a pre- to post-ACA IRR of 1.132 (95% CI, 1.07-1.198). Similarly, the change in incidence rates was significantly greater in early vs locally advanced/metastatic stages (DID, 1.112; 95% CI, 1.030-1.200; P = .006). This pattern was not seen in cervical cancer.

Discussion | We found that incidence of early-stage breast and colorectal cancer increased after the adoption of the ACA, whereas it did not vary for late-stage cancer. Although screening itself was not assessed, the trend is consistent with modest but immediate increases in colorectal and breast cancer screening following the ACA. Our finding that there was no change in detection of early-stage cervical cancer is consistent with a previous report showing that the dependent coverage expansion to age 26 years did not affect the use of the Papanicolaou test in that population.3

Limitations of this observational study include assessment of only 1 year pre- and post-ACA, potential for unmeasured confounders, and unrelated background epidemiological trends, as well the inherent limitations of the difference-in-differences study design.

Despite these limitations, these results are consistent with a small but positive impact of the ACA on use of recommended cancer screening, which may vary by cancer site. Recent proposals for repealing the ACA would increase the uninsured population by tens of millions.6 This could easily erase these modest gains.

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