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Cost-Benefit Implication of Gene Expression Profiling and Adjuvant Therapy in Stage IIIA Melanoma

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Abstract

Background—Indiscriminate use of adjuvant therapy in stage IIIA melanoma is controversial. We sought to model the clinical impact and cost of implementing a gene expression profile (GEP) test to guide adjuvant therapy.

Methods—A Markov decision-analysis model was created to represent resected stage IIIA melanoma with three treatment options: observation (OBS), adjuvant pembrolizumab for all patients (ALL), and selective adjuvant therapy (SEL). In the SEL option, only high-risk patients based on GEP stratification are treated with pembrolizumab. Cost of adjuvant therapy was normalized to reflect Medicare reimbursement schedules. The primary outcome was cost per mortality avoided at 10 years.

Results—Model projections for 10-year overall survival were 68% for OBS, 73% for SEL, and 76% for ALL. The estimated incremental cost-per-mortality-avoided (compared to OBS) is \$2.1 million for SEL and \$2.4 million for ALL. These translate to costs of \$583.0K and \$697.1K per life-year for the SEL and ALL strategies, respectively.

Conclusion—Routine adjuvant pembrolizumab for stage IIIA melanoma is costly, and risk-stratification by GEP only marginally improves the value of therapy.

Graphical Abstract

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INTRODUCTION

Nearly 100,000 new diagnoses of cutaneous melanoma are made each year in the United States, roughly 10% of which involve regional nodal metastases (1, 2). Sentinel lymph node biopsy is an important component of the initial pathologic staging of patients with intermediate-thickness melanoma. Based on the American Joint Committee on Cancer (AJCC) 8th edition staging system, a positive sentinel node biopsy is considered stage III, with 10-year melanoma-specific survival (MSS, eTable 1) ranging from 60–88% (3). Among node-positive patients, those with a T1-T2a primary and up to 3 clinically-occult positive nodes (N1-N2a) are categorized as stage IIIA. Despite having non-localized disease, these patients have an overall good prognosis, with 10-year MSS of 88%.

Following results from the Multicenter Selective Lymphadenectomy Trial - 2 (MSLT-2) and German Dermatologic Cooperative Oncology Group (DeCOG-SLT) trial, management of sentinel node-positive melanoma has shifted away from completion lymph node dissection in favor of node basin surveillance (4, 5). Recent guidelines from the National Comprehensive Cancer Network recommend consideration of adjuvant systemic therapy for node-positive patients, except for those with very low-risk stage IIIA disease (≤ 2 mm thick non-ulcerated primary, sentinel node metastasis < 1 mm) (6). These recommendations are propelled in part by results from KEYNOTE-054, which reported an increase in relapse-free survival (RFS) among stage III patients treated with adjuvant pembrolizumab following lymphadenectomy (7). However, only 8% of patients within this trial were stage IIIA, and inclusion was limited to patients with nodal metastasis >1 mm. Within this stage IIIA subgroup, the hazard ratio for RFS was 0.38 favoring the pembrolizumab group, but the relationship was not statistically significant in this limited sample. Whether these findings apply to stage IIIA patients with node metastases < 1 mm is unknown. Following the report of KEYNOTE-054, pembrolizumab was approved in the adjuvant setting for all patients with stage III melanoma in 2019.

At 200 mg per dose for 18 doses, a standard twelve-month course of adjuvant pembrolizumab costs roughly \$300,000 USD at list price (8, 9). In addition, adjuvant anti-PD-1 carries risk of immune related adverse events, which may be permanent. Therefore,

there is an incentive to identify stage IIIA patients who are at high-risk for distant recurrence in order to enrich the population for those most likely to benefit from adjuvant treatment. Recently, a gene expression profile test of the primary melanoma (31-GEP) was shown to be prognostic for RFS and distant metastasis-free survival (DMFS) (10). The 31-GEP has potential roles for guiding surveillance intensity, need for sentinel node biopsy, and adjuvant systemic therapy (11). How this risk-stratification tool affects the cost-benefit balance of adjuvant pembrolizumab for patients with stage IIIA melanoma is unknown.

Due to the overall good prognosis of patients with stage IIIA melanoma, a prospective adjuvant trial in a risk-stratified cohort of these patients would require substantial accrual and follow-up in excess of 10 years. These considerations support the role for a decision-analysis modeling approach to estimate cost-benefit. The purpose of this study is to estimate the cost and oncologic outcomes of adjuvant therapy in stage IIIA melanoma, and to model the impact of using 31-GEP to guide therapy. While 31-GEP is itself a costly screening test at more than \$7000 per patient, it has the potential to be cost-saving if it could identify patients at low risk for recurrence who could avoid receiving adjuvant therapy. We hypothesized that, while universal adjuvant treatment (treatment of all stage IIIA patients regardless of individual risk) in this population would be prohibitively costly, the addition of 31-GEP could improve the cost-benefit ratio.

METHODS

Model Design

A Markov decision model was created to simulate three therapeutic strategies. In a Markov model, hypothetical patients transition between health states depending on potential outcomes represented in the model. Passage of time is captured through Markov cycles. Each Markov cycle represents 1 year spent within a specific disease state (for example, “disease-free survival”). Each cycle is associated with a set of costs relevant to the assigned disease state, including costs for treatment, surveillance and follow-up. Because the long-term survival of stage IIIA patients has not been well-reported beyond 10 years, analyses of the Markov model were restricted to 10-year outcomes.

In the observation strategy (OBS), resected stage IIIA patients receive no adjuvant treatment, and are surveilled for the development of distant metastases. Those patients who develop distant metastases are treated with therapeutic pembrolizumab per KEYNOTE-006 (12, 13). In the universal adjuvant group (ALL), stage IIIA patients are treated with adjuvant pembrolizumab per the treatment protocol described in KEYNOTE-054 (7). Over the course of subsequent surveillance, development of a distant recurrence is treated with ipilimumab monotherapy, based on protocols described in KEYNOTE-006 and CHECKMATE-067 (12–15). While alternative salvage therapies exist, ipilimumab was chosen because it is a broadly-applicable second-line therapy following anti-PD-1 treatment that has abundant prospective survival data in the stage IV setting. The combination of ipilimumab with nivolumab was considered, however, efficacy among patients previously treated with anti PD-1 is unclear (16). A parallel exploratory model was created to represent the treatment scenario for the V600E mutant population. In this scenario, adjuvant treatment is comprised of dabrafenib/trametinib based on the regimen in COMBI-AD (17), while metastatic

recurrence is treated with anti-PD-1 based on KEYNOTE-006 (13). In the selective adjuvant group (SEL), all patients undergo risk-stratification using 31-GEP. Only those patients who are stratified as high-risk for distant recurrence are selected for adjuvant treatment with pembrolizumab. Patients who are stratified as low-risk for recurrence undergo observation, and if recurrence develops, are then treated with pembrolizumab as first-line therapy for advanced/metastatic disease. The model schematic is presented in Figure 1.

Variable Estimates

Within a Markov model, progression through pre-defined disease states is dictated by transition probabilities. In this model, relevant transition probabilities are: 1) rate of distant recurrence, and 2) survival in the setting of metastatic disease. The therapeutic impact of adjuvant PD-1 antibody in reducing the likelihood of distant recurrence is captured by its relative risk reduction, estimated from KEYNOTE-054 (7). Survival in the setting of metastatic disease—treated either with pembrolizumab for patients who underwent up-front observation or ipilimumab for patients who received adjuvant pembrolizumab—was derived from the outcomes from KEYNOTE-006 and CHECKMATE-067. The prognostic accuracy of 31-GEP is represented by its ability to correctly categorize patients into those who will develop a distant metastasis (true positives), and those who will not (true negatives). These data, represented as the sensitivity and specificity of the test, were derived from data reported by Zager and colleagues (10).

Costs of clinic visits and surveillance imaging were acquired from facility limiting charges to Medicare (available at www.cms.gov). Cost of 31-GEP was based on the Medicare Clinical Laboratory Fee Schedule. Drug and drug administration costs for pembrolizumab, dabrafenib/trametinib, and ipilimumab were recently published (8, 9, 18). Radiographic surveillance in the setting of stage IIIA disease, and in the setting of distant metastases, was derived from National Comprehensive Cancer Network recommendations for stage IIB-IV disease (6). The surveillance protocol was comprised of a specialist clinic visit and positron emission tomography with computerized tomography (PET-CT) every 6 months for the first two years, and annually thereafter. Patients also undergo node basin ultrasound every 4 months for the first two years. Alternative surveillance strategies (i.e., CT for all patients, PET-CT for 31-GEP high-risk patients and CT for 31-GEP low-risk patients) did not significantly alter the study findings. A comprehensive list of probability estimates and costs is provided in Table 1.

Sensitivity Analysis

The primary outcome of the study is estimated cost per mortality avoided using the SEL and ALL strategies, relative to the OBS strategy. Baseline model analyses were performed using patterns of distant recurrence reported in the series by Zager and colleagues. However, this study included only 69 patients with stage IIIA melanoma. Thus, event-free survival may be susceptible to selection and referral biases. To account for this, a sensitivity analysis was performed in which the baseline estimate for distant metastasis-free survival (DMFS) was replaced with the weighted average of outcomes from MSLT-II and DeCOG-SLT (4, 5). These randomized trials provide high quality, long-term outcomes for stage IIIA patients from an era prior to approval of adjuvant PD-1 antibody and are therefore applicable to the

model scenario. Model analyses were performed using TreeAge Pro 2017 (TreeAge Software, Inc, Williamstown, MA).

RESULTS

Results of the baseline model—which incorporates recurrence patterns from the Zager et al. study—indicate that 10-year overall survival (OS) for the three strategies are: 0.68 for OBS, 0.73 for SEL, and 0.76 for ALL (Table 2). Using the OBS strategy as reference, the SEL strategy is associated with an absolute risk reduction in mortality by 5.2% over 10 years (67.6% versus 72.8%). On the other hand, an additional 23.5% of patients would be treated with at least one systemic therapy. Using the OBS strategy, a total of 47.5% of patients would be treated with pembrolizumab with 32.4% dying despite treatment and 15.1% of patients salvaged. The SEL strategy would treat a total of 53.6% of patients with adjuvant pembrolizumab based on 31-GEP high-risk stratification, and 20.7% of patients would receive ipilimumab following recurrence despite adjuvant treatment. Among patients stratified as low-risk by 31-GEP, 17.4% would go on to develop a distant recurrence and require salvage treatment. These patients could be interpreted as the cohort that was incorrectly spared up-front adjuvant treatment. They make up 46% of all patients (high- or low-risk) who develop distant recurrence. Compared to the SEL strategy, a universal adjuvant approach is associated with an absolute risk reduction in 10-year mortality of 3.6% (72.8% versus 76.4%). An additional 29% of patients would receive systemic therapy—17.9% with adjuvant pembrolizumab, 11.1% with pembrolizumab followed by ipilimumab for recurrence (Figure 2).

Associated costs of each strategy are listed in Table 2. Compared to the OBS strategy as reference, the incremental cost for each mortality avoided is \$2.10M for SEL and \$2.44M for ALL. The incremental costs per additional life-year are \$583.0K and \$697.1K, respectively. Recurrence estimates from the GEP profiling study were replaced with more robust estimates from MSLT-2 and DeCOG (10). This sensitivity analysis showed that SEL was associated with a cost-effectiveness ratio of \$581.4K per life-year, while ALL was associated with a ratio of \$795.7K per life-year. Results from the exploratory model that applies to the V600E mutant subpopulation is more favorable toward adjuvant treatment, with cost per additional life-year of \$258.4K and \$297.2K for the SEL and ALL strategies, respectively (eTable 2).

DISCUSSION

We used a Markov decision-analysis model to integrate 31-GEP performance data with clinical outcomes from several landmark randomized, prospective trials. Doing so allowed clarification of the role of adjuvant PD-1 antibody for stage IIIA melanoma. The model provided estimates of the cost and therapeutic value of selective and universal adjuvant strategies, relative to a strategy of observation.

In this study, a selective adjuvant approach—based on risk-stratification with 31-GEP—enriched the stage IIIA population modestly by selecting for patients at increased risk of recurrence. However, due to the relatively low specificity of 31-GEP in stage IIIA

melanoma, even with risk-stratification, most patients would still be treated unnecessarily, at an incremental cost of \$583K per additional life-year. A universal adjuvant strategy had an even greater incremental cost of nearly \$700K per additional life-year, relative to upfront observation. Model estimates for 10-year overall survival ranged from 68% to 76% across the three strategies. These projections were derived from survival outcomes published in randomized trials designed in the AJCC 7th edition era (4, 5, 7, 12, 13), and are lower than the 88% described by AJCC 8th edition (3). The exploratory model representing adjuvant BRAF/MEK inhibition for V600E mutant patients must be interpreted with caution, because SEL and ALL subgroups may receive two effective targeted therapies (adjuvant BRAF/MEK, salvage anti-PD-1), while OBS patients only receive salvage anti-PD-1. In reality, multiple lines of salvage therapy are available, but this more complex survival modeling was beyond the scope of our study. As a result, the survival outcomes of this model are significantly biased in favor of the ALL and SEL strategies.

The AJCC 8th edition survival estimate includes patients with < 1 mm node disease burden, who were excluded from many adjuvant trials such as KEYNOTE-054. The population of the 31-GEP risk-stratification study by Zager et al. more closely resembles the KEYNOTE-054 and the AJCC 7th edition stage IIIA population, with a DMFS rate of roughly 54–80% at 10 years (10). The same holds true for the studies used in the sensitivity analyses, MSLT-II and DeCOG-SLT. Because the absolute therapeutic impact of adjuvant treatment is generally lower for lower-risk populations, our results most likely underestimate the true cost-benefit ratio of PD-1 antibody in the adjuvant setting. While treatment toxicity was not the focus of this study, it is important to recognize that immune-related adverse events occur in over 15% of patients treated with anti PD-1 (14). These events can result in significant direct and intangible costs beyond the scope of our analysis.

This study's findings indicate that 31-GEP has limited potential to enrich the stage IIIA population for recurrence risk. Of course, thoughtful clinicians do not treat all stage IIIA patients the same. Number of nodes, nodal tumor burden, primary tumor thickness and ulceration are all important prognostic factors even within stage IIIA. The prognostic contribution of 31-GEP after adjustment for these traditional clinicopathologic variables requires further study. Our model also assumes availability of adequate primary tumor tissue, which may not be the case for small lesions, and a successful test procedure; the real-world clinical utility of a selective adjuvant strategy based on GEP testing may therefore be lower.

A recent cost-effectiveness study on adjuvant pembrolizumab for high-risk stage III melanoma reported an incremental cost-effectiveness ratio of \$57.5K per quality-adjusted life-year (QALY), relative to observation (8). However, this study is not pertinent to the stage IIIA population, which is more indolent than stages IIIB-C, and even high-risk stage II (19, 20). Moreover, the study made the assumption that recurrence-free survival curves from KEYNOTE-054 could be extended via parametric approximation indefinitely. In reality, only 2-year survival was published from this trial; therapeutic value beyond this period is speculative. Further, there is a paucity of prospective data on the outcomes of stage IIIA patients beyond 10 years. For these reasons, we believe that limiting model analyses to 10 years and representing the therapeutic effect of adjuvant pembrolizumab using its 2-year

relative risk-reduction is more valid. A number of groups have used Markov analyses to assess cost-effectiveness of PD-1 antibody in the setting of metastatic melanoma. Compared against reference strategies of either dacarbazine or ipilimumab, PD-1 antibody has been associated with incremental cost-effectiveness ratios ranging from \$30K-\$80K per QALY (9, 21–23). These findings suggest that cost-effectiveness of systemic therapy generally improves when a population is enriched for high-risk biology. Given the relative low risk of the stage IIIA population as a whole, the sensitivity and specificity required to produce a clinically useful test in this population are very high. The reported sensitivity of 31-GEP of 0.67 means that using the test to guide adjuvant therapy would result in failure to treat a third of patients who ultimately recur. More significant from a cost perspective is the specificity of 0.53, which translates into the unnecessary administration of one year of pembrolizumab to approximately half of all patients who were not going to recur anyway.

This study has several limitations. First, the prognostic power of 31-GEP was based on a retrospective cohort study of only 69 patients (10). Although we performed sensitivity analyses that incorporated prospective recurrence data, much larger series are needed to validate 31-GEP's performance statistics in stage IIIA patients. Our model adopted ipilimumab as salvage for patients who progress after adjuvant pembrolizumab. In reality, there are a variety of salvage options. However, this scenario of post-adjuvant progression applies to a very small subset of the model's ALL and SEL cohorts (5–8%), and alternative regimens are unlikely to significantly alter the study outcomes. Additionally, while KEYNOTE-054 indicated a relative risk-reduction of 60% by adjuvant pembrolizumab in stage IIIA patients, the trial was underpowered to reach significance in this subgroup (7). Thus, our model's assumptions are inherently biased in favor of the adjuvant arms. The true cost-benefit ratio of adjuvant pembrolizumab is most likely worse than presented here. Finally, we chose to censor model projections to 10 years to improve its validity. Because most melanoma-related mortalities among stage IIIA patients occur within 8 years (19, 24), the cost per mortality-avoided results remain valid. However, for young, healthy patients with much longer life expectancies, our model may not adequately represent the lifetime cost-benefit of adjuvant therapy.

CONCLUSIONS

Resected stage IIIA melanoma is characterized by a relatively favorable long-term prognosis. Indiscriminate adjuvant therapy in this population confers a small survival benefit but is associated with significant cost and patient morbidity. The use of 31-GEP to risk-stratify patients has the potential to marginally improve cost-effectiveness over a universal adjuvant approach, with a small trade-off in 10-year overall survival. However, the prognostic impact of 31-GEP beyond standard clinicopathologic risk stratification is unknown. At present, based on this model, the routine use of 31-GEP to risk-stratify patients with IIIA melanoma for adjuvant therapy cannot be recommended. In order for any risk-stratifying genetic profile test to be cost-effective, measurement of the degree of additional prognostic value above and beyond traditional clinicopathologic factors is necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Precis

Because patients with resected stage IIIA melanoma have an overall good prognosis, adjuvant systemic therapy has little impact on survival and adds a large cost burden. The 31-GEP risk-stratifying tool only marginally improves this cost-benefit ratio.

Figure 1.

Markov model design. Three treatment arms: observation (OBS), selective adjuvant treatment of patients classified as high-risk by 31-GEP results (SEL), and treatment of all patients with stage IIIA melanoma (ALL). After treatment of the primary melanoma, patients initially reside in a state of disease-free survival (DFS). Subsequent development of distant metastasis is treated with systemic therapy, after which patients reside in a state of stage IV survival. Likelihood of distant recurrence and survival rate in stage IV are specific to each treatment arm. Circular arrows indicate that modeled patients resided in the indicated state or progress to the subsequent state based upon the probability estimates shown in Table 1.

Figure 2.

Ten-year estimated overall survival associated with the various treatment strategies. Black signifies the proportion of patients deceased at 10 years (regardless of lines of treatment received). Yellow signifies the proportion of patients alive after treatment with at least 1 systemic therapy. Green signifies the proportion of patients alive without ever receiving systemic treatment. SEL and ALL strategies are associated with fewer deaths, at a cost of more patients being treated with at least one course of systemic therapy. OBS, initial observation; SEL, selective adjuvant treatment of patients classified as high-risk by 31-GEP results; ALL, adjuvant treatment of all stage IIIA patients.

Table 1:**Markov Model Variable Estimates**

Variable	N	Estimate*	Source
Probability estimate			
Distant metastasis-free survival (10Y, baseline)	69	0.48	Zager, et al (10)
Distant metastasis-free survival (10Y, randomized trials)	1303	0.40	MSLT-II, DeCOG-SLT (4, 5)
Stage IV overall survival (2Y, pembrolizumab)	556	0.55	KEYNOTE-006 (13)
Stage IV overall survival (2Y, ipilimumab)	278	0.43	KEYNOTE-006, CHECKMATE-067 (13, 15)
Risk reduction, adjuvant pembrolizumab	160	0.60	KEYNOTE-054 (7)
Risk reduction, adjuvant dabrafenib/trametinib	438	0.47	COMBI-AD (17)
31-GEP sensitivity	69	0.67	Zager, et al (10)
31-GEP specificity	69	0.53	Zager, et al (10)
31-GEP high-risk prevalence	69	0.54	Zager, et al (10)
Cost estimate, USD (\$)			
31-GEP		7193	CMS.gov
Pembrolizumab (adjuvant)		225,800	Bensimon, et al (8)
Pembrolizumab (metastatic)		303,505	Wang, et al (9)
Dabrafenib/trametinib (adjuvant)		184,179	Gerbasi, et al (18)
Ipilimumab (metastatic)		155,425	Bensimon, et al (8)
PET/CT		1500	CMS.gov
CT		1023	CMS.gov
Ultrasound		\$219	CMS.gov
Clinic follow-up		\$148	CMS.gov
Oncology consultation		\$211	CMS.gov

* Each estimate and cost displayed is the point estimate used as input into the Markov model.

31-GEP, gene expression profile

USD, United States dollar

Table 2:

Incremental Cost and Effect by Treatment Strategy

Strategy	OS (10-year)	Cost per patient, \$	Cost per death avoided, \$	Cost per life-year, \$
OBS _{WT}	0.68	77.2K	REF	REF
SEL _{WT}	0.73	182.1K	2.10M	583.0K
ALL _{WT}	0.76	272.4K	2.44M	697.1K

OS, overall survival; OBS, observation; SEL, selective adjuvant treatment of patients classified as high-risk by 31-GEP results; ALL, adjuvant treatment of all stage IIIA patients; REF, reference group – no deaths were avoided by adjuvant therapy as all these patients were observed.