2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Melanoma

In recent years, there has been an explosion of therapies for the treatment of melanoma, including *BRAF* mutation–guided therapy. With coverage by *The ASCO Post*, **Lisa Kottschade, APRN, MSN, CNP,** of the Mayo Clinic reviews clinical data supporting emerging targeted therapies and immunotherapies, and shares considerations on patient selection, education, and adverse event management.

Abstracts 2512 and 2517

Study Finds Immune-Related Adverse Events Herald Benefit With Adjuvant Pembrolizumab in Melanoma

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/172423/abstract and https://meetinglibrary.asco.org/record/172428/abstract to read the full abstracts and view disclosures.

In the EORTC 1325/KEYNOTE-054 trial of adjuvant pembrolizumab in patients with stage III melanoma patients, recurrences were reduced by 44% in the immunotherapy arm, vs placebo, but this benefit increased to a 63% reduction in risk among patients developing an immune–related adverse event on treatment (Eggermont et al., 2019a).

"This study shows that for patients who have an immune-related adverse event with pembrolizumab, outcomes are almost twice as good as for those who do not," said Alexander M.M. Eggermont, MD, PhD, of Gustave Roussy Cancer Centre and the Universite Paris–Saclay in France.

EORTC 1325/KEYNOTE–054 included 1,019 adults with complete resection of cutaneous melanoma metastatic to lymph node(s), classified as stage IIIA, IIIB, or IIIC (without in–transit metastasis). Consistent with the main analysis in the intent-to-treat population (Eggermont et al., 2018), recurrence-free survival for patients starting treatment was longer in the pembrolizumab than in the placebo arm (hazard ratio [HR] = 0.56). At 2 years, 75.5% of the pembrolizumab arm was recurrence-free, compared to 61.1% of the placebo arm, Dr. Eggermont reported.

The cumulative incidence of immune–related adverse events after 15 months of treatment was 37.3% in the pembrolizumab arm and 9.0% in the placebo arm. These were primarily endocrine disorders, which were observed in 23.4% and 5.0%, respectively; all but approximately 4% and 1%, respectively, were thyroid disorders. Vitiligo and rash were seen in about 5% of the pembrolizumab arm.

The occurrence of an immune–related adverse event was significantly associated with a longer recurrence–free survival in the pembrolizumab arm, whereas no such association was found among patients on the placebo arm. This was true for both males and females and regardless of disease stage.

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Compared to the placebo arm, the reduction in the hazard of recurrence or death in the pembrolizumab arm was greater after onset of an immune–related adverse event (HR = 0.37) than without one or before one (HR = 0.61), a significant difference (P = .028), he said.

Long–Term Outcomes With Adjuvant Ipilimumab

In the long–term (7–year) follow–up EORTC 18071, treatment of high–risk stage III melanoma patients with adjuvant ipilimumab provided a sustained improvement in the recurrence–free survival, distant metastasis–free survival, and overall survival, despite a 53% rate of discontinuation due to toxicity, in the latest analysis of the trial, also presented at ASCO by Dr. Eggermont (Eggermont et al., 2019b).

The phase III trial randomized 951 patients to ipilimumab 10 mg/kg or placebo given for 4 doses, then every 2 months for up to 3 years. The benefits, as assessed by local investigators, "were long–lasting, with almost a 10% difference observed vs placebo at 7 years, and were consistent across subgroups," Dr. Eggermont said.

The 7–year estimate of recurrence–free survival was 39.2% in the ipilimumab group and 30.9% in the placebo group (HR 0.75; P < .001). Distant metastasis–free survival was 44.5% and 36.9%, respectively (HR = 0.76; P = .002) and overall survival was 60.0% and 51.3%, respectively (HR = 0.73; P = .002).

"This study confirms that the overall survival benefit of adjuvant ipilimumab is real, because it's seen at 5, 6, 7, and 8 years," he said. "The difference in absolute terms at every time point is 8 to 10%, regardless of stopping therapy. Half the patients went off treatment after 4 doses, so you don't need maintenance therapy. It's all driven by 4 doses of ipi, just like we see in advanced disease."

With pembrolizumab, however, producing even greater benefits (recurrence–free survival rates of about 75% vs 40%), with fewer patients coming off treatment due to toxicity (14% vs 53%), pembrolizumab is "what patients are all getting now," he added. "But I think that eventually, for patients who do not develop an immune–related adverse event, we'll give them a low dose of ipi on top of pembro."

References

Eggermont, A. M. M., Kicinski, M., Blank, C. U., Mandalà, M., Long, G. V., Atkinson, V.,...Suciu, S. (2019a). Prognostic and predictive value of an immune–related adverse event among stage III melanoma patients included in the EORTC 1325/KEYNOTE–054 pembrolizumab vs placebo trial [Abstract 2517]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.2517

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The Advanced Practitioner Perspective

Lisa Kottschade, APRN, MSN, CNP, Mayo Clinic

For the first time in over a decade, we've seen several positively reported adjuvant trials in high-risk melanoma, including overall survival (OS) data. The long-term results of the adjuvant ipilimumab trial show continued response in patients compared to placebo. While the anti–PD-1 trials aren't as mature in terms of OS data, their impressive relapse-free survival rates (RFS) have led to their approval in high-risk resected stage III patients in the US.

Adjuvant Therapy Selection

Of note, while we have long-term data on RFS and OS in ipilimumab, initial RFS data comparing nivolumab vs. ipilimumab favored the nivolumab arm and had significantly less toxicity. Additionally, with the approval of targeted therapy in patients with *BRAF* mutations, it is important for APs to evaluate patients accordingly and have a frank discussion with them regarding the different adjuvant therapies that are currently available for use, as well as specific toxicity and possible lifelong toxicity (e.g., endocrine-related side effects).

Association of irAE Occurrence

However, with this in mind, it is also important to note that in EORTC 1325/KEYNOTE-054 patients with at least one immune-related adverse event (irAE) in the pembrolizumab-treated cohort had an increased RFS time, compared to

those who did not have an irAE. This may be important to note for the AP as ongoing follow-up for those patients who do not experience irAEs during adjuvant therapy.

Disclosure: Ms. Kottschade has acted as a consultant for Array BioPharma and Bristol-Myers Squibb and has received research funding from Bristol-Myers Squibb.

Abstract 9524

OPTiM Study on T-VEC for Unresectable Melanoma

By The ASCO Post

Visit https://meetinglibrary.asco.org/record/176444/abstract to read the full abstract and view disclosures.

New research on the immunotherapy talimogene laherparepvec (T-VEC)—an injectable oncolytic virus—for patients with unresectable melanoma was presented by Milhem et al at the 2019 ASCO Annual Meeting (Abstract 9524). Researchers reported the ad hoc analysis of progression-free survival for T-VEC compared to cytokine-based immunotherapy with granulocyte macrophage colony-stimulating factor (GM-CSF) in the phase III OPTiM trial.

OPTiM Trial Details

OPTiM included patients with unresectable stage IIIB–IV melanoma; ≥ 1 injectable cutaneous, subcutaneous, or nodal lesion; ECOG performance status ≤ 1; lactate dehydrogenase ≤ 1.5 times the upper limit of normal; ≤ 3 visceral metastases (excluding lung) with none > 3 cm.

Patients were randomly assigned 2:1 to receive intralesional T-VEC or GM-CSF. The primary endpoint was durable response rate.

Results

This analysis included 436 patients. Results show that single-agent T-VEC demonstrated an improvement in progression-free survival compared to GM-CSF in the overall intent-to-treat population, in whom 12-month progression-free survival was estimated to be 14.4% for patients treated with T-VEC and 4.6% for GM-CSF. The finding was driven primarily by patients with advanced (stage IIIB to stage IVM1a) melanoma, in whom 12-month progression-free survival was estimated to be 19.9% for T-VEC and 3.2% for GM-CSF.

"Our findings are consistent with previous data showing a more pronounced overall survival benefit with T-VEC for patients with local/regional melanoma, or disease that had not spread to other organs," said senior author Igor Puzanov, MD, Director of the Early-Phase Clinical Trials Program and Chief of Melanoma at Roswell Park Comprehensive Cancer Center. "Significantly, we observed no difference in median progression-free survival between patients with progression prior to response and those whose disease had not progressed prior to response."

A subgroup analysis showed that patients who did not have disease progression within 6 months of therapy with T-VEC had a 50% reduced chance of future progression compared to patients treated with GM-CSF.

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Milhem, M. M., Harrington, K. J., Collichio, F. A., Amatruda, T., Chesney, J. A., Agarwala, S. S.,...Puzanov, I. (2019). Progression-free survival (PFS) in unresectable melanoma patients (pts) treated with talimogene laherparepvec (T-VEC) versus granulocyte macrophage colony-stimulating factor (GM-CSF) in OPTiM [Abstract 9524]. *Journal of Clinical Oncology, 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.9524

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The Advanced Practitioner Perspective

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The approval of T-VEC for patients with metastatic melanoma was a new and exciting approval in the immunotherapy arena. However, this agent and its applicability to the larger melanoma population as a whole needs to be taken into consideration when choosing which patients to treat with T-VEC.

Study Design Considerations

First, the AP needs to be keenly aware that while patients with stage IV disease (including those with visceral metasteses) were included in the trial, these patients when analyzed by substage did not respond well in the visceral lesions, including both injected and noninjected lesions. Additionally, the control arm (GM-CSF) in this study is not an active control, so differences in PFS must be interpreted cautiously. However with that said, patients with cutaneous, subcutaneous, and lymph node involvement should be considered for therapy with T-VEC, especially in patients who are either not candidates for (poor performance status, other contraindications) or have had progression on immunotherapy and/or targeted therapy. Advanced practitioners also need to be aware of the special safe handling that is required for administration of this agent, and pertinent teaching for patients and caregivers.

There are several studies ongoing with T-VEC in combination with immune checkpoint inhibitors (ICI), several of which have been reported that show increased response rates, including in patients with visceral disease. We eagerly await more data on these combination studies, especially for patients who have previously progressed on single-agent ICIs and/or are not candidates for dual ICI therapy.

Disclosure: Ms. Kottschade has acted as a consultant for Array BioPharma and Bristol-Myers Squibb and has received research funding from Bristol-Myers Squibb.

Abstract 9507

Long-Term Survival With Dabrafenib Plus Trametinib in Metastatic *BRAF*-Mutated Melanoma

By Matthew Stenger

Visit https://meetinglibrary.asco.org/record/174754/abstract to read the full abstract and view disclosures.

In an extended analysis of the COMBI-d and COMBI-v trials reported at the 2019 ASCO Annual Meeting (Abstract 9507) and in *The New England Journal of Medicine*, Robert et al found a 5-year overall survival rate of 34% with the combination of dabrafenib and trametinib in previously untreated metastatic melanoma with a *BRAF* V600E or V600K mutation.

Study Details

The analysis included 563 patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation randomly assigned to receive the BRAF inhibitor dabrafenib 150 mg twice daily plus the MEK inhibitor trametinib 2 mg once daily in the COMBI-d trial (n = 211) and the COMBI-v trial (n = 352).

Progression-Free and Overall Survival

Median duration of follow-up was 22 months. Progression-free survival was 21% at 4 years and 19% at 5 years. Overall survival was 37% at 4 years and 34% at 5 years. In multivariate analysis, baseline factors associated with improved overall survival included Eastern Cooperative Oncology Group performance status (hazard ratio [HR] = 0.49 for 0 vs 1, $P < .001$), age (HR = 0.92 per 10-year increment, $P = .04$), sex (HR = 0.68 for female vs male, $P < .001$), number of organ sites with metastasis (HR = 0.58 for < 3 vs ≥ 3, $P < .001$), and lactate dehydrogenase level (HR = 0.47 for normal vs elevated, $P < .001$); these factors were also associated with prolonged progression-free survival. Complete response occurred in 109 patients (19%) and was associated with 5-year overall survival of 71%.

The investigators concluded, "First-line treatment with dabrafenib plus trametinib led to long-term benefit in approximately one-third of the patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation."

Reference

Nathan, P. D., Robert, C., Grob, J. J., Stroyakovskiy, D., Karaszewska, B., Hauschild, A.,...Long, G. V. (2019). Five-year analysis on the long-term effects of dabrafenib plus trametinib (D + T) in patients with BRAF V600–mutant unresectable or metastatic melanoma [Abstract 9507]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.9507 37

The Advanced Practitioner Perspective

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Therapies targeting *BRAF* mutations in melanoma have brought response rates never previously seen in patients with aggressive metastatic disease, including many complete responses. Unfortunately, many of these profound responses were temporary, and patients can experience rapid progression once resistance has occurred. Consequently, researchers still struggle to identify what line in therapy targeted agents should be used.

Future of Combination Therapy

In this study, one notable feature is that in those patients who had a CR as their tumor response, their 5-year survival was approximately 71%. Current studies are now looking at the possibility of using immunotherapy in combination with targeted therapy in the hopes of maintaining that response and withdrawing the targeted agent prior to the development of resistance. However, to date, these combination therapies have shown increased toxicity over either therapy alone.

Side Effects

Unique side effects of this class of drugs that are not usually associated with other types of therapy include pyrexia and secondary cutaneous malignancies. We are also seeing cross-toxicity with immunotherapy when used in close proximity to ICI administration. Education is imperative in preventing significant side effects that could necessitate early discontinuation of therapy.

Financial Toxicity

Also notable is the financial toxicity that may be experienced by patients on oral targeted therapy. As targeted therapies fall almost universally under prescription drug plans, patients are required to pay a significant share of the cost of the drugs. Advanced practitioners should also be aware of financial and free drug assistance for patients.

Disclosure: Ms. Kottschade has acted as a consultant for Array BioPharma and Bristol-Myers Squibb and has received research funding from Bristol-Myers Squibb.