Melanoma: 2022 ASCO Annual Meeting Highlights for the Advanced Practitioner

Suzanne McGettigan, MSN, CRNP, AOCN®, of Abramson Cancer Center of the Hospital of the University of Pennsylvania, reviews data on adjuvant therapy in stage IIB or IIC melanoma and omitting lymph node dissection and adjuvant therapy in patients with resectable stage III melanoma with major pathologic response.

Abstract LBA9500

KEYNOTE-716: Adjuvant Pembrolizumab Significantly Improves DMFS and RFS in Patients With Stage II Melanoma

By JADPRO Staff

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After 27.4 months of follow-up, data from the KEYNOTE-716 study continue to support the benefit of adjuvant pembrolizumab in reducing the risk of recurrence and distant metastasis in patients with stage IIB or IIC melanoma. Georgina V. Long, MD, PhD, FRACP, of the Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospital, presented these results as part 1 of the KEYNOTE-716 trial at the 2022 ASCO Annual Meeting.

Study Details

976 patients with complete resection of cutaneous stage IIB or IIC melanoma and negative sentinel lymph node biopsy were randomized 1:1 to receive pembrolizumab 200 mg or placebo every 3 weeks for 17 cycles (approximately 1 year) in Part 1 of the study. Treatment continued until disease recurrence or unacceptable toxicity. Patients who received placebo in Part 1 or who did not experience disease progression within 6 months of completing Part 1 were eligible for additional cycles of pembrolizumab every 3 weeks at recurrence (Part 2). The primary endpoint was recurrence-free survival (RFS) according to the investigator. The second endpoint was distant metastasis-free survival (DMFS).

Study Results

Investigators for the KEYNOTE-716 trial found that adjuvant pembrolizumab significantly improved DMFS (hazard ratio [HR] 0.64) compared with placebo. The 24-month DMFS rate was 88.1% vs. 82.2%. There was consistent reduction in the risk of recurrence with pembrolizumab vs. placebo (HR 0.64) with further follow-up. The 24-month RFS rate was 81.2% vs. 72.8%.

Grade ≥ 3 any-cause adverse events (AEs) occurred in 137 (28.4%) vs. 97 (20.0%) patients in the pembrolizumab and placebo arms, respectively. Grade ≥ 3 drug-related AEs occurred in 83 (17.2%) vs. 24 (4.9%) patients. One patient in the pembrolizumab arm and 5 patients in the placebo arm died due to an any-cause AE. No deaths were drug related. Immune-mediated AEs occurred in 182 (37.7%) vs. 45 (9.3%) patients, most commonly hypothyroidism (17.2% vs 3.7%).

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The Advanced Practitioner Perspective

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The updated findings from KEYNOTE-716 further support the efficacy of pembrolizumab (Keytruda) in preventing recurrence and distant metastatic disease in high-risk stage IIB and IIC melanoma at 24 months. This is an important group of patients in whom to consider adjuvant immunotherapy, as the 5-year overall survival (OS) for patients with stage IIC melanoma is lower than the OS for patients with stage IIIA or IIIB melanoma, a group of patients in which adjuvant PD-1 therapies are routinely utilized. However, immune checkpoint inhibitor (ICI) therapy is not without side effects, which is an important consideration in all patients, but particularly important in the adjuvant setting and as these therapies are introduced in earlier-stage disease.

It is important for oncology advanced practitioners (APs) to be aware of the potential immune-related adverse events (irAEs) associated with pembrolizumab and other ICIs. This study did not identify new irAEs or a higher incidence of expected irAEs, but these known effects require intense monitoring by the AP and quick intervention to prevent more serious complications. In addition, comprehensive upfront patient education is essential, along with a thorough discussion of these risks. The most common irAEs noted in this study were endocrinopathies, which are not generally reversible and require lifelong replacement therapy. Despite concerns about irAEs, this is the first therapy approved since interferon for use in this high-risk patient population.

Disclosure: Ms. McGettigan has served on advisory boards and speakers bureaus for BMS, Merck, Pfizer, and Regeneron.

Abstract 9501

Lymph Node Dissection and Adjuvant Therapy Can Be Omitted for Some Patients With Resectable Stage III Melanoma

By JADPRO Staff

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The PRADO trial showed high pathologic response rates with neoadjuvant ipilimumab and nivolumab in stage III melanoma and that patients with major pathologic responses (MPR; ≤ 10% viable tumor) could achieve positive outcomes without undergoing therapeutic lymph node dissection (TLND) and adjuvant therapy. PRADO is an extension cohort of the phase II OpACIN-neo study aiming to confirm the pathologic response rate and safety of neoadjuvant ipilimumab 1 mg/kg and nivolumab 3 mg/kg and to test response-driven subsequent therapy.

Study Details

Patients with stage III melanoma were included to receive 2 cycles of neoadjuvant ipilimumab 1 mg/kg and nivolumab 3 mg/kg after marker placement in the index node (ILN). Index node resection was planned at week 6. Patients who achieved MPR in the ILN did not undergo TLND, patients with partial response underwent TLND, and patients with no pathologic response underwent TLND and received adjuvant nivolumab or dabrafenib plus trametinib for 52 weeks with or without radiotherapy. The primary endpoints were pathologic response rate in the ILN and recurrence-free survival (RFS) at 2 years.

Study Results

99 patients were enrolled and treated with at least 1 cycle of neoadjuvant ipilimumab and nivolumab. Investigators previously showed a pathologic response rate of 72%, including 60 (61%) patients with MPR and 11 (11%) patients with partial response. Omitting TLND in MPR patients resulted in significant reduced surgical morbidity and improved quality of life. There were 27 non-responder, of whom 6 developed distant metastasis before ILN resection. Of the other 21 pathologic non-responder patients, 7 received adjuvant nivolumab, 10 adjuvant dabrafenib and trametinib, 3 no adjuvant therapy, and 1 was lost to follow-up. After a median follow-up of 27.9 months, the estimated

2-year RFS rate for MPR patients was 93.3%, with 4 of 60 patients developing a regional relapse. Distant metastasis-free survival (DMFS) was 100%. Of the 11 patients with partial response, 4 developed a relapse (all distant), resulting in a 2-year RFS and DMFS rate of 63.6%. The 2-year RFS rate of the non-responder patients was 71.4%, with a DMFS of 76.2%. At data cutoff, relapse occurred in 2 of 7 non-responder patients with adjuvant nivolumab and 3 of 10 patients with adjuvant dabrafenib and trametinib.

Conclusions

Major pathologic response patients in whom TLND was omitted showed a 2-year RFS rate of 93.3% and DMFS of 100%, indicating that the ILN procedure and omitting adjuvant therapy could be a safe approach for these patients. Adjuvant systemic therapy in non-responder patients seems to improve RFS as compared with historic control and thus should be considered in this group. The DMFS rate of 63.6% observed in the partial response group supports the consideration of adjuvant therapy for this subgroup.

The Advanced Practitioner Perspective

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The OpACIN-neo trial randomized patients with macroscopic nodal involvement to one of three neoadjuvant ipilimumab (Yervoy) and nivolumab (Opdivo) dosing regimens, establishing that ipilimumab 1 mg/kg and nivolumab 3 mg/kg for 2 cycles followed by surgical resection was the optimal regimen for patients in this setting and that pathologic response rate could predict overall recurrence risk. Standard-dose ipilimumab 3 mg/kg plus nivolumab 1 mg/kg for 4 cycles followed by single-agent nivolumab (flat dose) has demonstrated an advantage in progression-free survival and overall survival for patients with metastatic melanoma; however, the risk of immune-related adverse events (irAEs) is significant, which has limited the introduction of this regimen in earlier-stage disease.

PRADO further explored the OpACIN-neo findings in patients with a major pathologic response (MPR) by eliminating therapeutic lymph node dissection (TLND) and finding a sustained 93% recurrence-free survival (RFS) at 2 years. Patients without an MPR underwent TLND with or without post-surgical adjuvant therapy. There are a number of studies that have demonstrated the concordance of pathologic response rate and overall RFS and distant metastasis-free survival (DMFS) in melanoma; however, many have been single-institution studies and have not eliminated standard adjuvant therapy. The modified regimen utilized in this study reduced the risk of grade 3/4 irAEs compared with standard-dose ipilimumab/nivolumab, but it remains higher than with a single-agent PD-1 inhibitor.

The oncology advanced practitioner (AP) needs to be aware of the variable dosing schedules used when administering the ipilimumab/nivolumab combination regimen in melanoma and other cancers. This study suggests the efficacy of yet another dosing regimen in a select group of melanoma patients. It is imperative that the AP remain knowledgeable of the planned dosing schedule for individual patients. Recognizing and initiating management of irAEs in the neoadjuvant setting is also essential so that patients are able to undergo planned surgical resection.

Disclosure: Ms. McGettigan has served on advisory boards and speakers bureaus for BMS, Merck, Pfizer, and Regeneron.