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MELANOMA: Updates from Brisbane, Australia

A CME Activity

OVERVIEW

Roxana S. Dronca, MD, and **Lisa A. Kottschade, APRN, MSN, CNP**, offer their expert insights into recent data on advanced melanoma presented at the joint meeting of the 9th World Congress of Melanoma and 14th International Congress of the Society for Melanoma Research. Listen to what these experts have to say about combination therapy in the adjuvant setting for metastatic melanoma, real-world utilization of checkpoint inhibitor therapy, sequencing options for BRAF +/- MEK inhibition following immunotherapy, and the management of rheumatological immune-related adverse events following treatment with checkpoint inhibitors.

CONTENT

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This activity is supported by an independent educational grant from Merck Sharp & Dohme Corp.

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MELANOMA: Updates from Brisbane, Australia

CE/CME Information

Target Audience

This activity was developed for oncologists, dermatologists and other health care professionals who have an interest in melanoma.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Review the latest data on advanced/metastatic melanoma
- Discuss how therapeutic developments in advanced/metastatic melanoma are guiding research into improved care

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Research Support	Bristol Myers Squibb
Consultant	Array BioPharma

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Roxana S. Dronca, MD

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MELANOMA: Updates from Brisbane, Australia

Introduction

Although the management of malignant melanoma remains a challenge for clinical management, treatment options continue to expand, with immunotherapy emerging as a fundamental component of patient care. This activity reviews 4 abstracts presented at the *14th International Congress of the Society for Melanoma Research/9th World Congress of Melanoma*, which took place in Brisbane, Australia. These abstracts address combination checkpoint inhibitor therapy in the adjuvant setting for metastatic melanoma, real-world utilization of pembrolizumab in advanced melanoma, sequencing options for BRAF +/- MEK inhibition following pembrolizumab, and the management of *de novo* rheumatological immune-related adverse events following treatment with checkpoint inhibitors.

Abstract 1: Mature results of combination nivolumab (NIVO) plus ipilimumab (IPI) as adjuvant therapy in stage IIIC/IV melanoma.

Eroglu Z, Kim Y, Gibney G, et al.

Lisa Kottschade, APRN, MSN, CNP: Metastatic melanoma is an aggressive tumor with a poor prognosis, few viable options for systemic therapy, and a median survival of 6–10 months.[1] In patients with resected stage IIIC and IV melanoma, there is a particularly high risk of recurrence.[2] Interferon remains approved in the US for stage III melanoma, as well as high dose (10 mg/kg) ipilimumab which is a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor. The efficacy of adjuvant nivolumab has also recently been studied. In patients with stage IIIC/IV melanoma (n=33), nivolumab combined with a peptide vaccine was associated with a median RFS of 44 months,[3] while adjuvant nivolumab was compared with ipilimumab (standard of care) in Checkmate-238. This randomized, double-blind phase 3 trial involved 906 patients with stage IIIB/C/IV melanoma who had a greater than 50% risk of relapse over 5 years.[4] The trial, which was stopped early, showed clear evidence of benefit for nivolumab, with RFS rates (primary endpoint) of 66.4% vs 52.7% for ipilimumab (hazard ratio 0.65, $p<0.0001$). With these recent results, nivolumab was recently approved by the USFDA in the adjuvant setting for stage IIIB/C and—for the first time—stage IV disease.

How significant are these findings for the development of combination regimens in the adjuvant setting, especially in terms of dose safety and efficacy?

I think in this study the rates of grade 3/4 immune-related adverse events was significantly high. However, this study was done in a population that's extremely high risk for recurrence as well. I think in having conversations with patients, that'll definitely need to be discussed, the risk vs benefit ratio. I think we're going to need to wait a little bit longer until we have some of the phase 3 data to decide if this is a regimen that warrants the toxicity for the improvement in relapse-free survival.

In metastatic disease, the combination of nivolumab plus ipilimumab has yielded higher response rates, PFS and OS, in patients compared to either agent alone, although benefit is associated with a significant increase in toxicity.[5,6] Accordingly, a recent single-arm, single center trial examined the safety and efficacy of 2 dose cohorts of combined nivolumab (NIVO) and ipilimumab (IPI) as adjuvant therapy in patients with resected stage IIIC/IV melanoma (20 patients in each cohort, rendered disease-free by surgery). Exhibit 1 represents the treatment schema.

Half the patients in both cohorts had resected stage IV melanoma. More patients in cohort B completed all 4 induction doses (65% vs 50%); 6 pts in each completed all planned therapy. A majority of patients in both cohorts (18/20, 14/20) experienced treatment-related grade 3/4 AEs, the most frequently reported of which were lipase elevation, ALT/AST elevation, and colitis, and, in cohort B, hyperglycemia and vomiting, although these AEs were higher in

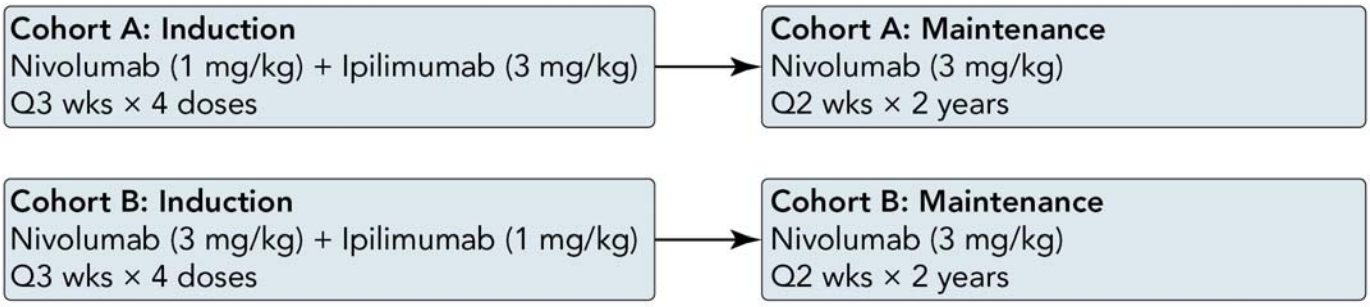

Exhibit 1. Induction and Maintenance of Nivolumab Plus Ipilimumab in 2 Patient Cohorts

cohort A. Hypophysitis was also higher in cohort A than cohort B in the maintenance phase (2/0). Median RFS and OS were not reached at median follow-up of 40 and 29 months respectively; 2-year RFS rates for cohort A were 80% (95% CI: 55-92) and 75% (50-89) for cohort B. In cohort A, 3-year RFS was 70% (45-85), and 75% (50-89) in cohort B. There were 6 relapses in cohort A and 5 in cohort B, with 1 death from recurrence in the former. In patients with stage IV melanoma, the 3-year RFS was 74% (48-88). Correlative analyses are ongoing.

Overall, this combination of nivolumab plus ipilimumab demonstrated a 3-year RFS of 71% in patients with high-risk resected stage IIIC and IV melanoma. However, the toxicity profile was significant, with better toleration in cohort B vs cohort A. It is not yet known how RFS or OS for adjuvant ipilimumab combined with nivolumab compares to anti-PD-1 therapy alone. Finally, this study was conducted with a small cohort. A randomized phase 3 trial of adjuvant ipilimumab (1mg/kg Q6 wks) plus fixed-dose nivolumab is currently being compared to nivolumab alone in patients with stages (AJCC v. 8.0) IIIB, C, D and IV melanoma (CheckMate 915/NCT03068455).

Where do these findings fit into current adjuvant treatment options in advanced metastatic melanoma?

I think the findings of this small study were actually fairly significant. The relapse-free survival in this study was slightly higher than in the study just recently reported in the New England Journal of Medicine by Jeff Weber and colleagues.[1] However, the one caveat with this study is that it did not compare dual checkpoint inhibition with single agent PD-1 alone, and I think that's where the CheckMate 915 Study will come in and help answer that question and look at both relapse-free survival rates as well as overall toxicity between the 2 cohorts.

I think this abstract fits in nicely with the overall conference. There were several other abstracts looking at combination therapy, both with novel immune checkpoint agents as well as other immunotherapy, and also targeted therapy was really talked about in combination with immunotherapy in this situation. I think it was nice to see another adjuvant study discussed at this conference because I think we've really had some milestones in the metastatic study, but it was nice to continue to see those milestones come through and that data translate from metastatic to the adjuvant study as well.

Abstract 2: Pembrolizumab (PEM) utilization and overall survival (OS) for patients with advanced melanoma: the real-world US experience.

Whitman ED, Liu FX, Cao X, et al.

Roxana S. Dronca, MD: Pembrolizumab was approved in the US in 2014 for treating patients with advanced melanoma based on phase 3 trials comparing this agent with chemotherapy in patients refractory to ipilimumab, and to ipilimumab in patients with no prior immunotherapy treatment.[7,8] First approved for second-line treatment of unresectable or metastatic melanoma, pembrolizumab is also approved for first-line therapy in patients with unresectable or metastatic melanoma, regardless of *BRAF* status. Compared with ipilimumab, pembrolizumab is associated with longer progression-free survival and overall survival.[8]

Despite the use of pembrolizumab for over 3 years, important questions remain about pembrolizumab utilization and associated patient outcomes in real-world settings. To this end, a retrospective analysis examined a longitudinal database comprised of cloud-based oncology electronic health records covering more than 265 US cancer clinics across approximately 800 sites of care (https://flatiron.com/life-sciences/). Researchers extracted de-identified patient level data for 1.7 million patients aged 18 years or older with a confirmed diagnosis of advanced melanoma who had received ≥1 dose of pembrolizumab between September 2014—June 2016, who had at least 2 clinical visits on or after January 1, 2011, and who were followed up to March 2017. Researchers excluded patients who had been enrolled in clinical trials.

What can clinicians learn about real-world studies that retrospectively examine longitudinal data?

I think these are the type of studies that are really useful for a practicing oncologist to help us put in context the clinical trial data and understand how randomized clinical trial findings apply to the real world of practice. Often our patients who do not meet the rigorous eligibility criteria are excluded from such clinical trials, and this is leaving practicing clinicians with incertitude as to how to manage these patients in the day-to-day practice.

Of 439 patients with advanced melanoma who had received at least 1 pembrolizumab administration, 73% were eligible for cohort inclusion and included in the analyses. The median age at pembrolizumab initiation was 69 years (range 30–84 years) and the majority of patients were male (66%). At initial melanoma diagnosis, 1%, 11%, 23%, 31%, and 34% were at stage 0, I, II, III, and IV, respectively. A majority (94%) received pembrolizumab monotherapy—55% in first line, 34% in second line, and 11% in third line or later. Of 105 patients receiving pembrolizumab as second-line therapy, 75% also received ipilimumab as first-line therapy. Over half (57%) of patients with *BRAF* mutant melanoma and 2% with *BRAF* wild-type melanoma received *BRAF*-targeted therapy, regardless of line of therapy. The median times on treatment were 5.6 months (95% CI, 4.4–7.2), 5.6 months (3.7–7.9), and 4.6 months (2.1–6.3) in first, second, and third line or later, respectively. The rates of censoring for the analyses of time on treatment were 36.4%, 32.4% and 22.0% in first, second, and third line or later, respectively. For patients receiving first-line pembrolizumab as monotherapy or combination therapy, the median OS from initiation of therapy was 22.7 months, with 1 year OS of 68.9% (95% CI, 68.83%-75.70%).

How do these real-world data compare with the clinical data for pembrolizumab, monotherapy and in combination?

I think that this data presented indeed confirms the fact that pembrolizumab is widely used in clinical practice irrespective of age. I think the median age in this study was 69 years with ranges from 30 to 84 years of age, so using patients irrespective of ECOG performance score. In this study about a quarter of patients had an ECOG performance score of 2 or higher irrespective of BirA mutation. So, I believe it reaffirms the fact that most clinicians are using PD-1 monotherapy, reserving anti-CTLA for end PD-1 combinations for patients with high-risk, high tumor burden melanoma. We also learned that patients do have durable clinical benefits despite treatment

discontinuation. As in this study, the median treatment duration was a little bit less than 6 months. And this is also, I think, reaffirming clinical trial findings.

Study limitations include the following: (1) In the time on treatment and overall survival analyses, many patients were censored because of relatively limited follow-up time (median, 6.9 months); (2) clinically important variables (ECOG PS status, LDH level) were not available for all patients; and (3) line-of-therapy assignments were dependent on availability of appropriate underlying EHR data triggering prespecified line-of-therapy definitions. Nonetheless, authors conclude that these preliminary results support the real-world effectiveness of pembrolizumab in advanced melanoma among patient populations that are more heterogeneous than patients treated in clinical trials.

Did any of the real-world sequencing options surprise you in this study?

I think what was surprising and also reassuring in this study is seeing how patients who were treated with anti-PD-1 monotherapy, even in second or third line, had durable benefit. The reported 1-year survival rate in patients who were treated with pembrolizumab as third-line therapy was more than 50%, and this was extremely reassuring, providing evidence that anti-PD-1 therapy works even in patients who were pretreated with prior lines of therapy.

Abstract 3: BRAF +/- MEK inhibition following pembrolizumab in KEYNOTE-006.

Long GV, Mortier L, Lotem M, et al.

Roxana S. Dronca, MD: Although BRAF inhibitors (BRAFi), MEK inhibitors (MEKi), and anti-PD-1 monoclonal antibodies are active therapeutic options for patients with advanced *BRAF*^{V600}-mutant melanoma, the most effective first-line treatment and optimal sequencing of these agents have not been well characterized. While first-line BRAFi + MEKi agents induce rapid response,[9] first-line PD-1 inhibition induces durable response.[10] Retrospective data suggest that patients may benefit regardless of the sequence of anti-PD-1 and BRAFi ± MEKi therapy,[11] although each therapy shows better outcomes when administered as first-line vs second-line therapy.[12] Combination therapy with BRAFi and MEKi has also demonstrated significant efficacy and manageable safety as first-line therapy for patients with advanced *BRAF*^{V600}-mutant melanoma,[13-16] while in KEYNOTE-006, pembrolizumab, an anti-PD-1 monoclonal antibody, showed improvement in OS, PFS, and ORR over ipilimumab in patients with *BRAF*^{V600}-mutant and wild-type advanced melanoma.[17,18]

KEYNOTE-006 was an open-label, phase 3 comparison study of pembrolizumab vs ipilimumab for patients who received ≤1 prior systemic therapy for unresectable, stage III/IV melanoma. Subsequently, Long et al used these data to explore best response and OS in patients who received BRAFi ± MEKi as the first subsequent systemic therapy following pembrolizumab. Analysis focused on patients who had discontinued pembrolizumab after receiving ≥1 dose and received BRAFi +/- MEKi as the first subsequent therapy (n=59). Radiation prior to or concurrent with BRAFi +/- MEKi was permitted, as was use of BRAFi +/- MEKi prior to pembrolizumab. Pembrolizumab doses (10 mg/kg once every 2 weeks or once every 3 weeks for 2 years) were pooled for analysis.

How does this study help clinicians sort out sequencing in advanced melanoma, the study that we're looking at, BRAF and MEK inhibitors, before and after pembrolizumab?

This exploratory analysis by Dr. Georgina Long and colleagues I think provides evidence that indeed BRAF and MEK inhibition does retain antitumor activity in patients who fail anti-PD-1 treatment, but it also shows that in patients with BRAF-mutant disease who are treated in second line with targeted therapy, the overall response rates and overall survival is slightly less than in patients who were treated with this therapy as first line.

Analysis showed antitumor activity for BRAFi ± MEKi following pembrolizumab in patients with advanced *BRAF*^{V600}-mutant melanoma (median duration = 6.5 months, range 11 days to 31.3 months). The ORR observed for subsequent BRAFi ± MEKi was similar for combination therapy (30%) and BRAFi monotherapy (Exhibit 2); however, the 31% ORR

observed for subsequent BRAFi ± MEKi was lower than the 64%-70% ORR observed in phase 3 studies of first-line BRAFi + MEKi.[9-12] Nonetheless, ORR with subsequent BRAFi ± MEKi was higher in patients who were naïve to BRAFi ± MEKi (42%) compared with those who received BRAFi ± MEKi before pembrolizumab (10%). A previous exploratory analysis of KEYNOTE-006 similarly found that ORR with pembrolizumab was higher in patients with *BRAF*^{V600}-mutant tumors who did not receive prior BRAFi ± MEKi (41%) vs those who did (21%).[19]

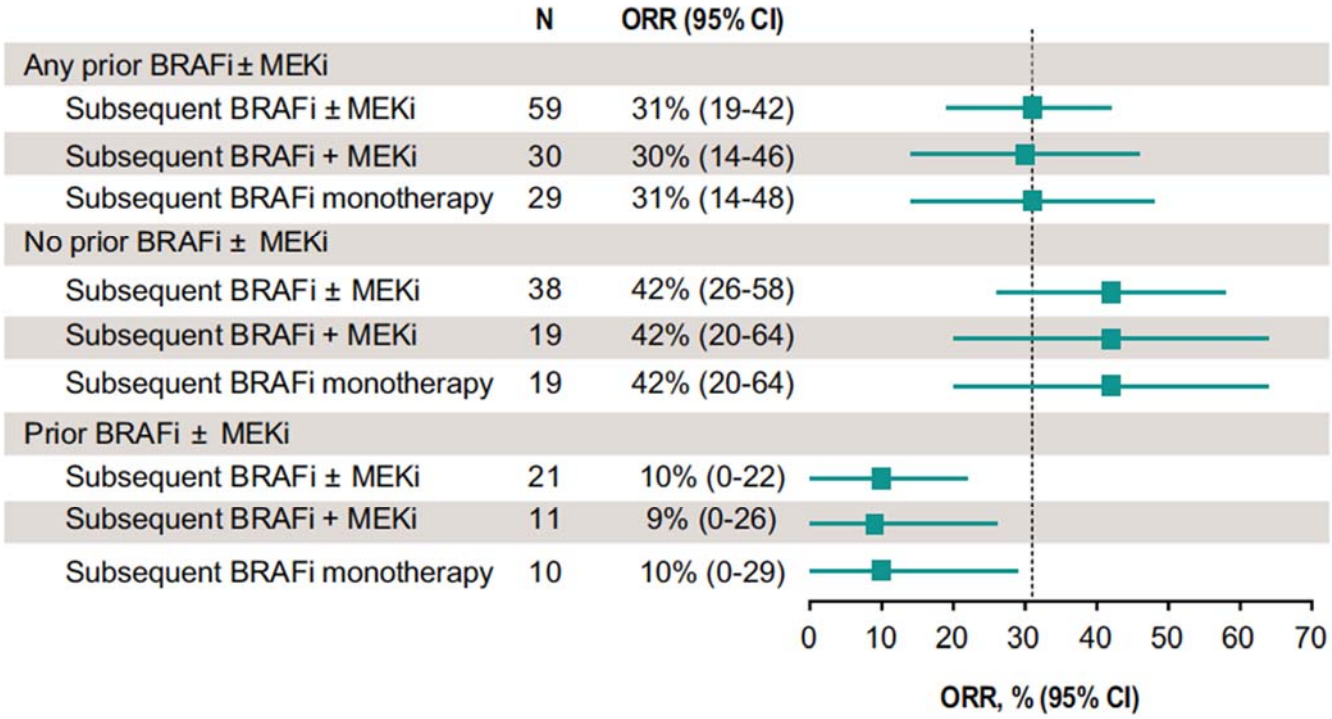

Exhibit 2. ORR to subsequent BRAFi ± MEKi

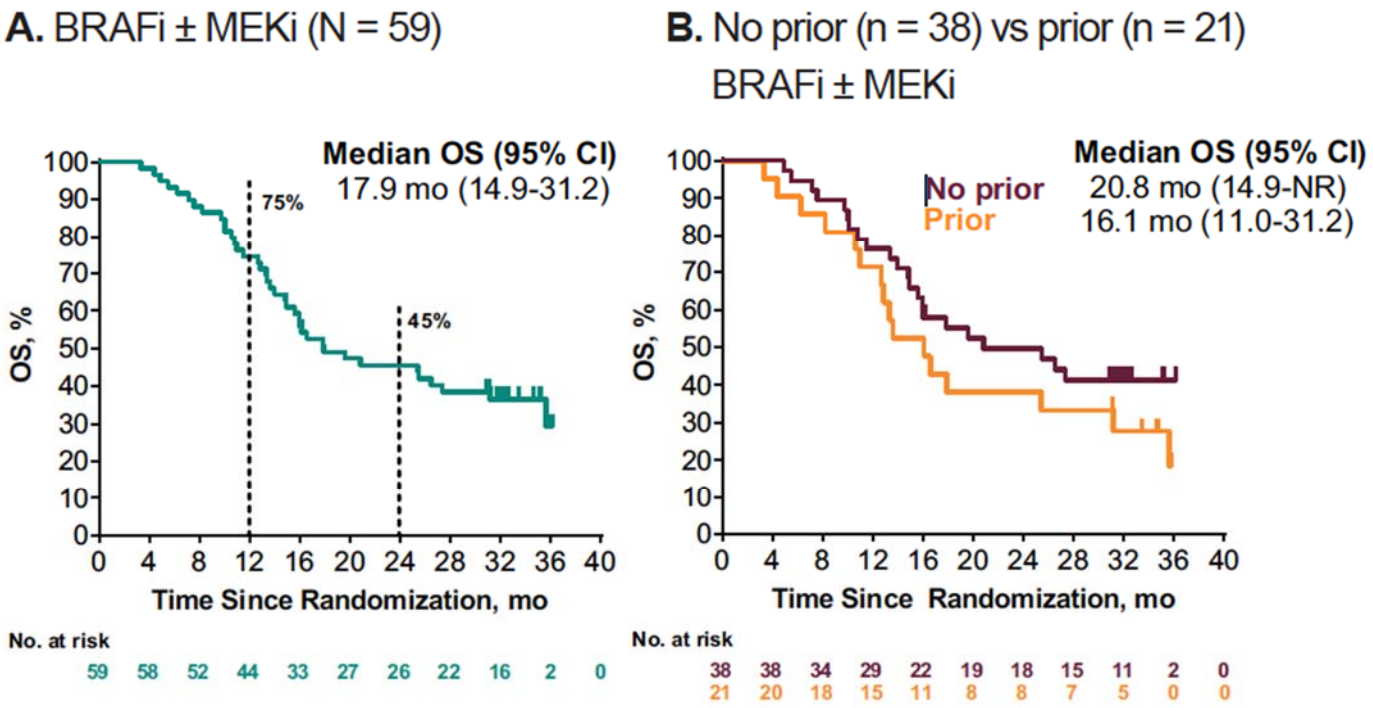

Exhibit 3. OS since time of study randomization for subsequent BRAFi ± MEKi

Where do these findings fit into current treatment options in advanced melanoma?

I believe these findings fit into the current practice patterns in the treatment of patients with metastatic BRAF-mutant melanoma, and those in-practice guidelines where patients with high tumor burden and high-risk disease are often offered targeted therapy up front, and indeed this is probably where the targeted therapy will show most benefit in terms of overall response rates, progression through survival, and overall survival. These findings reaffirm these patterns. The optimal sequencing between immunotherapy, targeted therapy, or even a combination of this approach—which now is an area of research in patients with metastatic BRAF-mutant melanoma—overall, remains a very active area of research and will likely require well-designed, randomized clinical trials to answer these questions. But studies like this, showing us how different treatments perform in first, second, and third line, really help us understand what best to offer to patients with metastatic BRAF-mutant disease.

In this small study, response to pembrolizumab did not appear to predict response to subsequent BRAFi ± MEKi treatment, and lack of response to pembrolizumab did not appear to preclude response to subsequent BRAFi ± MEKi treatment. Other retrospective data suggest patients may benefit regardless of the sequence of anti-PD-1 and BRAFi ± MEKi therapy,[10] although each therapy shows better outcomes when administered as first-line vs second-line therapy.[11,12] This exploratory analysis provides additional evidence that while sequencing anti-PD-1 agents to BRAFi ± MEKi or BRAFi ± MEKi, followed by anti-PD-1 agents, have similar activity, each individual therapy may have greater benefit when administered as first-line vs second-line therapy.

How did this particular study report align with some of the other presentations that you witnessed at this conference?

I think this study in general aligned very well with the overall theme of the conference, which focused on many practical aspects of management of patients with melanoma and also aligning the current practical issues with the research findings and the scientific advances and also giving us an insight into future directions of research in patients with melanoma.

The most active areas of research currently explore sequencing of therapies in patients with metastatic disease. Also, best combinatorial therapies, whether

combination immunotherapies with immune checkpoint inhibition and viral-based therapies, or combination of immunotherapy and targeted therapies. Also, a very active area of research is looking into biomarkers of response, predictive biomarkers, and also monitoring biomarkers to help us understand who are the patients who best benefit from these treatment approaches and what treatment should be offered to each patient.

Abstract 4: Management of rheumatological immune related adverse events in melanoma patients treated with anti-programmed cell death (pd) 1 antibodies.

Mitchell EL, Lau PK, Khoo C, et al.

Why is it important to characterize organ system specific immune-related adverse events in patients with melanoma?

Lisa Kottschade, APRN, MSN, CNP: I think as we continue to advance our treatments with immune checkpoint inhibitors, both singly and in combination, we need to be able to define immune-related adverse events by organ system, so we know how to better treat them. We're looking, moving forward, and trying to look at better ways to treat them, other than global immunosuppression with steroids. And, if we can tease out specific organs that can be targeted to suppress those adverse events, potentially to either continue therapy, or at least minimize global immunosuppression, this is really important.

Although anti-PD-1 antibodies such as pembrolizumab (P) and nivolumab (N) are established therapies for advanced melanoma, they are associated with a spectrum of immune-related adverse events (irAEs) that involve many organ systems. irAEs occur in up to 90% of patients receiving CTLA-4 agents and 7% of those receiving anti-PD-1/PD-L1 agents.[20,21] Gastrointestinal, hepatic, endocrine and dermatological are the most commonly reported irAEs.[22] Rheumatological (Rh) irAEs are infrequently reported, but approximately 5%-10% of patients treated with these agents develop arthralgias, inflammatory arthropathies, myopathies and other Rh irAEs. Management algorithms or protocols have been developed for endocrine, gastrointestinal, pulmonary and renal immune related AEs (irAEs), but not for Rh irAEs. This multicenter, retrospective study examined how clinicians are managing Rh irAEs in patients with melanoma being treated with anti-PD-1 antibodies.

Investigators obtained a range of clinical, demographic, response, and toxicity data, as well as data on treatment, duration of response, and reasons for stopping treatment, for 20 patients treated with anti-PD-1 antibodies who sustained Rh irAE (Exhibit 4).

Sex	Male = 13 Female = 7	
Median age	75 years	
Malignancy	M1a = 1 M1b = 1 M1c = 18	
Immunotherapy received	P or N = 19 N+I = 1	
irAE	***De novo* Rh irAE** Inflammatory arthritis = 9 Myositis = 2 PMR = 1 Fasciitis = 1	**Flare of existing Rh** Psoriatic arthritis = 1 Inflammatory arthritis = 1 PMR = 5
Time to irAE onset	15 weeks (range <1 - 113); myositis cases manifested within 6 weeks	

Exhibit 4. Patient and Disease Characteristics, Immunotherapy, and irAE

Of the 20 patients, 13 developed *de novo* Rh irAEs, 9 inflammatory arthritis, 2 myositis, 1 polymyalgia rheumatica (PMR), and 1 fasciitis. The other 7 sustained a flare of pre-existing Rh condition (5 PMR, 1 psoriatic arthritis, and 1 inflammatory arthritis). The median time to Rh irAE was 15 weeks (range <1 - 113) while myositis cases manifested within 6 weeks.

Twelve patients required high dose prednisolone (PNL) (≥10mg/day) and 5, lower doses. Disease modifying antirheumatic drugs including hydroxychloroquine, methotrexate, sulfasalazine, leflunomide, and mycophenolate, were used in 7 patients. Half of the patients completely responded

to anti-PD-1 (10), 8 partially responded, 1 had stable and 1 had progressive disease. Responses have been maintained despite ongoing low-dose PNL. Median duration of response has not been reached.

How can clinicians use the results from this kind of study to establish immune-related adverse event protocols in their cancer centers?

I think for overall general organ systems the protocols are pretty well defined. But, I think in this particular abstract, looking at patients with previous history of rheumatologic conditions and those that developed new kinds of *de novo* rheumatologic conditions, this is really important. While these conditions can respond to systemic steroids, they also can respond to other biologic modifiers that may, again, have less global immunosuppression than overall steroids do. So that these patients can, like I said, either continue treatment, or not have so many side effects from the steroids.

De novo Rh irAEs and flares of pre-existing rheumatological disease undoubtedly present a distinct challenge for clinicians managing patients being treated with anti-PD-1 therapy. Other single-center studies have shown that while glucocorticoids can be effective in treating Rh irAEs, nonetheless, some patients may require other measures such as biologic modifying agents, additional immunosuppressive therapy, or cessation of immunotherapy.[23]

What kind of challenge does the late appearance of rheumatological immune-related side effects present for clinicians and management?

I think the bigger problem is, are these truly bona fide rheumatologic conditions, or are they—could they be—side effects from other drugs that patients may have gone on after immune checkpoint inhibitor therapy? A lot of these patients also present seronegative. So, diagnosing these is very difficult. And, I think collaboration with a rheumatologist is absolutely imperative if patients are presenting with some of these vague myalgias, arthralgias. Some of them will present with increased inflammatory markers, and I think any of those patients that present with these types of things need to be further worked up by a rheumatologist. This needs to just be something in the back of oncologists' minds, primary care providers, as we're using these in the adjuvant setting, of melanoma as a possibility as a long-term late developing side effect.

While management of Rh irAEs remains an area of uncertainty, this small study shows that they appear to be steroid sensitive, and patients with melanoma whose irAEs are appropriately managed with steroids continue to respond to anti-PD-1 therapy.

How familiar are rheumatologists with these kinds of side effects, specifically related to checkpoint inhibitors?

I think at first they were not very familiar. They are increasingly seeing more of these, so they have started educating themselves. There have been a number of meetings about this with some of the world's leading rheumatologists across the country. I know our rheumatologists here have been going to their, kind of, annual meetings, and this topic has been discussed. So, I think they're becoming more and more familiar with these types of things. But, I think even in the oncologist's mind, this is where we need to work collaboratively with a rheumatologist to just discuss this possibility and make them aware that these are coming. There's more case reports out in the literature, which I think is helping. And, I think, again, just working collaboratively with the rheumatologists, primary care providers, and ourselves, to help these patients.

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