Bristol Myers Squibb
Independent Medical Education
Request for Educational Support (RFE)

Date	January 9, 2023
RFE Requestor Information	Name: Maria Deutsch E-mail: maria.deutsch@bms.com
RFE Code	RFE-23-ONC-102
Therapeutic Area	Oncology - Melanoma
Area of Interest	Advanced disease – immunotherapy in the treatment of early to late advanced stage melanoma
Educational Design	Bristol Myers Squibb is interested in supporting an innovative, comprehensive educational initiative that includes the following: • Virtual – A live, video web broadcast presentation and panel discussion with time for live Q&A/interaction with faculty held during 2023 ASCO Meeting, June 2-6, 2023 • On-demand – Web-based enduring activity leveraging the content from the live webcast presentation • Online resources and tools Knowledge and competency-based objective outcome measures according to Moore's Level 5 is preferred.
Intended Audience (may include, but not limited to)	Medical oncologists, dermatologists, surgical oncologists, and other allied HCPs involved in the treatment of patients with melanoma
Budget/Budget Range	The anticipated program is expected to be achieved with a BMS budget of no more than $185K. Single and multi-supported initiatives will be considered.
Accreditation	ACCME and others as appropriate to the audience(s).
Geographic Coverage	United States
Deadline for Submission (Date and Time)	2/10/2023 EOB 5pm EST

Background:

Melanoma (early disease)

Patients with stage IIB and IIC disease have poorer 5-year and 10-year melanoma-specific survival than those with stage IIIA disease.[1] Limited evidence of OS benefits has contributed to a lack of consensus on adjuvant immunotherapy in high-risk stage II melanoma, which includes stage IIB and stage IIC disease.[2] In the phase 3 KEYNOTE-716 trial, researchers showed that adjuvant pembrolizumab substantially improved RFS compared to placebo in resected high-risk stage II disease, leading to the FDA approval of this agent as adjuvant therapy in stage IIB/C disease.[3] Nivolumab is also being assessed in conjunction with surgery in patients with stage IIB-IIC melanoma in the CheckMate -76K trial (NCT04099251), as well as in the NivoMela study (NCT04309409).

Researchers have also attempted to assess the potential of neoadjuvant checkpoint blockade in stage III melanoma; in the OpACIN-neo trial, a tolerable dosing schedule of dual checkpoint blockade with neoadjuvant ipilimumab plus nivolumab was identified that induced pathologic complete responses (pCRs) in a high proportion of patients.[4,5] In the neoadjuvant setting, the 'flipped dosing' schedule (2X ipilimumab 1 mg/kg + nivolumab 3 mg/kg) appears to maximize efficacy and limit toxicity of neoadjuvant immunotherapy. In the PRADO study, neoadjuvant dual checkpoint blockade was able to induce high rates of pathologic response and avoid therapeutic lymph node dissection in a major subset of patients, thus reducing surgical morbidity while leading to robust survival outcomes.[6] Emerging neoadjuvant regimens in melanoma include relatlimab-nivolumab in clinical stage III melanoma; the combination was found to include high pathologic and major CR rates with a favorable toxicity profile.

Researchers have validated several innovative options that have overcome the limitations of conventional adjuvant therapy in resectable melanoma, including targeted and immunotherapy options. For example, the combination of dabrafenib and trametinib was approved by the FDA for adjuvant melanoma treatment, based on the results of COMBI-AD, a study comparing dabrafenib + trametinib to placebo in patients with resected stage III BRAF-mutant melanoma, which found substantial improvements in 3-year RFS.[7]

In 2015, ipilimumab was approved as adjuvant therapy for patients with stage III disease at high risk for recurrence after complete resection; approval was based on phase 3 evidence showing improvements in RFS, distant metastasis–free survival, and overall survival with ipilimumab compared to placebo.[8] The phase 3 CheckMate -238 trial, which assessed the adjuvant use of the PD-1 inhibitor nivolumab versus ipilimumab in patients with stage IIIB, IIIC, or IV melanoma undergoing complete resection, found that RFS rates were significantly higher for nivolumab versus ipilimumab, even in subgroups defined by stage, PD-L1 expression, and BRAF mutation.[9] The results of this trial led to the FDA approval of nivolumab as adjuvant therapy in melanoma patients with lymph node involvement or metastatic disease after complete resection.[10] Three- and four-year efficacy and biomarker results from the CheckMate -238 study demonstrated a superior recurrence-free survival benefit with nivolumab vs ipilimumab; this was consistent regardless of disease stage, PD-L1 expression level, and BRAF status in patients with resected stage III/IV melanoma who had a high risk for recurrence.[11,12] New directions include the assessment of innovative

immunotherapy combination regimens in the adjuvant setting. Based on its activity in metastatic, unresectable disease,[13] the novel combination of nivolumab and the LAG-3 targeting agent relatlimab is being tested as adjuvant therapy versus nivolumab alone after complete resection of stage III-IV melanoma (RELATIVITY-098).

The PD-1 targeting agent pembrolizumab was approved as adjuvant treatment for patients with resected, high-risk stage III melanoma[14]; this approval was based on results from the phase 3 EORTC 1325-MG/KEYNOTE-054 trial, in which adjuvant pembrolizumab substantially reduced the risk for recurrence or death in patients with resected, high-risk stage III melanoma.[15] Long-term findings confirmed this initial RFS benefit (regardless of BRAF status).[16] Updated results from this study found that adjuvant pembrolizumab met the key secondary endpoint of distant metastasis-free survival (DMFS), substantially reducing the risk of distant metastasis or death versus placebo and maintained a significant recurrence-free survival benefit.[17]

Melanoma (advanced disease)

Early breakthroughs in the progress of immune checkpoint blockade in cancer involved the development of cytotoxic T lymphocyte antigen-4 (CTLA-4)–targeting antibodies (ie, ipilimumab) in patients with advanced melanoma.[18] This led to other advances including the validation of therapies (such as nivolumab and pembrolizumab) directed against programmed cell death protein 1 (PD-1).[19,20] In metastatic unresectable melanoma, dual checkpoint blockade (nivolumab plus ipilimumab) as well as single agent PD-1 inhibitor approaches (nivolumab or pembrolizumab) are among the current standards of care based on a wealth of robust evidence;[21,22] these options are category 1 recommendations in metastatic unresectable melanoma regardless of BRAF mutation statis.[23] Dual checkpoint blockade is also highly efficacious in challenging and aggressive disease settings; updated 5-year results of the ABC trial found that ipilimumab plus nivolumab produced durable responses in melanoma brain metastases in a majority of patients, including those with baseline BRAF mutations or those who had received prior targeted agents.[24] Evidence on the use of BRAF/MEK inhibitor combinations in BRAF mutation–positive advanced disease has also confirmed the role of targeted agents in this setting, including dabrafenib/trametinib,[25] vemurafenib/cobimetinib,[26] and encorafenib/binimetinib.[27,28] The clinical experience to date with BRAF/MEK targeting agents in melanoma includes challenges such as the development of drug resistance and the need for interventions such as dose interruptions/discontinuations to address adverse events (eg, pyrexia or fatigue).[29,30]

The PD-L1 inhibitor atezolizumab has been approved in combination with cobimetinib/vemurafenib in previously untreated patients with BRAF-mutant advanced melanoma (based on phase 3 evidence), representing the convergence of immune-based and targeted options in this setting.[31] The phase 3 DREAMseq trial showed that upfront use of nivolumab/ipilimumab followed by targeted therapy at progression in BRAF-mutated advanced melanoma produced superior OS compared with a treatment sequence beginning with targeted agents (dabrafenib/trametinib), leading to what researchers characterized as a new standard of care.[32] Findings from the SECOMBIT trial also showed that patients with BRAF-mutated advanced melanoma may benefit from receiving dual checkpoint blockade upfront or from a sequential upfront strategy of

targeted followed by immune-based combinations.[33] Collectively, this evidence has led to a new management model that features immune and targeted strategies as centerpieces of care for various advanced, unresectable melanoma populations.[23]

Despite new evidence supporting a preferred algorithm for upfront and sequential management of BRAF-mutated melanoma, the integration of strategies such as dual checkpoint blockade into such treatment settings remains suboptimal. The different elements of this needs assessment demonstrate that significant gaps and unmet needs exist related to the development of modern, optimized treatment plans for BRAF-mutant metastatic melanoma, including the selection of initial treatment and effective team-based management of toxicity associated with immunotherapy and targeted agents, and that further education is needed in this area.

Education Needs:

Medically accurate, fair-balanced learning programs are required to maximize transparency and minimize clinician bias in the provision of medical education. Applying evidence-based scientific knowledge significantly contributes to professional competencies of HCPs and improves patient outcomes.

This virtual, live stream webcast will ensure timely and effective communication of the latest science and clinical trial data surrounding current and emerging immunotherapies in first-line metastatic melanoma.

The following educational needs should be addressed through this educational program:

- Cite current evidence and guideline recommendations for the use of immunotherapy in resectable stage III/IV melanoma and unresectable, metastatic disease
- Summarize evidence on applications of immunotherapy in melanoma, including as neoadjuvant therapy, as an adjuvant option for stage II disease, or as part of novel combinatorial approaches
- Integrate immunotherapy into the management of patients with resectable and unresectable melanoma, including those with BRAF-positive or -negative disease
- Manage immune-related adverse events in patients with melanoma receiving immunotherapy across the spectrum of disease
- Collaborate with the multidisciplinary team to integrate immunotherapy into individualized multimodal treatment plans for eligible patients with melanoma

References:

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The content and/or the format of the CME/CE activity and its related materials must be designed in such a way that it addresses the educational needs of health care professionals and, if appropriate, tools/aids that can help health care practitioners communicate with or better manage their patients.

Presentations and content must give a scientifically sound, fair and balanced overview of new and emerging therapeutic options currently available or in development to manage or prevent this disease.

Note: The accredited provider and, if applicable, the medical education provider (MEP) or other third party executing the activities are expected to comply with current ethical codes and regulations. They must have a conflict-of-interest policy in place to identify and resolve all conflicts of interest from all contributors and staff developing the content of the activity prior to delivery of the program, and must have a separate company providing/accrediting independent medical education if they are also performing promotional activities.

If your organization wishes to submit an educational grant request, please use the online application available on the Bristol Myers Squibb Independent Medical Education website: http://www.bms.com/grantsandgiving

Grant Proposals should include, but not be limited to, the following information:

- **Executive Summary: The Executive Summary should consist of 1-2 pages and highlight the key areas as described below.**

- **Needs Assessment/Gaps/Barriers:** Needs assessment should be referenced and demonstrate an understanding of the specific gaps and barriers of the target audiences. The needs assessment must be independently developed and validated by the educational provider.

- **Target Audience and Audience Generation:** Target audience for educational program must be identified within the proposal. In addition, please describe methods for reaching target audience(s) and any unique recruitment methods that will be utilized. The anticipated or estimated participant reach should also be included, with a breakdown for each modality included in the proposal, as applicable (e.g., number of participants for the live activity, the live webcast, and enduring activity).

- **Learning Objectives:** The learning objectives must be written in terms of what the learner will achieve as a result of attending. The objectives must be clearly defined, measurable, attainable and address the identified gaps and barriers.

- **Educational Design and Methods:** Describe the approach used to address knowledge, competence, and performance gaps that underlie identified healthcare gaps. The proposal should include strategies that ensure reinforcement of learning through use of multiple educational interventions and include practice resources and tools, as applicable.

- **Communication and Publication Plan:** Provide a description of how the provider will communicate the progress and outcomes of the educational program to the supporter It is highly recommended to describe how the results of the activity will be presented, published, or disseminated.

- **Innovation:** Describe how this project is innovative and engages the learners to improve knowledge, competence and/or performance. Further describe how this project might build on existing work, pilot projects or ongoing projects developed either by your institution or other institutions related to this topic.

- **Program Evaluation and Outcomes Reporting:** Description of the approach to evaluate the reach and quality of the educational program. Describe methods used for determining the impact of the educational program on closing identified healthcare gaps.
    - Please refer to “Guidance for Outcomes Report” (on the BMS grants website) for a detailed explanation of preferred outcomes reporting methods and timelines.
    - Remember that knowledge, performance and competency based outcome measures according to Moore’s Levels 4 & 5 are required. Level 6 outcomes are highly favored and recommended when possible.

- **Budget:** Detailed budget with rationale of expenses, including breakdown of costs, content cost per activity, out-of-pocket cost per activity, and management cost per activity.