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

Date	10/30/2024
RFE Requestor Information	Name: Maria Deutsch Title: Worldwide Medical Oncology, Medical Education E-mail: maria.deutsch@bms.com
RFE Code	RFE-24-ONC-104
Therapeutic Area	Oncology – Pan Tumor
Area of Interest	Innovative drug delivery approaches with immune checkpoints inhibitors in immuno-oncology
Educational Design	Bristol Myers Squibb is interested in supporting an innovative, comprehensive educational initiative that includes the following: • Virtual – A live broadcast presentation with live Q&A/interaction with faculty • On-demand – Web-based enduring activity leveraging the content from the live/virtual meetings • Online resources and tools Knowledge and competency-based objective outcome measures according to Moore's Level 4 are required. *Performance-based Level 5 outcomes are highly preferred.*
Intended Audience (may include, but not limited to)	Medical oncologists, urologists, dermatologists, surgical oncologists, thoracic surgeons, NPs, PAs, nurses, pharmacists, and other healthcare professionals involved in the care of patients with cancer
Budget/Budget Range	The anticipated program is expected to be achieved with a BMS budget of **$185,000**. Single and multi-supported initiatives will be considered, ensuring occurrence of activity.
Accreditation	ACCME and others as appropriate to the audience(s), such as pharmacists and nurses
Geographic Coverage	United States

Deadline for Submission (Date and Time)	12/05/2024 EOB 5pm EST

Background:

Introduction

Over the last decade, immunotherapy research has become the fastest growing area in the field of oncology drug development.[1] Specifically, immune-checkpoint inhibitors (ICIs) have become popular in the field of tumor immunotherapy due to their impressive therapeutic outcomes across a diversity of tumor types and their strong anti-tumor outcomes.[2] Traditionally, ICIs have been administered via an intravenous (IV) infusion, which necessitates lengthy appointments and may even introduce complications for some patients with the need for infusion ports.[3] Therefore, alternative means of ICI administration that can reduce the treatment burden and increase adherence are needed.[3] Emerging evidence shows that cancer drugs administered by a subcutaneous (SC) route are associated with important time and resource savings for both the providers and patients compared to IV administration.[4]

The Advantages of Subcutaneous Immune Checkpoint Inhibitors

Although ICIs administered via the IV route are currently most used, studies have reported a consistent preference for SC over IV drug administration for both patients and providers, so the demands for these innovative delivery routes are increasing.[5] Namely, SC administration shows similar efficacy and safety data to IV administration, and can not only decrease time spent in the clinic for the patient, but can also decrease medical costs for the healthcare team overall.[5,6] This SC route of administration allows for more efficient use of resources while simultaneously improving patient experience and satisfaction.[5,6]

A phase 1 dose-escalation study compared the safety and efficacy as well as pharmacokinetics (PK) between IV and SC formulations of the same anti-PD-1 antibody, PF-06801591, in patients with various advanced solid tumors.[6] Patients were randomized to receive either IV administration of 0.5 to 10 mg/kg every 3 weeks or SC administration of 300 mg once monthly.[6] No dose-limiting toxicities were found in either group and most treatment-related adverse events (AEs) were grade 1 or 2.[6] Additionally, objective responses were observed in 5 patients treated intravenously and 2 patients treated subcutaneously for an overall objective response rate of 18.4%.[6] The PK analysis showed that the steady state exposure following SC administration of 300 mg of PF-06801591 once monthly fell within the range observed with IV dosing at 1 mg/kg and 3 mg/kg every 3 weeks, which is consistent with the dose range for anti–PD-1 antibodies as a class where additional efficacy benefit is not gained by higher doses.[6] Thus, it was concluded that this antibody appears to be safe and tolerable and demonstrated antitumor activity in a variety of tumor types with both IV and SC routes of administration.[6]

A systematic literature review to identify evidence relating to differences in the burden for medical centers and HCPs between SC and IV administration revealed consistent results in favor of SC routes of administration.[4] Time savings associated with preparation and administration of SC therapies, across both oncology biologics and other supportive therapies, compared to IV therapies was clear.[4] Reductions were seen in the HCP time and resource use, including drug waste, required for SC versus IV therapy administration.[4] Patient hospital time was also shorter with SC versus IV administration, which may lead to additional cost savings due to a reduction in the loss of productivity and more chair-time for the patient.[4] The substantially shorter administration times of therapies administered subcutaneously has the

potential to offer several advantages over IV administration, including shorter treatment times, a reduction in healthcare resource use, increased convenience for patients, and greater patient preference.[4]

The Latest Evidence Supporting the Use of Subcutaneous ICIs

IMscin001 is a two-part global study in patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC).[7] The first part, the phase Ib portion of the study, explored pharmacokinetics and aimed to find comparative serum trough concentrations of atezolizumab following IV and SC administration.[7] SC atezolizumab was well tolerated and exhibited a safety profile consistent with the established safety profile of the IV formulation, showing some preference for injection in the thigh versus abdomen.[7] These results led to the start of the second part of the trial, the phase III portion of the study, which studied subcutaneous atezolizumab co-formulated with recombinant hyaluronidase.[8] SC atezolizumab showed noninferior drug exposure and similar efficacy, safety, and immunogenicity data relative to the IV arm, which therefore supports the clinical viability of subcutaneous atezolizumab as an alternative to IV infusion.[8] As of September 2024, atezolizumab formulated with hyaluronidase-tqjs was approved in the US as a subcutaneous injection for all indications as the IV formulation of atezolizumab.[9]

CheckMate-8KX is a pharmacokinetic phase I/II multi-tumor study of the SC formulation of nivolumab monotherapy.[10] The results demonstrated that nivolumab co-formulated with recombinant human hyaluronidase PH20 enzyme (rHuPH20) had similar and consistent pharmacokinetic parameters, including drug exposure, as well as safety and tolerability to IV nivolumab.[10] Additionally, an exploratory subanalysis of CheckMate-8KX found that a majority of patients were very satisfied and reported minimal pain/discomfort associated with SC injection and that most patients preferred SC over IV nivolumab.[11] This data established the basis for the initiation of the phase III CheckMate-67T trial, evaluating PK and objective response rate (ORR) noninferiority of SC versus IV nivolumab in previously treated patients with advanced/metastatic clear cell renal cell carcinoma (ccRCC). Recent readouts show positive results; SC nivolumab + rHuPH20 demonstrated noninferior pharmacokinetics and objective response rate relative to IV nivolumab, alongside a similar, consistent safety profile.[12,13] Study results are consistent with the perceived time benefits of SC formulations, showing a less than five-minute administration time compared to the standard ~30-60 minutes required for IV infusions.[14] With a longer follow-up of the CheckMate-67T trial, consistent efficacy, safety, and immunogenicity data between the SC and IV formulations were observed.[15] Based on results from CheckMate-67T, the SC formulation of nivolumab co-formulated with rHuPH20 has a Prescription Drug User Fee Act (PDUFA) goal date of December 29, 2024 in the US.[16]

KEYNOTE-555 is a Phase I trial comparing SC and IV pembrolizumab, in which Cohort A studied patients with metastatic melanoma.[17] The PK of pembrolizumab in the SC formulation were consistent of that with the IV formulation as well as the SC formulation of other monoclonal antibodies; SC pembrolizumab was found to have similar absorption and bioavailability as IV pembrolizumab and was generally well tolerated with a consistent safety profile.[17] This phase I trial led the proof-of-concept groundwork for SC pembrolizumab which leads to KEYNOTE-D77.[18] This is a Phase 3 trial evaluating the efficacy of MK-3475A, a subcutaneous formulation of Keytruda, in combination with chemotherapy as a first-line treatment for NSCLC.[18] The primary hypotheses of this study are MK-3475A SC is noninferior to pembrolizumab IV with respect to PK parameters.[18] This study is expected to conclude in May 2028.[18]

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 activity will ensure timely and effective communication of the latest science and clinical trial data surrounding current and emerging routes of administration.

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

- Explain the advantages and disadvantages of IV and SC routes of administration and the potential for SC routes to address unmet needs when treating patients with cancer
- Describe the current clinical evidence on using innovative drug delivery methods when managing patients with cancer across different tumor types and treatment settings
- Select the most appropriate ICI-based treatment for patients with cancer across a variety of tumors, based on clinical evidence and guidelines, considering contraindications based on patient-related factors and disease characteristics as well as managing adverse events
- Utilize a multidisciplinary team approach to integrate SC routes of administration in real world practice based on latest clinical trial data and other healthcare system considerations
- Discuss best practices and evolution of workflow to optimize SC ICI implementation

References:

1. Thompson, G. (2016). *Switching on the Light: A Model Immunotherapy Program for Oncology Practices*. Oncology Practice Management. https://oncpracticemanagement.com/issues/2018/february-2018-vol-8-no-2/1072-switching-on-the-light-a-model-immunotherapy-program-for-oncology-practices
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3. Kobold S. Can new routes of administration have a place in the application of immunotherapy? September 12, 2022. https://dailyreporter.esmo.org/esmo-congress-2022/editorial/can-new-routes-of-administration-have-a-place-in-the-application-of-immunotherapy
4. McCloskey C, Ortega MT, Nair S, Garcia MJ, Manevy F. A Systematic Review of Time and Resource Use Costs of Subcutaneous Versus Intravenous Administration of Oncology Biologics in a Hospital Setting. Pharmacoecon Open. 2023;7(1):3-36. doi:10.1007/s41669-022-00361-3
5. Pivot X, Gligorov J, Müller V, et al.; PrefHer Study Group . Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. *Lancet Oncol*. 2013;14(10):962-970. doi: 10.1016/S1470-2045(13)70383-8
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Advanced Solid Tumors: A Phase 1 Dose-Escalation Trial. JAMA Oncol. 2019;5(7):999-1007. doi:10.1001/jamaoncol.2019.0836
7. Felip E, Burotto M, Zvirbule Z, et al. Results of a Dose-Finding Phase 1b Study of Subcutaneous Atezolizumab in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer. *Clin Pharmacol Drug Dev*. 2021;10(10):1142-1155. doi:10.1002/cpdd.936
8. Burotto M, Zvirbule Z, Mochalova A, et al. IMscin001 Part 2: a randomised phase III, open-label, multicentre study examining the pharmacokinetics, efficacy, immunogenicity, and safety of atezolizumab subcutaneous versus intravenous administration in previously treated locally advanced or metastatic non-small-cell lung cancer and pharmacokinetics comparison with other approved indications. *Ann Oncol*. 2023;34(8):693-702.
9. FDA Approves Atezolizumab and Hyaluronidase-tqjs for Subcutaneous Injection. Ascopost.com. Published 2024. Accessed October 7, 2024. https://ascopost.com/news/september-2024/fda-approves-atezolizumab-and-hyaluronidase-tqjs-for-subcutaneous-injection/
10. Lonardi S, Lugowska I, Jackson CGCA, et al. CheckMate-8KX: phase I/II multi-tumor preliminary analyses of a subcutaneous formulation of nivolumab (+/- rHuPH20). *J Clin Oncol*. 2021;39(suppl_15):2575.
11. Lonardi S, Bennett BM, Dixon M. 739P - Patient preference for subcutaneous nivolumab with/without recombinant human hyaluronidase PH20 (rHuPH20) vs. intravenous nivolumab: an exploratory subanalysis of a phase I/II pharmacokinetic multi-tumor study. *Ann Oncol*. 2022;33(suppl_7):S331-S355.
12. Phase 3 CheckMate -67T Trial of Subcutaneous Nivolumab (nivolumab and hyaluronidase) Meets Co-Primary Endpoints in Advanced or Metastatic Clear Cell Renal Cell Carcinoma. Bms.com. Published 2020. Accessed October 8, 2024. https://news.bms.com/news/corporate-financial/2023/Phase-3-CheckMate--67T-Trial-of-Subcutaneous-Nivolumab-nivolumab-and-hyaluronidase-Meets-Co-Primary-Endpoints-in-Advanced-or-Metastatic-Clear-Cell-Renal-Cell-Carcinoma/default.aspx
13. Subcutaneous Nivolumab (nivolumab and hyaluronidase) Shows Noninferiority Compared to Intravenous Opdivo (nivolumab) in Advanced or Metastatic Clear Cell Renal Cell Carcinoma in CheckMate -67T Trial. Bms.com. Published 2020. Accessed October 7, 2024. https://news.bms.com/news/corporate-financial/2024/Subcutaneous-Nivolumab-nivolumab-and-hyaluronidase-Shows-Noninferiority-Compared-to-Intravenous-Opdivo-nivolumab-in-Advanced-or-Metastatic-Clear-Cell-Renal-Cell-Carcinoma-in-CheckMate--67T-Trial/default.aspx
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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.