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CASE (CemiplimAb-rwlc Survivorship and Epidemiology) study in advanced cutaneous squamous cell carcinoma

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In 2018, cemiplimab-rwlc became the first systemic treatment approved by the US FDA for patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. In 2019, conditional approvals were granted by Health Canada and the European Commission for the same indications. Limited data exist pertaining to the clinical characteristics, disease progression and survivorship of patients with advanced CSCC in real-world clinical practice. CemiplimAb-rwlc Survivorship and Epidemiology (CASE) is a prospective Phase IV, noninterventional, survivorship and epidemiology study that will enroll patients with advanced CSCC who have recently initiated or who plan to receive cemiplimab in a real-world setting. Trial registration number: NCT03836105.

Lay abstract: Cutaneous squamous cell carcinoma (CSCC) is a common form of skin cancer that is usually cured by surgery. When it progresses to a form that is incurable by surgery and/or radiotherapy, it is classified as advanced CSCC. Cemiplimab is a therapy that unleashes the immune system to fight cancer. It is the only treatment approved in the USA, Canada and Europe for the treatment of advanced CSCC. Little information exists on cemiplimab clinical experience outside of clinical trials. CASE is a Phase IV study that will collect outcomes data from patients with advanced CSCC receiving cemiplimab in a real-world setting.

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Keywords: advanced CSCC • cemiplimab • CSCC • cutaneous squamous cell carcinoma • epidemiology • PD-1 inhibitor • real-world data • survivorship

Cutaneous squamous cell carcinoma (CSCC) is one of the most common cancers worldwide and is rivaled in incidence only by basal cell carcinoma as the most common cancer in the USA [1,2]. In most cases, early stage CSCC can be cured by surgery [3]. However, a small percentage of patients develop advanced CSCC, a term that comprises metastatic CSCC and locally advanced CSCC no longer amenable to curative surgery and/or curative radiation. Radiotherapy alone or in combination with chemotherapy is an option for some patients with locally advanced CSCC who are not amenable to surgery. However, radiotherapy alone is associated with a recurrence rate of 30% for these patients [4,5].

Advanced CSCC is associated with high mortality rate and poor prognosis [6,7]. Until recently, there was no approved systemic therapy for patients with advanced CSCC, and systemic treatment options were often adopted from head and neck squamous cell carcinoma treatment regimens. Limited evidence shows that patients with advanced CSCC may respond to cytotoxic chemotherapy or targeted therapy such as EGFR inhibitors. However, efficacy of these treatments is moderate, the responses are rarely durable and the treatments are associated with significant toxicity [6,8,9].

Cemiplimab is a high-affinity, human, hinge-stabilized IgG4 monoclonal antibody to the PD-1 receptor that potently blocks the interactions of PD-1 with PD-ligand 1 and PD-ligand 2 [10]. Cemiplimab demonstrated substantial antitumor activity with durable responses in patients with metastatic or locally advanced CSCC in Phase I expansion cohorts and a Phase II study [11–13].

In the USA, cemiplimab-rwlc is the only FDA-approved treatment for patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation [14]. The National Comprehensive Cancer Network (NCCN) has included the aforementioned indications in their guidelines as a systemic therapy option [5]. In April 2019 and July 2019, Health Canada and the European Commission (EC), respectively, granted conditional approvals for, and the Brazilian Health Authority recommended the use of, cemiplimab for the aforementioned indications [15–17]. The UK National Institute for Health and Care Excellence has also recommended the use of cemiplimab, within the Cancer Drugs Fund, as an option for the treatment of the aforementioned indications [18].

Background & rationale

Given that CSCC data are not collected in most national cancer registries, there are limited data on the presenting clinical characteristics, therapeutic sequence, disease course, patient-reported outcomes and survivorship of patients with advanced CSCC in the real-world clinical setting. Recent approval of cemiplimab for this patient population presents an opportunity to identify disease characteristics of patients with advanced CSCC in real-world practice, and prospectively describe this patient group and evolution of their disease.

In routine clinical practice settings, patients will likely receive cemiplimab at various timepoints (e.g., first-line, second-line) in their respective treatment pathway of advanced CSCC. Some patients receiving treatment are also expected to have clinically relevant comorbid conditions (e.g., immunosuppression due to transplant/autoimmune disease or hematologic cancers such as chronic lymphocytic leukemia) that are commonplace in real life, even though patients with these conditions were excluded from registrational trials. Data from real-world experience with cemiplimab in advanced CSCC will assist in identifying treatment patterns, survivorship and epidemiologic aspects of the disease that have not yet been studied.

CASE study

CASE (CemiplimAb-rwlc Survivorship and Epidemiology; NCT03836105) is a Phase IV, multicenter, prospective, noninterventional, survivorship and epidemiology cohort study of patients with advanced CSCC receiving cemiplimab in the real-world. CASE is the first survivorship and epidemiology study of patients with advanced CSCC and is planned to represent the largest cohort of such patients receiving cemiplimab in a real-world setting. Here, we describe the design and rationale for CASE, which will collect long-term data on characteristics and survivorship of patients with advanced CSCC being treated with cemiplimab in clinical practice as their standard-of-care treatment, and fill evidence gaps in the management of advanced CSCC.

Objectives

The objectives of this study are to describe the effectiveness of cemiplimab 350 mg administered every 3 weeks intravenously in eligible patients, including in those who are immunosuppressed or immunocompetent, after prior exposure to radiotherapy, and as a first-line or later systemic treatment; to evaluate the safety of cemiplimab (based on the incidence of grade ≥ 3 immune-related adverse events, grade ≥ 2 infusion-related reactions and treatment-related serious adverse events) in eligible patients; to describe patient and clinical characteristics and potential associations with outcomes; to describe the use patterns of cemiplimab for the treatment of advanced CSCC; and to describe patient experience, including patient-reported quality of life (QoL), functional status and clinician-reported performance status in a real-world setting for patients with advanced CSCC.

Table 1. Inclusion & exclusion criteria.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Patients aged 18 years or older were eligible for treatment with cemiplimab for advanced CSCC in accordance with approved prescribing information: <ul style="list-style-type: none"> Patients who are continuing treatment with cemiplimab after completing cemiplimab treatment on the Phase II clinical trial of cemiplimab in advanced CSCC are eligible to participate in this study at the time that they initiate treatment with cemiplimab in a real-world setting; It is recommended that patients are enrolled prior to administration of their third dose of cemiplimab. Willingness and ability to comply with standard clinical care for advanced CSCC; Ability to understand and complete study-related questionnaires; Provision of signed informed consent. 	<ul style="list-style-type: none"> Treatment with cemiplimab for an indication other than advanced CSCC; Any condition that, in the opinion of the investigator, may interfere with patient's ability to participate in the study (e.g., unstable social situation such as homelessness, or psychiatric conditions such as schizophrenia, advanced depression, active substance abuse or severe cognitive impairment or other comorbidities) or other comorbidities that would, in the opinion of the investigator, predictably limit compliance with the intended treatment plan, or prevent adequate completion of QoL assessments; Concurrent participation in any study including those that involve administration of investigational therapy (including cemiplimab) or procedure (including survival follow-up).

CSCC: Cutaneous squamous cell carcinoma; QoL: Quality of life.

Table 2. Estimated precision (95% confidence interval) for various outcome event rates by sample size after dropout.

End point	%	95% CI by sample size			
		n = 250	n = 300	n = 350	n = 400
Objective response rate	45	38.8–51.2	39.4–50.6	39.8–50.2	40.1–49.9
Disease control rate	65	59.1–70.9	59.6–70.4	60.0–70.0	60.3–69.7
Overall survival at 12 months	80	75.0–85.0	75.5–84.5	75.8–84.2	76.1–83.9
Overall survival at 2 years	55	48.8–61.2	49.4–60.6	49.8–60.2	50.1–59.9
Grade ≥ 3 irAEs [†]	8	4.6–11.4	4.9–11.1	5.2–10.8	5.3–10.7
Grade ≥ 2 infusion-related reaction [‡]	3.7	1.4–6.0	1.6–5.8	1.7–5.7	1.9–5.5

[†] Per the European Union risk management plan at day 180.

[‡] Per Phase II study of cemiplimab in advanced CSCC (data cut-off of 27 October 2017) and Phase I study of cemiplimab in advanced CSCC (data cut-off was 2 October 2017 for patients with advanced CSCC who received cemiplimab monotherapy, and data cut-off was 1 September 2017 for all other patients).

CI: Confidence interval; irAE: Immune-related adverse event.

Design

Study design

CASE is a prospective, noninterventional, noncomparative longitudinal survivorship cohort study of adult patients with advanced CSCC receiving cemiplimab in the real-world setting. The type and frequency of patient visits and all evaluations will be performed as done in real-world clinical practice. Patients will be enrolled at up to 100 study sites in the USA. Study sites in other countries may be initiated after the approval and availability of cemiplimab in those countries. Implementation of the study protocol and all amendments require approval by the institutional review board and the ethics committee at each participating study site. The study is being conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Informed consents will be provided by patients before enrollment.

Eligibility criteria

Patients in this study will include men and women ≥ 18 years of age who have recently initiated, or are about to initiate, treatment with commercially available cemiplimab for advanced CSCC. Patients who meet all eligibility criteria (Table 1) will be included in the study. Patients who do not initiate cemiplimab within 4 weeks of signing informed consent may not participate unless they undergo additional screening and consent procedures; the reason for not initiating cemiplimab will be documented. These patients will be eligible to participate in the study with no waiting period should they subsequently provide informed consent and decide to start treatment with cemiplimab at a later date.

Planned sample size & study period

CASE will target enrollment of 350 patients with advanced CSCC in the USA based on the assumptions summarized in Tables 2 and 3. The planned duration of enrollment is approximately 24 months (Figure 1). If the target of 350 patients is reached prior to the 24-month enrollment period, no more than 500 patients will be enrolled. Each patient will be followed up for up to 36 months.

Table 3. Estimated precision (95% confidence intervals) of event rates per observed incidences of adverse events of special interest from cemiplimab clinical trials by sample size after dropout.

Sample size (n)	Observed event incidence (%)				
	0.5	0.7	1.0	5.0	7.0
350	0.0–1.2	0.0–1.6	0.0–2.0	2.7–7.3	4.3–9.7
300	0.0–1.3	0.0–1.6	0.0–2.1	2.5–7.5	4.1–9.9
250	0.0–1.4	0.0–1.7	0.0–2.2	2.3–7.7	3.8–10.2

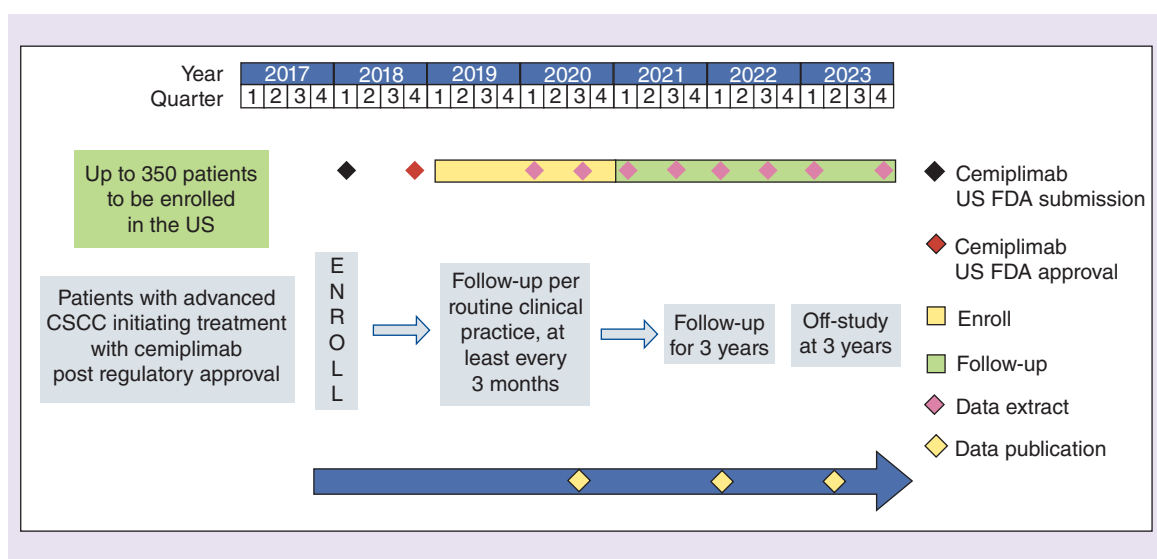


Figure 1. Study design. The target of 350 patients is for the US study only. CSCC: Cutaneous squamous cell carcinoma.

Study procedure

No investigational agents will be provided by the study sponsor to the patients enrolled in CASE. At each participating site, eligible patients will be screened and offered the opportunity to participate in the study until the enrollment goal is achieved. The decision to prescribe cemiplimab will be based solely on the clinical judgment of the treating physician per the participating investigator’s standard of care. Upon provision of informed consent and enrollment in the study, patients will be followed up by their treating physician per routine clinical practices with the longest or maximum elapsed time between clinical visits to be 3 months. All visits will be documented in the electronic case report forms.

After enrollment, patients will continue on study irrespective of cemiplimab treatment status (i.e., temporary or permanent discontinuation) for continued collection of data, unless consent is withdrawn by the patient. For patients who decline further participation from the study (i.e., decline to have data captured or decline to participate in patient-reported outcome documentation), information on survival will continue to be collected at 3-month intervals, for the full 36-month follow-up period, unless the patient withdraws consent to be followed up for survival. Patients may receive other therapies, in addition to cemiplimab, as deemed necessary by their physicians for the treatment of advanced CSCC or comorbid conditions.

Outcome measures

Patient and tumor baseline characteristics will be collected prior to the start of cemiplimab treatment in the real-world clinical treatment settings. Outcome measures of CASE include effectiveness of treatment, safety, treatment patterns and patient experience. Further details on each outcome measure are provided in [Box 1](#).

Statistical assumptions & analysis

Data will be requested for transcription to electronic case report forms. Records of laboratory tests, clinical notes, patient medical records, patient questionnaires and correspondence with other healthcare professionals (if

Box 1. Study outcomes of interest**Patient and tumor characteristics**

- Demographics;
- Comorbidity diagnoses and medication history;
- CSCC medical/surgical/radiation history;
- ECOG performance status;
- Other primary cancer with medical/surgical history;
- Baseline physical exam;
- HRQoL.

Treatment effectiveness

- Objective response rate per investigator assessment;
- Disease control rate per investigator assessment;
- Duration of response;
- Time to response;
- Progression-free survival;
- Overall survival;
- Time to treatment failure, including lack of response and discontinuation due to adverse events;
- Disease-specific death rate;
- Pattern of response and pattern of recurrence;

Safety

- Treatment-related irAEs and IRRs per physician assessments. Data will be coded and categorized using MedDRA and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5;
- Treatment-related SAEs per physician assessments, coded and categorized using MedDRA.

Treatment patterns & related outcomes

- Interventions for advanced CSCC treatment (e.g., surgery, radiation, drug therapy) prior to the initiation of cemiplimab treatment, if applicable;
- Pattern of response and pattern of recurrence;
- Concomitant medications;
- Treatment of irAEs (e.g., systemic corticosteroids, noncorticosteroid treatment and hormone-replacement therapies);
- Determinants of disease sequelae (recurrence, metastasis);
- Longitudinal effectiveness of advanced CSCC interventions;
- Duration of treatment prior to cemiplimab;
- Health services utilization;
- Reason for discontinuation of cemiplimab (e.g., lack of effectiveness, adverse events, complete response or prolonged partial response);
- Interventions for advanced CSCC treatment (e.g., surgery, radiation, drug therapy) following initiation of cemiplimab treatment, including dates of administration, premedications administered (if any), dosage and administration details, reasons for and dates of dose delays and reason for and dates of treatment discontinuation.

Patient experience

- HRQoL and disease-related symptoms will be captured at baseline and follow-up visits using the following tools:
 - EORTC QLQ-C30: to assess HRQoL across five functional scales (physical, role, emotional, cognitive, social), a global health status/QoL scale, three symptom scales (fatigue, nausea and vomiting and pain), and six individual symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties);
 - EORTC QLQ-ELD14: five scales (mobility, worries about others, worries about future, maintaining purpose, burden of illness), two single items (joint stiffness and family support);
 - SCI: three scales (emotional, social, appearance);
 - Pain NRS: to assess pain intensity;
 - SEBI: to assess exposure to sun.

CSCC: Cutaneous squamous cell carcinoma; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL: Health-related QoL; irAE: Immune-related adverse event; IRR: Infusion-related reaction; MedDRA: Medical Dictionary for Regulatory Activity; NRS: numeric rating scale; QoL: Quality of life; SAE: Serious adverse event; SCI: Skin cancer index; SEBI: Sun exposure and behavior inventory; .

applicable) in the patient files will be the original source documents. There is no formal statistical hypothesis to test nor a planned inferential comparison. Data will be summarized descriptively (for continuous variables), by frequencies and percentages (for categorical and ordinal data) or by Kaplan–Meier estimation and duration-adjusted statistics (for time to event).

Discussion

There is limited information on overall disease burden, health status, QoL and survivorship of patients with advanced CSCC and those receiving cemiplimab in the real-world clinical setting. While clinical trials are important for evaluating medical benefits of treatments for various cancers, real-world data are becoming increasingly important in healthcare decision making as they provide evidence on long-term treatment effectiveness and safety in clinical practice in a patient cohort more reflective of day-to-day clinical practice [19,20]. Currently available real-world evidence for advanced CSCC are mainly based on retrospective analyses [6,21]. A real-world study with prospective evaluation of patients, long study period and long patient follow-up, such as in CASE, provides an opportunity for collection of robust data on patients with advanced CSCC.

The Phase II study of cemiplimab in advanced CSCC was the largest prospective clinical trial of patients with advanced CSCC receiving systemic therapy [11]. However, there is still a need to continue to expand available clinical data on CSCC treatment outcomes including efficacy, safety, treatment patterns and QoL of patients treated with cemiplimab. Prior to September 2018, there was no approved systemic therapy for treating advanced CSCC. Furthermore, due to limited available evidence, there is lack of consensus on treatment approach (surgery, radiation, systemic therapy) for patients with this disease. Given that cemiplimab is the first systemic agent approved for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation [14], there is a need for a pragmatic study to better understand the disease and clinical benefit of the approved treatment outside of a clinical setting.

The drivers of this undertaking are relevant to clinical practice and outcomes-based investigation. While clinical trials often include eligibility criteria that aim to ensure homogenous and representative patient populations, these criteria may exclude patients with certain disease characteristics and/or comorbidities such that available evidence from the clinical trial can only be extrapolated to patients with a similarly narrow clinical makeup. As an example, in the Phase II study of cemiplimab in advanced CSCC, patients who had undergone solid organ transplantation or those who were immunosuppressed were excluded [11]. As such, the clinical benefit of cemiplimab in those groups of patients is unknown. In the real-world setting, treatment decisions are dependent on multiple patient factors. Strict eligibility criteria such as those imposed in a clinical study will most likely not apply in real-world clinical practice. Hence, CASE may be able to help bridge the evidence gap and provide clinicians with real-world data on the potential clinical benefit of cemiplimab in patient groups not included in the clinical trials.

Given the rapidly evolving treatment landscape but limited supporting evidence for broad, population-based cancer care, a multidisciplinary working group (consisting of the American College of Surgeons Commission on Cancer, the American Society for Radiation Oncology, the American Society of Clinical Oncology, the Society of Interventional Radiology, and the Society of Surgical Oncology) recently provided consensus recommendations on approaches to fill knowledge gaps where a controlled randomized clinical trial is absent, not achievable or not necessary in cancer research [22]. The recommendations include promotion of cross-disciplinary research, conduction of more pragmatic studies, use of health information technology to facilitate observational research and use of reimbursement strategies to incentivize evidence development [22].

CASE is a prospective analysis of outcomes and long-term effectiveness of cemiplimab in patients with advanced CSCC, and moreover promotes cross-disciplinary research between treating dermatologists, surgeons, radiation oncologists and medical oncologists. Furthermore, CASE will not only collect real-world evidence relating to cemiplimab, but also collect and analyze additional information such as the medical history, prior treatments, outcomes and progression patterns of patients participating in the study. Finally, CASE will also collect patient-reported outcomes, a patient perspective that provides a value-based assessment of treatment [23], and thus supplement evidence generated during clinical trials.

CASE is currently only opened for enrollment in the USA; additional study sites outside of the USA may be opened upon approval in those countries. Furthermore, as CASE is a survivorship study of cemiplimab in the real-world setting, the study may be extended to additional tumor types based upon approval within those indications.

Conclusion

Until recently, there was no approved systemic therapy for patients with advanced CSCC. Currently, cemiplimab-rwlc is the only systemic treatment approved by the US FDA for the treatment of patients with advanced CSCC [14]. It has also received conditional approval in the European Union and Canada, and a recommendation by the Brazilian Health Authority, for the aforementioned indications [15–17]. The UK National Institute for Health

and Care Excellence has also recommended the use of cemiplimab (within the Cancer Drugs Fund) for the same indications [18], and additional reimbursement approvals/recommendations in other countries are expected over time. With the emerging need for insight on the clinical characteristics, disease course and survivorship of patients with advanced CSCC receiving cemiplimab in the real-world clinical setting, CASE will provide an opportunity to collect long-term data on the use of cemiplimab in clinical practice and fill evidence gaps in the management of patients with advanced CSCC in the real world.

Executive summary

Advanced cutaneous squamous cell carcinoma

- A small percentage of patients with cutaneous squamous cell carcinoma (CSCC) develop advanced CSCC, a term that comprises metastatic CSCC and locally advanced CSCC not amenable to curative surgery and/or radiotherapy.
- Cemiplimab-rwlc is the only US FDA approved treatment for patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation.
- The NCCN guidelines have included the aforementioned indications in their guidelines as a systemic therapy option.
- Health Canada and the EC granted conditional approvals of, and the Brazilian Health Authority and the UK National Institute for Health and Care Excellence recommended cemiplimab for the aforementioned indications.

CASE study

- There is limited information on the presenting clinical characteristics, therapeutic sequence, disease course, patient-reported outcomes and survivorship of patients with advanced CSCC in real-world clinical practice.
- CASE is a prospective survivorship and epidemiology cohort study of patients with advanced CSCC receiving cemiplimab in the real-world setting.
- CASE will collect long-term data from patients with advanced CSCC being treated with cemiplimab in clinical practice and fill evidence gaps in the management of advanced CSCC.

Objectives

- To describe the effectiveness of cemiplimab 350 mg administered every 3 weeks intravenously in eligible patients, and:
 - In immunosuppressed and immunocompetent patients;
 - After prior exposure to radiotherapy;
 - As a first-line or later systemic treatment.
- To evaluate the safety of cemiplimab (based on the incidence of Grade ≥ 3 immune-related adverse events, Grade ≥ 2 infusion-related reactions and treatment-related serious adverse events) in eligible patients.
- To describe patient and clinical characteristics and potential associations with outcomes.
- To describe the real-world use patterns of cemiplimab for the treatment of advanced CSCC.
- To describe patient experience, including patient-reported QoL and functional status and clinician-reported performance status in a real-world setting.

Study design & eligibility

- Patients will include men and women ≥ 18 years of age who have recently initiated or who plan to initiate treatment with commercially available cemiplimab for the treatment of advanced CSCC in real-world clinical settings.
- The type and frequency of patient visits and all evaluations will be performed as done in real-world clinical practice.
- Approximately 350 patients will be enrolled at up to 100 study sites in the USA.
- No investigational agents will be provided by the study sponsor; the decision to prescribe cemiplimab will be based solely on the clinical judgment of the treating physician per the local standard of care.

Outcome measures of interest

- Patient and tumor characteristics.
- Treatment effectiveness.
- Safety.
- Treatment patterns and related outcomes.
- Patient experience.

Author contributions

All authors were involved in the conception and development of this clinical trial protocol article. All authors critically reviewed and provided approval of the final article.

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R Charnas from the study sponsors reviewed and provided editorial comments on the manuscript. The sponsor was involved in the study design and fact checking of information provided in the manuscript. The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

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Ethical conduct of research

The investigators are obtaining the appropriate institutional review board approval and will follow the principles outlined in the Declaration of Helsinki. In addition, informed consent will be obtained from the participants involved.

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