

Concurrent Radiotherapy and Ipilimumab Immunotherapy for Patients with Melanoma

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Abstract

Ipilimumab and radiotherapy are commonly used to treat unresectable and metastatic melanoma. Results from preclinical studies and case reports suggest a biologic interaction between these two treatments. To understand the clinical implications of the interaction, we carried out a retrospective study reviewing records of patients treated with ipilimumab and radiotherapy for melanoma at our institution between 2005 and 2011. The review included details of treatment, response, adverse events (AE), and overall survival (OS). Twenty-nine patients underwent 33 courses of non-brain radiotherapy between their first and last dose of ipilimumab. Immune-related AEs (ir-AEs) were observed in 43% of patients receiving ipilimumab at 10 mg/kg and in 22% of patients receiving 3 mg/kg; the frequency of ir-AEs was not significantly different compared with previous studies of ipilimumab alone. Radiotherapy-related AEs were significantly more common in patients receiving higher doses of radiation. Palliation of symptoms was reported by 77% of patients after radiotherapy. Median OS was 9 and 39 months in patients receiving radiotherapy during induction and maintenance with ipilimumab, respectively. In this retrospective study, concurrent ipilimumab and radiotherapy was neither associated with higher than expected rates of AEs nor did it abrogate palliative effects of radiotherapy or survival benefits of ipilimumab. Further studies to prospectively explore the efficacy of this therapeutic combination are warranted. *Cancer Immunol Res*; 1(2); 92–98. ©2013 AACR.

Introduction

Ipilimumab is a monoclonal antibody that blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a negative regulator of T-cell function, which is essential for maintaining immunologic homeostasis. By blocking CTLA-4, ipilimumab disinhibits T cells and increases the immune response to cancer. Ipilimumab was approved in March 2011 by the U.S. Food and Drug Administration (FDA) for treatment of patients with unresectable and metastatic melanoma based on results from two randomized controlled trials showing an improvement in overall survival (OS). Although response rates are modest (10–15%), ipilimumab is a standard management strategy for metastatic and unresectable melanoma (1, 2).

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Radiotherapy is used frequently in the management of metastatic melanoma. A recent study estimated that 45% of patients with metastatic melanoma receive radiotherapy during the course of their disease (3). A prospective study reported that palliative radiotherapy can be given to relieve symptoms (pain, neurologic impairment, hemorrhage, obstruction, dyspnea, or cough) or to prevent impending symptoms (pain, neurologic impairment, ulceration, or obstruction). Radiotherapy relieves pain in two-thirds of treated patients with melanoma (4).

Radiotherapy may modulate the immunotherapeutic effects of CTLA-4-blockade by ipilimumab. In a murine mammary carcinoma model, CTLA-4 blockade alone did not affect tumor growth or survival. However, when CTLA-4 blockade was combined with tumor radiotherapy, OS improved significantly. This effect seemed to be dependent on CD8⁺ T and invariant natural killer cells (5). Results from a follow-up study indicated that hypofractionated high-dose radiotherapy was necessary to elicit antitumor immune effects (6).

Little is known about the clinical effects of combining ipilimumab and radiotherapy. Previous studies reported high rates of adverse events (AE) when radiotherapy was combined with other immunotherapies, such as interferon (7–9). Moreover, lymphocytes are exquisitely sensitive to radiotherapy. As ipilimumab affects lymphocytes directly, radiotherapy could potentially diminish the immunotherapeutic effects.

Two recent case reports showed remarkable responses to ipilimumab only after non-brain radiotherapy treatment

(10, 11). This result supports the preclinical work described above and suggests synergy of this combination approach. Results from case series of palliative brain radiotherapy combined with ipilimumab for patients with metastatic melanoma have also indicated synergy (12–15). Therefore, we conducted a systematic, retrospective analysis of the toxicity and efficacy of ipilimumab and non-brain radiotherapy in records of patients with melanoma. The goal of the study was to analyze the safety profile of non-brain radiotherapy given during ipilimumab immunotherapy to establish a foundation for prospective trials assessing the efficacy of this promising combination for patients with melanoma.

Materials and Methods

Patients

Medical record review was conducted with permission of the institutional review board (WA0194-11). Patients with unresectable stage III and stage IV melanoma, who received ipilimumab immunotherapy between February 21, 2005 and August 16, 2011, were identified in our institutional databases. Among this group of patients, those who received treatment with non-brain radiotherapy between the first and last dose of ipilimumab were chosen for the study. Demographic information on patient, disease, and treatment characteristics at the time of starting ipilimumab (sex, age, type of melanoma, time since initial diagnosis of melanoma, presence of visceral or brain metastases, lactate dehydrogenase, courses of prior systemic and radiotherapies) were used for the analysis.

Therapy and adverse events

Medical record review focused on details of dose, date, and phase of ipilimumab administration. Radiotherapy was delivered during the induction or maintenance phase of ipilimumab administration. During the induction phase, radiotherapy occurred between the first and fourth doses of ipilimumab, or within 16 weeks of starting ipilimumab; during the maintenance phase, radiotherapy began after the last induction dose more than 16 weeks after starting ipilimumab. Common terminology criteria for AEs (CTCAE v4.0) grade 3 or higher

immune-related AEs (ir-AEs) were recorded. Radiotherapy record review focused on details including the target of treatment, treatment intent, total dose, fractionation, and dates of treatment. Equivalent radiation doses for melanoma in 2 Gy fractions (EQD2) were calculated using the α/β of melanoma (0.6). Irradiated organs were assessed for CTCAE (v4.0) grade 3 or higher AEs. Average absolute lymphocyte count (ALC) during the 12-week period before and after the initiation of radiotherapy was recorded.

Treatment response

The local effect of radiotherapy was recorded (in-field disease control for postoperative radiotherapy, improvement, or prevention of symptoms for palliative radiotherapy). Given the heterogeneous and delayed responses to ipilimumab, we focused on efficacy analyses of time to treatment failure (TTF) and OS (16). TTF was defined as the interval from ipilimumab start to last follow-up, death, or the start of a different systemic therapy. OS was defined as the interval from ipilimumab start to last follow-up or death.

Statistical analysis

Summaries of the statistical analysis are presented. Fisher exact test was used to calculate differences in the frequency of grade ≥ 3 AEs (two-sided, $\alpha = 0.05$). A paired *t* test (two-sided, $\alpha = 0.05$) was used to compare average ALC before and after radiotherapy. Kaplan–Meier methods were used to estimate TTF and OS. Statistical analyses were conducted using Win-STAT for Microsoft Excel, version 2009.1.

Results

Patients

Between February 21, 2005 and August 16, 2011, 333 patients received ipilimumab immunotherapy for melanoma at our institution (Fig. 1). Half (49.8%) of these patients also received linear accelerator-generated radiotherapy for melanoma. Many patients received several courses of brain and non-brain radiotherapy before, during, and after ipilimumab treatment. Radiotherapy was most frequently given to non-brain targets.

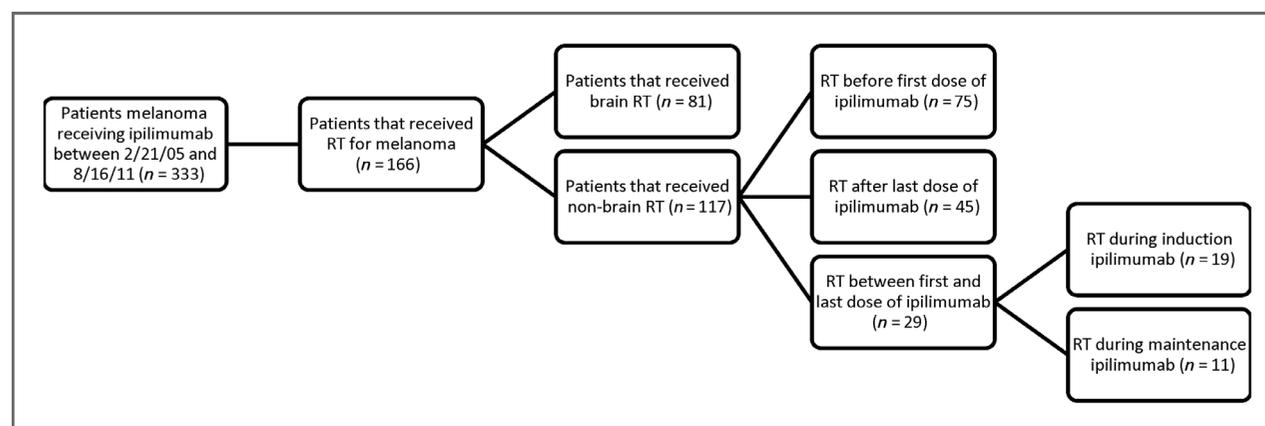


Figure 1. Distribution of patients that received ipilimumab and radiotherapy (RT) for melanoma. Patients with melanoma that received ipilimumab between February 21, 2005 and August 16, 2011 at our institution were studied.

Twenty-nine patients (8.7%) underwent 33 courses of non-brain radiotherapy between the first and last dose of ipilimumab. One patient (#21) received radiotherapy during induction and maintenance phases of ipilimumab. Most patients (22.5%) underwent non-brain radiotherapy before the first dose of ipilimumab, whereas other patients (13.5%) underwent non-brain radiotherapy after receiving the last dose of ipilimumab. Median follow-up of all patients after starting ipilimumab was 11 months. Median follow-up of survivors after starting ipilimumab was 34 months.

Characteristics of patients receiving radiotherapy during ipilimumab treatment are presented in Table 1. Most patients

were male, with recurrent, previously treated, metastatic cutaneous melanoma at the time of starting ipilimumab. Few patients had brain metastases when starting ipilimumab, but most had visceral metastases.

Treatment and adverse effects

The median doses of ipilimumab and radiotherapy were 10 mg/kg and 30 Gy, respectively. Most patients (69%) were treated on ipilimumab research protocols (CA184045, CA184087, CA184008, CA184078, CA184022, CA184042, and CA209004). Table 2 describes treatment parameters among patients experiencing a grade ≥ 3 AE.

Table 1. Patient and disease characteristics

	Radiotherapy during induction ipilimumab (n = 18 patients)	Radiotherapy during maintenance ipilimumab* (n = 11 patients)
Sex		
Male	14	8
Female	4	3 ^a
Age at start of ipilimumab, y		
Median (range)	60 (21–77)	57 (39–74)
Melanoma origin		
Cutaneous	12	9
Uveal	2	1 ^a
Mucosal	2	1
Unknown	2	0
Interval from diagnosis to M/R recurrence, mo		
Median (range)	11 (0–74)	55 (6–218)
Courses of therapies for M/R melanoma before ipilimumab		
Systemic		
Median (range)	1 (0–4)	1 (0–6)
Non-brain radiotherapy		
Median (range)	0 (0–1)	1 (0–2)
At start of ipilimumab		
ECOG performance status		
0	1	2
1	17	9 ^a
2	0	0
Brain metastasis		
No	13	9 ^a
Yes	5	2
Visceral metastasis		
No	2	1
Yes	16	10 ^a
Lactate dehydrogenase (IU/L)		
Median	259	195
Range	122–2292	154–599
AJCC M stage		
M0 (unresectable)	2	0
M1a	0	1
M1b	2	1
M1c	14	9 ^a

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; M/R, metastatic/unresectable.

^aIncludes one patient that received radiotherapy during induction and maintenance ipilimumab.

Table 2. Grade ≥ 3 adverse events during radiotherapy and ipilimumab

Patient number	Ipilimumab treatment dose (mg/kg)	Cumulative ipilimumab dose (mg/kg)	Cumulative ipilimumab dose (mg/kg) at start of radiotherapy	Phase of ipilimumab radiotherapy given	RT dose (Gy)	Number of radiotherapy fractions	EQD2 (0.6)	Radiotherapy site	Grade ≥ 3 AE	Time from ipilimumab start to AE (days)	Time from radiotherapy start to AE (days)	AE Attribution
1	10	40	10	Induction	24	1	227	T12 Vertebral metastasis	Grade 3 cytokine release	7	3	ir and/or rr
1	10	40	10	Induction	24	1	227	T7 Vertebral metastasis	Grade 3 cytokine release	7	2	ir and/or rr
3	3	6	3	Induction	25	10	30	Left base of skull tumor	Grade 3 diarrhea	36	32	ir
6	10	40	10	Induction	30	10	42	Right humeral metastasis	Grade 3 transaminase elevation	104	100	ir
7	10	20	0	Induction	62.5	25	75	Left axillary lymphadenopathy	Grade 3 transaminase elevation and rash	63	94	ir
9	3	12	6	Induction	30	10	42	Conus medullaris metastasis	Grade 3 maculopapular rash ^b	98	64	ir
13	3	12	6	Induction	28.5	3	111	Sacral metastasis	Grade 3 thrombocytopenia	50	22	rr
15	3	9	6	Induction	30	3	122	Right suboccipital lymphadenopathy	Grade 3 transaminase elevation	35	(Before radiotherapy)	ir
21	10	160	30	Induction	20	5	35	Base of skull metastasis ^a	Grade 4 uveitis	1,186	1,126	ir and/or rr
22	10	110	80	Maintenance	28.5	3	111	T7 Vertebral metastasis	Grade 3 radiculitis	927	477	rr
24	10	170	160	Maintenance	30	10	42	Upper abdominal lymphadenopathy	Grade 3 pruritus	1,328	293	ir
29	10	50	30	Maintenance	30	5	76	Right hilar lymphadenopathy	Grade 3 transaminase elevation	41	(Before radiotherapy)	ir

Abbreviations: EQD2, equivalent dose in 2 Gy fractions with α/β of 0.6; ir, immune related; rr, radiation related.^aSecond course of radiotherapy to this site.^bRash occurred outside radiotherapy field, after vemurafenib.

Grade ≥ 3 ir-AEs were more frequent in patients receiving ipilimumab at 10 mg/kg (43%) than at 3 mg/kg (20%; Supplementary Table S1). Comparing the present data with historic results, statistical analysis using Fisher exact test did not show significant difference in the frequency of grade ≥ 3 ir-AEs at 3 mg/kg ($P = 0.70$), or at 10 mg/kg ($P = 0.20$; refs. 1, 17).

The frequency of grade ≥ 3 AEs in irradiated organs was 15% for the 33 courses of radiotherapy given during ipilimumab treatment. One grade 4 event was noted in a previously irradiated organ that was reirradiated. Among patients not having the same target reirradiated, EQD2(0.6) more than 100 Gy was associated with radiation-related AEs by Fisher exact test (44% vs. 0%, $P = 0.004$).

Average ALC decreased after 27 of 33 courses (82%) of radiotherapy. The average ALC was significantly lower after radiotherapy (0.93 k/ μ L) than before radiotherapy (1.34 k/ μ L, $P < 0.005$).

Local treatment response, TTF, and OS

Symptom alleviation was noted after 17 of 22 (77%) courses of radiotherapy given for palliation; 3 patients were not reassessed for symptoms after radiotherapy and 2 patients experienced symptom progression. None of the 9 patients treated to prevent symptoms from metastatic melanoma developed symptoms. Two patients underwent postoperative radiotherapy after resection of metastatic melanoma and did not develop locoregional recurrence with follow-up of 5 and 56 months.

Twelve patients (41%) were treated with a different systemic therapy after receiving ipilimumab and radiotherapy, following clinician-determined treatment failure. Nine of the 19 patients (47%) receiving radiotherapy during the induction phase of ipilimumab treatment changed systemic therapy and 3 of 11 (27%) receiving radiotherapy during the maintenance phase of ipilimumab treatment also changed systemic therapy. Median TTF was 5 months for patients undergoing radiotherapy during induction ipilimumab and 39 months for patients undergoing radiotherapy during maintenance ipilimumab. Median OS was 9 months for patients undergoing radiotherapy during induction ipilimumab and 39 months for patients undergoing radiotherapy during maintenance ipilimumab (Fig. 2).

Discussion

This study was designed to assess the safety of concurrent non-brain radiotherapy and ipilimumab immunotherapy in patients with melanoma. Prior research suggested that radiotherapy during immunotherapy might be associated with high rates of AEs (7–9). Moreover, CTLA-4 blockade targets lymphocytes, which are known to be exquisitely sensitive to radiation, but it was not known whether radiotherapy might compromise the benefit of ipilimumab treatment. We found that the rates of local AEs or systemic ir-AEs were not increased with concurrent radiotherapy and ipilimumab treatment. Furthermore, combining these treatments did not compromise the local and survival benefits of radiotherapy and ipilimumab, respectively.

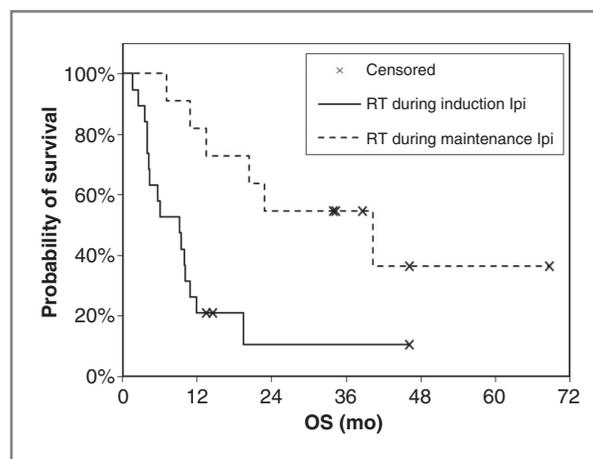


Figure 2. Overall survival in patients undergoing radiotherapy (RT) during induction or maintenance ipilimumab (ipi) immunotherapy. OS was calculated from time of start of ipilimumab to time of death or last follow-up.

Of the 333 patients who received ipilimumab immunotherapy for metastatic or unresectable melanoma at our institution, 49% also received radiotherapy. This is consistent with results from a previous study based on an analysis of a United States medical claims database indicating that 45% of patients with metastatic melanoma receive radiotherapy (3). However, of all patients receiving ipilimumab for melanoma, very few (8.7%) received non-brain radiotherapy between their first and last doses of ipilimumab. This could be because of the short duration of immunotherapy relative to the longer duration of time that many patients live with metastatic melanoma. Alternatively, radiotherapy may not have been permitted as part of the treatment on research protocols. Likewise, clinicians may have been reluctant to prescribe radiotherapy during ipilimumab immunotherapy because of concerns about excessive toxicity or compromised efficacy.

We found that ir-AEs were more common in patients receiving a higher dose of ipilimumab (10 mg/kg), which is not the dose currently approved for use by the FDA. In a randomized dose-finding study of ipilimumab, it was found that higher doses of ipilimumab were associated with higher rates of grade 3–4 ir-AEs (7% at 3 mg/kg, 25% at 10 mg/kg, $P = 0.005$ by Fisher exact; ref. 17). Results from another study indicated that the rate of grade 3–4 ir-AEs was 38% to 42% with ipilimumab at 10 mg/kg (18). In the present study, the frequency of grade ≥ 3 ir-AEs was higher (20% at 3 mg/kg and 43% at 10 mg/kg) than previously reported, but this was not statistically different from historical controls. Further study will be necessary to validate this finding.

In previous studies, high rates of AEs were found when combining immunotherapy with radiotherapy for melanoma. Several retrospective studies have shown high rates of radiation-associated necrosis, myelitis, and dermatitis when radiotherapy was given during or within 4 weeks of interferon administration (7–9). However, results from a recent prospective phase I/II trial indicated that acute and long-term toxicity were not associated with higher than expected rates of AEs

when combining interferon and adjuvant radiotherapy (19). Additional research is needed to determine whether combining radiotherapy and immunotherapy is associated with AEs.

Little data exist on the safety of combining ipilimumab and radiotherapy. A recent case series found higher than expected rates of brain necrosis after radiosurgery with 20 Gy in 1 fraction (EQD2 of 158 Gy; ref. 12). However, a prospective trial of patients with prostate cancer revealed no increase in toxicity with ipilimumab during 8 Gy in 1 fraction (EQD2 of 26 Gy; ref. 20). We found that the likelihood of AEs in radiotherapy is associated with higher radiation doses, which is consistent with these studies. Therefore, attention to radiation dose may be particularly important for patients receiving ipilimumab.

Therapies that block CTLA-4, such as ipilimumab, result in the activation and proliferation of lymphocytes. Ipilimumab treatment has been shown to lead to an increase in the ALC (17, 21). This effect may be important, as longer survival has been shown in patients with greater increases in ALC as well as higher levels of ALCs at various time points after the initiation of ipilimumab (21–24). As radiotherapy is known to be associated with lymphopenia, we explored the changes in ALC after radiotherapy. In the present study, a statistically significant reduction in 12-week average ALC was noted after radiotherapy. However, despite a reduction in the ALC after radiotherapy, there did not appear to be a negative effect on survival after treatment with ipilimumab. Future studies to characterize the immunologic response to radiotherapy and ipilimumab are necessary to better understand the significance of this finding.

The local symptomatic response to palliative radiotherapy in the present study was 77%, which is consistent with a 67% response rate found in a previous study of palliative radiotherapy for patients with metastatic melanoma (4). Postoperative locoregional radiotherapy was used infrequently among the present cohort, but no recurrences were noted in the irradiated targets, suggesting successful locoregional disease control.

Median OS of 9 months after radiotherapy during induction ipilimumab is comparable with the median survival of patients with unresectable or metastatic melanoma that failed a prior therapy and were treated with ipilimumab (3 mg/kg) alone (10.1 months, 95% confidence interval, 8.0–13.8 months; ref. 1). However, median OS among those receiving radiotherapy during maintenance ipilimumab (at 10 mg/kg) was 39 months. Previous studies have suggested longer OS in patients receiving ipilimumab at 10 mg/kg (median OS of 17.7–19.3 months), although studies comparing survival at these two doses are still ongoing (NCT01515189; ref. 18). The greater than expected median OS in patients receiving radiotherapy during maintenance ipilimumab is probably due to selection bias introduced by the protocol requirements. Maintenance therapy is not offered outside of a clinical trial and is not included in the FDA label for ipilimumab. However, the finding is provocative and suggests that if radiotherapy modifies the effect of ipilimumab, the timing and/or sequence of treatment may be important.

The present analysis has several limitations. First, the retrospective nature of the design may have led to under-reporting of AEs. Most patients treated with ipilimumab at our

institution were enrolled on clinical trial protocols. Therefore, follow-up and documentation of AEs and response is robust, but not prospectively recorded for the present analysis. Second, the present cohort is heterogeneous and the treatments rendered varied. This limitation is inherent in retrospective clinical research. As an exploratory and hypothesis-generating analysis, the present data may offer insight for the design of future studies combining radiotherapy and ipilimumab immunotherapy. Because ipilimumab is a relatively new therapy for melanoma, this series likely represents the largest experience with the combination of ipilimumab and radiotherapy at the present time.

The combination of ipilimumab and radiotherapy has generated considerable interest, and several prospective trials are currently underway to further characterize the safety and efficacy of this approach (Supplementary Table S2). Our retrospective study characterized the feasibility, toxicity, and preliminary efficacy of ipilimumab and radiotherapy given concurrently for patients with melanoma. We found that the AE rates for the combined regimen were not higher than expected, and that the local effect of radiotherapy or the survival benefit of ipilimumab immunotherapy was not compromised. These results suggest that future and ongoing studies combining radiotherapy and ipilimumab are warranted. Until results of ongoing studies are available, our experience suggests that combining radiotherapy with ipilimumab to treat patients with melanoma is safe if both are used cautiously.

Disclosure of Potential Conflicts of Interest

M.A. Postow has a commercial research grant and is a consultant/advisory board member of Bristol-Myers Squibb. Y. Yamada has honoraria from speakers' bureau from Institute for Medical Education and is a consultant/advisory board member of Varian Medical Systems. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: C.A. Barker, M.A. Postow, Y. Yamada
Development of methodology: C.A. Barker, M.A. Postow, Y. Yamada
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.A. Barker, M.A. Postow, K. Beal, Y. Yamada, N.Y. Lee, J.D. Wolchok
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.A. Barker, M.A. Postow, N.Y. Lee, J.D. Wolchok
Writing, review, and/or revision of the manuscript: C.A. Barker, M.A. Postow, K. Beal, P.K. Parhar, Y. Yamada, N.Y. Lee, J.D. Wolchok
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.A. Barker, S.A. Khan, J.D. Wolchok
Study supervision: C.A. Barker

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