after application, and an anti-itch effect persists at 2 hours after administration. A particularly favorable condition to be alleviated with this gel is urticaria. The standard treatment of urticaria is oral H_1 receptor antagonists, but antihistamines require at least 1 hour for the onset of drug action. Sometimes these drugs have poor patient adherence, such that symptoms of lack of sleep and itch persist. Patients may prefer a topical medication with instant relief of itch, within minutes if possible. Here, we present evidence that Cryosim-1 has the potential to be a drug for the immediate relief of itch, making it a valuable addition to the treatment of itching.

Min Je Jung, MD,[a] Jin Cheol Kim, MD,[a] Edward Tak Wei, PhD,[b] Tudor Selescu, PhD,[c] Bo Young Chung, MD, PhD,[a] Chun Wook Park, MD, PhD,[a] and Hye One Kim, MD, PhD[a]

From the Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea[a]; School of Public Health, University of California, Berkeley, California[b]; and Department of Anatomy, Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucuresti, Romania.[c]

Drs Jung and Kim contributed equally to this article.

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Correspondence to: Hye One Kim, MD, PhD, Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Korea

E-mail: hyeonekim@gmail.com

Chun Wook Park, MD, PhD, Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Korea

E-mail: dermap@daum.net

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Incidence of dermatologic adverse events in patients with cancer treated with concurrent immune checkpoint inhibitors and radiation therapy: A systematic review and meta-analysis

To the Editor: Among cutaneous adverse events (CAEs) from immune checkpoint inhibitors (ICIs), rash and pruritus are the most common.[1] It is unknown if concurrent ICIs and radiotherapy (RT) increase their frequency and severity. We performed a systematic review and meta-analysis to characterize the incidence of all-grade and severe (grade 3 or 4) rash and pruritus in patients on concurrent ICI and RT regimens.

Studies published on or before March 20, 2020, were identified by using the following search terms on PubMed: "(ipilimumab OR Yervoy OR pembrolizumab OR Keytruda OR cemiplimab OR Libtayo OR nivolumab OR Opdivo OR tremelimumab OR ticilimumab OR atezolizumab OR Tecentriq OR avelumab OR Bavencio OR durvalumab OR Imfinzi) AND (radiotherapy OR radiation) AND (adverse events OR adverse effects OR toxicity OR safety)."

The inclusion criteria were as follows: (1) clinical trial, (2) concurrent ICIs and RT, and (3) the outcomes examined included CAEs. Studies were excluded if they did not specify the type of CAE.

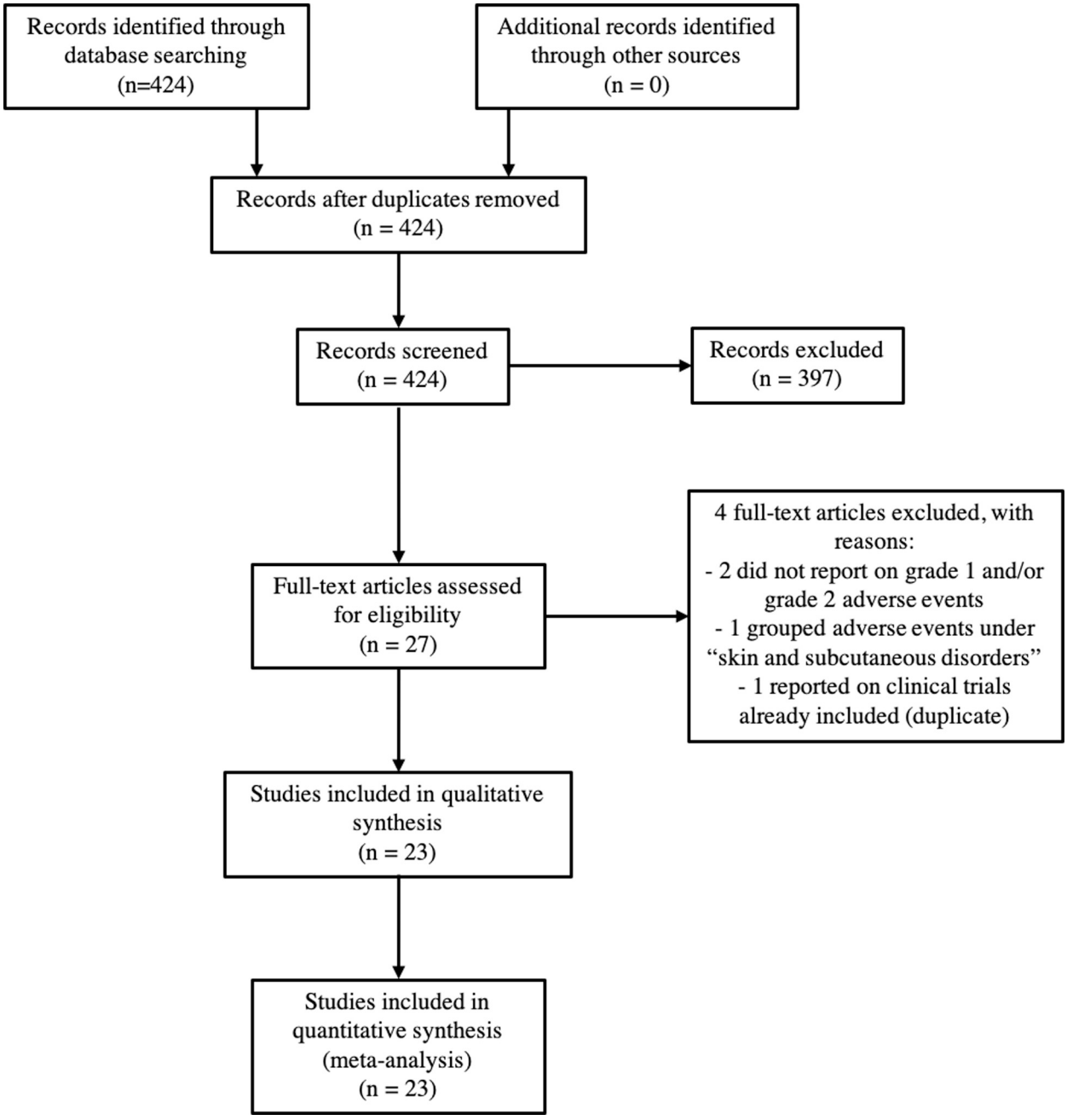

Fig 1. Flow diagram of study selection.

There were 424 eligible articles (Fig 1). A total of 23 articles, including 12 phase 1, 7 phase 2, 2 phase 1/2, and 2 phase 3 trials, were included, totaling 1504 patients (Table I). The most common cancers per study were non–small-cell lung cancer (26%) and various cancers (17%). The most common ICI classes were PD-1 inhibitors (48%) and CTLA-4 inhibitors (35%). The equivalent radiation dose if administered in 2-Gy fractions was calculated and classified as high or low by using a cutoff of 50 Gy. The time between ICI and RT administration was 0 to 42 days.

Using random-effects models, the overall incidences of all-grade and severe rash were 22% (95% confidence interval [CI], 16-29) and 3% (95% CI, 2-5), respectively. This is comparable to reported incidences of 14.3% to 24.3% and 1.2% to 2.4%, respectively, with ICI monotherapy.[2,3] Differences in rash incidence with varying ICI classes ($P = .47$) or radiation dose ($P = .29$) were not found.

The pooled incidences of all-grade and severe pruritus were 14% (95% CI, 10-19) and 2% (95% CI, 1-3), respectively, using random-effects models.

Table I. Characteristics of the 23 studies included in an analysis of rash and pruritus from concurrent treatment of advanced-stage malignancies with immune checkpoint inhibitors and radiation therapy

Study	Design	Cancer type	Intervention	ICI dose	EQD2, Gy	Timing	Follow-Up
1	Phase 3	NSCLC	Durvalumab + RT	10 mg/kg q2w	54-74	RT, then ICI within 42 days	25.2 months (range, 0.2-43.1 months)
2	Phase 2	Breast	Pembrolizumab + RT	200 mg q3w	23	ICI, then RT 2-7 days after	—
3	Phase 1	H&N	Avelumab + RT	10 mg/kg q2w	70	ICI, then RT 7 days after	12 months (range, 8-26 months)
4	Phase 2	NSCLC	Ipilimumab + RT	3 mg/kg q3w	40 (phase 1) 46 (phase 2)	Both ICI and RT started on day 1	Survivors: 43 months (range, 38-47 months)
5	Phase 2	Breast	Pembrolizumab + RT	200 mg q3w	40	RT, then ICI 1-3 days after	34.5 weeks (range, 2.1-108.3 weeks)
6	Phase 1	NSCLC	Pembrolizumab + RT	100 mg or 200 mg q3w	60	ICI given on day 1 or day 29 of RT	16.0 months (95% CI: 12.0-22.6)
7	Phase 1	Breast	Tremelimumab + RT	3, 6, 10, or 15 mg/kg	23	RT, then ICI on day 3	27.0 months (range, 4.8-101.7 months)
8	Phase 3	Prostate	Ipilimumab + RT	10 mg/kg q3w	12	RT, then ICI within 2 days	9.9 months (IQR, 4.3-16.7 months)
9	Phase 1/2	Multiple	Durvalumab + RT	10 mg/kg q2w	24	ICI, then RT 1-35 days after	15.6 months (range, 2.5-27.6 months)
10	Phase 1	RCC	Pembrolizumab + RT	200 mg q3w	8 or 23	RT, then ICI within 1 week	32.3 months (range, 9.3 to 46.6 months)
11	Phase 2	NSCLC	Atezolizumab + RT	1200 mg q3w	60-66	RT, then ICI after 3 weeks (part 1) or at the same time (part 2)	Part 1: 22.5 months (IQR, 19.0-29.1 months) Part 2: 15.3 months (IQR, 10.9-19.4 months)
12	Phase 1	Multiple	Pembrolizumab + RT	200 mg q3w	36 or 38	ICI, then RT 1 week after	—
13	Phase 1	NSCLC	Nivolumab + RT	3 mg/kg q2w	54	ICI within 2 weeks of RT	—
14	Phase 1	Multiple	Cemiplimab + RT +/- CPA	1, 3, or 10 mg/kg q2w	40 or 43	1 week after ICI	19.3 weeks (range, 2.3-84.3 weeks)
15	Phase 2	NSCLC	Nivolumab + RT	360 mg q3w × 4, then 480 mg q4w	66 or 72	Both ICI and RT on day 1	13.4 months (IQR, 9.0-18.4 weeks)
16	Phase 1/2	Prostate	Ipilimumab + RT	3 mg/kg or 10 mg/kg q3w	12	RT 2 days before ICI	15.7 months (range, 1.1-57.3 months)
17	Phase 1	Melanoma	Ipilimumab + RT	3 mg/kg q3w	36 or 50 or 66	RT, then ICI 1 day after	—

Continued

Table I. Cont'd

Study	Design	Cancer type	Intervention	ICI dose	EQD2, Gy	Timing	Follow-Up
18	Phase 2	Melanoma	Nivolumab + RT	3 mg/kg q2w	36	RT, then ICI 1 day after	13.1 months (IQR, 7.5-19.2 months)
19	Phase 1	Urothelial	Pembrolizumab + RT	200 mg q3w	36	RT, then ICI 1 day after	—
20	Phase 1	SCLC	Pembrolizumab + RT	100 mg, 150 mg, 200 mg	51	Both ICI and RT on day 1	7.3 months (range, 1-13 months)
21	Phase 2	Multiple	Ipilimumab + RT	3 mg/kg q3w	94 or 80	ICI, then RT within 10 days after	10.5 months
22	Phase 1	Melanoma	Ipilimumab + RT	3 mg/kg	33 or 60	ICI 2 days after RT	WBRT: 8.0 months (range, 3.5- 24.1 months) SRS: 10.5 months (range 1.8-36.8 months)
23	Phase 1	Pancreas	Durvalumab + RT	10 mg/kg q2w	12 or 33	Both ICI and RT on day 1	—

CI, Confidence interval, *EQD2*, equivalent dose in 2 Gy per fraction; *H&N*, head and neck; *ICI*, immune checkpoint inhibitor; *IQR*, interquartile range; *NSCLC*, non–small-cell lung cancer; *q2w*, every 2 weeks; *q3w*, every 3 weeks; *q4w*, every 4 weeks; *RCC*, renal cell carcinoma; *RT*, radiation therapy; *SCLC*, small-cell lung cancer; *SRS*, stereotactic radiosurgery; *WBRT*, whole-brain radiotherapy.

Previous studies have reported similar rates of all-grade (13.2%-30.7%) and severe (0.5%-2.3%) pruritus with ICIs alone.[3,4] Differences in pruritus incidence did not vary among ICI classes ($P = .25$). Subgroup analysis showed a lower pruritus incidence ($P = .009$) with higher radiation doses (8%; 95% CI, 4-14) compared to lower doses (14%; 95% CI, 11-20). A possible explanation may be that higher RT doses have a smaller target volume focused on deeper tumors, with a resultant lower effective dose to the skin.

To our knowledge, this is the first meta-analysis reporting on the incidence of CAEs in patients concurrently treated with ICIs and RT in clinical trials. We did not find an increased incidence of all-grade or severe rash or pruritus with concurrent therapy. Limitations include the lack of patient-level data, nonspecific characterization of rash and pruritus, and significant heterogeneity of the included studies. Given the relatively high incidence of rash and pruritus and their known negative effects on the quality of life of patients with cancer,[5] continued care must be taken to monitor for and treat CAEs resulting from ICIs and RT.

Bernice Y. Yan, MD,[a,b] Gloria Wasilewski, RN,[a] Mario E. Lacouture, MD,[c] and Christopher A. Barker, MD[a]

From the Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York[a]; Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, New York[b]; and Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York.[c]

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Reprint requests: Christopher A. Barker, MD, 1275 York Ave, New York, NY 10065

E-mail: barkerc@mskcc.org

Conflicts of interest

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Association between treatment center experience and survival after diagnosis of stage I to III Merkel cell carcinoma treated with surgery with or without postoperative radiation therapy

To the Editor: Merkel cell carcinoma (MCC) is a rare malignancy and variable management across institutions influences outcomes.[1,2] Prior studies demonstrated improved overall survival (OS) at institutions with high treatment center volume (TCV).[3,4] Yet, it remains unknown whether this OS benefit extends to all curative stages and across treatment approaches. This study characterizes TCV's impact on OS for stage I to III MCC treated with surgery alone or postoperative radiotherapy. Additionally, TCV was examined to identify the minimum number of annual cases needed to attain the OS benefit.

The National Cancer Database was used to identify patients with pathologically confirmed stage I to III MCC diagnosed from 2004 to 2015 and treated at one facility with curative-intent (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/d7y72gvcx9/1). Cox proportional hazards regression was used to model the association between TCV and OS. TCV was analyzed as a continuous variable to identify a statistically significant association with OS. In a preplanned exploratory analysis, TCV was then dichotomized into "low" or "high" at the 90th percentile (≥5 cases/y), which represented the facilities that treated ≥50% of the patients (ie, the top 10% of the institutions treated ≥50% of the patients). Sensitivity analysis of the dichotomous model at various percentiles (50th, 75th, 95th, and 99th) was performed to determine the minimum number of annual cases at which OS benefit could be detected.

Of the 11,119-patient cohort, 4952 (45%) were treated at high TCV facilities and 6167 (55%) at low TCV facilities. At median follow-up of 28.8 months, 2-year OS was higher at high TCV centers for the overall cohort (70.9% vs 63.6%, $P < .0001$), including stage I and II (76.8% vs 68.2%, $P < .0001$) and stage III MCC (59.2% vs 52.9% $P = .0013$) (Fig 1). The association between TCV and OS was also significant for surgery alone (69.8% vs 59.4%, $P < .0001$) or surgery and postoperative radiotherapy (73.1% vs 68.4%, $P < .0001$) (Fig 2). Each increment of 100 patients (9 cases/y) was associated with a 3% OS improvement (adjusted hazard ratio, 0.974; 95% confidence interval, 0.959-0.989; $P < .0010$). In the prespecified sensitivity analysis, improved OS was noted at the 75th (3 cases/y), 95th (9 cases/y), and 99th (20 cases/y) percentiles, but not at the 50th percentile (1 case/y) (Supplementary Table I).

This study demonstrates that the improvement in OS associated with high TCV facilities extends to all curative stages and for surgery alone or in combination with postoperative radiotherapy. OS improvement increases with number of patients treated per year: for every 3 additional patients, the risk of death decreases by 1%.

Increased familiarity with MCC streamlines care in a multidisciplinary setting through subspecialized providers in surgery, radiation oncology, medical oncology, and dermatology.[5] Physicians who treat patients with curable MCC may wish to consider referral to high-volume centers where there may be enhanced access to clinical trials and specialty expertise.

Limitations are due to the nature of the available database, which does not provide recurrence data or disease-specific survival. Despite these limitations, the study represents a robust finding that confirms prior studies and augments existing knowledge of the relationship between TCV and OS.

Fallon E. Chipidza, MD,[a,b] Manisha Thakuria, MD,[c,d] Jonathan D. Schoenfeld, MD, MPH,[b,c] Ann W. Silk, MD,[c,e] Paul J. Catalano, ScD,[f] Charles H. Yoon, MD PhD,[c,g] Glenn J. Hanna, MD,[c,e] James A. DeCaprio, MD,[c,e] Roy B. Tishler, MD, PhD,[b,c] and Danielle N. Margalit, MD, MPH[b,c]