American Head and Neck Society - Journal Club
Volume 60, May 2026

This issue of Journal Club is hosted by the Cutaneous Cancer Section – contributors: Justin Hintze, Jeffrey Liu, Samantha Tam, Harrison Cash and Neil Gildener-Leapman.

Table of Contents** – **click the page number to go to the summary and full article link.

Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma

Danny Rischin, Sandro Porceddu, Fiona Day, Daniel P Brungs, Hayden Christie, James E Jackson, Brian N Stein, Yungpo Bernard Su, Rahul Ladwa, Gerard Adams, Samantha E Bowyer, Zulfiquer Otty, Naoya Yamazaki, Paolo Bossi, Amarnath Challapalli, Axel Hauschild, Annette M Lim, Vishal A Patel, Joanna L Walker, Maite De Liz Vassen Schurmann, Paola Queirolo, Javier Cañueto, Flavio Augusto Ferreira da Silva, Alexander Stratigos, Alexander Guminski, Charles Lin, Fernanda Damian, Lukas Flatz, Anne E Taylor, David R Carr, Samuel Harris, Dmitry Kirtbaya, Gaëlle Quereux, Piotr Rutkowski, Nicole Basset-Seguin, Nikhil I Khushalani, Caroline Robert, Haisong Ju, Camryn Joseph, Shikha Bansal, Chieh-I Chen, Frank Seebach, Suk-Young Yoo, Israel Lowy, Priscila Goncalves, Matthew G Fury

New England Journal of Medicine, May 31, 2025

Background: Patients who have cutaneous squamous-cell carcinoma with high-risk features are at risk for recurrence after definitive local therapy. The benefit of systemic adjuvant therapy options has not been well established in clinical trials.

Methods: In a phase 3, randomized trial, we enrolled patients with local or regional cutaneous squamous-cell carcinoma, after surgical resection and postoperative radiotherapy, at high risk for recurrence owing to nodal features (extracapsular extension with largest node ≥20 mm in diameter or at least three involved nodes) or nonnodal features (in-transit metastases, T4 lesion [with bone invasion], perineural invasion, or locally recurrent tumor with ≥1 additional risk feature). Patients were assigned in a 1:1 ratio to receive adjuvant cemiplimab (350 mg) or placebo, administered intravenously every 3 weeks for 12 weeks, followed by a dose increase to 700 mg administered every 6 weeks for up to 36 weeks (≤48 weeks total). The primary end point was disease-free survival. Secondary end points included freedom from locoregional recurrence, freedom from distant recurrence, and safety.

Results: A total of 415 patients were assigned to cemiplimab (209) or placebo (206). The median follow-up was 24 months. Cemiplimab was superior to placebo with respect to disease-

free survival (24 vs. 65 events; hazard ratio for disease recurrence or death, 0.32; 95% confidence interval [CI], 0.20 to 0.51; P<0.001). The estimated 24-month disease-free survival was 87.1% (95% CI, 80.3 to 91.6) with cemiplimab and 64.1% (95% CI, 55.9 to 71.1) with placebo. Cemiplimab led to lower risks of locoregional recurrence (9 events, vs. 40 with placebo; hazard ratio, 0.20; 95% CI, 0.09 to 0.40) and distant recurrence (10 vs. 26 events; hazard ratio, 0.35; 95% CI, 0.17 to 0.72). Adverse events of grade 3 or higher occurred in 23.9% of the patients who received cemiplimab and in 14.2% of those who received placebo; discontinuation due to adverse events occurred in 9.8% and 1.5%, respectively.

Conclusions: Adjuvant cemiplimab therapy led to longer disease-free survival than placebo among patients at high risk for recurrence of cutaneous squamous-cell carcinoma. (Funded by Regeneron Pharmaceuticals and Sanofi; C-POST ClinicalTrials.gov number, NCT03969004.)

Summary:

- This is an International randomized trial of cemiplimab vs. placebo for high risk cutaneous squamous cell carcinoma (cSCC). AKA C-POST Trial Patients randomized to cemiplimab q3weeks (or q6weeks later in trial) vs. placebo 1:1
- High risk cSCC definition and inclusion criteria
  - high risk nodal disease (ENE in nodes) OR three or more positive nodes
  - in-transit metastasis
  - PNI of named nerves (clinical or radiological)
  - T4 primary tumors with bone invasion
  - local recurrence with at least one adverse feature (see paper)
- No immunosuppressed patients
- 415 patients enrolled with a median followup of 24 months
- Additional select demographics of the cohort:
  - 15-17% were N American, 43% were from New Zealand or Australia
  - 79-85% are HN patients
  - 50% of pts were included due to high risk ENE lymph nodes
- At 24 months, the cemiplimab arm had 87.1% DFS vs. 64.1%. HR for disease recurrence or death was 0.32.
- Treatment related adverse events for discontinuation was 9.8% in cemiplimab vs. 1.5% in placebo
- This study helped obtain data to support now FDA approval for adjuvant cemiplimab in appropriately selected high risk patients.

Strengths

- Randomized control trial
- Clear inclusion criteria
- Impactful findings with significant effect

Weaknesses

- Use of adjuvant radiation in the patient cohorts not clear. Radiation did not appear to be controlled for in the analysis
- Study was limited to immunocompetent patients, so management of immunosuppressed patients with immunotherapy still remains unknown/uncertain

back to top

Neoadjuvant PD-1 blockade in surgically resectable desmoplastic melanoma: cohort A of the phase 2 SWOG S1512 trial

Kari L Kendra, Shay L Bellasea, Zeynep Eroglu, Siwen Hu-Lieskovan, Katie M Campbell, William E Carson 3rd, David A Wada, Jose A Plaza, Gino K In, Alexandra Ikeguchi, John Hyngstrom, Andrew S Brohl, Bartosz Chmielowski, Nikhil I Khushalani, Joseph Markowitz, Marcus Monroe, Carlo M Contreras, Tawnya Bowles, Kurt Norman, Egmidio Medina, Cynthia R Gonzalez, Ignacio Baselga-Carretero, Ivan Perez Garcilazo, Agustin Vega-Crespo, Jia Ming Chen, Nataly Naser Al Deen, Sapna P Patel, Kenneth F Grossmann, Vernon K Sondak, Elad Sharon, James Moon, Michael C Wu, Antoni Ribas

Nature Cancer, Feb 7 2026

Abstract The phase 2 SWOG S1512 trial (NCT02775851) was designed to evaluate the response to pembrolizumab (anti-PD-1) in individuals with desmoplastic melanoma. Here we report the results of cohort A of the trial, evaluating the pathological complete response (pCR) rate of neoadjuvant PD-1 blockade in surgically resectable desmoplastic melanoma. Secondary endpoints included clinical response rate, overall survival and toxicities. Twenty-eight eligible individuals with resectable desmoplastic melanoma received intravenous pembrolizumab (200 mg) every 3 weeks three times, followed by excision. Tissue samples before treatment, at 3-5 weeks after treatment initiation and at the time of surgery were reviewed. The primary endpoint of pCR rate by local pathological review was 71% (95% confidence interval, 51-87%; $P < 0.001$), which met the prespecified endpoint. There were two (7%) grade 3 treatment-related adverse events. At three years of follow-up, four participants have died, none known to be from melanoma or adverse events. In conclusion, neoadjuvant pembrolizumab in individuals with resectable desmoplastic melanoma results in a high pCR rate with acceptable safety profile.

Summary statements

- This multicenter phase 2 cohort evaluated neoadjuvant pembrolizumab in 28 patients with surgically resectable desmoplastic melanoma, demonstrating a high pathological complete response rate of 71%, far exceeding the 25% null hypothesis and meeting the trial's primary endpoint.
- The regimen was well-tolerated, with only 2 patients (7%) experiencing grade 3 treatment-related adverse events and no grade 4/5 events; none of the patients in the cohort died from melanoma or treatment-related causes.
- At a median follow-up of 42 months, 3-year relapse-free survival was 74%, overall survival was 87%, and melanoma-specific survival was 95%, supporting durable benefit from this approach.

Strengths

- Prospective, multicenter (10 US sites) cooperative-group design addressing a rare melanoma subtype with a strong biological rationale for PD-1 sensitivity.
- The magnitude of pathological response was striking and clinically relevant, particularly given the morbidity of surgery for desmoplastic melanoma, which commonly involves the head and neck.
- Prespecified endpoints, centralized blinded pathological review, and whole-exome sequencing adds rigor and generalizability beyond single-institution series.

- The high concordance between local and central pathology reviews validates the primary endpoint assessment, and the serial biopsy design provided meaningful insight into the time-course of immunological response.

Weaknesses

- Small sample size (n=28) and single-arm design without a comparator arm limit the ability to draw definitive causal conclusions or formally quantify the benefit over surgery alone or adjuvant-only approaches.
- The study population was predominantly older, white men with head and neck primaries, which may limit generalizability.
- Survival conclusions should be interpreted cautiously because follow-up remains moderate, event numbers were low, and none of the patients received adjuvant pembrolizumab despite this being permitted and often standard in higher-risk melanoma.

back to top

Outcomes of Solid Organ Transplant Recipients With Advanced Cancers Receiving Immune Checkpoint Inhibitors: A Systematic Review and Individual Participant Data Meta-Analysis

Nida Saleem, Jiayue Wang, Angela Rejuso, Armando Teixeira-Pinto, Jacqueline H Stephens, Annabelle Wilson, Anh Kieu, Ryan P Gately, Farzaneh Boroumand, Edmund Chung, Billie Bonevski, Matteo S Carlino, Robert Carroll, Wai H Lim, Jonathan C Craig, Naoka Murakami, Germaine Wong

JAMA Oncology, Oct 2025

Importance Immune checkpoint inhibitors (ICIs) have improved overall survival in patients with advanced-stage cancers. However, data on their efficacy and safety in solid organ transplant recipients (SOTRs) are limited.

Objective To examine cancer-specific and patient survival among SOTRs with advanced-stage cancer receiving ICIs and identify factors associated with patient and graft outcomes.

Data Sources Electronic databases and clinical registries, including MEDLINE, Embase, ClinicalTrials.gov, Australia New Zealand clinical trials registry, and the World Health Organization International Clinical Trials Registry Platform, were searched from inception to June 2024 without language restriction.

Study Selection Case reports and series, observational studies, and clinical trials that described the treatment of advanced-stage cancers using ICIs in SOTRs were included.

Data Extraction and Synthesis Individual participant data were extracted and synthesized using a single-stage random-effect model.

Main Outcomes and Measures Time to cancer-related death was the primary outcome. The main secondary outcomes included time from ICI initiation to first rejection and cancer response according to Response Evaluation Criteria in Solid Tumors 1.1 criteria. Adjusted Cox proportional hazards regression models were conducted for time-to-event analyses.

Results Of 140 studies, 128 studies involving 343 SOTRs treated with ICI were included. Most participants were male (76.9%), kidney transplant recipients (70.9%), with a median (IQR) age of 63 years (14-88 years), and treated with programmed cell death protein-1 inhibitors (72.9%). Within 3 years of ICI initiation, 52.8% (95% CI, 43.9%-61.6%) died of cancers. Acute rejection occurred in 36.2% (95% CI, 30.7%-41.7%) at 1 year, and 18.4% (95% CI, 13.7%-23.1%) experienced graft loss at 1 year. Objective response at 1 year was 31.6% (95% CI, 25.0%-37.7%), with a higher response observed in patients with cutaneous squamous cell carcinoma (cSCC) (61.0% [95% CI, 45.5%-76.4%]) than melanoma (48.5% [95% CI, 26.8%-70.3%]), and other solid organ cancers (26.9% [95% CI, 14.5%-39.3%]). Transplant recipients with melanoma (hazard ratio [HR], 2.29; 95% CI, 1.31-3.99) and solid organ cancers (HR, 2.84; 95% CI, 1.70-4.74) experienced higher rates of cancer-related deaths than those with cSCC. Recipients with melanoma have a higher risk of acute rejection (HR, 2.88; 95% CI, 1.69-4.90) than cSCC. Maintenance with steroids and mammalian target of rapamycin inhibitors (mTORIs) was associated with a lower risk of rejection compared with other immunosuppressive agents (HR, 0.30; 95% CI, 0.14-0.63).

Conclusions and Relevance In this study, cancer outcomes in SOTRs receiving ICIs varied by cancer type, with a higher probability of achieving response among those with cSCC than other cancers. Concurrent use of mTORIs and steroids during ICI therapy may reduce the risk of acute allograft rejection.

Summary statements:

- **Efficacy and Safety of ICIs in SOTRs:** Immune checkpoint inhibitors (ICIs) show a comparable objective response rate in solid organ transplant recipients (SOTRs) with advanced cancers to that seen in the general population. However, survival outcomes remain limited, with over 80% of SOTRs dying within three years of ICI initiation.
- **Cancer Type Variability:** The response to ICIs varies significantly by cancer type. Patients with cutaneous squamous cell carcinoma (cSCC) demonstrated a considerably higher response rate compared to those with melanoma or other solid organ cancers.
- **Rejection Management:** Maintaining immunosuppression with mammalian target of rapamycin inhibitors (mTORIs) and steroids during ICI therapy may help reduce the risk of acute allograft rejection and subsequent graft loss. Melanoma patients, in particular, showed a higher risk of rejection.

Strengths

- Comprehensive review of studies involving SOTRs receiving ICI which captured a large dataset (n = 343) of patients.
- Individual participant data meta-analysis allowed for a robust method to analyze the potential efficacy and safety of ICIs than aggregation of summary study findings.

Weaknesses

- No comparator group for SOTRs not receiving ICI therapy and therefore can only be compared to literature regarding relative outcomes from separate studies.
- Many factors varied across studies including whether organ rejection was confirmed by biopsy, transplant and cancer types, immunosuppressive regimens, ICI dosing.
- Publication bias may lead to less favorable outcomes being underreported.

back to top

Vismodegib for Preservation of Visual Function in Patients with Advanced Periocular Basal Cell Carcinoma: The VISORB Trial.

Kahana A, Unsworth SP, Andrews CA, Chan MP, Bresler SC, Bichakjian CK, Durham AB, Demirci H, Elner VM, Nelson CC, Kim DS, Joseph SS, Swiecicki PL, Worden FP.

Oncologist, July 2021.

Background: Basal cell carcinoma (BCC) is a common skin cancer often curable by excision; however, for patients with BCC around the eye, excision places visual organs and function at risk. In this article, we test the hypothesis that use of the hedgehog inhibitor vismodegib will improve vision-related outcomes in patients with orbital and extensive periocular BCC (opBCC).

Materials and methods: In this open-label, nonrandomized phase IV trial, we enrolled patients with globe- and lacrimal drainage system-threatening opBCC. To assess visual function in the context of invasive periorbital and lacrimal disease, we used a novel Visual Assessment Weighted Score (VAWS) in addition to standard ophthalmic exams. Primary endpoint was VAWS with a score of 21/50 (or greater) considered successful, signifying globe preservation. Tumor response was evaluated using RECIST v1.1. Surgical specimens were examined histologically by dermatopathologists.

Results: In 34 patients with opBCC, mean VAWS was 44/50 at baseline, 46/50 at 3 months, and 47/50 at 12 months or postsurgery. In total, 100% of patients maintained successful VAWS outcome at study endpoint. Compared with baseline, 3% (95% confidence interval [CI], 0.1-15.3) experienced major score decline (5+ points), 14.7% (95% CI, 5 to 31.1) experienced a minor decline (2-4 points), and 79.4% experienced a stable or improved score (95% CI, 62.1-91.3). A total of 56% (19) of patients demonstrated complete tumor regression by physical examination, and 47% (16) had complete regression by MRI/CT. A total of 79.4% (27) of patients underwent surgery, of which 67% (18) had no histologic evidence of disease, 22% (6) had residual disease with clear margins, and 11% (3) had residual disease extending to margins.

Conclusion: Vismodegib treatment, primary or neoadjuvant, preserves globe and visual function in patients with opBCC. Clinical trial identification number.NCT02436408.

Implications for practice: Use of the antihedgehog inhibitor vismodegib resulted in preservation of end-organ function, specifically with regard to preservation of the eye and lacrimal apparatus when treating extensive periocular basal cell carcinoma. Vismodegib as a neoadjuvant also maximized clinical benefit while minimizing toxic side effects. This is the first

prospective clinical trial to demonstrate efficacy of neoadjuvant anti-hedgehog therapy for locally advanced periocular basal cell carcinoma, and the first such trial to demonstrate end-organ preservation.

Summary statements

- Vismodigib was used in a neoadjuvant fashion with variable time courses up to one year (depending on treatment tolerance) for 34 patients who had orbital or lacrimal threatening basal cell carcinoma.
- This allowed 27 out of 34 to progress to surgery, with 18 having no histologic evidence of malignancy. Only 3 patients had positive margins with residual disease.
- The key finding of the study was that only 1 patient had a significant worsening in their VAWS score. This demonstrated a high visual and ocular function preservation.

Strengths

- Focus of the study was on feasibility of vision and globe preservation which can often get left out of oncologic outcomes in periocular malignancies.
- Novel scale was introduced: Visual Assessment Weighted Score (VAWS) which emphasizes orbital and lacrimal system outcomes.

Weaknesses

- Was not designed to assess disease free survival, as microscopic deposits of tumor can be left behind peripherally in the neoadjuvant approach. After completion of the study 2 patients in continued follow up were noted to have local recurrence.
- No direct comparison to a standard of care approach (though it is inferred by the predicted surgical approach at trial entry)

back to top

Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial

Suzanne L Topalian, Shailender Bhatia, Asim Amin, Ragini R Kudchadkar, William H Sharfman, Celeste Lebbé, Jean-Pierre Delord, Lara A Dunn, Michi M Shinohara, Rima Kulikauskas, Christine H Chung, Uwe M Martens, Robert L Ferris, Julie E Stein, Elizabeth L Engle, Lot A Devriese, Christopher D Lao, Junchen Gu, Bin Li, Tian Chen, Adam Barrows, Andrea Horvath, Janis M Taube, Paul Nghiem

Journal of Clinical Oncology, August 2020

Purpose: Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer commonly driven by the Merkel cell polyomavirus (MCPyV). The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunosuppressive pathway is often upregulated in MCC, and advanced metastatic MCC frequently responds to PD-1 blockade. We report what we believe to be the first trial of anti–PD-1 in the neoadjuvant setting for resectable MCC.

Methods: In the phase I/II CheckMate 358 study of virus-associated cancer types, patients with resectable MCC received nivolumab 240 mg intravenously on days 1 and 15. Surgery was planned on day 29. Tumor regression was assessed radiographically and microscopically.

Tumor MCPyV status, PD-L1 expression, and tumor mutational burden (TMB) were assessed in pretreatment tumor biopsies.

Results: Thirty-nine patients with American Joint Committee on Cancer stage IIA-IV resectable MCC received ≥ 1 nivolumab dose. Three patients (7.7%) did not undergo surgery because of tumor progression (n = 1) or adverse events (n = 2). Any-grade treatment-related adverse events occurred in 18 patients (46.2%), and grade 3-4 events in 3 patients (7.7%), with no unexpected toxicities. Among 36 patients who underwent surgery, 17 (47.2%) achieved a pathologic complete response (pCR). Among 33 radiographically evaluable patients who underwent surgery, 18 (54.5%) had tumor reductions ≥ 30%. Responses were observed regardless of tumor MCPyV, PD-L1, or TMB status. At a median follow-up of 20.3 months, median recurrence-free survival (RFS) and overall survival were not reached. RFS significantly correlated with pCR and radiographic response at the time of surgery. No patient with a pCR had tumor relapse during observation.

Conclusion: Nivolumab administered approximately 4 weeks before surgery in MCC was generally tolerable and induced pCRs and radiographic tumor regressions in approximately one half of treated patients. These early markers of response significantly predicted improved RFS. Additional investigation of these promising findings is warranted.

Summary statements

- This paper reports on the neoadjuvant cohort of 39 patients with Merkel cell carcinoma (all had surgically resectable disease, including Stage IIa-IIIb locoregional disease, oligometastatic disease, or local recurrence >/=1 cm) from CheckMade 358; treatment generally well tolerated with three patients with Grade 3-4 treatment related adverse effects (1 rash, 1 autoimmune colitis, 1 increased lipase); The most common AE regardless of grade was skin reaction (10.3%).
- Three patients did not undergo surgery (due to disease progression (n=1), non-treatment related nausea (n=1), and treatment related grade 3 rash (n=1); one patient had delayed surgery (15 weeks) due to treatment-related autoimmune colitis.
- Of patients who underwent surgery, 17 (47.2%) had pathological complete response and 4 (15.4%) had major pathological response; pathologic completed response (HR=0.12, 95% CI 0.01 to 0.93) and radiographic response (HR=0.11, 95% CI: 0.01 to 0.87) were correlated significantly with relapse free survival.

Strengths

- Promising proof of concept clinical trial demonstrating promise for use of nivolumab in a neoadjuvant paradigm for patients with Merkel cell carcinoma.
- Response appeared to be agnostic of viral and PD-L1 expression.
- A significant portion of patients experienced robust pathological response, which was also correlated with disease outcome.

Weaknesses

- Short follow-up, small sample size, single-arm design do not allow for full conclusions to be drawn, but point to the need for future investigation.

- 3/36 patients who had initially surgically resectable disease were unable to make it to surgery.
- The role of response-adaptiveness of surgery was unclear – understanding the extent of surgical resection will be important for future studies.

back to top