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DREAMseq: A phase III trial of treatment sequences in BRAFV600-mutant (m) metastatic melanoma (MM) – Final clinical results

BRAF is one of the most commonly mutated oncogenes in melanoma[1]. Patients with BRAF-mutant MM can be treated either with targeted therapy (TT) or with combined immunotherapy (IO)[2-4] such as nivolumab and ipilimumab[5] both of which have demonstrated significant clinical benefit. However, the optimal sequencing of these treatments has remained unclear, with limited data available to guide clinical decision-making.

The DREAMseq, led by ECOG-ACRIN Cancer Research Group, was a phase 3, two-arm, two-step, open-label, randomized study. The trial enrolled treatment-naive patients with BRAFV600-mutant MM, who were stratified by ECOG performance status (PS) and lactate dehydrogenase (LDH) levels, and then randomized to arm A (combination nivolumab/ipilimumab) or arm B (dabrafenib/trametinib) in Step 1, and at disease progression, if eligible, they were enrolled in Step 2 receiving the alternate therapy, dabrafenib/trametinib (Arm C) or nivolumab/ipilimumab (Arm D).

The primary endpoint was 2-year overall survival (OS), with secondary endpoints including 3-year OS, overall response rate (ORR), response duration, progression-free survival (PFS), crossover feasibility, and safety.

The primary analysis–first presented at the 2023 ASCO inaugural virtual plenary session and published in JCO[6]–demonstrated a significantly higher 2-year OS for patients receiving IO first (72% vs. 52%; p = 0.01). The benefit of starting with IO was consistent across all clinical subgroups, leading to more durable and ongoing responses (88 vs. 48% still in response). TT showed similar efficacy in both first- and second-line settings, while IO showed reduced efficacy when used in second-line. The PFS and OS curves crossed at 6 and 19 months, respectively, reflecting a biphasic treatment effect. Notably, early deaths occurred more frequently in the IO-first group, typically among patients with poor prognosis who never received second-line TT. Adverse events (AEs) profiles differed between arms, but the rates of grade ≥ 3 were similar.

Updated results presented by Dr. Michael B. Atkins at ASCO 2025 (data cutoff: July 2024; median follow-up: 58 months) confirmed–and further reinforced–the survival advantage of initiating treatment with IO in patients with treatment-naive BRAFV600-mutant MM. Five-year OS was 63.3% in the IO-first arm compared to 33.3% in patients who received TT as first-line treatment. Similarly, 5-year PFS was significantly higher in the IO-first group (39.4%) versus the TT-first group (12.8%), with $p < 0.01$. These long-term benefits were consistent across all patient subgroups.

Notably, although the ORR was nearly identical between arms–51.5% with IO versus 51.1% with TT–the durability of response was markedly superior in the IO-first group. At 5 years, 76.4% of responders in the IO arm remained in response, compared to just 23.9% in the TT-first arm. Radiographic response durability also differed significantly. Among patients who received TT first, 41.2% of partial responses (PR) observed at 12 weeks were not confirmed at 24 weeks, compared to only 16.9% in the IO-first group. Investigators

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suggested that this apparent discrepancy in ORR may partly reflect differences in imaging intervals: the DREAMseq trial used longer scan intervals compared to earlier TT registration trials. If imaging had been performed at 8 and 16 weeks, as in earlier studies, the TT-first arm may have shown higher ORRs.

Patients in the IO-first group were also significantly less likely to develop central nervous system (CNS) metastases. At 2 years, 86.8% of patients in the IO arm remained free of CNS metastases, compared to 62.1% in the TT-first group. At 4 years, these rates were 76% and 62.1%, respectively.

These data are practice-changing and provide strong support for initiating treatment with IO in the majority of patients with treatment-naive BRAFV600-mutant MM.

Ongoing biomarker studies on blood and tumor samples aim to identify patients who might benefit from a short upfront course of TT; patients likely to progress early on fist-line IO and requiring earlier switch to TT; and patients who fail both modalities and may require alternative strategies.

A randomized phase 2 trial of encorafenib + binimetinib + nivolumab versus ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000 (NCT04511013)

The SWOG S2000 trial marks a significant advancement in the treatment of patients with BRAFV600-mutant melanoma and brain metastases (MBM). This randomized phase 2 study is the first of its kind to prospectively compare a triplet regimen of TT and IO with the current standard of dual immune checkpoint blockade in this high-risk population.

Patients with MBM, particularly those harboring BRAFV600 mutations, face a poor prognosis, with median survival < 12 months despite recent therapeutic advances[7,8]. Immune checkpoint inhibitors (ICI)–notably, the combination of nivolumab and ipilimumab–have shown durable intracranial responses in MBM, particularly in asymptomatic patients with limited corticosteroid requirements[9,10]. Separately, TT involving BRAF and MEK inhibitors has demonstrated rapid tumor responses, including intracranial activity, though durability has been a challenge[11-13].

Despite the efficacy of both IO and TT in MBM, the optimal sequencing or combination therapy remains unclear, especially in patients with symptomatic disease or active CNS involvement[14,15]. The SWOG S2000 trial was therefore designed to directly compare these two strategies–triplet IO/TT versus dual IO–in a randomized, prospective study, aiming to address a critical gap in the management of BRAFV600-mutant MBM.

SWOG S2000 was a multicenter, open-label, randomized phase 2 trial enrolling patients with histologically confirmed BRAFV600-mutant MM and measurable brain metastases, either untreated or progressing following local therapy. Eligible patients could have symptomatic disease or require steroids (dexamethasone ≤ 8 mg/day or equivalent). Participants were randomized to receive triplet therapy with encorafenib, binimetinib and nivolumab (Arm A) or nivolumab plus ipilimumab (Arm B).

The primary endpoint was 6-month PFS, with secondary endpoints including intracranial response rate (iORR), overall PFS, OS, duration of response, and safety.

A total of 37 patients were randomized in a 1:1 ratio. Baseline characteristics were generally well balanced between the two arms, including the number and size of brain metastases, presence of symptoms, and prior local CNS-directed therapies. However, the triple therapy arm included more patients with non-BRAFV600E mutations, while the IO arm had more proportion of patients with elevated LDH levels.

With a median follow-up of 18 months, the triplet therapy arm demonstrated superior efficacy across multiple clinical endpoints compared to the IO arm. At 6 months, the PFS rate was 54% in the triplet group compared to 20% in the IO group (hazard ratio [HR]: 0.47; 1-side 90% confidence interval [CI]: 0-0.82; p = 0.04). Median PFS was significantly longer with triplet therapy, reaching 6.2 months, compared to just 1.5 months in the IO arm.

Intracranial outcomes followed a similar trend. The iORR was notably higher in patients receiving triplet therapy, with 75% achieving a radiographic response, in contrast to 13% in the IO group. Median intracranial PFS was also prolonged in the triplet arm at 8.7 months versus 1.5 months in the IO group (HR: 0.39; 1-side 90% CI; 0-0.68; p = 0.01).

The triplet regimen led to earlier and more frequent responses, translating into improved control of both intracranial and extracranial disease. The ORR was 67% in the triplet therapy arm, compared to 14% in the IO arm.

Grade ≥ 3 treatment-related AEs occurred in 69% of patients in the triplet arm and 75% in the IO arm. Despite the higher incidence of dose modifications in the triplet arm (75% vs. 32%), treatment discontinuation

due to toxicity was lower (19% triplet vs. 32% IO). Most common AEs in the triplet arm were pyrexia, rash, fatigue, diarrhea, and elevated liver enzymes. Immune-related AEs predominated in the IO arm.

SWOG S2000 represents the first randomized, prospective comparison of TT combined with IO versus standard dual IO in patients with melanoma brain metastases. The results show a clear clinical advantage for triplet regimen, particularly in terms of iORR and PFS, key measures in the management of symptomatic CNS disease.

The rapid onset of response seen with BRAF and MEK inhibitors is particularly important in patients at risk of neurologic deterioration. The addition of nivolumab may contribute to more sustained disease control. These results build on prior single-arm studies and reinforce growing interest in combining IO/TT strategies in BRAF-mutant melanoma.

While OS data are still immature, the early PFS and iORR results support a potential role for triplet therapy in first-line treatment in selected patients. Further research is warranted to refine patient selection, optimize treatment sequencing, explore the addition of agents such as anti-angiogenic therapies, and evaluate the potential of intermittent dosing strategies.

In summary, this study shows that combining encorafenib, binimetinib, and nivolumab significantly improves intracranial disease control and PFS compared with nivolumab and ipilimumab in patients with symptomatic BRAFV600-mutant MBM. This triplet regimen offers a promising new option for patients with active CNS disease, particularly when rapid response is clinically necessary. Final survival data and correlative biomarker analyses are awaited.

Lifileucel in patients with advanced melanoma: 5-year outcomes of the C-144-01 study

ICIs have transformed the treatment landscape for MM offering durable responses for many patients. However, a significant proportion ultimately experiences disease progression due to either primary[16-18] or acquired resistance[18,19]. As a result, there remains a critical need for effective therapies capable of overcoming ICI resistance in this population.

Lifileucel is an autologous tumor-infiltrating lymphocyte (TIL) therapy, approved by the U.S. Food and Drug Administration for the treatment of patients with advanced melanoma who have progressed after anti-PD-1 therapy and, if BRAFV600 mutant, BRAF ± MEK TT. In the registrational phase 2 C-144-01 study, lifileucel previously demonstrated an objective response rate (ORR) of 31.4% in a treatment-refractory population[20].

At the ASCO 2025 Annual Meeting, Dr. Theresa Medina presented the final 5-year efficacy and safety results from C-144-01 trial–representing the longest prospective follow-up of TIL therapy in advanced melanoma to date.

The final analysis included 153 patients from Cohorts 2 and 4 of the C-144-01 trial. Eligible patients had unresectable or MM with prior progression on ICI and, if applicable, TT. All patients received a single infusion of lifileucel following non-myeloablative lymphodepletion (NMA-LD), and subsequent interleukin (IL)-2 administration. At the data cutoff on November 20, 2024 with a median follow-up of 57.8 months, all patients had completed the study, and 28 patients (8.3%) had reached the 5-year follow-up milestone. The median age was 56 years (range 20-79), 83% were male, and 26.8% harbored BRAF V600E/K mutations. Patients had received a median of 3 prior systemic therapies (range 1-9).

Lifileucel demonstrated durable and clinically meaningful responses with extended follow-up. The ORR was confirmed at 31.4%, including 5.9% complete responses (CR), and 25.5% PR, with 79.3% of patients experiencing a reduction in tumor burden. The median duration of response, as assessed by an Independent Review Committee, was 36.5 months (95% CI: 8.3–not reached [NR]). Notably, 15 of 45 responders (33.3%) maintained such response throughout the entire follow-up period, with the longest ongoing response lasting 58.7 months. Importantly, 16 patients initially categorized as having stable disease or PR showed deepening of responses over time, including four patients who converted from PR to CR as late as 3 years after treatment, highlighting the potential for delayed but durable responses with TIL therapy.

The median OS for the entire cohort was 13.9 months, with an estimated 5-year OS rate of 19.7%. These findings highlight the durable survival benefit attainable with a single lifileucel infusion in a heavily pretreated population with limited therapeutic alternatives.

The safety profile of lifileucel was consistent with the expected effects of NMA-LD and IL-2 administration, with AEs primarily attributable to these treatments. The incidence of AEs declined significantly after the first 2 weeks post-infusion, and no new or late-onset lifileucel-related toxicities were observed. Grade 3/4 cytopenias occurred in all patients but resolved to grade ≤ 2

in most cases within 30 days. Red blood cell and platelet transfusions were predominantly confined to the first 2 weeks following NMA-LD initiation.

In summary, the final 5-year results from the C-144-01 study confirmed the durability, safety, and long-term survival benefit of lifileucel in patients with ICI-refractory advanced melanoma. These findings represent the longest prospective dataset to date for any cellular therapy in this setting and support the role of TIL therapy as a 1-time treatment capable of inducing sustained clinical benefit in heavily pretreated patients.

Future research, including the ongoing phase 3 TILVANCE-301 trial, will further evaluate this option in earlier lines of therapy and help define its role in evolving melanoma treatment algorithms.

Phase 3 trial of adjuvant cemiplimab versus placebo for high-risk cutaneous squamous cell carcinoma (CSCC)

CSCC is one of the most common malignancies worldwide. While most cases are effectively treated with surgery and radiation, a subset of patients with high-risk features–such as nodal involvement, perineural invasion, or poor differentiation–remain at significant risk of recurrence[21]. At present, no systemic adjuvant therapies are approved for this high-risk population[22].

Cemiplimab, an anti–PD-1 antibody, is already established as a standard of care for patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or radiotherapy. In these advanced settings, cemiplimab has demonstrated an ORR of approximately 47%, with durable clinical benefit[23,24].

At the 2025 ASCO Annual Meeting, the results of the phase 3 C-POST trial were presented, providing compelling evidence that adjuvant cemiplimab may reduce recurrence and improve outcomes in patients with resected high-risk CSCC. The C-POST trial enrolled 415 patients with resected high-risk CSCC who had also completed adjuvant radiotherapy. Participants were randomized 1:1 to receive either cemiplimab (n = 209) or placebo (n = 206). Cemiplimab was administered at 350 mg intravenously every 3 weeks for 12 weeks, followed by 700 mg every 6 weeks, for a total treatment duration of up to 48 weeks.

Stratification factors included tumor location (head and neck vs. non-head and neck), geographic region (North America, Australia/New Zealand, Rest of World), high-risk classification (nodal vs. non-nodal), ECOG PS (0 vs. 1), and history of chronic lymphocytic leukemia. The primary endpoint was disease-free survival (DFS). Secondary endpoints included freedom from locoregional recurrence (FFLRR), freedom from distant recurrence (FFDR), OS, and safety. At data cutoff (October 4, 2024), the median follow-up was 24 months (range 2-64 months).

Baseline characteristics were well balanced between the two arms, including tumor location, geographic distribution, and risk classification. Cemiplimab demonstrated a statistically significant reduction in recurrence risk. DFS events occurred in 24 patients in the cemiplimab arm compared to 65 in the placebo arm (HR: 0.32; 95% CI: 0.20-0.51; $p < 0.001$). At 3 years, DFS was 83.1% with cemiplimab versus 60.4% with placebo. Median DFS was not reached in the cemiplimab group, compared to 49.4 months with placebo. The benefit was consistent across all pre-specified subgroups.

Cemiplimab also significantly improved FFLRR (HR: 0.2; 95% CI: 0.09-0.40) and FFDR (HR: 35; 95% CI: 0.17-0.72). OS data were immature at the time of analysis, with 25 deaths reported (HR: 0.86; 95% CI: 0.39-1.90). The efficacy and safety profile of cemiplimab was consistent regardless of dosing schedule, whether administered every 3 weeks or transitioning to every 6 weeks after induction.

Toxicity was manageable at the adjuvant setting. Grade ≥ 3 AEs occurred in 24% of patients receiving cemiplimab versus 14% in the placebo group. There was one treatment-related death (due to myositis) in the cemiplimab arm. The discontinuation rate due to AEs was 10% in the cemiplimab arm compared to 1% with placebo. Immune-related AEs grade ≥ 3 occurred in 7% of patients treated with cemiplimab versus none in the placebo group. Overall, the safety profile was consistent with prior experience, with most immune-related events being manageable but requiring vigilant monitoring.

These findings represent the first positive phase 3 data supporting adjuvant IO in high-risk CSCC. With a hazard ratio of approximately 0.32 and a 3-year DFS improvement of over 20% points, cemiplimab clearly outperformed placebo. Benefits were consistent across subgroups and dosing regimens, reinforcing the robustness of the results. Although immune-related toxicities and discontinuation rate were notable, serious AEs were uncommon and generally manageable.

Adjuvant cemiplimab therefore emerges as a potential new standard of care for patients at high-risk of CSCC recurrence.

Also presented at ASCO 2025 was Keynote-630, a phase 3 trial evaluating pembrolizumab in a similar

high-risk CSCC population. Unlike C-POST, this trial did not meet its primary endpoint of recurrence-free survival (HR: 0.76, p = 0.072) and was halted early for futility. Although some subgroups showed signals of benefit, the lack of overall statistical significance limits its clinical applicability. Notably, pembrolizumab was associated with lower rates of grade ≥ 3 AEs (~8%) compared to cemiplimab (~24%), and both agents had predictable immune-related toxicity profiles. Differences in inclusion criteria and baseline characteristics may help explain the divergent outcomes between the trials.

Conclusion

The C-POST trial demonstrated that adjuvant cemiplimab significantly improves DFS and reduces both locoregional and distant recurrence in patients with resected high-risk CSCC, establishing it as a strong candidate for first-line adjuvant therapy. In contrast, Keynote-630 did not meet its primary endpoint, highlighting the need for further research into patient selection, biomarkers, and optimal treatment timing. These findings underscore the evolving role of IO in CSSC and pave the way for more individualized treatment approaches.

References

1. Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol. 2016;34:871-78.
2. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19:1315-27.
3. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381:626-36.
4. Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF (V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17:1248-60.
5. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40:127-37.
6. Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced braf-mutant melanoma: the DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol. 2023;41:186-97.
7. Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer. 2011;117:1687-96.
8. Georgina V Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Alexander D Guminski, Michael P Brown et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018 May;19(5):672-681.
9. Tawbi HA, Forsyth PA, Hodi FS, Algazi AP, Hamid O, Lao CD, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021;22:1692-704.
10. Long GV, Atkinson V, Lo SN, Guminski AD, Sandhu SK, Brown MP, et al. Ipilimumab plus nivolumab versus nivolumab alone in patients with melanoma brain metastases (ABC): 7-year follow-up of a multicentre, open-label, randomised, phase 2 study. Lancet Oncol. 2025;26:320-30.
11. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib in patients with BRAF-mutant melanoma and brain metastases: subgroup analysis of the COLUMBUS study. Eur J Cancer. 2018;104:44-52.
12. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with $BRAF_{V600}$-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18:863-73.
13. Dummer R, Queirolo P, Gerard Duhard P, et al. Atezolizumab, vemurafenib, and cobimetinib in patients with melanoma with CNS metastases (TRICOTEL): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2023;24(12):e461-e471.
14. Margolin K. Treatment of brain metastases in melanoma: improving outcomes with targeted therapy and immunotherapy. Am Soc Clin Oncol Educ Book. 2019;39:e151-60.
15. Z. Eroglu, T.O. Topcu, H.M. Yu, K.A. Margolin. How I treat brain metastases of melanoma. ESMO Open 2022; 7,100598.
16. Amaral T, Seeber O, Mersi E, Sanchez S, Thomas I, Meiwes A, et al. Primary resistance to PD-1-based immunotherapy-a study in 319 patients with stage IV melanoma. Cancers (Basel). 2020;12:1027.
17. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23-34.
18. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA. 2016;315:1600-9.
19. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30:582-8.
20. Chesney J, Lewis KD, Kluger H, Hamid O, Whitman E, Thomas S, et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. J Immunother Cancer. 2022;10:e005755.
21. Chong CY, Goh MS, Porceddu SV, Rischin D, Lim AM. The current treatment landscape of cutaneous squamous cell carcinoma. Am J Clin Dermatol. 2023;24:25-40.
22. Killock D. Postoperative chemoradiotherapy versus radiotherapy for high-risk cutaneous disease. Nat Rev Clin Oncol. 2018;15:344.
23. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379:341-51.
24. Hughes BG, Guminski A, Bowyer S, Migden MR, Schmults CD, Khushalani NI, et al. A phase 2 open-label study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1): final long-term analysis of groups 1, 2, and 3, and primary analysis of fixed-dose treatment group 6. J Am Acad Dermatol. 2025;92:68-77.