

Dermatologists

in Cancer Care[®]

FDA Approval Sought for Lifileucel in Advanced Melanoma

KRISTI ROSA

A ROLLING BIOLOGICS license application (BLA) seeking the approval of lifileucel (LN-44) in patients with advanced melanoma who progressed on or after previous anti-PD-1/PD-L1 therapy, and if BRAF mutation positive, also previous BRAF or BRAF/MEK inhibitor therapy, has been submitted to the FDA.¹

The application is based on findings from the phase 2 C-144-01 trial (NCT02360579).

In cohort 4 (n = 87), the tumor-infiltrating

lymphocyte therapy elicited an objective response rate (ORR) of 29% (95% CI, 19.5%-39.4%) per independent review committee (IRC) assessment and by RECIST v1.1 criteria.² Among those who responded to treatment, 3 achieved complete responses (CRs) and 22 experienced partial responses (PRs). At a median follow-up of 23.5 months, the median duration of response (DOR) in this cohort was 10.4 months by IRC.

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Talimogene Laherparepvec Plus Pembrolizumab Misses Mark in Advanced Melanoma

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THE ADDITION OF talimogene laherparepvec (T-VEC) to pembrolizumab (Keytruda) did not significantly improve progression-free survival (PFS) or overall survival (OS) over pembrolizumab alone in patients with advanced melanoma, according to data from a phase 2 trial (NCT02263508) published in the *Journal of Clinical Oncology*.¹

In the planned PFS primary analysis,

which had a median follow-up of 25.58 months (range, 0.3-45.8), the doublet did not improve PFS over pembrolizumab alone per blinded independent central review (BICR) and RECIST 1.1 criteria (overall stratified HR, 0.86; 95% CI, 0.71-1.04; P = .13).

However, the PFS favored the combination arm over the monotherapy arm in those who were enrolled to the

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United States (overall HR, 0.59; 95% CI, 0.37-0.92), those with baseline lactate dehydrogenase (LDH) less than or equal to the upper limit of normal (overall HR, 0.76; 95% CI, 0.59-0.99), and in those with a baseline sum of the longest diameters of target lesions of less than or equal to the median (overall HR, 0.70; 95% CI, 0.51-0.96).

In the second OS interim analysis, which had a median follow-up of 31.0 months (range, 0.3-53.0), T-VEC plus pembrolizumab did not significantly improve OS vs pembrolizumab alone (HR, 0.96; 95% CI, 0.76-1.22; P = .74). Moreover, no OS improvement was observed with the doublet over the monotherapy in any

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These data are supported by findings from cohort 2 (n = 66), in which lifileucel produced an ORR of 35% (95% CI, 23.5%-47.6%) per IRC; this included 5 CRs and 18 PRs. The median DOR was not yet reached at a median follow-up of 36.6 months.

In pooled patients from cohorts 2 and 4 (n = 153), lifileucel induced an ORR of 31% (95% CI, 24.1%-39.4%) by IRC. At a median follow-up of 27.6 months, the median DOR was not yet reached.

“Initiating our rolling BLA submission for lifileucel is a significant step toward our goal to deliver the first individualized, one-time cell therapy for melanoma patients with significant unmet need,” Frederick Vogt, PhD, JD, interim president and chief executive officer of lovance Biotherapeutics, Inc., stated in a press release. “In parallel, we are executing our on-boarding and personnel training at authorized treatment centers, education and awareness initiatives, internal capacity planning, and launch readiness activities to prepare for commercialization. The FDA is supportive of our regulatory approach, and we look forward to continuing this collaboration throughout the submission and review process.”

The trial enrolled patients with unresectable or metastatic melanoma that was stage IIIC or IV who had confirmed

radiologic progression.³ Patients must have progressed after 1 or more previous systemic therapies, including a PD-1 inhibitor, and if BRAF positive, a BRAF inhibitor with or without a MEK inhibitor.

Study participants received a nonmyeloablative lymphodepletion regimen comprised of cyclophosphamide at 60 mg/kg once daily for 2 days followed by fludarabine at 25 mg/m² once daily for 5 days. Lifileucel was thawed and administered as a single infusion about 24 hours from the last dose of fludarabine. A short course of bolus interleukin-2 at 600,000 IU/kg was infused every 8 to 12 hours for up to 6 doses, starting within 3 to 24 hours of completing the infusion.

The primary objective of the trial was investigator-assessed objective response rate using RECIST v1.1 criteria. Secondary end points comprised DOR, overall survival, and safety.

Patients in cohort 4 were noted to have higher disease burden at baseline vs those in cohort 2. For example, a substantially higher proportion of patients had elevated lactate dehydrogenase levels at baseline in cohort 4 vs cohort 2, at 64.4% and 40.9%, respectively, and more baseline tumor lesions, at 83.9% vs 65.2%, respectively.

Those in cohort 2 also had about half of the cumulative duration of PD-1 therapy

prior to lifileucel vs those in cohort 4; a reduced duration of previous PD-1 therapy was linked with an increase in DOR with lifileucel.

Regarding safety, the treatment-emergent adverse effects experienced in both cohorts were noted to align with the underlying disease and the known safety profiles of nonmyeloablative lymphodepletion and IL-2. Safety findings also proved to be consistent between cohorts 4 and 2.

lovance shared plans to present additional data from C-144-01 at a medical conference later this year.

References

1. lovance Biotherapeutics initiates biologics license application (BLA) submission for lifileucel in advanced melanoma. News release. lovance Biotherapeutics, Inc. August 25, 2022. Accessed August 25, 2022. <https://bit.ly/3QSNyR1>
2. lovance Biotherapeutics announces positive clinical data for lifileucel in advanced melanoma. News release. lovance Biotherapeutics, Inc. May 26, 2022. Accessed August 25, 2022. <https://bit.ly/3RdbWMM>
3. Sarnaik AA, Hamid O, Khushalani NI, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. *J Clin Oncol*. 2021;39(24):2656-2666. doi:10.1200/JCO.21.00612

of the predefined subgroups.

“There is a continuing unmet need in the field for combination strategies to improve the efficacy of currently available therapies without added toxicities,” Jason A. Chesney, MD, PhD, of the University of Louisville School of Medicine, and colleagues, wrote in the paper. “Although the combination of T-VEC [and] pembrolizumab did not result in OS benefit compared with placebo [and] pembrolizumab in the frontline treatment of advanced melanoma, this combination is still under

active investigation in patients who are refractory to anti-PD-1 inhibitor therapy for melanoma and other tumor types.”

T-VEC is an oncolytic viral intratumoral therapy designed to produce granulocyte-macrophage colony-stimulating factor. When combined with pembrolizumab, it is hypothesized that T-VEC may have the potential to overcome immunotherapy failure.

Data from the single-arm, phase 1b MASTERKEY-265 trial (NCT02263508) showed that T-VEC plus pembrolizumab elicited an objective response rate (ORR) of 62%, which included a complete

response rate (CRR) of 43%, in 21 patients with advanced melanoma.² The combination was also found to be well tolerated, with no dose-limiting toxicities reported.

Based on these data, investigators launched the randomized, double-blind, placebo-controlled, multicenter, international phase 3 trial, which enrolled those with histologically confirmed stage IIIB to IV M1c, unresectable melanoma. To be eligible, patients were required to be at least 18 years of age, have an ECOG performance status of 0 or 1, and at least 1 visceral or nodal/soft

tissue melanoma lesion that could be measured in at least 1 dimension and for which the longest diameter was at least 10 mm.

If patients had active untreated brain metastases or primary uveal or mucosal melanoma, or if they previously received T-VEC or any other oncolytic viruses, previous PD-1/PD-L1/PD-L2 agents, previous tumor vaccine in the neoadjuvant setting, or had a history of autoimmune diseases, they were excluded.

Study participants (n = 692) were randomly assigned 1:1 to receive the combination of T-VEC and pembrolizumab (n = 346) or placebo plus pembrolizumab (n = 346). T-VEC/placebo was given via intratumor injection once at 106 PFU/mL for up to 4 mL on day 1 of week 0, followed by up to 4 mL of 108 PFU/mL on day 1 of week 3, and once every 2 weeks until the fifth injection at week 9. Every 3 weeks thereafter, T-VEC plus placebo was then given synchronously with pembrolizumab, which was administered at 200 mg once every 3 weeks.

PFS per modified RECIST (mRECIST) v1.1 criteria and BICR and OS served as the dual primary end points of the trial. Important secondary end points comprised CRR, PFS per modified immune-related response criteria (irRC)-RECIST and BICR, and OS in those with stage IIIB to IVM1b disease.

Other end points included ORR, best overall response, durable response rate (DRR), duration of response, and disease control rate per BICR and both mRECIST v1.1 and modified irRC-RECIST criteria, and safety.

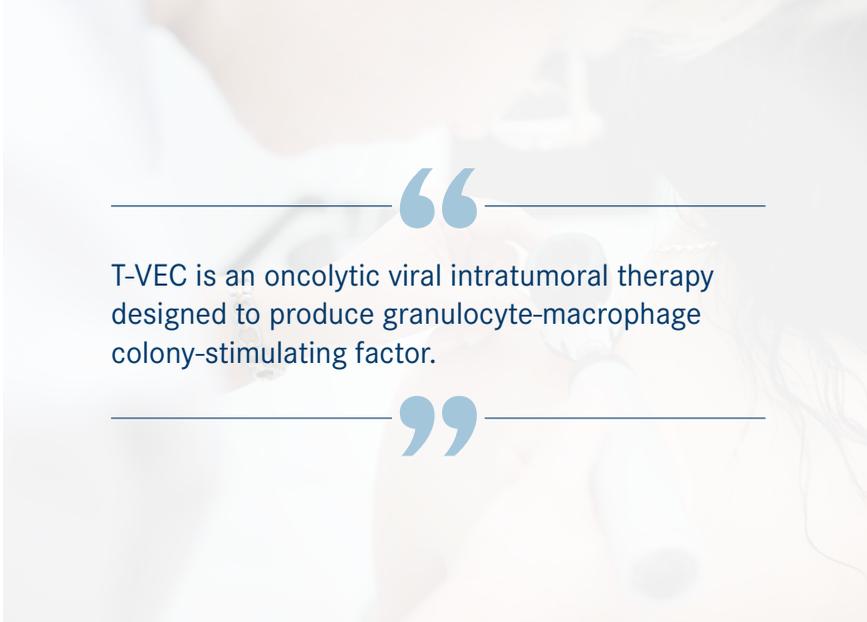
Baseline patient characteristics were noted to be balanced between the treatment arms. Across the arms, the median age was 64 years (range, 19-94). In the investigative and control arms, most patients were White (94.5% vs 96.8%, respectively), had an ECOG performance of 0 (74.9% vs 72.0%), were enrolled in a non-US region (74.9% vs 79.5%), had negative BRAF mutational status (61.0% vs 62.1%), had a baseline

LDH \leq ULN (61.8% vs 69.7%), were PD-L1 positive at baseline (66.8% vs 63.0%), and have IVM1c disease (41.9% vs 41.3%).

Additional data from the primary analysis showed that the ORR achieved with the doublet was 48.6% (95% CI, 43.3%-53.8%) by BICR and per RECIST v1.1 criteria; the CRR was 17.9% (95% CI, 13.9%-22.0%) and the DRR was 42.2% (95% CI, 37.0%-47.4%). The median DOR was 43.7 months (95% CI-not estimable [NE]). In the monotherapy arm, the ORR was 41.3% (95% CI, 36.1%-45.5%), the CRR was 11.6% (95% CI, 8.2%-14.9%),

fatal AE. Five of these effects were determined to be related to treatment. In the T-VEC/pembrolizumab arm, 1 patient experienced atypical pneumonia, 1 had cardiac arrest, and 1 had delirium, and 1 had pulmonary sepsis; in the pembrolizumab-alone arm, 1 patient had respiratory failure.

Any-grade immune-related AEs (irAEs) were reported in 27.5% of patients who received the doublet and 24.8% of those who were given the monotherapy. The most common irAEs in the investigative and control arms were hypothyroidism



T-VEC is an oncolytic viral intratumoral therapy designed to produce granulocyte-macrophage colony-stimulating factor.

and the DRR was 34.1% (95% CI, 29.1%-39.1%). The median DOR was not NE with pembrolizumab alone.

Regarding safety, treatment-related toxicities were reported by 88.4% of those who were given T-VEC plus pembrolizumab vs 74.6% of those given pembrolizumab alone. The most common adverse effects (AEs) reported in the investigative and control arms were pyrexia (35.1% vs 5.0%, respectively) and fatigue (31.3% vs 22.2%).

Grade 3 or higher treatment-related AEs were experienced by 20.3% of those in the doublet arm and 15.7% of those in the monotherapy arm. Five patients on the investigative arm and 42 patients on the control arm had a

(12.5% vs 13.4%) and hyperthyroidism (5.8% vs 5.0%).

References

1. Chesney JA, Ribas A, Long GV, et al. Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma. *J Clin Oncol*. Published online August 23, 2022. doi:10.1200/JCO.22.00343
2. Long G, Dummer R, Johnson D, et al. 429 Long-term analysis of MASTERKEY-265 phase 1b trial of talimogene laherparepvec (T-VEC) plus pembrolizumab in patients with unresectable stage IIIB-IVM1c melanoma. *J Immunother Cancer*. 2020;8(suppl 3). doi:10.1136/jitc-2020-SITC2020.0429

Relatlimab Plus Nivolumab Approaches EU Approval for Advanced Melanoma With PD-L1 of <1%

KRISTI ROSA

THE EUROPEAN Medicines Agency's Committee for Medicinal Products for Human Use has recommended the approval of the fixed-dose combination of nivolumab (Opdivo) and relatlimab (Opdualog) for the frontline treatment of adult and adolescents who are 12 years of age or older with advanced melanoma and a tumor cell PD-L1 expression of less than 1%.¹

The proposed indication was supported by findings from an exploratory analysis of patients with a PD-L1 expression of less than 1% who were examined in the phase 2/3 RELATIVITY-047 trial (NCT03470922).

Data presented during the 2022 ASCO Annual Meeting showed that the hazard ratio (HR) for progression-free survival (PFS) by blinded independent central review (BICR) in those with a PD-L1 expression of less than 1% (n = 209) was 0.68 (95% CI, 0.53-0.86). The HR for overall survival (OS) in this subset was 0.78 (95% CI, 0.59-1.04).²

"We are very proud of the role we have played in progressing the treatment of advanced melanoma over the years. As part of our mission to deliver new medicines for patients, we have continued to develop new dual immunotherapy combinations," Paul Basciano, development lead of relatlimab at Bristol Myers Squibb (BMS), stated in a press release. "This positive CHMP opinion marks the first step toward the potential approval of the first LAG-3-blocking antibody combination – and the third distinct checkpoint inhibitor for BMS – for advanced melanoma patients in the European Union."

The global, randomized, double-blind, gated, phase 2/3 RELATIVITY-047 trial enrolled patients with previously untreated, unresectable, or metastatic melanoma who had an ECOG performance

status of 0 or 1.

A total of 714 study participants were randomized 1:1 to receive the fixed-dose combination of nivolumab at 480 mg plus relatlimab at 160 mg intravenously (IV) every 4 weeks (n = 355) or IV nivolumab at 480 mg every 4 weeks (n = 359).

Patients were stratified by LAG-3 expression on immune cells in the tumor microenvironment, PD-L1 expression on tumor cells, BRAF mutational status, and AJCC v8 metastatic stage.

The primary end point of the trial was PFS by BICR, and secondary end points included OS and objective response rate (ORR) by BICR. Moreover, end points were hierarchically tested starting with PFS, followed by OS, and then ORR.

The median age of patients was 63 years (range, 20-94), and 41.7% were female. Regarding AJCC v8 M stage, 25.8% had M1A stage, 24.2% had M1B stage, 38.9% had M1C stage, and 2.4% had M1D stage. Additionally, 66.9% of patients had an ECOG performance status of 0, 36.1% had a serum lactate dehydrogenase level above the upper limit of normal, and 8.4% previously received neoadjuvant or adjuvant treatment.

Regarding LAG-3 expression, 75.2% of patients had expression of 1% or higher and 24.8% had expression of less than 1%. Forty-one percent of patients had a PD-L1 expression of 1% or higher and 59% had an expression of less than 1%. Regarding BRAF mutational status, 38.5% had mutated disease, and 61.5% had wild-type disease. Moreover, 65.7% of patients had AJCC M stage of M0/M1any[0] and 34.3% had M1any[1].

In March 2022, the FDA approved relatlimab plus nivolumab for the treatment of adult and pediatric patients aged 12 years and older with unresectable or metastatic melanoma.³ The decision

was supported by earlier findings from the trial, which showed that the doublet resulted in a median PFS of 10.1 months (95% CI, 6.4-15.7) compared with 4.6 months (95% CI, 3.4-5.6) with standard nivolumab monotherapy (HR, 0.75; 95% CI, 0.62-0.92; P = .0055).

Updated data showed that at a median follow-up of 19.3 months, the PFS benefits achieved with the combination were maintained.² The median PFS with nivolumab/relatlimab was 10.22 months (95% CI, 6.51-14.75) vs 4.63 months (95% CI, 3.48-6.44) with single-agent nivolumab (HR, 0.78; 95% CI, 0.64-0.94).

The 12-month PFS rates in the investigative and control arms were 48.0% (95% CI, 42.5%-53.4%) and 36.9% (95% CI, 31.7%-42.1%), respectively; at 24 months, these rates were 38.5% (95% CI, 32.7%-44.2%) and 29.0% (95% CI, 23.8%-34.4%), respectively.

With 19.3 months of follow-up, the doublet resulted in a clinically meaningful improvement in OS vs nivolumab monotherapy, although this improvement was not determined to be of statistical significance. In those who received the doublet, the median OS had not yet been reached (NR; 95% CI, 34.20-NR) vs 34.10 months (95% CI, 25.23-NR) in those who received nivolumab alone (HR, 0.80; 95% CI, 0.64-1.01; P = .0593).

The 12-month OS rates in the investigative and control arms were 77.0% (95% CI, 72.2%-81.1%) and 71.6% (95% CI, 66.6%-76.0%), respectively, and the 24-month OS rates were 63.7% (95% CI, 58.1%-68.7%) and 58.3% (95% CI, 52.7%-63.4%), respectively. The 36-month OS rates in these arms were 55.8% (95% CI, 49.8%-61.4%) and 48.8% (95% CI, 42.7%-54.7%), respectively.

Additionally, the doublet elicited an ORR of 43.1% (95% CI, 37.9%-48.4%) per BICR vs 32.6% (95% CI, 27.8%-37.7%) with nivolumab monotherapy, translating to a 10.3% difference between the arms (95% CI, 3.4-17.3) with an odds ratio of 1.6 (95% CI, 1.2-2.2). In the combination arm, 16.3% achieved a complete response (CR), 26.8% had a partial response (PR), and 18.2% achieved stable disease; in

the monotherapy arm, the CR rate was 14.2%, the PR rate was 18.4%, and the stable disease rate was 16.4%. Those in the investigative arm experienced a lower rate of progressive disease than those in the control arm, at 29.6% vs 41.5%, respectively.

Common treatment-related toxicities included pruritus, fatigue, rash, hypothyroidism, arthralgia, diarrhea, and vitiligo. Any-grade treatment-related adverse effects (TRAEs) were reported in 83.7% of those in the combination arm and 72.4% of those in the monotherapy arm; they led to discontinuation in 15.2% and 7.2% of patients, respectively.

Grade 3 or 4 TRAEs were reported in 21.1% and 11.1% of those in the investigative and control arms, respectively; these effects resulted in discontinuation in 9.0% and 3.6% of patients, respectively. Treatment-related deaths occurred in 4 patients in the investigative arm and 2 patients in the control arm.

Reference

1. Bristol Myers Squibb receives positive CHMP opinion recommending approval for LAG-3-blocking antibody combination Opdualag (nivolumab and relatlimab) for treatment of patients with unresectable or metastatic melanoma. News release. Bristol Myers Squibb. July 22, 2022. Accessed July 22, 2022. <https://bit.ly/3Ou0Ykn>

2. Long GV, Hodi FS, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma: overall survival and response rates from RELATIVITY-047 (CA224-047). *J Clin Oncol*. 2022;40(suppl 36):360385. doi:10.1200/JCO.2022.40.36_suppl.360385
3. US Food and Drug Administration approves first LAG-3-blocking antibody combination, Opdualag (nivolumab and relatlimab-rmbw), as treatment for patients with unresectable or metastatic melanoma. News release. Bristol Myers Squibb; March 18, 2022. Accessed July 22, 2022. <https://bit.ly/3wk6PDx>

Adjuvant Pembrolizumab Wins European Approval for Stage IIB/IIC Melanoma Following Complete Resection

CHRIS RYAN

THE EUROPEAN COMMISSION (EC) has approved pembrolizumab (Keytruda) for adjuvant treatment of adult and adolescent patients 12 years and older with stage IIB or IIC melanoma who have undergone a complete resection.¹

Furthermore, the EC expanded the indications for pembrolizumab to include adolescent patients aged 12 years and older with advanced unresectable or metastatic melanoma and stage III melanoma as an adjuvant treatment following complete resection.

“When melanoma recurs, patients often have a significantly worse long-term prognosis, especially if the cancer returns or spreads to distant sites,” Alexander Eggermont, MD, PhD, chief scientific officer of the Princess Máxima Center for Pediatric Oncology in the Netherlands, stated in a press release. “This approval further reinforces the important role of adjuvant therapy for patients 12 years and older with completely resected stage

IIB and IIC melanoma who now have a treatment option that has demonstrated the potential to significantly reduce the risk of their cancer returning.”

The commission based its approval on findings from the phase 3 KEYNOTE-716 trial (NCT03553836) in which pembrolizumab significantly prolonged recurrence-free survival (RFS) vs placebo. At a median follow-up of 20.5 months, pembrolizumab reduced the risk of recurrence or death by 39% (HR, 0.61; 95% CI, 0.45-0.82; P = .00046). Additionally, at a median follow-up of 26.9 months, pembrolizumab lowered the risk of distant metastasis by 36% vs placebo (HR, 0.64; 95% CI, 0.47-0.88; P = .00292).

In December 2021, the FDA approved pembrolizumab for the adjuvant treatment of adult and pediatric patients with stage IIB or IIC melanoma following complete resection based on data from KEYNOTE-716.²

The trial enrolled 976 patients who

were at least 12 years old with newly diagnosed, resected, high-risk, stage II melanoma with a negative sentinel lymph node biopsy. Patients were also required to have an ECOG performance status of 0 or 1.³

Patients were randomly assigned to 200 mg of intravenous (IV) pembrolizumab (n = 487) or IV placebo (n = 489) once every 3 weeks for 17 cycles. Stratification factors included T-category (3b, 4a, and 4b) and pediatric status.

The primary end point of the trial was RFS per investigator assessment. Secondary end points included distant metastasis-free survival, overall survival, and safety.

Additional data presented at the 2022 ASCO Annual Meeting showed that at a median follow-up of 37.2 months, patients in the pembrolizumab arm continued to see a benefit in RFS (HR, 0.64; 95% CI, 0.50-0.84).³The 24-month RFS rates in the pembrolizumab and placebo arms were 81.2% and 72.8%, respectively.

Investigators have evaluated single-agent pembrolizumab for safety in 7631 patients across multiple tumor types. The rate of any-grade immune-related adverse effects (IRAEs) in the adjuvant setting was 36.1% and the rate of grade 3-5 IRAEs

was 8.9%. Investigators observed no new IRAEs with adjuvant pembrolizumab.

“Melanoma continues to be a public health burden in Europe, claiming more than 26,000 lives in 2020, with rates rising annually,” Scot Ebbinghaus, MD, vice president of Global Clinical Development at Merck Research Laboratories, said in a press release. “[Pembrolizumab] has become the first anti-PD-1 adjuvant treatment option approved in the EU for patients 12 years and older across stage IIB, IIC and III melanoma following complete resection, based on data that

show the potential of [pembrolizumab] to help reduce the risk of recurrence, including as distant metastases, in these patients. This approval furthers our commitment to finding new effective options for even more patients with melanoma.”

Reference

1. European Commission approves KEYTRUDA® (pembrolizumab) as adjuvant treatment for adult and adolescent patients (≥12 years of age) with stage IIB or IIC melanoma following complete resection. News release. Merck. June 24, 2022.

2. FDA approves Merck's KEYTRUDA (pembrolizumab) as adjuvant treatment for adult and pediatric (≥12 years of age) patients with stage IIB or IIC melanoma following complete resection. News release. Merck; December 3, 2021. Accessed June 24, 2022. <https://bit.ly/3DrqYal>
3. Long GV, Luke JJ, Khattak M, et al. Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study. *J Clin Oncol*. 2022;40(suppl 17):LBA9500. doi:10.1200/JCO.2022.40.17_suppl.LBA9500

Cobolimab Plus Dostarlimab Achieves Clinical Responses in Advanced Melanoma

CAROLINE SEYMOUR

IMMUNOTHERAPY HAS LED a transformation for melanoma care but combinations of anti-PD-1 and CTLA-4 presentation by Caroline Robert, MD, PhD, at the 2017 World Congress of Melanoma.

Treatment with the combination of cobolimab and dostarlimab (Jemperli) led to an overall objective response rate (ORR) and immune-related ORR of 42.9% (n = 12/28) consisting of all partial responses (PRs) in patients with advanced or metastatic melanoma, according to data from the phase 1 AMBER study (NCT02817633) presented at the 2022 ASCO Annual Meeting.

“Cobolimab plus dostarlimab showed preliminary antitumor activity, supporting the rationale for dual TIM-3 and PD-1 blockade in advanced or metastatic solid tumors,” lead study author Antoni Ribas, MD, PhD, of the University of California, Los Angeles, said in a presentation of the data.

TIM-3 is an immune checkpoint receptor that is associated with inhibitory antitumor responses, but concurrent TIM-3 and PD-1 blockade is more effective at reducing tumor growth than either

pathway alone. Cobolimab is a selective anti-TIM-3 monoclonal antibody that activates immune cell function and induces substantial antitumor activity in combination with anti-PD-1 agents like dostarlimab.

As such, investigators evaluated the safety of cobolimab plus dostarlimab in patients with metastatic solid tumors (parts 1 and 2) and efficacy in patients with advanced or metastatic melanoma (parts 1C and 1E).

The open-label, multicenter study was split into 2 parts: a dose-escalation (part 1 A-H) and -expansion (part 2 A-D) phase.

To be eligible for enrollment, patients had to be at least 18 years of age and have an ECOG performance status of 0 or 1. In part 1C, patients had to have advanced or metastatic solid tumors, including immunotherapy-naïve melanoma and disease progression on or intolerance to prior therapy. In part 1E, patients had to have advanced or metastatic immunotherapy-naïve melanoma with or without prior treatment.

Key exclusion criteria included a

history of grade 3 or greater immune-related adverse effects (AEs) with prior immunotherapy and active autoimmune disease requiring systemic therapy. In part 1E, the 300-mg or higher dose levels for dostarlimab excluded patients with uveal melanoma.

In part 1C (n = 10), patients received 1 of 3 doses of intravenous (IV) cobolimab: 100 mg, 300 mg, or 900 mg plus 500 mg of IV dostarlimab. In part 1E (n = 18), patients received either 300 mg or 900 mg of IV cobolimab plus 500 mg of IV dostarlimab.

Parts 1A through C evaluated the efficacy and safety of cobolimab as a single agent and in combination with dostarlimab or nivolumab (Opdivo) in patients with advanced or metastatic solid tumors.

Treatment was continued every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or death for up to 2 years.

The primary end points in part 1C were safety and tolerability, as well as to identify the recommended phase 2 dose (RP2D) for the regimen. In part 1E, the primary end point was the ORR including PRs and complete responses (CRs) per RECIST v1.1 criteria.

The secondary end point in part 1C was the ORR per RECIST v1.1 criteria. Exploratory end points in both cohorts included the disease control rate (DCR)

including stable disease for at least 16 weeks, PR or CR per RECIST v1.1 criteria, and ORR and DCR per immune-related RECIST criteria.

Additional results showed that at the RP2D of 300 mg of cobolimab and 500 mg of dostarlimab, the ORR was 57.1% (n = 8/14).

In this population, the median patient age was 66.0 years (range, 30.0-90.0), and most patients were male (n = 162/273; 59.3%), Caucasian (n = 238/273; 87.2%), and had an ECOG PS of 1 (n = 171/273; 62.6%). In parts 1C and 1E, most patients had cutaneous melanoma (82.1%) and an ECOG performance status of 0 (67.9%).

“Cobolimab in combination with dostarlimab had a manageable safety profile, with no new toxicities identified, in an integrated safety analysis that included 273 patients with advanced or metastatic

solid tumors,” Ribas said.

Any-grade and grade 3 or greater treatment-related treatment-emergent adverse effects (TR-TEAEs) occurred in 57.4% (n = 159) and 13.4% (n = 37) of patients, respectively. The most common any-grade TR-TEAEs were fatigue (n = 48; 17.3%), rash (n = 21; 7.6%), diarrhea (n = 19; 6.9%), and dyspnea (n = 8; 2.9%). Serious TR-TEAEs and TR-TEAEs leading to discontinuation occurred in 8.7% (n = 24) and 4.7% (n = 13) of patients, respectively.

In the target-dose cohort (n = 167), the incidences were lower with regard to fatigue (n = 22; 13.2%), rash (n = 9; 5.4%), diarrhea (n = 10; 6.0%), and dyspnea (n = 0). Additionally, any-grade and grade 3 or greater TR-TEAEs occurred in 57.5% (n = 96) and 10.8% (n = 18) of patients, respectively. Serious TR-TEAEs and TR-TEAEs leading to discontinuation

occurred in 7.8% (n = 13) and 4.2% (n = 7) of patients in this cohort, respectively.

Ongoing research with the agent includes the randomized phase 2 COSTAR trial (NCT04655976), which is evaluating cobolimab plus dostarlimab and docetaxel vs docetaxel alone in relapsed/refractory non-small cell lung cancer following PD-1/PD-L1 inhibition, and a phase 2 study (NCT04139902) evaluating neoadjuvant cobolimab plus dostarlimab vs dostarlimab alone in high-risk, resectable melanoma.

Reference

1. Ribas A, Eroglu Z, Trigo Perez JMM, et al. AMBER parts 1c and 1e: A phase 1 study of cobolimab plus dostarlimab in patients (pts) with advanced/metastatic melanoma. *J Clin Oncol.* 2022;40(suppl 16):9513. doi:10.1200/JCO.2022.40.16_suppl.9513

Gibney Breaks Down the Evolving Treatment Landscape of Melanoma

JASON HARRIS

BRENTUXIMAB VEDOTIN (Adcetris) has been approved by the European Commission for the treatment of patients with CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

A lack of approved treatment options exist for patients with melanoma who have progressed on an anti-PD-1 therapy in later lines of treatment, according to Geoffrey T. Gibney, MD. However, new clinical trials evaluating agents such as tumor infiltrating lymphocyte (TIL) therapy, TLR-9 agonists, and combination therapies are working to address this unmet need.

“We look at the melanoma field, and we see a lot of exciting developments. This is clearly changing the course for patients. The treatment decisions are getting more complex, and this requires more of a multidisciplinary, integrated approach. This is particularly [true] when patients have multiple options that include surgery,

radiation, or systemic therapy,” Gibney said in an interview with OncLive® following an Institutional Perspectives in Cancer (IPC) webinar on melanoma.

In the interview, Gibney, who chaired the event, reviewed the topics from the meeting including current treatment options for patients with melanoma, clinical trials that have explored different agents and combinations, and developing treatment options in uveal melanoma. Gibney is a co-leader of the Melanoma Disease Group at the Georgetown Lombardi Comprehensive Cancer Center and the MedStar Cancer Network, and a member of the Developmental Therapeutics (Phase I) program.

OncLive®: What has been the most exciting advance in uveal melanoma in the past year?

Gibney: [At] the [IPC] meeting, we

discussed advanced melanoma, looking at both frontline [treatment], as well as the second- or third-line [treatment]. We then did a deeper dive into newer data for uveal melanoma, where there’s still a very large unmet need. Fortunately, we now have approval of the new immunotherapy, tebentafusp-tebn [(Kimmtrak) for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma], but still clearly a lot more work needs to be done.

Michael B. Atkins, MD, of Georgetown Lombardi Comprehensive Cancer Center, discussed newly diagnosed metastatic melanoma. How does the presence of a BRAF mutation affect how immunotherapy is sequenced?

My colleague, Michael Atkins, MD, presented on frontline data, and we fortunately have a number of frontline therapies to offer patients, particularly if there’s a BRAF mutation that’s present in the tumor.

Dr Atkins led a national study called the phase 3 DREAMseq study [NCT02224781] that set the bar for immunotherapy first in

this population. We then saw an improvement in the 2-year overall survival [OS] from that data. This has now set the standard for using combination immunotherapy with nivolumab [Opdivo] and ipilimumab [Yervoy] in the frontline setting in this population.

We now have another immunotherapy combination that has been FDA approved: nivolumab and relatlimab-rmbw [(Opdualag), based on findings from the phase 2/3 RELATIVITY-047 trial (NCT03470922)]. These combinations have not been compared head-to-head, but the data look equally impressive. [Relatlimab plus nivolumab] also has benefit in patients with BRAF mutations. The safety profile looks a little more favorable compared with nivolumab plus ipilimumab, but we don't have any long-term data yet, nor do we have brain metastases data. We don't have all the pieces we would like for utilizing nivolumab and relatlimab. That said, it's still a good option to offer patients, particularly in those who may have been hesitant for the ipilimumab toxicity, where we would just offer just [nivolumab] monotherapy. That would be a great patient to offer nivolumab and relatlimab to.

At the meeting, you presented on novel approaches for relapsed/refractory melanoma. What current novel approaches are utilized in this setting?

I spoke on the salvage setting in patients who progressed on an anti-PD-1 monotherapy. This could be a patient who received therapy in the adjuvant setting and relapsed, and also in the setting where a patient has active disease or stage IV disease and either did not respond or had a good response [before progressing]. Unfortunately, we see this often, and there's an unmet need of treating patients in the second and third line.

There have now been 2 studies looking at nivolumab/ipilimumab or pembrolizumab [Keytruda]/ipilimumab in the second-line setting. We're fortunate to have the data, and it lined up well, showing similar results where we have a response rate of almost 30%. Many of those responses look durable.

We saw in the phase 2 SWOG S1616

trial [NCT03033576] with nivolumab/ipilimumab that greater efficacy [is observed] when using the nivolumab/ipilimumab combination compared with ipilimumab monotherapy. Now that we have that data, it's settled the discussion that patients in the salvage setting should receive a combination of a PD-1 drug, such as nivolumab/ipilimumab.

What salvage regimens are under study that are generating excitement for these patients?

There are several agents that are in clinical investigations and some of them are far along. One [regimen] that we spent time talking about was adoptive T-cell therapy, or TIL therapy. Data from a phase 2 trial [NCT03645928] are probably the most mature, and we are hoping to have an FDA approval soon for this. This is a technique that has been around since the 1980s and now has become more of a commercialized product. We are excited to be able to offer this treatment to patients, hopefully soon, as a standard therapy.

[TIL therapy has produced a] response rate of 36%, and a large portion of the responses are durable, and we hope permanent. Past studies with TIL therapy have shown durable and long-lasting responses with a single course of treatment, and we anticipate that will be the same in the salvage setting. We are still waiting for long-term follow up on that data, but this is an exciting therapy to be able to offer patients, particularly after they've progressed through anti-PD-1 and anti-CTLA-4 therapy.

We also touched on other evolving data, such as with the TLR-9 agonist, vidutolimod [CMP-001]. This has shown activity in patients as monotherapy and in combination with anti-PD-1 therapy. We've seen a response rate of approximately 20% with both regimens, and it is more durable when you have a PD-1 drug in combination. We're hopeful that this will become another approved regimen for patients, which is currently only available in clinical trials.

There is a range of other options that look very exciting, and we are waiting for

more mature data. Looking at the NCCN guidelines, there's a number of other regimens that can be offered to patients, although we're still looking for even more effective therapies.

How is TIL therapy utilized as a post-PD-1 treatment?

When patients have been treated with an anti-PD-1 regimen and develop either relapse or progression, it is a challenge for those in the clinic. We see in the adjuvant setting that more than one-third of patients relapse after anti-PD-1 therapy, and in terms of patients with active disease, over half of patients won't respond up front, or will respond and then progress. This is an area where we need more therapy.

Adoptive T-cell therapy, or TIL therapy has been around for over 20 years, initially studied in patients that were not exposed to anti-PD-1 drugs. We now have data in the population where patients have previously been treated and had progression on anti-PD-1 therapy. This has now become an exciting area where we have seen objective responses in patients who have now progressed on an anti-PD-1 regimen.

We discussed data from the phase 2 trial [mentioned above] in anti-PD-1 refractory melanoma. In that study, using a standard TIL therapy technique of harvesting a tumor, TIL is manufactured in a laboratory, a patient is brought into the hospital, given lymphodepleting chemotherapy, their TIL therapy, and then a course of IL-2.

We've seen a response rate of 36% in that data set. This is one of the highest response rates seen in patients who have progressed on an anti-PD-1 therapy before being treated with another immunotherapy. This is very exciting. We have seen that many of these responses are durable with that single course of treatment. Potentially, these patients may not need any further therapy for their melanoma, and they can go on with the rest of their lives. Having this available as a salvage regimen, we're expecting and hoping that we will have FDA approval in this upcoming year, and we will be able to offer TIL therapy to patients as standard-of-care therapy.